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## Causes of failure in acute respiratory distress syndrome modeling and treatment in animal research and new approaches

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### Abstract

Acute respiratory distress syndrome (ARDS) is a major cause of morbidity, death and cost in intensive care

units. Despite intensive research, pharmacotherapy has not passed the experimental stage and mortality rates are still high. Animal models provide a bridge between patients and the laboratory bench. Different animal models have been developed in order to mimic human ARDS, but they have limitations. The purpose of this review was to summarize the properties of the most commonly used experimental animal models mimicking the causes and pathology of human ARDS, the limitations of ARDS models, treatment failure and new therapeutic approaches.

**Key words:** Acute respiratory distress syndrome; Lung injury; Animal models; Model limitations

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**Core tip:** Acute respiratory distress syndrome (ARDS) is a syndrome with multiple risk factors that trigger the acute onset of respiratory insufficiency. ARDS is still one of the most fatal diseases with a high mortality rate in intensive care units. Mortality rates remain unchanged, pharmacotherapies have a very limited role in the management of ARDS and additional treatments are sorely needed. Animal models provide a bridge between patients and the laboratory bench, but these models have certain limitations and to date, no single animal model reproduces all the characteristics of human ARDS. Despite these limitations, the complex pathogenesis of ARDS makes animal models necessary.

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## INTRODUCTION

Acute respiratory distress syndrome (ARDS) was first described in 1967<sup>[1]</sup>, and its description was developed into the Berlin definition in 2011<sup>[2]</sup>. In the clinical study cohort of the Berlin definition, the mortality rate was 27% for mild, 32% for moderate and 45% for severe ARDS<sup>[3]</sup>. Although worsening oxygenation is a risk factor for ARDS mortality, patients generally die from multisystem organ failure or a progressive underlying illness; only a minority of ARDS patients (13%-19%) die from refractory respiratory failure<sup>[4]</sup>. Currently, there is no effective medical treatment that improves the survival of adult patients with ARDS.

ARDS is a syndrome of inflammation and increased permeability of the blood-gas barrier<sup>[5]</sup>. It is characterized by rapid-onset respiratory failure following a variety of direct (e.g., bacterial and viral infections of the lungs, aspiration of gastric contents and inhalational injury) or indirect (e.g., systemic infections that cause sepsis syndrome, major trauma, pancreatitis, severe burns and blood transfusions) insults to the parenchyma or vasculature of the lungs<sup>[5-8]</sup>. Pneumonia and sepsis are the two most common predisposing conditions for the development of ARDS<sup>[5,6]</sup>.

There have been a number of studies addressing the pathogenesis of, and therapies for, ARDS (e.g., inhaled pulmonary vasodilators including nitric oxide and prostacyclins, corticosteroids, beta agonists, neuromuscular blocking agents, statins, macrolide antibiotics, aspirin, angiotensin converting enzyme inhibitors/angiotensin receptor blockers)<sup>[2,9,10]</sup>. However, despite intensive research, pharmacotherapy has not passed the experimental stage and supportive therapies represent the mainstay of ARDS treatment<sup>[2-5,9-11]</sup>. The current therapeutic strategy primarily emphasizes low tidal-volume mechanical ventilation and judicious fluid management, plus treatment of the initiating insult and any known underlying disease<sup>[2-4,9,10]</sup>. This dearth of therapeutic modalities is largely due to the complex pathogenesis of ARDS, where multiple overlapping signaling pathways are activated depending on the type of lung injury<sup>[2,9,10]</sup>. The development of experimental models and therapies is necessary for improving treatment and reducing the mortality rate.

## ARDS ANIMAL MODELS

Different animal models have been developed for ARDS research<sup>[5-8,12,13]</sup>. These models can be divided into two groups: direct, in which the lung is injured directly; and indirect, where models are generally based on the formation of sepsis (Table 1). To create a similar human ARDS model, various injury models can be combined<sup>[5,14,15]</sup>. Numerous different models have been developed, but there is no animal model which shows all the characteristics of human ARDS<sup>[5-8,12-15]</sup> (Table 1).

Creating a model to mimic the human ARDS definition is not practical in animals, particularly in

**Table 1 Animal models of acute respiratory distress syndrome**

Direct lung injury	Intratracheal or intranasal delivery of bacteria or bacterial product such as lipopolysaccharide Hydrochloric acid or gastric particles to create acid aspiration High inspired fraction of oxygen Surfactant depletion (0.9% NaCl lavage) Lung ischemia/reperfusion Mechanical ventilation at high tidal volumes
Indirect lung injury	Cecal ligation and puncture Intravenous bacteria or LPS administration Mesenteric ischemia/reperfusion Oleic acid model
Combination models	Cecal ligation and puncture followed by hemorrhage Saline lavage after mechanical ventilation Intraperitoneal LPS injection after intravenous oleic acid

LPS: Lipopolysaccharide.

small animals. Therefore, using histopathological criteria to define ARDS is a more accurate approach<sup>[8]</sup>. In humans, inflammatory cell infiltrates, thickening of alveolar septa and hyaline membrane depositions are the main characteristics of alveolar damage<sup>[5,10]</sup>. There is no animal model which shows all the characteristics of human ARDS, however, lacking one of these factors does not mean that this model is not a form of ARDS<sup>[8]</sup>. The most important factor is choosing an appropriate experimental model. Before choosing an animal model of ARDS, the target feature to be tested should be determined and then it should be created in the most appropriate model<sup>[7]</sup>. For example, if the passage of neutrophils into the lung is to be investigated, the lipopolysaccharide (LPS) instillation model characterized by alveolar neutrophilia would be appropriate. If epithelial damage is of interest, the acid instillation model would be considered suitable<sup>[7]</sup>.

## LIMITATIONS OF ARDS MODELS

Animal models of ARDS can mimic the clinical disorders, but there are certain limitations that affect the success of the modeling and treatment options<sup>[5-8,12-15]</sup> (Table 2).

Despite these limitations, animal models are needed. Matute-Bello *et al*<sup>[7]</sup> reviewed each model with its advantages, disadvantages and methodologies. Animal models also focus on interactions between systemic (e.g., renal failure, hepatic and hematologic dysfunction) and pulmonary injuries<sup>[7]</sup>.

## NEW APPROACHES IN ARDS

### TREATMENT

In the last decade, significant advances in the molecular mechanisms of ARDS have been recorded. However, these improvements could not be implemented successfully in clinical practice.

When considering new therapeutic opportunities and research, such therapies may come from mesen-



**Table 2** Limitations of acute respiratory distress syndrome models

Experiment period	The formation of pathology takes hours or days in humans, whereas the monitored period is shorter in animal models (monitoring difficulties)
Ventilation and fluid management	Ventilation and fluid management supports are lacking in animal experiments (these are crucial in humans)
The degree of pathology	Experimental models generally have milder pathology compared to human pathology
The species and the size of the animals	Larger animals (primates) can more easily mimic human disease, but these experiments require expertise. Smaller animals (mice) are much more widely used (this may allow for the study of complex pathways and genetic studies)
Treatment time	Therapeutic agents in experimental studies are usually given before the onset of acute respiratory distress syndrome, whereas the clinical diagnosis and treatment of ARDS is delayed
Animal age	Animal experiments are performed on young animals with no comorbidities; however, patients with ARDS are mostly elderly and may have many medical problems such as cardiovascular diseases, kidney or liver failure
Changes in response to therapy	The effects of therapeutic agents on survival in humans and animals are different. An agent may be effective on animal survival, but may not be effective in humans (there are many anatomical and physiological differences between animals and humans)
Coagulation and fibrinolytic status	Animal models cannot mimic the coagulation and fibrinolytic system changes during lung injury in humans
Correlation between biochemical markers and their biological activities	Biochemical markers measured in bronchoalveolar lavage fluid, plasma and edema fluid may not correlate with their biological activities
Combination treatment	Combined treatment should be developed. Combined treatment approaches are applied to a lesser extent in experimental models

ARDS: Acute respiratory distress syndrome.

chymal stem cells (MSCs; "adult stem cells") and gene therapies<sup>[2]</sup>.

MSCs could represent a promising new therapy for this syndrome, as recent animal research suggests that MSCs may ameliorate lung injury<sup>[16]</sup>. MSCs have several features which allow their use in the treatment of ARDS. MSCs are capable of regenerating damaged tissues and can differentiate into different cells. In addition, they can release immunomodulatory and anti-inflammatory molecules. These cells also lack HLA II molecules and this allows them to escape the immune reactions after transplantation<sup>[2]</sup>. Viral and non-viral methods for gene delivery to the lung have been developed. Recent studies have demonstrated that gene transfer of hemoxygenase-1, IL-10, and keratinocyte growth factor attenuate lung injury<sup>[2,17]</sup>. With the development of more efficient approaches, the use of therapeutic gene therapy will be safe and efficacious in the treatment of ARDS, leading to urgently needed, novel and safe therapies for ARDS. At this stage, further animal research will maximize therapeutic potency and safety of cell, gene or combined cell-based gene therapies and other pharmacotherapy agents in the treatment of ARDS.

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## Post splenectomy related pulmonary hypertension

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### Abstract

Splenectomy predisposes patients to a slew of infectious and non-infectious complications including pulmonary vascular disease. Patients are at increased risk for venous thromboembolic events due to various mechanisms that may lead to chronic thromboembolic pulmonary hypertension (CTEPH). The development of CTEPH and pulmonary vasculopathy after splenectomy involves complex pathophysiologic mechanisms, some of which remain unclear. This review attempts to congregate the current evidence behind our understanding about the etio-pathogenesis of pulmonary vascular disease related to splenectomy and highlight the controversies that surround its management.

**Key words:** Pulmonary hypertension; Thalassemia; Splenectomy; Thrombocytosis; Chronic thromboembolic pulmonary hypertension

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**Core tip:** Pulmonary hypertension is an often under-recognized non-infectious complication after splenectomy. The mechanisms for the development of pulmonary hypertension in this setting are multifactorial and are not clearly elucidated. We attempt to outline and highlight the current evidence behind these proposed mechanisms of post splenectomy related pulmonary hypertension.

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## INTRODUCTION

The spleen plays a key role in immune homeostasis through its ability to link innate and adaptive immunity. Splenectomy predisposes the individual to a life-long increased risk of severe infections<sup>[1]</sup>. Besides a risk of localized or generalized infection there is also a well known risk of thromboembolic events due to thrombocytosis post-splenectomy<sup>[2]</sup>. More specifically, in post-splenectomy patients there is a risk of pulmonary complications such as pneumonia, pleural effusion. Recently, there has been a growing interest about non-infectious complications such as thromboembolic events and pulmonary vasculopathies (Table 1). Pulmonary thromboembolic disease in the form of pulmonary embolism leading to chronic thromboembolic pulmonary hypertensive disease is one of the observed pulmonary complications of splenectomy. The pathophysiology of these conditions is complex and not yet clearly understood. Herein we attempt to describe the possible mechanisms of post-splenectomy pulmonary hypertension with a review of the literature.

## INDICATIONS FOR SPLENECTOMY

There are many indications for splenectomy but the most common cause remains traumatic injury leading to rupture of the spleen. In addition there are many benign and neoplastic conditions that may lead to removal of the spleen. Hematologic causes may include autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura (ITP), hereditary spherocytosis, pyruvate kinase deficiency, glucose-6 phosphate dehydrogenase deficiency or hypersplenism<sup>[3]</sup>. In addition there are neoplastic conditions that warrant splenectomy such as Hodgkin's disease, non-Hodgkin's lymphoma, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy cell leukemia and primary or metastatic tumors<sup>[3]</sup>. Other benign indications may be Gaucher's disease<sup>[4]</sup> and Chediak-Higashi Syndrome<sup>[5]</sup>. Complications post-splenectomy include acute complications of general surgery that include impaired wound healing, bleeding, post surgical infection due to high dose corticosteroids or possible gastric or pancreatic fistulas. However, splenectomy may be associated with an elevated risk for cardiovascular events such as myocardial infarction and stroke<sup>[6]</sup>. In addition to the aforementioned complications splenectomy predisposes patients for increased thromboembolic events<sup>[7]</sup> and pulmonary hypertension<sup>[8]</sup>.

## PULMONARY HYPERTENSION AND SPLENECTOMY

Pulmonary hypertension (PHTN) is characterized by a mean pulmonary arterial pressure (mPAP)  $\geq 25$  mmHg at rest<sup>[9]</sup>. The World Health Organization (WHO) has proposed a classification system for pulmonary

**Table 1 Medical complications after splenectomy**

Early
Lower lobe collapse of left lung
Left pleural effusion
Pneumonia
Venous thromboembolism
Subphrenic abscess
Delayed
Overwhelming infections: bacterial ( <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus</i> group B, <i>Salmonella</i> species, <i>Escherichia coli</i> and other coliforms, <i>Capnocytophaga canimorsus</i> and rarely <i>Pseudomonas aeruginosa</i> ), parasitic (Babesiosis <i>Plasmodium</i> species, Ehrlichiosis)
Venous thromboembolism
Pulmonary hypertension
Graft vs host disease <sup>[6]</sup>

**Table 2 World Health Organization's classification of pulmonary hypertension<sup>[10]</sup>**

Group I - PAH
Idiopathic PAH
Heritable PAH (BMPR2, ALK1, ENG, SMAD9, CAV1, KCNK3, Unknown)
Drug and toxin induced
Associated with (1) Connective tissue disease; (2) HIV infection; (3) Portal hypertension; (4) Congenital heart disease; and (5) Schistosomiasis
Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
Persistent pulmonary hypertension of the newborn
Group II - Pulmonary hypertension due to left heart disease
Left ventricular systolic dysfunction
Left ventricular diastolic dysfunction
Valvular disease
Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
Group III - Pulmonary hypertension due to lung diseases and/or hypoxia
Chronic obstructive pulmonary disease
Interstitial lung disease
Other pulmonary diseases with mixed restrictive and obstructive pattern
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitudes
Developmental lung disease
Group IV - Chronic thromboembolic pulmonary hypertension
Group V - Pulmonary hypertension with unclear multifactorial mechanisms
Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
Metabolic disorders: glycogen storage disease, Gaucher's disease, hypothyroidism
Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension

Adapted from Galie *et al*<sup>[62]</sup>. BMPR: Bone morphogenic protein receptor type II; CAV1: Caveolin-1; ENG: Endoglin; HIV: Human immunodeficiency virus; PAH: Pulmonary arterial hypertension.

hypertension based on common clinical features (Table 2)<sup>[10]</sup>. Patients with splenectomy can develop PHTN with histopathological changes similar to those with WHO Group 1 Pulmonary Arterial Hypertension (PAH)<sup>[8,11]</sup> and WHO Group 4 - Chronic Thromboembolic Pulmonary

**Table 3** List of splenectomy and pulmonary hypertension studies

Ref.	Patient cohort (n)	Study design	No. of patients with splenectomy	Method of PH diagnosis	Comment
Hoeper <i>et al</i> <sup>[8]</sup>	Unexplained PHTN (61)	Retrospective	7	RHC	3 patients had splenectomy for hereditary spherocytosis and trauma, one patient with ITP
Jaïs <i>et al</i> <sup>[11]</sup>	CTEPH (257)	Retrospective	22 (8.6%)	RHC	15 patients had splenectomy after trauma, 4 with hemolytic disorder
Jaïs <i>et al</i> <sup>[11]</sup>	Idiopathic PHTN (276)	Retrospective	7 (2.5%)	RHC	Lower prevalence of splenectomy in idiopathic PHTN compared to prior study
Phrommintikul <i>et al</i> <sup>[38]</sup>	PHTN in Thalassemia with Hb < 10 g/dL (29)	Retrospective	29 (75.8%)	TTE	Increased prevalence of PHTN with higher nucleated red cells, platelets and transfusion requirement in splenectomised patients than those with intact spleen
Elstein <i>et al</i> <sup>[16]</sup>	Gaucher's disease (134), 9 patients had PH	Retrospective	6	TTE	All patients with PHTN had enzyme replacement therapy
Stewart <i>et al</i> <sup>[15]</sup>	Hereditary stomatocytosis after splenectomy (9)	Retrospective	9	2 RHC 1 on autopsy	3 patients developed CTEPH, one portal hypertension
Palkar <i>et al</i> <sup>[63]</sup>	PHTN after splenectomy (9)	Retrospective	9	RHC	4 patients belonged to group 1, two to group 4 and one each in groups 2, 3 and 5

RHC: Right heart catheterization; TTE: Transthoracic echocardiography; ITP: Immune thrombocytopenic purpura; PHTN: Pulmonary hypertension.

Hypertension (CTEPH)<sup>[11-13]</sup>. In addition splenectomized patients developing PHTN in the setting of hemolytic disorders, trauma, sickle cell disease, Gaucher's disease are included in WHO Group 5 definition of pulmonary hypertension.

Initially the link between splenectomy and PHTN was suggested in patients with thalassemia and hereditary stomatocytosis<sup>[12,14,15]</sup>. It has been estimated that the time interval between splenectomy and the development of PHTN is long (range 2-35 years)<sup>[8,11]</sup>. Autopsy findings from 58 patients with thalassemia showed pulmonary vascular changes indicative of microthromboemboli in 54% splenectomized patients compared to 16% of those who had not had splenectomy<sup>[14]</sup>. In a study by Hoeper *et al*<sup>[8]</sup> the prevalence of asplenia (including traumatic asplenia) was significantly higher (11.5%) among 61 patients with unexplained PHTN. In a study by Jaïs *et al*<sup>[11]</sup> a cohort of 257 patients referred for the treatment of CTEPH, 22 patients (8.6%) had a history of splenectomy. In the control group of idiopathic PHTN in the same study, 2.5% of patients had splenectomy compared to 0.56% in patients with chronic lung conditions<sup>[11]</sup>. In another study of 134 adults with Gaucher's disease, PHTN was diagnosed on echocardiogram in 9 patients (7%) on enzyme replacement therapy; 6 patients had prior splenectomy<sup>[16]</sup>.

An increased incidence of PHTN has also been described in patients who have undergone splenectomy for trauma<sup>[8,11]</sup>, hemolytic disorders such as thalassemia, pyruvate kinase deficiency, hereditary spherocytosis, and stomatocytosis<sup>[14,17-20]</sup> and Gaucher's disease<sup>[16,21]</sup>.

Based on the literature it is difficult to differentiate if the hypercoagulability is caused by splenectomy or is due to the underlying hemolytic disorder. Even the risk of PHTN after splenectomy may differ between hemolytic disorders. This suggests that in

addition to the loss of splenic filter, the development of PHTN in post-splenectomy patients is likely a slow multifactorial process. In a study by Jaïs *et al*<sup>[11]</sup> only 4 of 22 patients had a hemolytic disorder, in most of the others, the spleen had been removed for trauma. In another study, of seven patients with unexplained PHTN after splenectomy, 3 patients had splenectomy due to trauma<sup>[8]</sup>. Thus, it is clear that splenectomy by itself is a risk factor for PHTN even in the absence of hematologic disorders. All studies on regarding PHTN have been summarized in Table 3.

## MECHANISMS FOR PULMONARY HYPERTENSION POST SPLENECTOMY

### *Venous thromboembolism and CTEPH*

Splenectomy is associated with venous thrombosis in general and in particular, with deep venous thrombosis and non-resolving and recurrent venous thromboembolism<sup>[22,23]</sup>. Deep venous thrombosis may be complicated by pulmonary embolism. Compared to the general population and appendectomy patients respectively, Thomsen *et al*<sup>[23]</sup> found a 19.8-fold (95%CI: 8.8-44.7) and 2.3-fold (95%CI: 1.3-4.1) increased risk of DVT and a 32.6-fold (95%CI: 13.9-76.3) and 3.2-fold (95%CI: 1.8-5.5) higher risk of PE in splenectomized patients within the first 90 d after splenectomy.

One late consequence of non-resolution of venous and pulmonary thromboemboli is CTEPH<sup>[24]</sup>. This condition is defined by the absence of thrombus resolution after one or more episodes of acute pulmonary embolism causing sustained vascular obstruction and subsequent pulmonary hypertension. In a study by Pengo *et al*<sup>[25]</sup> a cumulative incidence of 3% was found for symptomatic chronic thromboembolic pulmonary hypertension in patients with acute pulmonary embolism at 2 year



follow up. Autopsies in patients with thalassemia have confirmed microthromboembolism in the pulmonary vasculature<sup>[14]</sup>. Histologic examination of explanted lungs in patients with unexplained PHTN undergoing lung transplant showed abundant thrombotic lesions in conjunction with medial hypertrophy, plexiform lesions and marked intimal thickening<sup>[8]</sup>. In a study by Frey *et al*<sup>[26]</sup>, mass spectral analysis of human pulmonary endarterectomy specimens in CTEPH after splenectomy showed increased anionic phospholipids. These anionic phospholipids inhibit angiogenesis *in vitro* thereby delaying thrombus resolution<sup>[26]</sup>. In the same study, thrombi volumes and cross sectional areas were compared in splenectomized and sham-operated mice after inferior vena caval ligation to create stagnant flow venous thrombosis and model human deep vein thrombosis. Splenectomized mice showed larger initial thrombi and delayed thrombus resolution<sup>[26]</sup>. In the study by Jaïs *et al*<sup>[11]</sup> of the 22 patients with CTEPH who had had splenectomy, only eight were suitable for thrombo-endarterectomy. Also, in the same study, only 7 (2.5%) of 276 patients with idiopathic PHTN had splenectomy compared to prevalence of 11.5% of aplenia in patients with unexplained PHTN reported in an earlier study<sup>[8]</sup>. However, in the study by Hoeper *et al*<sup>[8]</sup>, splenectomized subjects had prominent thrombotic pulmonary arteriopathy. This raises the possibility of a continuum between CTEPH, thrombotic form of idiopathic PHTN and PAH without thrombosis<sup>[27]</sup>. Further, it suggests that PHTN after splenectomy occurs mainly through thromboembolic involvement of pulmonary microvasculature. This may occur by two mechanisms; (1) Increased thrombus formation; and (2) Delayed thrombus resolution as discussed below.

### Increased thrombus formation

Patients undergoing splenectomy may have significant enrichment of anion phospholipids and this has been proposed to be the key to thrombogenicity<sup>[26]</sup>. In animal studies, platelet-derived micro particles (MP) were significantly increased in the blood of the splenectomized mice<sup>[26]</sup>. These microparticles can act as pro-coagulants by providing a negative charged surface for the assembly of coagulation proteases thus contributing to thrombus formation<sup>[28]</sup>. A similar rise in platelet derived MPs was observed in humans after undergoing splenectomy<sup>[29]</sup>. Anionic phospholipids of the erythrocyte membrane phosphatidylserine (PS) are localized in the inner membrane leaflet of the cell membrane of red blood cells in normal individuals<sup>[30]</sup>. The translocation of such phospholipids (*e.g.*, PS) to the outer leaflets of the erythrocyte membrane supports coagulation by acting as cofactors for proteolytic reactions<sup>[31]</sup>. Kuypers *et al*<sup>[32]</sup> showed that number of erythrocytes with modified PS expression was 20 times higher after splenectomy. The loss of splenic filtering function allows abnormal red cells

to remain in circulation after splenectomy. Thus increased MPs and anionic phospholipids can enhance thrombogenicity, and result in CTEPH.

### Delayed thrombus resolution

In the mouse models of Frey *et al*<sup>[26]</sup> the anionic phospholipids PS and phosphatidylglycerol (PG) as well as the neutral phospholipid phosphatidylethanolamine (PE) were increased in the later phase of vascular remodeling along with delayed incidence of thrombus resolution. This supports the possibility that cellular effects of these phospholipids may be driving the delay in thrombus resolution. Angiogenesis is a key event in vascular remodeling. It has been demonstrated that non-resolution of the thrombus has been associated with low expression of angiogenesis associated genes. PS may inhibit angiogenesis *via* brain specific angiogenesis inhibitor 1. This adhesion type G protein coupled receptor binds PS on apoptotic cells. This has shown to inhibit *in vivo* neovascularization<sup>[33,34]</sup> that in turn leads to delayed thrombus resolution. While Frey *et al*<sup>[26]</sup> also demonstrated compromised lymphangiogenesis in splenectomized patients, whether it plays a role in thrombus non-resolution is a subject of further research.

In patients with thalassemia, the high oxidative state of the red blood cells due to iron accumulation in the membrane induces a similar high oxidative state in the platelets, leading to their activation<sup>[35]</sup>. Furthermore, rheological abnormality of the red blood cells also tends to favor their aggregation<sup>[36]</sup>. Garozzo *et al*<sup>[37]</sup> have reported increased adhesion molecules on nucleated red blood cells in patients with thalassemia intermedia and major, which may contribute to the hypercoagulable state. Splenectomized patients with thalassemia have more abnormal red blood cells and precursors thus possibly leading to thrombosis that in turn may lead to elevated pulmonary pressures<sup>[38]</sup>.

### Thrombocytosis

Reactive thrombocytosis immediately following splenectomy is due to decreased cell degradation and increases the risk of subsequent venous thromboembolism<sup>[39,40]</sup>. However, this association is likely due to additional risk factors of severely ill trauma patients included in these studies<sup>[41]</sup>. No increase in the incidence of thromboembolism was evident directly after splenectomy in another study<sup>[2]</sup>. Thrombocytosis normally diminishes following splenectomy, however pulmonary hypertension may develop if thrombocytosis persists<sup>[27]</sup>. Long standing thrombocytosis after splenectomy has been shown in one case to be associated with elevated fibrinopeptide A, thromboxane B2 and  $\beta$ -thromboglobulin levels resulting in endothelial damage, local platelet activation and thrombin generation leading to CTEPH. Treatment of the thrombocytosis led to improvement in the clinical condition as well as pulmonary symptoms<sup>[42]</sup>. In another case treatment with hydroxyurea improved

both vascular and cardiac function in a patient who developed pulmonary hypertension and right heart failure due to thrombocytosis following splenectomy<sup>[43]</sup>. Singer *et al*<sup>[44]</sup> also showed higher levels of sPECAM-1, which has a role in platelet activation, and adhesion signaling in splenectomized thalassemia intermedia patients. Thus besides thrombocytosis, increased platelet adhesion may contribute to the development of pulmonary vasculopathy.

### Megakaryocytes

There is strong indirect evidence indicating transmigration of intact megakaryocytes from the bone marrow into the circulation and the release of platelets from these megakaryocytes in the pulmonary capillary bed<sup>[45,46]</sup>. These large sized platelet precursors can contribute to distal *in situ* thrombosis leading to CTEPH after splenectomy. This explains the observation that many patients with CTEPH are not suitable for thromboendarterectomy<sup>[11,47]</sup>. In patients with hemolytic anemia and myeloproliferative disorders especially in the setting of splenectomy extramedullary hematopoiesis (EMH) occurs, where the megakaryocyte can play a key role<sup>[45]</sup>. EMH commonly involves the liver and the spleen. However after splenectomy, the lungs can become an alternate site of EMH. Pulmonary EMH has been observed in Gaucher's disease with the presence of Gaucher's cells and megakaryocytes in the lungs<sup>[48]</sup>. Thus the presence of increased megakaryocytes as a result of EMH in pulmonary bed can contribute to PHTN. "Pathologic emperipoiesis" is seen in myelofibrosis in which the megakaryocytes cause marrow fibrosis through the release of fibrogenic mediators like vascular endothelial growth factor, platelet derived growth factor (PDGF) and transforming growth factor- $\beta$ <sup>[49]</sup>. It has been proposed that megakaryocytes at sites of pulmonary EMH may be responsible for a similar phenomenon which leads to fibrosis of the pulmonary vasculature and PHTN<sup>[45]</sup>. In sickle cell disease, auto-splenectomy can lead to EMH in the lungs and PHTN. While possible mechanisms have been mentioned above, more studies are needed to ascertain the exact role of megakaryocytes in the pathogenesis of PHT after splenectomy.

### Nitric oxide

In patients with chronic hemolytic disorder, free hemoglobin released from lysed red cells can scavenge nitric oxide, an important pulmonary vasodilator<sup>[27]</sup>. Elevated cell-free hemoglobin is modestly correlated with mean pulmonary artery pressures and pulmonary vascular resistance in pulmonary arterial hypertension<sup>[50]</sup>. Splenectomy leads to impaired clearance of senescent red cells especially in patients with hemoglobinopathies. Thus, higher plasma hemoglobin levels and increased scavenging of nitric oxide in splenectomized patients may contribute to pulmonary vasculopathy and the development of

PHTN<sup>[51,52]</sup>. Nitric oxide also has an inhibitory function on megakaryocytes leading to their apoptosis<sup>[53]</sup>. Depletion of nitric oxide can lead to increased megakaryocytes in the pulmonary circulation and development of PHTN as mentioned above.

### Endothelin-1

In the study by Singer *et al*<sup>[44]</sup>, endothelin-1 (ET-1), a potent vasoconstrictor produced by vascular endothelial and smooth muscle cells was higher in non-transfused splenectomized thalassemia patients compared to the transfused group. ET-1 is known to cause pulmonary vasoconstriction and thus could play an important role in developing pulmonary vasculopathy after splenectomy. The role of ET-1 is even more crucial, since theoretically ET antagonists can also play a part in the treatment of PHTN in such patients.

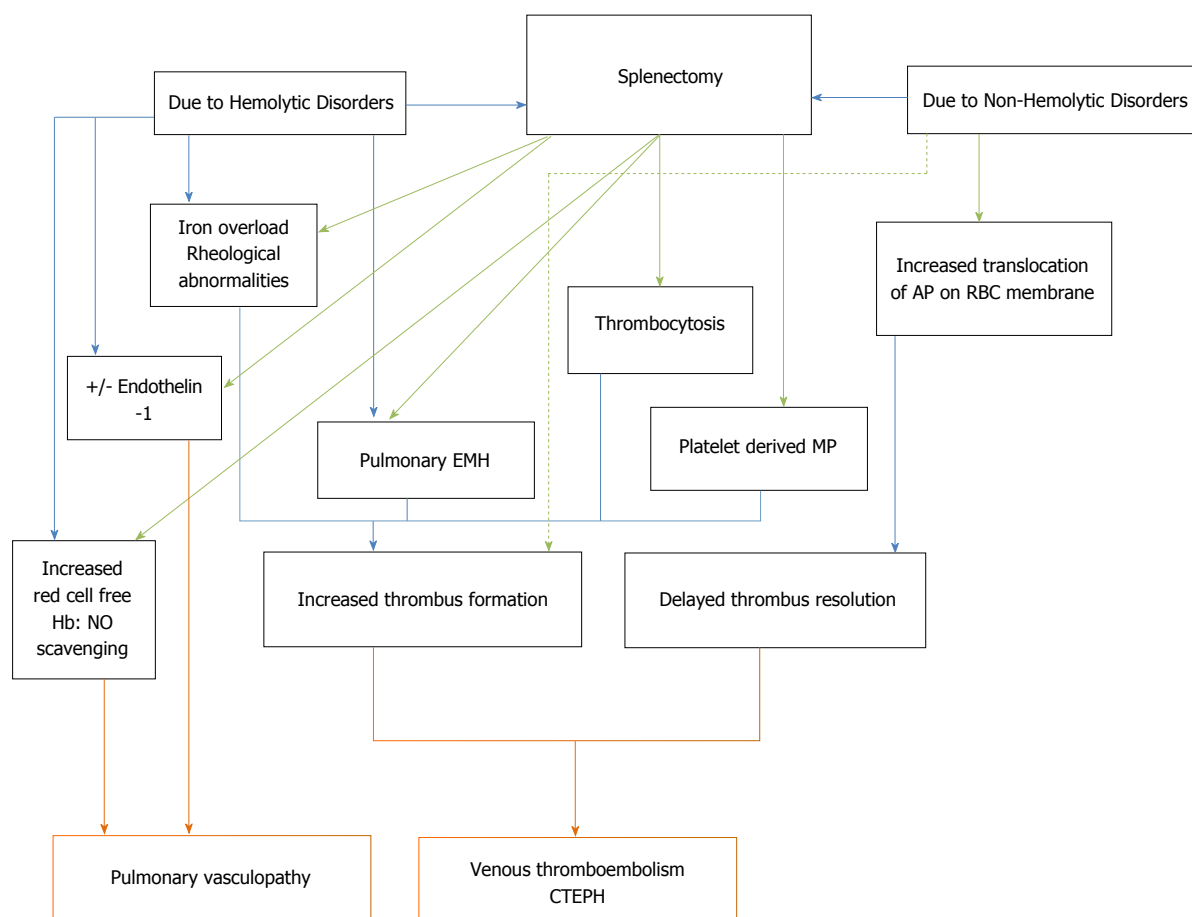
## DIAGNOSIS AND MANAGEMENT

Transthoracic doppler echocardiography in patients with hemoglobinopathies like thalassemia is cost effective and an established screening tool for PHTN. It is also suggested to screen patients with Gaucher's disease and at high risk for developing pulmonary hypertension<sup>[16]</sup>. Echocardiography may overestimate pulmonary artery pressure. Therefore elevated pulmonary artery systolic pressure on echocardiography should be confirmed by right heart catheterization. Although not all studies on splenectomized patients have used right heart catheterization for the diagnosis of PHTN (Table 3). Splenectomized patients may develop PHTN and hence should be screened for the development of exercise intolerance. However, currently there is no data to support routine screening in patients after splenectomy for non-hematologic disorders for the development of PHTN.

In patients with thalassemia, regular blood transfusions and iron chelation may reduce the need for splenectomy and prevent the development of PHTN<sup>[38,44]</sup>. Proper transfusion therapy likely restores tissue oxygen delivery and suppresses the synthesis of native defective erythrocytes, hence preventing rapid red cell turnover and hypercoagulability. Reduction of platelet counts with hydroxyurea or by the use of an anti-platelet agent has been suggested for the prevention of thrombotic complications in splenectomized non-transfused thalassemia intermedia patients<sup>[54]</sup>.

There is a paucity of large randomized, controlled clinical trials demonstrating benefit of currently available PHTN specific therapies in patients with hemolytic disorders as well as in the subset of these patients undergoing splenectomy. According to the WHO classification, patients with PAH are included in group 1, CTEPH in group 3, and those with PHTN due to hemolytic disorders or Gaucher's disease are included in group 5. Also, patients with PHTN in the setting of splenectomy without other predisposing co-





**Figure 1 Proposed mechanisms for the development of pulmonary vasculopathy after splenectomy.** Solid lines represents known mechanisms, Dotted line represents hypothesized mechanisms. Hb: Hemoglobin; NO: Nitric oxide; EMH: Extra medullary hematopoiesis; MP: Micro-particles; AP: Anionic phospholipids; RBC: Red blood cell; CTEPH: Chronic thromboembolic pulmonary hypertension.

morbidities are included in group 5. WHO treatment guidelines for PHTN for groups 1 and 4 are well defined. However, no recommendations yet exist for the use of PHTN specific therapy in patients with group 5 PHTN. Many patients with PHTN post-splenectomy are treated with vasodilators similar to patients with group 1 PHTN in the absence of overt thromboembolic disease. Therefore, the treatment algorithm for PHTN in post-splenectomy patients remains unclear given the complex interplay of mechanisms discussed previously.

PHTN associated with Gaucher's disease has been treated with enzyme replacement therapy and anecdotally with adjuvant vasodilator therapies such as prostacyclin, bosentan and/or sildenafil with improvement in clinical and hemodynamic parameters<sup>[55]</sup>. No data specifically addresses PHTN therapy of splenectomized patients with Gaucher's disease.

Sildenafil, a phosphodiesterase-5 inhibitor was studied in sickle cell disease associated PHTN in the walk-PHaSST trial<sup>[56]</sup>. This was the first multicenter randomized trial of sildenafil in sickle cell disease sponsored by the National Institute of Health. The study was prematurely terminated due to increased incidence of painful crises in the treatment group<sup>[56]</sup>.

The efficacy and safety of sildenafil in patients

with thalassemia is limited to small studies defining PHTN using Doppler echocardiography<sup>[57,58]</sup>. Sildenafil has been shown to be safe, improved pulmonary hemodynamics in patients in both studies while in the study by Derchi *et al.*<sup>[57]</sup>, Sildenafil improved exercise capacity.

Both non-selective dual action endothelin receptor antagonists including Bosentan and Macitentan and selective receptor antagonists of endothelin receptor A such as Ambrisentan are approved for treatment of group 1 PHTN. However, a trial with Bosentan in sickle cell disease with pulmonary arterial hypertension was also suspended early because of poor enrollment, and some of the beneficial effects observed were not statistically significant<sup>[59]</sup>. Anticoagulation is currently indicated for the treatment of patients with group 1 and 4 PHTN (CTEPH)<sup>[60]</sup>. However, there is no evidence to support routine use of anticoagulants for the treatment of post splenectomy group 5 PHTN.

Riociguat a soluble guanylate cyclase stimulator approved for CTEPH, and may be considered in patients developing pulmonary hypertension after splenectomy in the setting of pulmonary thromboembolic phenomenon. However, with mechanism of action being related to phosphodiesterase inhibition and lack

of safety data in splenectomized patients, routine use in this subgroup of patients is currently not recommended.

## CONCLUSION

Patients undergoing splenectomy are known to develop pulmonary complications including pneumonia and pleural effusion. However, the development of pulmonary hypertension after splenectomy also needs to be considered. The risk of development of PHTN after splenectomy is currently unknown for any given patient. Nevertheless, this complication does occur after splenectomy likely through a multitude of factors (Figure 1). Further research is required to identify markers or screening tools to predict the development of PHTN in this patient population. Whether therapies approved for specific groups of PHTN would be effective for treatment of patients with PHTN after splenectomy remains to be determined. It is clear that more studies are necessary to guide rational treatment strategies targeting specific mechanisms that lead to PHTN after splenectomy.

It is important for physicians to be vigilant about PHTN as it may develop years or decades after splenectomy. Since PHTN usually manifests with non-specific symptoms, patients should be screened for symptoms such as fatigue, exercise intolerance and dyspnea. Screening for PHTN cannot be under-emphasized for post-splenectomy patients with hematologic disorders given increased risk for the development of PHTN in this subgroup. Early recognition is essential to institute interventions that may improve outcome.

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## Mechanical circulatory support in lung transplantation: Cardiopulmonary bypass, extracorporeal life support, and *ex-vivo* lung perfusion

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### Abstract

Lung transplant is the standard of care for patients with end-stage lung disease refractory to medical management. There is currently a critical organ shortage for lung transplantation with only 17% of offered organs being transplanted. Of those patients receiving a lung transplant, up to 25% will develop primary graft dysfunction, which is associated with an 8-fold increase in 30-d mortality. There are numerous mechanical lung assistance modalities that may be employed to help combat these challenges. We will discuss the use of mechanical lung assistance during lung transplantation, as a bridge to transplant, as a treatment for primary graft dysfunction, and finally as a means to remodel and evaluate organs deemed unsuitable for transplant, thus increasing the donor pool, improving survival to transplant, and improving overall patient survival.



**Key words:** Lung transplant; Cardiopulmonary bypass; Extracorporeal membrane oxygenation; Extracorporeal life support; Extracorporeal lung assist; Interventional lung assist; *Ex-vivo* lung perfusion

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**Core tip:** Numerous modalities of mechanical lung assistance may be employed throughout the course of a lung transplant patient. The use of cardiopulmonary bypass for lung transplantation is controversial and should be employed only when necessary for hemodynamic stability. Extracorporeal membrane oxygenation or extracorporeal lung assist devices improve survival to transplant as well as improve survival in patients with primary graft dysfunction. These techniques should be implemented early and appropriately according to patient factors. *Ex-vivo* lung perfusion has been shown to be safe in clinical trials and holds promise for increasing the donor pool and thus decreasing waiting list mortality.

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## INTRODUCTION

Lung transplantation is the standard of care for end-stage lung disease refractory to medical management<sup>[1,2]</sup>. There are an increasing number of patients awaiting lung transplant despite increases in lung transplant surgeries performed each year<sup>[3]</sup>. Only 15%-20% of available donor lungs are deemed suitable for transplant<sup>[3]</sup>. The shortage of suitable donor organs and extensive wait times have led to further progression of the recipient's native lung disease at the time of transplant, increased respiratory failure prior to transplant, and increased mortality while awaiting transplantation. Patient mortality may reach as high as 20% the first year on the waiting list and up to 40% after 2 years<sup>[4]</sup>.

Mechanical circulatory support may be required in the course of lung transplantation whether pre-operatively, intra-operatively, or post-operatively. Mechanical lung assistance (MLA) whether extracorporeal membrane oxygenation (ECMO) or extracorporeal lung assist (ECLA) has been used as a bridge to transplant in those patients undergoing respiratory failure prior to donor lung availability. The possibility of using ECMO in potential donors to increase the number of viable organs has also been proposed<sup>[5]</sup>. The use of cardiopulmonary bypass (CPB) or ECMO during lung

transplant surgery is controversial. Lung transplant recipients who develop severe primary graft dysfunction (PGD) have increased early and late mortality, perioperative complications, and development of bronchiolitis obliterans syndrome<sup>[6,7]</sup>. For those patients with PGD, ECMO and ECLA have been used as salvage therapies similar to their use in acute respiratory distress syndrome (ARDS). Furthermore, *ex-vivo* lung perfusion (EVLP) is an innovative technique, which may increase available donor organs by reconditioning previously untransplantable organs while allowing for continuous assessment of suitability for transplant.

## USE OF CARDIOPULMONARY SUPPORT DURING LUNG TRANSPLANTATION

### Overview

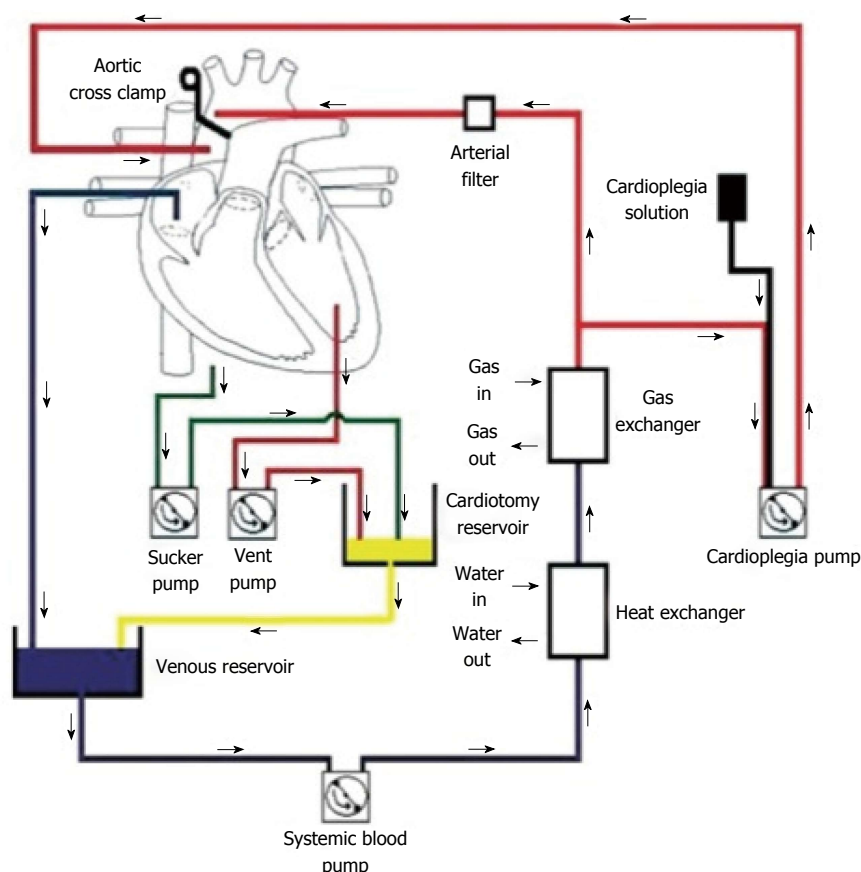
Mechanical circulatory support in the form of CPB or ECMO is frequently employed for lung transplantation<sup>[1]</sup>. However, due to improvements in single-lung ventilation techniques and hemodynamic support, neither is always necessary<sup>[1]</sup>. The components of a CPB circuit and an ECMO circuit are illustrated in Figures 1 and 2, respectively<sup>[8,9]</sup>. The requirement for mechanical circulatory support during lung transplantation depends upon right ventricular function, pulmonary hypertension, and ability to tolerate single-lung ventilation<sup>[1]</sup>.

### Indications

The most common indication for the use of CPB during lung transplantation is primary or secondary pulmonary hypertension, mean pulmonary artery pressure  $\geq 25$  mmHg<sup>[10-12]</sup>. CPB is used in patients with pulmonary hypertension to prevent sudden and further increase in pulmonary artery pressure, which may lead to acute right ventricular failure during clamping of the pulmonary artery. Another common indication for CPB is *en-bloc* double-lung transplantation<sup>[11,12]</sup>. Indications for unplanned CPB include: intra-operative hemodynamic instability, acute right ventricular failure, impaired gas exchange, technical difficulties, and increased pulmonary pressure<sup>[10,12]</sup>. Gammie *et al*<sup>[12]</sup> reports their most common indication for unplanned CPB as hypoxemia and hypotension during single-lung ventilation employed for contralateral hilar dissection, occurring in 5 out of 8 patients (62.5%). In their case series, Triantafillou *et al*<sup>[13]</sup> reported 11 out of 18 patients (61%) requiring CPB for instability after complete pulmonary perfusion was transferred to transplanted lung. Bronchiectasis has been flagged as a possible risk factor for requiring CPB with 3 out of 9 patients with this diagnosis (33%) requiring CPB in one series<sup>[12]</sup>. One could speculate that this may be secondary to associated pulmonary hypertension.

