

## Chapter 2

# Pulmonary Hypertension in Interstitial Lung Disease

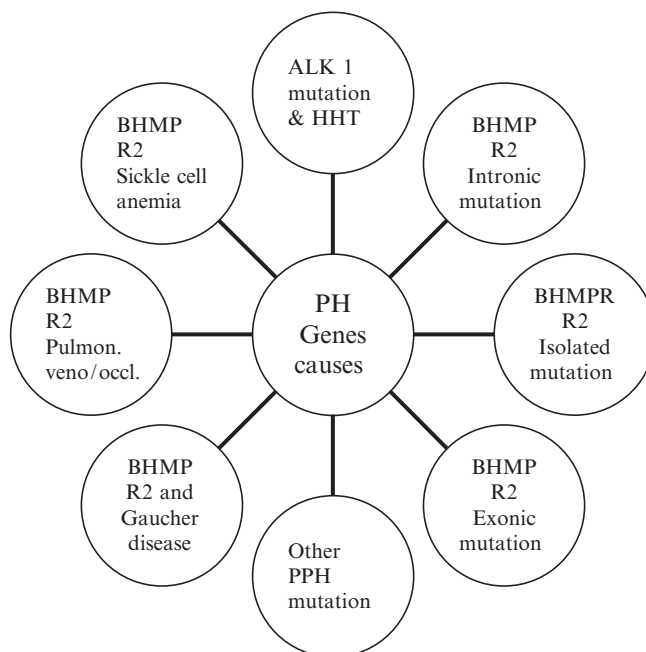
Roberto G. Carbone, Assaf Monselise, and Giovanni Bottino

### Genetic Factors Associated With Interstitial Lung Disease (ILD): View in Relation to Pulmonary Hypertension (PH)

The development of family registries and the banking of deoxyribonucleic acid has enabled researchers to search for a marker for familial PH on chromosome 2q 31/32. As a result, the bone morphogenetic protein factor receptor type 2 gene (BMPR2) on chromosome 2q 33, having 13 exons, was discovered. Mutations in familial PH have been reported in all exons except for 5 and 13. Humbert et al. [1] cited mutations of BMPR2 in PH associated with fenfluramine derivatives. These data are concordant with the working hypothesis that gene–gene or gene–environmental interactions are required for PH. Conversely, Morse et al. [2] and Tew et al. [3], who studied patients with scleroderma and PH, did not find the presence of BMPR2 mutations.

Recently, Trembart et al. [4] have found a second PH gene in some patients with hereditary hemorrhagic teleangiectasia lesions whose mutation in active/like kinase type/1 (ALK1) receptor confers a predisposition to PH and hereditary hemorrhagic teleangiectasia lesions. Both BMPR2 and ALK1 genes are two receptors in the transforming growth factor (TGF)- $\beta$  family. Multiple genetic causes associated with PH are summarised in Fig. 2.1.

Du et al. [5,6] have described the genetic mechanism of PH. According to their hypothesis, an unknown stimulus involved in the TGF- $\beta$  receptor pathway increases angiopoietin-1 and its receptor TIE2, which decreases the BMPR1A receptor. The latter is required for the optimization of the BMPR2A receptor. Mutant forms of BMPR2A and mALK1 are associated with familial forms of PH, and both are involved in signaling through growth promoting proteins, which finally stimulate vascular smooth muscle remodelling. The study of genes associated with the risk of acquiring PH is complex from a statistical point of view. PH is probably the result of an interaction between the BMPR2 genes with environmental factors and will be continue to be a subject of future investigations.



**Fig. 2.1** PH genetic causes

## View in Relation to ILD

Mutations of the surfactant protein C gene could be the cause of pathological forms of IPF, including nonspecific interstitial pneumonia (NSIP), desquamitive interstitial pneumonia (DIP), and usual interstitial pneumonia (UIP). Noguee et al. [7] showed that mature surfactant protein C is derived from the proteolysis of a 197 amino acid pro-protein. The surfactant protein C precursor protein is an integral membrane protein that is anchored to the membrane by a mature surfactant protein C. A deletion in the domain of the surfactant protein C precursor protein causes a disruption in the intracellular transport with a consequent degradation of this protein. A lack of mature surfactant protein C in lung tissue and bronchoalveolar lavage (BAL) fluid is an indication that the precursor protein has not being processed and secreted normally.

The absence of the surfactant protein/C (SP/C) or an abnormal production of the pro SP/C protein could both lead to severe ILD, as recently described by Amin et al. [8] in a family with ILD. In particular, the defective SP/C could be the cause of mechanical injury to the respiratory epithelial type II cells and thereby the alveoli, contributing to the pathogenesis of IPF. The clinical course of ILD as the result of surfactant protein C gene mutations appears could be quite long, ranging up to few decades. Evidence suggests a common viral respiratory infection as a trigger for the disease. Nineteen percent of patients who received a lung transplantation for IPF had

a positive family history. Studying IPF in families may be the most effective method for understanding this disease. Several studies have provided evidence for the importance of TGF- $\beta$ 1 gene polymorphism in disease progression of IPF [9–13].

A study of the distribution, concentration, and profibrotic effects of a mutant TGF- $\beta$ 1 protein in lung tissue of patients with IPF is expected in the near future. A hypothesis that suggests a potential role for a genetic variant of TGF- $\beta$ 1 in disease progression of IPF must be confirmed in larger studies [14].

## PH: Physiology in ILD

Pulmonary circulation is influenced by different physiologic conditions. Regional differences in blood flow occur during standing as the result of differences in the hydrostatic pressures between pulmonary artery, alveolar, and venous pressures. Blood flow does not depend on the pulmonary venous pressure but on a pressure gradient existing between pulmonary artery and alveolar pressure. For illustrative purposes, the lung can be divided in four zones: West zones I–IV in the standard position. In West zone I, the pulmonary artery pressure exceeds the alveolar pressure, and it is not present in human subjects under physiologic conditions because the pulmonary artery pressure always exceeds the alveolar pressure. The apex of the lung corresponds to West zone II. Blood flow in this zone follows the waterfall principle (Sterling resistance). The middle and lower portions of the lung correspond to West zones III and IV, respectively. Pulmonary vessels here are characterised by their capability to fully distend as a result of the augmented perfusion during physical activity.

In addition to this passive recruitment, an active vasodilation also could take place. The vasoconstrictive effect of hypoxia on pulmonary vessels is denominated hypoxic pulmonary vasoconstriction (HPV). HPV is mediated by cyclic AMP (cAMP) and cyclic GMP (cGMP) in smooth muscle cells of precapillary vessels. These two molecules regulate calcium concentration in the cytoplasm, thereby permitting the interaction of actin and myosin filaments. A cascade of events begins with the activation of G proteins by a series of ligands: caffeine, thromboxane  $A_2$ , noradrenaline, vasopressin ( $AVP_1$  receptor), angiotensin II, and endothelin ( $ETA$  receptor), or by membrane depolarization, which blocks the potassium channels. Activated G proteins lead to PLC (phospholipase C)-mediated breakdown of inositol polyphospholipids PIP<sub>2</sub> from membrane phospholipids, which give origin to inositol triphosphate IP<sub>3</sub> and diacylglycerol DG. The interaction of the former with the sarcoplasmic reticulum causes an efflux of calcium ions into the cytoplasm.

Potassium channels also play an important role in the mechanism of HPV by influencing the membrane potential, which leads to the generation of cAMP and cGMP [15–17]. Cyclic GMP (cGMP) is activated by nitric oxide (NO), a potent vasoactive mediator, as well as by atrial natriuretic peptide (ANP) and brain natriuretic peptide. Cyclic AMP (cAMP) is activated by prostacyclin via the IP receptor and by catecholamines via  $B_2$  adrenergic and  $D_1$  dopaminergic receptors).

Phosphodiesterases (PDE4 and PDE5) inactivate cAMP and cGMP by cleavage of the two molecules, thereby permitting vasodilation.

Different subtypes of potassium channels have been identified in pulmonary vessels. Of particular interest is the  $K_{DR}$  subtype, which is important for the control of pulmonary vascular resistance. One of the  $K_{DR}$  channel components is present in scarce quantities in patients with PPH and is therefore thought to predispose them to the disease. Some subtypes of potassium channels are inhibited by appetite suppressants, such as dexfenfluramine. It seems that HPV is regulated by  $O_2$  concentration, mechanism of which lies within pulmonary artery smooth muscle cells (SPAM cells). The mechanism is not well understood, but it appears to be related to an NADPH oxidase shown to exist also in oxygen-sensitive cells of the carotid body. During hypoxia, SPAM cells produce super oxide anions, which are converted by super oxide dismutase to hydrogen peroxide. The latter is degraded by a catalase to  $H_2O$  and  $O_2$ . It may be possible to block HPV by inhibiting the enzyme NADPH oxidase with diphenyleniodonium or by blocking the super oxide dismutase (Fig. 2.2) [18,19].

The final step in the chain of reactions bringing to HPV is dependent upon SPAM cell intracytoplasmatic concentration of calcium ions [20]. During hypoxia, the decrease in SPAM cells in the potassium concentration leads to membrane depolarisation, thereby permitting the influx of calcium ions into the cytoplasm, which leads to a cascade of events terminating in vasoconstriction.

Oxygen may be a direct activator of the potassium channels; otherwise, its effect could be mediated by intracellular changes in the redox potential with the formation of super oxide and peroxide anions, calcium ions. Indeed, it has been suggested that the NADPH oxidase is part of this oxygen-sensitive potassium channel. Recent studies have demonstrated that calcium channel antagonists, endothelin, and alpha-adrenergic antagonists block HPV. Some vasodilators, such as prostacyclin and NO, are able to counteract HPV [21].

Prostacyclin is an endothelium-derived antiaggregator molecule with vasodilating properties. Prostaglandin  $I_2$  is a potent vasodilator with antiproliferative effects on smooth muscle fibres and fibroblasts [6]. It is an unstable molecule with a half-life of 2–3 min in the circulation, necessitating a continuous infusion while treating patients with PH.

Endothelin 1 (ET-1), a polypeptide synthesised by endothelial cells, is considered to be the most potent vasoconstrictor among the vasoactive peptides known.

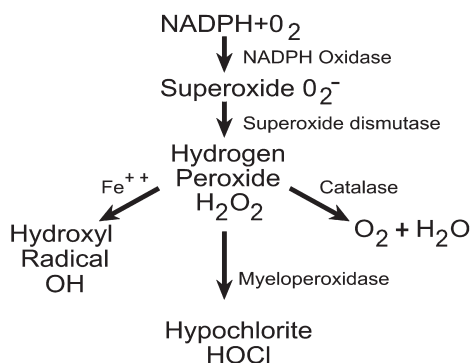


Fig. 2.2 Structure

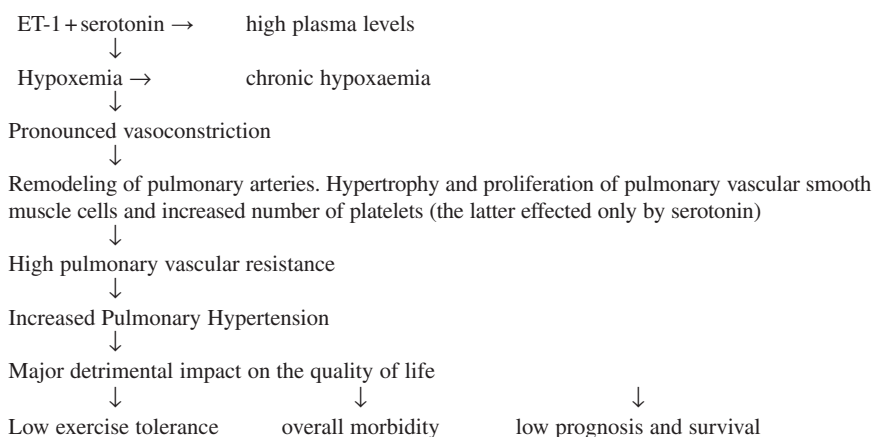
The profibrotic, proinflammatory, proliferative, and vasoconstrictive effects of ET-1 are mediated through ET receptors [22,23]. Increased pulmonary vascular tone in PH is caused by a combination of factors: (1) enhanced ET-1 activity, a result of increased circulating ET-1 and increased expression of ET<sub>A</sub> receptors, which mediates pulmonary vasoconstriction; (2) a decrease in vasodilators such as prostacyclin and NO; (3) vascular remodeling through the proliferation of pulmonary artery smooth muscle cells, resulting in medial hypertrophy and intimal hyperplasia; and (4) ET-1-induced platelet aggregation and hypoxia, which lead to an increase in endothelin secretion and stimulation of fibroblast proliferation. Stimulation of the ET-1R is a feature common to many disorders characterised by abnormal vasoconstriction, cell proliferation, and fibrosis, such as PH, pulmonary fibrosis, scleroderma, chronic heart failure, hypertension, and chronic renal failure (Table 2.1).

Two subtypes of ET-1 receptors are known: ET<sub>A</sub> and ET<sub>B</sub> [24,25]. The ET<sub>A</sub> isoform is selective in that it binds ET-1 and ET-2 with a higher affinity than ET-3, whereas the ET<sub>B</sub> R binds, in addition, a peptide named sarafotoxin S6c. Both subtypes are widely expressed on endothelial cells in lung and brain tissue. The expression ratio of the ET<sub>B</sub>R/ET<sub>A</sub>R in the lung interstitium, alveolar epithelium, and large pulmonary vessels is in favor of the former. Furthermore, an increased

**Table 2.1** Pathophysiology of PH

a) Factors contributing to hypoxemia

Endothelin-1 (ET-1) and serotonin play an important role in pulmonary vasoconstriction in vivo:



b) Factors that antagonise the effects of hypoxaemia

1. O<sub>2</sub> therapy
2. Calcium antagonists
3. Inhaled nitric oxide
4. Prostaglandin infusion
5. Prostaglandin infusion in association with bosentan
6. Prostaglandin by aerosol

expression of ET-1 was shown to exist in the airway epithelium and type-II pneumocytes of patients with IPF [26,27], and the lungs of patients with scleroderma, as compared with subjects without [28]. In the rat model of bleomycin-induced pulmonary fibrosis, ET-1 was found to be increased in airway epithelial cells and inflammatory cells. An ET antagonist could attenuate the development of fibrosis, which could be the result of a decrease in the inflammatory process [29]. Further support for the role of ET-1 in pulmonary fibrosis comes from the observation that overexpression of ET-1 in the lung is associated with progressive pulmonary fibrosis and recruitment of inflammatory cells, predominantly CD4 lymphocytes.

