Pulmonary Hypertension

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Editorial Board

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Editorial

Pulmonary Hypertension

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Pulmonary hypertension is a hemodynamic and pathophysiological condition which is defined by right heart catheterization as an increase in mean pulmonary artery pressure above 25 mmHg at rest [1]. Several clinical conditions can result in increased pulmonary arterial pressure, therefore detailed evaluation and accurate diagnosis of the underlying disease is crucial for appropriate treatment [2]. The clinical classification of pulmonary hypertension (PH) advanced since its first version proposed by World Health Organization in 1973. The final version of the clinical classification was derived from the Dana Point Meeting in 2008 (Table 1). Pulmonary hypertension due to left heart disease (clinical group 2) is defined as postcapillary (pulmonary capillary wedge pressure $\geq$ 15 mmHg) while precapillary (pulmonary capillary wedge pressure $\leq$ 15 mmHg) pulmonary hypertension presents in other groups.

Echocardiography is a widely used screening method in patients with suspected pulmonary hypertension. However, right heart catheterization is required to confirm diagnosis of PH [2]. The evaluation of the patients should also include clarifying specific etiologies and assessment of the degree of functional and hemodynamic impairment. The majority of pulmonary hypertension cases are due to left heart disease and/or lung disease (clinical groups 2 and 3); idiopathic pulmonary arterial hypertension (PAH) remains a diagnosis of exclusion. Hence, diagnostic algorithms are suggested by several guidelines in order to prevent excessive diagnostic testing for a common disease or under-diagnosis of rare conditions [1, 3].

Pulmonary hypertension is common and difficult to manage in critical care units (ICU). In the present issue two specific patient populations admitted to ICU are described: pregnant women and newborns. The physiologic changes developing during pregnancy and after labor are poorly tolerated by the pregnant women. Also acute conditions associated with pregnancy such as pulmonary and amniotic fluid embolism may be complicated with severe pulmonary hypertension [4]. No standardized treatment strategies exist for the management of PH in pregnancy, and maternal mortality remains high despite lower death rates in the last decade compared with previous era.

PH occurring in the newborn may result from a variety of causes, most commonly; it presents immediately after birth and is referred to as persistent pulmonary hypertension of the newborn (PPHN), when pulmonary vascular resistance fails to decrease at birth. The majority of cases are associated with lung parenchymal diseases, such as meconium aspiration syndrome, and respiratory distress syndrome. The improvement in the prognosis and the survival in PPHN over the last decade is attributed to early admission to a tertiary centre, the use of new techniques of mechanical ventilation, extracorporeal membrane oxygenation, and the use of new pulmonary vasodilators [5].

Over the last decade, research in pulmonary vascular disease has revealed genetic mutations in heritable PAH, new methods and imaging techniques for diagnosis of PH, methods to assess right ventricular function and remodeling, and clinical impact of the disease and its prognosis in special conditions such as the pediatric population [6].

Table 1: The clinical classification of pulmonary hypertension [1].

Group 1	Pulmonary arterial hypertension (PAH)
	(i) Idiopathic (IPAH)
	(ii) Heritable (HPAH)
	(a) Bone morphogenetic protein receptor type 2 (BMPR2)
	(b) Activin receptor-like kinase 1 gene (ALK1), endoglin (with or without hereditary hemorrhagic telangiectasia)
	(c) Unknown
	(iii) Drug and toxin induced
	(iv) Associated with (APAH)
	(a) Connective tissue diseases
	(b) Human immunodeficiency virus (HIV) infection
	(c) Portal hypertension
	(d) Congenital heart disease (CHD)
	(e) Schistosomiasis
	(f) Chronic haemolytic anaemia
	(v) Persistent pulmonary hypertension of the newborn (PPHN)
Group 1′	Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary haemangiomatosis (PCH)
Group 2	Pulmonary hypertension due to left heart diseases
	(i) Systolic dysfunction
	(ii) Diastolic dysfunction
	(iii) Valvular disease
Group 3	Pulmonary hypertension due to lung diseases and/or hypoxemia
	(i) Chronic obstructive pulmonary disease (COPD)
	(ii) Interstitial lung disease (ILD)
	(iii) Other pulmonary diseases with mixed restrictive and obstructive pattern
	(iv) Sleep-disordered breathing
	(v) Alveolar hypoventilation disorders
	(vi) Chronic exposure to high altitude
	(vii) Developmental abnormalities
Group 4	Chronic thromboembolic pulmonary hypertension (CTEPH)
Group 5	PH with unclear and/or multifactorial mechanisms
	(i) Haematological disorders: myeloproliferative disorders, splenectomy
	(ii) Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, and vasculitis
	(iii) Metabolic disorders: glycogen storage disease, Gaucher disease, and thyroid disorders
	(iv) Others: tumoral obstruction, fibrosing mediastinitis, and chronic renal failure on dialysis

This special issue aims to identify current limitations as well as future goals to advance the approach to patients with pulmonary vascular disease. The readers will find concise reviews about pulmonary hypertension in newborns and pregnant women, under recognized etiologies of PH and functional impairment of the disease.

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Review Article

Etiopathogenetic Mechanisms of Pulmonary Hypertension in Sleep-Related Breathing Disorders

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Obstructive sleep apnea syndrome is a common disorder with significant health consequences and is on the rise in consonance with the obesity pandemic. In view of the association between sleep-disordered breathing and pulmonary hypertension as depicted by multiple studies, current clinical practice guidelines categorize obstructive sleep apnea as a risk factor for pulmonary hypertension and recommend an assessment for sleep disordered breathing in evaluating patients with pulmonary hypertension. The dysregulatory mechanisms associated with hypoxemic episodes observed in sleep related breathing disorders contribute to the onset of pulmonary hypertension and identification of these potentially treatable factors might help in the reduction of overall cardiovascular mortality.

1. Introduction

In consonance with the obesity pandemic, there is an increasing awareness of sleep-related breathing disorders (SRBDs) as a potentially treatable factor in reducing overall cardiovascular mortality. The spectrum of SRBD ranges from habitual snoring to obstructive sleep apnea (OSA) and increasing evidence shows that improved cardiovascular function may be obtained by early recognition and treatment of these disorders [1].

Over the past three decades, the pathophysiology of sleep-related breathing disorders (SRBDs) has been better understood and though the exact contributory pathways are still not clearly defined several studies allude to multifactorial mechanisms being involved in the development of pulmonary hypertension in relation to SRBD [1].

Sleep apnea occurs in about 12 million US adults in their 4th to 6th decades of life and about a quarter of all those are over the age of 65 yrs. Nearly half of all nursing home residents have sleep apnea and 38,000 deaths annually are directly attributed to SRBD. With the prevalence of SRBD currently exceeding that of asthma in adults, the cardiovascular consequences of its associated comorbidities especially pulmonary hypertension (PH) have been of significant interest in recent years [1].

The most recent classification system of pulmonary hypertension was published in the 2009 European Society of Cardiology Guidelines where the definition of PH was based on an increased mean pulmonary arterial pressure >-25 mmHg at rest. This broadly encompasses all clinical subgroups of PH as outlined by the 4th World Symposium on Pulmonary Hypertension in Dana Point, California, in 2008. This update classifies Group 1 as pulmonary arterial hypertension (PAH) due to idiopathic, heritable, or drug- and toxin-induced causes; it also includes PAH associated with specific disease conditions or persistent pulmonary hypertension of the newborn. Group 1[1] is PH due to pulmonary veno-occlusive diseases and/or pulmonary capillary haemangiomatosis. Group 2 includes PH due to left heart disease. Group 3 comprises PH due to lung diseases and hypoxia. Group 4 refers to chronic thromboembolic PH. Group 5 encompasses PH due to unclear or multifactorial mechanisms [2].

Pulmonary arterial hypertension though comparatively rare can be very devastating as it progresses rapidly to right heart failure and subsequent occurrence of death within

three years of diagnosis. Peak age of incidence is in the 4th and 5th decades of life with a female preponderance. Multiple studies have shown a higher prevalence of SRBD in patients with pulmonary hypertension [1] as well as an increased prevalence of pulmonary hypertension in patients with SRDB (17–53%); and factors such as daytime PO_2, BMI, and AHI are significantly associated with both [3].

This paper presents a review of the current literature on dysregulatory mechanisms in sleep-related breathing disorders which result in pulmonary hypertension. Emphasis will be placed on Group 3 PH where the broad principles which underlie etiopathogenesis have been elucidated.

2. Diagnosis

Accurate diagnosis of PH is based on the acquisition and precise analysis of invasive hemodynamic data as this ultimately determines appropriate treatment options. Current recommendations are for transthoracic echocardiography in the initial screening process with possible subsequent evaluation by right heart catheterization for diagnostic confirmation. Though PH refers broadly to a mean pulmonary artery pressure >25 mmHg from any cause, these invasive studies are crucial to excluding left heart causes of PH where vasodilator therapies should be avoided. For patients with a PCWP <15 mmHg, vasodilator challenge is a crucial diagnostic step for evaluation of vasoreactivity and this is commonly done with inhaled nitric oxide or intravenous agents such as adenosine, epoprostenol, or nitroprusside. All patients with PAH should also undergo routine biochemical, hematologic, immunologic, and thyroid function tests as well as high resolution CT to identify the specific associated condition [2–4].

In view of the association between sleep disordered breathing (SDB) and pulmonary hypertension as depicted by multiple studies [5–17], the American College of Chest Physicians (ACCP) categorizes obstructive sleep apnea (OSA) as a risk factor for PAH. The current ACCP Evidence-Based Clinical Practice Guidelines recommends an assessment for SDB in evaluating patients with PAH and the use of polysomnography when there is clinical suspicion of OSA as the etiology [18, 19].

3. Pathophysiology

The pathological changes observed in PH due to hypoxia and SRBD include medial hypertrophy and obstructive proliferation of the tunica intima within the distal pulmonary arteries. The severity of intimal and medial thickening is highly variable and results in near total occlusion of these vessels. This results in major increments in the pulmonary vascular resistance and considerably impedes blood flow through the lungs. Regions of the lungs with significant emphysematous changes or fibrosis may exhibit substantial destruction of the pulmonary vascular bed. The disordered mechanisms resulting in the observed pathophysiological manifestations are multifactorial (Figure 1). Crucial factors which play a pivotal role in these processes include hypoxic vasoconstriction, mechanical changes resulting from hyper-inflated lungs, capillary loss, and inflammation. New evidence also points to the importance of an imbalance between endothelium-derived factors responsible for vasoconstriction and vasodilation [20].

Compensatory changes occur in the right ventricle to overcome the maladaptive responses of these resistance vessels and improve pulmonary blood flow particularly in situations of increased oxygen demand. Eventually, the right ventricle becomes unable to maintain adequate blood flow and this heralds the onset of dyspnea on exertion. This progresses to overt right ventricular failure and poor cardiac output. Finally, severe debilitation sets in and significant dyspnea occurs at rest; ultimately death occurs in most untreated patients in less than 3 years after initial diagnosis [24, 25]. This drastic clinical course which culminates in significant clinical deterioration of the affected previously healthy individual has resulted in intensified research efforts in search of a definitive cure. Newer treatment modalities have shown moderate improvement in prognosis but fail to halt disease progression or alter eventual mortality data.

4. Breathing-Related Sleep Disorders

4.1. Normal Sleep. Under healthy conditions cardiovascular regulatory changes occur in specific stages of normal sleep. Nonrapid eye movement (NREM) sleep is associated with a generalized decrease in sympathetic drive; and deeper stages are associated with bradycardia, reduction in blood pressure, stroke volume, cardiac output, vasomotor tone, and systemic vascular resistance. Conversely, REM sleep is characterized by remarkable increases in sympathetic activity and thus labile heart rate and blood pressure values analogous to those observed while in the wakeful state [26]. Dysregulatory cardiovascular changes which characterize sleep-disordered breathing activate neural and circulatory responses with repetitive reflex increases in sympathetic activity. The subsequent vasoconstriction, which ensues, activates mechanisms which result in an eventual rise in mean pulmonary artery pressure [27].

4.2. Spectrum of Sleep Disorders. SRBD encompasses several overlapping disorders with varying degrees of severity. These include habitual snoring, increased upper airway resistance syndrome, hypoventilation syndromes, obstructive sleep apnea (OSA), and central sleep apnea (CSA). The most prevalent of the SRBD is OSA which occurs in 4% of all US adult males and 2% of the female population, thus it is the most studied of all SRBD [28]. Poor concentration, fatigue excessive sleepiness, and unrefreshing sleep are some of the characteristic symptoms of these disorders.