### Advantages of CPB

Proponents of CPB note maintenance of circulation and gas exchange, controlled reperfusion, and



**Figure 1** Cardiopulmonary bypass circuit is an open circuit in which venous blood drains into the venous reservoir by gravity (40-70 cm below the level of the heart) or siphonage. Cardiopulmonary bypass circuit is considered an open circuit: blood from the cardioplegia reservoir, blood transfusions, or other fluids may be added into the circuit. Blood then passes through an oxygenator or gas-exchanger and is returned to the arterial system by utilizing a roller or centrifugal pump<sup>[8]</sup>. Figure from Machin *et al*<sup>[9]</sup>, with permission of Oxford University Press.

immunosuppressive effects as advantages of this approach<sup>[11,14]</sup>. Marczin *et al*<sup>[11]</sup> argue that controlled partial pulmonary reperfusion allowed by CPB may improve graft function. Studies have shown that reducing initial lung perfusion pressure can improve graft function<sup>[11,14]</sup>. This then raises the question of sequential double lung transplant, in which the first lung transplanted will have to accommodate 100% of cardiac output during the implantation of the second lung, sometimes leading to PGD. In this situation, some authors suggest initiation of CPB after the implantation of the first lung, allowing for shorter CPB time and controlled reperfusion<sup>[11]</sup>. Pharmacologic agents such as prostacyclin or nitric oxide have also been used to control reperfusion pulmonary artery pressures<sup>[11]</sup>. Inhaled nitric oxide and inhaled prostacyclin are selective pulmonary vasodilators which decrease pulmonary vascular resistance through increases in intracellular cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) respectively thus decreasing pulmonary artery perfusion pressure<sup>[7,15]</sup>. Szeto *et al*<sup>[16]</sup> retrospectively reviewed 50 patients undergoing lung transplant for chronic obstructive pulmonary disease (COPD). They aimed to remove possible confounding of multiple disease processes and use of unplanned CPB. They

compared 14 patients undergoing elective CPB to 36 controls. They found no significant differences in duration of mechanical ventilation, ICU stay, length of stay, creatinine levels,  $\text{PaO}_2:\text{FiO}_2$  at 1, 24, or 48 h, 30-d mortality, or 1 and 3-year survival. They concluded that CPB has no deleterious effects on early lung function or clinical outcome<sup>[16]</sup>. Burdett *et al*<sup>[17]</sup> performed a larger retrospective review comparing 53 CPB patients to 206 non-CPB patients. They similarly found no difference in  $\text{PaO}_2:\text{FiO}_2$  ratios at 1 and 24 h post-transplant and no differences in duration of mechanical ventilation or transbronchial biopsy at 30 d<sup>[17]</sup>. Pochettino *et al*<sup>[18]</sup> found no significant differences in the following clinical outcome measures: duration of mechanical ventilation, re-intubation, re-operation for bleeding, sepsis, PGD, renal dysfunction, length of stay, or mortality. de Boer *et al*<sup>[14]</sup> showed a significant survival benefit in emphysema patients when CPB was employed. This survival benefit was observed in patients with 2 HLA-DR mismatches as compared to those with 0 or 1 mismatches with immunosuppressive effects of CPB implicated as the source of survival benefit.

### Airway management

Marczin *et al*<sup>[11]</sup> suggest that CPB provides advantages



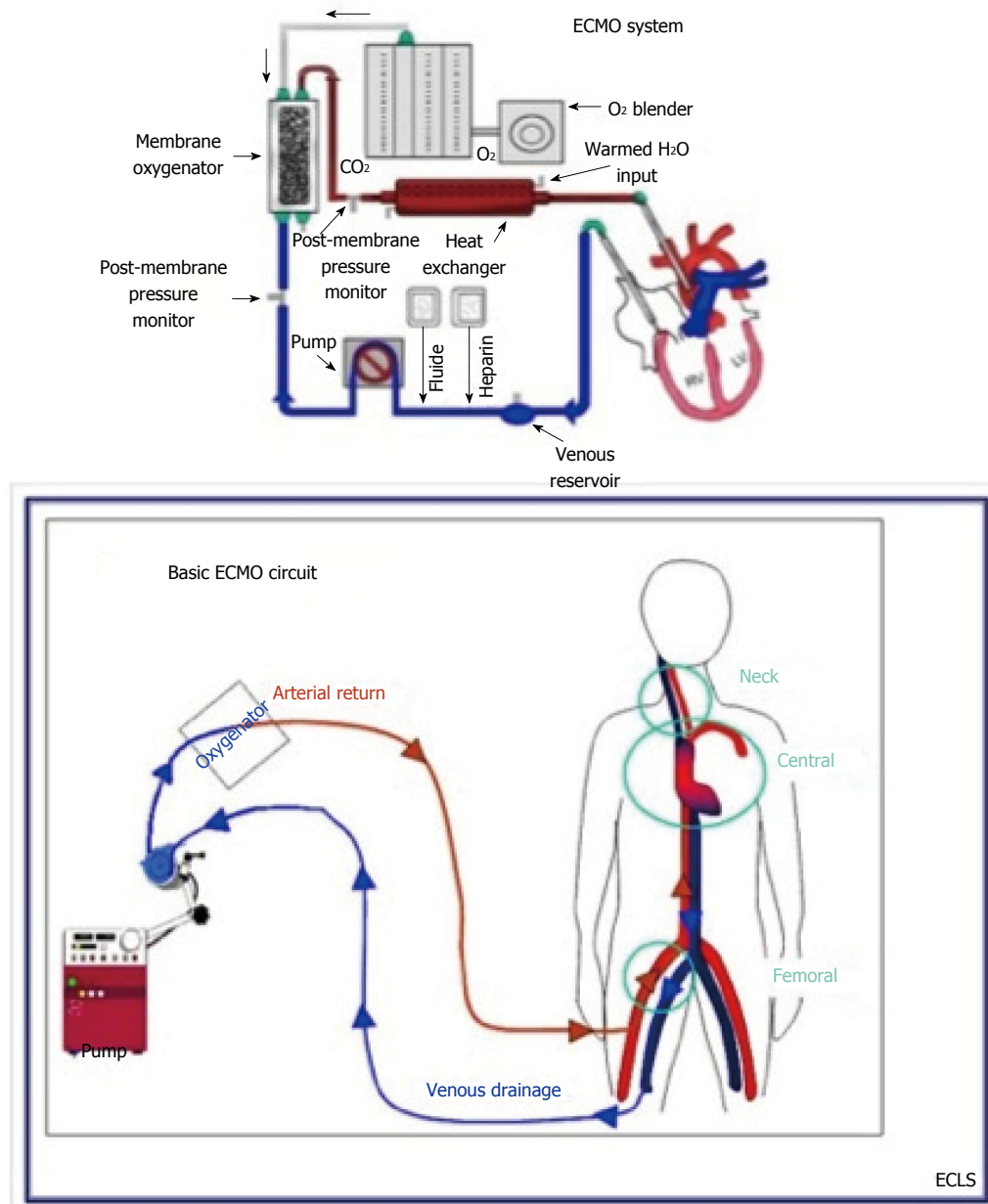


Figure 2 Schematic illustrating the components of an extracorporeal membrane oxygenation circuit: centrifugal pump, membrane oxygenator, inflow and outflow cannulas or cannula, and tubing with the potential to add ports for hemodialysis or ultrafiltration<sup>[9]</sup>. ECMO: Extracorporeal membrane oxygenation.

in airway management, especially for small patients and those with suppurative lung disease in which double-lumen endotracheal tubes may present difficulties<sup>[11]</sup>. They state a single-lumen endotracheal tube provides better access for removal of thick secretions. Pochettino *et al.*<sup>[18]</sup> reported decreased perioperative pneumonia post-bilateral lung transplant in cystic fibrosis patients when CPB was employed ( $P = 0.02$ ). They attributed this to decontamination of the operative field facilitated by CPB. CPB allows for simultaneous explantation of both infected lungs followed by lavage of native tracheal bronchial airways. Pochettino *et al.*<sup>[18]</sup> commented on a different technique employed by the University of North Carolina in a similar study. Their group performed vigorous bronchoscopic washing of native lungs prior to explantation, thus

allowing for single-lung ventilation and avoidance of CPB.

#### Drawbacks of CPB

Use of CPB has been associated with early graft dysfunction due to activation of inflammatory mediators, increased operative and ischemic times, longer post-operative mechanical ventilation, increased pulmonary edema, increased mortality, as well as increased bleeding complications due to systemic heparinization<sup>[1,10,12,19]</sup>. Pochettino *et al.*<sup>[18]</sup> reported significant increase in fresh frozen plasma and platelet transfusions in patients undergoing CPB. Burdett *et al.*<sup>[17]</sup> showed significant increases in blood transfusions ( $P < 0.02$ ), and Szeto *et al.*<sup>[16]</sup> showed significant increase transfusions of platelets and fresh frozen

plasma, each with ( $P < 0.001$ ) in CPB groups<sup>[16,17]</sup>. Gammie *et al*<sup>[12]</sup> reported 11.4 units of perioperative blood transfusions in their CPB group compared to 6.0 units in their no-CPB group, ( $P = 0.01$ ). Dalibon *et al*<sup>[19]</sup> again showed significant differences in blood transfusions as well as duration of graft ischemia, duration of mechanical ventilation, pulmonary edema, and mortality at 48 h, 1 mo, and 1 year all being greater in CBP groups.

### Inflammatory response to CPB

Inflammatory manifestations of CPB have been implicated in respiratory failure, ARDS, renal insufficiency, neurological deficits, and systemic inflammatory response syndrome (SIRS)<sup>[20]</sup>. CPB alone invokes an inflammatory response thus far indistinguishable from ARDS and ischemia-reperfusion injury (IRI), including: activation of polymorphonuclear neutrophils (PMNs), macrophages, and monocytes; release of cytotoxic and chemotactic factors; increase in circulating cytokines such as endotoxin, interleukins, and tumor necrosis factor; complement activation; platelet activation and sequestration; and endothelial damage<sup>[20-23]</sup>. Hypo-oncotic pressure resulting from large crystalloid priming volumes has been associated with endotoxin translocation<sup>[24]</sup>. In recent years decreased priming volumes and use of colloid priming have been implemented in attempt to reduce this response. Reintroduction of activated blood from the surgical field into the CPB circuit leads to increased tissue plasminogen activator (tPA) and fibrinolytic activity<sup>[24]</sup>. Interaction of blood cells with the CPB circuit results in complement activation. The balance of coagulation and anticoagulation remains a constant debacle in both ECMO and CPB. Thrombin plays an integral role in inflammation and coagulation and results in chemoattraction of monocytes and thus production of tissue factor as well as activation of endothelial cells, neutrophil adherence, and endothelial damage<sup>[20,21]</sup>. Tissue factor leads to diffuse fibrin deposition throughout the microvasculature, followed by fibrinolysis which in turn leads to increased thrombin production, platelet aggregation and consumption<sup>[21]</sup>. Anti-thrombin III (ATIII), identified as having potential anti-inflammatory and protective effects, may deficient post-CPB as well, possibly due to heparinization, hemodilution, or consumption<sup>[20]</sup>. Systemic anticoagulation required for CPB compounded with often friable parenchyma and significant pleural adhesions may be directly responsible for increased peri-operative blood transfusions which come with their own share of inflammatory reactions, including transfusion related acute lung injury (TRALI). Transplanted lungs inevitably undergo cold and warm ischemia. Ischemia-reperfusion injury (IRI) has been shown to lead to pulmonary vasomotor dysfunction due to constriction of pulmonary vascular smooth muscle in the absence of hypoxia thus increasing

pulmonary vascular resistance (PVR)<sup>[23]</sup>. Reperfusion of the transplanted lung with activated blood components from CPB circuit has been shown to exacerbate pulmonary vasomotor dysfunction in a dog model of autologous lung transplantation<sup>[23]</sup>.

Strategies are underway to help confront the inflammatory response to CPB. Aprotinin is a serine protease inhibitor, which has been shown to reduce bleeding and need for peri-operative transfusions, with possible anti-inflammatory effects related to inhibition of leukocyte transmigration through vascular endothelium<sup>[20]</sup>. Heparin-coated circuits have reduced but not ameliorated complement activation<sup>[22,24]</sup>. Baufreton *et al*<sup>[24]</sup> prospectively evaluated the inflammatory response in 29 patients undergoing coronary artery bypass grafting and found that centrifugal pumps (CFP) resulted in increased intra-operative complement and neutrophil activation in comparison to roller pumps. Both groups showed significant increases in TNF- $\alpha$ , IL-6, and IL-8; however IL-8 was significantly greater at 2 h in the CFP group ( $P = 0.02$ )<sup>[24]</sup>. Leukocyte depletion, and monoclonal antibodies are also being investigated<sup>[21]</sup>.

There is sufficient evidence to implicate CPB in lung damage on both a cellular level and in clinical outcomes. Both a multi-center prospective trial and a systematic review and meta-analysis found CPB to be a significant independent risk factor for PGD<sup>[25,26]</sup>. A 10-year retrospective analysis yielded increased time on mechanical ventilation, pulmonary edema, blood transfusions, as well as 48 h, 1 mo, and 1-year mortality when CPB was compared to non-CPB<sup>[19]</sup>. High-volume centers such as the University of Toronto are aiming to avoid CPB, which may be justified.

### CPB and early graft dysfunction

The effects of CPB on early graft dysfunction is not a new question as evidenced by the retrospective review performed by Aeba *et al*<sup>[27]</sup> on 100 lung transplant recipients from 1990-1992. They found significantly lower arterial/alveolar oxygen tension ratios of  $0.48 \pm 0.19$  in the CPB group compared to  $0.60 \pm 0.22$  in non-CPB group ( $P = 0.025$ ). The CPB had more severe pulmonary infiltrates within 12 h after reperfusion than non-CPB group ( $P = 0.034$ ). Prolonged intubation,  $> 7$  d occurred in 29/55 in CPB compared to 8/45 in non-CPB group ( $P = 0.003$ ). The non-CPB group showed better graft ( $P = 0.05$ ) and patient ( $P = 0.033$ ) survival at one month. Gammie *et al*<sup>[12]</sup> retrospectively reviewed 94 double-lung transplantations and showed similar results. The reported significantly longer mean ischemic times ( $P = 0.04$ ), increased perioperative blood transfusions ( $P = 0.01$ ), worse arterial/alveolar oxygen tension ratios ( $P = 0.001$ ), more severe pulmonary infiltrates ( $P = 0.005$ ), and longer median duration of intubation in the CPB group ( $P = 0.002$ )<sup>[12]</sup>. However, despite these findings, Gammie *et al*<sup>[12]</sup> found no significant differences in 30-d mortality or

1-year survival between the two groups. It has been argued by proponents of CPB, that CPB groups are heavily weighted with patients having pulmonary hypertension, and perhaps the poor outcomes are not due to CPB. Gammie *et al.*<sup>[12]</sup> performed a multivariate logistic regression analysis to address this concern, and pulmonary hypertension was not found to be an independent predictor of early graft dysfunction. Oto *et al.*<sup>[28]</sup> noted that 80% of their patients requiring ECMO for PGD had undergone CPB, as compared to CPB use in only 16% of the patients not requiring ECMO for PGD, ( $P = 0.0001$ ). Hartwig *et al.*<sup>[29]</sup> similarly showed 66.7% of patients requiring ECMO for primary graft failure (PGF) had undergone CPB, compared to 16.2% in non-ECMO group ( $P < 0.001$ ).

### PGD

PGD a severe form of acute lung injury (ALI) occurs in approximately 10%-25% of lung transplant patients, with an 8-fold increase in 30-d mortality<sup>[26]</sup>. Multiple strategies may be employed to minimize ischemia-reperfusion injury (IRI) and PGD. The Toronto group first removes the native lung with the least perfusion<sup>[30]</sup>. Alveolar recruitment by holding sustained inspiration is thought to improve capillary recruitment and lead to decreased pulmonary vascular resistance (PVR). Toronto holds sustained inflation twice with a peak pressure  $< 25$  cmH<sub>2</sub>O, and positive end-expiratory pressure (PEEP) of 5 cmH<sub>2</sub>O. They also remove their pulmonary artery clamp gradually over a 10-min period<sup>[21]</sup>. Liu *et al.*<sup>[26]</sup> performed a systematic review and meta-analysis of the clinical risk factors for PGD after lung transplant. Upon evaluation of 10042 patients, the following recipient risk factors showed a significant association with PGD: female gender, African American race, idiopathic pulmonary fibrosis (IPF), sarcoidosis, PPH, BMI  $\geq 25$  kg/m<sup>2</sup>, and use of CPB. The following recipient factors were not found to significantly correlate with PGD: age, cystic fibrosis, secondary pulmonary hypertension (SPH), intra-operative inhaled nitric oxide (iNO), nor type of transplant, single vs bilateral<sup>[26]</sup>. Diamond *et al.*<sup>[25]</sup> performed a 10-center, prospective cohort study from March 2002 to December 2010, collecting data on 1255 patients, 211 (16.8%) of which developed grade 3 PGD by International Society for Heart and Lung Transplantation (ISHLT) criteria. They evaluated recipient and donor factors, finding the following independent risk factors for PGD to be significant: donor smoking, FiO<sub>2</sub> during reperfusion, single lung transplant, use of CPB, overweight/obese BMI, sarcoidosis, and pulmonary artery hypertension (PAH)<sup>[25]</sup>.

### CPB vs ECMO for lung transplant

ECMO has been used as an alternative to CPB in lung transplantation. The key differences between ECMO and CPB are peripheral vs central cannulation and duration of support. The details of ECMO circuits are discussed later in the ECMO section. ECMO

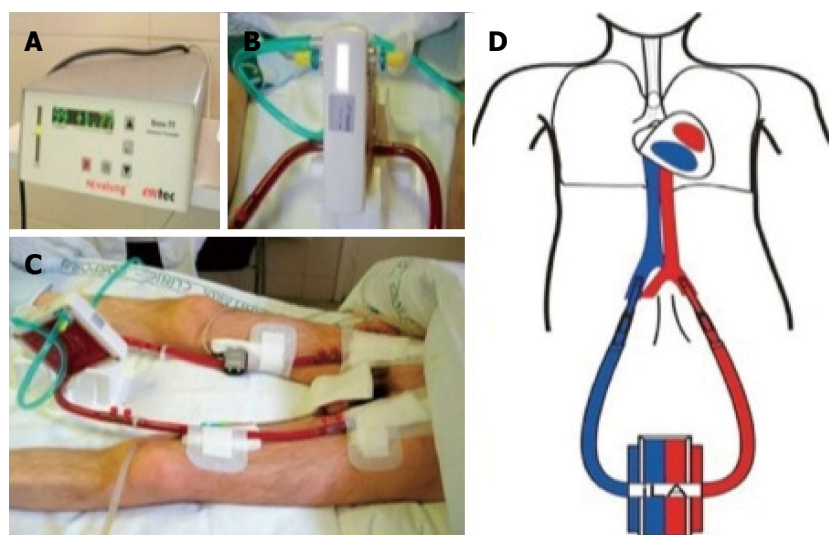
supports hemodynamic stability and gas exchange while allowing for lower doses of heparinization thus presumably decreasing bleeding complications. It also has the added benefit being able to provide support in all phases of transplantation.

Bittner *et al.*<sup>[1]</sup> retrospectively reviewed 47 lung transplants performed at a single institution between 2003 and 2005. The purpose of their study was to compare the use of ECMO and CPB in lung transplant. Patients who underwent a combined heart-lung or lung-kidney transplant, coronary artery bypass, atrial septal defect repair, or emergency CPB support were excluded. Seven patients underwent CPB and 8 employed ECMO. Despite presumed benefits of decreased bleeding complications with ECMO, transfusion requirements for during the operation and 72 h afterward were  $13.25 \pm 1.6$  units of PRBC for ECMO group vs  $5.1 \pm 2.8$  for CPB group ( $P = 0.02$ ). Activated clotting time (ACT) was kept  $> 450$  s for CPB and between 160-220 s for ECMO group. Patients undergoing lung transplant without extracorporeal support received  $2.7 \pm 0.9$  units PRBC in the same time period ( $P = 0.001$ ). Indication for transfusion was hematocrit  $< 30\%$ ; however later they state liberal blood product administration for intravascular volume. Weaning from mechanical ventilation was shorter in CPB group  $3.9 \pm 3.7$  d vs  $10.8 \pm 6.6$  d in the ECMO group ( $P = 0.03$ ). Severe graft ischemia-perfusion injury, defined as ISHLT grade III, occurred in 9% CPB vs 13% in ECMO group, which is one patient per group. The ECMO patient survived after clot evacuation from thorax whereas CPB patient required ECMO support, massive blood transfusions, and passed on post-operative day 10 due to resistant coagulopathy, right heart failure, and intracranial bleeding. Similarly, Ko *et al.*<sup>[31]</sup> concluded in their series of 10 single and 3 bilateral sequential lung transplantations that ECMO rather than CPB should be used.

## MECHANICAL CIRCULATORY SUPPORT AS A BRIDGE TO TRANSPLANT

Due to extensive wait times, deterioration in pulmonary status while awaiting lung transplantation, and detrimental effects of mechanical ventilation, MLA is increasingly employed as a bridge to lung transplantation<sup>[2,4]</sup>. There are two main forms of MLA, or extracorporeal life support (ECLS), which we will discuss, ECMO and ECLA. Let us first define each.

ECMO has become a general term, which now encompasses venoarterial (VA) and venovenous (VV) extracorporeal blood oxygenation and CO<sub>2</sub> removal. While venovenous ECMO is typically thought of for respiratory support, it may not be sufficient in pre-lung transplant patients, many of which have concomitant pulmonary hypertension and right heart failure. An ECMO circuit (Figure 2) contains a centrifugal pump,



**Figure 3** Extracorporeal lung assist, Interventional Lung Assist, or the NovaLung® System. A: Flow measure across the system, in this case 1.77 L of blood per minute; B: Arterial and venous lines, oxygen inflow, and extracorporeal membrane made of polymethylpentene which provides gas exchange by simple diffusion; C: Exchange membrane and arterial and venous cannulations; D: AV cannulation diagram for extracorporeal lung assist, note the absence of a pump<sup>[32]</sup>.

membrane oxygenator, inflow and outflow cannulas or cannula, and tubing with the potential to add ports for hemodialysis or ultrafiltration if needed<sup>[3,9]</sup>. Peripheral cannulation for ECMO usually employs a combination of the following vessels depending on whether VA- or VV-ECMO is indicated: femoral artery, femoral vein, carotid artery, and internal jugular vein. A bicaval dual-lumen cannula is now available, which is inserted *via* the internal jugular vein, and potentially allows for increased mobility in awake VV-ECMO patients.

ECLA, the NovaLung® System (NovaLung GmbH, Heilbronn, Germany), sometimes referred to as Interventional Lung Assist (iLA) is illustrated in Figure 3<sup>[32]</sup>. It is a pumpless, extracorporeal, biocompatible, membrane composed of polymethylpentene (PMP) fibers, which provides gas exchange *via* simple diffusion<sup>[3]</sup>. ECLA is designed to function without a mechanical pump; however, one may be added if higher flows are needed. The device is typically implanted across an arteriovenous shunt between the femoral artery and femoral vein after heparinization. Flow rates of up to 2.5 L/min can be achieved depending on size of cannula and mean arterial pressure. Flow rates of 5.5 L/min may be achieved with the addition of an external pump. Because this device only receives approximately 15%–20% of cardiac output, it only oxygenates approximately 1/5 of venous return to the heart and is not recommended for severe hypoxia ( $\text{PaO}_2/\text{FiO}_2 < 80 \text{ mmHg}$ )<sup>[33,34]</sup>.

### ECMO as a bridge to lung transplant

Early data on ECMO as a bridge to LTx were unfavorable<sup>[33,35,36]</sup>. Fischer *et al.*<sup>[4]</sup> reported a perioperative mortality of up to 60% in patients bridged to LTx with ECMO.

This could be attributed to the early attempts being in post-LTx patients with severe PGD, a pa-

tient population with severe immunocompromise and numerous other comorbidities. Over the last decade, technical advances in extracorporeal circuits such as centrifugal pumps, heparin-coated circuits, and polymethylpentene membrane oxygenators, among other advances have contributed to improved outcomes<sup>[33]</sup>. Hayes *et al.*<sup>[5]</sup> reports 1-year survival rates between 58% to 92% for patients bridged to LTx with ECMO.

Jackson *et al.*<sup>[35]</sup> reported 3 cases in which ECMO was used successfully as a bridge to LTx; however each of these cases were complicated by bleeding requiring reoperation and massive transfusion in the post-operative period.

Bermudez *et al.*<sup>[37]</sup> performed a single-center retrospective analysis of 1305 patients undergoing lung or heart-lung transplant between 1991 and 2010. Seventeen patients (1.3%) were bridged with ECMO, 5/17 (29%) between 1991–1993 and 12/17 (71%) after 2005. These patients were compared to non-ECMO control group. Statistically significant differences between the two groups included: double lung transplant 88% of ECMO group vs 54%, mean ischemic time 344 min for ECMO group vs 244, 48% of ECMO group required ECMO post-operatively due to PGD compared to 7.3% in control group. Increased post-operative ECMO for PGD was attributed to longer ischemic times and CPB or ECMO during transplantation. While ECMO group had increased perioperative morbidity, there were no significant differences in 30 d, 1-year, or 3-year survival or allograft function at 1-year<sup>[37]</sup>.

Lehmann *et al.*<sup>[2]</sup> concluded that veno-arterial (VA) ECMO can be successfully used as a bridge to LTx as well as being utilized during LTx as a means for circulatory support. Lehmann *et al.*<sup>[2]</sup> performed a retrospective analysis of 143 patients undergoing



LTx at their institution, 15 patients received MLA preoperatively, 14 ECMO, and 1 ECLA. Of the 5 ECLA patients, 4 were converted to ECMO after 10 d and one was weaned from MLA and went on to LTx. Two of the fifteen patients died prior to LTx due to intracranial hemorrhage and multi-organ failure (MOF). Eight patients from the MLA group were on mechanical ventilation, while 5 were awake and extubated. Six patients from the non-MLA group were on mechanical ventilation pre-transplant. Length of mechanical assistance pre-LTx ranged from 6 h to 30 d. There were no significant differences in demographic data, ischemia times, or intraoperative pulmonary arterial pressure (PAP). There were more sternotomies and bilateral sequential LTx performed in MLA group as well as 5 stroke events and 4 reoperations for bleeding. There was no significant difference in 30-d, 90-d, 1-year, and 5-year survival between MLA and non-MLA groups. Ten/13 (76.9%) survived to discharge<sup>[2]</sup>.

### **ECLA as a bridge to lung transplant**

Fischer *et al.*<sup>[4]</sup> reported on 12 patients with severe ventilation-refractory hypercapnia and respiratory acidosis, which were bridged to lung transplant with ECLA. At the time of Medical Advisory Secretariat Systematic Review in 2010, the Fisher case series was the only one to describe use of iLA as a bridge to LTx. It was compared to six studies using iLA for treatment of ARDS. While all studies showed an improvement in hypercapnia and acidosis, the pre-LTx group showed a drastic improvement over the first 6 h with PaO<sub>2</sub>, pH, and PaCO<sub>2</sub> improving from 71 ± 27 mmHg, 7.21 ± 0.1, 128 ± 42 mmHg to 83 ± 17 mmHg, 7.34 ± 0.1 (*P* < 0.05), and 52 ± 5 mmHg (*P* < 0.05), respectively. However, these drastic improvements level off after 6 h whereas other groups continue to have significant improvements over subsequent days. These plateaus in the pre-LTx group may represent the inability of end-stage lungs for further improvement as compared to acute respiratory conditions associated with ARDS. Furthermore, PaO<sub>2</sub>/FiO<sub>2</sub> ratio dropped after 24 h on iLA in pre-LTx group while continuing to improve in all other groups (135 pre, 150 2-6 h, 168 24 h, 139 2-7 d). Similarly, there was also an increased in PEEP requirements between 3-7 d in pre-LTx group from 6.8 ± 2.7 to 8.2 ± 1.4. iLA may be an effective bridge to LTx, improved survival and outcomes may be dependent on optimal timing of implementation<sup>[4]</sup>.

ECLA with a pulmonary artery to left atrial shunt (PA-LA) ECLS has also been proposed. Strueber *et al.*<sup>[38]</sup> reported 4 cases of the use of PA-LA ECLS as a bridge to lung or heart-lung transplantation. All 4 patients survived to transplantation with mean time on ECLS of 17.5 d. Two patients required VA-ECMO for hemodynamic stabilization prior to PA-LA cannulation. They found that with PA-LA ECLS right ventricular function was able to recover, potentially eliminating the need for heart-lung transplantation. Extubation is

possible with PA-LA ECLS<sup>[38]</sup>.

Nosotti *et al.*<sup>[39]</sup> reported on 4 cases in which ECMO was used as a bridge to transplant. While this is a small number of patients, they highlighted several key concerns in this patient population. Out of their 4 patients one had reoperation for hemothorax, one died from an ischemic stroke, and one had caval thrombosis adequately treated with heparin. This highlights the fine balance of coagulation management necessary in ECMO patients. They also commented on critical illness myopathy, which would likely be similar with mechanical ventilation in this same patient population, but again an important consideration. Furthermore, they commented that formerly healthy patients posted for emergent transplant do not have time to cope with being listed for organ transplantation and thus have significant psychiatric disturbances and depression<sup>[39]</sup>. It could be argued that any patient undergoing salvage therapies such as ECMO may experience such disturbances. Awake ECMO may address the later two issues as well as avoidance of complications associated with general anesthesia, intubation, and mechanical ventilation such as hemodynamic collapse on induction and pulmonary and systemic inflammation associated with long-term ventilation<sup>[40,41]</sup>.

### **Awake/ambulatory ECMO as a bridge to lung transplant**

This brings us to Olsson *et al.*<sup>[42]</sup> who in 2010 were the first to report on five patients with cardiopulmonary failure secondary to pulmonary hypertension in which VA-ECMO was used in awake, spontaneously breathing patients. All patients were cannulated under local anesthesia without sedation, and with the exception of two patients who later required intubation secondary to bleeding complications, all patients were able to eat, drink, and participate in active physical therapy as well as psychotherapy. In this series, there were no reports of limb ischemia, hemolysis, platelet activation, systemic inflammatory response, or clinically evident embolic events; however 60% (3/5) of patients had significant bleeding events, two of which necessitated endotracheal intubation and one requiring repeat blood transfusions.

Fuehner *et al.*<sup>[40]</sup> went on to report on 26 patients receiving awake ECMO as a bridge to LTx and compared these to 34 patients in whom mechanical ventilation (MV) was used as a bridge to LTx. Of note, 18 patients (53%) in the MV group were placed on ECLS prior to LTx (4 VV-ECMO, 12 AV-ECLA, and 2 PA-LA ECLA). Eight patients in the awake ECMO group (31%) required blood transfusion for bleeding complications (puncture sites, *n* = 6; epistaxis, *n* = 1; hemoptysis, *n* = 1). Seven patients (27%) required intubation and only 3 of these survived to discharge. Five (19%) developed sepsis, 1/5 survived to LTx. Patients in the ECMO group required significantly less days on MV after LTx (*P* = 0.04). ECMO group had an improved survival to transplant, improved survival

**Table 1 Comparison of mechanical circulatory support modalities**

	Open/closed	Pump	Cannulation	Indications	Phase of transplant
CPB	Open	Yes (Centrifugal or Roller)	Central (intrathoracic)	Hemodynamic instability Pulmonary hypertension Right ventricular failure <i>En bloc</i> double-LTx	Intraoperative
ECLS/iLA	Closed	No (Pump may be added)	Usually peripheral (also PA-LA)	Refractory: Hypercarbia (PCO <sub>2</sub> > 80 mmHg)	Bridge to Tx (Awake)
VV-ECMO	Closed	Yes (Centrifugal or Roller)	Peripheral (BCDLC)	Refractory: Hypoxia (PaO <sub>2</sub> :FiO <sub>2</sub> < 80 mmHg) Hypercarbia PCO <sub>2</sub> > 80 mmHg	Bridge to Tx (Awake) Graft Salvage
VA-ECMO	Closed	Yes (Centrifugal or Roller)	Peripheral (sometimes Central)	Hemodynamic instability Pulmonary hypertension Right heart failure	Bridge to Tx Intraoperative Graft Salvage

CPB: Cardiopulmonary bypass; ECLS: Extracorporeal lung support; iLA: Interventional lung assist; VV: Venovenous; VA: Venoarterial; ECMO: Extracorporeal membrane oxygenation; PA-LA: Pulmonary artery-left atrium; BCDLC: Bi-caval dual lumen cannula.

post-transplant, with overall 6-mo survival 62% ECMO group vs 35% MV group, ( $P = 0.05$ ). If only those patients who received LTx are considered 80% ECMO group vs 50% MV group at 6-mo, ( $P = 0.02$ ). Patients in the ECMO group also trended towards shorter ICU stays and shorter hospital stays<sup>[40]</sup>.

The myriad of extracorporeal support strategies available as a bridge to lung transplantation should be employed in the following order if possible: iLA (hypercarbia, respiratory acidosis), VV-ECMO (severe hypoxia, hypercarbia), VA-ECMO or PA-LA ECLS (need for hemodynamic support, pulmonary HTN, right heart failure) (Table 1). Oxygenation requires flows 3–5 L/min whereas CO<sub>2</sub> removal requires flows (0.5–1.0 L/min)<sup>[43]</sup>. It has been suggested that even VA-ECMO does not successfully unload the right ventricle<sup>[33]</sup>. Proponents of PA-LA ECLS state that this cannulation strategy may be employed in those patients who would benefit from an atrial septostomy as this decreases the work of the right ventricle and uses the elevated pulmonary artery pressure to drive flow across the oxygenator. By creating an oxygenating shunt PA-LA ECLS decreases right ventricular work while avoiding central hypoxemia created by an atrial septostomy. It is noted that patients with this degree of right ventricular failure will likely need peripheral VA-ECMO cannulation for hemodynamic support prior to induction of anesthesia.

Awake MLA has many benefits and should be employed whenever possible. In patients with pure respiratory failure VV-ECMO and ECLA offer safe bridging strategies. Hypercarbic respiratory failure may be bridged with ECLA, whereas hypoxic respiratory failure benefits from the higher flows provided by VV-ECMO. In patients with concomitant pulmonary hypertension and right ventricular failure, VA-ECMO and PA-LA ECLA are the two main options for bridging these patients to transplant. Olsson *et al.*<sup>[42]</sup> were able to achieve cannulation and successful bridging to transplant with VA-ECMO without sedation, intubation, or mechanical ventilation thus avoiding

the potential drawbacks of each. PA-LA ECLS provides immediate decrease in right ventricular afterload but has the necessity of general anesthesia, endotracheal intubation, and sternotomy or thoracotomy. None of the current case series provide hemodynamic data to assess improvement in right ventricular function. Further studies need to be done to assess the pros and cons of these two potential bridging strategies for this frequent scenario of pulmonary hypertension and right heart failure.

### Post-transplant

Severe graft failure is the most common cause of death in the first 30 d post-lung transplant<sup>[2]</sup>. The incidence of pulmonary graft failure (PGF) in patients post-lung transplant ranges from 13%–35%<sup>[28]</sup>. PGF requiring ECMO support ranges from 2.1%–7.4% of lung transplants performed in the reported series<sup>[2,28]</sup>. Use of MLA has been reported in 2.1%–5.5% of lung transplants for treatment of severe graft failure. PGF is defined as the inability of a pulmonary allograft to sustain ventilation and oxygenation despite full mechanical support<sup>[44]</sup>. There are varying definitions of early PGF with some authors classifying it as < 7 d post-LTx and others within 24 h<sup>[44]</sup>. Multiple factors have been associated with early PGF, including: prolonged ischemic time, ischemia-reperfusion injury, prolonged CPB, blood transfusions, circulatory arrest, significant active infection in recipient pulmonary bed, technical complications, and quality of donor lung<sup>[28,44]</sup>. Of the possible contributors to early PGF, ischemia-reperfusion injury (IRI) is one of the most well-recognized complications of LTx, accounting for approximately one-third of 30-d mortality<sup>[29]</sup>. Patients experiencing IRI may present with worsening compliance, hypoxemia, diffuse pulmonary infiltrates, and copious airway secretions<sup>[29]</sup>. Late PGF is often multifactorial and may be irreversible<sup>[28,44]</sup>.

Glassman *et al.*<sup>[44]</sup> concluded that ischemia-reperfusion injury and acute graft dysfunction could be successfully reversed with early aggressive intervention.

They reported on 17 cases of ECMO support for severe graft failure in 16 patients between 1991 and 1993. These patients represented 7.4% of the 215 patients who underwent transplant during this time period. They noted significant differences in outcome depending on early (< 7 d post-LTx) or late ( $\geq$  7 d post-LTx) initiation of ECMO support. In the early group, 80% (8/10) patients were weaned from ECMO and 70% (7/10) were long-term survivors, and 71% (5/7) had normal long-term lung function. In the late group, 0% (0/7) survived to discharge<sup>[44]</sup>.

Oto *et al.*<sup>[28]</sup> reported on 10 (2.1%) of 481 LTx patients at their institution that were placed on ECMO for severe PGF. They compared 4 patients from (1990-1999) and 6 patients from (2000-2003). There was a significantly different time from transplant to initiation of ECMO support between these two groups with mean of 21 d in "early" group to a mean of 0.5 d for the recent group, ( $P = 0.01$ ). PaO<sub>2</sub> 12 h post-initiation was significantly better in recent group  $341 \pm 90$  mmHg vs  $90 \pm 23$  mmHg, ( $P = 0.03$ ). There was improved survival between "early" and recent groups; however this could be explained by observation of Glassman *et al.*<sup>[44]</sup> above that ECMO is effective in early PGF, but not in late PGF. Oto *et al.*<sup>[28]</sup> have the lowest reported incidence of ECMO use for PGF of any of the reported series, at 2.1% of their LTx cases. They attribute this to: (1) pretreatment of donor lungs with prostacyclin; (2) prospective T-cell and B-cell crossmatching; (3) less use of CPB; (4) inhaled nitric oxide during implantation; and (5) use of differential ventilation for unilateral PGF. While the incidence of bleeding improved from 50% in "early" group to 32% in recent group, the mortality rate for patients with bleeding complications was 100% suggesting that even with improved ECMO technology bleeding is still a significant problem<sup>[28]</sup>.

Hartwig *et al.*<sup>[29]</sup> reported 23 patients requiring ECMO support for PGF. They compared those receiving VA- vs VV-ECMO. There were no significant differences in patient demographics, underlying pulmonary disease, or type of transplant between the two groups. However, there were significantly larger numbers of COPD/A1AT, Retransplant, and PPH patients in the ECMO group compared to non-ECMO group, with relative risk (RR) 0.272, 5.93, 5.76, respectively. CPB was used in 66.7% of those patients needing ECMO post-op as compared to 6.6% in the non-ECMO group, ( $P < 0.001$ ). While not reaching statistical significance, ( $P = 0.062$ ), donor/recipient BSA ratios indicated that the donor was smaller than the recipient in the majority of ECMO cases. VA-ECMO group had more complications, 30 of 39. VV-ECMO group had 87.5% 30-d survival, and a 3-year survival comparable to non-ECMO group. Survival data for VA-ECMO group was not explicitly provided. They concluded that VV-ECMO was associated with fewer complications and improved outcomes in comparison to VA-ECMO

and recommend early initiation of VV-ECMO in all LTx patients with severe IRI unless severe cardiac dysfunction refractory to VV-ECMO is present<sup>[29]</sup>.

### **Blood stream infections associated with mechanical circulatory support**

Of the studies reviewed, very few comment on blood stream infections or the incidence thereof. Fischer *et al.*<sup>[41]</sup> reported positive blood cultures in 7/12 (58.3%) of patients bridged to LTx with the NovaLung® iLA. In their case series of awake ECMO as a bridge to LTx, Olsson *et al.*<sup>[42]</sup> reported 2/5 (40%) patients with infectious complications: one who died of septic multiorgan failure on the 8<sup>th</sup> day of ECMO support and one who died 2 mo post-LTx of septic multiorgan failure. Similarly, Bermudez *et al.*<sup>[37]</sup> reported sepsis in 7/17 (41%) of patients bridged to LTx with ECMO. Of these 3 were bacterial and 4 fungal. Of the fungal infections 3/4 (75%) were caused by *Aspergillus*.

Fuehner *et al.*<sup>[40]</sup> reported 5/26 (19.2%) with sepsis-like syndrome, all with negative blood cultures, 4 who went on to die of multisystem organ failure prior to transplant. In patients requiring ECMO post-transplant due to primary graft failure had the following reported rates of sepsis: Hartwig *et al.*<sup>[29]</sup> 5/23 (21.7%); Oto *et al.*<sup>[28]</sup> reported 2/10 (20%); Wigfield *et al.*<sup>[45]</sup> 4/22 (18.2%). Fischer *et al.*<sup>[46]</sup> queried the ELSO database and found 151 patients who underwent ECMO for PGD post-LTx, of these 15% were found to have septic complications.

Aubron *et al.*<sup>[47]</sup> performed a retrospective review of 146 ECMO cases lasting greater than 48 h. They reported a 16.4% occurrence of blood stream infections (BSI), with *Candida* being the most common pathogen. Sequential Organ Failure Assessment (SOFA) score prior to cannulation [Odds ratio (OR) 1.23] and the duration of ECMO therapy (OR 1.08) were independent predictors of BSI. While BSI was associated with significant increase in ICU and overall hospital length of stay, it was not associated with increased mortality. Of note, these patients were not given prophylactic antibiotics but likely received antibiotics for underlying disease processes or surgical procedures. This study is of all ECMO patients at one institution and does not specifically represent lung transplant patients.

In a similar study, Pieri *et al.*<sup>[48]</sup> retrospectively identified 46 patients undergoing ECMO (24 VA and 22 VV) for greater than 48 h in the time period reviewed. This study similarly found infection rate to correlate with SOFA score, duration of ECMO therapy, as well as ICU and hospital length of stay. Blood stream infection was identified in 8/46 (17.4%) of ECMO patients (4 VA and 4 VV). Causative organisms included: *Candida albicans* (2), *Candida parapsilosis* (2), *Klebsiella pneumonia* (2), *Candida tropicalis* (1), *Corynebacterium minutissimum* (1), *Staphylococcus epidermidis* (1), and *Acinetobacter baumannii* (1). They note that 42% of ECMO centers use



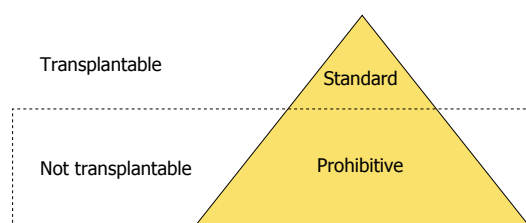


Figure 4 Only 15%-20% of donor organs meet standard criteria for lung transplant.

prophylactic antibiotics while only 2% report routine use of antifungal agents.

There have been no randomized controlled trials to evaluate the most appropriate prophylactic antimicrobial regimens for patients undergoing ECMO. This data could be beneficial in management of ECMO patients and could be combined with institutional antibiograms to provide the best possible prophylactic regimens for these patients.

## EVLP

### Shortage of suitable donor organs

The issue of critical organ shortage for lung transplantation has already been previously mentioned. In 2013, 1923 lung transplants were performed in the United States, and 174 patients died while on the waiting list<sup>[49]</sup>. Only 15%-20% of offered organs meet criteria for transplantation<sup>[3,50,51]</sup>. Figure 4 demonstrates the disparity between available organs and those meeting criteria for transplant. The International Society for Heart and Lung Transplantation (ISHLT) lists the following as the currently accepted "ideal" lung donor criteria: age < 55 years, ABO compatible, clear chest radiograph, approximate size match, clear chest X-ray,  $\text{PaO}_2/\text{FiO}_2 > 300$  on 100%  $\text{FiO}_2$  and positive end expiratory pressure (PEEP) of 5  $\text{cmH}_2\text{O}$ , < 20 pack-year smoking history, absence of chest trauma, no evidence of aspiration/sepsis, no prior cardiopulmonary surgery, absence of organisms on sputum gram stain, and clear bronchoscopy<sup>[52]</sup>. Failure of donor lungs to meet criteria is largely due to events leading up to death which result in poor organ, including: barotrauma, pulmonary edema, aspiration, and pneumonia as well as direct effects of brain death<sup>[53]</sup>. Brain death is thought to lead to neurogenic pulmonary edema and inflammatory lung injury due to hemodynamic changes and cytokine storm associated with brain death<sup>[53]</sup>.

EVLP is an innovative use of mechanical circulatory support in an attempt to expand the available donor pool<sup>[50]</sup>. This technology utilizes components of CPB or ECMO to isolate the lung and evaluate its function outside the body as a means of assessing suitability for transplant. The theorized mechanisms of benefit are removing interstitial fluid, washing out of inflammatory mediators, and allowing for alveolar recruitment at low airway pressures. Similar to the benefits observed

when ECMO is utilized for PGD, EVLP aims to provide a platform for organ reconditioning which will allow previously untransplantable organs to meet criteria for transplantation.

### History of ex-vivo perfusion

First written ideas of ex-vivo perfusion are tracked back to 1812. In 1866, a frog heart was kept alive ex-vivo for 48 h, and a perfused liver ex-vivo was capable of producing urea. In 1935, Alexis Carrel successfully perfused a cat thyroid for 18 d using the Lindbergh pump, placing both men on the front of Time magazine<sup>[54]</sup>. They performed several experiments showing that whole organs including ovary, thyroid, kidney, and heart could maintain functionality and cell proliferation ex-vivo<sup>[53]</sup>.

### Support for use in humans

Animal models of EVLP showed no detrimental effects to the organ or recipient and additionally showed improved oxygenation, decreased mean airway pressure, pulmonary artery pressure, and inflammatory markers<sup>[55]</sup>. In our own rat and porcine models, EVLP provides a platform for organ evaluation, reconditioning, disease modeling, and administration of therapeutic agents<sup>[56]</sup>. Preclinical porcine models by Cypel *et al.*<sup>[57]</sup> showed that normal and injured donor lungs could be maintained on EVLP for up to 12 h with excellent post-transplant lung function.

In 2001, Steen *et al.*<sup>[58]</sup> published on the first ex-vivo perfused human lung transplant, a non-heart-beating donor lung transplanted into a 54 years old female with COPD yielding excellent function. Cypel *et al.*<sup>[53]</sup> went on to perform a prospective, non-randomized clinical trial in which 23 high-risk donor lungs were placed on EVLP for 4 h and if physiologically appropriate, transplanted into human recipients. Three patients first underwent a safety and logistic feasibility study in which standard criteria donor lungs were transplanted, one with conventional methods and one after 1 h of EVLP with similar outcome. Twenty of the 23 high-risk donor lungs met criteria for transplant with improvement in median  $\text{PO}_2:\text{FiO}_2$  from 335 mmHg donor lung to 414 and 443 mmHg at 1 and 4 h of EVLP, respectively ( $P < 0.001$ ). These 20 lungs were transplanted and compared to 116 conventional lung transplants performed during the same time period. The incidence of PGD within 72 h of transplant was 15% for EVLP group, while 30% for control group. The EVLP group had no significant differences in length of stay, mechanical ventilation requirements, bronchial complications, and 1-year survival.