In this study by Hoher et al. [30], there was no significant development of PH. At present, there are a few studies in which the authors addressed the inflammatory and proliferative properties of ET[101–103]. Data regarding ET effects on angiogenesis related to pulmonary fibrosis are lacking. Indeed, the histopathological characteristics of IPF show features of dysregulated and abnormal repair with exaggerated angiogenesis, fibroblast proliferation, and deposition of extra cellular matrix, leading to progressive fibrosis and restrictive damage, as expressed in pulmonary function tests.

The first evidence of neovascularization in IPF was identified by Turner-Warwick et al. [31], who examined lungs of patients affected with interstitial lung diseases, and demonstrated neo vascularization leading to anastomoses between the systemic and pulmonary microvasculature.

Peao et al. [32] confirmed the evidence of neovascularization in the pathogenesis of bleomycin-induced pulmonary fibrosis after the perfusion of rat lungs with methacrylate resin. Using electron microscopy, Peao et al. [32] showed that the major vascular alterations that were located in the peribronchial regions consisted of the remodelling of the alveolar capillaries. The neovascularization was closely associated with regions of pulmonary fibrosis, similar to the findings in human lungs. However, further studies are necessary to investigate factors involved in angiogenetic regulation in pulmonary fibrosis.

In two reports, Kean et al. [33,34] demonstrated an imbalance of the CXC chemokine promoters of angiogenesis (CXCL5 and CXCL8) and inhibitors of angiogenesis (CXCL10) in IPF lung tissue. The chemokine imbalance, which promotes angiogenic activity in the lung tissue of patients with IPF, was reflected by increased levels of CXCL5 and CXCL8, in comparison with control patients. Lung epithelium was the source of CXCL5, whereas pulmonary fibroblasts were the predominant interstitial source of CXCL8. The increased angiogenic activity attributed to CXCL8 was accompanied by a decrease in the angiostatic factor CXCL10.

Hyde et al. [35] proposed that interferon (IFN)- $\gamma$ , a major inducer of CXCL10, could be an inhibitor of wound repair because of its angiostatic properties. However, at the same time, it has been shown to reduce fibrosis in bleomycin-induced pulmonary fibrosis. Kean et al. [36] confirmed that the imbalance of CXC chemokines was relevant to the process of pulmonary fibrosis: CXCL2 and CXCL10 were measured during bleomycine-induced pulmonary fibrosis in whole lung tissues and were found to be directly and indirectly correlated, respectively, with hydroxyproline concentration, a measure of collagen deposition. Indeed, these findings give further support to the theory that CXC chemokine regulated angiogenesis, is an important factor in the process of pulmonary fibrosis.

It is important to mention the interactions between ET-1 and ANP, an antagonist of the former. The importance of the vasoconstrictive effects of ET-1 are of particular concern in the phase of increased ANP levels. ANP suppresses ET-1 by a negative feedback mechanism, preventing endothelin-induced hypertension.

## Pathophysiology

PH, which is characterised by vasoconstriction and structural changes in the small pulmonary muscular arteries and arterioles, is a devastating disease, with progressive elevation of pulmonary artery pressure (PAP) and pulmonary vascular resistance, ultimately producing right heart failure and death [37].

Two facts are accepted to be related with the disease: (1) PH and the subsequent development of cor pulmonale are recognised consequences of ILD and (2) the presence of PH in patients with ILD results from hypoxic vasoconstriction. New data suggest that the PH mechanism is much more complex than it seemed to be. The mechanism leading to the development of PH involves primarily the obliteration of lung microvasculature caused by pulmonary thromboembolism and mechanical stress, the result of heart defects. Second, any form of PH, which may be caused by inflammatory diseases of the lung, collagen vascular diseases, toxic oil syndromes, and hypoxic pulmonary vasoconstriction, occurs with hypoxia and alveolar hypoventilation. The different types of etiopathogenesis cited lead to vasoconstriction and pulmonary vascular remodeling, aggravated by in situ thrombosis of the small pulmonary arteries.

PH is classified into three categories, based on the severity of the pulmonary hemodynamics: (1) latent PH, (2) manifest PH, and (3) severe or very severe PH. If one rules out the passive PH caused by an increase in left ventricular filling pressure, the possible causes of PH are (1) vasoconstriction, (2) loss of vascular cross-sectional area as the result of remodeling and the occlusion of small arteries, (3) the loss of parenchymal elasticity, and (4) a reduction in the active vasodilation mechanism.

### *Latent PH*

In patients with PH, at rest, the mean PAP remains normal (<21 mmHg). During physical exercise, the PAP increases to 28–30 mmHg. Patients are asymptomatic or manifest dyspnoea during strenuous physical activity.

### *Manifest PH*

In patients with manifest PH, PH is within normal range at rest. The majority of patients with a mean PAP between 21 and 30 mmHg exhibit lung diseases with secondary pulmonary hypertension (SPH). The maximum cardiac output shows a distinct limitation in the unadapted patient. The PAP increases to 30 mmHg or

greater during exercise. Cardiac output is limited during physical exercise only in adapted patients. The patients suffers from dyspnoea.

### ***Severe or Very Severe PH***

In patients with severe or very severe PH, a mean PAP of 30–45 mmHg at rest correlates with decompensation and lung diseases. A mean PAP of 40–70 mmHg at rest correlates with decompensation and chronic pulmonary embolism. Finally, a mean PAP of between 65 and 120 mmHg at rest correlates with Eisenmenger's Syndrome. When patients are at rest, there is reduced cardiac output.

Right ventricular adaptation is one of the most important prognostic factors in pulmonary hypertension. Initially, right ventricular hypertrophy compensates for the increased after load. The chamber decompensates when the pressure increases more rapidly than the adaptation mechanism. A moderate increase of pulmonary resistances and a slow progression of disease are good conditions for the development of right ventricular adaptation. On the whole, the factors that influence right ventricular remodeling are largely unknown.

There is evidence that the local ACE system of the heart might be activated during PH [38]. Pulmonary arteries develop structural changes in parallel with the chronic vasoconstriction. In situ thrombosis develops, accelerating the remodeling of small cells. As a consequence, there is a reduction of the vascular cross-sectional area and a loss of compliance. Structural changes in pulmonary arteries differ between small and large vessels: the latter assume aneurismal forms, whereas the lumen of the former is progressively diminished as the result of the remodeling process.

The term remodelling is used to describe changes in small diameter pulmonary vessels [39,40]. Normal-appearing pulmonary arterial vessels have a continuous media down to a diameter of approximately 80 µm. Distally to this point, vessels are partially muscular and contain so-called intermediate cells, which range in their properties somewhere between pericytes and smooth muscle cells. In the most peripheral vascular areas, there are only few pericytes, and the remaining cell population consists of endothelial cells.

The process of vessel remodeling results in (1) intimal fibrosis, (2) hypertrophy of the media, and (3) the formation of myocytes ex novo. The smooth muscles of the media grow distally, initially in a longitudinal direction, providing a complete muscular layer to smaller pulmonary arterial vessels having a diameter down to 15 µm. The smooth muscle cells produce extracellular matrix proteins such as glycoprotein and elastin. At same time, there are changes in other vascular layers, such as the adventitia and intima. The adventitia shows a proliferation of fibroblasts with migration of these cells in the vessel wall. The intimal cells responsible for fibrosis are poorly characterised and are described as my fibroblasts secreting extracellular matrix proteins such as collagen type I and III. As for the intima, changes involve the glycocalyx layer of the endothelial cells, with a reduction of heparan sulphate, which can trigger smooth muscle proliferation.



It seems that endothelial cell mediators shift from an anticoagulatory to protrombotic profile. The internal elastic lamina is fragmented and allows cells to migrate into the intimal layer.

The plexogenetic arteriopathy is characterised by a formation of multiple endoluminal channels in small, thin-walled branches of pulmonary arteries that appear similar to glomeruli in the kidney. Tudor et al. [41] described the channels as multi-layer endothelial cells. They named the process “misguided angiogenesis.” According to their hypothesis, endothelial proliferation could be the result of a frustrated attempt to build new vessels. In contrast, Yi et al. [42] described the plexiform lesion as a subtype of intimal fibrosis, consisting of the same cells types. Plexiform lesions occur in PPH and SPH. The latter is also associated with congenital heart defects and liver cirrhosis. The cells in lesions of SPH were polyclonal, whereas monoclonal lesions were found in PPH and dexfenfluramine-induced PH. The presence of monoclonal lesions suggests that all the cells stem from a single cell and show properties of tumour-like proliferation.

Today, we know that two elements are involved in the pathogenesis of PPH and SPH: cellular calcium concentration and vessel remodelling. Although the former could be reversible within a short time, the latter, if reversible at all, would need a considerably longer period of time. PH leads to a vicious circle of disordered endothelial function: mechanical obstruction by thrombi corroborates vascular remodeling by the release of fibrin degradation products and thrombin which are potent growth factors. Vascular remodelling enhances mechanical obstruction. Furthermore, an alteration of gene expression in association with hypoxia and reduced endothelial concentration of NO synthase was documented in patients with severe PPH [43].

Arterial hypoxia is a cause of polycythemia, which occurs as a result of many reasons: high altitudes, lung disease, heart disease, chronic pulmonary embolism, and PH. The primary mechanism involves hypobaric hypoxia, hypoventilation, ventilation/perfusion mismatch, shunting of pulmonary blood flow and vessel, or structural heart defects. The increase in viscosity resulting from polycythemia increases the perfusion resistance and pulmonary pressure. Arterial supply of  $O_2$  is increased as the result of a high concentration of haemoglobin and a decline in cardiac output.

The increased tension on blood vessels in PH depends upon different factors: static and hydrostatic forces, shear stress that is dependent on blood viscosity and the diameter of the vessel. Vessels that are exposed to hydrostatic strain are subjected to infiltration of different cells and secretion of matrix proteins and growth factors, which together act on the remodelling process. Vascular adaptations protect vessels from dilation and the interstitial space from extravasation of plasma, hereby increasing pulmonary resistance, which might culminate in PE. The concomitant presence of endothelin and prostacyclin maintains the vascular tone balanced, even though remodeling has taken place. Increased levels of plasminogen activator-inhibitor explain the tendency for the local development of thrombosis. Repeated distension of fibroblasts leads to their activation with an increase of fibrosis.

Pressure-induced endothelial injury leads to penetration of the vessel wall by serum factors, which induce the liberation of endogenous vascular elastase, followed by a cascade of events in which the glycoprotein tenascin, as well as fibronectin, plays an important role. It is yet unclear whether humoral mediators cause PH or whether PH induces these factors; however, it seems that the endothelium has an important role in this process. Three groups of mediators have been individualised. The first comprises Thromboxan A<sub>2</sub>, angiotensin II, thrombin, and platelet activating factor, which interact with the vessel wall but do not have vasoconstrictive effects. The second group of mediators have few or no vasoactive properties but contribute to the remodelling process of the vascular wall. Among the third group, NO, ANP, and prostaglandin I<sub>2</sub> have antiproliferative and vasodilative properties.

Fibrosis in patients with ILD is a slow, progressive process, leading eventually to remodelling of the connective and vascular tissue and ending finally with PH. Many recent studies suggest that alveolar type II cell injury and apoptosis may be an important early feature in the pathogenesis of ILD.

Wang et al. [44] have suggested that fibroblasts in the lungs of patients with IPF produce angiotensin-related peptides that promote epithelial cell apoptosis. Kuwano et al. [45] showed that TGF- $\beta$  promotes epithelial cell apoptosis. Hagimoto et al. [46] explained the mechanism in ILD as the result of the increased production of oxidants in the phase of glutathione deficiency. In addition, Wang et al. [47] described an increase of tumour necrosis factor (TNF)- $\alpha$ , which promotes the apoptosis of alveolar epithelial cells. These data suggest a potential role for TNF- $\alpha$  in the pathogenesis of ILD, especially in IPF. The use of anti-TNF- $\alpha$  agents could, therefore, be a possible therapeutic approach for ILD.

The studies reported herein propose a pathogenetic mechanism for ILD, which includes epithelial cell injury and the consequent accumulation of a variety of growth factors (keratocyte growth factor, TGF- $\alpha$  and  $\beta$ , insulin-like growth factor-1, platelet-derived growth factors, fibroblast growth factor), that promote epithelial cell proliferation. Many growth factors activate tyrosine kinase, which induces fibroblast proliferation and matrix production, a process culminating in epithelial cell regeneration with recruitment of fibroblast and myofibroblasts. Keane et al. [48] hypothesised that the progressive fibrosis stems from an angiogenetic process attributed to an imbalance of pro- and anti-angiogenetic chemokines. Vascular endothelial growth factor, a potent inhibitor of endothelial cell apoptosis, has a role in promoting angiogenesis and fibrosis. In contrast, Renzoni et al. [49] and Koyama et al. [50] suggested a decreased concentration of vascular endothelial growth factor in ILD with less angiogenesis in IPF in comparison with the granulation tissue in organizing pneumonia. The early stages of IPF are characterised by enhanced angiogenesis, whereas the late stages are dominated by paucity of blood vessels.

The initiation and maintenance of pulmonary fibrosis may be perpetuated by a sequence of host cytokine responses. Initially, high concentrations of IFN- $\gamma$ , a type 1 cytokine, cause the activation of phagocytes (i.e., neutrophils, monocytes, and macrophages) as well as the induction of MHC class II expression on antigen-presenting cells. Moreover, IFN- $\gamma$  suppresses fibroblast proliferation and collagen deposition. Subsequently, type 2 cytokines (interleukin [IL]-4, IL-5, and IL-13) predominate, with activated fibroblasts and fibrosis.

The authors of numerous recent studies have demonstrated a role for IL-4 and IL-5 in fibroblast activation. Weller et al. [51] described a correlation between fibroblast activation and the production of eosinophils. The authors of several studies have showed an increase of eosinophils in association with pulmonary fibrosis. In fact, the evolution of chronic immune-mediated lung diseases depends first on an abortive type 1 (high IFN- $\gamma$ ) response and, second, on a shift to a type 2 response with high levels of IL-4 and IL-13, IgE antibodies, eosinophils, and Th2 cells. A persisting insulting agent activates a type 2 response with the production of fibroblasts resulting in matrix deposition to “wall-off” the agent from the host.