Sleep apnea can be defined as repetitive, prolonged airflow cessation with associated sleep arousal and occasional oxygen desaturation. Variants of sleep apnea include obstructive sleep apnea, with persistent respiratory effort in spite of oropharyngeal airway occlusion; central sleep apnea, involving cessation of both airflow and all respiratory effort; and a mixed pattern of both [29]. The term obstructive sleep apnea syndrome is used to refer to the occurrence of obstructive sleep apnea in conjunction with excessive sleepiness and

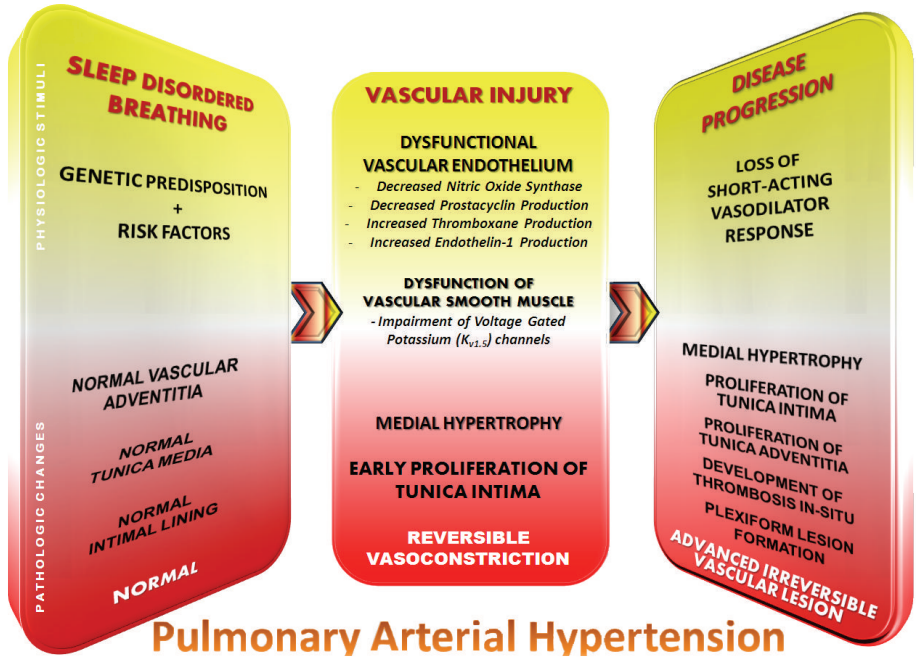

Figure 1: Pathogenesis of pulmonary hypertension [19, 21–23].

oxygen desaturation. Sleep apnea is commonly characterized by episodes of apnea, hypopnea, intermittent hypercapnia and hypoxia, increased sympathetic activity, and variations in sleep-associated baroreceptor reflex responses. Hypopnea is a reduction in airflow of ≥50% accompanied by an arousal or oxygen desaturation of ≥3%. Respiratory effort-related arousals occur when arousal from sleep result from increasing respiratory effort in the absence of overt apnea or hypopnea; this characterizes increased upper airway resistance syndrome. Change in pulse transit time, nasal pressure measurements, and respiratory inductance plethysmography are common modalities implemented in the assessment of sleep-related respiratory effort. A seemingly "normal" polysomnogram in a symptomatic patient does not rule out the presence of SRBD as the occurrence of respiratory events varies widely in milder variants. A consensus statement by the American Thoracic Society and the American Academy of Sleep Medicine specifies criteria for the diagnosis of SRBD. A diagnosis of obstructive sleep apnea-hypopnea syndrome can only be made in the presence of excessive daytime sleepiness which cannot be better explained otherwise, in the presence of ≥5 obstructed breathing events (including effort-related arousals, apnea, or hypopnea) per hour during sleep (referred to as the respiratory disturbance index (RDI)). Thus, an RDI of 5–15 is mild, 15–30 is moderate; and ≥30 hourly events is classified as severe [30, 31].

4.3. Obstructive Sleep Apnea. Obstructive sleep apnea is a common chronic SRBD that is characterized by complete or partial airway obstruction with resultant episodes of apnea or hypopnea, respectively. One-fifth of all adults in Western nations have mild OSA, while 1 in 15 adults has moderate to severe OSA. The prevalence is highest in older males with a high body-mass index and features of the metabolic syndrome; yet this disorder is seldom diagnosed and undiagnosed cases are as high as 85% in certain communities. These values are expected to rise in parallel with the current rising trend in obesity worldwide, leading to a resultant increase in the associated cardiovascular comorbidities, depression, and reduced quality of life of affected individuals [32–34].

5. Etiopathogenetic Mechanisms

An abrupt withdrawal of the nonchemical respiratory drive accompanies the transition from the wakeful state to NREM sleep resulting in a sudden decline in minute ventilation and $pO_{2,}$ as well as a concurrent rise in pCO_2 [35]. The decline in sympathetic drive is associated with a reduction in heart rate and cardiac output; normal individuals in NREM sleep experience a decline of up to 20% in systemic blood pressure [36]. In contrast, parasympathetic tone and pulmonary artery pressure rise during sleep [37]. In REM sleep however, the respiratory drive is influenced by behavioral changes and inhibition of the resting muscle tone in the upper airway musculature and accessory muscles, resulting in irregular breathing patterns which may worsen the hypoxemia and hypercapnia. About 80% of sleep time is spent in the NREM phase while 20% is in REM [28].

5.1. Changes in Cardiovascular Physiology in Sleep-Disordered Breathing. Recent studies have shown that individuals with OSA are at significant risk of developing systemic hypertension, cerebrovascular events, and ischemic heart disease. These result from acute cardiovascular changes which gradually become chronic and lead to cardiac remodeling and altered cardiovascular hemodynamics [38, 39]. Key factors

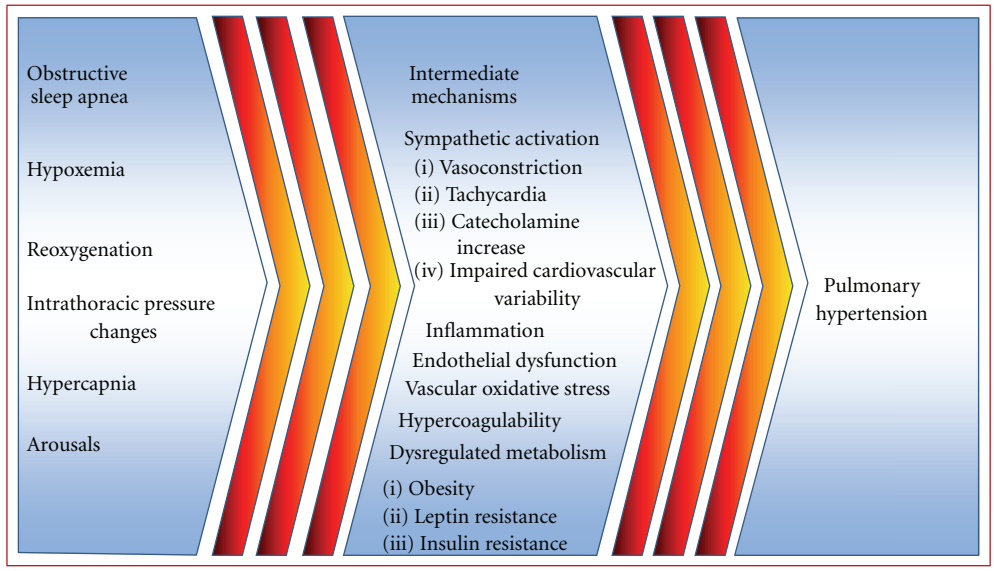

Figure 2: Intermediate mechanisms which potentially increase the risk of developing pulmonary hypertension in obstructive sleep apnea. These intermediate mechanisms in obstructive sleep apnea may contribute to initiating and perpetuating pathologic cardiovascular changes which result in pulmonary hypertension.

influencing these alterations include an abnormal amplification of negative intrathoracic pressure in the presence of a closed glottis as well as hypoxemic episodes and sleep arousals. These changes fluctuate acutely between episodes of apnea and ventilation, with variable chronotropic and vasomotor responses among individuals, and ultimately result in autonomic dysfunction, hypercoagulability, and a predisposition to thromboembolic events [21, 40–42].

5.2. Acute and Transient Cardiovascular Effects. A physiologic reduction in systemic blood pressure of up to 15% occurs during stages 3 and 4 of NREM sleep accompanied by a 10% reduction in cardiac output; this results in an overall decline in systemic vascular resistance. More complex hemodynamic responses occur in response to apneic stimuli which causes pulmonary and systemic hypertension, increased afterload, and reduction in cardiac output (Figure 2). These alterations to normal physiology are a consequence of changes in intrathoracic pressure, sympathetic activation, and episodes of hypoxia and hypercapnia [43, 44].

5.2.1. Negative Intrathoracic Pressure. A hallmark of sleep apnea is the Mueller maneuver (inspiration against a closed upper airway) which could generate negative intrathoracic pressures with values as low as -80 cm H_2O. The altered cardiac configuration and chamber filling pressures may consequently increase left ventricular transmural pressure and afterload, while LV relaxation is impaired by the exaggerated negative intrathoracic pressure thus worsening LV filling. This reduces stroke volume and cardiac output while the negative intrathoracic pressure stretches the aortic wall and activates intramural baroreceptors with episodic inhibition of sympathetic outflow with each Mueller maneuver. Increased venous return which occurs as the individual resumes breathing causes right ventricular distention and a leftward interventricular septal shift (ventricular interdependence) compromising LV diastolic filling and compliance [45–51].

5.2.2. Sympathetic Activation. Transient rises in sympathetic activity with vasoconstriction and hypertension accompany episodes of apnea with the lowest blood pressure values recorded at the midpoint of these episodes. Blood pressure then rises gradually with a sudden elevation at onset of breathing. Apneic episodes that exceed 35 seconds are characterized by decline in cardiac output of about 33%; however cardiac output rises by up to 15% above baseline at resumption of breathing [52–55]. Elevated systemic blood pressure and reduced cardiac output indicate apnea-related increase in systemic vascular resistance, with alpha-sympathetic neurons mediating vasoconstriction. Pulmonary artery pressures are noted to rise acutely in hypoxia and at onset of breathing in conjunction with systemic blood pressure; these neuronal effects are primarily in response to hypoxemia and hypercapnia [56–59]. With prolonged apnea and increasing hypoxemia, bradycardia worsens. Though tachy and bradyarrhythmias, sinus pauses, ventricular ectopy, and complete heart block are frequently observed in patients with obstructive sleep apnea syndrome, ventricular arrhythmias become more frequent at significant hypoxemia [60–64].

5.2.3. Effects of Hypoxia. Activation of carotid chemoreceptors by hypoxemia triggers arteriolar vasoconstriction and systemic catecholamine secretion. This response is most marked in the systemic vascular bed at oxyhemoglobin saturation levels lower than 65% and leads to transient hypertension [65].

Conversely, pulmonary vasoconstriction is a direct response to alveolar hypoxia in a physiologic attempt to

minimize ventilation perfusion mismatch. The recurrence of hypoxemic episodes in sleep apnea result in repetitive increases in pulmonary artery pressures; however, about 1 in 5 patients develops sustained pulmonary hypertension during the daytime [66–70]. More severe OSA and hypoxia may lead to right ventricular hypertrophy culminating in daytime pulmonary hypertension and right ventricular failure in the presence of hypercapnia and chronic alveolar hypoventilation [71–74].

5.3. Mechanisms Linking Obstructive Sleep Apnea to Chronic Cardiovascular Disease

5.3.1. Oxidative Stress. Repetitive bouts of nocturnal hypoxemia and intermittent reperfusion which accompany apneic episodes may generate highly reactive superoxide radicals as well as reperfusion-mediated endothelial damage, thus increasing susceptibility to atherosclerosis. Several polymorphonuclear leukocytes respond to hypoxemia with the release of free oxygen radicals; the cumulative effect of repetitive cycles of hypoxia followed by reoxygenation occurring multiple times in each hour of sleep over decades in patients who remain untreated may further worsen this preexisting vascular oxidative stress. The use of CPAP in patients with sleep apnea has been shown to reduce superoxide production [73–79].

5.3.2. Sympathetic Activation. A high level of sympathetic tone has been observed in patients with sleep apnea and administration of 100% oxygen results in deactivation of the chemoreceptor reflex response and significant reduction in sympathetic activity [80–82]. This has also been linked to increased resting heart rate and blood pressure variability and a reduced heart rate variability which all increase cardiovascular risk. The decrease in heart rate variability has been associated with an increase in cardiovascular mortality [83–87].

5.3.3. Vascular Endothelial Dysfunction. The release of vasoactive substances and vascular endothelial dysfunction may follow recurrent bouts of hypercapnia, hypoxia, and changes in vasomotor tone. Surges in plasma endothelin levels may help sustain vasoconstriction and endothelial dysfunction as observed in hypertension, dyslipidemia, and smoking, and diabetes has also been demonstrated in persons with OSA in the absence of other overt cardiovascular co-morbidity [88–90].