In a similar study conducted in Italy, incidence of PGD immediately after transplant and at 72 h was evaluated in EVLP ( $n = 8$ ) and standard ( $n = 28$ ) lung transplant groups<sup>[59]</sup>. Eleven donor lungs initially underwent EVLP, 3 failed to meet criteria for transplantation, 2 secondary to infection, and 1 due

to poor gas exchange. They note that EVLP allowed for identification and confirmation of right lower lobe infection that was not evident on xray or CT scan performed on the day of donation. Increase in mean  $\text{PaO}_2:\text{FiO}_2$  showed significant improvement at 1, 2, 3, and 4 h on EVLP ( $P < 0.05$ ). Lung radiographs performed post-EVLP showed resolution of edema. In the standard lung transplant group, 50% (14/28) patients had PGD 3 at time zero, 7 of which continued through 72 h. Consistent with early mortality associated with PGD 3, 4 of these 7 patients did not survive to hospital discharge. In the EVLP group, 37.5% (3/8) patients had PGD 3 at time zero, all of which resolved by 72 h resulting in 0% PGD 3 at 72 h.

Sage *et al.*<sup>[60]</sup> performed a similar study in France in which 32 pairs of unsuitable donor lungs were reconditioned with *ex-vivo* perfusion per the Toronto technique. Of these, 31 were deemed suitable for transplant. One pair of lungs became progressively edematous with decreasing  $\text{PaO}_2:\text{FiO}_2$ . Reconditioned lungs were compared with 81 double-lung transplants performed during the same time period. EVLP resulted in a significant improvement in median  $\text{PaO}_2:\text{FiO}_2$  ( $P < 0.0001$ ). There were no significant differences in PGD at 72 h, length of mechanical ventilation, ICU or hospital length of stay, 30-d mortality, or one-year survival.

In utilizing unsuitable donor lungs reconditioned with EVLP, increased incidence of PGD was one of the primary concerns. These studies have shown that this concern is not validated, and in fact lungs reconditioned with EVLP may have lower incidence of PGD when compared with standard lung transplant controls.

### Donor selection

EVLP seeks to make marginal donors a viable option. Marginal donors can be defined as those with arterial oxygen tension : fraction of inspired oxygen ( $\text{PaO}_2:\text{FiO}_2$ ) ratios  $< 300$ , pulmonary edema, blood transfusions  $> 10$  units, donation after cardiac death (DCD), pneumonia, or poor inflation/deflation at the time of procurement. Those with pneumonia or other active infection, severe mechanical lung injury contusions in more than one lobe, or gross gastric aspiration remain excluded.

### DCD

In controlled DCD donors, graft assessment may occur prior to life support and therefore, EVLP is not typically employed for organ assessment<sup>[61,62]</sup>. In uncontrolled DCD donors, duration of warm ischemia is often unknown and assessment prior to cardiac arrest is not possible. In these donors, EVLP provides a means of organ assessment and remodeling. Snell *et al.*<sup>[63]</sup> used a dog model to compare all Maastricht categories with varying preservation techniques with all groups achieving a  $\text{PaO}_2:\text{FiO}_2$  between 472 to 586 mmHg without a significant increase in lung weight.

Similarly, Inokawa *et al.*<sup>[64]</sup> used a rat EVLP transplant model to compare four groups: heart beating donors (HBD), non-heart-beating donors (NHBD) without *ex-vivo* perfusion, NHBD perfused with Earle's solution, and NHBD perfused with Earle's solution supplemented with washed porcine erythrocytes<sup>[64]</sup>. Blood samples obtained from the transplanted left pulmonary vein did not show significant differences in oxygenation between the two groups. At explantation wet-to-dry ratios were greater in left transplanted lungs as compared to native right lungs; however, there were no significant differences between the four groups. Steen *et al.*<sup>[58]</sup> were the first to report on clinical transplantation of DCD donor lungs after assessment by EVLP. In their review, Yeung *et al.*<sup>[62]</sup> list the following advantages provided by EVLP: (1) facilitates recruitment of atelectatic lung; (2) facilitates bronchoscopic clearance of airway secretions; (3) removal of clots *via* transient retrograde perfusion; and (4) improves ventilation/perfusion matching by avoiding interference of stiff chest wall and immobile diaphragm. As EVLP strategies improve, they are providing not only a means of assessment but a platform for organ remodeling and delivery of therapeutic agents.

### Clinical trials

The HELP trial was a prospective, non-randomized performed from September 2008 through September 2009, which enrolled 102 lung transplant patients. Donor lungs initially rejected for transplant based on current criteria were placed on EVLP with Steen at 37 °C for 4 h. Rejected organs reaching a  $\text{PaO}_2/\text{FiO}_2 > 400$  mmHg while on EVLP were transplanted into 16 recipients. These patients were compared to 86 controls receiving standard lung transplants during this same period. PGD scores, 30-d mortality, duration of intubation, length of ICU stay, and length of hospital stay were found to be equivalent in both groups<sup>[50]</sup>.

A multi-center prospective trial, NOVEL, is currently underway at 6 US lung transplant centers: New York Presbyterian-Columbia University Hospital, University of Colorado Medical Center, Brigham and Women's Hospital, Duke University Medical Center, University of Pennsylvania Medical Center, and University of Maryland Medical Center. This phase I clinical trial is funded by XVIVO Perfusion (Vitrolife, Inc, Englewood, CO) and will evaluate 30-d mortality, PGD, ICU length of stay, mechanical ventilation and ECLS utilization, and survival. We anxiously await the results of this trial in hopes that EVLP will achieve FDA support and help us decrease the number of patients dying while awaiting lung transplant.

## CONCLUSION

There are numerous established and emerging mechanical circulatory support modalities that may be employed throughout the course of a lung transplant

patient. The use of CPB during lung transplantation is controversial. There are a paucity of randomized controlled trials to evaluate the utility of CPB in lung transplantation. The trials that have been reviewed here are inconsistent in their findings; further proving the need for higher powered studies. While the detrimental effects of CPB are well documented, right ventricular failure and/or hemodynamic instability are indications for the use of mechanical circulatory support during lung transplantation. VA-ECMO may also be used for this purpose and has the added benefits of peripheral cannulation and ability to span multiple phases of care, from bridging to post-operative support. Randomized controlled trials need to be performed to further investigate this controversial issue.

Extracorporeal support may also be required as a bridge to lung transplant as long wait times may result in respiratory failure prior to organ availability. To this avail, the least invasive modality should be employed if possible for the relative indication: iLA (hypercarbia, respiratory acidosis), VV-ECMO (severe hypoxia, hypercarbia), VA-ECMO or PA-LA ECLS (need for hemodynamic support, pulmonary HTN, right heart failure). These same modalities may be applied with the same order of preference for post-operative support or PGF. All of these modalities may be performed in awake patients and should be whenever possible.

While increased wait times necessitate bridging with mechanical circulatory support, EVLP may be emerging as the answer to increasing organ utilization and thus decreasing wait times. EVLP has shown excellent results in animal models as well as reproducible results in human studies around the world. We now anxiously await the results of ongoing clinical trials that may lead to the approval of EVLP for widespread use.

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## Collagen vascular disease-associated interstitial lung disease

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### Abstract

Interstitial lung disease (ILD) is an important mani-

festation of collagen vascular diseases. It is a common feature of scleroderma, and also occurs in dermatomyositis and polymyositis, mixed connective tissue disease, Sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, and Antineutrophil cytoplasmic antibody-associated vasculitis. When present, it is associated with increased morbidity and mortality, thus making early diagnosis important. In fact, in many patients, ILD may be the first manifestation of a collagen vascular disease. The most common symptoms are cough and dyspnea. The diagnosis is made based on pulmonary function tests showing restrictive lung disease and impaired oxygen diffusion and chest imaging showing ground glass infiltrates, interstitial thickening, and/or fibrosis. The most common histologic finding on lung biopsy is non-specific interstitial pneumonia, though organizing pneumonia and usual interstitial pneumonia may also be seen. Treatment is focused on addressing the underlying collagen vascular disease with immunosuppression, either with corticosteroids or a steroid-sparing agent such as cyclophosphamide, azathioprine, or mycophenolate, although the optimal agent and duration of therapy is not known. There are few clinical trials to guide therapy that focus specifically on the progression of ILD. The exception is in the case of scleroderma-associated ILD, where cyclophosphamide has been shown to be effective.

**Key words:** Interstitial lung disease; Collagen vascular disease; Connective tissue disease; Rheumatoid arthritis; Scleroderma; Myositis; Sjogren's syndrome; Systemic lupus erythematosus; Antineutrophil cytoplasmic antibody-associated vasculitis; Mixed connective tissue disease

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**Core tip:** Interstitial lung disease (ILD) is a significant manifestation of collagen vascular diseases due to its association with increased morbidity and mortality. Thus it is important for clinicians to consider and be able to recognize collagen vascular disease-associated

ILD and initiate appropriate treatment. This review will discuss the clinical features, histologic findings, and treatment options of collagen vascular disease-associated ILD.

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## INTRODUCTION

Collagen vascular diseases (CVD) are a diverse group of autoimmune diseases which can have a myriad of manifestations. These include cardiac (pericarditis), musculoskeletal (myositis, inflammatory arthritis), dermatologic (rashes), ophthalmic (uveitis), and pulmonary [interstitial lung disease (ILD), pulmonary arterial hypertension]. ILD is a frequent manifestation of CVD, although the prevalence varies between each disease. ILD is most commonly seen in scleroderma, where it is found in up to 70% of patients, and least commonly in lupus where it occurs in 5%-10% of patients<sup>[1-4]</sup>. ILD may also be the initial presentation of a CVD. Based on the experience at the Johns Hopkins ILD clinic, 15% of patients presenting with a new diagnosis of ILD have an undiagnosed CVD<sup>[5]</sup>. Regardless of the associated CVD, when ILD does occur, it is associated with increased morbidity and mortality<sup>[3,4,6-14]</sup>. Thus it is critical that ILD is identified early so that treatment can be initiated. In this review, the clinical presentations, histologic features, and treatment of collagen vascular disease-associated ILD (CVD-ILD) will be discussed. A summary of the key features of CVD-ILD can be found in Table 1.

## OVERVIEW

### *Clinical presentation*

Clinically, ILD typically manifests with progressive dyspnea on exertion and dry cough. However, given the existence of concomitant joint disease and mobility issues, patients often attribute the early symptoms to the CVD or deconditioning and have frequently lost considerable lung function prior to diagnosis. CVD-ILD is diagnosed based on clinical presentation, loss of lung function and demonstration of interstitial scarring on chest imaging. Pulmonary function testing (PFT) reveals restrictive lung disease with diminished total lung capacity (TLC), decreased forced vital capacity (FVC), and impaired diffusion capacity of the lung for carbon monoxide (DLCO). Chest imaging demonstrates ground glass, inter- and intra-lobular interstitial thickening, and in many cases end stage fibrosis and scarring<sup>[15]</sup>. Imaging may also show other manifestations of the underlying CVD such as

enlargement of the pulmonary artery or dilation of the esophagus<sup>[15]</sup>. Bronchoscopy is often used to rule out alternative diagnoses such as infection but is not typically diagnostic of CVD-ILD.

### *Histology and imaging findings*

Lung biopsy may show a variety of histopathology, most commonly non-specific interstitial pneumonia (NSIP), though organizing pneumonia (OP) and usual interstitial pneumonia (UIP) may be present depending on the CVD<sup>[16]</sup>. However, due to the risks of the procedure, surgical lung biopsy is not routinely part of the workup of CVD-ILD. Diagnosis is based upon clinical presentation, history, PFTs and high-resolution computed tomography (HRCT) scan. The typical HRCT findings for a patient with UIP are intralobular septal thickening, honeycombing, traction bronchiectasis, and subpleural, peripheral reticular opacities<sup>[17]</sup>. In contrast, NSIP is characterized by subpleural ground glass opacities, predominantly in the lower lobes<sup>[17]</sup>. There may be interlobular septal thickening and honeycombing, but the honeycombing is typically microcystic<sup>[17]</sup>. In OP, the HRCT shows patchy, peripheral ground glass opacities or consolidations, which may be migratory<sup>[17]</sup>. Lymphoid interstitial pneumonia (LIP) is characterized by diffuse ground glass opacities with intermixed central or perivascular cysts<sup>[17]</sup>. Thus, HRCT is essential in not only diagnosing CVD-ILD but also in suggesting potential histologic patterns that may alter prognosis.

Due the association between esophageal dysmotility and CVD, particularly in patients with scleroderma, there can also be evidence of chronic aspiration in the lungs. Studies have found that chronic aspiration is associated with a bronchocentric distribution of noncaseating granulomas, basophilic intraluminal contents and foreign-body containing multinucleated giant cells on histopathology<sup>[18-21]</sup>. On HRCT, patients with chronic aspiration have centrilobular nodules, tree-in-bud opacities, and bronchial wall thickening with or without fibrosis, predominantly in the lower lobes, often times with dilation of the esophagus as well<sup>[18-21]</sup>.

### *Treatment*

Generally speaking, treatment of CVD-ILD is focused on addressing the underlying CVD, and there are not many randomized-controlled trials looking at the ILD specifically to guide therapy. The exception to this is in the case of scleroderma-associated ILD, where studies have shown cyclophosphamide to be effective<sup>[22,23]</sup>.

## FEATURES OF SPECIFIC CVD-ILD

### *Clinical presentation*

Scleroderma is a CVD with skin, cardiac, pulmonary, gastrointestinal, and renal involvement<sup>[24]</sup>. The pulmonary manifestations include pulmonary arterial



**Table 1 Summary of key features of collagen vascular-Interstitial lung disease**

	Prevalence	Histology	Other pulmonary findings	Treatment
Scleroderma	> 70%	NSIP	Pulmonary arterial hypertension	<sup>1</sup> Cyclophosphamide <sup>[22,29]</sup> Mycophenolate, azathioprine used for maintenance
Dermatomyositis/ Polymyositis	20%-30%	NSIP	Diaphragmatic weakness	Corticosteroids Azathioprine Mycophenolate Calcineurin inhibitors Rituximab IVIg
Mixed connective tissue disease	30%-60%	NSIP	Diaphragmatic weakness	Corticosteroids ± cyclophosphamide
Sjogren syndrome	25%-40%	NSIP, UIP, OP, LIP		Corticosteroids ± cyclophosphamide
Rheumatoid arthritis	10%-20%	UIP	May have obstructive lung disease, necrobiotic nodules, pulmonary arterial hypertension	Corticosteroids ± cyclophosphamide or azathioprine
Systemic lupus erythematosus	5%	NSIP, OP	Pulmonary arterial hypertension, Pleural effusion	Corticosteroids ± cyclophosphamide or azathioprine
ANCA-associated vasculitis	7%-47%	UIP	Pulmonary hemorrhage	Induction with corticosteroids + cyclophosphamide or rituximab <sup>[84-86]</sup> Maintenance with methotrexate or azathioprine Plasmapheresis for pulmonary hemorrhage

<sup>1</sup>Use in collagen vascular disease-associated- interstitial lung disease supported by multicenter clinical trials.

hypertension and ILD<sup>[24]</sup>. ILD is a significant cause of mortality in patients with scleroderma<sup>[6,7,13]</sup>. Lung involvement portends a worse prognosis, and more severe fibrosis is correlated with higher mortality<sup>[6,7,12,13]</sup>. The prevalence of pulmonary fibrosis varies between studies. When diagnosed by either restrictive physiology on PFTs or characteristic findings on HRCT scan, ILD is present in 25%-40% of patients<sup>[12,13,24,25]</sup>. However, this likely underestimates the true prevalence of disease as at autopsy, ILD is present in at least 70% of cases<sup>[1,16]</sup>. Due to its association with pulmonary arterial hypertension and esophageal dysmotility, other common findings on HRCT scan are enlargement of the pulmonary artery and dilation of the esophagus<sup>[15]</sup>. PFTs may also show evidence of pulmonary arterial hypertension with reduction in DLCO out of proportion to the reduction in TLC.

### Histology and imaging findings

The most common histopathology pattern is NSIP. Rarely UIP or OP are seen<sup>[16,26,27]</sup>. HRCT most commonly shows confluent ground glass, a fine reticular pattern of interstitial markings, and traction bronchiectasis<sup>[15]</sup>.

### Treatment

The most established treatment for scleroderma-associated ILD is cyclophosphamide<sup>[28]</sup>. In two multicenter randomized placebo-controlled trials, treatment with cyclophosphamide for one year showed improvement in lung function<sup>[22,29]</sup>. In the Scleroderma Lung Study, cyclophosphamide was shown to improve FVC and TLC after 12 mo of therapy compared to

placebo<sup>[22]</sup>. Follow up analysis of this study identified a group of patients with an enhanced response to treatment, who were characterized by more severe fibrosis at baseline based on HRCT scan and/or more severe skin involvement<sup>[23]</sup>. The other study compared prednisolone plus cyclophosphamide for 6 mo followed by azathioprine and found at 12 mo a trend towards improvement in FVC<sup>[29]</sup>. Other studies have shown similar results<sup>[30-33]</sup>. One question that remains, however, is the optimal duration of treatment. The Scleroderma Lung Study found that following 12 mo of therapy, the benefit persisted 6 mo after treatment was stopped, with lung function returned to pre-treatment levels 12 mo after therapy was ended<sup>[22,23]</sup>. Additional studies with longer follow up have shown persistent stability in lung function up to 3-4 years after the end of therapy<sup>[32,34]</sup>. However, not all patients have such a prolonged benefit. One study found that 4 years after therapy, although 69% of patients had stable lung function, 32% of patients had experienced progression of their disease<sup>[32]</sup>. Due to the side effects of cyclophosphamide, other drugs have been explored for use as maintenance therapies. Azathioprine and methotrexate are commonly used as maintenance<sup>[26,33,35,36]</sup>. However, concern remains of using methotrexate in patients with CVD-ILD as the drug itself may cause drug-induced-ILD that may complicate the picture.

As monotherapy, mycophenolate has also been shown in retrospective studies to stabilize lung function after at least 6 mo of therapy<sup>[37-39]</sup>. Azathioprine as monotherapy was shown to stabilize FVC and improve dyspnea after treatment for at least 12 mo in a

retrospective study<sup>[40]</sup>. However, a subsequent study comparing cyclophosphamide to azathioprine showed worsening of lung function with azathioprine compared to stability of lung function with cyclophosphamide<sup>[41]</sup>.

Due to the association between corticosteroids and scleroderma renal crisis, corticosteroids have been used less commonly than for other CVD-ILD. However, a retrospective cohort analysis of two medical centers in Japan showed that corticosteroid monotherapy as compared to no therapy was associated with improvement in FVC without any change in 5 or 10-year survival<sup>[42]</sup>.

Another medication that has been evaluated is rituximab. Rituximab is a monoclonal antibody against B cells and has been shown in a few case reports and one randomized controlled trial of 14 patients to be associated with improvement in lung function<sup>[43]</sup>.

Recently, pirfenidone has been shown in patients with idiopathic pulmonary fibrosis (IPF) to slow decline in FVC<sup>[44]</sup>. Pirfenidone has antifibrotic effects, and in mouse models of IPF has been shown to reduce pro-fibrotic cytokines such as transforming growth factor beta (TGF- $\beta$ ) and to inhibit fibrocyte accumulation in the lungs<sup>[45,46]</sup>. This drug is now being studied in patients with scleroderma-ILD to see if it has the same effects as in patients with IPF.

These trials have not examined responses based on histology patterns, as most patients do not require a lung biopsy to make the diagnosis. One exception is in patients who have fibrotic lung disease with predominantly features of chronic aspiration. Esophageal dysmotility, which can predispose one to chronic aspiration, is a common feature of scleroderma. One study differentiated patients with scleroderma-ILD into those with features of NSIP vs those with features of chronic aspiration based on lung biopsy, with those found to have NSIP treated with cyclophosphamide for one year and those found to have chronic aspiration treated with aggressive proton pump inhibitor therapy, prokinetic medications, and lifestyle modifications for GERD<sup>[21]</sup>. After one year of therapy, both groups had stability in their FVC, FEV1, and DLCO, suggesting that in a subset of patients with ILD related to chronic aspiration, antireflux therapy may be critical in slowing or halting disease progression<sup>[21]</sup>.

## DERMATOMYOSITIS AND POLYMYOSITIS

### *Clinical presentation*

ILD is also commonly found in patients with dermatomyositis and polymyositis, and is a significant cause of mortality<sup>[9,10,14]</sup>. Studies have found that 20%-30% of patients with myositis have ILD, and ILD may precede muscle and skin findings in about 20% of patients<sup>[9,10,14,47]</sup>. There is a strong association between ILD and the presence of antisynthetase antibodies (most commonly

anti-Jo-1)<sup>[9,10,47]</sup>. Because of associated muscular weakness and deconditioning, dyspnea on exertion may go unrecognized for some time. Additionally, muscular weakness can affect the diaphragm, causing a diminished TLC out of proportion to the DLCO, which is more pronounced in the supine position.

### *Histology and imaging findings*

The most common histology is NSIP, but OP or UIP may also be seen<sup>[10,16,26]</sup>. HRCT typically shows confluent ground glass consolidation in the lower lobes with reticular interstitial changes and traction bronchiectasis, consistent with NSIP<sup>[15]</sup>.

### *Treatment*

Treatment is based on the underlying histologic pattern. Organizing pneumonia and NSIP are most responsive to steroids compared to UIP<sup>[10,26]</sup>. For those patients who do not respond to corticosteroids, retrospective studies and case series have shown stabilization or improvement in pulmonary function with the use of cyclophosphamide<sup>[47,48]</sup>, mycophenolate<sup>[39,49]</sup>, azathioprine<sup>[14,50]</sup>, and calcineurin inhibitors<sup>[51-53]</sup>. Azathioprine and mycophenolate are also used for maintenance therapy following cyclophosphamide<sup>[10]</sup>. Case reports have also shown improvement with intravenous immunoglobulin (IVIG)<sup>[54,55]</sup>.

## MIXED CONNECTIVE TISSUE DISEASE

### *Clinical presentation*

Mixed connective tissue disease (MCTD) is a unique collagen vascular disease characterized by the presence of anti-ribonucleoprotein (anti-RNP) antibodies and clinical features similar to lupus, scleroderma, and dermatomyositis/polymyositis, including myositis, sclerodactyly, Raynaud's phenomenon, and polyarthritides<sup>[8,56,57]</sup>. ILD is present in approximately 30%-60% of patients<sup>[8,57]</sup>. As in other CVD, the presence of severe fibrosis has been associated with increased mortality<sup>[8]</sup>. In addition to ILD, MCTD is also associated with pleural thickening, pleural effusions, and pericardial effusions, all of which may be seen on HRCT scan<sup>[15]</sup>.

### *Histology and imaging findings*

The most common pathology seen is NSIP, with UIP and OP seen less commonly<sup>[16,26]</sup>. HRCT shows ground glass predominantly in the lower lobes<sup>[15]</sup>.

### *Treatment*

Similar to other CVD-ILD, therapy is guided by treatment of the underlying CVD. Corticosteroids have shown some efficacy, with one uncontrolled study showing that 50% of patients treated with corticosteroid monotherapy had improvement in lung function, and an additional 20% improving with corticosteroids plus cyclophosphamide<sup>[57]</sup>.

## SJOGREN'S SYNDROME

### Clinical presentation

Sjogren's syndrome is a disease primarily affecting exocrine glands, with ILD representing a major extraglandular manifestation<sup>[11]</sup>. Studies have found a wide range in the prevalence of ILD, from 25%-40%<sup>[11,58-60]</sup>. As with other CVD-associated ILD, the presence of ILD is associated with poor survival<sup>[11]</sup>.

### Histology and imaging findings

The most common pathology pattern is NSIP, but UIP, OP, and LIP can be present as well<sup>[16,26,61-63]</sup>. The typical HRCT findings are consistent with NSIP, patchy ground glass and microcystic honeycombing predominantly in the lower lobes<sup>[15]</sup>. When LIP is present, the HRCT shows ground glass, cysts (5-30 mm), and peribronchovascular, centrilobular, and subpleural nodules<sup>[15]</sup>. Other findings that can be seen in patients with Sjogren's syndrome in general are bronchial wall thickening, bronchiectasis, air trapping, cysts, and nodules<sup>[15]</sup>.

### Treatment

Corticosteroids are the primary treatment, with case series showing the majority of patients improving with this therapy<sup>[61]</sup>. There are also reports of corticosteroid and cyclophosphamide used with the majority of patients demonstrating improvement or stabilization of lung function<sup>[63]</sup>.

## RHEUMATOID ARTHRITIS

### Clinical presentation

ILD is the most common pulmonary manifestation of rheumatoid arthritis (RA), affecting approximately 10%-20% of patients<sup>[3,4,64-66]</sup>. Development of ILD is associated with increased mortality<sup>[3,4]</sup>. Although most patients with rheumatoid arthritis are women, male gender confers an increased risk of developing ILD<sup>[64,67,68]</sup>. Smoking, anti-citrullinated protein (anti-CCP) antibodies, and rheumatoid factor (RF) antibodies have also all been associated with an increased risk of developing ILD<sup>[3,68,69]</sup>. In addition to ILD, pulmonary manifestations of rheumatoid arthritis include pulmonary arterial hypertension, necrobiotic nodules, and obliterative bronchiolitis, and thus HRCT may show enlargement of the pulmonary artery, mosaic attenuation with air trapping, and/or pulmonary nodules<sup>[15]</sup>. On PFTs, reduction in DLCO out of proportion to the reduction of TLC suggests the presence of pulmonary arterial hypertension as well. There also may be obstruction if there is concomitant airways disease.

Drugs used to treat RA have also been associated with pulmonary toxicity, and it is important to differentiate between drug-induced lung disease and RA-ILD. Agents known to cause pulmonary toxicity include methotrexate, gold, penicillamine, leflunomide,

and anti-tumor necrosis factor alpha (anti-TNF- $\alpha$ ) agents<sup>[65,70-72]</sup>. Indeed, biologic agents, specifically anti-TNF- $\alpha$  agents have been associated with both new and exacerbation of underlying ILD<sup>[73]</sup>. Increased mortality rates in up to two-thirds of patients with existing ILD were reported<sup>[73]</sup>. It is unclear if the drugs caused the worsening ILD or that the patients had underlying aggressive disease necessitating use of more aggressive ILD therapy with biologic agents. Drug-induced pulmonary toxicity should be suspected based on the timing of symptoms and use of a suspect medication. Labs may or may not be helpful. In the case of penicillamine, patients develop a peripheral eosinophilia, but in the case of other drugs, labs and BAL findings are nonspecific<sup>[72]</sup>. The treatment is to stop the offending agent and in severe cases start steroids.

### Histology and imaging findings

Unlike the other CVD, UIP is the most common histopathology, though NSIP can also be seen<sup>[16,26,71]</sup>. The UIP pattern is associated with an increased mortality and a poor response to therapy compared to the NSIP pattern<sup>[68,74]</sup>. However, the prognosis with a UIP pattern associated with rheumatoid arthritis is less severe than in patients with IPF<sup>[74]</sup>. HRCT findings in RA-ILD are most commonly a UIP pattern, similar to IPF, with basal predominant, subpleural, peripheral distribution of interstitial fibrosis and honeycombing<sup>[15]</sup>. Given that it does not change management, surgical lung biopsy is not typically performed to differentiate between UIP and NSIP.

### Treatment

For patients with NSIP and OP pathology, corticosteroids are first line therapy<sup>[71,75]</sup>. However, UIP has not been shown to be steroid responsive<sup>[71]</sup>. Typically patients are treated with a combination of corticosteroids and cyclophosphamide, or corticosteroids and azathioprine, though there are not studies to evaluate the efficacy of these regimens<sup>[70]</sup>. Medications used for RA that are associated with causing lung injury or worsening ILD should be avoided<sup>[70]</sup>. As noted above, due to concerns with anti-TNF- $\alpha$  either initiating or exacerbating ILD, there have yet to be any clinical trials evaluating use of biologic anti-TNF- $\alpha$  agents to treat RA-ILD.

## SYSTEMIC LUPUS ERYTHEMATOSUS

### Clinical presentation

Systemic lupus erythematosus (SLE) can have a variety of pulmonary manifestations, including pleuritis with or without a pleural effusion, pulmonary arterial hypertension, thromboembolic disease, and diaphragmatic weakness<sup>[76]</sup>. ILD is a rare manifestation of lupus, occurring in approximately 5%-10% of patients<sup>[2]</sup>. However, this number may underestimate the true prevalence, as an autopsy study revealed a

prevalence of approximately 15%<sup>[77]</sup>. Other studies have found evidence of ILD on HRCT in up to 30% of patients<sup>[78]</sup>.

SLE patients can also develop an acute pneumonitis, characterized by acute onset of fever, dyspnea, cough, and pleuritic chest pain<sup>[76,78]</sup>. HRCT shows diffuse ground glass and consolidations<sup>[15,76,78]</sup>. Patients with acute pneumonitis are critically ill, and there is a high mortality rate. Treatment is based on case reports, and high dose corticosteroids are most commonly used<sup>[76]</sup>.

### Histology and imaging findings

SLE-ILD is associated with an NSIP or OP pattern<sup>[16,26]</sup>. HRCT shows subpleural ground glass opacities, or patchy consolidation and air bronchograms consistent with NSIP or OP respectively<sup>[15]</sup>.

### Treatment

There are no placebo-controlled trials to guide treatment for lupus-associated ILD<sup>[76,78]</sup>. Corticosteroids have been used with some efficacy in slowing or improving ILD<sup>[2]</sup>. Other immunosuppressants such as azathioprine and intravenous cyclophosphamide have also been used<sup>[76]</sup>.

## ANCA-ASSOCIATED VASCULITIS

### Clinical presentation

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are pauci-immune vasculitides that includes granulomatosis with polyangitis (GPA, formerly called Wegener's granulomatosis), microscopic polyangitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGP, formerly called Churg-Strauss syndrome). These conditions, particularly MPA, have been associated with ILD. Studies have found the prevalence of ILD in patients with MPA to range from 7%-47% of patients<sup>[79-81]</sup>. The presence of myeloperoxidase-ANCA (MPO-ANCA) rather than proteinase 3-ANCA (PR3-ANCA) is associated with ILD<sup>[80]</sup>. Other pulmonary manifestations of AAV are pulmonary hemorrhage, pulmonary nodules, and tracheobronchial stenosis or masses<sup>[79,81]</sup>. Asthma is also a feature of EGP.

### Histology and imaging findings

On histology, the most common pattern is UIP, with NSIP also seen, as well as vasculitis of bronchial and pulmonary arterioles<sup>[82]</sup>. HRCT typically shows a UIP or NSIP pattern, with thickened interlobular septa, honeycombing, traction bronchiectasis and ground glass infiltrates<sup>[79,81,82]</sup>.

### Treatment

The mainstay of treatment of ANCA-associated vasculitis is induction therapy with either cyclophosphamide and prednisone or rituximab and prednisone, followed by maintenance with methotrexate or azathioprine<sup>[83-87]</sup>.

Plasmapheresis is used only for patients with severe pulmonary hemorrhage<sup>[87]</sup>.

## CONCLUSION

ILD is a manifestation of CVD that causes significant morbidity and mortality. It typically presents with dyspnea and cough, though due to other symptoms such as systemic weakness and deconditioning, symptoms may become apparent only after significant lung function has been lost. The most common histology is NSIP, although OP and UIP are also seen<sup>[16]</sup>. UIP is most commonly seen in RA-ILD and AAV-ILD and is associated with less response to treatment and worse prognosis compared to NSIP<sup>[16,26,71,82]</sup>. In terms of therapy, the only randomized-controlled trials are in patients with scleroderma-associated ILD, where cyclophosphamide has been shown to be effective in halting progression of disease<sup>[22,29]</sup>. For other CVD-ILD, therapy is targeted at controlling the underlying CVD, most commonly with steroids, cyclophosphamide, mycophenolate, and azathioprine. Given the significant morbidity and mortality associated with CVD-ILD, future studies are needed to evaluate the optimal therapy for these diseases. Additionally, it is important to explore the pathogenesis underlying development of ILD in order to provide future targets for new therapies.

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## Advanced non-small cell lung cancer in elderly patients: A review

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### Abstract

Over 50% of patients diagnosed with non-small-cell lung cancer (NSCLC) are 65 years old while 30% exceed 70 years old. Comparing elderly patients to their younger counterpart they poorly tolerate chemotherapy due to progressive reduction of organ function and age-related co-existing pathologies. Due to this reason elderly are usually excluded from platinum-based chemotherapy, which still represent the standard of care for advanced NSCLC. In every-day practice, single-agent schedule with a third-generation drug is the recommended option for elderly patients with advanced NSCLC. A modest increase in toxicity for elderly patients has been demonstrated by subgroup analyses concluding for platinum-based combination chemotherapy being similar in young patients and fit elderly. Even though the cited evidence, feasibility of chemotherapy based on platinum remains an open question. Prospective randomised trials are warranted in order to change guide lines and give the clinicians a new therapeutic option. Recent emerging role of molecular target in selecting patients for new targeted therapies suggest dedicated trials for elderly patients. The same is for more accurate evaluation of elderly patients with increasing evidence for a comprehensive geriatric assessment as a valid tool for customized treatment in NSCLC elderly patients. Suitable evidences for the treatment of elderly patients affected by advanced NSCLC together with more appropriate and validated tools for patients selection are reviewed along the manuscript.

**Key words:** Lung cancer; Elderly; Chemotherapy; Target therapy

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**Core tip:** Due to progressive ageing of population in the next few years a consistent proportion of non-small-cell lung cancer (NSCLC) patients will be diagnosed over the age of 70 years old. Guide lines indications together with results from most recent phase III trials dedicated to elderly patients are discussed along the review. Special attention has been deserved to toxicity profile. Recent emerging role of molecular target in selecting patients for new targeted therapies suggest dedicated trials as for more accurate evaluation with increasing evidence for a comprehensive geriatric assessment as a valid tool for treatment selection in NSCLC elderly patients.

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## INTRODUCTION

Non-small-cell lung cancer (NSCLC) still represents the most frequent cause of cancer-related deaths in Europe and many western countries. Median age at diagnosis of NSCLC is around 70 years old with 50% and more diagnosed over 65 and 30% over 70<sup>[1,2]</sup>. Continuous shifting toward an older population will cause oncologists seeing more elderly patients with lung cancer in years to come.

The highest percentage of patients presents with metastatic disease at diagnosis with chemotherapy standing for the gold standard of management. It is demonstrated that many older patients with metastatic NSCLC are not treated due to many reasons<sup>[3,4]</sup>. Aging is cause of physiological changes in organ functions, as for example renal and liver function. Co-morbidities and consequent drugs intake which may condition chemotherapy administration and toxicity profile<sup>[5]</sup>. An immediate consequence is a sort of under-treatment for this setting of patients<sup>[6]</sup>.

It is known that these patients are not candidated to clinical trials causing difficulty in reaching evidence-based clinical recommendation. In current clinical practice the choice of treatment is still very often based on a old-believe that cancer in older people behave in a less aggressive manner<sup>[7]</sup>.

A significant difference has been documented on a survey which considered trials for cancer drug registration from 1995 to 2002 with only 35% of elderly patients enrolled on clinical trials<sup>[8]</sup>. Such a discordance can greatly affect the reproducibility of trial results.

Chronological age should be no more considered the correct parameter on which candidate patients to receive specific treatment. Biological age should be defined through laboratory tests and geriatric assessment evaluation. However chronological age still represent a reference for clinical trials: 70 years old is considered a reasonable cut-off considering the incidence of age-related variations starts to increase after the age of 70<sup>[9]</sup>. Many evidences suggest an advanced median age of elderly patients in dedicated trials with milder reported toxicity respect to that reported in age-unspecified studies<sup>[10]</sup>.

## SINGLE-AGENT CHEMOTHERAPY

The ELVIS trial was the first phase III trial conducted in advanced NSCLC patients aged  $\geq 70$  years old. Patients were randomized to receive vinorelbine at a dose of 30 mg/m<sup>2</sup> on days 1 and 8 or best supportive care. Advantage in term of survival and increased quality of life (QoL) were demonstrated for vinorelbine arm<sup>[11]</sup>.

Regarding the role of gemcitabine in the treatment of elderly patients affected by advanced NSCLC many specifically addressed phase II trials confirmed its interesting role with an overall response rates (ORR) of 18% to 38% and MST of 6.8 to 9 mo. Toxicity was mild with only sporadic grade 3 to 4 hematologic toxicities in two of them<sup>[12-15]</sup>.

Other specific trials demonstrated satisfying data regarding both activity and feasibility for paclitaxel and docetaxel: ORR 3%-23% and MST 6.8-10.3 mo<sup>[16]</sup>. Overall response rate (ORR) and median survival time (MST) were as follow: 3%-23% and 6.8-10.3 mo, respectively, with acceptable toxicity<sup>[16-21]</sup>.

When docetaxel was compared to vinorelbine in a randomized phase III trial no significant difference in MST was encountered, while longer progression-free survival (PFS) and higher ORR were demonstrated for docetaxel<sup>[22]</sup>.

## NON-PLATINUM-BASED POLICHEMOTHERAPY

Among non-platinum-based regimen the association of gemcitabine plus vinorelbine has been widely studied. At least two phase III trials compared the combination with single agent schedule. Frasci *et al*<sup>[23]</sup> obtained survival advantage for combination respect to single agent in term of MST and ORR.

The Multicenter Italian Lung cancer in the Elderly Study (MILES) trial with its 700 elderly patients affected by advanced NSCLC, represents a milestone in this setting. Patients were randomised to receive vinorelbine or gemcitabine or combination. Considering ORR, time to progression (TTP), MST or QoL no advantage was demonstrated over single-agent therapy in favour of combination therapy. Single-agent therapy confirmed



**Table 1 Results from phase III trials of advanced non-small-cell lung cancer in elderly patients: Non-platinum based chemotherapy**

Ref.	Regimen	Age (yr)	No. of patients	RR (%)	MST (mo)
Gridelli <sup>[11]</sup>	Vinorelbine	70	76	20	6.5
	<i>vs</i>				
	Best Supportive Care		78	NA	4.8
Fraschi <i>et al</i> <sup>[23]</sup>	Vinorelbine	70	60	15	4.2
	<i>vs</i>				
	Vinorelbine + Gemcitabine		60	22	6.7
Gridelli <i>et al</i> <sup>[24]</sup>	Vinorelbine or	70	233	18	8.3
	Gemcitabine		233	16	6.5
	<i>vs</i>				
	Vinorelbine + Gemcitabine		232	21	6.9
Kudoh <i>et al</i> <sup>[22]</sup>	Vinorelbine	≥ 70	91	9.9	9.9
	<i>vs</i>				
	Docetaxel		88	22.7	14.3
Quoix <i>et al</i> <sup>[54]</sup>	Vinorelbine or Gemcitabine	≥ 70	226		10.3
	<i>vs</i>				
	Carboplatin/paclitaxel		225		6.2
Hainsworth <i>et al</i> <sup>[25]</sup>	Docetaxel	≥ 65	171	17	5.1
	<i>vs</i>				
	Docetaxel/gemcitabine		174	25	5.5

RR: Response rate; MST: Median survival time; NA: Not applicable.

its role in this setting<sup>[24]</sup>.

Hainsworth *et al*<sup>[25]</sup> demonstrated that docetaxel plus gemcitabine *vs* weekly docetaxel alone did not improve survival in a population of 350 accrued and randomized elderly patients affected by advanced NSCLC. Moreover, in these two trials the doublet was slightly more toxic than single agent treatment<sup>[25]</sup> (Table 1).

## PLATINUM-BASED CHEMOTHERAPY

Cisplatin represents standard treatment for advanced NSCLC. Nephrotoxicity, ototoxicity and neurotoxicity are the most common non-haematological toxicities attributed to cisplatin in addition to haematological ones.

Carboplatin is responsible for lower incidence of nausea, nephrotoxicity and neurotoxicity, although safety remains an issue also due to its administration in combination with other myelotoxic agents.

**Retrospective analyses of platinum-based chemotherapy**  
In the last decade many data were collected from large randomised trials not selected for elderly patients.

No significant differences in terms of efficacy were shown in retrospective analysis from ECOG 5592 comparing effects of two different platinum-based schedules in patients older than 70 years respect to younger counterpart. In terms of toxicity elderly patients had worse leukopenia and neuropsychiatric disorders<sup>[26]</sup>. ECOG 1594 trial compared four treatment combinations in first-line with no significant differences for RR and MST in retrospective subset analysis for the 227 patients (20%) aged ≥ 70. Significant ( $P = 0.04$ ) major grade 4 toxicities were reported in the elderly subgroup<sup>[27]</sup>. Always referring to retrospective analysis the Southwest Oncology Group (SWOG) 9509 trial,

and the SWOG 9308 trial, documented no significant age influence on MST, TTP and toxicity<sup>[28]</sup>.

In more recent years, the CALGB compared carboplatin plus paclitaxel with paclitaxel. MST was similar between patients aged > 70 and their younger counterpart. A secondary analysis evidenced a survival advantage for the doublet in the elderly patients<sup>[29]</sup>.

TAX 326 compared first-line cisplatin plus vinorelbine or docetaxel. In the subset analysis considering patients aged ≥ 65 increase in survival was obtained with docetaxel plus cisplatin respect to vinorelbine/cisplatin. Lowest incidence in toxicity was registered for docetaxel plus carboplatin arm<sup>[30]</sup>.

Comparing weekly paclitaxel or standard dose paclitaxel in combination with carboplatin in the elderly, the fractionated regimen produced higher RR, TTP and MST. Significant less neuropathy was encountered in the experimental arm<sup>[31-34]</sup> (Table 2).

## Platinum-based chemotherapy: Prospectives studies

Many prospective phase II trials evaluating third-generation cytotoxic agents with modified platinum-based schedules were performed in the last 20 years. Cisplatin and gemcitabine combination was tested in four phase II trials reaching an ORR around 40% and a MST of 10 mo<sup>[35-38]</sup>. At least three phase II trials tested cisplatin/vinorelbine schedule with similar ORR and MST<sup>[39-41]</sup>. Both combinations demonstrated to be safe. Better results in terms of ORR and MST were demonstrated by Ohe *et al*<sup>[42]</sup> in patients aged ≥ 75 years by adding docetaxel to weekly cisplatin<sup>[42,43]</sup>.

In 2007 Gridelli *et al*<sup>[44]</sup> tested in the MILES 2P the feasibility of cisplatin with gemcitabine or vinorelbine in elderly patients. Both combinations were feasible and active with the former combination being the preferred one for a direct comparison with standard single-agent



**Table 2 Retrospective data analyses of elderly patients enrolled in phase III trials with cisplatin- or carboplatin-based chemotherapy**

Ref.	Treatment	Age (yr)	No. of patients	RR	MST (mo)	P value
Nguyen <i>et al</i> <sup>[27]</sup>	CDDP + GEM	≥ 70	53	15%	7.7	NS
		< 70	207	29%	9.4	
Kelly <i>et al</i> <sup>[28]</sup>	CBDCA + TAX	≥ 70	117	NR	6.9	0.06
	CDDP + VNR	< 70	491	NR	8.6	
Langer <i>et al</i> <sup>[26]</sup>	CDDP + VP-16	≥ 70	86	23.3%	8.5	NS
	CDDP + TAX	< 70	488	21.5%	9.1	
Rocha Lima <i>et al</i> <sup>[32]</sup>	CDDP + VBL	≥ 70	31	16%	5.7	NS
		< 70	222	31%	8.0	
Hensing <i>et al</i> <sup>[33]</sup>	CBDCA + TAX	≥ 70	67	27%	7.1	NS
		< 70	163	20%	7.8	
Belani <i>et al</i> <sup>[30]</sup>	CDDP + TXT	≥ 65	149	NR	12.6	NS
		All ages	408	32%	11.3	
	CDDP + VNR	≥ 65	134	NR	9.9	NS
		All ages	404	25%	10.1	
	CBDCA + TXT	≥ 65	118	NR	9.0	NS
		All ages	406	24%	9.4	
Belani <i>et al</i> <sup>[30]</sup>	CBDCA + TAXw	≥ 70	70	25.7%	9.2	NR
		< 70	147	28.6%	9.6	
	CBDCA + TAX	≥ 70	63	19%	7.7	NR
		< 70	151	19.2%	11.4	
Lilenbaum <i>et al</i> <sup>[29]</sup>	CBDCA + TAX	≥ 70	77	36%	8.0	NS
		< 70	207	30%	8.5	

CDDP: Cisplatin; CBDCA: Carboplatin; TAX: Paclitaxel; TXT: Docetaxel; VNR: Vinorelbine; GEM: Gemcitabine; VBL: Vinblastine; VP-16: Etoposide; RR: Response rate; MST: Median survival time; S: Survival; NR: Not reported; NS: Not significant.

**Table 3 Phase II trials of cisplatin-based chemotherapy with third-generation agents and modified schedules or attenuated doses of cisplatin**

Ref.	Regimen	CDDP dose	Age (yr)	No. of patients	RR	MST (mo)
<sup>1</sup> Mattioli <i>et al</i> <sup>[39]</sup>	CDDP + VNR	25 mg/m <sup>2</sup> , weekly	> 65	36	36%	11
Pereira <i>et al</i> <sup>[40]</sup>	CDDP + VNR	60-90 mg/m <sup>2</sup>	> 70	44	50%	7.5
Buffoni <i>et al</i> <sup>[41]</sup>	CDDP + VNR	30 mg/m <sup>2</sup> , day 1 and 8	≥ 70	30	33%	7.4
Lippe <i>et al</i> <sup>[35]</sup>	CDDP + GEM	35 mg/m <sup>2</sup> , weekly	≥ 65	29	48%	10
Berardi <i>et al</i> <sup>[36]</sup>	CDDP + GEM	35 mg/m <sup>2</sup> , weekly	≥ 70	48	31.8%	9
Feliu <i>et al</i> <sup>[37]</sup>	CDDP + GEM	50 mg/m <sup>2</sup>	≥ 70	46	35%	10.2
Moscetti <i>et al</i> <sup>[38]</sup>	CDDP + GEM	75 mg/m <sup>2</sup> , day 2	≥ 65	46	45.6%	15
Ohe <i>et al</i> <sup>[42]</sup>	CDDP + TXT	25 mg/m <sup>2</sup> , weekly	≥ 75	33	52%	15.8

<sup>1</sup>Including 3 unfit patients; CDDP: Cisplatin; VNR: Vinorelbine; GEM: Gemcitabine; TXT: Docetaxel; RR: Response rate; MST: Median survival time; S: Survival.

chemotherapy in this setting (Table 3).

Carboplatin plus vinorelbine combination was tested in two phase II studies without any clinical benefit compared to standard treatment<sup>[45,46]</sup>. More favourable results were reported for the combination of low-dose carboplatin (AUC 4) and gemcitabine accompanied by acceptable toxicity<sup>[47]</sup>.

Modified carboplatin/paclitaxel schedules reached in many trials 70% RR and 14 mo MST<sup>[10,48-53]</sup>.