### ***Summary***

The pathophysiology of IPF is characterised by a shift towards the increased production of Th2 and the decreased production of Th1 cytokines as the result of an as-yet-unknown lung injury. Overexpression of the Th2 cytokine TGF- $\beta$  leads to angiogenesis, activation of lung fibroblasts with fibrogenesis, and deposition of extracellular matrix, all hallmarks of IPF. The Th1 cytokine IFN- $\gamma$  produces biological effects opposite from those of TGF- $\beta$ . IFN- $\gamma$  inhibits the proliferation of lung fibroblasts and, in the bleomycin-induced model of lung fibrosis, down-regulates the transcription of the gene for TGF- $\beta$  [52,53]. Production of IFN- $\gamma$  may be decreased in patients with IPF [54]. Therefore, IFN- $\gamma$  may have a potential therapeutic role in the management of IPF.

### **Clinical Role of High-Resolution Computed Tomography (HRCT)**

Numerous reports have shown that HRCT is significantly more accurate than chest x-ray in the diagnosis of ILD. The use of Thin-section or HRCT increases spatial resolution, facilitating visualization of the pulmonary parenchyma to the level of the lobule, thereby permitting the ability to discern the different anatomical patterns of ILD.

According to studies, HRCT is 10–20% more accurate in the diagnosis of ILD as compared with a chest x-ray [55,56]. A correct diagnosis was made in 65% of cases when chest x-rays are used versus 74% of cases when low-dose HCRT is used ( $p < 0.02$ ) and 80% when conventional HRCT is used ( $p < 0.05$ ) [57]. A high confidence level in diagnosis was obtained in 42% of chest x-rays, 61% of low-dose HRCT, and 63% of conventional-dose HRCT, which were correct in 92%, 90%, and 96% of the studies, respectively [57].

Despite the overall similarity in the results of different studies, important drawbacks, highlight the differences in the reported accuracies of HRCT, including scanning techniques, retrospective design, lack of clinical correlation, lack of correlation with disease stage, referral bias, inconsistent definition of degrees of confidence, and poor interobserver concordance. The radiological findings of pulmonary fibrosis on HRCT

correlate strongly with fibrosis on histology ( $p=0.0001$ ). Also, a ground-glass appearance correlates well with interstitial inflammation ( $p=0.03$ ). The use of HRCT could play an important role in the selection of optimal sites for lung biopsy and to exclude patients with severe end-stage fibrosis, who may not benefit from biopsy [58]. In contrast, no significant correlation was found between the presence of pulmonary nodules as detected by HRCT and disease activity in the assessment of patients with sarcoidosis when the authors of several publications compared the efficacy of HRCT to pulmonary functional tests, histology, BAL, and serum angiotensin-converting enzyme in assessing disease.

Nevertheless, the presence of “ground glass” in HRCT studies proved to be of value as a predictor both of response to therapy as well as overall prognosis in patients with ILD [59]. Wells et al. [60] found that the presence of ground glass opacity was related to prognosis and likelihood of response to treatment. In this study, HRCT abnormalities were interpreted as predominantly ground glass (group 1), mixed ground glass and reticular pattern (group 2), or opacities that were predominantly reticular pattern (group 3). The 4-year survival rate was greatest in patients who had predominantly ground-glass opacity and greater in patients who had mixed opacities as opposed to those who had reticular abnormalities; these findings were independent of the duration of symptoms or severity of pulmonary function abnormalities ( $p<0.001$ ). Similarly, the response rate to therapy in previously untreated patients was significantly greater in patients who had predominantly ground-glass opacity and greater in group 3. The study concludes that the evolution of disease is correlated with histology and independent of its extension. In fact, a patient with an 80% ground glass opacity pattern who is a responder to therapy has a 40% survival rate greater than a patient with a fibrotic or reticular pattern.

HRCT findings in group 1 patients, described by Wells et al. [60], bear a striking resemblance to HRCT findings in patients who had NSIP, raising the possibility that the improved survival in at least some of the patients in this group is related to variations in the underlying pathology. NSIP pathology is divided in two histological subsets: cellular (plasma cells and lymphocytes) and fibrotic findings [60]. The former, which is less common than the latter, has a better prognosis, with good survival in patients at 5 and 10 years. Imaging with HRCT of cellular NSIP shows that the thickening of alveolar septa is caused by inflammatory cells, whereas the fibrotic variant is characterised by homogeneously thickened septae with scarce inflammatory cells.

IPF, a chronic progressive ILD that can be fatal within 3 years of diagnosis, probably is the most common IIP, accounting for 62% of the cases. When a peripheral reticular pattern consistent with fibrosis by histology is present, the results of HRCT are reported to be approximately 90% accurate in the diagnosis of patients who have suspected IPF.

A reticular pattern or honeycombing are always more prominent in the lower lung zones, but they may involve the whole lung in advanced disease. Honeycombing, described by Zerhouni et al. [61], when associated with an intermediate reticular pattern typical of an intralobular interstitial thickening, gives rise to the morphology of IPF (97%). Hunninghake et al. [62] reported that the positive predictive value of

a diagnosis of IPF made with HRCT by experienced radiologists is 96%. McDonald et al. [63] suggested that a biopsy is not always necessary when HRCT can be used to visualised the typical features of UIP (reticular pattern with little or any ground glass abnormality). Daniil et al. [64] noted that patients with a typical HRCT pattern of IPF had reduced survival as compared with those who have an atypical HRCT pattern. Flaherty et al. [65] concluded that the survival of patients with a positive HRCT and histological features of UIP was significantly worse as compared with those with a histological pattern of UIP and an indeterminate HRCT. HRCT features correlated closely with the histological pattern of UIP, but an indeterminate HRCT could be correlated with UIP or NSIP. The greatest mortality was described among patients with typical features of UIP as visualised by HRCT [65].

Gay et al. [66] proposed an HRCT fibrosis score for predicting survival of patients with IPF. The authors determined scoring by considering the severity of ground glass and fibrosis patterns by evaluating the correlation between HRCT, histology, and survival. Thirty-eight patients with IPF were recruited; all were treated with steroids for at least 3 months. The major importance of this study was in proposing predictive factors of outcome that may be important in selecting a subset of patients for lung transplantation. There was a good correlation between the histologic and HRCT fibrosis scores, which validates the use of HRCT scoring in the assessment of patients with IPF. The major drawback of this study was the small group of patients observed. In two prospective studies, King et al. [67,68] examined factors influencing survival in IPF patients: A clinical radiological physiological score was calculated.

The strength of these studies are supported by many factors: a histologic support, the numbers of cases, duration of follow-up, and an accurate statistical analysis. The major drawbacks were the absence of HRCT imaging and that all patients completed maximum exercise testing and  $DL_{CO}$ . For the authors, the HRCT results would likely strengthen the clinical radiological physiological score, because the assessment score and detection of PH with the use of a chest x-ray is subjective. Wells et al. [69] developed a composite physiologic index, where patients with IPF were evaluated with HRCT and pulmonary functional tests (i.e., forced vital capacity, forced expiratory volume in 1 second, and diffusion capacity of the lung for carbon monoxide [ $DL_{CO}$ ]). The strength of the composite physiologic index lies in the fact that it does not require a complete exercise test nor the presence of experienced radiologists for the interpretation of HRCT. This index could be a useful clinical guide for staging disease severity and predicting outcome in patients with ILD.

The importance of HRCT was further emphasised by Mogulkoc et al. [70], who demonstrated that the HRCT fibrosis score was an independent predictor factor of survival in IPF. The Joint Statement of American Thoracic Society (ATS) and European Respiratory Society has approved that, in the absence of an open lung biopsy, HRCT should be one of the four major criteria necessary for the diagnosis of IPF, that is, after excluding other causes of ILD established by history, transbronchial biopsy, BAL, and abnormal pulmonary functional tests. The additional presence of at least three of four minor criteria (age >50 years, insidious onset of dyspnoea, duration of disease greater than 3 months, bibasilar crackles) is necessary [71].

Because features of NSIP on HRCT may significantly overlap with IPF/UIP, DIP, and cryptogenic organizing pneumonia (COP), NSIP is commonly misdiagnosed on HRCT. Cellular and fibrotic NSIP subtypes appear differently. The former exhibits a prominent ground-glass appearance (70–100%), whereas the latter has a fine reticular fibrosis, thickened septal lines, and honeycombing. The pattern is very similar to that of IPF (Fig. 2.3). Radiological and clinical features can be used to differentiate between fibrotic NSIP and IPF; the former shows an improvement in patients after steroid therapy. The Joint Statement of ATS and European Respiratory Society suggests that NSIP should be considered at first a provisional clinical diagnosis (Fig. 2.4). NSIP could be regarded as idiopathic only after excluding possible associations with collagen vascular diseases, drugs, and extrinsic allergic alveolitis.

On HRCT, the features of respiratory bronchiolitis/ILD and DIP (Fig. 2.5) typically overlap. The use of HRCT reveals areas of dense ground glass in association with mild reticulations in the upper zone of the lung with centrilobular emphysema. Mild bronchiol ectasias and centrilobular nodules are present in particular in the upper zones of the lungs. Honeycombing is uncommon. Both types of ILD have a good response to the use of steroids and the cessation of smoking.

The features of COP on HRCT typically show a mixed consolidation area of ground glass distributed in different patterns: triangular, patchy, and peripheral (Fig. 2.6). Approximately 85% of patients have a rapid response to steroid therapy, but in the remaining 10–15%, the disease is progressive. The relationship between UIP and COP has not been fully studied, but a reticular HRCT pattern in COP, similar to that of UIP, portends poor prognosis.

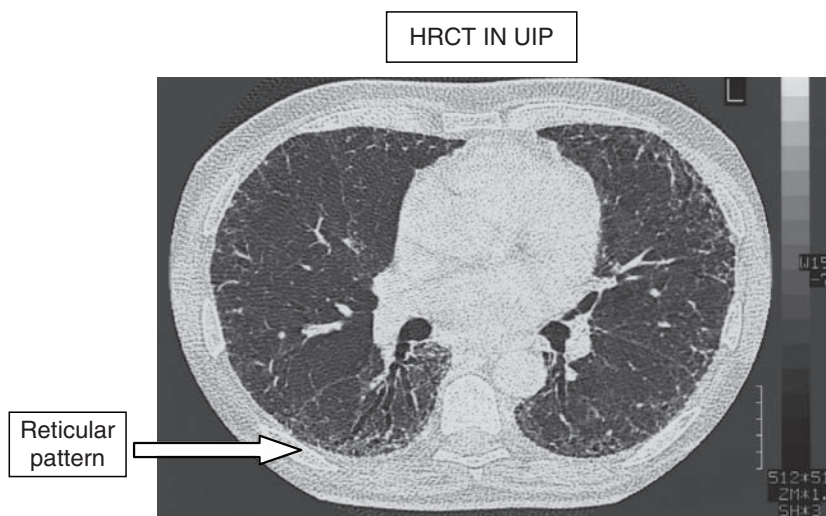


Fig. 2.3 UIP



## HRCT IN NSIP

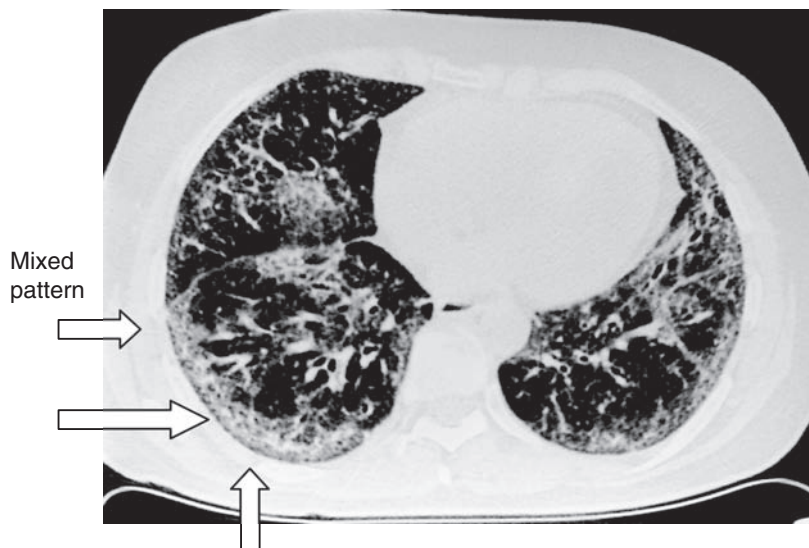


Fig. 2.4 NSIP

## HRCT IN DIP

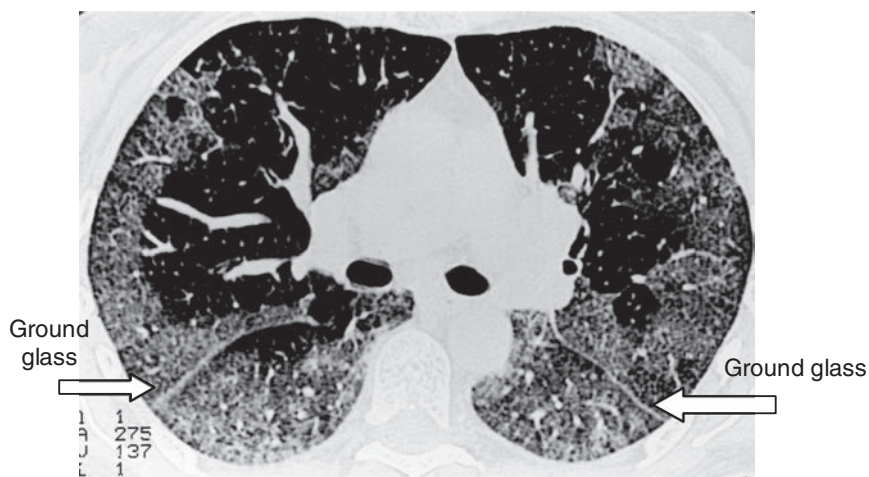
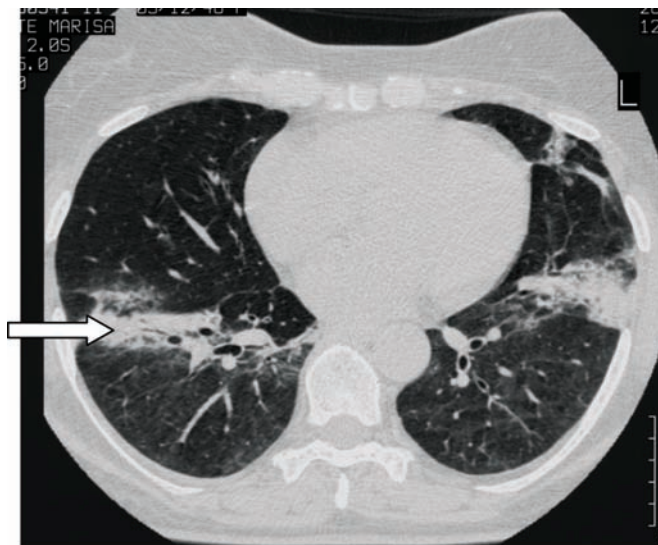


Fig. 2.5 DIP

The features of acute interstitial lung disease on HRCT are characterised by ground glass extended a random (100%), and partially consolidated (overall 60%). Honeycombing is uncommon. Acute interstitial lung disease has a mortality rate of approximately 60%; the remainder of patients experience long-term survival. LIP



**Fig. 2.6** COP

on HRCT appears as ground glass and numerous parenchymal fine nodules with a centrilobular distribution.