5.3.4. Metabolic Dysregulation. Dysregulation of metabolic pathways associated with OSA may heighten cardiovascular risk and increase the predilection for weight gain. Leptin, a hormone derived from adipocytes and primarily responsible for appetite suppression, demonstrates increased levels in obesity possibly from resistance to its metabolic effects. This hormone, which has been identified as an independent cardiovascular risk marker and might induce platelet aggregation, has been observed to occur at much higher levels in OSA than in obesity. Moreover, patients with OSA have been observed to develop significant weight gain in the year immediately preceding diagnosis, and treatment of OSA with CPAP decreases leptin levels and accumulation of visceral fat, further implicating leptin resistance in the predisposition to weight gain [91–97].

Impaired glucose tolerance may also result from OSA. Elevated fasting blood glucose, serum insulin, and HbA_{1c} have been observed in these individuals with a direct correlation between severity of insulin resistance and OSA; patients with severe OSA are five times more likely to develop overt diabetes mellitus than the general population [22, 98–101].

5.3.5. Inflammation. Serum levels of C-reactive protein (CRP) and inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α may be increased in response to hypoxia and sleep deprivation, both of which are present to varying degrees in patients with OSA. Patients with OSA have also shown elevated levels of these cytokines. The inhibition of nitric oxide synthase mediated by CRP which also increases the expression of certain cell adhesion molecules may worsen endothelial dysfunction and further aggravate preexisting vascular disease [102–111]. The expression of cell adhesion molecules which mediate leukocyte adhesion to endothelial cells may be directly modulated by hypoxic stress, thus leading to elevated levels of cell adhesion molecules in persons with moderate to severe OSA. This elevation may be reversed with the use of CPAP therapy.

5.3.6. Coagulation. Increased nocturnal catecholamine levels in conjunction with other factors increase the tendency for platelet aggregation in OSA; a condition almost completely reversed by the use of CPAP. Similarly, an increase in fibrinogen level, hematocrit and hyperviscosity of blood result in a predilection for thromboembolism and atherosclerosis. The reversal of these hypercoagulable phenomena with CPAP therapy suggests a causal relationship to OSA [23, 112–118].

6. Right Heart Dysfunction and Pulmonary Hypertension in Sleep-Disordered Breathing

OSA is frequently regarded as an independent risk factor in the development of pulmonary hypertension and subsequent cor pulmonale. However, studies show a stronger association between PH and obstructive ventilatory patterns observed on pulmonary function testing as well as daytime hypercapnia and hypoxemia; where most of this association is attributed to coexisting obstructive airway disease. PH correlates highly with elevated waking pCO_2, reduced waking pO_2, coexisting obstructive pulmonary disease, and body mass index, particularly in severe cases [119–121]. Patients with pulmonary hypertension have also been shown to have more lengthy periods of hypoxemia. The high correlation of PH with increased BMI, reduced vital capacity, expiratory reserve volume, and total lung capacity suggest that the association between PH and OSA is strongest in the presence of the mechanical consequences of obesity on respiration [8, 14, 122]. Recurrent and persistent pressure and volume strains on the right heart increase wall tension in the right ventricle facilitating myocardial hypertrophy. Chronic hypoxemia

resulting from episodic nocturnal oxygen desaturations potentiates the development of permanent PH by the induction of vascular remodeling [67, 123, 124].

7. Treatment of Pulmonary Hypertension in Sleep-Related Breathing Disorders

Pulmonary vascular response to hypoxia has been shown to reduce with significant drop in the mean pulmonary artery pressures after the therapeutic use of nasal CPAP, suggesting potential reversibility of pulmonary hypertension upon treatment of OSA [125–127]. Other therapeutic strategies implemented in recent times include the use of hemodialysis in patients with coexisting chronic renal failure to reduce the severity of OSA [128]. Surgical alternatives and cardiac atrial pacing have also been explored as therapeutic alternatives [129]; in patients with less tolerance for conventional treatment strategies, the use of agents that limit effects of inflammatory mediators such as aspirin or statins may be beneficial [130–134].

8. Summary

SRBD encompasses conditions which range from habitual snoring to obstructive sleep apnea and may be associated with considerable morbidity and mortality. Increasing evidence points to the significant association between SRBD and PH. Though the majority of research endeavors in recent times have focused on left heart hemodynamics, few studies have attempted to outline the effects of SRBD on the pulmonary vascular system and multiple studies are ongoing to further elucidate the specific pathways underlying these mechanisms. Available evidence indicates that the development of pulmonary hypertension in patients with SRBD involves the complex interplay of multiple factors and correlates strongly with the severity and duration of nocturnal desaturations as well as associated risk factors. Early recognition and treatment may effectively reduce these complications.

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Clinical Study

Significant Differences in Markers of Oxidant Injury between Idiopathic and Bronchopulmonary-Dysplasia-Associated Pulmonary Hypertension in Children

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While oxidant stress is elevated in adult forms of pulmonary hypertension (PH), levels of oxidant stress in pediatric PH are unknown. The objective of this study is to measure F_2-isoprostanes, a marker of oxidant stress, in children with idiopathic pulmonary hypertension (IPH) and PH due to bronchopulmonary dysplasia (BPD). We hypothesized that F_2-isoprostanes in pediatric IPH and PH associated with BPD will be higher than in controls. Plasma F_2-isoprostanes were measured in pediatric PH patients during clinically indicated cardiac catheterization and compared with controls. F_2-Isoprostane levels were compared between IPH, PH due to BD, and controls. Five patients with IPH, 12 with PH due to BPD, and 20 control subjects were studied. Patients with IPH had statistically higher isoprostanes than controls 62 pg/mL (37–210) versus 20 pg/mL (16–27), $P < 0.01$). The patients with PH and BPD had significantly lower isoprostanes than controls 15 pg/ml (8–17) versus 20 pg/mL (16–27), $P < 0.02$. F_2-isoprostanes are elevated in children with IPH compared to both controls and patients with PH secondary to BPD. Furthermore, F_2-isoprostanes in PH secondary to BPD are lower than control levels. These findings suggest that IPH and PH secondary to BPD have distinct mechanisms of disease pathogenesis.

1. Introduction

It has long been recognized that patients with pediatric idiopathic pulmonary hypertension (IPH) have poor long-term survival. More recently pulmonary hypertension (PH) associated with bronchopulmonary dysplasia (BPD) has been identified as a significant cause of mortality among BPD patients [1, 2]. Few studies have evaluated the mechanisms and optimal treatment of PH due to BPD, resulting in management strategies for these patients which mirror the better studied pharmacologic treatments of IPH. The use of similar therapeutic strategies in these two populations relies on the unproven assumption that the diseases share similar molecular pathophysiologies.

Oxidant stress appears to play a role in the molecular mechanism of adult IPH. Multiple studies measuring F_2-isoprostanes, a stable marker of oxidant stress resulting from the oxidation of cell-membrane arachidonic acid, have shown adult IPH patients, have higher F_2-isoprostane levels than do control patients [3, 4]. Elevated F_2-isoprostane levels suggest enhanced oxidant stress in IPH patients and may also directly contribute to pulmonary vasoconstriction [5]. There are no published data on oxidant stress or F_2-isoprostane levels in pediatric patients with PH secondary to BPD or IPH. The objective of this study is to measure F_2-isoprostanes in children with IPH and PH due to BPD and to compare them to normal controls to assess the role of oxidant stress in pediatric populations with PH. We hypothesize that children with IPH and PH due to BPD will have F_2-isoprostane levels higher than those measured in healthy control subjects. Evidence supporting similar biochemical mechanisms between these pediatric populations with PH would support the practice of utilizing similar therapeutic strategies in these children.

2. Materials and Methods

2.1. Study Population. All patients who presented to the pediatric catheterization laboratory at Vanderbilt Children's Hospital for evaluation of pulmonary hypertension between December 2007 and December 2008 were approached for participation in the study. Patients were excluded if they had ventricular septal defects; patients with an atrial septal defect or hemodynamically insignificant patent ductus arteriosus were allowed. Other exclusion criteria were pulmonary vein stenosis, valvar stenosis of any kind, aortic arch obstruction, left ventricular dysfunction, active infection of any kind, and autoimmune disease. All catheterizations were performed for clinical reasons in accordance with the standard of care at the Vanderbilt Pulmonary Hypertension Center.

Two groups of control patients were enrolled. The primary control group was recruited from the general pediatric clinic at Vanderbilt Children's Hospital. Patients without acute or chronic illness who required a routine blood draw for health maintenance were approached for enrollment in the study. In addition, in order to assess the effect of general anesthesia and the general impact of the catheterization on F_2-isoprostane levels, patients presenting to the pediatric catheterization laboratory for atrial septal defect (ASD) device closure were also approached to participate as controls. Patients undergoing device ASD closure were chosen because they typically do not have elevation of their pulmonary artery pressure and are in good general health. Exclusion criteria for both control groups were a history of prematurity, ventricular septal defect, pulmonary vein stenosis, valvar stenosis of any kind, aortic arch obstruction, left ventricular dysfunction, active infection of any kind, and autoimmune disease.

2.2. Echocardiography. All consenting control subjects recruited from the general pediatric clinic underwent echocardiography to screen for undiagnosed pulmonary hypertension. Right ventricular pressure was assessed by interrogation of the tricuspid regurgitation jet and utilization of the Bernoulli equation. The right atrial pressure was assumed to be 5 mmHg. Any right ventricular pressure measurement of greater than 30 mmHg was deemed elevated. In the absence of tricuspid regurgitation, flattening of the ventricular septum during systole in the parasternal short axis was defined as evidence of elevated right ventricular pressure. The echocardiograms were independently reviewed by two pediatric cardiologists. Evidence of elevated right ventricular pressure found by one or more reviewer excluded a patient from participation as a control subject.

2.3. Cardiac Catheterization. At the Vanderbilt Pediatric Pulmonary Hypertension Center, the timing of cardiac catheterization is specific to each type of PH. IPH patients undergo cardiac catheterization with vasodilatory testing at diagnosis and every 3–12 months thereafter depending on their clinical status and changes in therapy. Patients with PH and BPD are not routinely catheterized at diagnosis unless structural abnormalities are suspected such as pulmonary vein stenosis. Our center uses echocardiography to identify and follow elevated pulmonary artery pressure in neonates with BPD in the neonatal ICU and in follow up after discharge from the ICU. Tricuspid regurgitation velocity and systolic flattening of the ventricular septum are the primary echocardiographic features used to assess pulmonary artery pressure. BPD patients with persistent echocardiographic evidence of elevated pulmonary artery pressure are followed in the PH clinic as outpatients and undergo catheterization within 3–6 months if on vasodilator therapy. BPD-PH patients may also undergo catheterization prior to discontinuation of vasodilator therapy.

Consenting participants with PH and the ASD control patients underwent their clinically indicated cardiac catheterization under general anesthesia. All patients underwent a right heart catheterization with directly measured saturations and pressures at the lowest FiO_2 were required to maintain oxygen saturations of above 95% by pulse oximetry. In patients with an ASD, a catheter was placed across the ASD from the right heart to obtain a pressure in the left atrium and a saturation measurement from a pulmonary vein. A femoral artery sheath was placed in all patients to directly measure the systemic blood pressure and the descending aortic saturation. Pulmonary flows were calculated using the Fick equation with assumed oxygen consumption in all BPD patients, in the IPH patients with an atrial septal defect, and in all the ASD control patients. Thermodilution was used to measure pulmonary flow in IPH patients without an atrial septal defect. All pulmonary flows were indexed to body surface area. Pulmonary vascular resistance (PVR) was calculated in Woods units (WU) and indexed to body surface area.

2.4. Blood Sampling. In control patients recruited from the general pediatric clinic, 5 mLs of study blood was drawn by routine phlebotomy. ASD control patients and PH patients had 5 mls of study blood drawn during the baseline hemodynamic measurements. If patients undergoing catheterization had a pulmonary venous sample obtained, the study blood was taken from a pulmonary vein. Catheterized patients without an ASD had study blood obtained in the descending aorta through the femoral arterial sheath or arterial catheter. All blood samples were obtained before any pulmonary vasodilator testing was performed. All study blood was collected on ice in an EDTA tube and immediately transported to the laboratory for isoprostane analysis.

2.5. F_2-Isoprostane Analysis. F_2-isoprostanes were measured using a method pioneered by Drs. Morrow and Roberts [6]. Briefly this involves passing the sample through two Waters Corporation Sep-Pak cartridges to remove much of the unwanted impurities. First one uses a C-18 packing material and the second uses a silica packing material. The final elution is then esterified with pentafluorobenzyl bromide and silated with bis(trimethylsilyl)trifluoroacetamide before being subjected to GC/MS analysis on an Agilent 5973 inert

Table 1: Subjects' demographics.