Recently IFCT-0501 confronted attenuated carboplatin-paclitaxel schedule vs standard single agent monotherapy. Combination and standard treatment showed respectively 10.3 and 6.2 mo in terms of OS. Regarding toxicity, grade 3-4 neutropenia and thrombocytopenia were 54.3% and 6.3% for doublet respect to 14.3% and 1% for single agent. Considering non-hematological toxicity, neuropathy resulted significantly more frequent in the doublet arm

vs single agent arm. Considering QoL, role functioning and fatigue were worse in the doublet group than in single agent. Authors concluded that despite increased toxic effects for doublet, this should be considered as standard treatment in first line setting<sup>[54]</sup>.

For the future better CDDP-based schedule in terms of activity and tolerability should be tested by direct comparison and considering emerging strong data about histology (Table 4).

## TARGETED THERAPIES

### Bevacizumab

The SAIL study assessed the addition of bevacizumab to standard chemotherapy in terms of safety and efficacy in the first-line. When evaluating incidence of anti-VEGFR related side-effects in a planned analysis including elderly patients no difference was

**Table 4 Prospective trials of first line platinum-based chemotherapy in elderly patients affected by advanced non-small-cell lung cancer**

Ref.	Regimen	Phase	Age (yr)	No. of patients	Efficacy
Gridelli <i>et al</i> <sup>[44]</sup>	CDDP + GEM	I / II	≥ 70	159	OS 43.6 wk
					PFS 25.3 wk
					RR 43.5%
	CDDP + VNR				OS 33.1 wk
Abe <i>et al</i> <sup>[43]</sup>	CDDP + DOC	III	> 70	221	PFS 21.1 wk
	<i>vs</i>				RR 36.1%
	DOC				OS 13.3 wk
					OS 17.3 wk
Biesma <i>et al</i> <sup>[53]</sup>	CARBO + GEM	III	≥ 70	181	OS 8.6 mo
	<i>vs</i>				RR 27%
	CARBO + PAC				OS 6.9 mo
					RR 19%
Quoix <i>et al</i> <sup>[54]</sup>	GEM or VNR	III	≥ 70	451	OS 6.2 mo
	<i>vs</i>				RR 10.9%
	CARBO + PAC				OS 10.3 mo
					RR 29.5%

CDDP: Cisplatin; VNR: Vinorelbine; GEM: Gemcitabine; CARBO: Carboplatin; RR: Response rate; OS: Overall survival.

encountered. OS (14.6 mo in both groups), TTP (8.2 mo vs 7.6 mo), RR (49.3% vs 52.4%) and disease control rate (89.3% vs 88.4%) were similar in both arms<sup>[55]</sup>.

The ARIES trial evaluated bevacizumab in clinical practice. Six hundred and fifty enrolled patients were older than 70 and experienced similar adverse events than total population except for arterial thromboembolic events (slightly increased in patients ≥ 70 years old). Median PFS and OS were similar in both subgroups<sup>[56]</sup>.

### EGFR tyrosine kinase inhibitors

**Gefitinib/erlotinib:** Gefitinib and erlotinib are reversible inhibitor of EGFR that competitively inhibits the binding of ATP.

Antitumor activity of single-agent gefitinib in patients unselected for EGFR status has been tested in many trials. When gefitinib was dispensed in the second line setting in an unselected populations with NSCLC obtained 5.3 mo of MST<sup>[57]</sup>.

In the subgroup of elderly patients gefitinib maintained its activity and good tolerance with no grade 3 or 4 side effects experienced<sup>[58]</sup>. Cavina *et al*<sup>[59]</sup> reported encouraging efficacy data with only 10% of grade 3 skin toxicity and 3% of diarrhoea. Gridelli *et al*<sup>[60]</sup> reported in the same setting of patients similar MST and favourable safety profile. Cappuzzo *et al*<sup>[61]</sup> observed reported 5 mo MST and mild side effects. Hotta *et al*<sup>[62]</sup> studied gefitinib on patients aged ≥ 75 years: RR 17%; SD 43%; MST 7.6 mo. Grade 3-4 toxicity was encountered in 9% of patients (Table 5).

Gefitinib addition to chemotherapy has been tested. Stinchcombe *et al*<sup>[63]</sup> combined weekly docetaxel plus daily oral gefitinib: RR 31%, MST 6.5

mo, 1-year survival 27%. The schedule resulted in excessive toxicity for elderly patients<sup>[63]</sup>. Bepler *et al*<sup>[64]</sup> added daily gefitinib to three-weekly docetaxel: RR 38%, SD 24%, MST 12.4 mo, and 1-year survival of 60%. Better tolerance was reported even if adverse effects required hospitalization in 6 patients<sup>[64]</sup>. A phase II trial evaluated gefitinib with vinorelbine or gemcitabine. Vinorelbine plus gefitinib produced 72% of grade 3-4 neutropenia and 3 treatment-related deaths while the association with gemcitabine reported a lower activity (RR 5.7%, SD 14%, MST 9.1 mo) but a better safety profile (grade 3-4 neutropenia 11.4%; thrombocytopenia 8.6%, asthenia and diarrhoea 5.7%)<sup>[65,66]</sup> (Table 6).

At least three single-arm trials tested the role of gefitinib in patients with EGFR mutation positive tumors. A phase II study conducted with erlotinib in patients older than 70 years in I line setting, showing encouraging activity (RR of 10.9%, SD of 54.5%) and MST (10.5 mo). Adverse events were mild. EGFR mutations have been detected in 3 out of 5 responsive patients to erlotinib treatment<sup>[67]</sup>. Erlotinib improved also QoL and many disease related symptoms<sup>[68]</sup> (Table 7).

The EURTAC trial population with its median age of 65 years old represent an older population respect to common trial population. This trial showed that erlotinib yielded a longer progression-free survival than chemotherapy<sup>[69]</sup>.

An age-unspecified trial in patients not selected for mutation status, the BR21, showed that in a second or third line setting, erlotinib improves survival but at a cost to older patients. Although older and younger patients achieved comparable PFS, OS and RRs, older patients suffered worse toxicity due to rash, fatigue and dehydration<sup>[70]</sup>.

Erlotinib performed better than vinorelbine in a subgroup of EGFR mutation positive elderly patients as shown in a prospective phase II trial while failed to gain advantage when added to gemcitabine or compared to it in molecularly not selected elderly patients<sup>[71,72]</sup>.

## SECOND-LINE CHEMOTHERAPY

Retrospective subgroup analysis on elderly patients from phase III trials testing pemetrexed vs docetaxel obtained: TTP 4.6 mo vs 2.9 mo, MST 9.5 mo vs 7.7 mo, 12-mo survival was 20.4% vs 23.1%, 24-mo survival 6.1% vs 10.6%, respectively. Neutropenia, febrile neutropenia and anemia were more consistent in docetaxel arm<sup>[73]</sup>. Second-line cytotoxic therapy appeared feasible for good performance status elderly patients.

Pemetrexed produced a more favourable toxicity profile compared to docetaxel. In a phase II trial a modified schedule of docetaxel (37.5 mg/m<sup>2</sup> on days 1 and 8 every three weeks) reported encouraging activity and acceptable toxicity profile<sup>[74]</sup>.

**Table 5 Retrospective analyses of gefitinib in the treatment of unselected elderly patients with advanced non-small-cell lung cancer**

Ref.	Previous chemotherapy	Age (yr)	No. of patients	RR (%)	SD (%)	MST (mo)	Toxicity G $\geq$ 3
Copin <i>et al</i> <sup>[58]</sup>	Yes (61%) No (39%)	$\geq$ 70	61	2 (3)	16 (26)	NR	None
Cavina <i>et al</i> <sup>[59]</sup>	Yes (64.5%) No (35.5%)	$\geq$ 70	31	0 (0)	18 (58)	3.0	G3 skin 10% G3 diarrhoea 3%
Gridelli <i>et al</i> <sup>[60]</sup>	Yes (94.5%) No (5.5%)	$\geq$ 70	18	0 (0)	2 (11)	4.4	None
Cappuzzo <i>et al</i> <sup>[61]</sup>	Yes (100%)	$\geq$ 70	40	2 (5)	18 (45)	5.0	G4 diarrhoea 2.5%
Hotta <i>et al</i> <sup>[62]</sup>	Yes (57%) No (43%)	$\geq$ 75	92	16 (17)	40 (43)	7.6	G3-4 toxicity 9%

RR: Response rate; SD: Stable disease; MST: Median survival time; G: Grade; NR: Not reported.

**Table 6 Studies with gefitinib (250 mg/d) plus chemotherapy in the treatment of elderly patients (age  $\geq$  70 years) with advanced non-small-cell lung cancer**

Ref.	Treatment	Study phase	No. of patients	RR (%)	SD (%)	MST (mo)	Toxicity G $\geq$ 3
Stinchcombe <i>et al</i> <sup>[63]</sup>	TXT 30-36 mg/m <sup>2</sup> , days 1, 8, 15, Q4W	I / II	26	8 (31)	-	6.5	G3-5 toxicity 42%
Beppler <i>et al</i> <sup>[64]</sup>	TXT 75 mg/m <sup>2</sup> , day 1, Q3W	II	21	8 (38)	5 (24)	12.4	G3-4 toxicity 28.5%
Scagliotti <i>et al</i> <sup>[65]</sup>	GEM 1200 mg/m <sup>2</sup> , days 1, 8, Q3W	II	35	2 (5.7)	14 (40)	9.1	G3-4 neutropenia 11.4%
	vs VNR 30 mg/m <sup>2</sup> , days 1, 8, Q3W	Random	25	0 (0)	11 (44)	12.2	G3-4 neutropenia 72% 3 toxic deaths

RR: Response rate; SD: Stable disease; MST: Median survival time; G: Grade; TXT: Docetaxel; GEM: Gemcitabine; VNR: Vinorelbine; Q4W: Every 4 wk; Q3W: Every 3 wk; Random: Randomised.

**Table 7 Phase II study of single-agent erlotinib in the treatment of advanced non-small-cell lung cancer elderly patients**

Ref.	Previous chemotherapy	Age (yr)	No. of patients	RR (%)	SD (%)	MST (mo)	Toxicity G $\geq$ 3
Jackman <i>et al</i> <sup>[67]</sup>	No (100%)	$\geq$ 70	58	6 (10.9)	30 (54.5)	10.5	G $\geq$ 3 toxicity 30%

RR: Response rate; SD: Stable disease; MST: Median survival time; G: Grade.

Second-line cytotoxic therapy appeared feasible for good performance status elderly patients.

A recent retrospective review of elderly patients receiving a second line therapy analyzing 293 young patients (age < 70) and 168 patients (> 70) treated with second-line treatment (both chemotherapy and EGFR TKIs) showed no differences in both efficacy and toxicity between the two age group<sup>[75]</sup>.

## GERIATRIC ASSESSMENT

As elderly patients represent a very heterogeneous group, their functional status cannot be established only basing on chronological parameters. Comprehensive Geriatric Assessment (CGA) is a multidisciplinary and multidimensional approach including many items: co-existing diseases, socioeconomic status, nutritional status, medicine intake, and the presence of geriatric syndromes.

Many works demonstrated to add very useful informations regarding functional assessment of elderly

patients permitting better evaluation in terms of prognostic aspects<sup>[76]</sup>.

A meta-analysis based on 28 trials demonstrated that CGA, when applied together with geriatric interventions is capable to reduce early re-hospitalization and mortality. Nowadays no phase III randomized trials are available.

More recent studies attributed to many CGA issues the power to predict the risk of chemotherapy toxicity<sup>[77]</sup>.

Puts *et al*<sup>[78]</sup> reported data on CGA in cancer patients collected from 73 trials. Six reported a significant association with chemotherapy toxicity, 8 demonstrated association with mortality and other 2 a change of treatment indications after CGA assessment. CGA is recommended by the International Society of Geriatric Oncology (SIOG) and the EORTC<sup>[78]</sup>.

## CONCLUSION

NSCLC remains the major cause of cancer-related

deaths.

Altered organ functions and higher incidence of co-morbidities usually affect treatment decisions. Platinum-based treatment while is a mainstay for advanced NSCLC in younger patients is still considered questionable for elderly patients due to higher risk of toxicity. However many retrospective subset analyses demonstrated only minimal or none differences between elderly and younger counterpart patients.

Dedicated trials for elderly population are anyway needed. Research must be empowered looking for new tools and items capable of better define "biological" and "chronological" aspects of ageing. At the same time several treatment options should still be evaluated as for example: doublets with and without platinum, maintenance strategies and biologic agents<sup>[73]</sup>.

A third-generation agent given alone is at the time the recommended option for elderly advanced NSCLC patients<sup>[79-81]</sup>.

The choice for the best agent should consider together expected toxicities, pharmacokinetics aspects, liver-kidney function and co-existing illnesses.

Doublets employing platinum could be consider a valid indication for fit elderly patients with normal organ function. Each patient should receive a functional assessment at baseline in order to better define the therapeutic options.

Considering continuous elucidation of mechanisms that contribute to the malignant phenotype and subsequent molecular targets for anticancer therapy several biologic agents have been introduced in the treatment of NSCLC and many are still under investigation.

Trials performed with new targeted agents in molecularly selected younger population evidenced very good toxicity profile. So new biologic drugs are better candidates than chemotherapy to be tested in elderly patients. Gefitinib and erlotinib have already proven to be effective in chemotherapy-refractory NSCLC patients. Their mild toxicity profile, experienced in elderly patients with advanced disease, makes them some of the best candidates to test prospectively as single-agent first-line treatment in molecularly selected elderly population, as an alternative to chemotherapy.

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## Effectiveness of adaptive servo-ventilation

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### Abstract

Adaptive servo-ventilation (ASV) has been developed as a specific treatment for sleep-disordered breathing, in particular Cheyne-Stokes respiration with central sleep apnea (CSA). Heart failure patients often have sleep-disordered breathing, which consists of either obstructive sleep apnea (OSA) or CSA. Other medical conditions, such as stroke, acromegaly, renal failure, and opioid use may be associated with CSA. Continuous positive airway pressure (CPAP) therapy is widely used for patients with OSA, but some of these patients develop CSA on CPAP, which is called treatment-emergent CSA. CPAP can be useful as a treatment for these various forms of CSA, but it is insufficient to eliminate respiratory events in approximately half of patients with CSA. As compared to CPAP, ASV may be a better option to treat CSA, with sufficient alleviation of respiratory events as well as improvement of cardiac function in heart failure patients. In patients without heart failure, ASV can also alleviate CSA and relieve their symptom. Recently, ASV has been widely used for patients with various forms of CSA. ASV may be also used in the setting without CSA, but it should be assessed more carefully. Clinicians should have a better understanding of the indications for ASV in each setting.

**Key words:** Adaptive servo-ventilation; Central sleep apnea; Cheyne-Stokes respiration; Continuous positive airway pressure; Heart failure; Positive airway pressure; Sleep disordered breathing

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**Core tip:** Adaptive servo-ventilation (ASV) is a form of positive airway pressure device that is used to treat Cheyne-Stokes respiration and central sleep apnea with various etiologies. Accumulating evidence supports the use of ASV in patients with heart failure. However, some existing data suggest that ASV should be used in other situations. In this review, we highlight the clinical applications and effectiveness of ASV and describe future perspectives regarding its applications.

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## INTRODUCTION

Adaptive servo-ventilation (ASV) is one form of non-invasive positive airway pressure (PAP) therapy and was originally developed to treat sleep disordered breathing (SDB), or more precisely Cheyne-Stokes respiration with central sleep apnea (CSR-CSA), which is typically observed in patients with heart failure (HF)<sup>[1]</sup>. Teschler *et al.*<sup>[2]</sup> first mentioned ASV in 2001 and reported that it was superior to other treatment options including supplemental oxygen, continuous PAP (CPAP) and bi-level PAP in the suppression of CSR-CSA in patients with HF. Furthermore, several studies have shown that treatment of CSR-CSA with ASV improved underlying cardiac dysfunction in patients with HF<sup>[3,4]</sup>. ASV can also be used to treat various forms of central sleep apnea (CSA), such as idiopathic CSA, treatment-emergent CSA, opioid-induced CSA and CSA observed in patients with other medical conditions<sup>[4-7]</sup>.

CSA often coexists with obstructive sleep apnea (OSA), another form of SDB, especially in patients with HF. Because ASV provides expiratory positive airway pressure (EPAP), which can maintain an open upper airway, in addition to inspiratory pressure support (PS), it can alleviate coexisting OSA and CSA<sup>[8]</sup>.

More recently, ASV has been applied in various clinical settings beyond just SDB treatment. Some Japanese groups have suggested the use of ASV for the treatment of pulmonary congestion and improvement of hemodynamics in patients with HF regardless of the presence or absence of SDB<sup>[9-13]</sup>. Another group reported the efficacy of ASV use combined with deep sedation during the pulmonary vein isolation procedure for atrial fibrillation. Thus, ASV is widely used in the field of cardiology and respiratory medicine.

In this review, we describe the fundamental mechanisms and effects of ASV on respiratory and cardiovascular systems, the utility of ASV in various clinical settings, and future perspectives.

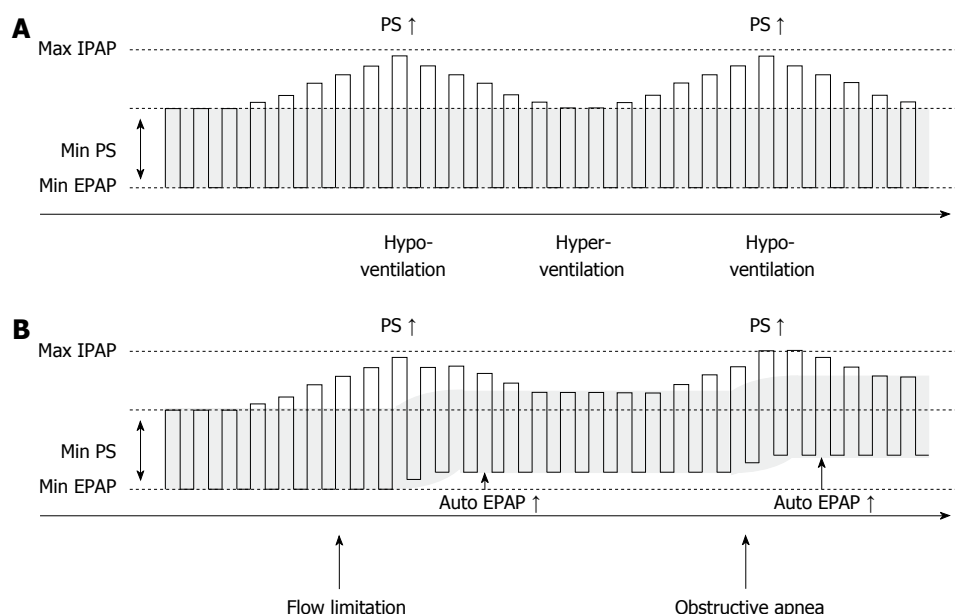
## FUNDAMENTALS OF ASV

ASV can be considered as an advanced mode of bi-level PAP. ASV devices automatically provide altering PS for each inspiration, ranging from a pre-set minimum to a pre-set maximum level to maintain the moving target ventilation determined by the current breathing of the patient, in addition to back-up ventilation with automatically determined respiratory rates (Figure 1A). ASV devices also provide an EPAP that is sufficient to maintain an open upper airway. More recent ASV devices can automatically alter EPAP levels based on algorithms that aim to alleviate snoring, flow limitation, and obstructive apneas and hypopneas (Figure 1B).

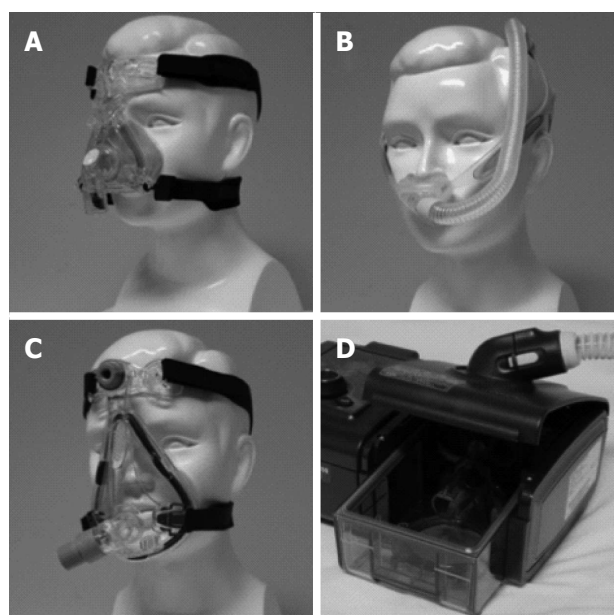
Three ASV devices are manufactured by ResMed Inc., Philips-Respironics Inc. and Weinmann Geräte für Medizin GmbH+Co. KG (Table 1). In the latest version of all of the devices, EPAP automatically varies to eliminate obstructive events. PS is also dynamically adjusted breath-to-breath as necessary to ensure that the actual ventilation matches the target value in addition to the auto-titration of EPAP to maintain airway patency. The main differences between devices are the triggers to determine the target level. ResMed and Weinmann devices provide volume-triggered ASV. The ResMed device establishes a target minute-ventilation that is 90% of the recent average minute volume from a 3-min collection period and attempts to maintain ventilation at the target level. The Weinmann device has no fixed target level of minute volume, but it calculates the relative minute volume of the current breath and attempts to predict future values of minute volume based on a moving window that is focused by 50% on the last 2 min and by 50% on the previous time to stabilize the relative minute volume. The Philips-Respironics device is a flow-triggered ASV that monitors the peak inspiratory flow of the patient over a recent moving 4-min window, calculating an average peak flow at every point within this window to establish a target peak flow. It compares these data to an internal target and maintains a target peak inspiratory flow. There are some minor differences in other features across these three devices.

Other than ASV devices themselves, the important equipment necessary for ASV therapy is patient interfaces include nasal masks, nasal pillows, and oro-nasal (full-face) masks that cover the nose and mouth, and the optional heated humidifier system (Figure 2). The choice of mask rather than the choice of device is the most important issue for patient comfort and tolerance to ASV therapy. Poorly fitted masks decrease the efficacy and adherence to ASV therapy. In addition to the mask itself, headgear or straps are used as a harness. Headgear that are too tight may worsen the air leak and interfere with patient comfort and adherence. The optional heated humidifier can be easily connected to the ASV device and helps to minimize the effects of nasal dryness.





**Figure 1** Adaptive servo-ventilation can be considered as an advanced mode of bi-level positive airway pressure. A: In response to central events, adaptive servo-ventilation increases pressure support during hypoventilation and decreases pressure support during hyperventilation, with the goal of stabilizing ventilation; B: In response to obstructive events (apneas, airflow limitation, and snoring), adaptive servo-ventilation increases expiratory positive airway pressure, with the goal of suppressing obstruction.



**Figure 2** Several types of masks are available as an adaptive servo-ventilation interface for patients to discover a more comfortable fit: nasal masks (A), a pillow mask (B), an oro-nasal mask (C), and an optional heated humidifier connected to an adaptive servo-ventilation device (D).

## EFFECTS OF ASV ON RESPIRATORY AND CARDIOVASCULAR SYSTEMS

### Effects on the respiratory system

ASV devices, which provide EPAP (more recently auto EPAP), auto-adjusted PS and servo-ventilation, have several effects on the respiratory system.

EPAP prevents alveoli from collapsing in the end-expiratory phase and improves gas exchange and

oxygenation through alveolar units, which is a common effect across PAP devices<sup>[14]</sup>. EPAP also prevents upper airway obstruction in patients with OSA<sup>[15]</sup>, consequently decreasing respiratory events and arousals and improving sleep architecture. Auto-adjusted PS, which is provided based on the target minute volume or target peak flow, can reduce respiratory muscle loading of breathing<sup>[16]</sup> and alleviate CSR-CSA and other forms of CSA. Each ASV device has different algorithms, but all of them provide auto-adjusted PS during inspiration and servo-ventilation, with the goal of stable ventilation. Because breathing instability leads to enhanced sympathetic nervous system activity (SNA)<sup>[17,18]</sup>, ASV may reduce SNA by alleviating CSR-CSA and other forms of CSA and maintaining stable ventilation<sup>[9]</sup>. Such sympathoinhibitory contributions of ASV may provide beneficial effects on hemodynamics, which may be unique to ASV<sup>[19]</sup>.

### Effects on the cardiovascular system

ASV devices have several direct effects on the cardiovascular system. Some small studies in patients with HF suggest acute effects of the short-duration use of ASV, whereas wakefulness will help us understand the hemodynamic effects of ASV. After 30 min of ASV, blood pressure and heart rate were significantly decreased, whereas stroke volume and cardiac output were significantly increased<sup>[19]</sup>. These findings indicate that in patients with HF, ASV can reduce systemic vascular resistance and consequently reduce left ventricular (LV) afterload, potentially by maintaining a consistent ventilation and providing a related reduction of SNA. ASV also reduces right ventricular (RV) preload, thus diminishing the systemic venous

**Table 1** An overview of the features of the three adaptive servo-ventilation devices

Manufacturer	ResMed	Philips-Respironics	Weinmann
Current version	S9 VPAP Adapt, AutoSet CS-A	BiPAP autoSV Advanced System One	Prisma LINE CR
EPAP (default)	4-15 cmH <sub>2</sub> O auto	4-15 cmH <sub>2</sub> O auto	4-20 cmH <sub>2</sub> O auto
(min EPAP)	4-15 cmH <sub>2</sub> O	4-25 cmH <sub>2</sub> O	4-20 cmH <sub>2</sub> O
(max EPAP)	min EPAP-15 cmH <sub>2</sub> O	min EPAP-25 cmH <sub>2</sub> O	min EPAP-20 cmH <sub>2</sub> O
IPAP	Max 30 cmH <sub>2</sub> O	Max 25 cmH <sub>2</sub> O	Max 30 cmH <sub>2</sub> O
PS	0 to 30-prevailing EPAP	0 to 25-prevailing EPAP	0 to 30-prevailing EPAP
Calculation	The recent 3-min average minute volume	The recent 4-min average peak flow	The average of the minute volume in the recent 2-min and an earlier interval
Target for PS	90% of the average minute volume	90%-95% of the average peak flow (without SDB) 60% percentile of peak flow (with SDB)	Relative minute volume of the current breath to the average
	Approximate the minute volume to the target	Approximate the peak inspiratory flow to the target	Stabilize the relative minute volume
Backup rate	Auto (cannot be established manually)	Auto (default) or fixed rate	Auto (default) or fixed rate

EPAP: Expiratory positive airway pressure; IPAP: Inspiratory positive airway pressure; PS: Pressure support; SDB: Sleep disordered breathing.

return by increasing the intrathoracic pressure. These cardiac unloading effects are favorable in HF patients. However, in subjects without HF who are usually dependent on preload<sup>[20]</sup>, the cardiac output may decrease in response to ASV.

Another favorable effect of ASV on the cardiovascular system is the improvement of SDB. Both OSA and CSR-CSA, or other forms of CSA, may lead to a deterioration of cardiac function. OSA exaggerates the negative intrathoracic pressure during inspiratory efforts against upper airway obstruction<sup>[21]</sup>. Therefore, the LV transmural pressure increases (*i.e.*, intraventricular minus intrathoracic pressure), leading to an elevated LV afterload. The sympathetic nervous system is activated in patients with OSA as well as CSA<sup>[22,23]</sup>, leading to a surge in BP and HR. An absence of breathing eliminates the sympathoinhibitory reflex from pulmonary stretch receptors, enhancing SNA. Intermittent hypoxia and arousals also lead to cyclical surges in SNA. Attenuation of SDB by ASV will alleviate these adverse effects on hemodynamics. However, the maintenance of a consistent respiration by auto PS and servo-ventilation, even in cases without SDB, may play a role in the attenuation of SNA.

## UTILITY OF ASV IN VARIOUS CLINICAL SETTINGS

### SDB in heart failure

As mentioned previously, ASV was originally developed to treat CSR-CSA in patients with HF. CSR-CSA is characterized as a cyclic pattern of crescendo-decrescendo respiration superimposed by central apnea or hypopnea.

HF patients with an increased left ventricular filling pressure are likely to present CSR-CSA<sup>[22]</sup>. An elevated pulmonary capillary wedge pressure (PCWP) results in pulmonary congestion, stimulating pulmonary vagal irritant receptors and leading to hyperventilation in association with an increased chemosensitivity<sup>[24]</sup>.

This effect is observed in patients with HF and is most likely due to an increase in SNA<sup>[25]</sup>. When PaCO<sub>2</sub> falls below the apneic threshold due to such hyperventilation because of an increase in the apneic threshold during the transition from wakefulness to sleep<sup>[24]</sup>, central apnea ensues. Apnea persists until PaCO<sub>2</sub> rises above the apneic threshold; subsequently, ventilation resumes, ventilatory overshoot occurs, and PaCO<sub>2</sub> decreases below the apneic threshold in association with arousal during the ventilatory phase and increased chemosensitivity. The length of the ventilatory phase following central apneas is directly proportional to the lung-to-chemoreceptor circulation time<sup>[26]</sup> and inversely proportional to cardiac output<sup>[27]</sup>, reflecting a delayed transmission of change in arterial blood gas tension from the lungs to the chemoreceptors in association with impaired cardiac output in HF patients. This phenomenon could also contribute to the pathogenesis of the Cheyne-Stokes respiration (CSR) pattern by facilitating a ventilatory overshoot and undershoot.

As described above, CSR-CSA occurs secondary to HF, but CSR-CSA itself also contributes to the deterioration of cardiac function. HF patients with CSA exhibit an increased SNA during sleep, and this effect persists during wakefulness<sup>[23]</sup>. In HF, patients with CSR-CSA are associated with a worse prognosis. Thus, CSR-CSA could be a therapeutic target in patients with HF. However, treatment for CSR-CSA in patients with HF should be considered after optimization of HF therapy because CSR-CSA results from HF and pulmonary congestion. Because HF patients with CSR-CSA have associated pulmonary congestion and increased LV filling pressures, CPAP was initially applied to improve pulmonary congestion and decrease the LV filling pressure *via* cardiac unloading<sup>[28]</sup>. However, studies regarding the effects of CPAP on the suppression of CSR-CSA in HF patients produced inconsistent results: some of them alleviated CSR-CSA significantly, but others did not<sup>[29]</sup>. Nevertheless, if CPAP was titrated gradually, then CSR-CSA was alleviated in most of the

**Table 2** Clinical trials assessing the effects of adaptive-servo ventilation on cardiac function in heart failure patients with central sleep apnea

Ref.	Study design	n	Duration (mo)	Baseline		Device usage (h)	Changes	
				AHI	EF		AHI	EF
Pepperell <i>et al</i> <sup>[36]</sup>	RCT							
	Subtherapeutic	15	1	17.7	35.7	3.9	-3	0.5
	Therapeutic	15		21.9	36.5	5.0	-16.5	1.8
Philippe <i>et al</i> <sup>[3]</sup>	RCT							
	CPAP	13	6	40.5	30.0	4.2	-20	-2
	ASV	12		47.0	29.0	5.8	-45	7
Fietze <i>et al</i> <sup>[37]</sup>	RCT							
	Bi-level PAP	15	1.5	34.9	25.5	4.8 <sup>1</sup>	-18.5	5.6
	ASV	15		31.7	24.6		-20.5	1.9
<sup>1</sup> Kasai <i>et al</i> <sup>[4]</sup>	RCT							
	CPAP-mode	11	3	23.0 <sup>2</sup>	33.0	3.3	0.1	-1
	ASV-mode	12		25.0 <sup>2</sup>	32.0	4.7	-23	5.8

<sup>1</sup>Patients with residual AHI  $\geq 15$  on CPAP were included; <sup>2</sup>AHIs on CPAP were described. AHI: Apnea-hypopnea index; ASV: Adaptive-servo ventilation; Bi-level PAP: Bi-level positive airway pressure; CPAP: Continuous positive airway pressure; EF: Ejection fraction; RCT: Randomized controlled trial.

cases<sup>[30]</sup> accompanied by an increase in PaCO<sub>2</sub><sup>[31]</sup>, a reduction in SNA<sup>[32]</sup>, and improvements in respiratory muscle function<sup>[33]</sup> and LV systolic function<sup>[34]</sup>.

However, The Canadian Continuous Positive Airway Pressure for Treatment of Central Sleep Apnea in Heart Failure (CANPAP) trial<sup>[34]</sup>, which included 258 patients with HF and CSA to assess the long-term survival benefit of CPAP treatment for CSR-CSA, reported that CPAP did not improve survival. A post-hoc analysis of the CANPAP trial<sup>[35]</sup> revealed that patients with CSR-CSA that was sufficiently suppressed [*i.e.*, apnea-hypopnea index (AHI)  $< 15$ ] by CPAP at 3 mo had a significantly better survival, which indicated that treatment that can suppress CSR-CSA more sufficiently and consistently might improve survival in HF patients with CSR-CSA. Because ASV has been recognized as the most effective technique to suppress CSR-CSA, even in patients with an AHI  $\geq 15$  on CPAP, the effects of ASV on cardiac function during the treatment of CSR-CSA were assessed in several short-term randomized controlled trials (RCTs). Small RCTs investigating the effects of ASV on cardiac function in HF patients with CSR-CSA are summarized in Table 2. Pepperell *et al*<sup>[36]</sup> reported that ASV decreased AHI, improved excessive daytime sleepiness and lowered the level of brain natriuretic peptide (BNP) and urinary metadrenaline excretion compared with subtherapeutic use of ASV. However, there was no difference in improvement of cardiac function.

Philippe *et al*<sup>[3]</sup> compared ASV with CPAP and concluded that ASV provided a greater benefit in attenuating CSR-CSA and improving cardiac function. Although volume-targeted ASV devices were used in these two studies, Kasai *et al*<sup>[4]</sup> investigated the effects of flow-targeted ASV devices on cardiac function by comparing two settings for the same ASV: ASV-mode and CPAP-mode. This study included only patients with CSR-CSA that was not sufficiently suppressed (*i.e.*, AHI  $\geq 15$  on CPAP) despite  $\geq 3$  mo of CPAP. In

these populations, ASV-mode was superior to CPAP-mode in reducing AHI and improving cardiac function. Bi-level PAP has also been reported to be effective in attenuating CSR-CSA. Fietze *et al*<sup>[37]</sup> compared the effects of ASV and Bi-level PAP using the standard spontaneous/timed (S/T) mode. They concluded that both PAPs could reduce AHI and increase LVEF. Between the two PAPs, AHI decreased more in the ASV group, whereas LVEF increased more in the Bi-level PAP group, although these differences were not significant. Based on these studies, ASV can attenuate CSR-CSA more than other PAPs in HF patients with CSR-CSA. ASV can also improve LVEF in HF patients with CSR-CSA after 3 to 6 mo use with good adherence, which indicates that the nightly usage is more than 4 h.

The effects of ASV treatment for CSR-CSA on the long-term prognosis of HF patients will be determined by two ongoing large-scale RCTs: Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure (Serve-HF)<sup>[38]</sup>; Effect of Adaptive Servo Ventilation (ASV) on Survival and Hospital Admissions in Heart Failure (ADVENT-HF)<sup>[39]</sup>.

The prevalence of OSA is also high in patients with HF, and coexisting OSA with CSR-CSA is common in patients with HF. Therefore, CPAP may not sufficiently alleviate SDB, particularly in patients with a greater proportion of CSR-CSA than OSA. However, ASV can suppress OSA by modifying the EPAP levels in addition to suppressing CSR-CSA. Thus, ASV, particularly more recent ASV devices equipped with auto-titrating EPAP, may be a therapeutic option for SDB without the need to distinguish between OSA and CSR-CSA. Several short-term RCTs have assessed the effects of ASV on cardiac function in HF patients with coexisting CSR-CSA and OSA (Table 3). Two studies comparing the effects of CPAP and ASV on cardiac function suggested different results. Kasai

**Table 3** Clinical trials assessing the effects of adaptive-servo ventilation on cardiac function in heart failure patients with central sleep apnea and coexisting obstructive sleep apnea

Ref.	Study design	n	Duration (mo)	Baseline		Device usage (h)	Changes	
				AHI	EF		AHI	EF
Kasai <i>et al</i> <sup>[40]</sup>	RCT							
	CPAP	15	3	38.6	36	4.4	-23.2	1.9
	f-ASV	16		36.3	35.7	5.25	-35.4	9.1
Randerath <i>et al</i> <sup>[41]</sup>	RCT							
	CPAP	34	12	41	43	4.3	-24.0	4.9
	f-ASV	36		47	47	5.2	-36.0	-1.9
Yoshihisa <i>et al</i> <sup>[42]</sup>	RCT							
	Control	18	6	36	54	-	-8.2	-2.0
	v-ASV	18		37	56.1	5.6	-30.2	5.1
Birner <i>et al</i> <sup>[43]</sup>	RCT							
	Control	35	3	43	29	-	0	3.0
	f-ASV	37		52	30	4.2	-41.0	1.0

AHI: Apnea-hypopnea index; ASV: Adaptive-servo ventilation; CPAP: Continuous positive airway pressure; EF: Ejection fraction; f-ASV: Flow-targeted ASV; v-ASV: Volume-targeted ASV; RCT: Randomized controlled trial.

*et al*<sup>[40]</sup> reported that ASV significantly reduced AHI more completely and significantly increased LVEF compared with CPAP. Randerath *et al*<sup>[41]</sup> reported that ASV reduced AHI and BNP levels, but there were no significant differences in exercise performance and cardiac functions. Another two studies<sup>[42,43]</sup> comparing an ASV group and a control group without ASV failed to show an improvement of LVEF, although ASV improved SDB in both studies. However, both studies demonstrated a significantly greater reduction of the BNP level in the ASV group, and a study by Yoshihisa *et al*<sup>[42]</sup> demonstrated significant improvements in diastolic function and event-free survival (against cardiac death and worsening HF). We should note that the studies by Randerath *et al*<sup>[41]</sup> and Yoshihisa *et al*<sup>[42]</sup> included HF patients with preserved LVEF, whereas the studies by Kasai *et al*<sup>[40]</sup> and Birner *et al*<sup>[43]</sup> included only HF patients with reduced LVEF (LVEF < 50%, < 40%). Moreover, residual AHI on ASV was higher than 10/h in the studies conducted by Randerath *et al*<sup>[41]</sup> and Birner *et al*<sup>[43]</sup>. Differences in the etiology of HF could have led to differences in LVEF improvement. The studies reported by Randerath *et al*<sup>[41]</sup> and Birner *et al*<sup>[43]</sup> contained a high proportion of ischemic heart disease, whereas those by Kasai *et al*<sup>[40]</sup> and by Yoshihisa *et al*<sup>[42]</sup> included only 26% and 28%, respectively. The long-term prognostic effects of SDB were greater in HF patients with ischemic heart disease<sup>[44]</sup>. However, greater short-term reductions in RV and LV volumes were observed in HF patients with idiopathic dilated cardiomyopathy compared with those with ischemic cardiomyopathy<sup>[45]</sup>. Based on the findings of these studies showing that ASV provides consistent effectiveness to reduce AHI and maintain good compliance in HF patients with coexisting OSA and CSR-CSA, ASV should be recommended to patients with symptoms that are related to their SDB and be considered to improve cardiac functions if the SDB can be alleviated with ASV (*i.e.*, AHI on ASV < 10/h), as well as in some select cases (possibly HF

patients with non-ischemic etiologies). Kasai *et al*<sup>[40]</sup> also showed a significant correlation between the nightly usage of devices (*i.e.*, ASV and CPAP) and the increase in LVEF; the longer the nightly usage, the greater was the increase in LVEF. This finding indicates that maintenance of better adherence to devices is more important for improvement of cardiac function than the type of device that is used. We should note that OSA can be alleviated by CPAP and that CPAP can alleviate CSR-CSA in approximately 50% of the patients with CSR-CSA<sup>[34]</sup>. In addition, considering the difference in cost between CPAP and ASV, CPAP should be attempted as a first-line therapy. The effects of ASV on both types of SDB will be determined in an ongoing large-scale RCT that includes HF patients with predominant OSA in addition to those with CSR-CSA (*i.e.*, ADVENT-HF)<sup>[39]</sup>.

Although most of the previous data regarding SDB involve HF patients in the chronic phase, it has been recently reported that hospitalized patients with HF following acute decompensated HF (ADHF) also frequently have SDB and that the presence of either severe OSA or moderate-to-severe CSR-CSA identified during hospitalization following ADHF is a predictor of readmission and mortality<sup>[46]</sup>. Thus, ASV therapy can be considered in such patients. An ongoing study, Cardiovascular Improvements With MV ASV Therapy in Heart Failure (CAT-HF), may elucidate whether ASV therapy improves outcomes in these patients<sup>[47]</sup>.

### Treatment-emergent CSA

Some patients with OSA develop central respiratory events or a periodic breathing pattern similar to CSR after the removal of upper airway obstruction. This phenomenon has been reported in patients with OSA treated by CPAP and described in various ways, such as "treatment-emergent CSA", "CPAP-emerged CSA", "complex SDB", or "complex sleep apnea syndrome (SAS)". The term "complex SAS" was first used by Morgenthaler *et al*<sup>[48]</sup> and has been most widely applied



since that time. However, this term is sometimes misunderstood as solely a mixture of OSA and CSA observed in one patient during a diagnostic sleep study rather than CSA that has emerged in response to treatment. Thus, we use “treatment-emergent CSA” in this review, which is consistent with the term in the third edition of the International Classification of Sleep Disorders (ICSD-3).

In general, studies including patients with CPAP therapy for OSA have found that the prevalence of treatment-emergent CSA ranged from 1.6%-18.0%<sup>[6,49-52]</sup>. Most residual events during the initial CPAP titration are transient and may disappear over 2 to 3 mo of continued CPAP use<sup>[53]</sup>. Residual events lead to CPAP intolerance, and therefore, patients with treatment-emergent CSA may sometimes discontinue CPAP prior to alleviating the residual respiratory event. The residual respiratory events that emerged in response CPAP were associated with dyspnea and inadvertent mask removal<sup>[54]</sup>. More careful follow-up is needed to continue CPAP for such patients.

A prospective study<sup>[55]</sup> suggested that patients with treatment-emergent CSA were significantly older, but some other studies found no significant difference between patients with and without treatment-emergent CSA. In several retrospective studies<sup>[48-50]</sup>, treatment-emergent CSA was more frequently observed in men than in women. In addition, most epidemiological investigations suggested that body mass index (BMI) did not differ between patients with and without treatment-emergent CSA<sup>[49,50,53,55]</sup>. In terms of polysomnographic findings, although some studies suggested that greater AHI, central apnea index, or the arousal index during diagnostic sleep studies could be predictors for the development of treatment-emergent CSA, these results were not consistent with those of other studies. One case report suggested that dissociation between apnea termination and arousal during diagnostic sleep study might be suggestive of the presence of treatment-emergent CSA<sup>[56]</sup>. However, this phenomenon should be studied using a larger sample size.

Bitter *et al*<sup>[6]</sup> described that 18% of patients with HF develop treatment-emergent CSA defined as more than 15 episodes of central apnea or periodic breathing per hour when undergoing CPAP titration. When defined as more than 5 episodes, 37% of the patients presented treatment-emergent CSA, which indicates that treatment-emergent CSA is quite common in patients with HF. However, Westhoff *et al*<sup>[57]</sup> assessed the prevalence of treatment-emergent CSA among patients with CPAP treatment for OSA with BNP levels that were within the normal range. The prevalence (1.6%) was much lower than that in patients with HF. Thus, HF is one of the risk factors for the development of treatment-emergent CSA. However, this feature may be explained by an underlying CSR pattern of respiratory events with an obvious obstructive phenotype. Such respiratory events were scored as

obstructive during diagnostic studies. However, in a CPAP titration study, alleviation of the upper airway obstruction resulted in a prominent underlying CSR<sup>[56]</sup>.

The mechanism underlying the development of treatment-emergent CSA remains to be elucidated and is assumed to be multifactorial. Minute ventilation is determined by the level of PaCO<sub>2</sub> via stimulating chemoreceptors. When PaCO<sub>2</sub> falls below the apnea threshold, central apnea occurs. Patients with treatment-emergent CSA may be susceptible to frequent arousal due to the intolerance to CPAP, and this effect is secondary to an elevated nasal resistance<sup>[58]</sup>, including a mask leak and mouth breathing<sup>[59]</sup>. Other comorbidities of the patients can also trigger frequent arousals, leading to unstable sleep and oscillation of PaCO<sub>2</sub>, which may cause treatment-emergent CSA<sup>[60]</sup>. Excessive pressure may activate lung stretch receptors, which inhibit central respiratory motor output, and lead to central apnea via the Hering-Breuer reflex<sup>[61]</sup>. The efficiency of CO<sub>2</sub> excretion in patients with OSA is usually reduced but is improved with the application of CPAP. Even if the pressure is appropriate, improved CO<sub>2</sub> excretion can induce transient hypocapnia, triggering CSA. The CO<sub>2</sub> apnea threshold, which is usually 2–6 mmHg below the eucapnic sleeping CO<sub>2</sub> level, may improve to the lower level as the eucapnic sleeping CO<sub>2</sub> level decreases over several weeks of CPAP use, resulting in a resolution of the central apnea<sup>[62]</sup>. This phenomenon may be one of the reasons why most treatment-emergent CSA is transient and may disappear over several weeks<sup>[53]</sup>.

ASV has been reported to be effective for the treatment of treatment-emergent CSA. However, the success rate, defined as the total AHI that was attenuated under 10 events per hour, varies from 76% to 92%<sup>[63,64]</sup>. Supplemental oxygen plus CPAP or the use of bi-level PAP alone rather than CPAP have also been reported to be effective, but Allam *et al*<sup>[63]</sup> reported that ASV was more successful than either CPAP with oxygen or bi-level PAP (including either spontaneous/timed-mode or spontaneous-mode). A retrospective study<sup>[65]</sup> in which the mean nightly use of ASV was assessed at the first visit (at 4–6 wk following initiation of ASV) revealed good adherence to ASV (5.0–6.0 h per night). In another retrospective study, attenuation of residual AHI on CPAP using ASV resulted in an improvement of sleep fragmentation and a reduction of the arousal index<sup>[64]</sup>. These findings do not indicate that all patients with treatment-emergent CSA should be treated with ASV because CSA may disappear over several months<sup>[53]</sup>, but they suggest that some patients with treatment-emergent CSA will benefit from ASV in reducing AHI and improving sleep architecture and adherence. In general, we should try to optimize the setting of CPAP, improve nasal resistance, and control mask leaks. Following these efforts and after the confirmation that treatment-emergent CSA remains after several weeks, an upgrade from CPAP to ASV could be considered. We should also consider the cost effectiveness of ASV in patients with treatment-emergent CSA.