The features of UIP/IPF on HRCT may mimic UIP secondary to collagen vascular diseases asbestosis and limited bibasilar fibrosis resulting from recurrent aspiration. A granulomatous appearance on HRCT is typical of sarcoidosis (small hard nodules) and hypersensitivity pneumonia (soft centrilobular nodules). Moreover, hypersensitivity pneumonia may exhibit a patchy consolidation and therefore could be confused with respiratory bronchiolitis/ILD or COP. Finally, neoplastic ILD (lymphangitic metastasis) may appear as a reticular and ground glass pattern.

When considering the differential diagnosis of ILD, one should take into account other HRCT findings, such as a dilated esophagus in patients with systemic scleroderma, pleural plaques in asbestosis, lymph nodes in sarcoidosis and, in lymphangitic metastasis, hepatomegaly in amiodaron-induced lung disease. A score capable of predicting survival could be a useful tool for evaluating ILD. Other means currently available for the follow-up of patients with ILD are not accurate:  $DL_{CO}$  lacks standardization; the HRCT fibrosis score is a semiquantitative visual score. A CT score combining the ground glass severity scale, fibrosis, and periaxial score at different sections could be solution.

Some cases of ILD may present on HRCT with increased periaxial deposition of connective tissue. The evaluation in these cases is based on scoring of different CT sections where the ratio of airway wall thickness (T) to bronchial diameter (D) [T/D] is considered. We have studied the correlation of HRCT periaxial with pulmonary function tests,  $DL_{CO}$ , the 6-minute walk test (6MWT), dyspnea, and PH. In CT, periaxial score T/D, the normal value of which is 0.23, was not different in small and large airways [72].



Our evaluation of the 0 score is  $\chi=0.15-0.23$  and pathological values have been calculated, by defining the extent of the disease by means of the ratio between the areas  $A$  and  $A_0$  of the cross sections of the sick and the normal bronchi, respectively. In this way, we have obtained the following formula:

$$T/D=0.50-\chi\sqrt{(A/A_0)}$$

The results of this work concluded that the HRCT periaxial score in patients with ILD had a good correlation to a restrictive pattern of pulmonary function tests, a normal  $DL_{CO}$  and PH, a negative 6MWT, and mild dyspnea.

Indeed, HRCT is a useful and noninvasive tool for the diagnosis and evaluation of ILD. It is important to bear in mind that a normal HRCT does not always exclude early and clinically significant ILD, especially in the phase of abnormal physiological tests.

## ***Summary***

A HRCT scan with a basal pattern of honeycombing (reticular pattern) and traction bronchiectasis is highly suggestive of IPF and carries with it a poor prognosis. In this setting, an open-lung biopsy is not necessary, although some clinicians perform bronchoscopy to exclude other diseases. On the other hand, the absence of a reticular pattern or fibrosis and the predominance of a ground glass pattern suggest NSIP. Here, the prognosis and response to treatment are better, and open lung biopsy is often performed. The HRCT fibrosis score is still a semiquantitative visual score. Therefore, we suggest that calculating a CT score based on a ground glass severity scale and CT fibrosis and periaxial score, at different sections, would be more accurate.

## **Clinical Role of BAL in ILD**

BAL in combination with HRCT imaging and the clinical setting can play an important role in the differential diagnosis of ILD. A recently published study on a large cohort of patients ( $n=3,118$ ), showed the importance of the predictive value of BAL in the diagnosis of ILD. BAL cell counts were most useful for the diagnosis of relatively common entities, such as sarcoidosis, in contrast to rare forms of ILD. The ratio of T lymphocytes  $CD4+:CD8+$  BAL is usually increased in patients with clinically active pulmonary sarcoidosis. However, although older age may be a contributing factor for a high ratio, many patients do not have an increased ratio. Thus, the sensitivity of an increased  $CD4+:CD8+$  ratio for sarcoidosis is relatively low. A decreased  $CD4+:CD8+$  ratio has been reported in patients with hypersensitivity pneumonitis (HP), drug-induced lung disease, COP, eosinophilic pneumonia (EP), and IPF. A BAL lymphocyte differential count greater than 25% could be indicative of an ILD associated with granuloma formation, (e.g., sarcoidosis and

hypersensitivity pneumonitis), or drug toxicity, that is, after excluding other diseases such as mycobacterial or fungal infection.

An exposure history to an antigen known to cause HP, when combined with BAL rich in lymphocytes (especially with differential counts equal or greater than 50%), is strongly suggestive of this disease. An eosinophil count equal or greater than 25% could be caused by an eosinophilic lung disease, especially EP, if the presentation is acute. In contrast, an extreme increase in the BAL content of neutrophils is likely caused by infection or an acute and diffuse lung injury. Because infection can cause the subacute onset of diffuse lung infiltrates or coexist with noninfectious ILD, BAL should be examined and screened for mycobacterial or fungal infection when performed to evaluate diffuse infiltrates.

Increased numbers of mast cells have been associated with HP, drug reactions, sarcoidosis, ILD associated with collagen vascular disease, IPF, COP, EP, or malignancy. Plasma cells have been observed in BAL in HP, drug reactions, EP, malignancy, or infection. Alveolar macrophages may also display morphological changes, such as a foamy appearance in HP, markedly vacuolated cytoplasm positively staining for fat in chronic aspiration pneumonitis, cytoplasmic inclusions associated with viral infection (e.g., cytomegalovirus pneumonia), ingested red blood cells with diffuse alveolar haemorrhage, or ingested asbestos bodies. Bloody lavage fluid is characteristic of diffuse alveolar haemorrhage. BAL fluid that has a milky or light brown to whitish color suggests the diagnosis of pulmonary alveolar proteinosis. A BAL with CD1a-positive cells in the right clinical setting and imaging can support a diagnosis of pulmonary Langerhans cell histiocytosis.

Acute-onset ILD is defined as an illness of less than 4 weeks' duration, with symptoms of shortness of breath, hypoxaemia, and diffuse radiographic infiltrates. The patient should have no history of previous lung disease, and no obvious risk factors for acute respiratory distress syndrome, such as sepsis or trauma. Diagnostic considerations in acute-onset ILD include infection and noninfectious ILD (i.e., acute interstitial pneumonia, acute EP, diffuse alveolar haemorrhage, acute HP, acute COP, drug toxicity, or acute exacerbation of previously undiagnosed IPF). Bronchoscopy with BAL at the time of acute presentation may facilitate the diagnosis and avoid the need for a surgical lung biopsy.

Recent advances in ILD assessment have demonstrated that the BAL procedure is an excellent tool in the clinical diagnosis of IPF when surgical lung biopsy is not performed. To make a diagnosis of IPF without a surgical lung biopsy, all four major criteria (exclusion of other known causes of ILD, a restrictive ventilatory defect and impaired gas exchange on pulmonary function testing, bibasilar reticular abnormalities with little or no ground-glass opacities on HRCT, and transbronchial biopsy or BAL showing no features to support an alternative diagnosis) and at least three of the four minor criteria (age > 50 years, the insidious onset of otherwise-unexplained dyspnea on exertion, duration of illness  $\geq 3$  months, and chest auscultation showing bibasilar inspiratory crackles) must be present [73].

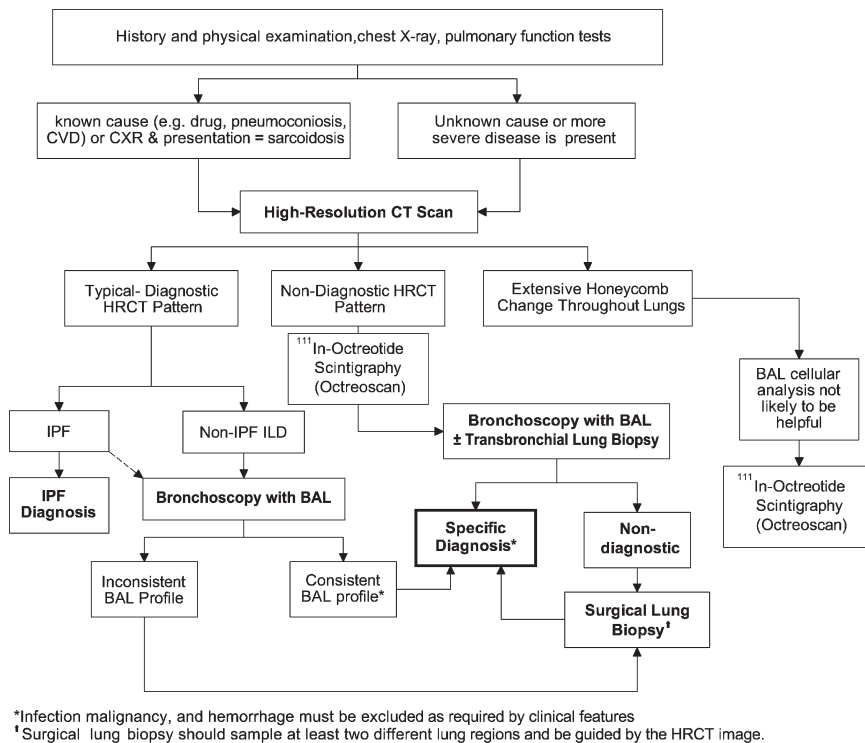
Some experts suggest, however, that when lower lung honeycombing occurs and upper lung zone reticular lines are present, the positive predictive value of these HRCT findings for a diagnosis of IPF/UIP is at least 85%, and a confident diagnosis of UIP can be made when these findings are present [73].

We suggest that, in cases of atypical HRCT, nondiagnostic patterns, or in elderly patients with extensive honeycombing and advanced disease, that the IPF diagnosis be made with the use of a minimally invasive approach such as BAL or indium-111 octreotide scanning (Octreoscan, Mallinckrodt Medical, Inc., St. Louis, MO). The latter seems to show a close correlation with IPF (UIP histological features).

Furthermore, clinicians should be aware that radiographic imaging, including HRCT, may not show pathologic changes, particularly when certain forms of ILD (e.g., non-IPF interstitial pneumonias or HP) are present. If BAL is performed on a symptomatic patient who has undergone radiographic imaging that is not suspicious of ILD, an abnormal cell profile consistent with the presence of an alveolitis can indicate the need for additional investigation including lung tissue biopsy [73].

## Summary

The role of the BAL procedure in the diagnosis and staging of ILD has been subject to intense study and will continue to increase in importance. The ATS and guidelines for BAL in ILD are currently being completed. The algorithm described below describes an updated approach to BAL in the diagnosis of ILD (Fig. 2.7).



**Fig. 2.7** Flowchart

## **Clinical Role of the Scintigraphy (i.e., Gallium-67 and Indium-111 Octreotide Scan [Octreoscan])**

The evaluation of patients with sarcoidosis (unlike those affected with IPF) requires a combination of clinical, radiographic, scintigraphic, or bronchoscopic data. Given the contradictory results of these studies, it is apparent that a definitive conclusion regarding the role of HRCT in diagnosis and assessment of disease activity in patients with sarcoidosis remains to be determined. Leung et al. [74] demonstrated a poor correlation between the extent of nodular involvement on HRCT and the intensity of lung gallium uptake ( $r=46$ ;  $p<0.02$ ), BAL lymphocytes ( $r=50$ ;  $p<0.01$ ), and serum angiotensin-converting enzyme levels ( $r=38$ ,  $p<0.05$ ).

Gallium-67 scintigraphy routinely was used for the study of ILD, especially sarcoidosis [75,76]. This test, whose sensitivity is now known to be suboptimal, was used in the past for its prognostic value [77]. Today, it is known that gallium imaging has no proven value for evaluation of IPF [77]. It is an expensive ancillary test, is associated with radiation exposure, and requires two hospital visits by the patient, the first for injecting the contrast and the second for scanning. The interpretation of gallium scans is difficult, and a negative scan does not exclude disease. Confounding factors such as steroid treatment must be considered, and patients should be instructed to stop therapy 1 week before the procedure [78,79].

Turner-Warwick et al. [80] had suggested that if no symptoms caused by extrapulmonary disease are present, then the evaluation of disease extent in sarcoidosis can be limited to clinical history, chest-X-ray, and pulmonary function tests. Although HRCT is more sensitive than chest-X-ray for detecting ILD, it is of limited value because worsening of symptoms and a decrease in lung function tests are not correlated with CT imaging [81].