	Control	IPH	PH due to BPD	*P* value
N	18	4	12	
Age[§] (years)	7.5 (3.8–15.3)	11 (3–16.8)	2 (1–2.8)	<.01*
Gender (# male)	10	2	10	.63**, .12[†], .25[¶]
BMI[§] (kg/m^2)	17.9 (16.6–25.2)	23.1 (15.4–27.1)	16.1 (15.7–16.7)	.02*
Race (# Caucasian)	10	4	8	.14**, .41[†], .27[¶]

* *P* value based on the Kruskal-Wallis test.
** *P* value based on the Fisher's exact test of control versus IPH.
[†] *P* value based on the Fisher's exact test of control versus PH due to BPD.
[¶] *P* value based on the Fisher's exact test of IPH versus PH due to BPD.
[§] Data expressed as median (IQR).

MSD coupled with and Agilent 6890N Network GC from Agilent Technologies in Wilmington, Delaware.

2.6. Statistical Analysis. Study data were collected and managed using the REDCap electronic data capture tools hosted at Vanderbilt University [7]. Data are presented as medians with interquartile ranges (IQR) due to lack of normal distribution. The Mann-Whitney *U* test was performed to determine the statistical significance of the difference between any two groups. The Kruskal-Wallis test was used to analyze differences between all three groups. Categorical variables between groups were assessed with the Fisher's exact test. Spearman's test was used to analyze correlations. A two-tailed α of <0.05 was considered statistically significant. Bonferroni correction was not used due to its conservative nature and the small number of comparisons done in this study. SPSS was used to perform the statistical analysis (IBM SPSS statistics, version 20).

This study was approved by the Institutional Review Board of the Vanderbilt University Medical Center.

3. Results

We enrolled 5 patients with IPH and 12 patients with PH secondary to BPD. All PH patients approached consented to participate in the study. Twenty controls, including 5 ASD patients and 15 healthy controls from the primary care clinic, consented to participate in the study. Three eligible control patients approached in the primary care clinic refused to participate because they did not have time to undergo echocardiography. All ASD patients approached to participate consented. None of the healthy control subjects had abnormal echocardiograms. One of the 5 IPH patients underwent diagnostic catheterization while the remainder underwent routine follow-up catheterizations. All of the BPD patients were catheterized for purposes of treatment follow-up. The F_2-isoprostane data could not be obtained in one IPH patient and two controls due to sample problems.

Table 1 describes the baseline characteristics of the study groups. The median age of control patients did not statistically differ from IPH patients ($P = 0.99$), but those with PH due to BPD were significantly younger than controls ($P < 0.01$). There was no statistical difference in gender distribution between the controls and the two PH groups. While the body mass index (BMI) of the IPH patients did not significantly differ from the controls, the BMI of those with PH due to BPD was significantly less than controls ($P = 0.01$).

Table 2: Medical therapy of pulmonary hypertension patients.

	IPH	PH due to BPD	*P* value
N	4	12	
Home Oxygen (No. of patients)	1	8	.13*
Epoprostenol (No. of patients)	3	2	.06*
Bosentan (No. of patients)	1	1	.52*
Sildenafil (No. of patients)	3	11	.45*
Months on Therapy[†]	17.5 (4–27.5)	20 (12–29)	.99**

* *P* value based on Fisher's exact test.
** *P* values based on Mann-Whitney *U* test.
[†] Data expressed as median (IQR).

The medical treatments of patients with PH are described in Table 2. There were significantly more IPH patients treated with epoprostenol than patients with PH due to BPD, although this did not reach statistical significance ($P = 0.06$). There was no difference in the number of subjects on bosentan, sildenafil, and home oxygen in the two PH groups.

The hemodynamic data from the cardiac catheterizations are presented in Table 3. The control patients undergoing ASD device closure had normal right ventricular pressure and pulmonary vascular resistance which were significantly lower than in both the IPH group ($P < 0.01$) and the BPD-PH group ($P < 0.01$). The right and left ventricular end diastolic pressures, cardiac index, and baseline FiO_2 in ASD controls were not different from either PH group. As expected, those undergoing ASD device closure had a larger pulmonary to systemic blood flow ratio than those with IPH ($P < 0.01$) and PH due to BPD ($P < 0.01$). The median right ventricular pressure as a percentage of left ventricular pressure (RVP/LVP ratio) and the median PVR were distinctly lower in those with PH due to BPD

Table 3: Hemodynamics of subjects in catheterization laboratory¶.

	IPH	PH due to BPD	ASD controls	*P* value IPH versus BPD
N	4	12	5	
RVP/LVP (%)	83 (80–1.1)	46 (38–59)	.24 (.22–.25)	.08*
Pulmonary vascular resistance (WUs)†	17.2 (16.2–19.6)	4 (3.5–5.4)	1.4 (1.1–1.6)	.08*
Mean PAP†† (mmHg)	61 (53–63)	25 (22–36)	17 (14–19)	.08*
RVEDP‡ (mmHg)	10 (8–10)	7.5 (6.3–9)	8 (7.5–8.5)	.26*
LVEDP6 (mmHg)	8 (8–9)	8 (7–9)	10 (8–10)	.99*
Cardiac index (L/min/m^2)	3.6 (3.1–3.6)	3.6 (3.5–3.8)	3.0 (2.7–3.5)	.99*
Qp : Qs§	.87 (0.8-.94)	1.0 (1.0-1.0)	2.1 (1.6–4.1)	.53*
Baseline FiO_2(%)	21 (21–26)	21 (21-22)	21 (21–21)	.52*
ASD (# patients)	2	7	5	.62**

*Value based on Mann-Whitney *U* test.
**Value based on Fisher's exact test.
†Indexed to body surface area.
††Pulmonary artery pressure.
‡Right ventricular end diastolic pressure.
‡‡Left ventricular end diastolic pressure.
§Ratio of pulmonary to systemic blood flow.
¶Interval data expressed as median (IQR).

compared to those with IPH, but the differences did not quite reach statistical significance. The median right ventricular end diastolic pressure (RVEDP), left ventricular end diastolic pressure (LVEDP), and baseline FiO_2 were not significantly different among the two groups with PH. A patent foramen ovale was found in 5 patients with PH secondary to BPD, and a moderate atrial septal defect was found in one patient with PH secondary to BPD. One patient with PH secondary to BPD had a patent foramen ovale in addition to a small patent ductus arteriosus. In those with IPH, two patients had small atrial septal defects.

Patients with IPH had significantly higher F_2-isoprostanes than controls (62 pg/mL (37–210) versus 20 pg/mL (16–27), $P \leq 0.01$) (Figure 1) . The patients with PH due to BPD had significantly lower F_2- isoprostanes than controls (15 pg/mL (8–17) versus 20 pg/mL (16–27), $P = 0.02$). F_2-Isoprostane levels in IPH patients were significantly higher than those with PH secondary to BPD ($P = 0.002$). No correlation was found between F_2-isoprostane levels and age ($R_S^2 = 0.02$) or between F_2-isoprostane levels and BMI ($R_S^2 = 0.09$) in the study cohort. Among all PH patients, no correlation was found between F_2-isoprostanes and RVP/LVP ratio ($R_S^2 = 0.02$) or any other hemodynamic measure. When analyzing only BPD patients with RVP/LVP >50%, those with PH due to BPD still had lower F_2-isoprostanes ((8.7 pg/mL (6.3–12.7)) than controls ($P \leq 0.01$) and those with IPH ($P = 0.02$). No significant difference was found between the F_2-isoprostane levels of the control subjects undergoing ASD device closure and those undergoing routine phlebotomy ($P = 0.95$). Similarly, the F_2-isoprostanes drawn from the pulmonary veins were not significantly different from those drawn from the descending aorta among those with PH due to BPD ($P = 0.09$) or among those with IPH ($P = 0.44$).

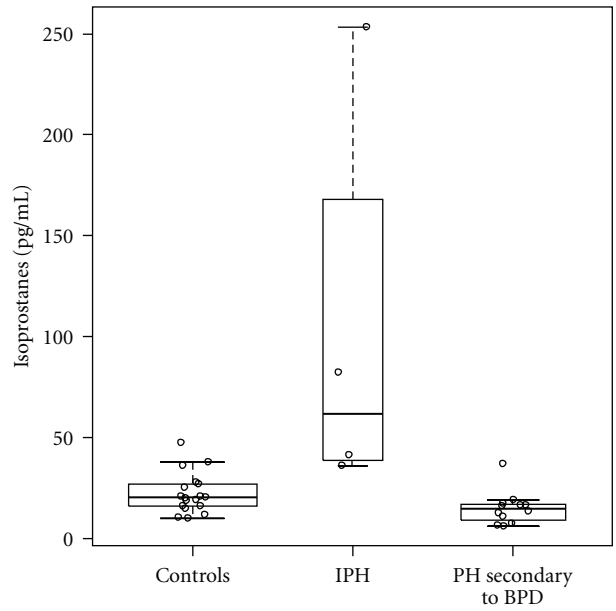

Figure 1: Box plot of plasma F_2-isoprostanes in IPH, PH due to BPD, and controls. F_2-Isoprostanes are significantly higher in children with IPH compared to pediatric controls and children with PH secondary to BPD. Plasma F_2-isoprostanes are statistically lower in children with PH secondary to BPD compared to those with IPH and pediatric controls.

Both the IPH and BPD-PH groups had one outlier with a high F_2-isoprostane level. The BPD patient with the high isoprostane value had only mildly elevated pulmonary artery pressures with a RVP/LVP ratio of .38 and a PVR of 3.6 WU and was only being treated with sildenafil and home oxygen. The IPH patient with the high isoprostane value

had similar hemodynamics to the other IPH patients with a RVP/LVP ratio of .83, a PVR of 17.1 WU, a RVEDP of 10 mmHg, and a LVEDP of 10 mmHg. This IPH patient was on epoprostenol and sildenafil similar to the remaining IPH patients but was the only one on bosentan. When repeating the analysis without the two outlier, the F_2-isoprostanes of the IPH group are still significantly higher than the BPD-PH group ($P = 0.01$), and the control F_2-isoprostanes are still significantly lower than the IPH group ($P = 0.02$) and higher than the BPD-PH group ($P < 0.01$).

4. Discussion

F_2-isoprostanes are elevated in pediatric patients with IPH but not in those with PH secondary to BPD. In fact, F_2-isoprostanes in the BPD-PH group seem to be lower than controls. Anesthesia and the general effect of the catheterization did not appear to influence F_2-isoprostane levels as there was no difference between the ASD controls and the clinic controls. To our knowledge, this is the first time F_2-isoprostane levels have been studied in pediatric patients with IPH and PH secondary to BPD. Different F_2-isoprostane levels suggest that IPH and PH secondary to BPD have distinct molecular pathophysiologies with different degrees of chronic oxidant injury. This suggests that these entities may be amenable to different pharmacologic approaches. The finding of elevated F_2-isoprostanes in children with IPH is consistent with the elevated levels previously reported in the adult populations with IPH [3]. F_2-isoprostanes have been shown to have a direct role in producing pulmonary vasoconstriction by the activation of thromboxane receptors and increasing the production of potent vasoconstrictors such as thromboxane A_2 and endothelin 1 [3, 8]. Our finding of elevated circulating F_2-isoprostane levels in pediatric patients with IPH suggests enhanced oxidant stress in these patients which may directly contribute to pulmonary vasoconstriction.

The low levels of F_2-isoprostanes in PH secondary to BPD was an unexpected finding. Two groups have previously shown elevated levels of F_2-isoprostanes in premature infants in the first weeks of life [9, 10]. Impaired and disordered angiogenesis and resultant impaired alveolarization due at least in part to oxidant damage is thought to underlie much of the BPD phenotype [11]. The natural history of oxidant stress in premature infants with or without PH due to BPD is unknown. In this study, there was no difference in months on treatment between the IPH group and the BPD-PH group suggesting the two cohorts are at reasonably similar points in disease time course. Even if the F_2-isoprostane levels are elevated early in the course of PH secondary to BPD, the low levels we found in these established BPD-PH patients is in marked contrast to the elevated levels we found in IPH patients at a similar point in disease course.