In the study by Bitter *et al.*<sup>[6]</sup> of HF patients with treatment-emergent CSA, all 34 HF patients with treatment-emergent CSA used ASV, and only one of them failed to show a reduction of AHI below 15 events per hour of sleep at 3 mo following the initiation of ASV. As described above, HF patients with treatment-emergent CSA may include some patients with a clear obstructive phenotype and underlying CSR. In such patients, ASV should be recommended in those patients with symptoms that are related to their residual SDB and be considered in cases in which SDB can be successfully alleviated with ASV, as well as in some select cases, similar to HF patients with coexisting OSA and CSR-CSA. Even in these populations, the patients should continue to use CPAP for several weeks with careful observation to exclude "transient" treatment-emergent CSA.

### Idiopathic CSA

Idiopathic CSA is categorized as one form of primary CSA with underlying causes or disorders (*i.e.*, HF, cerebrovascular disease, and renal failure) that are not identified. The prevalence of idiopathic CSA is not reported. Although it is not strictly limited to "idiopathic", the prevalence of CSA in the general population has been reported to be only 0.4%<sup>[66]</sup>, which suggests that the prevalence of idiopathic CSA could be much lower than other forms of primary CSA. The prognosis of idiopathic CSA is also unknown, but it is speculated to be a relatively benign condition due to the absence of other comorbidities<sup>[67]</sup>.

The pathogenesis of idiopathic CSA has not been fully elucidated. However, it has been reported that increased ventilatory responses and hypocapnia play important roles<sup>[68]</sup>. Arousal and the accompanying hyperventilation have also been reported to be one of the mechanisms that triggers hypocapnia<sup>[69]</sup>.

The patterns and features of respiratory events in patients with idiopathic CSA are not the same as those of typical CSR. Patients with idiopathic CSA exhibit a periodic breathing pattern with a shorter cycle length<sup>[26]</sup> and less severe desaturations associated with central apneas<sup>[70]</sup>. In patients with idiopathic CSA, insomnia (difficulty in initiating and maintaining sleep) or hypersomnolence have not been reported to be common presenting symptoms<sup>[70,71]</sup>.

ASV may also be effective for idiopathic CSA. However, there are no solid reports in which the effectiveness of ASV in patients with idiopathic CSA was completely evaluated. Three cases of idiopathic CSA that did not respond well to either CPAP or oxygen were reported to benefit from ASV<sup>[5]</sup>. In that case series, ASV decreased the mean abnormal breathing event index from 35.2 to 3.5 per hour of sleep, and it also reduced the mean number of arousals caused by the abnormal breathing events from 18.5 to 1.1 per hour of sleep. Moreover, subjective daytime alertness and mood improved after 6 to 12 mo of using ASV.

These cases indicated that ASV could be effective in improving symptoms for idiopathic CSA and should be used to relieve symptoms. The efficacy must be verified in larger numbers of patients.

### Opioid-induced CSA

Individuals who are either acute or chronic opioid users can develop CSA<sup>[72,73]</sup>. The prevalence of opioid-induced CSA is unknown, but previous reports suggested that CSA was present in 30%-60% of patients who received methadone, a long-acting  $\mu$ -opioid agonist, for the treatment of substance abuse<sup>[74,75]</sup>. It has been reported that methadone overdose is associated with the presence of CSA and a worse prognosis, but whether the reported worse prognosis in association with methadone overdose indicates the presence of CSA or underlying comorbidities remains unclear<sup>[76]</sup>.

Walker *et al.*<sup>[73]</sup> reported that symptoms of sleep apnea in the opioid group and in the control group were similar. There were no significant differences in the Epworth Sleepiness Scales or prevalence of comorbidities between the two groups. Specific symptoms of opioid-induced CSA have not been reported. The pattern of CSA observed in patients with opioid use is not similar to that observed in patients with HF, who typically display a CSR pattern. However, the pattern of CSA observed in patients who are taking opioids is similar to ataxic breathing. Ataxic breathing is distinguished from CSR by its irregularity. In addition, there is no cyclical change in tidal volume like that in CSR. The pathophysiology of developing CSA as a result of opioid use is unknown. However, it has been suggested that the inhibitory effects of opioids on the  $\mu$ -opioid receptor of carotid bodies may play an important role in the development of CSA.

Various forms of PAP have been used for opioid-induced CSA. A systematic review<sup>[77]</sup> based on five articles including a total of 127 patients who were using opioids for at least 6 mo showed the effectiveness of PAP for the treatment of opioid-induced CSA. In most of the cases, CPAP therapies were ineffective for the alleviation of CSA. However, ASV was more effective than CPAP. Approximately 60% of the patients with opioid-induced CSA attained a central apnea index of < 10 per hour of sleep on either the bi-level PAP or ASV<sup>[77]</sup>. In general, the presence of ataxic breathing can be a predictor of a poor response to PAP therapy<sup>[77]</sup>. Javaheri *et al.*<sup>[7]</sup> reported the results of a study in which twenty patients with chronic opioid therapy who showed persistent CSA on CPAP underwent ASV titration. In that study, the diagnostic polysomnography showed an average central apnea index (CAI) of 32 per hour of sleep. On the CPAP, in contrast, CSA was not attenuated, and the average CAI was 20 per hour of sleep. However, during ASV titration, the average CAI was 0 per hour of sleep for the final pressures. During the follow-up for a minimum of 9 mo and up to 6 years in 17 of the 20 patients, the adherence to ASV was

good (average nightly usage was > 5 h). Long-term RCTs are needed to validate the mortality benefit of ASV in patients with CSA associated with opioid use.

### Ischemic stroke-related CSA

SDB is common after ischemic stroke and can be found in more than half of the patients, especially in the acute phase<sup>[78,79]</sup>. Preexisting OSA has been reported to be a predictor of the development of ischemic stroke. A longitudinal cohort study suggested that a higher obstructive AHI could be predictive of future incident ischemic stroke<sup>[80]</sup>. Such OSA remains in the acute phase following the stroke attack. In contrast, CSA is likely to occur in the post-acute period of ischemic stroke, and there might be a cause and effect relationship between stroke and CSA during the acute phase following the stroke. This hypothesis is supported by observations in which SDB disappeared after the acute phase of stroke<sup>[78,81]</sup>. However, there are reports showing that CSA remains in approximately 50% of the ischemic stroke patients at 3 mo after the onset of stroke<sup>[78,82,83]</sup>. Injury in the brain or central nervous system, which may or may not be reversible, could be a possible explanation for such inconsistent results. In addition, a prospective study assessing 93 patients with stroke demonstrated that the presence of CSA was associated with a decrease in LVEF but was not related to the location or type of stroke. This study suggested that CSA after stroke was only a coexisting phenomenon of underlying cardiovascular diseases<sup>[84]</sup>.

Limited data suggest that the presence of CSA during the acute stroke phase might have a prognostic impact. Rowat *et al.*<sup>[85]</sup> reported that central periodic breathing patterns, such as CSR, were common in acute stroke (24%) and were independently associated with a poor outcome after stroke. They found that 91% of the patients with central periodic breathing were dead or physically dependent compared with 53% of those without this condition.

However, the treatment of CSA related to stroke has not been well established. ASV has also been applied for CSA related to stroke. Speculation regarding the similarities of the pathophysiology of CSA in relation to stroke and HF has led to the consideration that ASV may be effective in the treatment of CSA after stroke. A single-center retrospective analysis of ASV treatment for CSA in post-acute ischemic stroke patients suggested that ASV was well tolerated and clinically effective in such patients<sup>[86]</sup>. In that study, the role of ASV was evaluated in the treatment of CSA in post-acute stroke patients, most of whom were treated with other PAPs with insufficient reduction of AHI. ASV significantly improved AHI and reduced daytime sleepiness after 3 to 6 mo.

### Other clinical applications of ASV

HF patients without SDB may also benefit from PAP therapy as a result of its cardiac unloading effects.

In fact, the short-term application of CPAP (*i.e.*, 5-10 cm H<sub>2</sub>O) can increase cardiac output in stable HF patients with pulmonary congestion<sup>[87]</sup>. This possibility has been further assessed in a subgroup analysis of a small randomized trial investigating the effects of CPAP on cardiac function and clinical outcomes in HF patients with and without CSA<sup>[88]</sup>. In a subgroup analysis of patients without CSA, CPAP had no effect on either LVEF or the composite endpoint of mortality and the cardiac transplantation rate. However, based on recent data showing the acute beneficial effects of the short-term application of ASV on sympathetic nervous system activity<sup>[9,89]</sup> and hemodynamics<sup>[11,19]</sup>, it has been suggested that ASV and not CPAP may be an effective option for HF patients beyond just as a treatment for SDB. In fact, Takama *et al.*<sup>[10]</sup> reported that ASV treatment for HF patients resulted in almost equal improvements in BNP levels and LVEF regardless of the severity and type of SDB. Moreover, Koyama *et al.*<sup>[13]</sup> reported that ASV was associated with better clinical outcomes regardless of the presence or absence of moderate CSA (*i.e.*, AHI < 20 or ≥ 20). In addition, a multicenter, retrospective, observational study that included 115 Japanese HF patients treated with ASV, regardless of the presence or absence of SDB, examined the effects on their symptoms and hemodynamics. Improvements in LVEF and New York Heart Association (NYHA) class after ASV therapy were not influenced by the severity of SDB<sup>[90]</sup>. The possible benefits of ASV on cardiac function are being assessed in an ongoing randomized clinical trial in which HF patients with and without SDB are being randomized to either ASV treatment or medical therapy to assess changes in the LV ejection fraction at 6 mo (SAVIOR-C)<sup>[91]</sup>.

In general, the acute hemodynamic effects of PAP therapy are more prominent in HF patients with pulmonary congestion or increased LV filling pressure (*i.e.*, pulmonary capillary wedge pressure ≥ 12 mmHg)<sup>[11]</sup>. Therefore, HF patients with a low filling pressure and those without hypervolemia should not be treated with PAP therapy including ASV, or they should at least be treated with caution<sup>[90]</sup>.

The acute effects of ASV in patients with acute cardiogenic pulmonary edema have also been evaluated<sup>[12]</sup>. In an observational study, Nakano and colleagues found that after one hour of ASV with supplemental oxygen, plasma catecholamine concentrations fell significantly with declines in blood pressure, heart rate and respiratory rate compared with supplemental oxygen alone. These findings suggest that the use of ASV, in comparison to supplemental oxygen alone, may relieve dyspnea and improve hemodynamics, possibly through the modulation of sympathetic nerve activity. However, this hypothesis remains to be confirmed in a larger-scale randomized study comparing ASV and other PAPs.

In Japan, ASV is sometimes used during pulmonary

**Table 4** Summary of recommendations for the use of adaptive-servo ventilation in various settings

Settings	Indication	Improvement other than AHI	Supporting evidence
With SDB			
HF	After optimization of HF, with CSA not suppressed by CPAP	Daytime sleepiness LVEF BNP Event-free survival	RCTs ( <i>vs</i> CPAP) <sup>[3,4,40,41,43]</sup> RCTs ( <i>vs</i> control) <sup>[36,42]</sup> RCT ( <i>vs</i> Bi-level PAP) <sup>[37]</sup>
Treatment-emergent CSA	With HF Without HF	Same as HF Sleep architecture Adherence of PAP	Retrospective studies (pre-post study, <i>vs</i> CPAP) <sup>[64,65]</sup>
Idiopathic CSA	With symptoms	Daytime alertness and mood	Case series (pre-post study, <i>vs</i> CPAP or oxygen) <sup>[5]</sup>
Opioid-induced CSA	Benefit unknown		
Stroke-related CSA	Post-acute phase	Daytime sleepiness	A single-center retrospective study (pre-post study) <sup>[86]</sup>
Without SDB			
HF	Regardless of the presence or absence of SDB	LVEF NYHA class	A multi-center retrospective study (pre-post study) <sup>[91]</sup>
Acute cardiogenic pulmonary edema	With elevated filling pressure	Dyspnea High blood pressure	An observational study ( <i>vs</i> supplemental oxygen alone) <sup>[12]</sup>
Atrial fibrillation	During PVI	Procedural time	On-off study <sup>[93]</sup>

AHI: Apnea-hypopnea index; ASV: Adaptive-servo ventilation; BNP: Brain natriuretic peptide; CPAP: Continuous positive airway pressure; CSA: Central sleep apnea; HF: Heart failure; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; PAP: Positive airway pressure; PVI: Pulmonary vein isolation; RCT: Randomized controlled trial; SDB: Sleep disordered breathing.

vein isolation (PVI) by catheter ablation for atrial fibrillation to maintain stable respiration. During the PVI procedure, the use of deep sedation with analgesia (propofol and pentazocine hydrochloride) suppresses respiration and/or results in upper airway collapse, leading to unstable respiration with a large variation that interferes with the PVI procedure, such as catheter positioning. The use of deep sedation with analgesia in combination with ASV lowers the frequency of restless body movements and stabilizes respiration, leading to a decreased total electrical energy supply, shorter fluoroscopy and procedural times, and a decreased rate of recurrence of atrial fibrillation<sup>[92]</sup>. These findings should be confirmed in a larger-scale randomized study comparing ASV and other PAPs.

## FUTURE PERSPECTIVES

We should note that indications for ASV and anticipated clinical outcomes in response to ASV are different in each situation (Table 4).

In HF patients with SDB, one can anticipate improvements with ASV use in cardiac function in addition to symptom relief due to SDB. If the long-term prognostic impacts of ASV for such patients are demonstrated in the future, a benefit of ASV will be more pronounced. Still, we should not overlook the following points: CPAP or ASV should be chosen appropriately, considering the cost-benefit of CPAP rather than ASV because approximately half of the HF patients with CSA can be sufficiently attenuated by CPAP; efforts to maintain adherence to devices should be implemented to derive the maximal benefit from them. In terms of maintaining adherence, intensive support for CPAP use, including a 3-night

trial of CPAP in the sleep center, education regarding home use of CPAP for patients and their partners and an additional home visit after initiating home use of CPAP, increased the duration of usage and improved symptoms compared with standard support<sup>[93]</sup>. Thus, the strategy of initiating ASV for HF patients following admission due to acute decompensated HF is reasonable because more intensive support is available during hospitalization for ADHF. RCTs investigating the application of ASV for ADHF patients are needed, and we should also validate the usefulness of this strategy in the maintenance of adherence.

When treatment-emergent CSA is observed in HF patients, the same indication for HF patients with SDB can be applied. However, in patients without HF, we should avoid the routine use of ASV for treatment-emergent CSA, considering the high cost of ASV. We can apply ASV in such patients only to relieve symptoms of treatment-emergent CSA. We must determine the long-term prognostic impact of changing from CPAP to ASV for HF patients with treatment-emergent CSA. We must also determine which patients will experience prognostic benefits following such changes.

The impacts of ASV for idiopathic CSA or opioid-induced CSA are limited. ASV can attenuate CSA in such patients, but the significance of the effect for patients with no symptoms should be investigated further. The regular use of ASV in these situations may represent overuse and should be avoided.

Other situations of ASV use have been introduced in several reports. However, whether the clinical benefits of ASV exceed those of other PAP devices remains to be clarified. At present, additional evidence is needed to support the use of ASV rather than that of other PAP devices in such situations.



## CONCLUSION

As discussed herein, the effectiveness of ASV in the field of cardiovascular and respiratory care is currently being established, and it will be more widely used if positive results are obtained in several large-scale RCTs. Therefore, clinicians should have a better understanding, for instance, of which patients should be targeted for ASV, how to apply it, and what is the anticipated outcome of ASV, with insightful consideration of the cost-effectiveness in each case.

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## Caveolae, caveolin-1 and cavin-1: Emerging roles in pulmonary hypertension

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### Abstract

Caveolae are flask-shaped invaginations of cell membrane that play a significant structural and functional role. Caveolae harbor a variety of signaling molecules and serve to receive, concentrate and transmit extracellular signals

across the membrane. Caveolins are the main structural proteins residing in the caveolae. Caveolins and another category of newly identified caveolae regulatory proteins, named cavin, are not only responsible for caveolae formation, but also interact with signaling complexes in the caveolae and regulate transmission of signals across the membrane. In the lung, two of the three caveolin isoforms, *i.e.*, cav-1 and -2, are expressed ubiquitously. Cavin protein family is composed of four proteins, named cavin-1 (or PTRF for polymerase I and transcript release factor), cavin-2 (or SDPR for serum deprivation protein response), cavin-3 (or SRBC for sdr-related gene product that binds to-c-kinase) and cavin-4 (or MURC for muscle restricted coiled-coiled protein or cavin-4). All the caveolin and cavin proteins are essential regulators for caveolae dynamics. Recently, emerging evidence suggest that caveolae and its associated proteins play crucial roles in development and progression of pulmonary hypertension. The focus of this review is to outline and discuss the contrast in alteration of cav-1 (cav-1), -2 and cavin-1 (PTRF) expression and downstream signaling mechanisms between human and experimental models of pulmonary hypertension.

**Key words:** Caveolae; Caveolin-1; Cavin-1; Pulmonary hypertension; Lipid rafts

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**Core tip:** Pulmonary hypertension is a disease condition that is associated with a wide range of underlying medical conditions and environmental exposures. Currently, the exact molecular mechanisms underlying the pathogenesis of pulmonary hypertension remain unclear. This review is to outline and discuss the current understandings on the novel roles of a group of cell surface proteins, cav-1, -2 and cavin-1, on the development of pulmonary hypertension and vascular remodeling.

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## INTRODUCTION

The cell membrane is a dynamic, fluid structure containing lipids and proteins that are asymmetrically distributed between the outer and inner leaflets of the membrane. It functions not only as a protective boundary to the cell, but also aids in selective molecular transport and transduction of signals across the membrane. These processes are facilitated by membrane proteins that form macromolecular complexes and are highly organized with respect to time and position. In some cases, these complexes are localized to specific regions of the cell membrane, such as lipid rafts and caveolae<sup>[1]</sup>. Caveolae are (Ω)- or flask-shaped invaginations of the plasma membrane. While the surrounding plasma membrane contains mostly lipids with kinked-unsaturated fatty acids, the caveolae have a high concentration of saturated straight chain fatty acids and cholesterol, which makes the structure rigid and highly organized<sup>[1]</sup>. This organization is maintained by proteins called caveolin, lining the inner leaflet; sometimes referred to as "caveolin-coat". Three distinct caveolin proteins have been identified in humans: caveolin-1 (cav-1), caveolin-2 (cav-2) and caveolin-3 (cav-3)<sup>[2]</sup>. Cav-3 is mostly expressed in skeletal and smooth muscle cells, while cav-1 and -2 are widely expressed in many cell types.

In addition to the coat protein caveolin, caveolae also have an inner lining of adapter proteins called cavins. The cavin family consists of four members (cavin-1 to -4) with common structural features including leucine zipper motifs, PEST (Pro-Glu-Ser-Thr-rich) sequence and phosphoregulatory sites<sup>[3]</sup>. Among the different cavins, cavin-1 is the most abundantly expressed and extensively studied.

As discussed above, signaling protein complexes are organized and concentrated in the caveolae which serve to receive, concentrate and transmit extracellular signals across the cell. And since caveolae are covered with a "caveolin-coat", it is imperative that caveolin plays an important role in transmitting these signals *via* interaction with the signaling protein complexes.

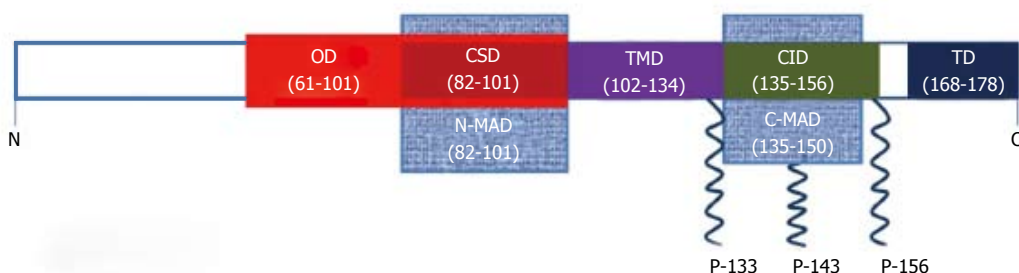
In this review we will discuss the role of cav-1 and cavin-1 as a regulator in lung disease, specifically pulmonary hypertension.

Pulmonary hypertension is a chronic and progressive disease characterized by high mean pulmonary arterial pressure (> 25 mmHg at rest). Common symptoms include shortness of breath, dizziness, edema and fatigue. Right heart catheterization and six-minute walk test are often performed to diagnose the disease.

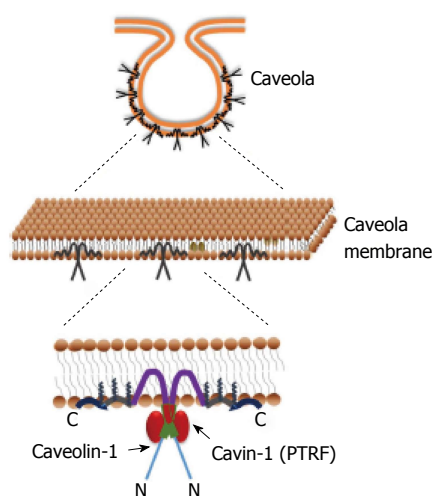
However, due to the non-specific nature of symptoms of the disease, by the time patients are diagnosed, frequently, they are at an advanced stage of the disease. Endothelial dysfunction, pulmonary vasoconstriction and vascular remodeling are the common features of pulmonary hypertension of different etiologies. Dysfunctional endothelial cells in PH patients have an altered production of endothelial vasoactive mediators such as NO, endothelin-1, prostacyclin, thromboxane and serotonin<sup>[4]</sup>. Pulmonary vasoconstriction in response to airway hypoxia is a physiological response to redirect blood flow from poorly ventilated regions of the lungs to well oxygenated regions<sup>[5]</sup>. Pulmonary vascular remodeling refers to a process that causes thickening of the arterial wall, wherein phenotypic and morphological changes occur in all three layers of the vessel wall: intima, media and adventitia. In more severe forms of PH, such as that in idiopathic and heritable PAH, the additional formation of complex cellular and fibrotic neointimal and plexiform lesions in distal pulmonary arteries is often identified, which involve the proliferation of both PSMCs and PAECs<sup>[6-8]</sup>. Without treatment, these conditions lead to right ventricular hypertrophy, right heart failure and premature death. Currently, the exact molecular mechanisms underlying the development of pulmonary vasoconstriction and pulmonary arterial remodeling are still unclear. This is mostly due to the fact that pulmonary hypertension is a disease condition that is associated with a wide range of underlying medical conditions and environmental exposures<sup>[9]</sup>. Interestingly, many of the signaling proteins implicated in the pathobiology of PH such as eNOS, VEGF receptor and prostacyclin receptors are known to interact with the membrane protein, cav-1 in caveolae of endothelial cells<sup>[10-13]</sup>, as reviewed below in detail.

## CAV-1 STRUCTURE AND FUNCTION

Cav-1 is a 22 kDa phosphoprotein present in many cell types in the lung including endothelial cells, type I epithelial cells, airway and vascular smooth muscle cells, fibroblasts, macrophages and neutrophils<sup>[14]</sup>. The *CAV1* gene on chromosome 7 encodes a 178 amino acid protein<sup>[15]</sup>. Cav-1 protein exists in two isoforms: cav-1 $\alpha$  and cav-1 $\beta$  that are derived from the use of two distinct transcription initiation sites<sup>[16]</sup>. Pulse-chase analysis studies have shown that soon after the cav-1 protein is synthesized in the ER, it forms homo-oligomers of approximately 14-16 monomers before being translocated to the plasma membrane<sup>[17,18]</sup>. The oligomerization is brought about by a series of 40 amino acids from residues 61-101 of cav-1. This is called the oligomerization domain (OD). The OD also contains the caveolin scaffolding domain (CSD) which spans from residues 82-101 (Figure 1). The CSD interacts with several other membrane proteins, most of which are signaling proteins that have a cav-1 binding motif<sup>[19]</sup>. Cav-1 also has a membrane spanning segment (residues



**Figure 1** Diagram summarizing the different functional domains of caveolin-1 protein. Cav-1 contains seven known functional domains. It contains an oligomerization domain (OD), a caveolin scaffolding domain (CSD), a transmembrane domain (TMD), a caveolin inhibitory domain (CID) (eNOS, Src kinase and PKA), a terminal domain (TD), an N-terminal membrane association domain (N-MAD), and a C-terminal membrane association domain (C-MAD). P-133, 143, 156: Palmitoylation sites.



**Figure 2** Structural organizations of a caveola, caveolin-1 and cavin-1. Caveola are specialized lipid raft that are structurally maintained by caveolin-1 to form flask-shaped invaginations. In addition to these coat protein caveolin, caveolae contains an inner lining of adapter proteins called cavins, which regulate caveolin. PTRF: Polymerase I and transcript release factor.

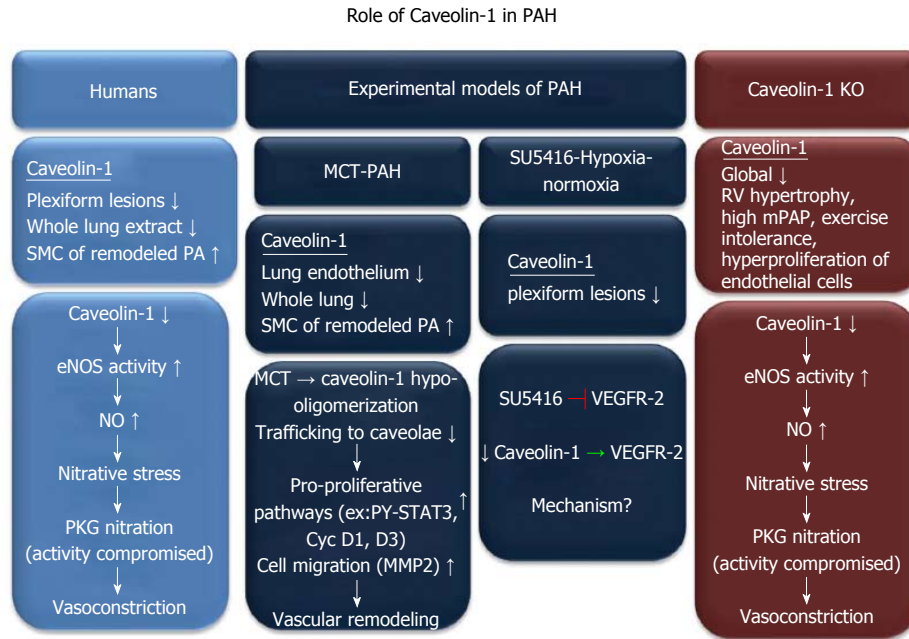
102-134), also called the transmembrane domain (TMD), formed by a hydrophobic loop configuration exposing the N- and C-termini to the cytoplasm<sup>[17,20]</sup>. The TMD is flanked by membrane attachment domains on each side called the N-terminal membrane attachment domain (N-MAD, residues 82-101) and C-terminal membrane attachment domain (C-MAD, residues 135-150) (Figure 1). Interestingly, N-MAD and C-MAD are minimal regions required to mediate attachment to the membrane. While the N-MAD targets cav-1 attachment to caveolae membrane, C-MAD facilitates trans-golgi targeting<sup>[21]</sup>. Additionally, the C-terminus has three palmitoylation sites on cysteine residues (133, 143 and 156)<sup>[22]</sup>, and the N-terminus has a phosphorylation site on tyrosine-14<sup>[23]</sup> (Figure 1).

Various studies have shown that cav-1 plays an important role in the formation of caveolae (Figure 2). Most importantly: (1) Mice lacking the CAV1 gene (CAV1<sup>-/-</sup>) do not have caveolae on the plasma membrane<sup>[24]</sup>; (2) Cells that do not have detectable cav-1 and endogenous caveolae on their membranes,

were able to form plasma membrane invaginations *de novo*, upon transient expression of cav-1 in these cells<sup>[25,26]</sup>. Cav-1 also aids in cellular transport namely, transcytosis<sup>[27,28]</sup>, endocytosis<sup>[29,30]</sup> and exocytosis<sup>[31]</sup>. Caveolins have also been implicated in cholesterol homeostasis. Since its discovery, cav-1's association with cholesterol has been demonstrated in several studies<sup>[32-34]</sup>. Cholesterol binds to cav-1 in the ER and is then transported to caveolae where it can be either released outside the cell or added to the plasma membrane layer<sup>[35,36]</sup>. The three palmitoylation sites on C-terminus are required for cholesterol binding of cav-1 and transport to caveolae<sup>[37]</sup> (Figure 2). Numerous plasma membrane-signaling protein complexes have been reported to concentrate in caveolae in different cell types. These proteins have caveolin binding sequence motif that allows them to interact with CSD on cav-1. Some of the cav-1-associated proteins that have been reported are: endothelial-NO synthase (eNOS), G-protein  $\alpha$ -subunits, insulin receptor, Rho A and TGF $\beta$  receptors<sup>[34,38-41]</sup>.

## CAV-1 IN HUMAN PULMONARY HYPERTENSION

Geraci *et al.*<sup>[42]</sup> in 2001, first reported a decrease in cav-1 mRNA level, in lung tissue samples from severe PH patients, in a gene expression profiling study. Further, immunohistochemical studies in lungs from severe PH patients show a lack of cav-1 staining in complex plexiform lesions and muscularized pre-capillary arterioles. Cav-2, a protein that normally co-localizes with cav-1 also shows decreased expression in plexiform lesions<sup>[43]</sup>. Plexiform lesions are mainly composed of highly proliferative endothelial cells and are characteristic features of pulmonary vascular remodeling<sup>[44,45]</sup>. Dysfunctional endothelial cells of pulmonary arteries play a key role in initiation and progression of PAH<sup>[46,47]</sup>. Interestingly, endothelial and smooth muscle cells of the surrounding normal-appearing vessels in the severe PH lungs express cav-1 ubiquitously<sup>[43]</sup>. In contrast, the increase in cav-1 staining is specifically seen in the vascular



**Figure 3** Schematic representation of alterations in caveolin-1 and the downstream pathways affected by caveolin-1 in human idiopathic pulmonary arterial hypertension and experimental models of pulmonary hypertension. Cav-1 expression is decreased in the lung. Downstream signaling pathways that are affected by cav-1 are diverse in different animal models of pulmonary hypertension (PH) and in humans. However, they eventually lead to vasoconstriction, vascular remodeling and development of PH. PAH: Pulmonary arterial hypertension; VEGFR: Vascular endothelial growth factor receptor; Cav-1: Caveolin-1.

smooth muscle cells lining the remodeled arteries<sup>[48]</sup>. In whole lung tissue extract, cav-1 expression (by immunoblotting) is lower in IPAH lungs as compared to normal lungs<sup>[11]</sup>. This could be due to the fact that human IPAH is a complex disease and the changes in cav-1 expression are cell-specific. Endothelial cells are the majority cell type in the lung expressing abundant cav-1<sup>[49]</sup>. Therefore, the decreased cav-1 level in whole lung tissue extract reflects mainly the level of cav-1 in endothelial cells. In the pulmonary artery smooth muscle cells (PASMC) of IPAH patients, increase in cav-1 and caveolae formation enhances the capacitative calcium entry and  $[Ca^{2+}]_i$  which is attributable to the up-regulation of TRPC channels and localization to caveolae<sup>[48,50,51]</sup>. A sustained increase in  $[Ca^{2+}]_i$  is known to trigger vasoconstriction in PASMCs and also stimulate cell growth<sup>[48,52]</sup>. Therefore cav-1 up-regulation in PASMCs may also contribute to increase in pulmonary vascular resistance and pulmonary vascular remodeling.

Another interesting observation in the lungs of IPAH patients is the high level of eNOS derived NO<sup>[11]</sup> (Figure 3). NO can have beneficial or adverse effect in a disease setting like PH depending on the relative amounts of NO and reactive oxygen species (ROS)<sup>[53]</sup>. eNOS activity in the lungs of IPAH patients is substantially increased because of the reduction in cav-1 levels. Under basal conditions, cav-1 interacts with eNOS and inhibits NO production. eNOS binds to Cav-1 at a specific amino acid stretch (90-99 residues) in the caveolin scaffolding domain and inhibits its activity<sup>[54]</sup>. Loss of cav-1 in the lungs of IPAH patients leads to high NO levels and hypoxia-independent ROS

production which causes peroxynitrite formation. This induces nitration of PKG at tyrosine (residues 345, 549) which impairs its kinase activity<sup>[11]</sup>, subsequently, leads to pulmonary vasoconstriction and vascular remodeling of the pulmonary arteries. Taken together, the decrease of cav-1 expression in endothelial cells and increase of cav-1 level in smooth muscle cells may both contribute to the development of severe pulmonary vascular remodeling in the pathogenesis of human PAH.

## CAV-1 IN EXPERIMENTAL MODELS OF PULMONARY HYPERTENSION

Involvement of cav-1 in pulmonary hypertension has also been demonstrated in different rodent models of severe pulmonary hypertension. Decreased cav-1 and cav-2 expression has been reported in SU5416-hypoxia-normoxia<sup>[43,55]</sup> and myocardial infarction<sup>[56]</sup> models. SU5416 {3-[(2,4 dimethylpyrrol-5-yl) methylidenyl]-indolin-2-one}, is a vascular endothelial growth factor receptor-2 (VEGFR-2/Flk-1/KDR) inhibitor<sup>[57]</sup>. In the SU5416- hypoxia-normoxia model, many complex plexiform lesions show diminished immunohistochemical staining for cav-1 (Figure 3). However, in chronic hypoxia model of PH (without adding SU5416), there is no diminution in cav-1 expression<sup>[58]</sup>. Given that the plexiform lesions are prominent features in SU5416-hypoxia-normoxia models, this observation suggests that cav-1 may play an essential role in regulating pulmonary vascular remodeling. Interestingly, cav-1 has been shown to regulate the activity of VEGFR-2. Cav-1 forms a complex with VEGFR-2 in the caveolae



of endothelial cells and inhibits its basal activity<sup>[12]</sup>. Similarly, overexpression of cav-1 in endothelial cells blocks VEGF-dependent activation of Elk-1 promoter activity<sup>[41]</sup>. Conversely, treatment of endothelial cells with VEGF causes a marked decrease in cav-1 protein expression<sup>[41]</sup>. Furthermore, endothelial cells isolated from cav-1 knockout mice, as compared to WT endothelial cells, show a robust and sustained increase in the tyrosine phosphorylation of VEGFR-2 upon stimulation with VEGF<sup>[59]</sup>. Apparently, although SU5416 and cav-1 depletion have opposite effects on VEGFR-2, both of these factors play a role in development of pulmonary hypertension. Further studies are required in order to dissect the signaling between SU5416 inhibition of VEGFR-2, and role of cav-1 in the SU5416- hypoxia-normoxia model of severe PAH.

In the relatively older monocrotaline (MCT) model of PAH, a decrease in caveolae was first reported in 1988 where, a reduction in percent volume of caveolae was observed in endothelial cells<sup>[60]</sup>. Later on, another study showed a decrease in cav-1 protein in the caveolae fraction of MCT treated rat lungs<sup>[61]</sup>. This was accompanied by hyperactivation of the transcription factor STAT3 (PY-STAT3) and an increase in DNA synthesis (Figure 3). As seen in human IPAH lungs, there is an increase in cav-1 expression in smooth muscle cells of remodeled pulmonary arteries<sup>[62]</sup>. In this report, the authors studied the sequential events occurring after administration of MCT through the progression of PAH up to 4 wk. After administration of MCT, there is a progressive decline in endothelial cav-1, PECAM-1 and soluble guanylate cyclase (sGC) along with a progressive increase in PY- STAT3 and pro-survival protein, Bcl-xl up to 4 wk. However, endothelial vWF and smooth muscle cav-1 remain unchanged until 2 wk post-MCT. With further loss of endothelial cav-1 at 4 wk post-MCT, there is severe endothelial deterioration indicated by loss of vWF. This exposes the smooth muscle cells to shear stress and high pressure prevalent in the hypertensive pulmonary arteries. Further, this leads to an increase in smooth muscle cav-1 expression in 70% of the vWF-lacking arteries, accompanied by an increased expression and activation of MMP2 which facilitates the proliferation and migration of smooth muscle cells, eventually leading to vascular remodeling<sup>[62]</sup> (Figure 3). eNOS protein expression increases soon (48 h) after MCT administration up to one week and then decreases by about 50% by 3-4 wk post MCT<sup>[63,64]</sup>. Similarly, NO production in the lung is decreased by about 50% by 3-5 wk post-MCT<sup>[65,66]</sup>. Mechanistically, MCT treatment in endothelial cells *in vitro* leads to hypo-oligomerization of cav-1 (< 8-mers) in the Golgi compartment and inhibits its trafficking from the Golgi compartment to caveolae on the plasma membrane<sup>[61]</sup>. Interestingly, administration of a peptide corresponding to cav-1 scaffolding domain to MCT rats is able to restore cav-1 expression in whole lung extracts and subsequently normalize right ventricular hypertrophy and pulmonary artery medial hypertrophy

that is seen in MCT-PAH rats. Hyperactivation of STAT3 and increase in cyclin D1, D3 protein expression is also suppressed in the lungs of MCT treated rats after the administration of this peptide<sup>[67]</sup>.

## CAV-1 KNOCKOUT MOUSE AND PULMONARY HYPERTENSION

Cav-1 knockout mice are viable and fertile. The lung parenchyma of these mice show a multilayered, thickened alveolar septa due to increased pulmonary endothelial cell proliferation and fibrosis<sup>[24,68]</sup> possibly due to the lack of inhibition of mitogenic signals in the absence of cav-1. The highly disorganized alveolar septum comprise of mostly incompletely differentiated cells as evidenced by lack of vWF (differentiated endothelial cell marker) staining and prominent Flk-1 staining (endothelial progenitor marker)<sup>[68]</sup>. In the absence of cav-1, cav-2 expression is also reduced by up to 95%. Cav-1 is known to hetero-oligomerize with cav-2 and recruit it to the caveolae on plasma membrane. Depletion of cav-1 halts the trafficking of cav-2 to the plasma membrane thereby sequestering the residual cav-2 mostly in the Golgi compartments<sup>[24]</sup>. However, depletion of cav-2 in the cav-2 knockout mouse does not affect the expression and trafficking of cav-1 to plasma membrane. Also, caveolae formation is not affected by the absence of cav-2. But cav-2 knockout mice demonstrate alveolar septal thickening, endothelial hyperproliferation and exercise intolerance similar to cav-1 knockout mice, without any altered lipid homeostasis and vascular dysfunction<sup>[69]</sup>. This observation suggests that cav-2 has selective function in lung homeostasis and is independent of caveolae formation. The depletion of cav-1 gene in the knockout mice however, does not affect the presence of clathrin-coated pits in the cells of these animals<sup>[24]</sup>. This could be one of the work-around mechanisms by which these cells overcome the lack of caveolae that could make the cav-1 knockout mice viable. These cav-1 knockout mice also exhibit remarkable exercise intolerance as assessed by a forced swimming test. Cav-1 knockout mice develop marked right ventricular hypertrophy indicating a chronic elevated pulmonary artery pressure<sup>[70]</sup>. Indeed pulmonary artery pressure is increased in cav-1 knockout mice by 90% as compared to wild type mice.

As observed in MCT-PAH rat models, cav-1 knockout mice lungs also showed increased tyrosine phosphorylation of STAT3 and a dramatic upregulation of cyclin D1 and D3 levels<sup>[56]</sup>, that could promote cell proliferation and perhaps contribute to structural remodeling in the lung. Unlike in the MCT-PAH model, in cav-1 knockout mice there is 5-fold increase in systemic NO, while in the lungs, eNOS derived NO is increased by at least 3-fold as compared to wild type mice<sup>[11,70,71]</sup>. However eNOS protein expression is not changed in the heart and lungs of these mice. Mechanistically,

the high NO levels from impaired eNOS activity leads to tyrosine nitration of PKG and thereby decreasing PKG bioavailability (figure 3). This could abolish its vasodilatory effect, perhaps contributing to development of PH<sup>[11]</sup>. This speculation is supported by the fact that NOS inhibition or superoxide scavenging in cav-1 knockout mice is able to rescue the PH phenotype in these mice. Similarly, PKG-1 overexpression in the lungs of these mice significantly decreases the right ventricular systolic pressure and pulmonary vascular resistance. Furthermore, endothelial specific reconstitution of cav-1 in cav-1 knockout mice not only restores eNOS activity to normal levels, it is also able to suppress pulmonary hypertension and right ventricular hypertrophy<sup>[72]</sup>. Taken together, these observations clearly demonstrate that loss of cav-1 plays an important role in the development of pulmonary hypertension in mouse PH models.

## CAVIN-1 AND PULMONARY HYPERTENSION

Cavin-1, also called as polymerase I and transcript release factor (PTRF), is known to be expressed mostly in endothelial cells, fibroblasts and epithelial cells in the lungs and also in heart, adipocytes and skeletal muscle<sup>[73]</sup>. Since its discovery in 1998, cavin-1 was known to aid in the dissociation of paused ternary transcription complexes in the nucleus<sup>[3]</sup>. However, in recent years cavin-1/PTRF has been associated with caveolae and reported to regulate caveolae membrane curvature by anchoring cavin-1 to the cytoskeleton *via* its C- terminal region<sup>[74]</sup>. Also, cavin-1 is required to mediate the normal oligomerization of cav-1<sup>[73]</sup>. More recent evidence suggests that cavin-2 plays an important role in generating caveolae specifically in the endothelial cells of the lung which is supported by the fact that endothelial cells lacking cavin-2 have flattened or shallow caveolae, but show cavin-1 co- localizing with oligomerized cav-1<sup>[73]</sup>. While cav-1 knockout mice have almost no cavin-1 expression<sup>[73,75]</sup>, cavin-1 knockout mice also have diminished cav-1 expression<sup>[73]</sup> suggesting that the expression of cav-1 and cavin-1 are interdependent. Cavin-1 knockout mice have increased lung tissue density and show hypertrophic remodeling of pulmonary arteries. They also exhibit symptoms of pulmonary hypertension, *i.e.*, increased RV-to-RV+LV ratio and increased pulmonary artery pressure as assessed by right ventricular systolic pressure<sup>[76]</sup>. Microarray analysis in new born lungs of cavin-1 knockout mice show changes in Arg1 (arginase 1) and Ddah1 (dimethylarginine dimethylaminohydrolase) genes. Increase in Arg1 and decrease in Ddah1 have been previously implicated in acquired forms of PAH<sup>[77,78]</sup>. Although the reciprocal changes in Arg1 and Ddah1 are known to limit the increase in NOS activity decreasing NO levels, this study did not measure changes in NO levels after cavin-1 knockout. Interestingly, silencing cavin-1 in endothelial cells *in*

*vitro* enhances basal NO release from these cells, which could possibly be the effect of subsequent decrease in cav-1 levels<sup>[79]</sup>. Collectively, these data suggest that cavin-1 plays an important role in caveolae function in the lungs and could contribute to the development of pulmonary hypertension. However, changes in cavin-1 have not yet been studied in human and experimental models of PAH to date and these studies will help us better understand the role of cavin-1, as well as cav-1, in the development of pulmonary hypertension.

## CONCLUSION

As evidenced in several reports summarized here, cav-1 plays a central role in the development and progression of PH and PAH. The signaling pathways that are affected by cav-1 are diverse in different animal models and in humans, while chronic hypoxia-induced PH mice do not show any change in cav-1 levels. Although the cav-1 knockout mouse is not an experimental model of PH, these mice do exhibit symptoms of PH among other abnormalities. Similar effects are seen in cavin-1 knockout mice whose expression is also diminished in cav-1 knockout mice. SU5416-hypoxia-normoxia PAH mice and IPAH lungs in humans show a decrease in cav-1 in plexiform lesions but not in surrounding normal pulmonary arteries. Moreover, there is a robust increase in cav-1 in the medial smooth muscle of remodeled pulmonary arteries in both animal models and in humans. Therefore, the differential expression and function of cav-1 in specific cells (*i.e.*, endothelial cell vs smooth muscle cell) may all together contribute to the development of pulmonary vascular remodeling, subsequently resulting in PH.

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## Management of recurrent malignant pleural effusions with a tunneled indwelling pleural catheter

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### Abstract

In this review, we report on the use of indwelling pleural catheters in the treatment of malignant pleural effusions. We describe the most commonly used catheter. Also, treatment with indwelling pleural

catheters as compared to talc pleurodesis is reviewed. A comparison of efficacy, costs, effects on quality of life, and complications is made. Only one randomized controlled trial comparing the two is available up to date, but several are underway. We conclude that treatment for malignant pleural effusions with indwelling pleural catheters is a safe, cost-effective, and patient-friendly method, with low complication rates.

**Key words:** Malignant pleural effusion; Talc pleurodesis; Indwelling pleural catheter; Palliation; Review

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**Core tip:** Indwelling pleural catheters appear to be as efficient and cost-effective as talc pleurodesis in the treatment of malignant pleural effusions with a low complications rate. A great advantage is that terminally ill patients can be treated at home in the last stage of their lives.

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### INTRODUCTION

Indwelling pleural catheters (IPCs) are used worldwide, mostly in oncology centers, for the management of recurrent malignant and also non-malignant pleural effusions (MPE). Since their development approximately 15 years ago, increasing knowledge and expertise has developed. They offer the potential of increasing quality of life in terminally ill patients, and reducing length and number of hospital stays. A great advantage

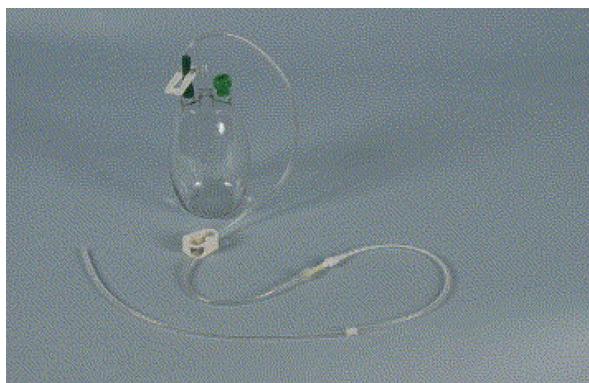


Figure 1 The Denver PleurX pleural catheter.

is that patients, who are terminally ill, can remain at home and be treated there in the last phase of their lives. This review aims to give an overview of the indications, complications and costs of indwelling pleural catheters. The alternative, *i.e.*, chest tube drainage with pleurodesis, will also be discussed.