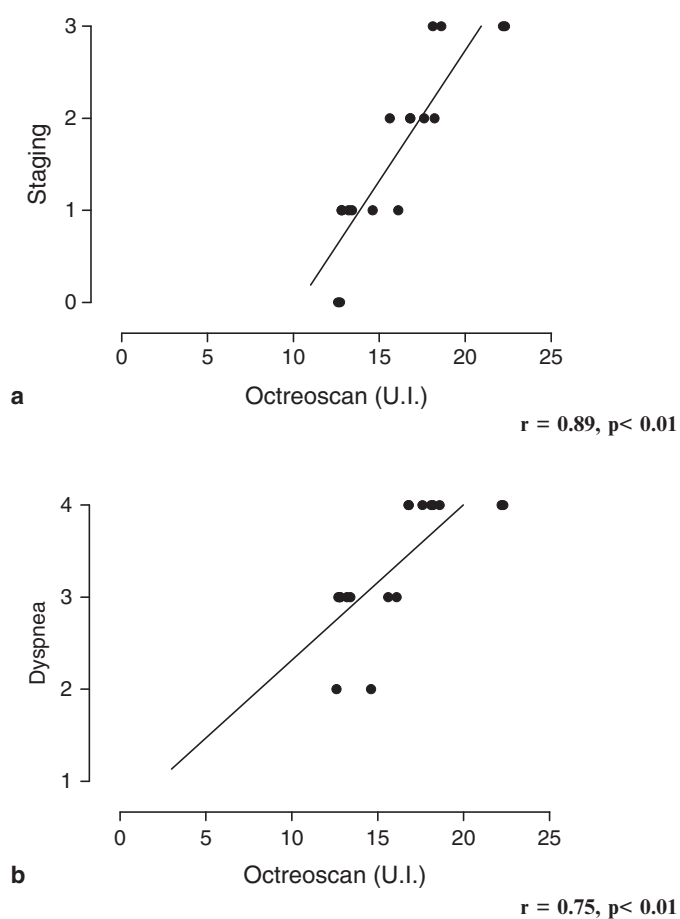
In the face of a lack in imaging techniques capable of providing adequate information on the disease extent and predict its severity disease, the use of somatostatin receptor imaging could be promising. Octreotide is a somatostatin derivate that binds to granuloma somatostatin T lymphocyte receptors, especially CD4-T cells, thereby demonstrating active granulomatous disease in sarcoidosis. Somatostatin receptors (subtype 2) are also present in epithelioid cells and giant cells [78,82]. Somatostatin receptor whole-body scintigraphy was obtained at 4 and 24 h after the administration of 5mCi of  $^{111}\text{In}$ -DTPA-D-Phe1-octreotide (Octreoscan). Thoracic imaging was obtained with single-photon emission computed tomography. The Octreoscan uptake index (UI) was defined as the ratio between normal and pathologic accumulation of the tracer in lung tissue. Octreoscan UI was scored by the use of a similar procedure described in literature used for gallium-67 and compared with the data of a group of healthy individuals. Normal values at 4 and 24 h were considered for  $\text{UI} \leq 10$ .

As for patients with sarcoidosis, the use of Octreoscan was shown to be a more sensitive diagnostic tool than gallium-67 scintigraphy, particularly when lymph nodes and spleen were imaged. Octreoscan is useful for the identification of disease activity and extension of lung disease (Fig. 2.8) [78,79,83]. Lebthay et al. [78]

confirmed that the use of Octreoscan also was more accurate than gallium-67 scintigraphy for evaluating the extent of sarcoidosis in patients receiving steroid therapy. Finally, the increased costs associated with Octreoscan, are outweighed by the accuracy of this test.

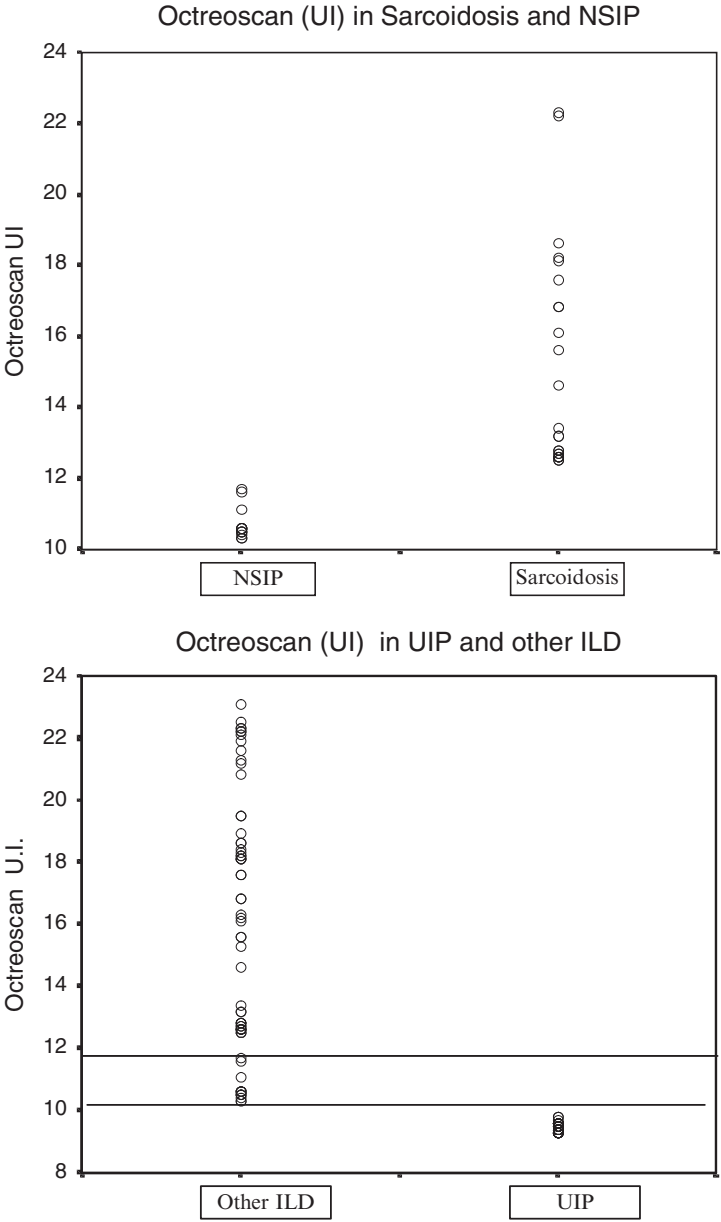
## Summary

The Octreoscan UI is strongly correlated with the degree of dyspnea in patients with sarcoidosis and can effectively quantify pulmonary involvement (Fig. 2.8). Further studies are warranted to evaluate Octreoscan as an early test in the prediction of disease.



**Fig. 2.8** Octreoscan in sarcoidosis. Correlation with staging (a) and degree of dyspnea (b)

The Octreoscan UI could be particularly useful in monitoring extrathoracic sarcoidosis and NSIP, probably because these two conditions are characterised by a preponderant inflammatory infiltrate (particularly lymphocytes) and less fibrosis (Fig. 2.9a). As for UIP, HRCT is still the most prevalent imaging technique for



**Fig. 2.9** a Octreoscan in sarcoidosis and NSIP. b Octreoscan (IU) in UIP and other ILD

assessing the extension of disease. Larger studies are necessary to evaluate the substitution of HRCT by Octreoscan in the assessment of UIP (Fig. 2.9b, Figs. 2.10–2.18, Octreoscan imaging).