The etiology of low levels of F_2-isoprostanes in children with PH secondary to BPD is unknown. F_2-isoprostanes are formed by the free-radical-induced peroxidation of arachidonic acid in cell membranes [4, 12]. This would suggest that PH secondary to BPD does not generate the oxidant stress seen in IPH at the molecular level and/or that BPD enhances compensatory mechanisms to scavenge free radicals. An alternative possibility would be the preferential production of other isoprostane molecules from arachidonic acid, such as E_2 and D_2 isoprostanes, in children with BPD-associated PH. Polyunsaturated fatty acids such as linoleic acid, DHA, and EPA may be oxidized to form isoprostane like molecules more efficiently than arachidonic acid [12]. Children with PH due to BPD may have an unknown mechanism to encourage oxidation of these polyunsaturated fats over arachidonic acid. This is another potential explanation of the low F_2-isoprostane levels in children with BPD-associataed PH, although there is no data on this possibility. Another alternative is inhibition of F_2-isoprostane formation by very high oxygen tension with diversion to isofuran production; however, those with BPD-associated PH in this study were not on significantly higher FiO_2 than the other groups [13]. In fact, all of the groups were breathing a FiO_2 of near 21% making hyperoxic suppression of F_2-isoprostanes very unlikely. The inevitable pO2 difference between the pulmonary venous samples and systemic venous samples did not appear to influence F_2-isoprostane levels as there was no difference in the F_2-isoprostane levels between the ASD controls, who all had pulmonary venous samples, and the clinic controls, who all had systemic venous samples. Regardless of any potential mechanism to lower F_2-isoprostane levels below normal controls, this study strongly supports the absence of a high level of uncompensated oxidant stress in this population of children with PH secondary to BPD.

The limitations of this study include the fact that the patients with PH due to BPD are younger and have a lower BMI than both the controls and those with IPH. The age difference is difficult to remedy as IPH typically presents later in childhood while PH due to BPD is a disease of infants and toddlers. If the patient survives infancy, PH secondary to BPD tends to improve or even resolve with age leaving few older children with active disease to study [2]. The lower BMI in the PH due to BPD is likely a function of both the younger age in this group and the commonly seen feature of failure to thrive early in life in patients with BPD. The absence of correlation of age or BMI with F_2-isoprostane level suggests the age and BMI differences do not explain the difference in F_2-isoprostanes seen in this study.

Another limitation of the study is the different PH severity among the IPH group and those with PH due to BPD. If infants survive the initial malignant phase of PH secondary to BPD, pulmonary artery pressures tend to decrease over time [2]. This natural history of improvement in PH due to BPD explains the lower pulmonary vascular resistance and RVP/LVP in those with PH secondary to BPD compared to those with IPH. The fact that no correlation exists between hemodynamic measures of elevated pulmonary pressures and F_2-isoprostanes suggests the F_2-isoprostane difference between IPH and PH due to BPD is not caused by the difference in PH severity. Similarly, analysis of only the BPD PH patients with RVP/LVP >50% continues to show significantly lower F_2-isoprostanes than IPH patients and controls. While clinical function data, such as New York

Heart Association class, was not collected due to the difficulty in applying these measures to infants and toddlers, normal ventricular filling pressures, and normal cardiac outputs in both groups demonstrate similar stable hemodynamic states despite the difference in PH severity. A greater percentage of those with IPH were on treatment with epoprostenol when compared to those with PH due to BPD. Evidence exists that this drug lowers F_2-isoprostane levels in patients; thus, this bias would act to lessen the difference between IPH patients and the other 2 study groups [3]. Finally, it would be optimal to increase the number of patients in the IPH group, but the rarity of this disease in children makes obtaining larger numbers difficult.

5. Conclusion

We found that pediatric patients with IPH have elevated F_2-isoprostane levels while children being followed for PH secondary to BPD have low F_2-isoprostane levels. This marked difference in oxidant stress suggests each disease has a unique pathophysiology. Future studies are needed to better elucidate these differences thereby leading to better targeted therapies for pediatric patients with a broad spectrum of pulmonary hypertensive diseases.

Abbreviations

PH:	Pulmonary hypertension
IPH:	Idiopathic pulmonary hypertension
BPD:	Bronchopulmonary dysplasia
ASD:	Atrial septal defect
PVR:	Pulmonary vascular resistance
WU:	Woods units
IQR:	Interquartile range
RVP/LVP:	Right ventricular pressure as a percentage of left ventricular pressure
RVEDP:	Right ventricular end diastolic pressure
LVEDP:	Left ventricular end diastolic pressure.

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Review Article

Pulmonary Hypertension in Pregnancy: Critical Care Management

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Pulmonary hypertension is common in critical care settings and in presence of right ventricular failure is challenging to manage. Pulmonary hypertension in pregnant patients carries a high mortality rates between 30–56%. In the past decade, new treatments for pulmonary hypertension have emerged. Their application in pregnant women with pulmonary hypertension may hold promise in reducing morbidity and mortality. Signs and symptoms of pulmonary hypertension are nonspecific in pregnant women. Imaging workup may have undesirable radiation exposure. Pulmonary artery catheter remains the gold standard for diagnosing pulmonary hypertension, although its use in the intensive care unit for other conditions has slowly fallen out of favor. Goal-directed bedside echocardiogram and lung ultrasonography provide attractive alternatives. Basic principles of managing pulmonary hypertension with right ventricular failure are maintaining right ventricular function and reducing pulmonary vascular resistance. Fluid resuscitation and various vasopressors are used with caution. Pulmonary-hypertension-targeted therapies have been utilized in pregnant women with understanding of their safety profile. Mainstay therapy for pulmonary embolism is anticoagulation, and the treatment for amniotic fluid embolism remains supportive care. Multidisciplinary team approach is crucial to achieving successful outcomes in these difficult cases.

1. Introduction

Pregnancy in women with pulmonary hypertension is known to be associated with significantly high mortality rate between 30% and 56% [1]. The physiologic changes that occur during pregnancy and the peripartum period are poorly tolerated in these patients. There are also acute conditions associated with pregnancy that may be complicated by severe pulmonary hypertension, such as, pulmonary and amniotic fluid embolism. Majority of maternal deaths occur during labor or within 1 month postpartum [2].

Pulmonary hypertension is defined as an increase in mean pulmonary artery pressure (PAP) (mPAP) >25 mmHg at rest as assessed by right heart catheterization (RHC). Recent developments have been made in the treatment of pulmonary hypertension, and advances in the multidisciplinary approach are believed to have an impact on the high maternal mortality rate [3]. However, management of critically ill patients with hemodynamically significant pulmonary hypertension remains challenging. In this paper we review the diagnosis and treatment of critically ill parturient with pulmonary hypertension of different etiologies and discuss treatment strategies.

2. Pregnancy and Labor Physiology

During pregnancy, several physiologic changes further impact on the hemodynamic ramifications in pulmonary hypertension [PH] (Figure 1). Virtually every organ system is affected in pregnancy. The most significant change in the cardiovascular system is increase in blood volume, which can increase in a normal, healthy pregnant female almost 50% above the nonpregnant level at it peaks during 20–32 weeks of gestation [4]. In addition, heart rate and stroke volume are also increased with higher cardiac output. Systemic and

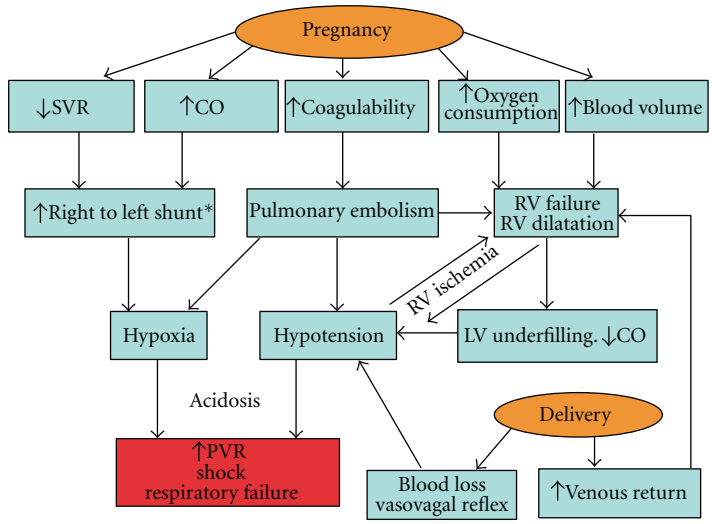

Figure 1: The physiologic response to pregnancy in pulmonary arterial hypertention* = right to left shunt increases in Eisenmenger's patients and patients with a patent foramen ovale [7].

pulmonary vascular resistances (PVRs) are decreased. However, in women with pulmonary hypertension, pulmonary vascular disease prevents the fall in PVR, leading to further rise in PAP with increased cardiac output [5]. Due to the stimulation of progesterone, tidal volume is increased despite the elevation of the diaphragm, whereas respiratory rate is unchanged. The rise in tidal volume accounts for increased minute volume and respiratory alkalosis with a mean arterial partial carbon dioxide pressure (PCO_2) of 30 mmHg and a decreased functional residual capacity [6].

Labor and delivery feature a further increase in cardiac output and blood pressure particularly during uterine contractions. These hemodynamic modifications are heavily influenced by the mode of delivery. Normal vaginal delivery is associated with a 34% increase in cardiac output at full cervical dilation [4]. At the point of cesarean section delivery and in response to spinal anesthesia, a 47% increase in cardiac index and 39% decrease in SVR have been recorded [6, 8]. Following delivery, several factors lead to hemodynamic instability in the PH patients, including decreased preload from blood loss and anesthesia, increased preload from relief of caval obstruction, or additional blood return from the contracting uterus, abrupt increase of SVR and PVR to nonpregnancy state, and reduced ventricular contractility [2, 4, 9].

A normal pregnancy induces a hypercoagulable state due to a combination of physical and hormonal factors, as well as hematologic changes. Progesterone-mediated increases in venous distensibility and capacity lead to increased venous stasis. The enlarging uterus may also induce a selective compressive effect on the common iliac vein. Pregnancy causes hematologic changes including increased circulating levels of clotting factors, decreased protein S levels and resistance to activated protein C [10]. The generation of fibrin is increased, and fibrinolytic activity is decreased. The combination of these factors results in a hypercoagulable state.

3. Pathophysiology

Multiple molecular pathways have been implicated in the pathogenesis of pulmonary hypertension. Vaso-affective molecules produced in the pulmonary vascular endothelium include nitric oxide and prostacyclin, which are vasodilators. Endothelin-1 acts as a vasoconstrictor and is involved in vascular smooth muscle proliferation [11]. Thus, dysfunction of the molecular pathways and dysregulation of their production can lead to imbalance between vasodilation and vasoconstriction and between apoptosis and proliferation. These molecular alternations are thought to be the underlying disease mechanisms for chronic pulmonary arterial hypertension [12].

In acute pulmonary hypertension, hypoxic pulmonary vasoconstriction plays an important role and can be the inciting or perpetuating factor for increased pulmonary pressures. In acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), both hypoxic vasoconstriction and deposition of intravascular fibrin and cellular debris contribute to vascular obliteration and PH [13]. Endotoxin release in sepsis has been shown in animal studies to cause PH by causing constriction of proximal pulmonary arteries and decreased compliance of the distal pulmonary vasculature [12]. In massive acute pulmonary embolism, the increase in pulmonary vascular resistance is related to the mechanical obstruction from the thrombosis load and subsequent vasoconstriction [14]. Vascular obstruction was historically thought to be also the pathophysiology in amniotic fluid embolism (AFE). However, more recent evidence suggests pulmonary hypertension is due to vasoactive substances (prostacyclin, endothelin) or immunologic factors. The latter supported by decreased complement level measured in postpartum AFE patients compared to control. These findings indicate AFE may result from biochemical mediators released after the embolization occurs and have led some authors to propose renaming the entity "anaphylactoid syndrome of pregnancy" [15].

Pulmonary hypertension of different causes can lead to a final common pathway of right ventricular strain or failure. Right ventricle is a thin walled structure that tolerates poorly acute increase in afterload. This is because right ventricular stroke volume decreases proportionately to acute increase in afterload, and it cannot acutely increase the mean PAP to more than 40 mmHg [11]. The RV subsequently becomes dilated, which is in contrast to chronic pulmonary hypertension, where RV hypertrophy is the main feature reflecting an adaptive mechanism. RV distention in turn results in increase oxygen consumption and reduction in contractility. It could also impair left ventricular (LV) filling with paradoxic interventricular septal movement, leading to decreased cardiac output and oxygen delivery [16]. Perfusion of the right coronary artery is usually dependent on adequate aortic root pressure and a pressure gradient between the aorta and RV [17]. In setting of increased RV pressure and decreased cardiac output, RV ischemia may ensue, with further severe hemodynamic decompensation.

4. Classification and Etiologies of PH

The world health organization (WHO) classification of pulmonary hypertension has been redefined and updated in 2009 (Table 1) [18]. Idiopathic PAH and PAH associated with connective tissue disease affect predominantly women of childbearing age [18]. Idiopathic PAH is rare and a rapidly progressive disease with an untreated survival of only 2.8 years [19]. The association of PAH with connective tissue disease is a common phenomenon. The highest incidence of the development of PAH is known in scleroderma patients, especially with the CREST syndrome (10–20% develop PAH) followed by systemic lupus erythematous (SLE, 10%) [20]. Patients with PAH in connective tissue disease have a deleterious clinical course and a worse prognosis [18].