## BACKGROUND

The most commonly used catheter for permanent drainage of pleural effusions is a flexible fenestrated silicone catheter with a cuff and a valve (Figure 1). The fenestrated portion of the catheter is inserted into the pleural space utilizing a peel away introducer (Seldinger technique). The portion of the catheter containing the cuff is tunneled subcutaneously, where it becomes fixed, thereby reducing the risk of dislocation. Also, because the catheter is tunneled, risk of infection is low. The remaining portion is left external to the body (Figure 2). Drainage occurs by connecting disposable vacuum bottles to the catheter. At the end is a one-way valve that can be attached to the vacuum drainage bottles. The most commonly used catheter is the 15.5 Fr PleurX catheter. The Food and Drug Administration (FDA) approved it for the use in malignant pleural effusions<sup>[1]</sup> and 4 years later the license was extended to include all recurrent pleural effusions<sup>[2]</sup>.

Before the availability of indwelling pleural catheters, symptom relieve was mostly achieved through repetitive drainage of pleural fluid, which resulted in frequent hospital visits. In some cases, partial pleurectomy was performed. However, only a small number of selected patients is eligible for such an invasive procedure, and it can be complicated by significant morbidity, especially before the era of video-assisted thoracoscopy (VATS)<sup>[3,4]</sup>. In a randomized controlled trial, Rintoul *et al*<sup>[5]</sup> recently compared video-assisted thoracoscopic partial pleurectomy to talc pleurodesis in patients with malignant mesothelioma. They showed that partial pleurectomy did not improve overall survival, and was associated with significantly more complications, longer hospital stay and more costs compared to talc pleurodesis in these patients.

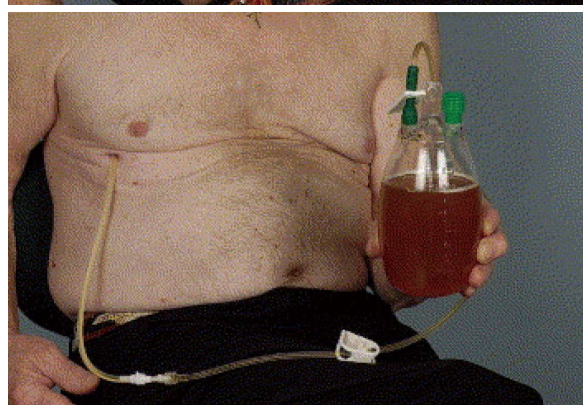
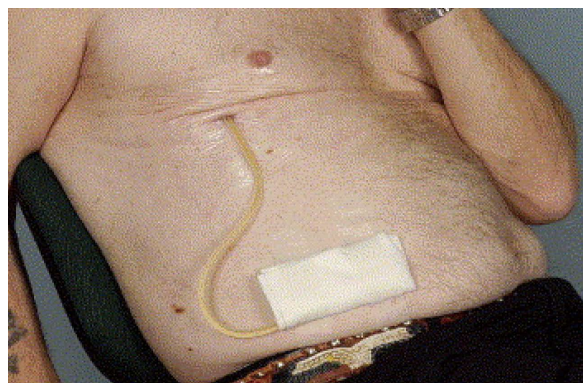


Figure 2 A patient with the catheter showing the removal of fluid. Printed with permission.

It is therefore not recommended as a standard alternative for pleurodesis or IPC<sup>[5,6]</sup>.

## INDWELLING PLEURAL CATHETERS VS TALC PLEURODESIS

The guideline of the British Thoracic Society states that in patients with malignant pleural effusions with a life expectancy of > 1 mo, drainage should be performed with subsequent pleurodesis, whereby talc is the most effective sclerosant<sup>[6]</sup>. It also states that the use of IPCs is an effective alternative method in selected cases. Although talc pleurodesis can have relevant success rates, it is not without complications and is not an option for patients with a trapped lung, which is often the case in malignant pleural effusion<sup>[7]</sup>. Complications include tachycardia, dyspnea, fever, pain and in rare instance ARDS<sup>[8]</sup>. Also for patients with malignant pleural effusions, who generally have a short life expectancy and mostly are in poor condition, it is highly favorable to reduce the emotional and physical burden of repetitive hospital visits or the length of hospital stay. In a retrospective study, Putnam *et al*<sup>[9]</sup> demonstrated that patients treated with IPC had shorter hospital stay, and lower early mean charges as compared to those with chest tube drainage followed by pleurodesis. In another retrospective study of a large number of patients, who all underwent IPC insertion, it was shown that IPC resulted in good

symptom control and shorter hospital stay. Also, a low complication rate was noted, the most severe being empyema in 3.2% of cases<sup>[10]</sup>. Moreover, the literature shows that spontaneous pleurodesis occurs in up to 51% of IPC cases, allowing removal of the catheter<sup>[10,11]</sup>.

In the only randomized controlled trial comparing IPC to chest tube and talc pleurodesis, the TIME2 trial, no significant difference in dyspnea was noted in the first 42 d after insertion between the two groups (primary endpoint)<sup>[11]</sup>. Only after the 6 mo-point a clinically and statistically significant decrease in dyspnea in favor of the IPC group was seen. A decrease in chest pain was observed in both groups, but no significant difference was noted. There was a statistically significant difference in days in hospital for drainage or drainage-related complications over 12 mo in favor of the IPC group<sup>[11]</sup>. Significantly more adverse events, albeit non-serious, were noted in the IPC group; most of these were cellulitis around the site of insertion and catheter blockage.

A Dutch multicenter randomized controlled trial was designed comparing indwelling pleural catheters to talc pleurodesis in 120 patients with malignant pleural effusions (NVALT 14). The primary objective of the study is to compare the patient reported outcome of talc pleurodesis and indwelling pleural catheter, assessed by the Modified Borg dyspnea Score. Secondary objectives include the number of interventions and visits for MPE, adverse events, costs, overall survival, quality of life, and treatment outcome at 1, 3 and 6 mo. The inclusion phase has now successfully been concluded<sup>[11]</sup>. Other studies investigating indwelling pleural catheters are also ongoing at the moment<sup>[12-14]</sup>.

## COMPLICATIONS

In a study published almost 10 years ago, describing our own experience with IPC, we showed that in 70%-80% of patients, catheter use was uncomplicated and provided significant symptom relief. Infection was only seen in two (12%) patients, dislocation of the catheter in three (18%). In the final analysis, catheter use was unsatisfactory in two patients (12%)<sup>[15]</sup>. More recent experience with indwelling pleural catheters in our Lung Oncology Center is still very positive, as even more expertise has been acquired over the years.

Early complications directly associated with IPC insertion are rare. Some degree of pain in the first days following insertion is normal and can be treated by oral analgesics. Also, bruising in the subcutaneous catheter tract almost always occurs; potentially life-threatening bleeding is very rare. Oral anticoagulants can be restarted immediately after insertion<sup>[16]</sup>.

Several studies have focused on the long-term complications of IPC. Thomas *et al*<sup>[17]</sup> retrospectively studied the incidence of catheter tract metastasis associated with IPC. In 10% of patients, catheter tract

metastasis developed. Eighty-two percent of these patients had mesothelioma and all had prior pleural interventions before IPC insertion. The only significant variable associated with higher risk for catheter tract metastasis was a longer interval post-IPC insertion<sup>[17]</sup>.

Another potential complication is pleural infection. In a multicenter retrospective study of 1021 patients, Fysh *et al*<sup>[18]</sup> reported an incidence of pleural infection of only 4.9%. The majority (94%) was successfully treated with antibiotics and in 54% of patients the IPC did not have to be removed. The most frequent causative agent of the infections was *Staphylococcus aureus*<sup>[18]</sup>. Other studies have shown similar results<sup>[19]</sup>. Patients undergoing chemotherapy with an IPC in place do not develop more infections than those with IPC not receiving chemotherapy<sup>[20]</sup>. Therefore chemotherapy does not have to be a contraindication for IPC placement.

## QUALITY OF LIFE

A major question of course is whether IPC insertion improves quality of life. In a multicenter observational study of 51 patients, quality of life was assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13. A significant improvement of symptoms scale was seen<sup>[21]</sup>. Changes in the mean scores between baseline and 30 d, as assessed with the EORTC QLQ-C30, for global, functional, and symptoms scales were: + 9.21, + 6.93, and -9.59, respectively.

In the TIME2 trial, global quality of life as measured by the QLQ-30 was measured<sup>[11]</sup>. Quality of life was improved in both the IPC and the chest tube drainage with talc pleurodesis group.

## COSTS

IPC insertion usually can be done as an outpatient procedure. Therefore, little or no costs are made for hospital stay. However, IPCs cost about 700 Euros compared to 30 Euros for a simple Pleura Cath. Also, IPC treatment is associated with the use of many disposables, especially relatively expensive vacuum bottles. Also, in some cases home care is needed to help the patient with drainage. These factors push the total cost of IPC treatment. Several studies have investigated the cost of IPC treatment, often compared to test tube drainage and pleurodesis. Universal comparison remains a difficult task, because of different insurance systems and hospital management in different countries.

Boshuizen *et al*<sup>[22]</sup> looked at the direct costs of IPC treatment in one Dutch hospital; they concluded that the costs of IPC treatment are reasonable as compared to direct costs of hospitalization for pleurodesis. In a randomized controlled trial comparing IPC to talc pleurodesis, no difference in overall comparative costs was noted. Higher initial hospital bed costs were seen in the talc pleurodesis group, whereas in the IPC group



most of the costs were made for ongoing drainage<sup>[23]</sup>. In patients with limited survival (< 14 wk), IPC was less costly with mean cost difference of -1719 US Dollars. In another study, this effect was seen in patients surviving less than 6 wk<sup>[24]</sup>. However, this financial benefit disappeared when substantial home care was needed for IPC treatment<sup>[23]</sup>. Taking these results together with the results of the earlier referred to TIME2 trial<sup>[11]</sup>, the authors conclude that the use of either IPC or talc pleurodesis should be based on patients' preferences after discussion of risks and benefits of each therapy<sup>[23]</sup>.

## CONCLUSION

Nowadays, IPC are used more frequently in the management of recurrent malignant pleural effusions and increasing expertise has been developed. Many studies show that IPC treatment has similar positive effects on dyspnea and quality of life as (repeated) chest tube drainage with talc pleurodesis. Effects on quality of life of a single intervention in this group of terminally ill patients with poor performance score have shown to be limited because of the many factors that influence these patients' well being in the last stage of their life.

IPC treatment is generally well tolerated with hardly any serious complications reported. Also, the costs of IPC treatment are comparable to those of chest tube drainage with talc pleurodesis. In patients with limited survival, IPC treatment even appears less costly. However, as far as we know, only one randomized controlled trial investigating the difference between IPC treatment and talc pleurodesis is available up to date, but several are underway. More research should be performed to investigate which groups of patients will benefit most from IPC treatment. However, we can conclude that the use of IPC is a safe, cost-effective and equally effective intervention to treat recurrent malignant pleural effusion as compared with pleural drainage followed by talc pleurodesis.

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## Unresectable stage III non-small-cell lung cancer: Have we made any progress?

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### Abstract

Lung cancer is responsible for the most cancer deaths worldwide with an incidence that is still rising. One third of patients have unresectable stage IIIA or stage IIIB disease. The standard of care for locally advanced

disease in patients with good performance status consists of combined modality therapy in particular concurrent chemoradiotherapy. But despite a lot of efforts done in the past, local control and survival of patients with unresectable stage III non-small-cell lung cancer (NSCLC) remains poor. Improving outcomes for patients with unresectable stage III NSCLC has therefore been an area of ongoing research. Research has focused on improving systemic therapy, improving radiation therapy or adding a maintenance therapy to consolidate the initial therapy. Also implementation of newer targeted therapies and immunotherapy has been investigated as well as the option of prophylactic cranial irradiation. This article reviews the latest literature on improving local control and preventing distant metastases. It seems that we have reached a plateau with conventional chemotherapy. Radiotherapy dose escalation did not improve outcome although increasing radiation dose-intensity with new radiotherapy techniques and the use of newer agents, *e.g.*, immunotherapy might be promising. In the future well-designed clinical trials are necessary to prove those promising results.

**Key words:** Stage III non-small-cell lung carcinoma; Chemoradiotherapy; Induction chemotherapy; Molecular targeted therapy; Consolidation chemotherapy; Dose-escalation; Altered fractionation; Advanced radiotherapy techniques; Prophylactic cranial irradiation

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**Core tip:** Lung cancer is responsible for the most cancer deaths. One third of patients have unresectable stage IIIA/IIIB disease. Despite a lot of efforts, local control and survival of these patients remains poor. Improving the treatment is therefore one of the biggest challenges in respiratory oncology. This review gives an overview of the important clinical studies that were performed the last decade in the treatment of unresectable stage III non-small-cell lung carcinoma and focuses on improvement of systemic therapy, with the exciting area

of implementation of newer agents (targeted therapy and immunotherapy) and improvement of radiotherapy, including the potential of prophylactic cranial irradiation.

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## INTRODUCTION

Lung cancer is responsible for most cancer deaths worldwide with an incidence that is still rising. Non-small-cell lung cancer (NSCLC) accounts for the majority of cases of lung cancer (85%)<sup>[1]</sup>. Stage III disease encompasses a heterogeneous group of patients with a variety in tumour size, lymph node location and prognosis for which treatment remains a major challenge. One third of all NSCLC patients have unresectable stage IIIA or stage IIIB disease<sup>[2]</sup>. This review will concentrate on the treatment of this group of patients.

The current standard of care for fit patients with unresectable stage III NSCLC is concurrent treatment with platinum-based doublet chemotherapy and radiotherapy<sup>[3]</sup>, yielding a 5-year overall survival (OS) of 15.1%, which is superior to the sequential approach<sup>[4]</sup>. Earlier randomized trials and meta-analyses had already proven that the combination of chemotherapy and radiotherapy, either concurrent or sequential, is superior to radiotherapy alone. During the last decade, strategies to increase survival have focused on improving systemic therapy, radiation therapy or adding a maintenance therapy to consolidate the initial therapy. Numerous trials have therefore investigated different agents, treatment sequences, and radiation schedules and doses.

The purpose of this review is to give an overview of the most important clinical studies that were performed the last decade in the treatment of unresectable stage III NSCLC.

## LITERATURE STUDY

A literature search was performed using PubMed, MEDLINE, the Cochrane Database of Systematic Reviews and Science Direct databases since 2005 up to June 2014 with the search term: "stage III", "non-small-cell lung carcinoma/cancer", "locally advanced lung cancer". Guidelines (ESMO, ACCP, NICE, NCCN) were manually searched as well as abstracts of the major conferences since 2005 and the reference sections of selected papers to retrieve relevant publications. Primarily randomized trials, meta-analyses, reviews and practice guidelines were

included. When lacking, additional articles were identified searching for outcomes like progression free survival (PFS), OS and objective response rate (ORR). Non-English articles were excluded.

## IMPROVING SYSTEMIC THERAPY

In the mid-nineties, two meta-analysis reviewing more than 50 trials confirmed the survival benefit of combining platinum-based chemotherapy with radiotherapy over radiotherapy alone in locally advanced unresectable NSCLC<sup>[5,6]</sup>. Numerous clinical trials were conducted afterwards to determine the best combination of chemotherapy and radiotherapy and to examine whether concomitant chemoradiotherapy was appropriate in this setting. Systemic chemotherapy is used to achieve two goals: it acts as a radiosensitizing agent to increase the effects of radiotherapy and as a cytotoxic agent to prevent or eradicate distant metastases. A Cochrane meta-analysis comparing concurrent to sequential chemoradiotherapy or radiotherapy alone performed in 2004<sup>[7]</sup> was updated in 2010<sup>[8]</sup> and confirmed the beneficial results of concurrent therapy seen in 2004 namely a hazard ratio (HR) of 0.74 (95%CI: 0.62-0.89) and a 10% absolute survival benefit at 2 years in favour of the concurrent approach, but at the expense of higher acute oesophageal toxicity. Aupérin *et al.*<sup>[4]</sup> in 2010 confirmed these results. In this meta-analysis a significant survival benefit of concurrent therapy was seen (HR = 0.84; *P* = 0.004) with an absolute benefit of 5.7% at 3 years (23.8% vs 18.1%). Here too significantly increased grade 3/4 oesophageal toxicity was reported, but no higher rates of pneumonitis were reported. Despite the higher toxicity, since these publications, concurrent chemoradiotherapy has been accepted as the standard of care. With improved staging, omission of elective node irradiation and more modern radiotherapy techniques, toxicity can be reduced. But also numerous trials have been performed to find more optimal chemotherapy combinations that can further improve the results obtained with the cisplatin-based doublets combined with continuous radiotherapy, as used in the trials included in the meta-analyses. Most commonly used chemotherapy regimens (*e.g.*, platinum/gemcitabin) administered to patients with metastatic disease cannot be safely administered at full doses in combination with radical doses of thoracic radiation because of the risk of pulmonary toxicity. Cisplatin/etoposide concurrent regimens allow the delivery of full doses of chemotherapy compared with third-generation doublets. This is a well-documented regimen with good survival data and acceptable toxicity particular in the control arm of the Hoosier trial<sup>[9]</sup>. Another well-known schedule is weekly carboplatin and paclitaxel. However three studies<sup>[10-12]</sup> show a lower median survival with the low-dose carboplatin. Until now there have been no randomized studies designed to investigate the optimal



**Table 1** Survival data from randomized trials comparing induction chemotherapy followed by concurrent chemoradiation therapy with concurrent chemoradiation therapy alone of chemotherapy followed by radiation therapy alone in non-small-cell lung cancer

Trial	Patients (n)	Schedule	Median survival (mo)	Survival (%)
Vokes <i>et al</i> <sup>[11]</sup>	366	CP × 2 → weekly CP + 66 Gy Weekly CP + 66 Gy	23 19	31 (3 yr) 29
Huber <i>et al</i> <sup>[16]</sup>	214	CP × 2 → weekly P + 60 Gy CP × 2 → 60 Gy	18.7 14.1	33 (3 yr) 14 (3 yr)
Gervais <i>et al</i> <sup>[14]</sup>	584	PVi × 2 → daily C + 66 Gy PVi × 2 → 66 Gy	14 11	- -
Clamon <i>et al</i> <sup>[13]</sup>	283	PVb × 2 → weekly C + 60 Gy PVb × 2 → 60 Gy	13.4 13.5	13 (4 yr) 10
Scagliotti <i>et al</i> <sup>[15]</sup>	89	DC × 2 → D + 60 Gy DC × 2 → 60 Gy	14.9 14	55.8 (1 yr) 58.7

CP: Carboplatin/paclitaxel; P: Paclitaxel; PVi: Cisplatin/vinorelbine; PVb: Cisplatin/vinblastin; DC: Docetaxel/cisplatin; D: Docetaxel.

chemotherapy regimen so no recommendation can be given whether cisplatin/etoposide is better than the combination with vinorelbine or carboplatin and paclitaxel. These regimens are used commonly.

### Induction chemotherapy

To further improve survival, control of micrometastatic disease must be optimised. Therefore induction chemotherapy preceding concurrent therapy has been examined. Randomized controlled trials did however not provide any significant improvement in survival<sup>[11,13-16]</sup> (Table 1).

### New drugs

**Pemetrexed:** Cisplatin/etoposide is until now the only regimen that can be given at full systemic dose in concurrent therapy. It has a known, predictable and acceptable side effect profile. More modern doublets with paclitaxel, docetaxel or gemcitabine cannot be given at full doses with concurrent high dose radiotherapy. The antifolate, pemetrexed, can be combined in full dose with thoracic radiotherapy up to 66 Gy. This has been demonstrated in phase I and II trials<sup>[17-20]</sup>. Cisplatin with pemetrexed was delivered at full dose concurrently with radiotherapy in the PROCLAIM trial, a randomized phase III trial comparing cisplatin/etoposide with cisplatin/pemetrexed. Unfortunately the phase III trial was stopped because the primary endpoint (improvement of OS) could not be reached.

### Targeted therapy

Addition of cetuximab, the monoclonal antibody targeting epidermal growth-factor receptor (EGFR) showed promising results in head and neck cancer better locoregional control and OS compared with radiotherapy alone<sup>[21]</sup> and in advanced NSCLC longer OS when cetuximab was added to chemotherapy<sup>[22]</sup>. Concurrent cetuximab with radical radiation therapy in stage III NSCLC has shown to be safe with acceptable toxicities<sup>[23-26]</sup>. The Cancer and Leukemia Group B (CALGB) 30407<sup>[27]</sup> evaluated the OS of patients with

unresectable stage III NSCLC treated with pemetrexed, carboplatin and thoracic radiotherapy with or without cetuximab in a phase II study. Unfortunately the overall response rate (73% without and 71% with cetuximab) and median survival (22.3 mo without vs 18.7 mo with cetuximab) were lower in the cetuximab group. Recently in the RTOG 0617 trial, patients were randomized to standard-dose (60 Gy) or high-dose (74 Gy) radiotherapy. Concurrent chemotherapy included weekly carboplatin and paclitaxel alone or with cetuximab. This RTOG 0617 trial also did not show any significant improvement of OS (18 mo OS with cetuximab 60.8% vs 60.2% without cetuximab;  $P = 0.484$ ; HR = 0.99)<sup>[28]</sup>. The radiotherapy related results are discussed later in this review.

When given with radiotherapy, EGFR tyrosine kinase inhibitors (TKIs) act as radiation sensitizer. Phase I and II data showed acceptable toxicity profiles<sup>[29-32]</sup> except for a possible higher risk of pulmonary toxicity<sup>[33]</sup> but the OS results have been less promising and variable (the latter probably reflecting differences in patients enrolled in the trials). A possible explanation and concern is that concurrent chemotherapy and EGFR TKI may be antagonistic, predominantly in wild-type EGFR<sup>[34]</sup>. Further investigation is needed to see if separate administration of chemotherapy and EGFR TKI can overcome this barrier<sup>[32]</sup> and to confirm that patients with EGFR mutations have improved outcomes when treated with combined modality treatment including EGFR inhibition by TKIs<sup>[32]</sup>.

Multi-targeted TKI's and mTOR inhibitors also show promising results in combination with radiation in cell lines acting as radiosensitizers although more clinical evidence is needed regarding efficacy and safety<sup>[35,36]</sup>.

Very disappointing results were seen in several trials where bevacizumab (the recombinant humanized monoclonal antibody that produces angiogenesis inhibition by inhibiting vascular endothelial growth factor A) was combined with chemoradiation. Preclinical and clinical data suggested that antiangiogenesis therapy and radiotherapy would be additive<sup>[37,38]</sup>. Combination of platinum-based therapy with bevacizumab in stage

**Table 2** Survival data from phase II and III trials using concurrent chemoradiation therapy followed by consolidation chemotherapy in non-small-cell lung cancer

Trial	Patients (n)	Schedule	Median survival (mo)	Survival (%)
Belani <i>et al</i> <sup>[10]</sup>	92	Weekly CP + 63 Gy → CP × 2	16.3	17 (3 yr)
Albain <i>et al</i> <sup>[96]</sup>	50	PE × 2 + 61 Gy → PE × 2	15	15 (5 yr)
Gandara <i>et al</i> <sup>[43]</sup>	83	PE × 2 + 61 Gy → D × 3	26	29 (5 yr)
Lau <i>et al</i> <sup>[97]</sup>	34	Weekly C + biweekly P + 61 Gy → CP × 2	17	40 (2 yr)
Hanna <i>et al</i> <sup>[44]</sup>	73	PE × 2 + 59.4 Gy → D × 3	21.2	27.1 (3 yr)

CP: Carboplatin/paclitaxel; P: Paclitaxel; PE: Cisplatin/etoposide; D: Docetaxel.

III B and IV had shown a longer OS in one trial and also higher response rate and longer progression free survival in all other trials<sup>[39-41]</sup>. However, the development of tracheoesophageal fistulae has led to early closure of phase II trials combining chemoradiotherapy and bevacizumab in NSCLC and SCLC<sup>[42]</sup>.

### Consolidation therapy

**Consolidation chemotherapy:** To improve OS in unresectable stage III NSCLC, the strategy of consolidation chemotherapy was investigated. Several phase II studies have assessed the safety and efficacy of concurrent chemoradiotherapy followed by consolidation chemotherapy. The phase II SWOG 9504 trial delivering docetaxel after concurrent chemoradiotherapy with platinum/etoposide showed the most promising median survival (26 mo)<sup>[43]</sup>. A phase III trial was therefore performed using the doublet cisplatin/etoposide concurrently with standard dose radiotherapy. Patients with response or stable disease were subsequently randomized to consolidation chemotherapy with docetaxel or best supportive care. Unfortunately there was no difference between the 2 arms [median survival time (MST) 21.2 mo for docetaxel arm and 23.2 mo for observation arm] and moreover there was more toxicity in the group that received docetaxel<sup>[44]</sup>. Recently another multinational phase III randomized trial using docetaxel and cisplatin as consolidation chemotherapy after concurrent chemoradiation also did not show an improvement in PFS (8 mo in observation arm vs 9.1 mo in consolidation arm;  $P = 0.38$ )<sup>[45]</sup> (Table 2).

### Maintenance targeted therapy

As the EGFR TKIs erlotinib and gefitinib are proven agents in advanced NSCLC in disease progression after chemotherapy and in first-line in patients with activating EGFR mutation positive tumours, maintenance therapy was investigated with gefitinib after concurrent chemoradiotherapy and consolidation docetaxel in the phase III SWOG S0023 trial<sup>[9]</sup>. The trial was designed to prospectively evaluate the role of gefitinib in improving OS and PFS in unselected patients. Unfortunately the gefitinib group had significantly worse survival (more rapid tumour progression, same toxicity) (HR = 0.633; 95%CI:

0.44-0.91;  $P = 0.013$ ; median survival times of 23 mo and 35 mo, respectively).

For maintenance with erlotinib a phase III trial investigating erlotinib after concurrent chemoradiotherapy showed no difference in progression-free survival interval<sup>[46]</sup>.

Also for maintenance with cetuximab no evidence exists to prove benefit in the multimodality treatment of unresectable stage III NSCLC.

Consolidation therapy with the anti-angiogenesis agent bevacizumab was also investigated but because of a high toxicity rate and lack of improvement in OS, no data underscore the further development in stage III treatment<sup>[47,48]</sup>.

### Maintenance immunotherapy

**Vaccine therapy:** Turning to the potential advantage of adding immunotherapy, promising results were seen in a randomized phase II B trial using a mucin 1 antigen-specific immunotherapy, tecemotide or L-BLP25. The MUC1 glycoprotein is overexpressed and abnormally glycosylated in NSCLC and other cancers. Tecemotide induces a T-cell response to MUC1 and therefore inhibits the abnormal interactions that trigger inappropriate activation of intracellular signalling pathways (promotes growth, proliferation and survival of cancer cells). In the randomized phase II B trial of tecemotide maintenance therapy vs best supportive care, a potential survival benefit was reported in patients with stage III B and IV NSCLC [MST L-BLP25 + best supportive care (BSC) 30.6 mo vs 13.3 mo for BSC only (HR = 0.548; 95%CI: 0.301-0.999)]<sup>[49,50]</sup>. In 2010 Butts reported similar survival results [1-year survival rate 82% (95%CI: 66%-98%), 2-year survival rate 64% (95%CI: 44%-84%)] in a single-arm phase II trial investigating tecemotide after chemoradiotherapy<sup>[51]</sup>. Because of these promising results, the randomized placebo controlled double-blind phase III START trial was initiated, the results of which have been published recently<sup>[52]</sup>. Tecemotide or placebo were given every week for 8 wk to patients with stable disease or objective response after chemoradiotherapy (concurrent vs sequential), and then every 6 wk until disease progression or withdrawal. The primary endpoint was OS. Tecemotide was very well tolerated yet there was no difference in median OS. What was

of interest, however, was the improvement of 10.2 mo in median OS in the concurrent chemoradiotherapy subgroup treated with tecemotide. In contrast there was no benefit in the group treated with sequential chemoradiation. It remains to date unclear what explains this difference: is it the heterogeneity in patient population between the groups of concurrent chemoradiation and sequential chemoradiation (e.g., performance status, tumour size)? The START trial threw a new light on the treatment of unresectable stage III NSCLC and especially on the possible effect of immunotherapy in multimodality treatment. Another phase II trial administering GV 1001, a telomerase peptide vaccine, after chemoradiotherapy, also demonstrated improved PFS and significantly improved OS in immune responders<sup>[53]</sup> and therefore a phase III study is planned. Unfortunately the START II trial designed to further investigate the potential benefit of tecemotide in maintenance after concurrent chemoradiation, will not be conducted because the pharmaceutical company is allocating resources to other immunotherapy strategies.

**Checkpoint inhibitors:** Promising results have been reported with the checkpoint inhibitors targeting cytotoxic T-lymphocyte-associated antigen 4 and the programmed death-1 pathway with achievement of durable clinical responses with manageable toxicity in advanced NSCLC and also in previously heavily treated lung cancer patients. Moreover recently there have been indications that combination of radiation treatment and immune checkpoint modulators could be beneficial in the treatment of malignant processes. Several investigators have shown the systemic effects of radiation therapy due to radiation-enhanced antitumoral immune responses<sup>[54,55]</sup>. The oxidative stress induced by radiation, augments the antigenicity of the irradiated tumor cells, more activating signals for dendritic cells become available. Dendritic cells produce neoantigens and together antitumoral immunity is induced even at sublethal doses of radiotherapy. This is called the immunomodulatory effect of radiation. Because of this mechanism cancer cells are efficiently recognized by the immune system and cleared. For this reason radiation could augment the antitumor immune responses elicited by checkpoint immunomodulators anti-CTLA-4 and anti-PD-L1<sup>[56]</sup>. Trials are currently ongoing evaluating the effect of checkpoint inhibitors in locally advanced unresectable stage III NSCLC following completion of treatment with chemoradiotherapy and no evidence of tumour progression (ClinicalTrials.gov Identifier NCT02125461).

## IMPROVING RADIOTHERAPY

With the current standard treatment of chemotherapy delivered concurrently with continuous radiotherapy up to a dose of 60 Gy over 6 wk, 2-year loco-regional control rate of 20%-44% has been reported<sup>[4,57,58]</sup>. As

the meta-analysis of Aupérin highlighted<sup>[4]</sup>, superior OS is related to better locoregional control. Therefore strategies that focus on improving local control by optimising radiotherapy may potentially enhance OS outcomes.

### Dose escalation

A meta-analysis of six trials of concurrent chemoradiotherapy showed better local control and survival with increased dose of radiation<sup>[57]</sup>. These findings laid the base for performing several prospective phase I / II cooperative group studies<sup>[59-61]</sup>. These trials all showed encouraging OS results and manageable side effects with total radiotherapy doses up to 74 Gy in 2 Gy fractions. Because of these favourable results, the randomized phase III RTOG 0617 trial<sup>[62]</sup> was launched to compare the standard-dose (SD: 60 Gy) vs high-dose (HD: 74 Gy) radiotherapy, both delivered in 2 Gy daily fractions. Unfortunately, 74 Gy did not prove superior in terms of OS, even more so, there was a trend towards lower 1-year survival in the 74 Gy arm [MST 28.7 mo (SD) vs 19.5 mo (HD); 18 mo OS rates 66.9% (SD) vs 53.9% (HD)] concluding that prolonging conventionally fractionated radiotherapy for dose escalation was not sufficient to create a better local tumour control. Although there is no clear evidence of higher toxicity in the 74 Gy arms, the percentage of grade V toxicity was higher when combining 74 Gy to chemotherapy and cetuximab. It has been unclear why the results of previous phase I - II trials did not translate into better outcome in the randomized trial, nor what might have caused this inferior outcome. The phase I - II studies might have been biased by a more favourable patient selection (more restrictive dose constraints enrolling patients with limited tumour burdens, first trial with use of FDG PET-CT imaging for staging). A possible explanation for the inferior outcome that was put forward was that in patients with larger tumours, the dose to the target might have been compromised in order to meet the dose constraints on the organs at risk. The RTOG performed a very detailed analysis of the quality aspects of the delivered radiotherapy that was published very recently<sup>[63]</sup>. The poorer outcome of the 74 Gy arm seems to be the result of a combination of factors: concurrent therapy was more difficult to complete, there was more non-compliance to radiotherapy planning, planning target volume coverage was poorer, there were more treatment-related deaths and higher doses on the heart. Further analyses will be performed to investigate the effect of the heart dose-volume on overall survival.

### Altered fractionation

While extending the overall treatment time (OTT) is not the way to go to enhance efficacy, counteracting tumour repopulation by increasing the dose intensity and/or accelerating the OTT is presumably a better approach. A meta-analysis of Mauguén<sup>[64]</sup> showed a

significant OS benefit from modified (accelerated or hyperfractionated, *i.e.*, different smaller fractions per day) radiotherapy in patients with locally advanced, nonmetastatic NSCLC. In the past continuous hyperfractionated accelerated radiotherapy (CHART) showed promising results. Both phase III trials of Saunders *et al.*<sup>[65]</sup> [54 Gy/1.5 Gy TID (three times daily) in 12 d] and Belani *et al.*<sup>[66]</sup> (57.6 Gy/1.5 Gy TID for 2.5 wk except for the weekend) showed a significant better OS and median survival with accelerated radiotherapy. Saunders *et al.*<sup>[65]</sup> showed an improvement in 2-year survival of 9% (20% to 29%) and Belani *et al.*<sup>[66]</sup> showed an improvement in MST from 14.9 mo to 20.3 mo. This could not be confirmed by the randomized phase III CHARTWEL trial (60 Gy in 40 fractions for 2.5 wk except for the weekend)<sup>[67]</sup>. These experiences have not widely translated into clinical practice, partly because of practical reasons (treatment with radiotherapy several times a day is difficult to implement), but also because greater toxicity in combination with chemotherapy remains an important challenge.

A shortened OTT can also be achieved by administration of a higher daily dose (hypofractionated radiotherapy). In a retrospective study of Pemberton<sup>[68]</sup>, a hypofractionated radiotherapy schedule (55 Gy in 2.75 Gy daily fractions) appeared as promising as CHART. Another retrospective trial of Amini *et al.*<sup>[69]</sup> concluded that accelerated hypofractionated radiotherapy (ACRT, 45 Gy in 15 fractions over 3 wk) showed significantly lower toxicity profiles in elderly receiving only radiotherapy compared to standard radiotherapy (60 Gy or more). Mehta *et al.*<sup>[70]</sup> developed a dose per fraction escalation schedule in NSCLC using advanced radiotherapy delivery technologies. This strategy was used by Donato *et al.*<sup>[71]</sup> in the context of combined (induction, sequential and concurrent) chemo-radiotherapy and showed that hypofractionated radiotherapy could be safely administered with or without chemotherapy. Outcomes (local tumour control and survival) were comparable with prospective data from phase II trials<sup>[72,73]</sup>. These promising results were confirmed in the meta-analysis of Manguen<sup>[64]</sup>, which was based on individual patient data from phase III trials. Higher 5-year OS rates [OS absolute benefit of 2.5% at 5 years (8.3% to 10.8%)] were seen in patients treated with a non-concurrent schedule but at the expense of transient acute oesophagitis. In non-concurrent setting, accelerated radiotherapy (*e.g.*, 66 Gy in 24 fractions) is therefore recommended in the ESMO guidelines<sup>[3]</sup>.

### Advanced radiotherapy techniques

The face of radiotherapy for lung cancer has changed by the introduction of advanced techniques allowing to conforming the delivered dose to the target volume better, thus translating into reduced rates of radiation-associated toxicity.

The introduction of FDG PET-CT has not only resulted in better patient selection by a better detection of extra-thoracic disease, but for radiotherapy planning, FDG PET-CT offers the potential of better target delineation. It allows distinguishing atelectasis from malignant tissue and to differentiate involved from uninvolved nodes, necessary for selective node irradiation. Both advantages translate into reduced treatment volumes, hence, lower radiation-induced toxicity<sup>[74]</sup>.

Intensity-modulated radiotherapy (IMRT) has improved the conformality of radiotherapy by modulating the intensity profile of the radiation beam. IMRT has been shown to decrease mean lung dose (MLD),  $V_{lung20}$  (percentile volume of total lung receiving 20 Gy) and maximal spinal cord dose compared to 3-dimensional conformal radiotherapy (3DCRT)<sup>[75]</sup>. This again yields the potential of delivering higher doses to the target volume while sparing the organs at risk or conversely delivering the same target dose with lower organs at risk doses. There are until now no prospective data comparing the efficacy and safety of IMRT to 3DCRT. Retrospective data comparing the outcome of patients treated with concurrent chemoradiation either with IMRT/4DCT (4-dimensional-CT, taking respiratory motion into account) or 3DCRT, show less acute and late pulmonary and oesophageal toxicity and a median survival of 21.6 mo<sup>[75-77]</sup>. There is a phase II randomized trial ongoing to investigate pulmonary toxicity and loco-regional progression in patients treated with concurrent chemo-radiotherapy and IMRT/4DCT/IGRT (image guided radiotherapy), vs 3DCRT (ClinicalTrials.gov Identifier: NCT00520702). IGRT has been optimized by the use of cone-beam CT that acquires 3-dimensional images of the patient pre-treatment allowing evaluation of the patient's anatomy in the treatment position.

Another interesting technique is adaptive radiotherapy (AR), which uses changes in tumour volume (*e.g.*, using CT or FDG-PET imaging during therapy) to adjust the radiotherapy treatment plan during therapy. It has been facilitated by the adoption of daily image guidance. In planning studies, this technique has demonstrated a significant reduction of the GTV (gross tumour volume) during treatment, with consequently a lower dose delivered to the organs at risk<sup>[78,79]</sup>. Ongoing trials are investigating the impact of this technique (ClinicalTrials.gov Identifier: NCT01507428).

A last interesting approach is to deliver the highest possible radiation dose to every individual patient: individualised accelerated radiotherapy (INDAR). In the Mastro clinic, this strategy is used with selective nodal irradiation based on FDG PET CT and accelerated radiotherapy in order to increase the biological effectiveness<sup>[80]</sup>. Each individual patient receives the highest possible biological radiation dose with the best therapeutic ratio based on his/her specific tumour and anatomical constraints. INDAR is not only feasible with



radiotherapy alone or with sequential chemoradiation, resulting in acceptable toxicity and promising survival rates that come close to results of concurrent chemoradiation schedules<sup>[81]</sup>, but in the concurrent approach as well. Recently published results of a phase II trial with INDAR in concurrent chemoradiation show acceptable toxicity and very promising 2 year OS reaching 52.4%<sup>[82]</sup>.

### Proton therapy

Proton therapy is of interest because it could further improve the therapeutic ratio for NSCLC through even better dose-conformality and reduction of the integral dose delivered to normal tissues, thus allowing dose escalation. This is mediated by the characteristic properties of protons: low doses upon tissue penetration, maximal dose deposition towards the end of the beam's path and finite range with minimal dose beyond the tumour.

Preliminary results of an ongoing phase II trial of concurrent CRT show a median survival of 24.9 mo and low rates of grade 3 pneumonitis (2%), and oesophagitis (11%)<sup>[83]</sup>. Sejpal *et al.*<sup>[84]</sup> retrospectively analyzed toxicity of concurrent platinum-based chemotherapy with proton therapy and showed lower rates of pneumonitis and oesophagitis compared to 3DCRT or IMRT, even if the latter were delivered at lower total doses.

Higher capital investments and operational costs of proton centres compared to photon therapy however still preclude wide access to proton therapy and therefore also hamper wide-spread investigation<sup>[85]</sup>. Another challenge for proton therapy in the treatment of pulmonary malignancies, due to the protons' finite range, is the respiratory tumour motion and size variability during radiotherapy which could lead to target miss or delivery of higher doses to the normal tissue<sup>[86]</sup>. In this respect, a study of Mohan *et al.*<sup>[87]</sup> showed inferior conformality of proton therapy compared to IMRT in highly irregular tumours. Therefore further research is ongoing - and warranted - to assess the feasibility, safety and efficacy and value for money of proton radiotherapy in stage III NSCLC.

## PROPHYLACTIC CRANIAL IRRADIATION

Brain metastases in patients with NSCLC are one of the most frequent sites of progression in previously treated locally advanced NSCLC<sup>[88]</sup>. Brain metastases moreover have a profound impact on survival and quality of life. Studies have shown that prophylactic cranial irradiation (PCI) is successful in decreasing the incidence of brain metastases but there is no proven survival advantage nor advantage in disease free survival<sup>[37,89]</sup>. There is still a trial ongoing comparing PCI to observation in stage III NSCLC (ClinicalTrials.gov Identifier: NCT01282437).

## POOR-RISK PATIENTS

It is important to mention that poor-risk factors influence the choice of treatment and the outcome in locally advanced NSCLC. The risk factors include age, performance status, comorbidities and weight loss<sup>[90]</sup>. It has been seen moreover that lung cancer incidence is strongly related to age, with the highest incidence rates being in older men and women. In the United Kingdom, *e.g.*, between 2009 and 2011, an average of more than four in ten cases were diagnosed in men and women aged 75 years and over underlining the importance of treatment according to age (cancer-researchuk.org). In advanced NSCLC advanced age alone has not been shown to influence response or survival with therapy<sup>[91]</sup>. In unresected stage III NSCLC it has been shown that despite toxicity, radiotherapy alone may improve the outcomes of elderly patients<sup>[92]</sup>. After concurrent chemoradiotherapy fit older patients have increased hematologic toxicity but renal toxicity, pulmonary toxicity, oesophagitis differed between trials. These patients do seem to have the same survival benefit though studies only included small amounts of elderly patients, mostly having good performance status and few comorbidities, and were not designed to make these conclusions for age-specific subgroups<sup>[93-95]</sup>. In conclusion fit elderly might benefit from concurrent chemoradiotherapy but there is a great need to develop trials including an important number of older patients with certain comorbidities and poorer performance status to develop tolerable combinations of systemic therapy with radiotherapy. Also there is a need to develop an applicable geriatric assessment tool to select the right patient for the right therapy.

## CONCLUSION

Despite a lot of efforts done over the last decade, local control and survival of patients with unresectable stage III NSCLC remains poor. Improving the treatment is therefore one of the biggest challenges in respiratory oncology. Staging has improved tremendously with FDG PET-CT and endobronchial ultrasound and this probably has contributed to improved outcomes in recent trials. But the improvement in radiotherapy techniques in the last decade will undoubtedly improve the therapeutic ratio and prognosis for the patients with unresectable stage III NSCLC. Dose escalation with conventional fractionation recently showed no promising results, but further research needs to be done towards altered fractionation schedules, individualised radiotherapy and proton therapy. What we are also still missing are trials investigating how the knowledge on radiation biology can help to improve patient selection and outcomes. In the context of systemic therapy, it seems that we have reached a plateau with conventional chemotherapy. The results

of targeted therapy concurrent with chemoradiation were so far not promising. Further investigation is needed to see if separate administration of chemotherapy and EGFR TKI can improve outcome and to confirm that patients with EGFR mutations have improved outcomes when treated with combined modality treatment including EGFR inhibition by TKIs. Newer agents such as multi-targeted TKIs and mTOR inhibitors should also be further investigated to confirm promising results *in vitro* when combined with radiation. The promising results of the START trial with the tumour vaccine tecemotide, threw a new light on the treatment of unresectable stage III NSCLC and especially on the effect of immunotherapy in multimodality treatment. To finalise the last decade it has become more clear that individual treatment protocols considering for instance age, health status, EGFR mutations, tumor size variability, *etc.*, have to be used to reach better results.

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## Role of hydrogen sulphide in airways

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### Abstract

The toxicity of hydrogen sulfide (H<sub>2</sub>S) has been known for a long time, as it is prevalent in the atmosphere. However accumulative data suggest that H<sub>2</sub>S is also endogenously produced in mammals, including man, and is the third important gas signaling molecule, besides nitric oxide and carbon monoxide. H<sub>2</sub>S can be produced *via* non enzymatic pathways, but is mainly synthesized

from L-cysteine by the enzymes cystathionine-γ-lyase, cystathionine-β-synthetase, cysteine amino transferase and 3-mercaptopyruvate sulfurtransferase (3MTS). The formation of H<sub>2</sub>S from D-cysteine *via* the enzyme D-amino acid oxidase and 3MTS has also been described. Endogenous H<sub>2</sub>S not only participates in the regulation of physiological functions of the respiratory system, but also seems to contribute to the pathophysiology of airway diseases such as chronic obstructive pulmonary disease, asthma and pulmonary fibrosis, as well as in inflammation, suggesting its possible use as a biomarker for these diseases. This review summarizes the different implications of hydrogen sulfide in the physiology of airways and the pathophysiology of airway diseases.

**Key words:** Hydrogen sulfide; Airways; Asthma; Chronic obstructive pulmonary disease; Inflammation

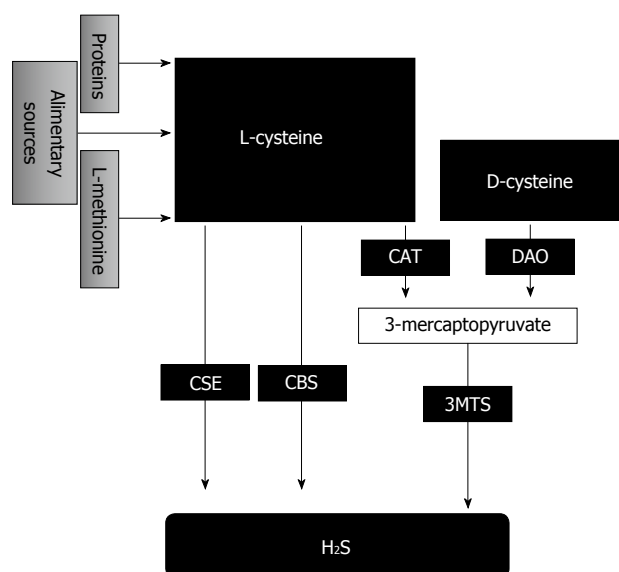
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**Core tip:** Hydrogen sulfide (H<sub>2</sub>S) is a metabolite produced in mammalian organisms both in physiological and in pathological conditions. The measured levels appear differentiated in inflammatory airway diseases, showing the need to acknowledge H<sub>2</sub>S not only as a metabolic mediator but as a signaling biomarker as well. This could be of clinical importance since H<sub>2</sub>S levels could be used in order to access staging or treatment efficiency in patients suffering from airway diseases.