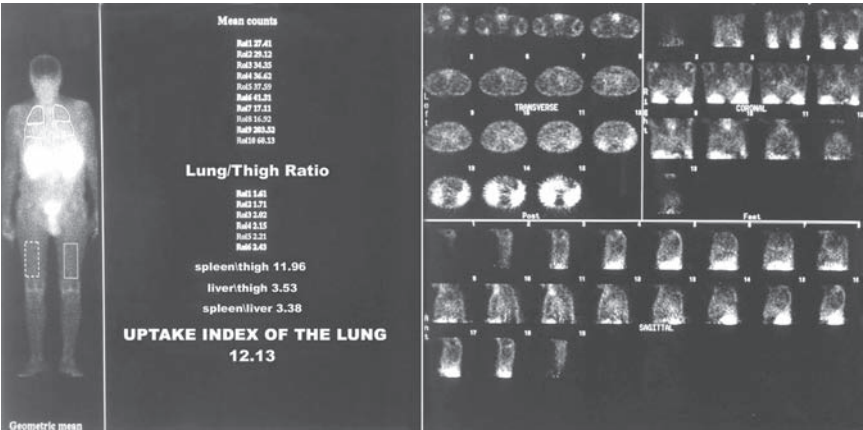


Fig. 2.10 Octreoscan of NSIP

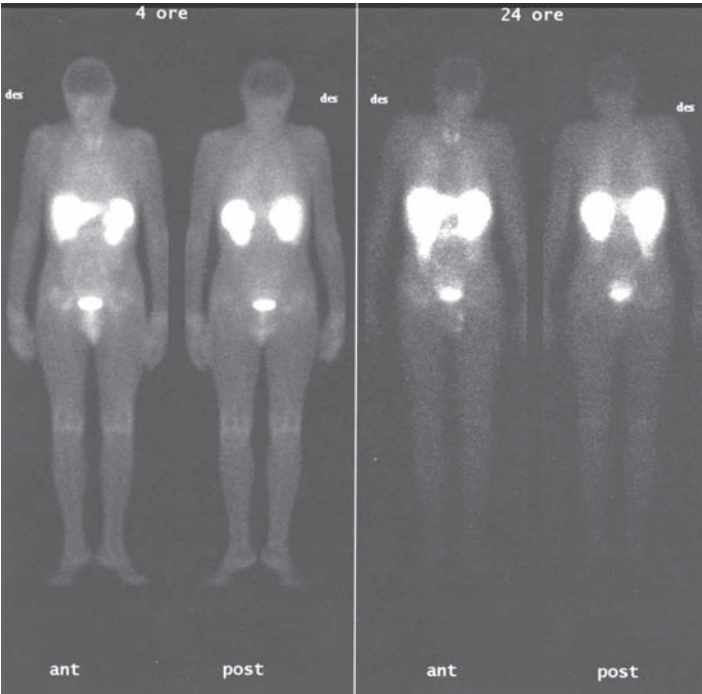


Fig. 2.11 Anterior and posterior Octreoscan scans of NSIP

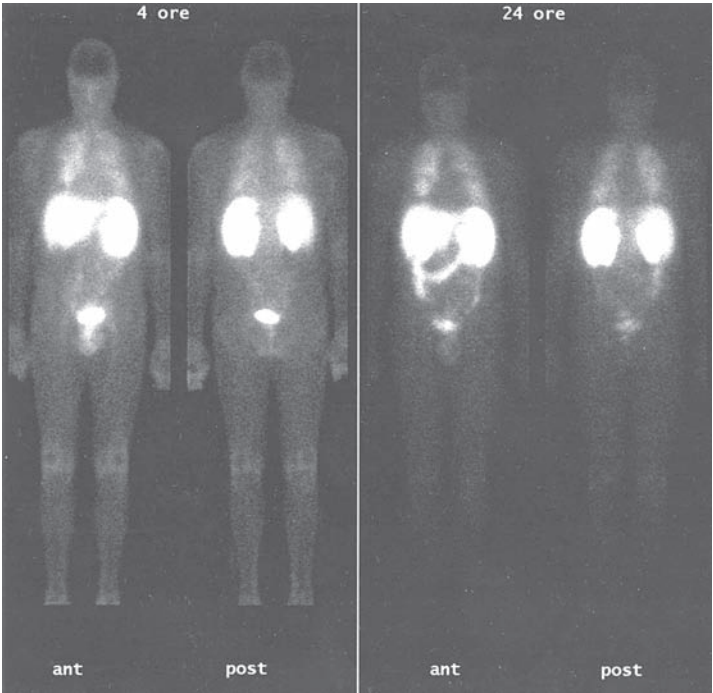


Fig. 2.12 Osteoscan of sarcoidosis

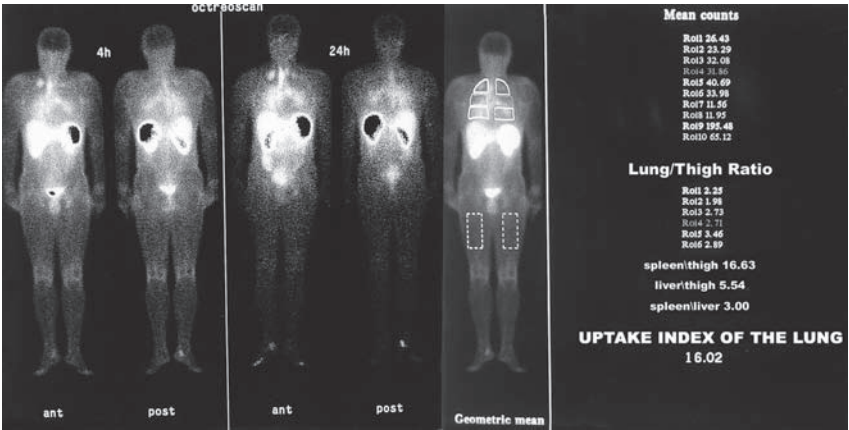


Fig. 2.13 Anterior and posterior Osteoscan scans of sarcoidosis



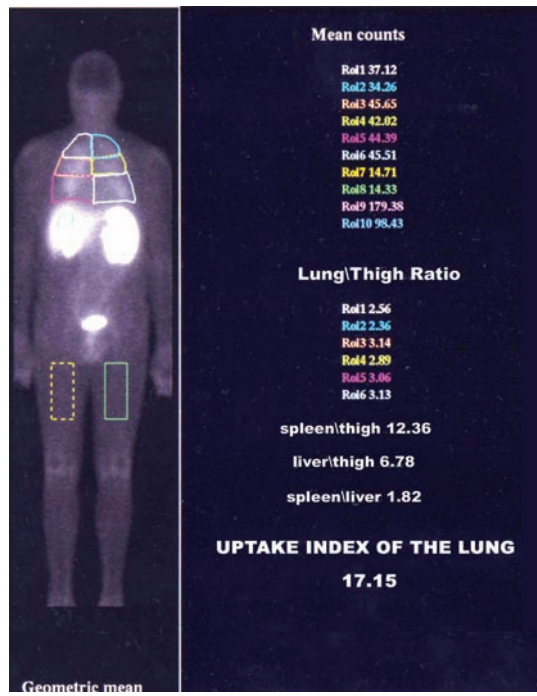


Fig. 2.14 Octreoscan of sarcoidosis

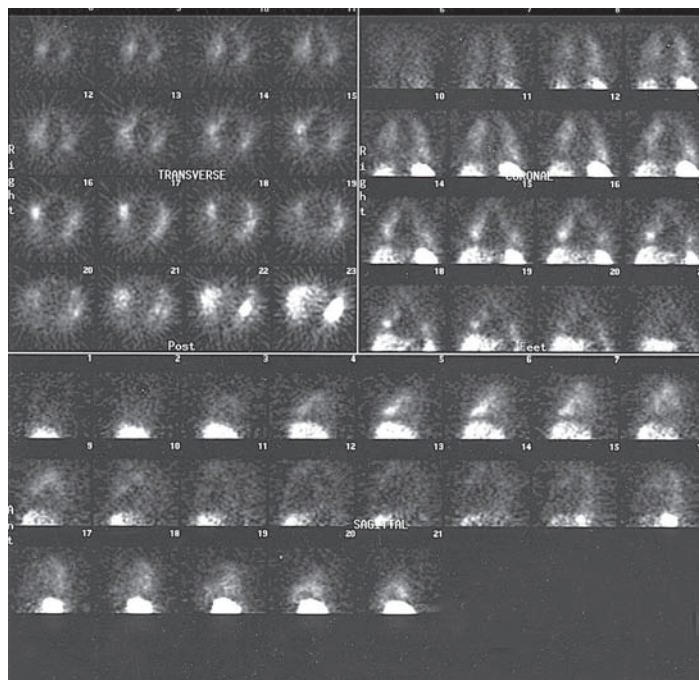


Fig. 2.15 Sarcoidosis on single-emission photon computed tomography

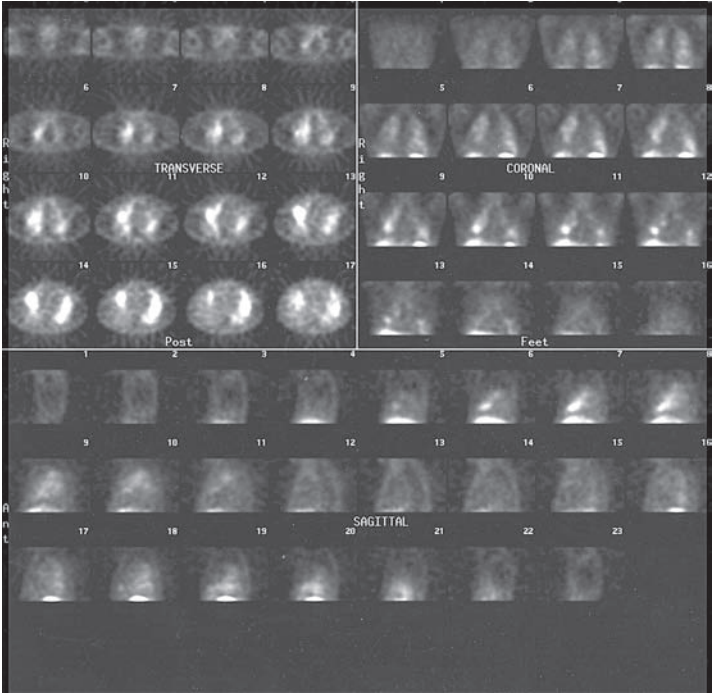


Fig. 2.16 Sarcoidosis on single-emission photon computed tomography

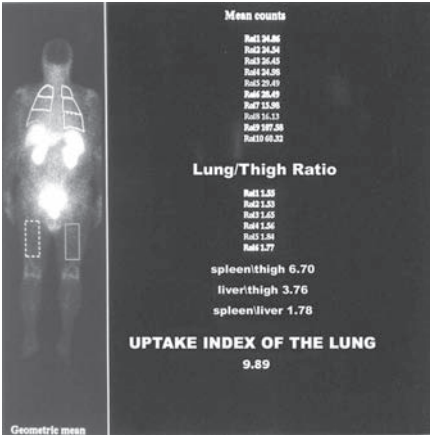
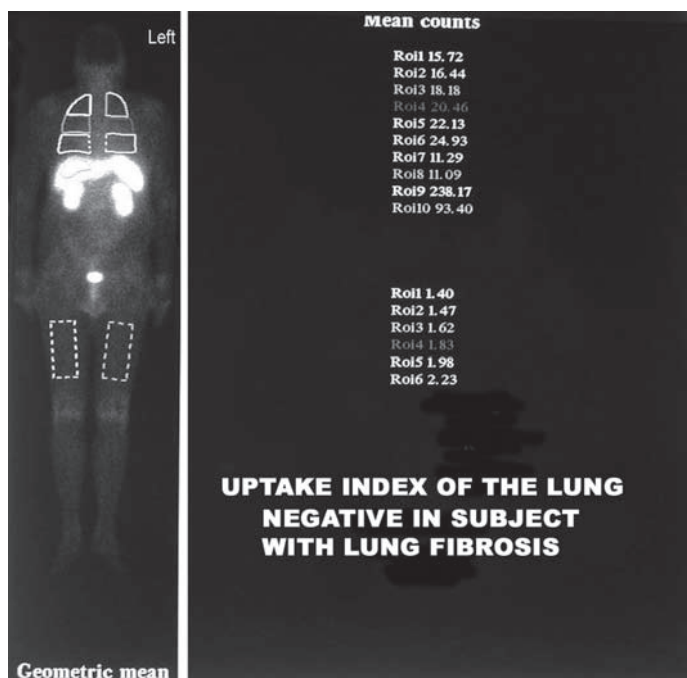


Fig. 2.17 Osteoscan of UIP



**Fig. 2.18** UIP on single-emission photon computed tomography

## Correlation Between Heart and Lung in ILD: Cardiological Procedures

Pulmonary arterial hypertension has been observed in all connective tissue diseases, but most frequently in systemic sclerosis (SSc). A good correlation between HRCT and pulmonary arterial hypertension could improve the clinical assessment, therapy, and survival prediction of patients with ILD. The development of pulmonary hypertension is a marker of poor prognosis. Up to 80% of patients affected with IPF and up to 50% of those with SSc develop secondary pulmonary artery hypertension, which begins with extravascular inflammation.

In the latter, echocardiography is a good screening test for early PH; it has a high sensitivity and specificity [84]. Echocardiography, as an adjunct to clinical evaluation, is currently the optimal screening approach for evaluating patients with SSc-related pulmonary arterial hypertension, which carry a worse prognosis than those with idiopathic pulmonary hypertension [85]. Burdt et al. [86] found that PH secondary to mixed connective tissue diseases, in particular overlap of scleroderma, systemic lupus erythematosus, and myositis, was the most common cause of death, occurring in 38% of patients. Increased pulmonary arterial pressure occurred less frequently in patients

with systemic lupus erythematosus, polymyositis, and rheumatoid arthritis. PH was associated with Raynaud's phenomenon in each of the cases, suggesting a similar pathogenesis of these vasculopathies.

When PH is suspected clinically, Doppler echocardiography should be performed as soon as possible. Systolic pulmonary arterial pressure (sPAP), which is considered equal to right ventricular systolic pressure in the absence of pulmonary valve stenosis or outflow tract obstruction, can be evaluated by Doppler echocardiography with a sensitivity and specificity that ranges from 0.79 to 1, and 0.6 to 0.98, respectively.

McQuillan et al. [87] assessed the clinical correlates of sPAP on a large echocardiographic database of 102,818 patients: the mean sPAP was  $28.3 \pm 4.9$  mmHg (95% confidence interval 18.7–37.9 mmHg). The author concluded that the evolution of Doppler techniques during the last decade has permitted the detection of minimal tricuspid valve regurgitation (TR) and thereby has made the estimation of sPAP more accurate.

The percentage of normal echocardiographic tests in which less-than-moderate TR was detected has increased from 48% in 1990 to 80% in 1999. Barst et al. [88] defined PH for values  $\text{sPAP} > 35$  mmHg. According to this author a Doppler examination by an experienced sonographer yields quantifiable TR in 74% of cases. Other studies reported absent or non quantifiable TR in 39% of patients, but pulmonary diastolic pressure also can be estimated by the use of Doppler echocardiography and correlates well with invasive measurements ( $r=0.92$ ) [89]. The authors of many studies use correlation coefficients as measures of accuracy, for example, comparing echo estimate and the value measured by right-catheterization.

Screening examinations depend not only on the sensitivity and specificity of the test used, but also on the prevalence of disease in the study population. False-positive results will be more frequent when the prevalence of disease is low. Consequentially Doppler echocardiography may underestimate the sPAP in patients with severe PH and overestimate sPAP in populations comprising mostly subjects with normal pressures.

The debate between experts about the efficiency of echocardiography as an accurate examination for the diagnosis of PH resides in the fact that the use of this examination results in an underestimation of the disease. According to Baughman et al. [90], the use of echocardiography could be a useful tool in ruling out significant PH in patients with sarcoidosis only if a TR jet is clearly visualised. This group confirmed the presence of PH in more than half of sarcoidosis patients with persistent dyspnea. Sulica et al. [91] reported the detection of PH by echocardiography in 40% of patients with sarcoidosis.

Arcasoy et al. [92] studied a group of 374 patients with advanced lung disease who underwent echocardiography and right heart ventricular catheterization within 72 h of each other: the use of echocardiography had a sensitivity of 85% in diagnosing PH, the specificity was lower, and a large percentage of patients were misclassified as having PH, especially when the estimated right ventricular systolic pressure was close to the cut-off point of 40 mmHg. Furthermore, Nadrous et al. [93] described

a subgroup of patients in which PH could not be estimated because of a lack of TR. This patient group did not survive for a long time. The authors of a study that evaluated mortality in association with PH found that subjects with IPF had a very poor survival rate, especially those with concomitant left ventricular dysfunction. The preservation of cardiac output can be an important factor in IPF associated PH as well as in idiopathic pulmonary hypertension.

Doppler echocardiography should be performed as a noninvasive effective tool that can detect, in some cases, an interstitial lung disease developed after cardiac surgery. It is known that cardiopulmonary surgery is associated with an acute inflammatory process that leads to lung damage caused by ischemia/reperfusion injury [94–96]. The latter is not limited to cardiomyocytes but also extends to the entire organism and especially in the alveolar/capillary unit and the interstitial lung tissue. Our clinical investigations hypothesised an injury of the capillaries and, most generally, of the interstitium of the lung with an inflammatory response 2 months after beginning cardiac surgery and often remaining at chronic clinical levels without treatment, probably leading to progressive fibrosis with definitive damage of pulmonary interstitium.

In the early inflammatory cellular phase after cardiac surgery, an interstitial lung process was shown: (1) BAL fluid containing a decrease of T-helper CD4 lymphocytes and an increase in T-suppressor CD8 lymphocytes, (2) pulmonary function tests with a restrictive pattern often involving the small airways and DLco ( $77.9\% \pm \text{SD}16$ ), (3) a moderately increased mean sPAP ( $44 \pm \text{SD} 10 \text{ mmHg}$ ), and (4) a significant response after treatment with steroids.

Therefore, a Doppler echocardiography accurate study must be conducted to diagnose and exclude left cardiac failure and/or diastolic dysfunction. In fact, the vascular/alveolar units are vulnerable to injury as a result of disorders affecting the heart, releasing endotoxin, secretion of metabolic markers, and generation of oxygen-derived free radicals by polymorph nuclear neutrophils. At the anatomic level, the interstitium is defined as the alveolar walls, including epithelial cells and capillaries, septae, and perivascular, perilymphatic, and peribronchiolar connective tissues. This structure is characterised from a wall extremely thin of alveolar–interstitial–capillary–plasma–erythrocyte and at same time immensely strong to withstand the stresses caused from the changes of the internal and external pressure.

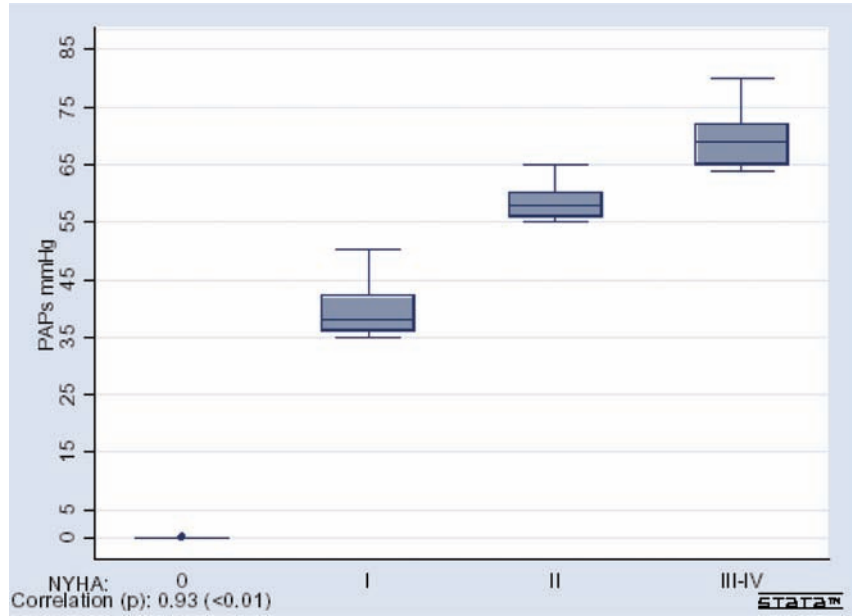
The stress leads to multiple events of injury/inflammation of the alveolar–capillary constituents compromising the normal basement membrane integrity. In response to injury, an intraalveolar exudative process takes place with infiltration of macrophages, fibroblasts, and other inflammatory cells. The resistance to stress is guaranteed from collagen IV of basement membranes enmeshed in an extracellular matrix that defends the alveolar–capillary barrier. Nevertheless, the physiologic and pathophysiologic phenomena can lead to chronic inflammation with remodeling of the extracellular matrix structure, progressing inevitably to end-stage pulmonary fibrosis.

Remodeling about the stress related to the larger pulmonary arterial and venous system is known, vice versa it's also needed to demonstrate the pathophysiological

mechanism of injuries related to capillary section. Another potential mechanism of disrepair seems to be the result of injuries caused from exchanges of capillary pressures and regulated from a modified gene for various procollagen formations and for the development the other grown factors. [97,98].

The 6MWT is a submaximal exercise test used to assess functional capacity in congestive heart failure. It is also useful for evaluating patients with PH for the following reasons: (1) the ease of reproducibility, (2) the good correlation with maximal exercise testing, and (3) the fact that most patients reach the end point of the test [99]. The 6MWT correlates with cardiovascular mortality and morbidity and helps a clinician to predict survival in patients with idiopathic pulmonary arterial hypertension.

The New York Heart Association (NYHA) classification is a simple method for classifying patients with congestive heart failure. NYHA has been used as a predictor of survival in several studies of patients with PH; however, its significance was proved in only three studies of SSc and idiopathic pulmonary hypertension. Little is known about the correlation between the NYHA classification and ILD associated PH. Carbone et al. [100] reported that NYHA could estimate survival and be used as a substitute for PAP in ILD (Figs. 2.19–2.23). Future prospective studies with mortality as an end point could shed more light on the utility of this classification.