WHO group 1 also includes PAH associated with congenital heart disease (CHD). The disease could be further classified based on anatomic pathophysiology of shunts or clinical phenotypes (Tables 2 and 3). A significant proportion of patients with CHD, in particular those with relevant systemic-to-pulmonary shunts, will develop PAH if left untreated [18]. Hemodynamic changes during pregnancy can exacerbate the problems associated with CHD as well. In the Eisenmenger syndrome, right to left shunting increases during pregnancy because of systemic vasodilation and RV overload with decrease in pulmonary blood flow and increase cyanosis. The outcome is related to functional class (NYHA classification), the nature of the disease, and previous cardiac surgery. Any patient in functional class III or IV during pregnancy is at high risk whatever the underlying condition as this means there is no remaining cardiovascular reserve [5]. The high-risk conditions are fragile aortas as in Marfan syndrome, left sided obstructions, and already dilated poorly functioning left ventricles [9].

Pregnancy is often fatal for a PAH patient. In a retrospective review study from 1978 to 1996, mortality was 30% in IPAH, 36% in Eisenmenger's syndrome, and 56% in PH secondary to other conditions [1]. A systemic review of all published reports from 1997 to 2007 of pregnancies in women with PAH found that overall maternal mortality was lower than previous reports, thought may be attributable to use of targeted PAH therapies and improved understanding of the disease. Mortality was 17% in IPAH, 28% in PAH associated with congenital heart disease, and 33% in PAH of other etiologies [21]. A recent prospective, multinational registry that included 26 pregnancies reported

Table 1: Venice clinical classification of pulmonary hypertension (2003).

(1) Pulmonary arterial hypertension (PAH)
- (1.1) Idiopathic (IPAH)
- (1.2) Familial (FPAH)
- (1.3) Associated with (APAH)
  - (1.3.1) Collagen vascular disease
  - (1.3.2) Congenital systemic-to-pulmonary shunts
  - (1.3.3) Portal hypertension
  - (1.3.4) HIV infection
  - (1.3.5) Drugs and toxins
  - (1.3.6) Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
- (1.4) Associated with venous or capillary involvement
  - (1.4.1) Pulmonary venoocclusive disease (PVOD)
  - (1.4.2) Pulmonary capillary hemangiomatosis (PCH)
- (1.5) Persistent pulmonary hypertension of the newborn

(2) Pulmonary hypertension with left-heart disease
- (2.1) Left-sided atrial or ventricular heart disease
- (2.2) Left-sided valvular heart disease

(3) Pulmonary hypertension associated with lung diseases and/or hypoxemia
- (3.1) Chronic obstructive pulmonary disease
- (3.2) Interstitial lung disease
- (3.3) Sleep-disordered breathing
- (3.4) Alveolar hypoventilation disorders
- (3.5) Chronic exposure to high altitude
- (3.6) Developmental abnormalities

(4) Pulmonary hypertension owing to chronic thrombotic and/or embolic disease
- (4.1) Thromboembolic obstruction of proximal pulmonary arteries
- (4.2) Thromboembolic obstruction of distal pulmonary arteries
- (4.3) Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)

(5) Miscellaneous

Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Table 2: Anatomic-pathophysiologic classification of congenital systemic-to-pulmonary shunts associated with pulmonary arterial hypertension.

(1) Type
(1.1) Simple pretricuspid shunts
(1.2) Simple posttricuspid shunts
(1.3) Combined shunts
(1.4) Complex congenital heart disease
(2) Dimension (specify for each defect if >1 congenital heart defect)
(2.1) Hemodynamic (specify Qp/Qs)*: restrictive or nonrestrictive
(2.2) Anatomic defect size: small, moderate or large
(3) Direction of shunt
(3.1) Predominantly systemic-to-pulmonary
(3.2) Predominantly pulmonary-to-systemic
(3.3) Bidirectional
(4) Associated cardiac and extracardiac abnormalities
(5) Repair status
(5.1) Unoperated
(5.2) Palliated
(5.3) Repaired

Table 3: Clinical classification of congenital systemic-to-pulmonary shunts associated with PAH.

A. Eisenmenger syndrome
Includes all systemic-to-pulmonary shunts resulting from large defects that lead to severely increased PVR and a reversed or bidirectional shunt: multiple-organ involvement are present
B. PAH associated with systemic-to-pulmonary shunts
Includes moderate to large defects: PVR is mildly to moderately increased, systemic-to-pulmonary shunt is still prevalent, no cyanosis at rest
C. PAH with small defects
Small defects (usually VSD <1 cm and ASD <2 cm): clinical picture is similar to idiopathic PAH
D. PAH after corrective cardiac surgery
Congenital heart disease has been corrected, but PAH is still present without significant postoperative residual lesions

PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; VSD: ventricular septal defect; ASD: atrial septal defect.

improved mortality in well-controlled and particularly long-term responders to calcium channel blockers [22]. Venous thromboembolism affects pregnant women 5 times more frequently than nonpregnant women of similar age [10]. Pulmonary embolism has surpassed infection, hemorrhage, and preeclampsia/eclampsia to become a leading cause of manternal mortality in the United States [10]. Amniotic fluid embolism (AFE) is a rare but catastrophic complication unique to pregnancy. Despite variation in reported incidence and mortality, AFE remains a life-threatening condition with significant morbidity and mortality for the pregnant women [15, 23–25]. It is the 5th most common cause of maternal mortality in the world [15].

5. Diagnosis and Evaluation

5.1. History and Physical Examination. Symptoms of pulmonary hypertension include chest pain, cough, and shortness of breath. With right heart failure patients may also have lower extremity swelling, dizziness, or syncope. Many of these symptoms overlap with that of normal pregnancy. Physical examination of patients with pulmonary hypertension and right ventricular failure reveals a prominent pulmonic component of the second heart sound and an elevated jugular venous pulse. Other findings may include a palpable right ventricular heave and systolic murmur of tricuspid regurgitation along the left lower sternal border. Accentuation of this murmur during inspiration (Carvallo's sign) distinguishes it from the murmurs of mitral regurgitation and aortic stenosis [11]. The lung examination may suggest underlying lung disease. Patients with isolated right ventricular failure do not have pulmonary edema, which if found, suggests left ventricular dysfunction, pulmonary venous hypertension, or ARDS.

5.2. Blood Tests. Biomarkers, such as, brain natriuretic peptide (BNP) are useful in monitoring chronic PAH [26]. In pulmonary embolism, BNP can stratify patients regarding risk for development of right ventricular failure [27] and troponin I leak may predict mortality [28]. Measurement of renal, liver, and neurological function will provide some information about the adequacy of cardiac function and tissue perfusion.

5.3. Chest X-Ray. Plain chest radiography (CXR) is of limited utility in diagnosing pulmonary hypertension in the ICU. Typical findings of right ventricular hypertrophy, right atrial enlargement, and obscuring of the aortopulmonary window by enlarged pulmonary arteries are less obvious on portable radiographs. Nonetheless, diffuse severe pulmonary parenchymal abnormalities may suggest an underlying cause of pulmonary hypertension. In pregnant women with suspected pulmonary embolism, CXR is recommended as the first radiation-associated imaging work-up; lung scintigraphy as the preferred test in the setting of a normal CXR, followed by computed-tomographic pulmonary angiography (CTPA) if the ventilation-perfusion result is nondiagnostic [29].

5.4. Right Heart Catheterization. Right heart or pulmonary artery (PA) catheterization is the gold standard for the diagnosis of pulmonary hypertension. Its use has fallen out of favor in the critically ill patients in general due to lack of studies with positive outcomes. However, there have been no studies targeting specifically the "pulmonary vascular" subpopulation. Most authors recommend the placement of PA catheters for patients admitted to the ICU with severe PH and RV failure, allowing for continuous measurement of RA and pulmonary pressures, cardiac output and mixed venous oxygen saturation [11, 14, 16, 30]. Certain technical

and interpretive limitations should be recognized. Severe tricuspid regurgitation and elevated PAP can make catheter placement challenging. Determination of cardiac output by thermodilution may be erroneously low because of tricuspid regurgitation. The Fick's method may be more accurate but requires determination of oxygen consumption, which is challenging in critically ill patients. PVR is a composite index of pulmonary pressure and cardiac output. However, PVR may not accurately reflect right ventricular afterload. Ultimately the response to a treatment strategy should be guided by the adequacy of tissue oxygen, which is partly reflected by central venous oxygen saturations.

5.5. Ultrasound. Compression ultrasound (CUS) is a noninvasive test with sensitivity of 97% and a specificity of 94% for the diagnosis of symptomatic, proximal deep venous thrombosis (DVT) in the general population [10]. CUS does not involve any radiation exposure and is recommended for evaluation of venous thromboembolism in pregnant women with signs and symptoms of DVT, with or without suspected PE [29]. Goal-directed bedside ultrasound has gained recognition in critical care. It can also be applied to the evaluation of patients with pulmonary hypertension. Echocardiography provides direct and noninvasive visualization of the right ventricle allowing intermittent repetitive followup of the dynamics of therapeutic responses. A recent statement of the American College of Chest Physicians (ACCPs) and the French Society of Intensive Care Medicine (SRLF) reported that a simple evaluation of the right ventricle can be done by nonexpert physicians or a more sophisticated evaluation by experts [31]. Right ventricular systolic pressure can be estimated from the tricuspid regurgitation velocity, assuming no significant right ventricular outflow tract obstruction [32]. The most usual echocardiographic sign of RV dilatation is the loss of its typical triangular shape. Right ventricular size can also be assessed by calculating the RV/LV end-diastolic area ratio in the four-chamber view. A normal ratio is below 0.6. When the RV is larger than the LV, the RV is defined as severely dilated. Another specific sign of RV failure is the paradoxical septal motion in systole with shifting to the left ventricle (D shaped septum), reflecting RV overload [16]. Lung ultrasonography may be integrated into bedside evaluation as an adjunct to the standard chest radiograph and CT scan. Normally aerated lung shows an A-line pattern, which is a reverberation artifact. The presence of A-line pattern indicates that the pulmonary artery occlusion pressure is <18 mm Hg and rules out cardiogenic pulmonary edema. B lines indicate an abnormality in the interstitial or alveolar compartment. These are comet-tail artifacts project from the pleural line, move with respiration, and extend to the bottom of the ultrasound screen. Diffuse B-line pattern may result from cardiogenic pulmonary edema and is associated with a smooth pleural line. B lines resulting from noncardiogenic lung injury, such as, ARDS, or interstitial lung disease, are associated with an irregular pleural surface and a nonhomogeneous B-line distribution with small subpleural areas of lung consolidation [33]. Lung ultrasonography may help differentiate the causes of pulmonary hypertension in critical care and minimizes radiation exposure in pregnant patients.

6. General Management in the Intensive Care Unit

Improved survival in pregnancy and pulmonary hypertension in recent years is attributable in addition to the new treatment modalities, incorporation of a multidisciplinary approach is equally important [2, 20, 21, 34]. Pulmonary hypertension in pregnancy and critical care is a complex clinical entity that requires collaborative efforts between obstetricians, anesthesiologists, cardiologists, pulmonologists, and intensivists. There is no standardized approach to the management of PH in pregnancy, successful outcomes are heavily dependent on a methodical approach individualized to each patient developed by a multidisciplinary team in a dedicated intensive care unit.

6.1. Fluid Management. Fluid management of these patients is often difficult, as both hypovolemia and hypervolemia can have detrimental effects. Unmonitored fluid challenges may further impair RV function and are not recommended. RV volume overload may be identified by a rising V wave on the central venous pressure (CVP) trace or by increased tricuspid regurgitation seen on echocardiography. In the situation with predominantly diastolic RV dysfunction, management involves fluid removal by diuresis or hemofiltration.

6.2. Inotropic Augmentation of RV Myocardial Function. Systolic RV failure with low cardiac output and hypotension may require inotropic agents. For sympathomimetic agents, desirable cardiac β_1 effects may be offset by chronotropic effects precipitating tachyarrhythmias, as well as worsening pulmonary vasoconstriction at higher doses through-agonism. Dobutamine has favorable pulmonary vascular effects at lower doses, although it leads to increased PVR, tachycardia, and systemic hypotension at doses exceeding 10 mcg/kg/min. Dopamine may increase tachyarrhythmias and is not recommended in the setting of cardiogenic shock. Alternatively, agents that do not have chronotropic properties, such as, phosphodiesterase (PDE)-3 inhibitors, may be preferable. PDE-3 usually deactivates intracellular cyclic adenosine monophosphate (cAMP), and PDE-3 inhibitors therefore increase cAMP and augment myocardial contractility while dilating the vasculature. Milrinone is frequently used, and nebulized milrinone, through pulmonary selectivity, has less systemic hypotension and V/Q mismatch compared with intravenous use [16]. Levosimendan, a calcium-sensitizing agent with positive inotropic and vasodilatory effects, holds promise for patients with PH and RV failure, but it has not yet been thoroughly investigated in these patients [17].