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### INTRODUCTION

Hydrogen sulfide (H<sub>2</sub>S) is prevalent in the atmosphere since it is generated from sources both manmade and natural. Therefore organisms may need to either



**Figure 1** Schematic presentation of pathways for hydrogen sulfide synthesis from L- and D-cysteine via the enzymes cystathionine- $\gamma$ -lyase, cystathionine- $\beta$ -synthetase, cysteine amino transferase, D-amino acid oxidase and 3-mercaptopyruvate sulfurtransferase. H<sub>2</sub>S: Hydrogen sulfide; CSE: Cystathionine- $\gamma$ -lyase; CBS: Cystathionine- $\beta$ -synthetase; CAT: Cysteine amino transferase; DAO: D-amino acid oxidase; 3MTS: 3-mercaptopyruvate sulfurtransferase.

protect themselves from H<sub>2</sub>S or respond to it, but not particularly in a true signaling way. Although its production in mammalian tissues has been long known, H<sub>2</sub>S was largely ignored as a metabolic waste. Its toxicity seems to depend mainly on the concentration and considerably less on the duration of H<sub>2</sub>S exposure<sup>[1]</sup>. Importantly, accumulating data suggest that H<sub>2</sub>S is indeed endogenously produced in mammals, including man, and it represents the third important gas-signaling molecule, besides nitric oxide (NO) and carbon monoxide (CO). Even more, a possible interaction between gas-signaling molecules, especially NO and H<sub>2</sub>S, has been described<sup>[2,3]</sup>. Endogenously produced H<sub>2</sub>S affects many biological processes in most human systems, including gastrointestinal, cardiovascular, nervous, endocrine system and kidneys<sup>[4-6]</sup>. Available data suggest that main cellular targets of H<sub>2</sub>S are ion channels, such as ATP-sensitive potassium channels (K<sub>ATP</sub>) and transient receptor potential vanilloid channels (TRPV)<sup>[7]</sup>, transcription factors, such as heme oxygenase-1 (HO-1) and nuclear factor kappa B (NF- $\kappa$ B)<sup>[8,9]</sup>, as well as kinases like mitogen-activated protein kinases (MAPK)<sup>[10]</sup>. These biological effects of H<sub>2</sub>S have led to the study of its implication in many diseases and the development of H<sub>2</sub>S-donating drugs with a possible clinical potential<sup>[6,11]</sup>. The involvement of H<sub>2</sub>S in the early stages as well as in the development of inflammatory diseases of the respiratory system makes it important to identify it as a biomarker that could be helpful in the prediction or the treatment of such pathological conditions. This review focuses on

the effects of H<sub>2</sub>S on the respiratory system and its implication in airway diseases.

## H<sub>2</sub>S METABOLISM

The metabolic pathways of H<sub>2</sub>S production in mammals, have been extensively described and are summarized elsewhere<sup>[11-13]</sup>. Briefly, H<sub>2</sub>S can be synthesized from L-cysteine, a sulfur-containing amino acid derived from alimentary sources, synthesized from L-methionine through the so-called "trans-sulfuration pathway" with homocysteine as an intermediate, or released from endogenous proteins<sup>[1]</sup> (Figure 1). H<sub>2</sub>S is synthesized from L-cysteine by the enzymes cystathionine- $\gamma$ -lyase (CSE) and cystathionine- $\beta$ -synthetase (CBS). These enzymes are responsible for the majority of the endogenous production of H<sub>2</sub>S and their expression appears to be tissue specific<sup>[14]</sup>. Furthermore, the enzyme cysteine amino transferase (CAT) catalyzes the formation of 3-mercaptopyruvate from L-cysteine that is converted to H<sub>2</sub>S by the enzyme 3-mercaptopyruvate sulfurtransferase (3MTS). H<sub>2</sub>S can also be synthesized from D-cysteine via the enzyme D-amino acid oxidase (DAO) that converts D-cysteine to 3-mercaptopyruvate, followed by its conversion to H<sub>2</sub>S by 3MTS<sup>[13]</sup>. H<sub>2</sub>S can also be produced via non enzymatic pathways but these pathways account only for a small portion of the total H<sub>2</sub>S production<sup>[5]</sup>.

H<sub>2</sub>S, once produced in mammalian cells, can be stored as bound sulfane sulphur and released later in response to a physiological stimulus<sup>[12]</sup>. H<sub>2</sub>S is removed quickly from the cellular environment via three main catabolic pathways: (1) H<sub>2</sub>S oxidation, which takes place mainly in mitochondria, initially to thiosulfate, followed by its conversion to sulfite and sulfate; (2) H<sub>2</sub>S methylation by thiol S-methyltransferase (TSMT) to methanethiol and dimethylsulfide; and (3) sulfhemoglobin formation by H<sub>2</sub>S binding to methemoglobin<sup>[7]</sup> (Figure 2).

## H<sub>2</sub>S EFFECT ON AIRWAYS PHYSIOLOGY

Many different methods have been used in order to estimate H<sub>2</sub>S physiological levels in the plasma or validate its use as a biomarker for a variety of pathophysiological conditions. This effort is not always easy, due to artifacts, which often lead to inconsistent and contradicting measurements<sup>[15]</sup>. However, there are studies showing that in healthy adults between the age of 56.6 to 75.0 years, the median H<sub>2</sub>S serum concentration is approximately 35  $\mu$ mol/L<sup>[16]</sup>, while H<sub>2</sub>S plasma concentration seems to be higher in 6-12 years old children (Table 1)<sup>[17]</sup>. H<sub>2</sub>S concentration in exhaled air of healthy adult subjects was found to be 8-16 ppb<sup>[18]</sup>. On the other hand, H<sub>2</sub>S concentration in lungs, at least in rat, is approximately 30  $\mu$ mol/L<sup>[19]</sup>. H<sub>2</sub>S levels appear altered in some pathological conditions of the airways, like asthma, Chronic Obstructive



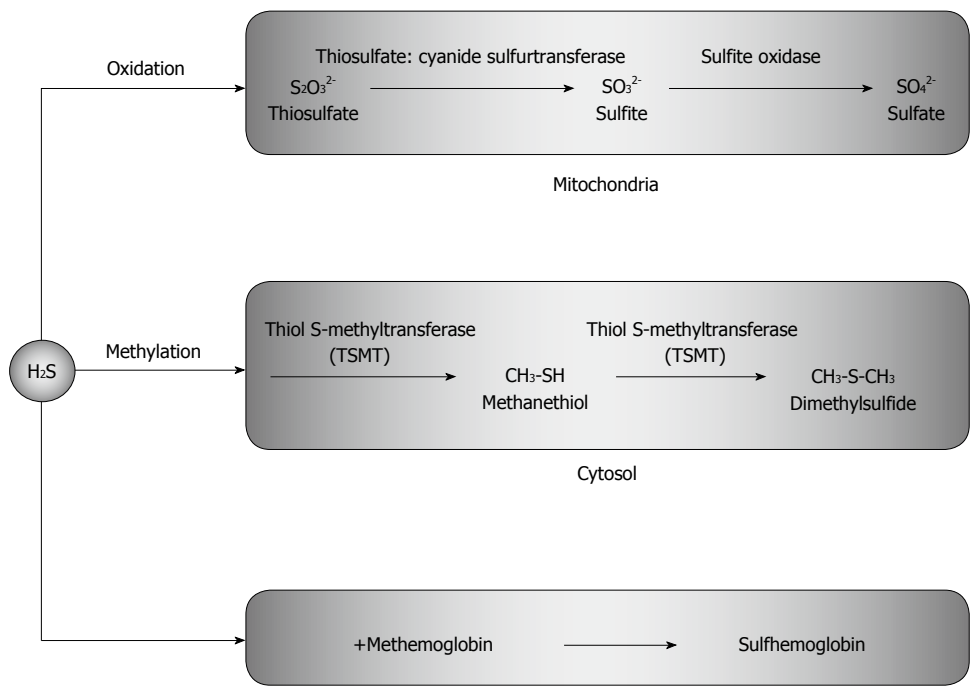


Figure 2 Main catabolic pathways of hydrogen sulfide. H<sub>2</sub>S: Hydrogen sulfide.

Table 1 Hydrogen sulfide concentration in healthy subjects and patients with asthma, chronic obstructive pulmonary disease or pneumonia			
Subjects	Age (yr)	H <sub>2</sub> S concentration in serum/plasma (μmol/L)	Ref.
Healthy	71-80	35.7 ± 1.2	[16]
	61-70	34.0 ± 0.9	[16]
	50-60	36.4 ± 1.1	[16]
	64.1 ± 8.7	35.4 ± 5.3	[43]
	9.22 ± 1.80	52.60 ± 5.56	[17]
Patients with bronchial asthma			
Bronchial asthma	6-12	44.17 ± 10.95	[17]
Neutrophilic group	53.0 ± 13.9	8.8 ± 4.7	[46]
Paucigranulocytic group	45.5 ± 15.7	6.9 ± 2.0	[46]
	9.03 ± 1.84	44.17 ± 10.95	[17]
Patients with stable COPD			
Patients with acute exacerbations of COPD			
	73.9 ± 8.3	33.8 ± 18.6	[43]
Patients in stage I to II	65.6 ± 1.6	40.5 ± 6.3	[16]
Patients in stage III		33.4 ± 2.9	[16]
Patients in stage IV		27.6 ± 1.6	[16]
Patients with pneumonia	57.6 ± 20.4	22.7 ± 14.6	[43]
H <sub>2</sub> S concentration in exhaled air (ppb)			
Healthy	52.86 ± 19.81	8.0-16.0	[18]
Patients with bronchial asthma			
Eosinophilic group	46.0 ± 15.2	7.7 ± 4.2	[46]
Paucigranulocytic group	45.5 ± 15.7	11.1 ± 4.6	[46]
Patients with COPD			
Acute exacerbations	67.5 ± 11.47	8.0-13.0	[18]
Stable COPD	64.11 ± 8.79	9.0-12.0	[18]

H<sub>2</sub>S: Hydrogen sulfide; COPD: Chronic Obstructive Pulmonary Disease.

Pulmonary Disease (COPD) and pneumonia (Table 1) suggesting that H<sub>2</sub>S is probably involved in the pathophysiology of some airways diseases. Therefore, like exhaled NO, H<sub>2</sub>S may be a possible biomarker for pulmonary diseases and/or a potential target for new therapeutic approaches for these diseases. Recent studies suggest that H<sub>2</sub>S participates in the relaxation of airway smooth muscle (Table 2). As far as the ability of airways to produce H<sub>2</sub>S is concerned, it has only been showed in porcine airways that H<sub>2</sub>S can be produced endogenously and that the H<sub>2</sub>S precursor, L-cysteine caused a concentration-dependent relaxation in peripheral bronchioles<sup>[20]</sup>. Most of the studies concerning the effect of H<sub>2</sub>S on airways are focused on the effect of exogenous H<sub>2</sub>S, using H<sub>2</sub>S donors. Contractility studies regarding the effect of the rapidly releasing H<sub>2</sub>S donor, sodium hydrosulfide (NaHS) demonstrated that H<sub>2</sub>S caused a concentration-dependent relaxation in porcine<sup>[20]</sup>, mouse and guinea pig bronchi<sup>[21]</sup>, as well as in rat trachea<sup>[22]</sup>. This relaxant effect did not depend on epithelium integrity, K<sub>ATP</sub> channels opening or NO release<sup>[22]</sup>. On the other hand, in guinea pig bronchi<sup>[23]</sup>, as well as mice lung<sup>[24]</sup>, H<sub>2</sub>S seems to induce the release of sensory neuropeptides, due to the activation of TRPV1 receptors, resulting to the contraction of these bronchi. Therefore, when sensory nerves were desensitized by capsaicin treatment, H<sub>2</sub>S induced a slight relaxation<sup>[23]</sup>. Deviations from these findings emerged from the study of Kubo *et al.*<sup>[21]</sup>, which showed that NaHS did not cause contraction in guinea pig bronchi, but a slight relaxation. Recently, an *in vivo* study revealed that

**Table 2** The effect of hydrogen sulfide on airway smooth muscle function

Tissue	H <sub>2</sub> S effects	Involved mechanism	Ref.
Porcine peripheral bronchiols	Relaxation	Alteration in K <sup>+</sup> channels activity	[20]
Guinea pig main bronchus	Slight relaxation		[21]
Guinea pig airways	Neurogenic inflammatory responses	Stimulation of TRPV1 receptors on sensory nerves endings	[23]
Mouse main bronchus	Relaxation	Independent of NK <sub>1</sub> /NK <sub>2</sub> tachykinin receptors, K <sub>ATP</sub> channels, production of NO, cGMP and prostaglandins	[21]
Mouse lung	Neurogenic inflammation	Stimulation of NK <sub>1</sub> and Substance P release	[24]
Mouse small intrapulmonary airways	Relaxation	Inhibition of Ca <sup>2+</sup> release from intracellular stores through InsP <sub>3</sub> receptors	[27]
Mouse tracheal smooth muscle cells	Relaxation	Activation of BK <sub>Ca</sub> channels	[26]
Rat trachea	Relaxation	Independent of K <sub>ATP</sub> channels, $\beta$ -adrenoceptors, epithelium and production of NO, cGMP and prostaglandins	[22]
Human ASMCs	Relaxation	Opening of K <sub>ATP</sub> channels	[29]
Isolated human airway smooth muscle cells	Relaxation Decrease of cell proliferation and IL-8 release	Inhibition of ERK-1/2 and p38 MAPK phosphorylation	[30]

H<sub>2</sub>S: Hydrogen sulfide; TRPV: Transient receptor potential vanilloid channels.

**Table 3** Implication of hydrogen sulfide in the pathophysiology in human airway diseases - its use as a biomarker

Disease	
COPD	Higher serum H <sub>2</sub> S level in patients with COPD compared with healthy subjects <sup>[16]</sup> Acute exacerbation of COPD decreases serum H <sub>2</sub> S level compared to patients with stable COPD <sup>[16,42]</sup> Higher sputum H <sub>2</sub> S levels in patients with acute exacerbation of COPD compared to those with stable COPD <sup>[42]</sup> Higher sputum-to-serum ratio of H <sub>2</sub> S in COPD subjects with acute exacerbation comparative with those with stable disease <sup>[42]</sup> Lower serum H <sub>2</sub> S levels in patients with COPD who required antibiotics treatment <sup>[43]</sup>
Asthma	In children, serum H <sub>2</sub> S concentration was significantly decreased compared to healthy subjects and correlated positively with FEV <sub>1</sub> <sup>[17]</sup> In adults, exhaled H <sub>2</sub> S was lowest in eosinophilic asthma correlated positively with FEV <sub>1</sub> <sup>[46]</sup>
Pulmonary fibrosis	H <sub>2</sub> S suppress human fibroblast migration, proliferation and phenotype transform stimulated by fetal bovine serum and growth factors and inhibits the TGF- $\beta$ <sub>1</sub> -induced differentiation of fibroblasts to myofibroblasts <sup>[53]</sup>

H<sub>2</sub>S: Hydrogen sulfide; COPD: Chronic Obstructive Pulmonary Disease; FEV<sub>1</sub>: Forced expiratory volume during first second; TGF- $\beta$ <sub>1</sub>: Transforming growth factor beta 1.

NaHS treatment inhibited the ozone-induced bronchial hyperresponsiveness in mice<sup>[25]</sup>. Studies regarding the mechanisms involved in H<sub>2</sub>S-induced relaxation of airways showed that H<sub>2</sub>S exerts its effect mainly by decreasing intracellular calcium levels. This is due both to reduced calcium influx<sup>[26]</sup> and to inhibition of Ca<sup>2+</sup> release from intracellular stores through InsP<sub>3</sub> receptors<sup>[27]</sup>.

It has also been shown, that H<sub>2</sub>S is involved in the relaxation of different smooth muscle types, by affecting a variety of ion channels. For example, in

vessels, H<sub>2</sub>S induces smooth muscle relaxation *via* its effect on K<sub>ATP</sub> channels located on vascular smooth muscle cells, or on small to medium conductance K<sup>+</sup> channels located on vascular endothelial cells, which results to membrane hyperpolarization and smooth muscle relaxation<sup>[28]</sup>. Similarly, in airways, evidence suggests the implication of K<sup>+</sup> channels in the relaxant effect of H<sub>2</sub>S<sup>[20]</sup>. Moreover, in primary cultured mouse tracheal smooth muscle cells NaHS seems to activate large conductance calcium activated potassium channels (BK<sub>Ca</sub>) causing an increase in potassium outward currents, cell hyperpolarization and inhibition of Ca<sup>2+</sup> influx<sup>[26]</sup>. Furthermore, H<sub>2</sub>S caused relaxation by opening K<sub>ATP</sub> channels in isolated human airway smooth muscle cells<sup>[29]</sup>.

Finally, both endogenous and exogenous H<sub>2</sub>S decreased human airway smooth muscle cell proliferation and interleukin (IL)-8 release induced by FCS, *via* the inhibition of the phosphorylation of extracellular signal-regulated kinase (ERK)-1/2 and p38 MAPK<sup>[30]</sup>. The effects of H<sub>2</sub>S donors that have been described were not affected by the inhibition of CSE, the blockade of K<sub>ATP</sub> channels or NO production.

## H<sub>2</sub>S IN THE PATHOPHYSIOLOGY OF AIRWAY DISEASES

Endogenous H<sub>2</sub>S participates in the regulation of physiological functions of the respiratory system (Table 3) and seems also to contribute in the pathophysiology of airway diseases such as COPD, asthma and pulmonary fibrosis (Table 3), suggesting its possible use as a biomarker for these diseases. Apart from the specific features of the pathophysiology, inflammation is a common theme of these diseases. Over the past decade, research data support a key role for H<sub>2</sub>S in acute or chronic inflammation in different

clinical conditions<sup>[31]</sup> and suggest that H<sub>2</sub>S has anti-inflammatory and cytoprotective effects that could be beneficial in lung diseases. Animal studies suggest that H<sub>2</sub>S in the lung increases the anti-inflammatory cytokine, IL-10, while it decreases the pro-inflammatory cytokine, IL-1 $\beta$  in burn and smoke-induced acute lung injury murine models<sup>[32]</sup> or hyperoxia-induced acute lung injury models in mice<sup>[33]</sup>. Animal studies also revealed that treatment with H<sub>2</sub>S attenuated lung injury and prolonged the subjects' survival<sup>[32,33]</sup>. Similarly, inhalation of H<sub>2</sub>S appears to be protective against ventilator-induced lung injury, in mice, by limiting cytokine release and neutrophil transmigration<sup>[34]</sup>. This protective role is associated with down-regulation of genes related to oxidative stress and inflammation and up-regulation of anti-apoptotic and anti-inflammatory genes<sup>[35]</sup>. Activating transcription factor 3 (Atf3), a protein that limits pro-inflammatory cytokine expression and controls the balance between proliferative and apoptotic signals<sup>[36,37]</sup>, may have an important role in H<sub>2</sub>S mediated lung protection, since H<sub>2</sub>S inhalation up-regulated *Atf3* gene<sup>[35]</sup>. Finally, in mice, NaHS treatment reduced the ozone-induced increase of the total cell number, including neutrophils and macrophages; the levels of cytokines, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), chemokine ligand 1, IL-6 and IL-1 $\beta$ <sup>[25]</sup>, as well as the increase of the bronchial alveolar lavage (BAL) fluid. On the other hand, inhalation of H<sub>2</sub>S protects against ventilator-induced lung injury by preventing edema formation, apoptosis, proinflammatory cytokine production, neutrophil accumulation, and inhibits heme oxygenase-1 expression<sup>[34]</sup>.

Although most of the studies suggest that H<sub>2</sub>S has an anti-inflammatory role, some studies have showed that it may contribute to neurogenic inflammation in airways<sup>[38]</sup>. Thus, both in guinea pig<sup>[23]</sup> and mouse<sup>[24]</sup> H<sub>2</sub>S induced the release of sensory neuropeptides, while only in mice, it also affected the level of substance P in the lungs, in sepsis-associated lung injury<sup>[39]</sup>.

### COPD

Despite inflammation, smoking is the main contributory factor for developing this disease. Animal studies suggest that H<sub>2</sub>S is protective against smoking-induced lung injury. Namely, exposure of rats to cigarette smoke resulted to an increase in CSE levels and the subsequent H<sub>2</sub>S administration reduced the number of inflammatory cells, as well as airway hyperresponsiveness<sup>[40]</sup>. Similar findings were reported in mice with tobacco smoke-induced emphysema<sup>[41]</sup>. Clinical studies showed evidence that H<sub>2</sub>S may be implicated in the pathophysiology of COPD and alteration of its levels may be connected with the severity of the disease. In humans, H<sub>2</sub>S serum levels were significantly higher in patients with COPD compared to healthy subjects and a positive correlation between the severity of COPD and H<sub>2</sub>S serum levels has been shown. Namely, in patients with stable COPD,

H<sub>2</sub>S serum levels were lower in patients with stage III than in those with stage I obstruction. Additionally, in patients either with or without COPD H<sub>2</sub>S correlated positively with the percentage of predicted forced expiratory volume (FEV<sub>1</sub>)<sup>[16]</sup>. On the other hand, acute exacerbation of COPD decreases H<sub>2</sub>S serum levels compared to those of patients with stable COPD<sup>[16,42]</sup>. On the contrary, H<sub>2</sub>S sputum levels were significantly higher in patients with acute exacerbation of COPD compared to those with stable COPD, which resulted in a higher sputum-to-serum level ratio of H<sub>2</sub>S in COPD subjects with acute exacerbation in comparison to those with stable disease<sup>[42]</sup>. As far as COPD treatment is concerned, measured H<sub>2</sub>S serum levels were significantly lower in patients with COPD who required antibiotics treatment<sup>[43]</sup>, while theophylline treatment did not alter significantly H<sub>2</sub>S serum levels of COPD patients<sup>[44]</sup>.

### Asthma

Clinical studies indicate that H<sub>2</sub>S serum levels were decreased in patients with either stable asthma or severe acute exacerbations. Even more the changes in H<sub>2</sub>S serum<sup>[45]</sup> or exhaled air<sup>[25]</sup> levels correlated positively with FEV<sub>1</sub> and negatively with the count of sputum cells, neutrophils<sup>[46]</sup> or eosinophils<sup>[25]</sup>. Similarly in children with asthma, H<sub>2</sub>S serum concentration was significantly decreased compared to healthy children and the concentration was positively correlated with lung function indices<sup>[17]</sup>. Whether the decrease of H<sub>2</sub>S serum levels in patients suffering from asthma is the cause or the consequence is not yet clear. Therefore, it is not clear if H<sub>2</sub>S levels could be used as a biomarker for the disease, like exhaled NO. However, Tian *et al*<sup>[17]</sup> proposed that decreased H<sub>2</sub>S serum levels might be used to indicate decreasing lung function and Wang *et al*<sup>[45]</sup> suggested that nasal H<sub>2</sub>S could be a way of accurately detecting H<sub>2</sub>S metabolism in the respiratory system since its levels will not be affected by oral conditions.

Additional evidence for the possible implication of H<sub>2</sub>S in the pathophysiology of asthma comes from animal studies. In the lungs of OVA-treated rats with asthma H<sub>2</sub>S serum levels and H<sub>2</sub>S production from the lungs were decreased in correlation with the decreased CSE expression level and CSE activity in lung tissues<sup>[47]</sup>. Even more the administration of NaHS or the CSE blocker, D,L-propargylglycine, alleviated or aggravated, respectively, airway hyper-responsiveness in both cigarette smoke exposure model and OVA-induced asthma rat models<sup>[40,47]</sup>.

### Pulmonary fibrosis

Pulmonary fibrosis is the final common pathway of a diverse group of lung disorders and is characterized by accumulation and abnormal activation of fibroblasts and myofibroblasts, resulting in excess extracellular matrix deposition and alveolar disruption<sup>[48]</sup>. Idiopathic pulmonary fibrosis (IPF) is caused by unknown reasons

and its pathophysiology has not yet been clarified, while there is a controversy among researchers whether inflammation constitutes the initial stimulus. Nevertheless, the initial stage is quickly followed by abnormal wound healing<sup>[49]</sup> and the main protein involved in this process seems to be epithelial cell-derived transforming growth factor beta 1 (TGF- $\beta_1$ )<sup>[50,51]</sup>. Evidence suggests that the endogenous CSE/H<sub>2</sub>S pathway may participate in the pathogenetic process of pulmonary fibrosis. Myofibroblasts have a main role in the pathogenesis of this disease and although they are generally considered to be differentiated from existing interstitial fibroblasts or bone marrow-derived stem/progenitor cells, epithelial cells also seem to be an important source of myofibroblasts in pulmonary fibrosis<sup>[25]</sup>. H<sub>2</sub>S seems to facilitate the maintenance of alveolar epithelial cell phenotype, since TGF- $\beta_1$  induces epithelial-mesenchymal transition and this effect is suppressed by H<sub>2</sub>S through a decrease in Smad2/3 phosphorylation, in lungs<sup>[52]</sup>. Fang *et al.*<sup>[53]</sup> reported that H<sub>2</sub>S suppressed human fibroblast migration, proliferation and phenotype transform that was stimulated by fetal bovine serum and growth factors and more specifically inhibited the TGF- $\beta_1$ -induced differentiation to myofibroblasts. These effects on pulmonary fibroblasts were partially mediated by decreased phosphorylation of ERK. Animal studies showed that NaHS administration ameliorated the bleomycin induced pulmonary fibrosis in rats<sup>[54,55]</sup>. This protective effect of H<sub>2</sub>S is due, partly, to inhibition of NF- $\kappa$ B p65 expression and regulation of Th1/Th2 balance<sup>[55]</sup>.

Last but not least it is important to point out the potential therapeutic use of H<sub>2</sub>S. Studies show that both the metabolite itself and its donors could be potentially used in the treatment of various diseases. Specifically, the H<sub>2</sub>S donor GYY4137 exhibits antihypertensive activity<sup>[1]</sup>, while other donors have anti-inflammatory<sup>[56]</sup> and antioxidant properties<sup>[57]</sup>. As far as respiratory diseases are concerned, there are studies showing that the donor-induced elevated levels of H<sub>2</sub>S are useful in the treatment of respiratory distress syndrome as well as other pathological conditions, since H<sub>2</sub>S can reduce the oxidative stress that is present in such disorders<sup>[1]</sup>.

## CONCLUSION

H<sub>2</sub>S appears to play a role both in the physiological function and the pathobiological conditions of the respiratory system. Its presence as a metabolite in inflammatory diseases, as well as the correlation that is found between H<sub>2</sub>S and inflammation mediators such as cytokines or growth factors, support its use as a biomarker of pathological conditions in both the lungs and the airways. However, determining H<sub>2</sub>S levels in body fluids is not an easy task, because H<sub>2</sub>S levels are influenced by H<sub>2</sub>S inhaled from atmospheric air. Such artifacts make its use as a biomarker difficult. Therefore, further studies are required in order to

determine the physiological H<sub>2</sub>S levels and their correlation with the phase, arising or deteriorating, of inflammatory diseases. Overall, it seems that H<sub>2</sub>S is not a cell waste, but an important metabolite that has yet to receive the proper attention.

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## Screening for lung cancer with chest computerized tomography: Is it cost efficient?

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### Abstract

Despite lung cancer (LC) screening by low-dose computerized tomography (LDCT) gaining many proponents worldwide, for many years it was not recognized as a life-prolonging and cost-effective procedure, until recently. Prospective observational studies had not been able to prove that this screening prolongs survival, but they helped to specify the inclusion and exclusion criteria. Long-awaited results of a prospective, randomized trial finally provided the evidence that LC screening with LDCT can prolong survival of the screened population. Several cost-effectiveness analyses were performed to justify mass introduction of this screening. Results of these analyses are equivocal, although conclusions highly depend upon inclusion and exclusion criteria, methods of analysis and prices of medical procedures which differ between countries as well as the incidence of other pulmonary nodules, especially tuberculosis. Therefore, cost-effectiveness analysis should be performed separately for every country. Cost-effectiveness depends especially upon the rate of false-positive results and the rate of unnecessary diagnostic, screening and treatment procedures. To ensure high cost-effectiveness, LC screening should be performed in accordance with screening protocol, in dedicated screening centers equipped with nodule volume change analysis, or as a prospective non-randomized trial, to ensure compliance with the inclusion and exclusion criteria. To ensure high cost-effectiveness of LC screening, future research should concentrate on determination of high-risk groups and further specifying the inclusion and exclusion criteria.

**Key words:** Lung cancer; Non-small cell lung cancers; Screening; Cost-effectiveness; Computerized tomography; Low-dose computerized tomography

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**Core tip:** Results of prospective, randomized trial finally provided the evidence that lung cancer screening with computerized tomography prolongs survival of the screened population. Several cost-effectiveness analyses were performed to justify mass introduction of this screening, but their results differ between countries. Cost-effectiveness depends especially upon the rate of false-positive results which increase the number of unnecessary medical procedures. Therefore, to ensure high cost-effectiveness, lung cancer screening should be performed in accordance with screening protocol, in dedicated screening centers equipped with nodule volume change analysis, or as a prospective non-randomized trial, to ensure compliance with the inclusion and exclusion criteria.

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## INTRODUCTION

Computerized tomography is today widely available in most, even moderately developed, countries. When used for screening of lung cancer (LC), it allows to detect neoplasm which is the leading cause of cancer death<sup>[1]</sup> in an early stage, which dramatically improves cure rate of newly diagnosed LC from 12%<sup>[2]</sup> to over 80%<sup>[3]</sup>. Despite that, the only country where LC screening with low-dose computerized tomography (LDCT) is widely used is Japan, where such programs are officially supported since 30 years ago. The main reasons why computerized tomography (CT) screening has not become popular worldwide are, developed in the United States, the principles of Good Clinical Practice (GCP) and Evidence-Based Medicine (EBM), which require new diagnostic and therapeutic methods to be well tolerated and to improve survival of the group in which they are administered, and finally, to confirm this in a prospective, randomized trial<sup>[4]</sup>.

These rules of GCP and EBM are a cornerstone of modern medical science and do well in the implementation of new therapeutic procedures and medicines, but their administration to new screening procedures is controversial, for several reasons. Firstly, it is not clear what poor toleration of a screening procedure means: can it be, *e.g.*, discomfort caused by detection of a benign nodule? Also, performing prospective randomized trial on a screening procedure never assesses a new method of screening, but always compares two methods of screening of different intensity, because it is believed unethical

not to administer any screening in the control arm. An exception is an ongoing in Holland, Belgium and Denmark NELSON trial, in which control arm receives only community care<sup>[5]</sup>. Moreover, participants often change arms of trial arbitrarily. Finally, since the primarily criterion of the effectiveness of cancer treatment is a 5-year survival, to assess the impact of screening on the survival of the study population, at least one generation should be sacrificed. Meeting the requirements for obtaining recommendation for new screening procedures is so difficult that several consecutive international randomized trials assessing the value of mammography in detecting breast cancer showed no effect on survival of the study population<sup>[6]</sup>. Fortunately for breast cancer patients, despite lack of proven impact on survival, mammography programs were not discontinued and subsequent randomized trials provided expected evidence<sup>[7]</sup>.

From this perspective, LC patients are less lucky than breast cancer patients. Despite early detected LC having a higher cure rate than breast cancer of similar size, and a 5-year survival almost inevitably meaning cure (unlike in breast cancer which can recur more than 20 years after radical treatment), despite it being inappropriate to call LC a "deserved" disease (most new cases develop in patients who never smoked cigarettes or stopped smoking over 10 years ago<sup>[8]</sup>), programs for LC screening in most countries are still waiting for official support and recommendations.

Due to reasons mentioned above, waiting for results of a prospective randomized trial on chest LDCT screening performed in the United States<sup>[9]</sup> did not satisfy supporters of this screening. They have organized, mostly in the United States, non-randomized observational studies<sup>[10]</sup>, to show that LDCT is able to increase resectability rate, cure rate and prolong survival in the screened population<sup>[3]</sup>. Finally, the National Lung Screening Trial provided evidence of a 20% reduction in lung cancer mortality and a 6.7% decrease in all-cause mortality among current and former smokers at high risk<sup>[11]</sup>. As a result, the United States Preventive Services Task Force (USPSTF) has recommended this screening, allowing coverage of LDCT to private health insurers under provisions of the Affordable Care Act which states that LDCT must be covered without cost-sharing by qualified health plans starting January 1, 2015. Because private insurers cover medical expenses mostly for population below 64 years, while 70% of new lung cancer cases are diagnosed above that age, the decision of Centers for Medicare and Medicaid Services which provides medical insurance for elderly population, will be of key importance<sup>[12]</sup>. Following USPSTF recommendations, appropriate recommendations have been adopted by other organizations with an interest in LC, including the National Comprehensive Cancer Network, American Association for Thoracic Surgery, American College of Radiology, Society of Thoracic Surgeons, International



**Table 1** Results of baseline screening with low-dose chest computerized tomography in asymptomatic smokers

Institution, country	Number of participants	Number (%) of positive results	Number (%) of diagnosed lung cancer	NSCLC	Stage I disease	Mean age of participants
Early Lung Cancer Action Project (ELCAP), United States <sup>[10,14]</sup>	1000	233 (23)	27 (2.7)	96%	85%	67
New York Early Lung Cancer Action Project (NY-ELCAP), United States <sup>[15]</sup>	6295	906 (14)	101 (1.6)	94%	97%	66
International Early Lung Cancer Action Project (I-ELCAP), United States <sup>[3]</sup>	31567	4186 (13)	405 (1.3)	-	86%	61
Mayo Clinic, United States <sup>[9,16,17]</sup>	1520	782 (51)	30 (2)	93%	75%	59
Anti-Lung Cancer Association (ALCA), Japan <sup>[18]</sup>	1611	186 (11.5)	13 (0.9)	100%	77%	60
University of Munster, Germany <sup>[19,20]</sup>	817	350 (43)	11 (1.3)	91%	70%	53
Pomeranian Pilot Program of Lung Cancer Screening, Poland <sup>[21]</sup>	2002	982 (49)	11 (0.5)	100%	91%	59
Total	44812	7625 (17)	598 (1.3)			
Median	6402	1089 (17)	85 (1.3)			

NSCLC: Non-small cell lung cancers.

Association for the Study of Lung Cancer, American College of Chest Physicians, and the American Cancer Society<sup>[13]</sup>.

## DISCUSSION

Lung cancer is diagnosed in about one out of 75 LDCT baseline examinations, as shown in the results of studies presented in Table 1.

In Table 1 only results of single baseline screenings for LC are presented. The age of participants varied between studies, in a Japanese study patients accrued were 40-79 years old, but most studies did not include patients below 50 years old. Screening was addressed to persons who had smoked at least 10 pack-years of cigarettes, but in a Japanese study 16% of patients did not have smoking history<sup>[18]</sup>. The rate of pulmonary lesions also varies. On average, in one out of 6 examinations pulmonary lesions are found, but they are more common in populations which had a common contact with tuberculosis half century ago (Poland)<sup>[22]</sup> and less common in countries where tuberculosis was less common that time (Japan)<sup>[23]</sup>. Comparison of consecutive data from observational studies (ELCAP, NY-ELCAP and I-ELCAP) shows that the rate of false-positive results decreases in subsequent studies, which can be explained by growing experience of radiologists which resulted in protocol change. According to International Early Lung Cancer Action Program (I-ELCAP) protocol, only solid lesions at least 15 mm in diameter require immediate evaluation [positron-emission tomography (PET-CT), biopsy], while in most earlier studies tumors at least 10 mm in diameter were send for an immediate evaluation.

Decision trees developed by I-ELCAP are different for baseline and annual screenings and are designed to minimize the risk of unnecessary repeat LDCT in order to improve cost-effectiveness. Figure 1 shows steps for a new patient during the first year after the baseline screening, whereas Figure 2 shows steps for the subsequent annual screenings<sup>[13]</sup>.

Results of meta-analysis presented in Table 1 show that 96% of neoplasms diagnosed with LDCT are non-small cell lung cancers (NSCLC), and only 4% are small-cell lung cancers (SCLC). According to data from the Table 1, about 86% of NSCLC diagnosed with screening are stage I disease.

Another way to convince decision-makers to support LC screening programs are pharmacoeconomical analyses, which aim to find out whether LC screening is cost-effective. The most important parameters which are measured in these studies are incremental cost-effectiveness ratio (ICER) and an incremental cost per quality-adjusted life-year (QALY) gained, which is the cost of prolonging the life of a patient by one year. In most countries, the new medical procedure is believed to be cost-effective when cost per QALY is less than 3 times growth domestic product (GDP) per capita<sup>[24]</sup>. Cost-effectiveness analyses have to be performed separately for every country (and maybe even bigger region), not only because GDP per capita is different, but also because rate of lung cancer, rate of other pulmonary diseases than lung cancer (for example tuberculosis), methods of calculation and reimbursement of medical expenses, prices for medical procedures and medicines vary between countries. It must be stressed, that prices of medicines (chemotherapy) and radiotherapy are similar throughout the World, regardless of the wealth level of a country, unlike prices of surgery, LDCT and follow-up which are lower in countries where labor is less expensive. Therefore, paradoxically, LDCT screening for lung cancer can be more cost-effective in middle-income than in high-income countries. During the last decade, prices of LDCT screening procedures decreased, similarly as it has happened to prices of all CT procedures in market-oriented economies, unlike prices of medical treatment of advanced cancer which tend to grow because of development of new medicines.

An important parameter for calculation of cost-effectiveness is lead time. Lead time is a time span between detection of cancer with a screening

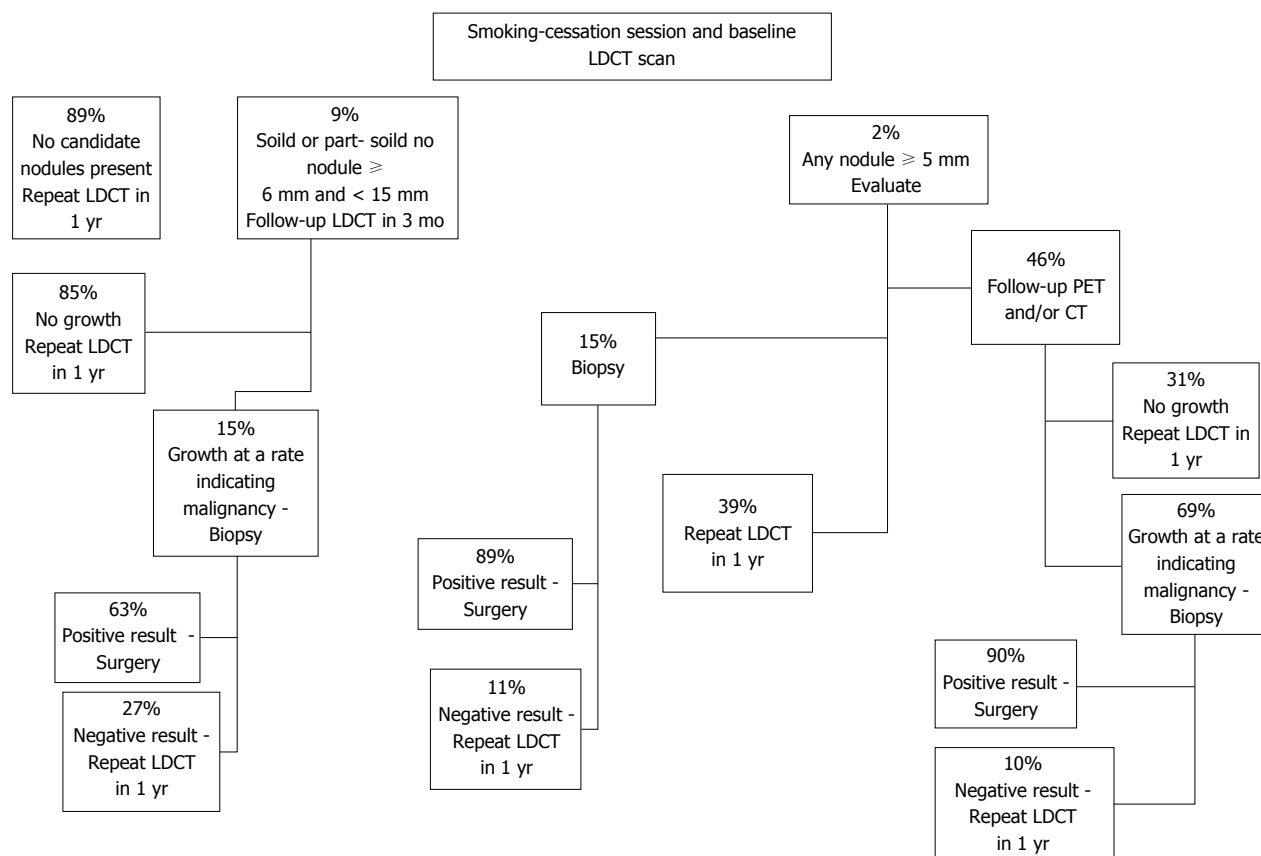


Figure 1 Decision tree within one year after baseline screening<sup>[13]</sup>. LDCT: Low-dose computerized tomography.

procedure and time when cancer would have been discovered without screening. It is often assumed that lead time for NSCLC cancer is about 3 years, *e.g.*, 6 doubling times (with assumption, that doubling time is 180 d)<sup>[14]</sup>. However, even without screening, most curable LC cases are detected before onset of clinical manifestations, by radiological procedures performed due to other reasons (*e.g.*, in follow-up CT-scans performed due to other cancers, after chest injuries, due to cardiac chest pain, pneumonia, *etc.*). In such cases lead time is much shorter than 3 years, usually it can be assumed that it is equal zero. On the other hand, solid pulmonary adenocarcinomas or SCLC can develop metastases and become unresectable and incurable even when the primary tumor is less than 5 mm in diameter. In such cases lead time is also zero. On the other hand, lead time can be even longer than 3 years in slowly growing cancers, especially peripheral squamous cell carcinoma and subtype A and B adenocarcinomas, according to Noguchi classification (pre-invasive adenocarcinoma, which grows not as a solid tumor but grows in interfollicular spaces creating so-called ground-glass opacities on chest CT scans)<sup>[25]</sup>. Therefore, it is questionable whether lead time should be as long as 3 years. We believe that the assumption that lead time for LC is 3 years is either not necessary at all or lead time should be decreased.

Results of cost-effectiveness analyses concerning LDCT for LC are equivocal. In our data which are

ahead of print<sup>[26]</sup>, ICER calculated for year 2008 prices was about \$1575. The borderline cost-effectiveness of medical procedure in Poland is set at 3 times GDP (gross domestic product) per capita per one year of life gained. In year 2014 it was 27845.25 EUR<sup>[24]</sup>, therefore the implementation of low-dose chest CT for screening of LC is cost-effective. This is similar to results of the study from Israel, where QALY gained was \$1464<sup>[27]</sup>. On the other hand, in the study performed in Australia cost per QALY gained depended upon age of participants and number of pack-years of cigarettes smoked, and varied from Aus\$32617 to Aus\$114056, and authors concluded that LC screening with LDCT is not cost-effective<sup>[28]</sup>.

Cost-effectiveness analysis of the National Lung Screening Trial performed in the United States varies depending upon methods used. While some authors calculated that the additional cost of screening to avoid one LC death is \$240000<sup>[29]</sup>, later calculations performed by the similar group of authors but after administration of different methods found LC screening with LDCT as highly cost-effective, at cost per QALY gained less than \$19000<sup>[13,30]</sup>.

## CONCLUSION

Comparison of cost-effectiveness analyses allows to formulate the conditions that must be met in order to achieve high profitability of LC screening. The

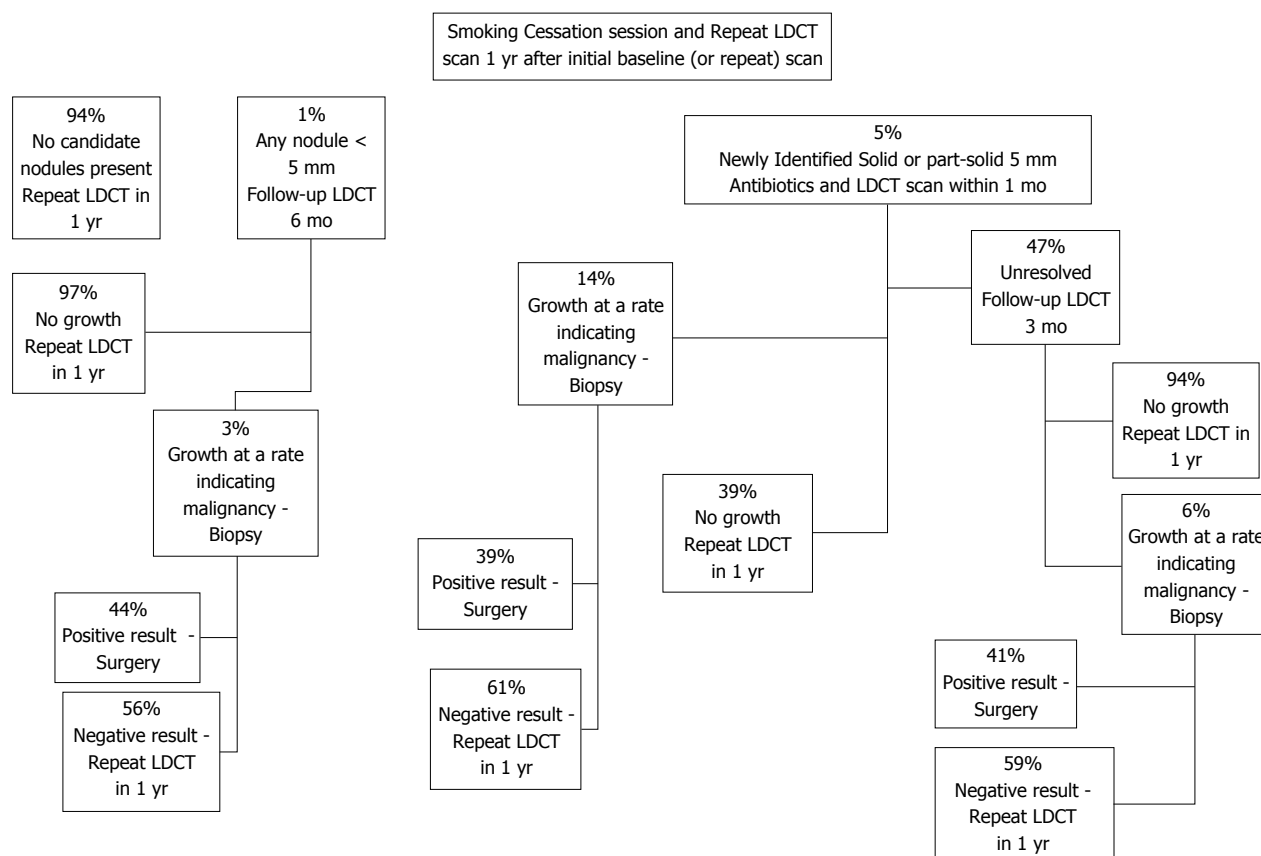


Figure 2 Decision tree one year after initial baseline or repeat scan<sup>[13]</sup>. LDCT: Low-dose computerized tomography.

first condition is careful formulation and observance of inclusion and exclusion criteria for the screening program which will ensure that screening will be performed only in high risk population, excluding patients who are not suitable for radical surgical treatment. Currently it seems that to ensure high cost-effectiveness, screening should be addressed to participants at least 55 years old, suitable for surgery, who smoked at least 20 pack-years and quit smoking not more than 20 years ago. Secondly, LDCT should be performed in specialized centers where radiologists are trained in detecting early LC and differentiating it from benign lesions, which would minimize the risk of false-negative and false-positive results. Thirdly, radiologists should be equipped with modern computerized programs allowing to analyze changes in nodule volume, which will decrease the number of repeat LDCT, ideally to only one procedure. Taking into account a Japanese experience, it should also be recommended to organize specialized screening centers, dedicated to performing screening procedures according to protocol, *e.g.*, in accordance with inclusion and exclusion criteria. Before such centers are organized, following inclusion and exclusion criteria could be ensured by performing LDCT screening for detection of LC within non-randomized clinical trials. Comparison of cost-effectiveness analyses from Australia, US, Israel and Poland shows

that LC screening can be more cost-effective in developed, middle-income countries, where prices of chemotherapy and radiotherapy are similar to those in high-income countries, but cost of labor (*i.e.*, cost of screening, surgery and follow-up) is lower.