**Fig. 2.19** Correlation PAPs: NYHA in ILD (94 patients)

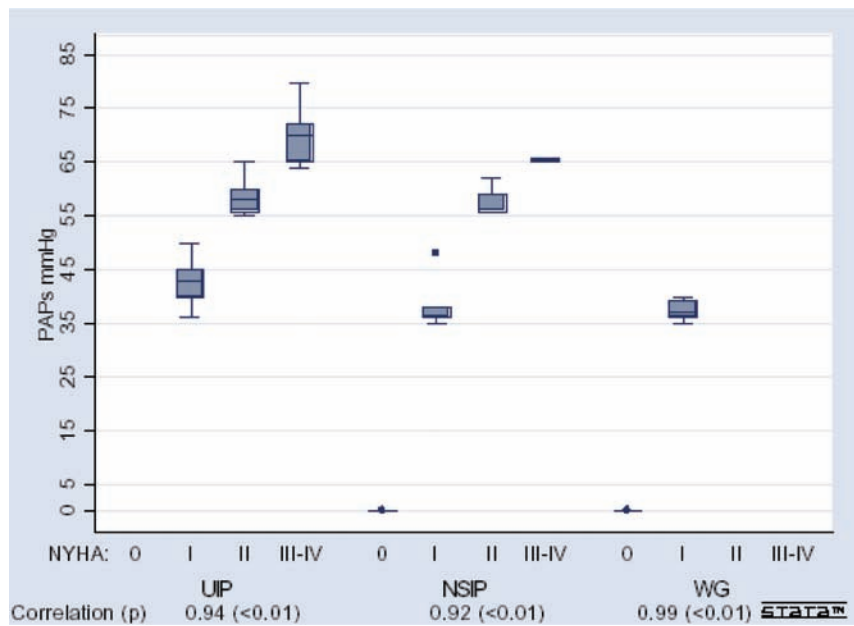


Fig. 2.20 Correlation PAPs: NYHA by diagnosis

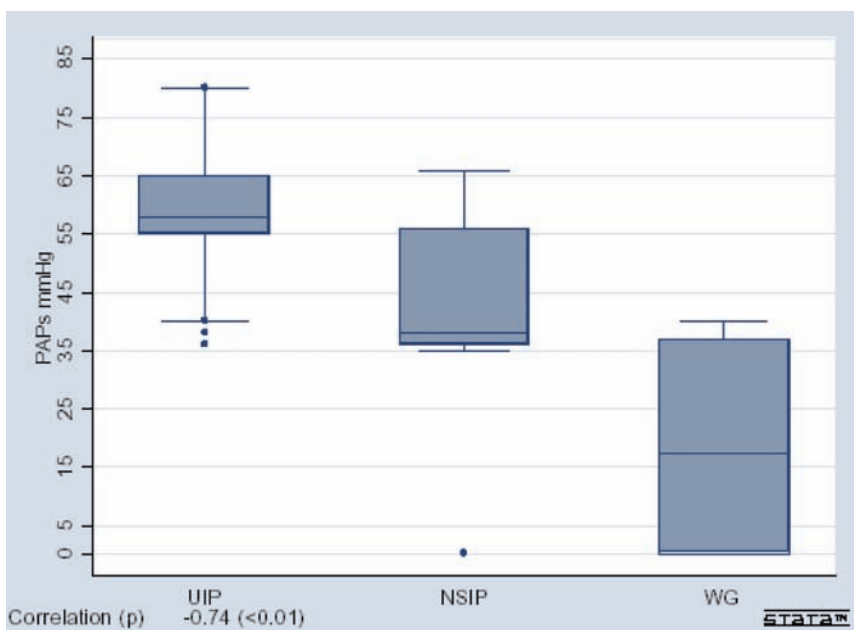
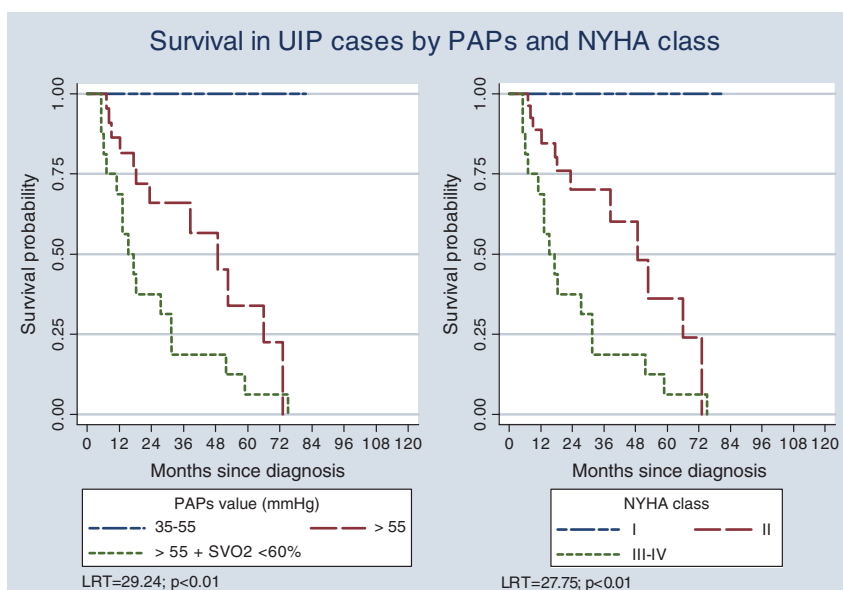
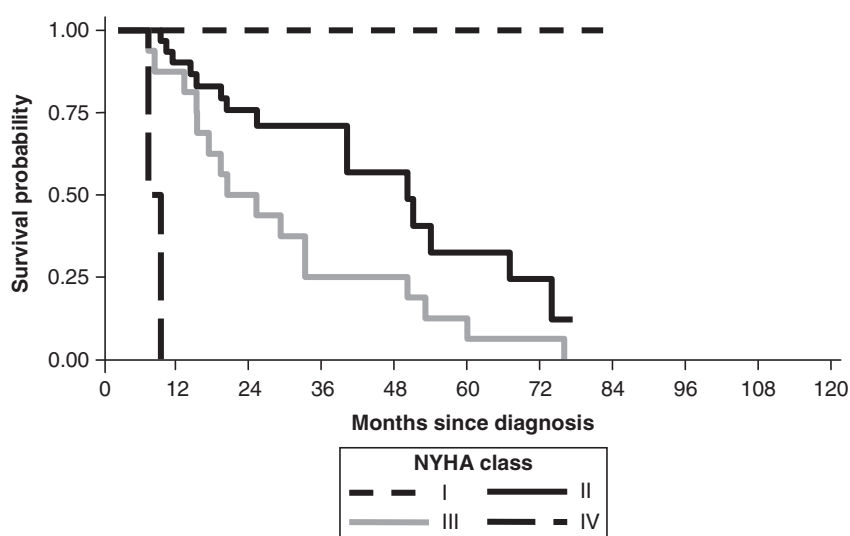


Fig. 2.21 PAPs by diagnosis





**Fig. 2.22** Survival in UIP cases by PAPs and NYHA class

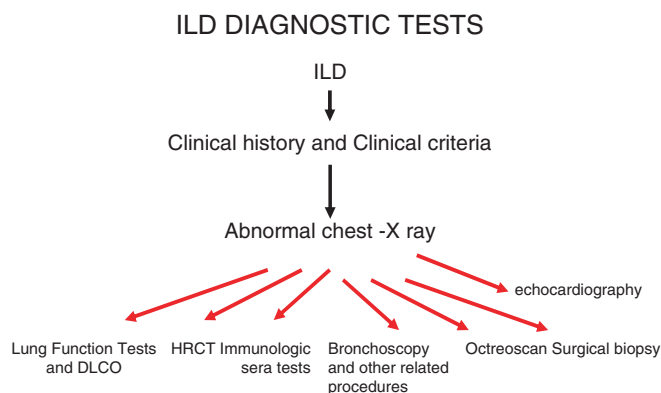


**Fig. 2.23** Kaplan Meyer survival estimates in 104 patients with interstitial lung disease according to NYHA functional class

## Summary

This section reviews the approach to diagnosis of PH in correlation with ILD diagnostic tests (Fig. 2.24). Cardiac parameters used for screening patients with suspected ILD





**Fig. 2.24** Diagnostic tests for ILD

are discussed. Echocardiography, when a TR jet is visible, is an important tool both in terms of diagnosis and prognosis. Patients with suspected PH in whom a TR jet is not visible, could be considered for right ventricular catheterization. The 6MWT is a useful quantitative test for evaluating the prognosis of patients with ILD-associated PH. The utility of the NYHA classification as a prognostic factor of survival and mortality in ILD should be further evaluated in larger studies.

## References

1. Humbert M, Deng Z, Simmoneau G, et al. BMPR2 germline mutations in pulmonary hypertension associated with fenfluramine derivatives. *Eur Respir J* 2002;20:518–523.
2. Morse J, Barst R, Horn E, et al. Pulmonary hypertension in scleroderma spectrum of disease lack of bone morphogenetic protein receptor-2 mutations. *J Rheumatol* 2002;29:2379–2381.
3. Tew MB, Arnett PC, Reveille JD, et al. Mutation of bone morphogenetic protein receptor type 2 are not found in patients with pulmonary hypertension and underlying connective tissue diseases. *Arthritis Rheum* 2002;46:2829–2830.
4. Trembart JRC, Thomson JR, Machado RD, et al. Clinical and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasis. *N Engl J Med* 2001;345:325–334.
5. Du I, Sullivan CC, Chu D, et al. Signaling molecules in non familial pulmonary hypertension. *N Eng J Med* 2003;92:984–991.
6. Farber HW, Loscalzo J. Pulmonary arterial hypertension. *N Eng J Med* 2004;351:1655–1665.
7. Nogee LM, Dunbar, III, AE, Wert SE, et al. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. *N Eng J Med* 2001;344:573–579.
8. Amin RS, Wert SE, Baughman RP, et al. Surfactant protein deficiency in familial interstitial lung disease. *J Pediatr* 2001;139:85–92.
9. Khalil N, Parekh TV, O'Connor R, et al. Regulation of the effect of TGF-beta 1 by activation of latent of TGF-beta 1 and differential expression of TGF-beta receptors /T-beta R-1 and T beta R-2) in idiopathic pulmonary fibrosis. *Thorax* 2001;56:907–915.
10. Sime PJ, Xing Z, Graham FL. Adenovector-mediated gene transfer of active transforming grown factor-beta 1 induces prolonged severe fibrosis in rat lung. *J Clin Invest* 1997;100:768–777.

11. Whyte M, Hubbard R, Meliconi R, et al. Increased risk of fibrosing alveolitis associated with interleukin-1 receptor antagonist and tumor necrosis factor- $\alpha$  gene polymorphisms. *Am J Respir Crit Care Med* 2000;162:755–758.
12. Zorzetto M, Ferrarotti I, Trisolini R, et al. Complement receptor 1 gene polymorphisms are associated with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;168:330–334.
13. Pantelidis P, Fanning GC, Wells AU, et al. Analysis of tumor necrosis factor- $\alpha$ , lymphotoxin- $\alpha$ , tumor necrosis factor receptor II, and interleukin-6 polymorphisms in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2001;163:1432–1436.
14. Xaubert A, Marin-Arguedas A, Lario S, et al. Transforming growth factor- $\beta_1$  gene polymorphisms are associated with disease progression in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;168:431–435.
15. Reeve HL, Archer SL, Weir EK. Ion channels in the pulmonary vasculature. *Pulm Pharmacol Ther* 1997;10:243–252.
16. Weir EK, Reeve HL, Talorova S, et al. Oxygen sensing in the pulmonary vasculature. In: Lopez-Barneo J, Weir EK, editors. *Oxygen regulation of ion channels and gene expression*. Armonk, NY: Futura Publishing Company, Inc.; 1998. p. 193–206.
17. Yuan JX, Aldinger AM, Juhaszova M, et al. Dysfunctional voltage-gated  $K^+$  channels in pulmonary artery smooth muscle cells of patients with primary pulmonary hypertension. *Circulation* 1998;14:1400–1406.
18. Marshall RB, Mamary CAJ, Verhoeven AJ, et al. Pulmonary artery NADPH-oxidase is activated in hypoxic pulmonary vasoconstriction. *Am J Respir Cell Mol Biol* 1996;15:633–644.
19. Weissmann N, Tadic A, Winterhalder S, et al. Inhibition of hypoxic pulmonary vasoconstriction by superoxide dismutase inhibitors in isolated rabbit lungs. *Am J Respir Crit Care Med* 1999;159:A 569.
20. Robertson TP, Hague D, Aaronson PI, et al. Voltage-independent calcium entry in hypoxic pulmonary vasoconstriction of intrapulmonary arteries of the rat. *J Physiol* 2000;525:669–680.
21. Yuan JX, Tod M, Rubin L, et al. Deoxyglucose and reduced glutathione mimic effects of  $H_2$  hypoxia on  $K^+$  and  $Ca^{++}$  conductances in pulmonary artery cells. *Am J Physiol* 1994;267:L52–L63.
22. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 1988;332:411–415.
23. Giaid A, Yanagisawa M, Langleben SD, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Eng J Med* 1993;328:1732–1739.
24. Arai S, Hori S, Aramori I, et al. Cloning and expression of a cDNA encoding an endothelin receptor. *Nature (Lond)* 1990;348:730–732.
25. Sakurai T, Yanagisawa M, Takawa Y, et al. Cloning of a cDNA encoding a non-isopeptide-selective subtype of the endothelin receptor. *Nature (Lond)* 1990;348:732–735.
26. Giaid A, Michel RP, Stewart DJ, et al. Expression of endothelin-1 in patients with cryptogenic fibrosing alveolitis. *Lancet* 1993;341:1550–1554.
27. Uguccioni M, Pulsatelli L, Grigolo B et al. Endothelin-1 in idiopathic pulmonary fibrosis. *J Clin Pathol* 1995;48:330–334.
28. Abraham DJ, Vancheeswaran R, Dashwood MR, et al. Increased levels of endothelin-1 and differential endothelin type A and B receptor expression in scleroderma-associated fibrotic lung disease. *Am J Pathol* 1997;151:831–841.
29. Park SH, Saleh D, Giaid A, et al. Increased endothelin-1 in bleomycin-induced pulmonary fibrosis and the effect of an endothelin receptor antagonist. *Am J Respir Crit Care Med* 1997;156:831–841.
30. Hochar B, Schwartz A, Fagan KA, et al. Pulmonary fibrosis and chronic lung inflammation in ET-1 transgenic mice. *Am J Respir Cell Mol Biol* 2000;23:19–26.
31. Turner-Warwick M. Precapillary systemic-pulmonary anastomoses. *Thorax* 1963;18:225–237.
32. Peao MND, Aguas AP, DeSa CM, et al. Neof ormation of blood vessels in association with a rat lung fibrosis induced by bleomycin. *Anat Rec* 1994;238:57–67.
33. Keane MP, Arenberg DA, Lynch JP 3rd, et al. The CXC chemokines, IL-8 and IP-10, regulate angiogenic activity in idiopathic pulmonary fibrosis. *J Immunol* 1997;159:1437–1453.