6.3. Vasopressors. An essential goal of using vasopressor is to maintain systemic blood pressure above pulmonary arterial pressures, thereby preserving right coronary blood flow and preventing shunt. Vasopressors will, however, inevitably

have direct effects on the pulmonary circulation as well as myocardial effects. Norepinephrine improves RV function both by improving SVR and CO although may increase PVR at higher doses. Phenylephrine is a direct alpha agonist, it improves right coronary perfusion in RV failure without causing tachycardia, although this benefit may be offset by worsening RV function due to increased PVR. Arginine vasopressin (AVP) causes systemic vasoconstriction via the vasopressinergic (V1) receptor. At low dose it has demonstrated vasodilating properties that manifest clinically as a reduction in PVR and PVR/SVR ratio. Low-dose AVP may be useful in difficult cases with vasodilatory shock and pulmonary hypertension, but further investigation is required [11].

The pregnant uterus has both α and β adrenergic receptors. The α receptor activation causes an increase in uterine muscle tone, whereas β receptor stimulation causes a decrease in uterine muscle activity. The vasculature of the uterus has only α receptors, so while β stimulating agents do not affect uterine blood flow, α receptor activators can cause uterine vasoconstriction with a decrease in blood flow [35].

6.4. Pulmonary Vasodilators. One of the important interventions to reverse RV failure is to reduce RV afterload through the use of pulmonary vasodilators. PAH-targeted therapies have revolutionized the care of patients with PAH. Agents are classically subdivided according to their action on the cyclic GMP, prostacyclin, or endothelin pathways. Endothelin receptor antagonists are pregnancy category X drugs and are contraindicated in pregnancy. These agents have been associated with profound craniofacial, cardiovascular, and visceral malformations in the rat model [2]. Calcium channel blockers are recommended for "responders" to vasodilator testing [36]. Their prolonged half life and negative inotropic effects, however, limit their use in treatment of acute pulmonary hypertension [30]. In addition, nifedipine, amlodipine, and diltiazem are all pregnancy category C drugs.

6.5. Prostaglandins. There have been only case reports describing successful use of targeted pulmonary vasodilator therapy. In pregnant patients presenting with PH and RV failure, intravenous epoprostenol is the initial treatment of choice [2, 7, 37–39], although care must be taken to avoid systemic hypotension. Both epoprostenol and treprostinil are classified as pregnancy category B. Most of the published case reports describe initiating intravenous epoprostenol several weeks before or near the time of delivery in parturients with PH [2, 7, 37, 38]. However, IV epoprostenol may inhibit platelet aggregation, so bleeding should be monitored particularly during delivery and postpartum period [40]. Nebulized Iloprost (category C) has also been used with positive outcomes although with more limited evidence [34, 39, 40].

6.6. PDE-5 Inhibitors. Sildenafil causes vasodilation of the pulmonary vascular bed and in the systemic circulation. It also has a positive inotropic effect on the hypertrophic right ventricle. It is a category B medication. Using sildenafil to treat PH in pregnancy has been described in case reports and appears to be safe, but experience is still limited [7, 39, 40].

6.7. Inhaled NO. Inhaled nitric oxide is a direct pulmonary vasodilator. It has been shown to have a beneficial effect on outcome of postoperative critically ill patients with severe pulmonary hypertension and/or right ventricular failure [17]. However, prolonged administration is associated with several adverse effects, such as, rebound pulmonary hypertension after withdrawal, production of NO_2, and development of methemoglobinemia [14].

6.8. Preventing Thromboembolic Events. The practice of thromboprophylaxis or anticoagulation in pregnant women with PH is not standardized. Most case reports of pregnant patients with PH place patients on thromboprophylaxis during pregnancy and continue through postpartum, with only brief interruption around time of delivery [2, 3, 21, 34]. Exceptions are for those who have idiopathic PAH and history of thromboembolic diseases where higher levels of anticoagulation may be required, and in patients with PAH associated with congenital heart disease, where caution should be exercised if prior history of bleeding exists [21, 34, 40].

6.9. Delivery and Anesthesia. Mode of delivery and anesthetic management remain debated. Vaginal delivery may be preferred over cesarean section to minimize postsurgical fluid shifts [2] or increased anesthetic risks [5]. Cesarean section, on the other hand, provides for a more controlled setting, avoids a prolonged second stage of labor [5], the potential for uncontrolled vaginal hemorrhage, and the adverse hemodynamic effects of bearing down [3]. If vaginal delivery is used, it should be performed in the ICU or the operating room [7]. Delivery in the lateral position avoids fetal compression of the inferior vena cava. The goals of anesthetic management are to avoid pain, hypoxemia, hypercapnia, and acidosis; all of which lead to increased PVR and thus hypertension [20]. Spinal and general anesthesia causes peripheral vasodilatation and may worsen the patient's hemodynamic. Regional anesthesia may be advantageous, however, when used in large dosages, may produce a decrease in venous return because of a sympathetic block [3, 7]. Investigators have reported using combined spinal-epidural anesthesia to provide a better sensory block than epidural anesthesia alone and no additional risk of hypotension with the use of very low-dose spinal anesthesia [3, 6, 7].

7. Management for Specific Diseases Causing Acute PH

(A) Pulmonary Embolism. The mainstay of therapy for acute venous thromboembolic disease during pregnancy is heparin [10], which does not cross the placenta, so does not carry risks of fetal hemorrhage or teratogenesis. Low molecular

weight heparin (LMWH) also does not cross the placenta and therefore may be safe during pregnancy. However, they may require monitoring of anti-Xa levels and frequent dose adjustments, negating their logistic benefits over unfractionated heparin. Coumadin derivatives cross the placenta and are associated with warfarin embryopathy and can cause fetal hemorrhage.

In massive pulmonary embolism (MPE), anticoagulation alone may be insufficient. Hemodynamic instability and right-heart strain may ensue. Subsequent treatment options, with variable level of evidence supporting their uses, include thrombolytics, embolectomy, and IVC filter. IVC filters have been successfully used during pregnancy, and the indications for their use are the same as for the nonpregnant population. These include recurrent embolism on adequate medical therapy, strong contraindications to full anticoagulation after a thromboembolism, and critically ill patients at high risk for recurrent embolism, in whom recurrent embolism is likely to be fatal [10]. IVC filters have been associated with a small but real risk of complications, especially over the long term. Risks include migration of the filter, perforation of the aorta, duodenum, or renal pelvis, and penetration of nearby structures including the vertebrae and the retroperitoneum [41]. For these reasons, retrievable filters can be an attractive alternative in this patient population, who are likely to be young and are at higher risk of long-term complications from indwelling filters.

The evidence on thrombolytic therapy in pregnant patients is limited to case reports [41, 42], and in fact, pregnancy is considered a relative contraindication for thrombolytic therapy. Systemic thrombolytic has high risk of major bleeding; however, some of the pregnancy-specific complications have not been reported, and it is not clear whether they are caused by the underlying disease or treatment. The risks and benefits of thrombolytics for MPE in pregnancy should be considered carefully on an individual basis. Data from the nonpregnant population indicate that thrombolytics can be considered for the treatment of patients who are hemodynamically unstable [43]. Recombinant tissue plasminogen activator and streptokinase do not cross the placenta, and their use is recommended if thrombolytic therapy is employed. Urokinase is a small molecule purified from human urine and crosses the placenta. It is not currently known whether urokinase induces a fetal coagulopathy [10]. Catheter-directed thrombolytic therapy carries the theoretical advantages of more rapid clot lysis and a lower risk of bleeding, because of a higher local concentration drug; however, there is no convincing evidence proving its superiority over systemic therapy [44]. On the other hand, disadvantages are radiation exposure associated with fluoroscopy. More experience is needed before catheter-directed therapy can be recommended for pregnant patients.

In a review on recent findings on management of PH, embolectomy and cardiopulmonary bypass was associated with a higher rate of fetal loss compared to thrombolytic therapy [14]. Although these data must be interpreted carefully, as they are limited to case studies and case reports, it suggests that embolectomy must be restricted to cases in which the life of the woman is endangered.

(B) Amniotic Fluid Embolism. The management of amniotic fluid embolism is supportive and focuses initially on rapid maternal cardiopulmonary stabilization [23]. The most important goal of therapy is to prevent additional hypoxia and subsequent end-organ failure. Supportive treatment modalities directed towards the maintenance of oxygenation, circulatory support with fluid resuscitation, vasopressors, and/or inotropes, and correction of the coagulopathy provide the basis for care. Several newer therapies for AFE have been described in case reports. Cardiopulmonary bypass, extracorporeal membrane oxygenation, and intra-aortic balloon counterpulsation have been used successfully [45] Right ventricular assist device (RVAD) has been described in successful management of AFE with severe pulmonary hypertension and RV failure [24]. Fetal delivery, if not yet occurred at time of diagnosis, should be performed immediately to prevent further hypoxic damage to the fetus and to facilitate cardiopulmonary resuscitative efforts [23].

8. Conclusion

In conclusion, PH in pregnancy carries a high mortality. The management of these patients in the ICU is challenging with unique pregnancy-related physiologic changes and concern for fetal safety. During the past decade, new advanced therapies for pulmonary hypertension and cardiopulmonary support devices have emerged. Their application in pregnant women is based on limited evidence and data extrapolated from the nonpregnant population. Improved maternal and fetal survival in recent years is attributable to improved understanding of pulmonary hypertension, advanced therapies, and adoption of a multidisciplinary treatment approach.

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Review Article

Exercise Intolerance in Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is associated with symptoms of dyspnea and fatigue, which contribute to exercise limitation. The origins and significance of dyspnea and fatigue in PAH are not completely understood. This has created uncertainly among healthcare professionals regarding acceptable levels of these symptoms, on exertion, for patients with PAH. Dysfunction of the right ventricle (RV) contributes to functional limitation and mortality in PAH; however, the role of the RV in eliciting dyspnea and fatigue has not been thoroughly examined. This paper explores the contribution of the RV and systemic and peripheral abnormalities to exercise limitation and symptoms in PAH. Further, it explores the relationship between exercise abnormalities and symptoms, the utility of the cardiopulmonary exercise test in identifying RV dysfunction, and offers suggestions for further research.

1. Introduction

Pulmonary arterial hypertension is a condition defined by primary abnormalities in the precapillary pulmonary arteries and arterioles. It forms group 1 of the World Health Organization classification of pulmonary hypertension (PH) [1]. This classification system identifies PAH as a specific entity, with a characteristic pathophysiology, clinical presentation, and response to therapy that helps separate it from other forms of pulmonary hypertension.

The most commonly reported symptoms on presentation in individuals with PAH are dyspnea and fatigue. These symptoms limit physical function, and, by the time of diagnosis, most individuals have marked functional limitation and are in the New York Heart Association (NYHA) Functional class III or IV [2]. The New York Heart Association reflects disease severity and prognosis, and disease progression is associated with worsening symptoms and functional capacity [1]. Recent development of pharmaceutical therapies, which address the specific pulmonary vascular abnormalities associated with PAH, has resulted in improved hemodynamics, exercise capacity [3, 4], and prognosis [3] for individuals with PAH. However, despite therapy, many individuals continue to have exertional symptoms, functional limitation and impaired quality of life (QoL) [5].

Exercise training has well-established safety and efficacy for improving exercise capacity and QoL in chronic obstructive pulmonary disease (COPD) [6] and left heart failure (LHF) [7]. Although, historically, physical activity and exercise training were discouraged for individuals with PAH,

interest has recently developed in the role of exercise training for individuals with PAH who have persistent functional impairments, despite pharmaceutical therapy. Evidence from several small studies suggests that well-designed exercise training programs improve exercise capacity and QoL, without major adverse events or clinical deterioration, in individuals who are stable on PAH-specific pharmaceutical therapy [8–12]. These studies reporting exercise training have utilized moderate-intensity exercise.

In a study using a monocrotaline rat model of PAH, which investigated moderate intensity aerobic training [13], RV myocardial capillary density increased and exercise capacity improved following exercise training in rats with stable PAH. However, in rats in which progressive PAH had been induced with a higher dose of monocrotaline, signs of RV inflammation and poorer survival occurred following exercise training, in comparison with sedentary rats and rats with stable PAH which had undergone exercise training [13].