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## Current methods of staging and restaging of the mediastinal nodes in non-small-cell lung cancer

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### Abstract

To analyze the current methods of primary staging and repeated staging (restaging) of the mediastinal nodes in non-small-cell lung cancer (NSCLC), all methods currently used for staging of NSCLC are analyzed. These methods include imaging techniques [computer tomography (CT), positron emission tomography (PET) combined with CT (PET/CT)], endoscopic/ultrasound techniques (endobronchial ultrasound/

transbronchial needle aspiration) and endoscopic ultrasound/fine needle aspiration and surgical techniques [standard cervical mediastinoscopy, video-assisted mediastinoscopy, extended mediastinoscopy, video-assisted mediastinoscopic lymphadenectomy, transcervical extended mediastinal lymphadenectomy, anterior mediastinotomy (Chamberlain procedure) and video-assisted thoracic surgery]. The diagnostic yield of Chest CT is regarded insufficient for both, primary staging and restaging. The PET/CT became a standard imaging technique preceding curative surgery of radical chemoradiotherapy. The issue of intraoperative staging is also described. Finally, the author's proposed algorithm of staging, both for primary staging and restaging after neoadjuvant therapy is presented. Detailed staging of NSCLC enables selection of patients with early stage disease for curative surgical/multimodality treatment and helps to avoid unnecessary surgery in advanced disease.

**Key words:** Lung cancer; Staging; Endoscopy; Surgery; Mediastinum

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**Core tip:** All methods currently used for staging of non-small-cell lung cancer are analyzed. These methods include imaging techniques [computer tomography (CT), positron emission tomography (PET) combined with CT (PET/CT)], endoscopic/ultrasound techniques endobronchial ultrasound/transbronchial needle aspiration and endoscopic ultrasound/fine needle aspiration and surgical techniques standard cervical mediastinoscopy, video-assisted mediastinoscopy, extended mediastinoscopy, video-assisted mediastinoscopic lymphadenectomy, transcervical extended mediastinal lymphadenectomy, anterior mediastinotomy (chamberlain procedure) and video-assisted thoracic surgery. The issue of intraoperative staging is also described. Finally, the author's proposed algorithm of staging, both for primary staging and restaging after neoadjuvant therapy is presented.

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## INTRODUCTION

The prognosis of lung cancer is still very bad with only 16.3% of all patients with of treatment for individual patients in aim to provide the best chance of cure in the lung cancer surviving 5 years<sup>[1]</sup>. One of the main important issues is a proper choice early stage of the disease and to avoid unnecessary invasive surgical or multimodality treatment in cases with the advanced disease. Estimation of the TNM factors is the key of the process of staging. Because non-small-cell lung cancer (NSCLC) is often found in a disseminating phase this is most important to rule-out distant metastases (M1). Even in stage IV, however NSCLC is a treatable, although not curable disease due to the survival advantage and improvement in quality of life over best supportive care (BSC) after platinum-based chemotherapy<sup>[2]</sup>. In patients with M1 there is no role for any curative approach like surgery or radical chemo-radiotherapy and chemotherapy or best supportive care are the only reasonable options. The only exception from this rule are the isolated brain metastases without any other symptoms of loco-regional or distal dissemination in patients who are otherwise amenable to treatment with surgery or irradiation. In the part of these patients subsequent surgical treatment is undertaken with reported 5-year survival 13% (7%-21%)<sup>[3]</sup>.

For patients with IIIB NSCLC with good performance status radical chemoradiotherapy is the preferred treatment option<sup>[4]</sup>.

The limits of effectiveness of surgery are also clearly understood with more benefit than harm in stage I amenable to resection alone because radical surgery still offers the best chance of cure despite recent reports on effectiveness of stereotactic body radiotherapy (SBRT), also described as Stereotactic ablative radiotherapy (SABR) emerging as an alternative to surgery<sup>[5-8]</sup>. SABR was shown to be superior to conventional radiotherapy in regard to local control and overall survival<sup>[9]</sup>. In patients with stage II NSCLC surgery with adjuvant chemotherapy is regarded the standard of care with neoadjuvant chemotherapy followed by surgery as an alternative in patients with N1 nodes discovered preoperatively<sup>[10]</sup>. The most controversial group are patients with stage IIIa, N2 metastatic mediastinal nodes for whom multimodality treatment with or without subsequent surgery should be considered<sup>[3,11]</sup>.

Therefore, the critical issue in planning of the treatment in patients with NSCLC is a proper staging

allowing for choice of the best therapy for individual patients. Staging of the mediastinal nodes is critical to differentiate between patients in stage I and II who could benefit from curative surgery or radiotherapy, stage IIIA who should undergo multimodality treatment and stages IIIB-IV managed without operation. Repated staging (restaging) regards patients who underwent neoadjuvant treatment and are considered candidates for subsequent radical surgery.

In the clinical practice, mediastinal nodal staging include imaging, endoscopic and surgical techniques. Recently, there has been an increasing interest in genetic and proteomic which are still experimental, however. The results of current studies are promising and it is possible that in the future circulating subtypes of micro RNA, DNA and the other biomarkers might be very useful in staging of NSCLC<sup>[12-14]</sup>. However, currently, these techniques does not allow for accurate staging of the mediastinal nodes, however. Therefore the issue of biomarkers will not be addressed in this article.

The aim of this study is to summarize current experience on staging and restaging of NSCLC.

## LITERATURE RESERCH

This article is based on the search made in PubMed for English language publications on staging of NSCLC from the period 2009-2014. Keywords: lung cancer, nsclc staging, nsclc invasive staging, ebus, eus, mediastinoscopy, vats were used. Some other important earlier publications were considered, as well. Only the publications in a peer-reviewed journals, the publications including large numbers of patients, with clearly presented methodology and results were used in this study. The results of the prospective randomized trials, practice guidelines, systematic reviews, and meta-analyses were regarded especially important were included preferentially. This is not a systematic review because the choice of the articles cited in this paper was dependent on the subjective opinion of the author. Therefore, the methodology of a Systematic Review was not obeyed, like the one presented by the PRISMA methodology<sup>[15]</sup>. All methods currently used for staging of NSCLC are analyzed. These methods include imaging techniques [computer tomography (CT), positron emission tomography (PET) combined with CT (PET/CT)], endoscopic/ultrasound techniques [endobronchial ultrasound/transbronchial needle aspiration (EBUS/TBNA) and endoscopic ultrasound/fine needle aspiration (EUS/FNA)] and surgical techniques [standard cervical mediastinoscopy (CM), video-assisted mediastinoscopy (VAM), extended mediastinoscopy, video-assisted mediastinoscopic lymphadenectomy (VAMLA), transcervical extended mediastinal lymphadenectomy (TEMLA), anterior mediastinotomy (Chamberlain procedure) and video-assisted thoracic surgery (VATS)].

## RESULTS

### Primary staging

**Imaging studies:** Chest CT is generally the preliminary step of diagnosis of NSCLC providing important information on staging of the disease. A staging process is continued in patients with clinical stages I - IIIb who are candidates for surgery or multimodality treatment. Chest CT is most often performed with the use of the contrast-enhanced (CE) technique allowing for differentiation of the mediastinal nodes from the mediastinal and hilar structures. The most common criterion of abnormality of the mediastinal nodes is the short-axis diameter of ( $> 1.0$  cm) on a transverse scan. The reported pooled sensitivity, specificity and Negative Predictive Value (NPV) of chest CT were 55% (20%-91%), 81% (50%-97%) and 83% (54%-97%)<sup>[16]</sup>. There is a general agreement that Computer Tomography is insufficient in reliable staging of the mediastinal nodes.

**PET:** Introduction of PET has been a major progress in diagnosis and management of NSCLC. There are several advantages of use of PET including improvement of the primary staging and restaging after neoadjuvant chemotherapy or chemoradiotherapy. PET was useful in discovery of the clinically silent distant metastases which was dependent on the clinical stage of the disease: such metastases were found in 19% of patients, including 7.5% of those with stage I disease, 18% of those with stage II disease and 24% of those with stage III disease by CT<sup>[17]</sup>. Pooled sensitivity and specificity and NPV of PET/CT for staging of the mediastinal nodes were approximately 77% (33%-100%), 86% (43%-100%) and 91% (79%-100%), respectively<sup>[16]</sup>. Generally, PET was found to be more sensitive than CT for identifying the mediastinal lymph node involvement in patients with known or suspected NSCLC, although this advantage was denied by the Danish authors<sup>[18]</sup>. The limitation of PET was a small diameter of the malignant lesion ( $< 4$  mm)<sup>[19,20]</sup>. Due to this limitation PET is less sensitive in normal size mediastinal nodes. In one study, the sensitivity was 32.4% for the small nodes ( $< 1$  cm) and 85.3% for the nodes  $> 1$  cm<sup>[21]</sup>. The reported sensitivity and specificity of PET in discovery of the mediastinal nodes metastases were 80% and 88%, respectively<sup>[16]</sup>. Mediastinal nodes which are positive on PET should be confirmed by biopsy due to the possible false positive results, especially in case of inflammatory process in the lungs. The use of PET is indicated especially in patients with large, centrally-located adenocarcinomas, as well as in patients with hilar nodal enlargement<sup>[4,20]</sup>.

The therapeutic impact of PET/CT has been studied in regard to the number of futile thoracotomies, defined as surgery for a benign lesion, intraoperative detection of N2, N3 or other stage III B disease, exploratory thoracotomy for some other reason, or tumor recurrence or death within 1 year<sup>[21,22]</sup>.

It was reported that the risk of death was twice as

high when the Standardized Uptake Value (SUV) was above the median value and the greater FDG uptake was independently associated with a worse prognosis among patients with malignant nodules that were surgically resected, even after adjusting for age, tumor size, histology and type of resection<sup>[23-28]</sup>.

Restaging of NSCLC after neoadjuvant treatment is another application of PET/CT.

In one review, sensitivity and specificity of PET for identifying residual N2 disease were only 64% and 85%, respectively which suggested that the diagnostic yield of PET/CT was inferior in restaging in comparison to the primary staging<sup>[29]</sup>.

Another issue is reduction of SUV after neoadjuvant treatment. According to the results of one study, reductions in FDG uptake of at least 75% in the primary tumor and at least 50% in the involved lymph nodes were strongly associated with a complete response<sup>[30]</sup>. In the recent ACCP guidelines and ESTS guidelines PET/CT was recommended for staging of NSCLC before curative-intent treatment. In case positive results of PET tissue confirmation by biopsy is necessary<sup>[11,16,17]</sup>.

**Endoscopy/ultrasound:** EBUS/TBNA and EUS/FNA are now considered the next phase of the mediastinal staging after CT and PET/CT. EBUS and EUS are complementary techniques allowing for visualization and biopsy of most of the mediastinal nodes. EBUS is better for examination of the right paratracheal nodes (stations 2R and 4R), for the upper paratracheal nodes (station 2L) and for the bilateral hilar nodes (N1). EUS is preferable for the lower paratracheal nodes (station 4L), and for the periesophageal and pulmonary ligament nodes (stations 8 and 9). Staging of the aorta-pulmonary window nodes (station 5) and paraaortic nodes (station 6) with EUS is a controversial issue. For the subcarinal nodes (station 7) both techniques are possibly equally good. In several studies combination of EBUS and EUS, so called combined ultrasound (CUS) were shown to be the best diagnostic yield<sup>[31,32]</sup>. With current EBUS endoscopes it is possible to perform both studies with one EBUS instrument introduced sequentially to the trachea and bronchi and then to the esophagus during one procedure performed in mild sedation. During the EBUS, EUS and CUS studies 1-4 nodal stations are usually needle-biopsied. Some authors recommend on site cytological examination to confirm that the proper cytological material has been taken during biopsy, the other authors questioned such policy, however<sup>[33-36]</sup>. Serious complications of EBUS and EUS were found in 0.3% and 0.05%, respectively in the review reported by von Bartheld *et al*<sup>[37]</sup>. The reported diagnostic yield for EBUS and EUS were dependent on the prevalence of the mediastinal metastases and was the lowest in the normal mediastinal nodes on CT and PET/CT. The reported sensitivity, specificity and NPV for EBUS were 89% (46%-97%) 100% (96%-100%) and 91% (60%-99%), and for EUS were

89% (45%-100%), 100% (90%-100%) and 86% (68%-100%), respectively<sup>[16]</sup>.

### **Surgical staging**

Current ACCP and ESTS guidelines recommend to omit surgical staging in patients with small tumors (< 3 cm) localized in the peripheral (outer third of the lung) without positive mediastinal and hilar (N1) nodes on PET/CT. In these patients the risk of false negative mediastinal nodes is low and the patients can be referred directly to pulmonary resection. Surgical staging is necessary in patients with larger tumors (> 3 cm), centrally located, with positive N1 nodes and with the positive mediastinal nodes on CT or PET/CT (even if negative on EBUS/EUS). In such patients the risk of mediastinal nodes metastases is at least 20%-25% so it is necessary to confirm the absence on such metastases with surgical staging.

Cervical mediastinoscopy formerly described as a gold standard of the mediastinal staging is still widely used<sup>[38-40]</sup>. Currently, VAM is a recommended version of mediastinoscopy, due to the improved technology, allowing for better view, simultaneous observation of the procedure on the screen with trainees and possible recording of the procedure. Both CM and VAM require general anaesthesia and can be performed as outpatient procedures. CM and VAM enable visualization and biopsy of the paratracheal nodes, bilaterally (station 2R,4R,2L,4L) and the subcarinal nodes (station 7). The other nodal stations are out the reach of CM and VAM. Reported sensitivity and NPV are 78% (32%-92%) and 91% (80%-97%) for CM and 89% (78%-97%) and 92% (83-96%) for VAM, respectively<sup>[16]</sup>. The advantage of VAM vs CM regards mainly better training and comfort of the surgeon, diagnostic superiority of VAM over CM is less clear<sup>[41]</sup>.

The diagnostic yield of EBUS/EUS and mediastinoscopy was compared in the prospective randomized multi-institutional ASTER study<sup>[42]</sup>. It was found that EBUS/EUS followed by mediastinoscopy had greater sensitivity for mediastinal nodal metastases in comparison to mediastinoscopy alone 94% (62/66; 95%CI: 85%-98%) vs 79% (41/52; 95%CI: 66%-88%) ( $P = 0.02$ ) and resulted in fewer unnecessary thoracotomies 18%; (95%CI: 12%-26%) in the mediastinoscopy group vs 7%; (95%CI: 4%-13%) in the endosonography/mediastinoscopy group ( $P = 0.02$ )<sup>[39]</sup>. Contrary results were reported in the retrospective study comparing EBUS and EUS with TEMPLA (see below)<sup>[43]</sup>. Primary staging was performed in 623 patients: EBUS in 351, EUS in 72 and CUS in 200 patients. TEMPLA was performed for primary staging in 276 patients. There was no mortality and morbidity after EBUS/EUS. One patient died after TEMPLA and morbidity rate after TEMPLA was 7.2%. There was a significant difference between EBUS/EUS and TEMPLA for sensitivity (87.8% and 96.2%;  $P < 0.01$ ) and negative predictive value (NPV) (82.5% and 99.6%;  $P < 0.01$ )

in favor of TEMPLA. The undisputed benefit of EBUS is possibility to differentiate between N0 and N1 for NSCLC<sup>[44]</sup>.

There are several techniques allowing for biopsy of the paraaortic nodes (station 6) and the aortopulmonary window nodes (station 5) including extended mediastinoscopy, anterior mediastinotomy, VATS and TEMPLA.

Extended mediastinoscopy is technique added to the standard mediastinoscopy to reach and biopsy the station 5 and 6 nodes. The key of this procedure is to perform a finger dissection to create a tunnel in the mediastinum in front of the ascending aorta and to introduce a mediastinoscope through this tunnel to visualize and biopsy the stations 5 and 6 nodes. The pooled reported sensitivity and specificity of the Extended Mediastinoscopy were 71% and 91%, respectively<sup>[16,45,46]</sup>.

The anterior mediastinotomy (chamberlain procedure) is performed in general anaesthesia to reach station 5 and 6 on the left side or the station 3A,4R and 10R on the right side. The mediastinum is entered from the front after resection of the second or third costal cartilage or intercostally, without resection of ribs. This technique does not allow to reach the other mediastinal nodal stations. The reported pooled sensitivity and specificity of the Chamberlain procedure were 71% (44%-81%) and 91% (89%-95%), respectively<sup>[16]</sup>.

VATS is a technique allowing to reach virtually all mediastinal nodal stations but only unilaterally, although an access to the left paratracheal nodes is very challenging and limited. The disadvantages of VATS include greater invasiveness in comparison to mediastinoscopy, the use of general anaesthesia, selective lung ventilation and several VATS ports and the use of postoperative chest drainage. These reasons limit the use of VATS for preoperative staging. The additional advantage of VATS is the possibility to evaluate T stage and to rule-out pleural dissemination. The reported sensitivity and specificity and NPV of VATS for mediastinal staging were 99% (58%-100%), 100% and 96% (88%-100%), respectively<sup>[16,47]</sup>.

VAMLA and TEMPLA are new techniques intended for performance of the mediastinal lymphadenectomy (complete removal of the whole mediastinal nodes with the surrounding adipose tissue) to improve the accuracy of staging instead of obtaining the pieces of the nodes obtained with the CM<sup>[48-50]</sup>.

Due to this advantage, the diagnostic yields of VAMLA and TEMPLA were much higher in comparison to the standard mediastinoscopy (as was proved for TEMPLA)<sup>[51]</sup>. VAMLA and TEMPLA are performed through the neck incision (like mediastinoscopy). Both techniques became feasible after introduction of the two-blade Linder-Dahan mediastinoscope which enabled much wider access to the mediastinum, however, contrary to the VAMLA most part of the TEMPLA procedure is performed in the open technique,



**Table 1** Diagnostic yield of staging procedures in non-small-cell lung cancer (%)

Diagnostic technique	Sensitivity Mean (range)	Specificity Mean (range)	Negative predictive value Mean (range)
Chest CT	55 (20-91)	81 (50-97)	83 (54-97)
PET/CT	77 (33-100)	86 (43-100)	91 (79-100)
EBUS/TBNA	89 (46-97)	100 (96-100)	91 (60-99)
EUS/FNA	89 (45-100)	100 (90-100)	86 (68-100)
Mediastinoscopy	78 (32-92)	100	91 (80-97)
Video-mediastinoscopy	89 (78-97)	100	92 (83-96)
VATS	99 (58-100)	100	96 (88-100)
VAMLA	93.8	100	96
TEMLA	96.2	100	98.9

CT: Computer tomography; PET: Positron emission tomography; EBUS/TBNA: Endobronchial ultrasound/transbronchial needle aspiration; EUS/FNA: Endoscopic ultrasound/fine needle aspiration; VAMLA: Video-assisted mediastinoscopic lymphadenectomy; TEMLA: Transcervical extended mediastinal lymphadenectomy; VATS: Video-assisted thoracic surgery.

without the use of a mediastinoscope. The nodal stations 1,3A, 3P, 5 and 6 are not removed with VAMLA but can be removed by TEMLA. In case of VAMLA, however stations 5 and 6 can be reached with use of additional Extended Mediastinoscopy. The other differences between VAMLA and TEMLA include more nodal stations and the mean number of nodes removed with TEMLA in comparison to VAMLA (11 vs 5 nodal stations and 20.8 vs 37.9 nodes, respectively) but also shorter mean operative time (54 min for VAMLA vs 128 min for TEMLA) and lesser invasiveness of VAMLA. There was no mortality and lower morbidity after VAMLA and 0.3% mortality and 6.6% morbidity for TEMLA, it was not clear however, if the results of VAMLA represented 30-d mortality and morbidity as was reported for TEMLA (the mortality of TEMLA was all due to no-surgical reasons). The diagnostic yield was slightly better for TEMLA than for VAMLA with reported sensitivity, specificity and NPV 96.2%, 100%, 98.9% and 93.8%, 100% and 96%, respectively<sup>[52,53]</sup>. It was not clear, however if the results for VAMLA were calculated for all nodal stations or only for those accessible for VAMLA. The other difference between VAMLA and TEMLA was the elevation of the sternum with a special retractor connected with the Rochard frame which widened the approach to the mediastinum and facilitated performance of TEMLA.

### Restaging of NSCLC after neoadjuvant treatment

Restaging of the mediastinal nodes is an extremely important part of multimodality treatment of stage IIIA NSCLC. In several studies it was found that the results of survival in patients with residual metastatic nodes much inferior in comparison to the patients in whom the nodes are N0-1 after neoadjuvant therapy. This is especially pronounced in patients with residual multi-

level metastatic nodes<sup>[54-56]</sup>. Therefore, a decision if to offer surgery to the patients after neoadjuvant therapy should be based on the reliable restaging. There are several methods of restaging of the mediastinal nodes after neoadjuvant treatment. Imaging studies include CT which has relatively low diagnostic yield (sensitivity 41%-59%, specificity 62%-75% and accuracy 58%-60%) and PET combined with CT (PET/CT) with sensitivity 61%-77%, specificity 85%-90% and accuracy 78%-83%<sup>[16,29,30]</sup>. PET/CT was found to be superior to CT (accuracy 89% vs 36% for stage I )<sup>[16]</sup>.

Restaging with endoscopic techniques include EBUS, EUS and combined EBUS/EUS. EBUS was used in the multi-institutional report (Copenhagen, Boston, Heidelberg, Chiba) on 124 patients restaged after induction therapy with sensitivity 76%, specificity 100%, PPV 100%, NPV 20%, accuracy 77%<sup>[57]</sup>. The results of the other study with use of EBUS were similar<sup>[19]</sup>. In the other study sensitivity and NPV of restaging with EBUS were 66.7% and 77.5%, respectively<sup>[58]</sup>. The reported sensitivity and NPV for restaging with EUS were 44% and 58%, respectively<sup>[59-61]</sup>.

Surgical techniques of restaging include repeated mediastinoscopy (remediastinoscopy), VATS and TEMLA. Generally, remediastinoscopy seems to be a technique of moderate diagnostic yield with sensitivity of 61%-83% (with exception of sensitivity 29% in the study published by De Leyn *et al*<sup>[62]</sup>).

Restaging with VATS was described in the recent multi-institutional study reporting sensitivity of VATS of 67% (95%CI: 47-83), and negative predictive value (NPV) of 73% (95%CI: 56-86)<sup>[47]</sup>.

The results of TEMLA in restaging of the mediastinal nodes reported sensitivity of 95.7% and NPV of 97.6%. In the retrospective study comparing the diagnostic yield of EBUS and EUS with TEMLA for restaging of NSCLC the endoscopic/ultrasound staging was performed in 88 patients and TEMLA in 78 patients. There was a significant difference between EBUS/EUS and TEMLA for sensitivity (64.3% and 100%,  $P < 0.01$ ) and NPV (82.1% and 100%;  $P < 0.01$ ) in favor of TEMLA<sup>[43,63]</sup>.

Diagnostic yield of staging and restaging techniques for NSCLC are shown in Tables 1 and 2.

### Intraoperative staging

Intraoperative biopsy or removal of the mediastinal nodes described as lymphadenectomy is a final step of staging. According to the ESTS guidelines there are several methods of intraoperative staging including selective biopsy of the piece of the nodes or nodes, sampling (removal of the whole node), systematic sampling (removal of the whole nodes from the nodal stations predetermined before an operation), systematic nodal dissection (systematic lymphadenectomy), lobe-specific nodal dissection and extended lymphadenectomy. Systematic nodal

**Table 2 Diagnostic yield of restaging procedures in non-small-cell lung cancer after neoadjuvant therapy (%)**

Diagnostic technique	Sensitivity Mean (range)	Specificity Mean (range)	Negative predictive value Mean (range)
Chest CT	55 (20-91)	81 (50-97)	83 (54-97)
PET/CT	77 (33-100)	86 (43-100)	91 (79-100)
EBUS/TBNA	89 (46-97)	100 (96-100)	91 (60-99)
EUS/FNA	89 (45-100)	100 (90-100)	86 (68-100)
Mediastinoscopy	78 (32-92)	100	91 (80-97)
Video-mediastinoscopy	89 (78-97)	100	92 (83-96)
VATS	99 (58-100)	100	96 (88-100)
VAMLA	93.8	100	96
TEMLA	96.2	100	98.9

CT: Computer tomography; PET: Positron emission tomography; EBUS/TBNA: Endobronchial ultrasound/transbronchial needle aspiration; EUS/FNA: Endoscopic ultrasound/fine needle aspiration; VAMLA: Video-assisted mediastinoscopic lymphadenectomy; TEMLA: Transcervical extended mediastinal lymphadenectomy; VATS: Video-assisted thoracic surgery.

dissection is recommended in all cases to ensure complete resection<sup>[64]</sup>. This technique includes removal of at least three mediastinal nodal stations with the surrounding fatty tissue are removed (the subcarinal nodes must be removed in every case). Additionally, hilar and intrapulmonary nodes should removed, as well. There is an general agreement that systematic lymphadenectomy enables the most detailed study of the mediastinum due to the largest number of the removed nodes, the therapeutic benefit of systematic lymphadenectomy has not been proved unequivocally, however. In the studies of Wu *et al*<sup>[65]</sup> and Keller *et al*<sup>[66]</sup> the authors found that systematic nodal dissection (SND) was superior to mediastinal lymph nodal sampling (MLS) in surgical treatment of non-small cell lung cancer (NSCLC).

The survival benefit was not confirmed by the results of the prospective randomized American College of Surgery Oncology Group Z0030 Trial reported by Darling *et al*<sup>[67]</sup> who concluded that in the clinical stage I NSCLC if systematic and thorough presection sampling of the mediastinal and hilar lymph nodes was negative, mediastinal lymph node dissection did not improve survival in patients with early stage non-small cell lung cancer, but these results were not generalizable to patients staged radiographically or those with higher stage tumors.

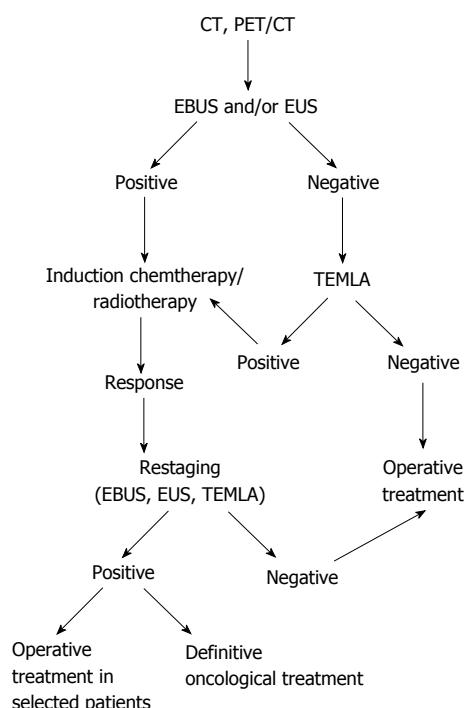
Lobe-specific systematic nodal dissection is a technique in which specific nodal stations according to the location of the tumor are removed. This procedure is acceptable for peripheral squamous T1 tumors, if hilar and interlobar nodes are negative on frozen section studies; it implies removal of, at least, three hilar and interlobar nodes and three mediastinal nodes from three stations in which the subcarinal is always included<sup>[68]</sup>. Ma *et al*<sup>[69]</sup> found no difference between Systematic Lymphadenectomy (SL) and Lobe-Specific

Lymphadenectomy (LL) in regard to migration of N staging, Overall Survival and Disease-Free Survival for cT1aN0M0 tumors with high rate of Ground-Glass Opacity (GGO). Shapiro *et al*<sup>[70]</sup> found that lobe-specific N2 nodal evaluation resulted in a recurrence rate similar to that of complete mediastinal evaluation. The authors concluded that lobe-specific mediastinal nodal evaluation appeared acceptable in patients with early-stage NSCLC.

Contrary results were reported by Maniwa *et al*<sup>[71]</sup> who found that the recurrence of mediastinal node cancer in patients undergoing Systematic Lymphadenectomy was significantly greater than that in those undergoing Lobe-Specific Lymphadenectomy. Selected lymph node biopsies and sampling are justified only to prove nodal involvement when resection is not possible, not for radical surgery<sup>[64]</sup>.

## DISCUSSION

Staging of NSCLC is currently an increasingly complex process with staging of the mediastinal nodes being a central part of this process. There is a general agreement that chest CT is insufficiently accurate to predict metastatic involvement in patients with a discrete enlargement of the nodes or normally looking mediastinum. PET/CT emerged as a standard of staging in the patients considered candidates for surgical treatment. The main value of PET/CT is discovery of possible clinically silent metastasis<sup>[32]</sup>. PET/CT will probably never replace CT completely, because anatomical details of the chest are visualized much more precisely on good quality CT than on PET/CT. In the clinical stage IA peripheral tumors negative PET/CT is possibly sufficient to refer patients directly to surgery. In all other patients with possibly curable tumors, invasive staging is necessary, however. During the last decade the role of EBUS and EUS rose substantially. These studies are currently recognized as the second step of staging after CT and PET/CT due to minimal invasiveness. It seems reasonable to combine endoscopic/ultrasound and surgical staging, this approach has been recently supported by results of our group<sup>[31]</sup>. The results reported by the leading experts on EBUS/EUS are impressive and lead them to claim that due to the advantages and possible superiority of EBUS and EUS in comparison to mediastinoscopy the latter one is no longer necessary. Herth *et al*<sup>[32]</sup> concluded that the combination of EBUS and EUS "may be able to replace more invasive methods as a primary staging method for patients with lung cancer". Tournoy *et al*<sup>[72]</sup> concluded that "EUS-FNA reduces the need for surgical staging procedures in patients with (suspected) lung cancer in whom a mediastinal exploration is needed". According to Vilman *et al*<sup>[73]</sup> "It seems therefore logical to assume that the combination of EUS-FNA and EBUS-TBNA will replace more invasive methods such as mediastinoscopy for diagnosis and staging of lung cancers in the near



**Figure 1** Institutional staging and restaging algorithm for non-small-cell lung cancer. CT: Computer tomography; PET: Positron emission tomography; EBUS: Endobronchial ultrasound; EUS: Endoscopic ultrasound; TELA: Transcervical extended mediastinal lymphadenectomy.

future<sup>[73]</sup>. The same authors called the combination of EBUS and EUS “the complete medical mediastinoscopy” and claimed that “A recent publication from our group has documented a sensitivity and specificity of 100% when EUS-FNA and EBUS-TBNA is used in combination for staging of the mediastinum”. However, surgical staging is not the past history. Even in some recent publication cervical mediastinoscopy was still regarded the gold standard of the mediastinal staging (Shrager)<sup>[40]</sup>. It is not clear if the results reported by the most experienced endoscopists could be achieved also by the average performers of EBUS and EUS. The reported results of mediastinoscopy pooled in the ACCP publication included broader number of publication, not only the best experts but also some poorer results that were compared to EBUS/EUS in aim to show superiority of endoscopy/ultrasound over surgical staging<sup>[16]</sup>. Therefore, the better results of EBUS/EUS might not be the proof that this modality was really better than mediastinoscopy. The final step of mediastinal nodal staging is a systematic lymphadenectomy performed during pulmonary resection of preoperatively, by means of VAMLA or TELA.

The importance of lymphadenectomy is limited not only to staging but this procedure may has also a therapeutic role, although the reported results are equivocal. The results of American College of Surgery Oncology Group Z0030 Trial did not confirm any beneficial influence of lymphadenectomy in comparison to sampling in clinical stage I NSCLC but it is still possible that there might be such influence in stage II

and III as was reported by Wu *et al*<sup>[65]</sup> and Keller *et al*<sup>[66]</sup> who found that lymphadenectomy improved the results of survival in comparison to sampling.

Due to the extremely large number of publication regarding mediastinal staging it is an imperative for every practitioner involved in diagnosis and treatment of NSCLC to form his/her own opinion how to choose the best possible way of staging. What was presented in this paper is a subjective view differing from the data presented in the most comprehensive systematic reviews<sup>[16]</sup>. For example, in my opinion, the value of relatively new techniques as PET/CT, EBUS or EUS is exaggerated, currently. In the past, the same happened to the chest CT. In the early 1980, it has been reported that sensitivity of chest CT in staging of lung cancer exceeded 80% to fall down to about 55%, according to the recent publications<sup>[74,75]</sup>. The time will solve if sensitivity of EBUS will still be around 90% as is being currently reported by the best experts. The real value of this technique will be shown in hands of an average endoscopist, who do not publish their results. In this article I made an attempt to present the staging and restaging algorithm which I recommended (Figure 1).

## CONCLUSION

Current staging for NSCLC which is a complex process including several imaging, endoscopy/ultrasound and surgical techniques enables optimal selection of patients with early stage disease for curative treatment and helps to avoid unnecessary surgical or multimodality treatment in the advanced disease.

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## Myasthenia gravis as a form of clinical presentation of thymic carcinoma

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### Abstract

Thymic carcinomas are rare tumors of the thymus arising in the thymic epithelium. They represent less than 1% of thymic malignancies. They often present with an advanced disease and metastasize to regional lymph nodes and distant sites. They have a worse prognosis with a 5-year survival rate of 30%-50%, while thymomas are much less invasive and have a 5-year survival of approximately 78%. We report a rare form of clinical presentation of a thymic carcinoma in which the diagnosis of myasthenia gravis was the cornerstone of the diagnosis of cancer. Surgery is considered the salvage treatment when possible. Radiotherapy is a second choice of salvage treatment, when possible depending on its localization and relation to nearby structures such as vascular structures. Molecular target therapy is a more directed, more expensive but less toxic treatment. Further studies need to be carried out for its approval worldwide, outside clinical trials.

**Key words:** Myasthenia gravis; Thymic carcinoma; Multidisciplinary approach; Clinical-molecular signature; Prognosis

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**Core tip:** We report a rare form of clinical presentation of a thymic carcinoma in which the diagnosis of myasthenia gravis was the cornerstone of the diagnosis of cancer. Surgery is considered the salvage treatment when possible. Radiotherapy is a second choice of salvage treatment, when possible depending on its localization and relation to nearby structures such as vascular structures. The prognosis is very reserved, when neither surgery nor radiotherapy can be accomplished. Having an unfavorable molecular signature, less than 10% of thymic carcinomas have c-kit mutations, and clinical outcome of these patients is detrimental.

de Macedo JE, Lopes S, Gouveia H, Oliveira S, Cunha J, Faria AL, Rego S, Oliveira A, Krug L, Bravo EM. Myasthenia gravis as a form of clinical presentation of thymic carcinoma. *World J Respirol* 2015; 5(2): 176-179 Available from: URL: <http://www.wjgnet.com/2218-6255/full/v5/i2/176.htm> DOI: <http://dx.doi.org/10.5320/wjr.v5.i2.176>

## INTRODUCTION

Thymic epithelial neoplasms are rare, but are nowadays well-classified according to the Masaoka-Koga system which is the currently most widely used classification<sup>[1]</sup>. Thymic epithelial neoplasms comprise thymomas, thymic carcinomas and thymic neuroendocrine tumors. Thymoma is the most common epithelial tumor in the anterior mediastinum in adults. Thymic carcinomas represent less than 1% of all thymic malignancies<sup>[2]</sup>. They have a worse prognosis with a 5-year survival rate of 30%-50%, while thymomas are much less invasive and have a 5-year survival of approximately 78%<sup>[2]</sup>. Treatment of thymic carcinomas may vary from complete surgical resection, being the gold standard, to chemotherapy and/or radiotherapy. The main aim of this case report is to share experience in dealing with the optimal treatment of a rare, indolent and malignant thymic carcinoma, where molecular pathways of thymic carcinomas are still on the verge of a new form of knowledge management.

## CASE REPORT

A 76-year-old white man with previously known ischemic heart disease, hypertension, dyslipidemia and obstructive sleep apnea syndrome (with domiciliary continuous positive airway pressure), complained of cervical pain, sore throat, dysphagia and mild dyspnea over the past 2 wk. Due to sudden clinical deterioration he was evaluated in the emergency department. The cervical-thoracic-abdominal scan showed an anterior mediastinal mass measuring 66 mm × 60 mm in

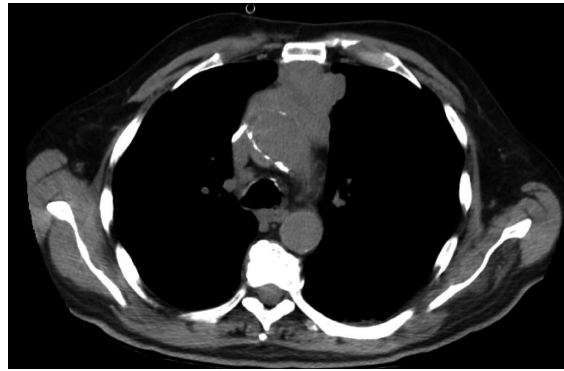


Figure 1 Computed tomography thoracic scan showing an anterior mediastinal mass with lobular contours measuring 60 mm × 66 mm.

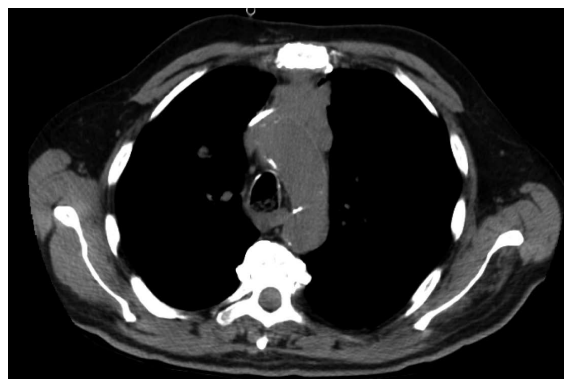


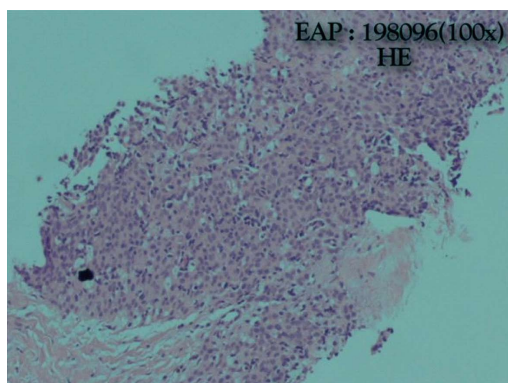
Figure 2 Computed tomography thoracic scan showing a 14-mm pulmonary nodule.

diameter, a slight pericardial effusion and a 14-mm pulmonary nodule in the right superior lobe (Figures 1 and 2).

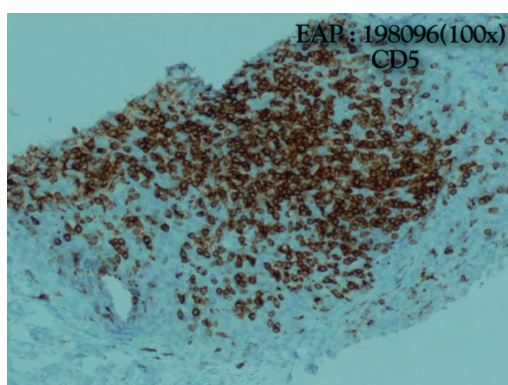
He was admitted to the Internal Medicine Department and started oxazepam. On the same day, he had a sudden worsening of conscious level and global respiratory insufficiency and was submitted to mechanical ventilation. The patient was transferred to the intensive care unit. The suspicion of myasthenic syndrome was confirmed by positivity to anticholinesterase antibodies. Two weeks later the patient improved and was extubated to spontaneous ventilation. An anterior mediastinal biopsy was performed and revealed a thymic carcinoma with squamous differentiation, which was poorly differentiated, positive for CD5 and negative for CD 117 and chromogranin. Thus, a type C (World Health Organization) stage IVB (Masaoka-Koga staging) (Figures 3 and 4) thymic carcinoma was diagnosed<sup>[1]</sup>. The laboratory testing revealed no abnormal values. The patient was transferred to the Internal Medicine Department, clinically improved and was discharged one week later.

The patient was evaluated by a multidisciplinary team and was diagnosed with a stage IVB disease (isolated pulmonary metastasis). Surgical hypothesis was rejected upfront given the vascular invasion of the tumor and highly suspected pulmonary metastasis.





**Figure 3** High-power view of poorly differentiated non-keratinizing squamous thymic carcinoma.



**Figure 4** Malignant epithelial tumor of the thymus positive for CD5 which favors thymic carcinoma over thymoma and tumors of non-thymic origin. A type C (World Health Organization) stage IVB (Masaoka- Koga Staging) thymic carcinoma was diagnosed.

He started chemotherapy with carboplatin (area under the curve 6; D1) and paclitaxel (225 mg/m<sup>2</sup> D1) every 3 wk. The patient completed the 4<sup>th</sup> cycle of chemotherapy with good tolerance and with a significant response on the computed tomography (CT) scan (Figures 5 and 6). No other secondary lesions were observed.

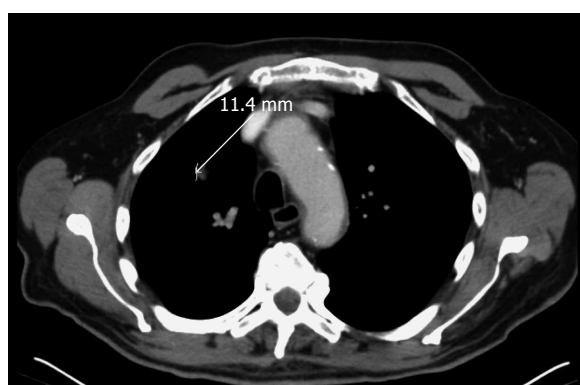
At this time he was evaluated by cardiothoracic surgery and due to his excellent response to chemotherapy, he was proposed for two more cycles and subsequent CT scan and PET-CT evaluation. Concerning a 76-year-old fit patient, surgery shall be considered at a later stage followed by postoperative radiotherapy if indicated.

## DISCUSSION

Thymic carcinomas are aggressive tumors which often metastasize to distant sites. In the case, the high suspicion of myasthenia syndrome was confirmed and associated to thymic carcinoma (30%-50% cases)<sup>[3]</sup>. Total thymectomy and complete surgical excision are the gold standard of treatments and cisplatin-based chemotherapy is recommended in locally advanced,



**Figure 5** Computed tomography thoracic scan showing a 27 mm x 28 mm anterior mediastinal mass.



**Figure 6** Computed tomography thoracic scan showing in the right superior lobe an 11-mm pulmonary nodule.

unresectable and metastatic setting.

Due to recent advances in technologies a better understanding of the molecular behavior of these tumors has been accomplished. Thymic carcinomas have a high frequency of KIT expression (73%-86%), but the rate of kit mutations remains low at 7%-9%<sup>[4]</sup>. Target therapies (imatinib or sunitinib) may be useful for patients with c-kit mutations besides its low expression<sup>[4]</sup>. Further molecular profiling for selecting the specific target therapy, is of utmost importance for defining the molecular signature of these tumors. Tumor characterization by clinical, imagiological and histological means are essential, but molecular profiling will allow us to treat our patients more efficiently, with better quality of life and lower toxicity profile.

Tumor stage, complete surgical resection and histology are the main prognostic factors of thymic carcinomas. Nevertheless, a very reserved prognosis when neither surgery nor radiotherapy can be accomplished is considered, but only 60% of the patients die from tumor progression. Other causes of death are autoimmune diseases and other non-malignant related disorders. Having an unfavorable molecular signature, less than 10% of thymic carcinomas have c-kit mutations, and clinical outcome of these patients is detrimental. Despite lacking data

on second-line chemotherapy, it remains an option for these patients who present themselves with a recurring disease, with no indication for alternative therapies, namely molecular, surgical or even radiotherapy.

## COMMENTS

### Case characteristics

A 76-year-old man complained of cervical pain, sore throat, dysphagia and mild dyspnea over the past 2 wk.

### Clinical diagnosis

Rapid clinical deterioration.

### Differential diagnosis

Other etiologies of anterior mediastinal masses.

### Laboratory diagnosis

An anterior mediastina biopsy was performed.

### Imaging diagnosis

The cervical-thoracic-abdominal scan showed an anterior mediastinal mass measuring 66 mm × 60 mm in diameter.

### Pathological diagnosis

A thymic carcinoma with squamous differentiation, which was poorly differentiated, positive for CD5 and negative for CD 117 and chromogranin. A type C (World Health Organization) stage IVB (Masaoka-Koga staging) thymic carcinoma was diagnosed.

### Treatment

Chemotherapy with carboplatin (area under the curve 6; D1) and paclitaxel (225 mg/m<sup>2</sup> D1) every 3 wk.

### Related reports

Thymic carcinomas have a high frequency of KIT expression (73%-86%), but

the rate of kit mutations remains low at 7%-9%. Target therapies (imatinib or sunitinib) may be useful for patients with c-kit mutations.

### Term explanation

Further molecular profiling for selecting the specific target therapy, is of upmost importance for defining the molecular signature of these tumors.

### Experiences and lessons

Tumor characterization by clinical, imagiological and histological means is still vital, but molecular profiling will allow us to treat our patients more efficiently, with better quality of life and lower toxicity profile.

### Peer-review

The paper is a report of a clinical case about thymic carcinoma that presented with signs and symptoms of a myasthenia gravis.

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