34. Keane MP, Belperio JA, Burdick M, et al. ENA-78 is an important angiogenic factor in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2001;164:2239–2242.
35. Hyde DM, Henderson TS, Giri SN, et al. Effect of murine gamma interferon on the cellular responses to bleomycin in mice. *Exp Lung Res* 1988;14:687–704.
36. Keane MP, Belperio JA, Arenberg DA, et al. IFN-gamma-inducible protein-10 attenuates bleomycin-induced pulmonary fibrosis via inhibition of angiogenesis. *J Immunol* 1999;163:5686–5692.
37. Rich S, editor. Primary pulmonary hypertension. Executive summary from the World Symposium: Primary Pulmonary Hypertension 1998. <http://www.who.int/ncd/cvd/pph.html>. Accessed 14 Aug 2008.
38. Morell NW, Morris KG, Stenmark KR. Role of angiotensin-converting enzyme activity and expression is increased during hypoxic pulmonary hypertension. *Cardiovasc Res* 1997;34:393–403.
39. Davis P, Burke G, Reid I. The structure of the wall of the rat interacinar pulmonary artery: an electron microscopic study of microdissected preparations. *Microvasc Res* 1986;32:50–63.
40. Jones RC. Role of interstitial fibroblasts and intermediate cells in microvascular remodelling in pulmonary hypertension. *Eur Respir Rev* 1993;3:569–575.
41. Tuder RM, Groves B, Badesch DB, et al. Exuberant endothelial cell growth and elements of inflammation are present in plexiform lesions of pulmonary hypertension. *Am J Pathol* 1994;144:275–285.
42. Yi ES, Kim H, Ahn H, et al. Distribution of obstructive intimal lesions and their cellular phenotypes in chronic pulmonary hypertension. A morphometric and immunohistochemical study. *Am J Respir Crit Care Med* 2000;162:1577–1586.
43. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *N Eng J Med* 1993;328:1732–1739.
44. Wang R, Ibarra-Sunga O, Verlinski L, et al. Abrogation of bleomycin-induced epithelial apoptosis and lung fibrosis by captopril or by a caspase inhibitor. *Am J Physiol Lung Cell Mol Physiol* 2000;279:L143–L151.
45. Kuwano K, Kunitake R, Maeyama T, et al. Attenuation of bleomycin-induced pneumopathy in mice by a caspase inhibitor. *Am J Physiol Lung Cell Mol Physiol* 2001;280:L316–L325.
46. Hagimoto N, Kuwano K, Inoshima M, et al. TGF-beta 1 as an enhancer of Fas-mediated apoptosis of lung epithelial cells. *J Immunol* 2002;168:6470–6478.
47. Wang R, Alam G, Zagariya A, et al. Apoptosis of lung epithelial cells in response to TNF-alpha requires angiotensin II generation de novo. *J Cell Physiol* 2000;185:253–259.
48. Keane MP, Arenberg DA, Lynch JP, Lynch JP 3rd, et al. The CXC chemokines, IL-8 and IP-10, regulate angiogenic activity in idiopathic pulmonary fibrosis. *J Immunol* 1997;159:1437–1443.
49. Renzoni EA, Walsh DA, Salmon M, et al. Interstitial vascularity in fibrosing alveolitis. *Am J Respir Crit Care Med* 2003;167:438–443.
50. Koyama S, Sato E, Haniuda H, et al. Decreased level of vascular endothelial growth factor. *Am Respir J Crit Care Med* 2002;166:382–385.
51. Weller PA. Eosinophils and fibroblasts: the medium in the mesenchyme. *Am J Respir Cell Mol Biol* 1989;1:267–268.
52. Elias JA, Freundlich B, Kern JA, Rosenbloom J. Cytokine networks in the regulation of inflammation and fibrosis in the lung. *Chest* 1990;97:1439–1445.
53. Gurujeyalakshmi G, Giri SN. Molecular mechanisms of antifibrotic effect of interferon gamma in bleomycin-mouse model of lung fibrosis: down regulation of TGF- $\beta$  and procollagen I and III gene expression. *Exp Lung Res* 1995;21:791–808.
54. Prior C, Haslam PL. In vivo levels and in vitro production of interferon-gamma in fibrosing interstitial lung diseases. *Clin Exp Immunol* 1992;88:280–287.
55. Gaensler EA, Carrington CB. Open biopsy for chronic diffuse infiltrative lung disease: clinical, roentgenographic, and physiologic correlation in 502 patients. *Ann Thorac Surg* 1980;30:411–426.

56. Padley SPG, Hansell DM, Flower CDR, et al. Comparative accuracy of high resolution computed tomography and chest radiography in the diagnosis of chronic diffuse infiltrative lung disease. *Clin Radiol* 1991;44:222–226.
57. Lee KS, Primack SL, Staples CA, et al. Chronic infiltrative lung disease: comparison of diagnostic accuracies of radiography and low- and conventional-dose thin-section CT *Radiology* 1994;191:669–673.
58. Kazerooni EF, Martinez F, Flint D, et al. Thin-section CT obtained at 10mm increments versus three-level thin-section CT for idiopathic pulmonary fibrosis: correlation with pathologic scoring. *AJR Am J Roentgenol* 1997;169:977–983.
59. Webb RW, Muller NL, Naidich DP. Clinical utility of high-resolution computed tomography. In: Webb RW, Muller NL, Naidich DP editors. *High-resolution CT of the lung*. Philadelphia PA: Lippincott William & Wilkins; 2001. p. 569–597.
60. Wells AU, Hansell DM, Rubens MB, et al. The predictive value of appearances of thin-section computed tomography in fibrosing alveolitis. *Am Respir Dis* 1993;148:1076–1082.
61. Zerhouni EA, Naidich DP, Stitik FP, et al. Computed tomography of the pulmonary parenchyma: part 2. Interstitial disease. *J Thorac Imaging* 1985;1:54–64.
62. Hunninghake GW, Zimmerman MB, Schwarz DA, et al. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2001;164:193–196.
63. McDonald SL, Rubens MB, Hansell DM, et al. Nonspecific interstitial pneumonia and usual interstitial pneumonia: comparative appearances at and diagnostic accuracy of thin-section CT. *Radiology* 2001;221:600–605.
64. Daniil ZD, Giltchrist FC, Nicholson AG, et al. A histologic pattern of nonspecific interstitial pneumonia is associated with a better prognosis than usual interstitial pneumonia in patients with cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med* 1999;160:899–905.
65. Flaherty KR, Twaite EL, Kazerooni EA, et al. Radiological versus histological diagnosis in UIP and NSIP: survival implications. *Thorax* 2003;58:143–148.
66. Gay SE, Kazerooni EA, Toews GB, et al. Idiopathic pulmonary fibrosis: predicting response to therapy and survival. *Am J Respir Crit Care Med* 1998;157:1063–1072.
67. King TE Jr, Schwarz MI, Brown K, et al. Idiopathic pulmonary fibrosis: relationship between histopathologic features and mortality. *Am J Respir Crit Care Med* 2001;164:1025–1032.
68. King TE Jr, Toozé JA, Schwarz MI, et al. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med* 2001;164:1171–1181.
69. Wells AU, Desai SR, Rubens MB, et al. Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography. *Am J Respir Crit Care Med* 2003;167:962–969.
70. Mogulkoc N, Brutsche MH, Bishop PW, et al. Pulmonary function in idiopathic pulmonary fibrosis and referral for lung transplantation *Am J Respir Crit Care Med* 2001;164:103–108.
71. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and management. International Consensus Statement. *Am J Respir Crit Care Med* 2000;161:646–664.
72. Awadh N, Muller NL, Park CS, et al. Airway wall thickness in patients with near fatal asthma and control groups: assessment with high resolution tomographic scanning. *Thorax* 1998;53:248–253.
73. Meyer KC. Bronchoalveolar lavage as a diagnostic tool. *Semin Respir Crit Care Med* 2007;28:546–560.
74. Leung AN, Brainer MW, Caillat-Vigneron N. Sarcoidosis activity: correlation of HRCT findings with those of <sup>67</sup>Ga scanning, bronchoalveolar lavage, and serum angiotensin-converting enzyme assay. *J Comput Assist Tomogr* 1998;22:229–234.
75. Sulavik SB, Spencer RP, Palestro CJ, et al. Specificity and sensitivity of distinctive chest radiographic and/or <sup>67</sup>Ga images in the noninvasive diagnosis of sarcoidosis. *Chest* 1993;103:403–409.
76. Alavi A, Palevsky HI. Gallium-67 citrate scanning in the assessment of disease activity in sarcoidosis. *J Nuc Med* 1992;33:751–755.
77. Grijm K, Verberne, Krowels FH, et al. Semiquantitative <sup>67</sup>Ga scintigraphy as an indicator of response to and prognosis after corticosteroid treatment in idiopathic interstitial pneumonia. *J Nucl Med* 2005;46:1421–1426.

78. Lebthai R, Crestani B, Belmatoug N, et al. Somatostatin receptor scintigraphy and gallium scintigraphy in patients with sarcoidosis. *J Nucl Med* 2001;42:21–26.
79. Carbone R, Filiberti R, Grosso M, et al. Octreoscan perspectives in sarcoidosis and idiopathic interstitial pneumonia. *Eur Rev for Med and Pharmacol Sci* 2003;7:97–105.
80. Turner-Warwick M, McAllister W, Lawrence R, et al. Corticosteroid treatment in pulmonary sarcoidosis: do serial lavage lymphocyte counts, serum angiotensin converting enzyme measurements and gallium-67 scan help management? *Thorax* 1986;41:903–913.
81. Clarke D, Mitchell AWM, Dick R, et al. The radiology of sarcoidosis. *Sarcoidosis* 1994;11:90–99.
82. Kwekkeboom DJ, Krenning EP, Kho GS, et al. Somatostatin receptor imaging in patients with sarcoidosis. *Eur J Nucl Med* 1998;25:1284–1292.
83. Carbone RG, Musi M, Cantalupi DP, et al. Somatostatin receptor versus gallium-67 scintigraphy in interstitial lung diseases. *Chest* 1999;119:315S.
84. McGoon M, Gutterman D, Steen V, et al. Screening early detection, and diagnosis of pulmonary arterial hypertension. ACCP evidence-based clinical practice guidelines. *Chest* 2004;126:14S–34S.
85. Mukerjee D, St George D, Knight C, et al. Echocardiography and pulmonary function as screening tests for pulmonary arterial hypertension in systemic sclerosis. *Rheumatology* 2004;43:461–466.
86. Burdt MA, Hoffman RW, Deutscher SL, et al. Long term outcome in mixed connective tissue disease: longitudinal clinical and serologic findings. *Arthritis Rheum* 1999;42:899–990.
87. Mc Quillan BM, Picard MP, Leavitt M, et al. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation* 2001;104:2797.
88. Barst RJ, McGoon M, Torbicki A, et al. Diagnosis and differential assessment of pulmonary hypertension. *J Am Coll Cardiol* 2004;43:40S–47S.
89. Stephen B, Dalal P, Berger M, et al. Noninvasive estimation of pulmonary artery diastolic pressure in patients with tricuspid regurgitation by Doppler echocardiography. *Chest* 1999;116:73–77.
90. Baughman R, Lower EE, Engel P. Echocardiography to detect pulmonary hypertension in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2005;22:244–245.
91. Sulica R, Teirstein AS, Kakarda S, et al. Distinctive clinical, radiological, and functional characteristics of patients with sarcoidosis-related pulmonary hypertension. *Chest* 2005;128:1483–1489.
92. Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiography assessment of pulmonary hypertension in patients with advanced lung disease. *Am Respir J Crit Care* 2003;167:735–740.
93. Nadrous HF, Pellika PA, Krowka MJ, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. *Chest* 2005;128:2393–2399.
94. Bourbon A, Vionnet M, Leprince P, et al. The effect of methylprednisolone treatment on the cardiopulmonary bypass-induced systemic inflammatory response. *Eur Cardiothorac Surg* 2005;27:729–730.
95. Gothard J. Lung injury after thoracic surgery and one-lung ventilation. *Curr Opin Anaesthesiol* 2006;19:5–10.
96. Ng CS, Wang S, Arifi AA, et al. Inflammatory response to pulmonary ischemia–reperfusion injury. *Surg Today* 2006;36:205–214.
97. Berg JT, Fu Z, Breen EC, et al. High lung inflation increases mRNA levels of ECM components and growth factors in lung parenchyma. *J Appl Physiol* 1997;83:120–128.
98. Berg JT, Breen EC, Fu Z, et al. Alveolar hypoxia increases gene expression of extra cellular matrix protein and platelet-derived growth factor-B in lung parenchyma. *Am Respir Crit Care Med* 1998;138:1920–1928.
99. Carbone R, Bossone E, Bottino G, et al. Secondary pulmonary hypertension- diagnosis and management. *Eur Rev for Med Pharmacol Sci* 2005;9:331–342.
100. Carbone R, Montanaro F, Bottino G. Outcome in interstitial lung disease. *Eur Respir J* 2005;26:268S.

101. Garbin U, Fratta Pasini A, Stranieri C, et al. Effects of nebivolol on endothelial gene expression during oxidative stress in human umbilical vein endothelial cells. *Mediators Inflamm.* 2008; 2008:367590.
102. Lee SH, Channick RN, Endothelin antagonism in pulmonary arterial hypertension. *Semin Respir Crit Care Med.* 2005 Aug;26(4):402–8. Review.
103. Ishaque A, Dunn MJ, Sorokin A, Cyclooxygenase-2 inhibits tumor necrosis factor alpha-mediated apoptosis in renal glomerular mesangial cells. *J Biol Chem.* 2003 Mar 21;278(12):10629–40.

Pulmonary Arterial Hypertension and Interstitial Lung  
Diseases

A Clinical Guide

Baughman, R.P.; Carbone, R.G.; Bottino, G. (Eds.)

2009, XVIII, 248 p., Hardcover

ISBN: 978-1-58829-695-5

A product of Humana Press