The paucity of literature reporting exercise training in PAH has resulted in uncertainty among healthcare professionals regarding appropriate levels of physical exertion for individuals with PAH, and which patients are suitable for exercise rehabilitation [14]. Furthermore, there is little in the literature regarding the causes and significance of dyspnea and fatigue associated with PAH. Consequently, healthcare professionals demonstrate inconsistency with respect to recommendations for appropriate levels of dyspnea and fatigue during the performance of daily activities in this population [14]. In light of the current interest in exercise training in PAH, it is timely that consideration be given to the hemodynamic consequences and origins and significance of the symptoms associated with physical exertion in PAH. This paper discusses the literature around exercise physiology in PAH, the likely impact of RV dysfunction and systemic and peripheral abnormalities on dyspnea, fatigue, and exercise limitation.

2. Central Hemodynamics in PAH

A fundamental endothelial abnormality is thought to play a key role in the pathogenesis and functional abnormalities associated with PAH. Imbalance in the production of pulmonary vasodilators and vasoconstrictors, abnormal proliferation of cells in the walls of the small pulmonary arteries and arterioles, and intra-luminal thrombus result in a marked reduction in the vasodilatory capacity, distensibility, and patency of the pulmonary circulation [15, 16]. The clinical outcome is a rise in pulmonary vascular resistance (PVR), pulmonary artery pressure (PAP), and RV afterload [17].

In a normal heart, the RV response to a sustained increase in afterload is adaptive myocardial hypertrophy. In PAH, with progressive vascular changes leading to an unrelenting increase in PVR, there is a transition from RV wall hypertrophy to RV dilatation [18]. The capacity for hypertrophic adaptation varies among individuals [19], and it has been proposed that the development of right heart failure in PAH is not only related to elevated RV afterload but also to intrinsic abnormalities of the RV wall [20] and may be related to myocardial inflammation [13]. Altered gene expression is thought to contribute to the development of RV dysfunction in some individuals [21]. In scleroderma, RV function can be further compromised by intrinsic abnormalities of the myocardium, which may be secondary to chronic inflammation [22]. However, the predominant cause of RV failure in PAH is believed to be RV ischemia due to imbalance between oxygen supply and demand associated with hypertrophy, increased RV workload and increased metabolic demand [23], without a concomitant increase in capillarization [13, 18, 20, 24] and blood supply [25].

Initially, dilatation of the right atrium and RV in PAH results in a compensatory increase in preload and maintenance of stroke volume (SV), but as contractile dysfunction worsens, diastolic dysfunction develops, filling pressures rise, and RV output falls [26]. The resultant decrease in left ventricular (LV) preload [27] and pressure-related movement of the interventricular septum to the left and LV compression [28], lead to a fall in LV output and systemic oxygen delivery [29, 30].

3. Exercise Abnormalities

Impairment in the distensibility and vasodilatory capacity and reduction in the size of the pulmonary vascular bed mean that an increase in pulmonary blood flow with exercise can only be achieved with a marked rise in PAP [31] and RV afterload [17]. Reduced RV contractility results in a reduced capacity for SV to augment cardiac output (CO) during exercise [30]. In addition to reduced SV, PAH is associated with chronotropic impairment [32], demonstrated by a failure to achieve a normal maximum heart rate at peak exercise [32–35]. Chronotropic impairment in PAH is related to downregulation of RV myocardial beta-adrenoreceptor activity [36] and reflects disease severity [32, 37]. The combined failure of SV and heart rate to increase normally during exercise results in an attenuated rise in CO and systemic blood pressure [38]. Prognosis in PAH is known to be closely associated with RV function [26] and the systemic blood pressure response during exercise [38]. Ultimately the RV fails to function adequately at rest, and, in the majority of cases, death occurs from RV failure [21].

4. The Influence of Right Ventricular Function on Exercise Capacity and Symptoms

There is increasing awareness that the primary cause of symptoms [39], functional impairment and mortality in PAH is RV dysfunction [23]. Along with being strongly associated with survival [40, 41], right atrial pressure has been identified as the hemodynamic measure that has the strongest (negative) correlation with exercise capacity in individuals with PAH [42]. Furthermore, indicators of RV function, SV and chronotropic response, are strong and independent factors in determining the six-minute walk distance (6MWD) [32]. Improvements in 6MWD are positively related to changes in SV, and chronotropic response [32] and cardiac index [17]

and negatively related to changes in PVR and the Borg scale rating of dyspnea following PAH-specific therapy [32]. Treatments that improve hemodynamics by unloading the RV, and/or improving RV contractility, have also been shown to improve NYHA functional class [17].

Further insights into the role of the RV in the generation of symptoms and reduction in exercise capacity can be gained from studies in patients with left heart failure (LHF). Pulmonary hypertension, due to elevated pulmonary venous pressure, is commonly associated with LHF [43, 44]. While there is a poor correlation between exercise capacity and left ventricular function in LHF [45], RV function influences both exercise capacity and prognosis in this condition [46]. Resting PAP and PVR correlate inversely, and right ventricular ejection fraction correlates positively with peak oxygen consumption (VO_2) [47, 48]. A high prevalence of PH has also been reported in chronic obstructive pulmonary disease (COPD) [49, 50] and pulmonary fibrosis [51, 52]. In these conditions, and in LHF, exercise capacity is lower and levels of dyspnea and fatigue are greater in individuals with pulmonary hypertension than those without [50, 52–55].

Recently, a study of individuals with normal hemodynamics at rest, but a persistent reduction in exercise capacity following successful pulmonary endarterectomy for chronic thromboembolic disease, was undertaken to investigate the cause of persistent exertional dyspnea and functional limitation [56]. This study identified elevated PVR and reduced pulmonary arterial compliance during exercise, and reduced exercise capacity in these individuals, in comparison with a control group. The combination of PVR and pulmonary arterial compliance reflects the hydraulic load imposed by the pulmonary circulation on the RV, and the findings of this study support the suggestion that elevated RV afterload negatively impacts on exercise capacity and contributes to exertional dyspnea [56].

The RV most likely contributes to the sensation of dyspnea via mechanoreceptors situated in the right atrium and RV. These receptors relay details of right atrial and RV pressure and volume and the amount of work performed by the RV [57, 58], via afferent sympathetic pathways, to the central nervous system. In PAH an increase in sympathetic activity [59] appears directly related to the degree of elevation of right atrial [60] or RV systolic pressure [61]. In animal models, sympathetic pathways have been implicated in mediating the association between RV work load and ventilatory response [62], with increased RV pressure, and stimulation of mechanoreceptors in the right atrium, directly resulting in increased ventilation [62, 63].

5. Other Abnormalities That Contribute to Reduced Exercise Capacity and Symptoms in PAH

5.1. Gas Exchange and Hypoxemia. Reduced diffusing capacity for carbon monoxide (DLCO) is a common finding in PAH [41, 64–67]. Reduced DLCO appears to be related primarily to impaired pulmonary membrane diffusing capacity and, to a lesser extent, reduced pulmonary capillary blood volume [66, 67]. Reduced DLCO has been shown to correlate with reduced exercise capacity and a higher functional class in PAH [68], likely reflecting disease severity. However, reduced DLCO also indicates a limited capacity for pulmonary gas exchange. In individuals with moderate to severe PAH, without a patent foramen ovale, a progressive fall in oxygen saturation occurs during exercise [35, 38]. It has been proposed that this results from reduced venous oxygen saturation secondary to reduced CO and tissue oxygen delivery [69]. At rest, mixed venous oxygen saturation has been shown to correlate with arterial oxygen tension (PaO_2) [70, 71]. However, reduced oxygen uptake in the lung secondary to rapid red cell transit time, diffusion impairment [66], and ventilation/perfusion mismatch [70, 72] also contributes to hypoxemia.

Hypoxemia stimulates ventilation through central chemoreceptors in the medulla and peripheral chemoreceptors in the carotid and aortic bodies. However, central chemoreceptors are generally only stimulated when PaO_2 is close to, or below, 50 mmHg [73]. There are conflicting data in the literature regarding a correlation between the ventilatory response (represented by the ventilatory equivalent for carbon dioxide [$\dot{V}E/\dot{V}CO_2$]) during exercise and arterial oxygen tension (PaO_2), in individuals with PAH. Although early studies identified no correlation between $\dot{V}E/\dot{V}CO_2$ and PaO_2 [74, 75], a recent study identified a correlation at rest and at the anaerobic threshold [71]. Both elevated $\dot{V}E/\dot{V}CO_2$ and reduced PaO_2 reflect disease severity in PAH [38, 71], and a direct link between the ventilatory response and hypoxemia in this condition has not been established. In LHF, hyperventilation during exercise occurs in the absence of hypoxemia [76]. Except in the presence of a patent foramen ovale or severe disease, the levels of hypoxemia in PAH are insufficient to stimulate hypoxia sensitive central chemoreceptors, and it is, therefore, unlikely that hypoxemia makes a significant contribution to hyperventilation in the majority of individuals with PAH.

Hypoxemia may, however, contribute to a sensation of dyspnea by predisposing the respiratory muscles to fatigue. In healthy individuals undergoing prolonged exercise, fatigue-induced changes in the contractile properties of the respiratory muscles contribute to a sensation of dyspnea through imbalance in inspiratory muscle effort relative to capacity [77]. The dyspnea associated with central nervous system's perception of inspiratory motor output, relative to capacity, is also influenced by a reduction in respiratory muscle strength [78]. Respiratory muscle weakness has been demonstrated in PAH [79, 80], and there is evidence of atrophy of type I and type II muscle fibres in the diaphragm of humans with PAH [81]. In the presence of hypoxemia, along with elevated ventilation, respiratory muscle weakness, and reduced CO, the respiratory muscles are predisposed to fatigue, which may contribute to the sensation of dyspnea during exercise in PAH.

5.2. Chemoreceptor Activation. It is likely that reduced oxygen delivery contributes to increased ventilation and dyspnea in PAH via activation of skeletal muscle chemoreceptors.

Reduced muscle cell pH associated with anaerobic metabolism stimulates intra- and extra-cellular chemoreceptors within the muscle and, via the ergoreflex, results in increased ventilation [82, 83]. In LHF, in the longer term, reduced CO during exercise, and chronic muscle acidosis [84] result in increased ergoreflex sensitivity [85–87] and increased ventilation and dyspnea [45]. It has been proposed that peripheral chemoreceptor stimulation [59] and possibly increased ergoreflex sensitivity also contribute to increased ventilation and dyspnea in PAH, although there are no data to confirm this possibility, to date.

5.3. Systemic Endothelial Dysfunction. Tissue oxygen delivery and aerobic metabolism depend upon adequate systemic vascular function, along with CO and arterial oxygen content. Due to the influence of the systemic endothelium on vascular tone and blood flow, endothelial dysfunction is believed to negatively impact on oxygen delivery to the periphery in LHF [88–90]. Evidence of systemic endothelial dysfunction in PAH [91] suggests that reduced peripheral blood flow may also be a source of impaired oxygen delivery, muscle acidosis, and elevated ventilation, during exercise, in PAH.

5.4. Skeletal Muscle Myopathy. Recent studies have identified muscle fibre changes and skeletal muscle weakness in individuals with PAH [92, 93]. The muscle fibre changes include a lower portion of type I muscle fibres and an enzyme profile compatible with a relatively higher potential for anaerobic than aerobic energy metabolism [93]. The cause of skeletal muscle dysfunction in PAH is uncertain, although it is likely related to chronic muscle acidosis, increased sympathetic activity [59, 61], systemic inflammation [94, 95], and neurohormonal changes [18], similar to the causes of skeletal muscle dysfunction in LHF [96]. Similarities in muscle dysfunction in LHF, COPD, and PAH also suggest that skeletal muscle atrophy and alterations in muscle morphology in PAH may contribute to an elevated ventilatory drive, and dyspnea, as described in LHF and COPD [45, 97, 98]. The improvement in muscle morphology and exercise capacity following exercise training in PAH [10, 11] suggests that deconditioning also contributes to exercise limitation in PAH.

6. Ventilatory Response in PAH

Characteristic ventilatory abnormalities have been well defined in PAH. Hyperventilation at rest and on exercise, identified by an elevated $\dot{V}E/\dot{V}CO_2$ and reduced arterial carbon dioxide tension ($PaCO_2$), is a well-recognised feature of PAH [35, 38, 74, 75, 99]. The elevated $\dot{V}E/\dot{V}CO_2$ in PAH describes a dissociation between carbon dioxide production, $PaCO_2$, and minute ventilation. The altered relationship between $\dot{V}E/\dot{V}CO_2$, $PaCO_2$, and arterial pH described in PAH [74] suggests that elevated $\dot{V}E/\dot{V}CO_2$ during submaximal exercise in PAH is not mediated by changes in arterial blood gases. Initial reports of an elevated $\dot{V}E/\dot{V}CO_2$ suggested that increased ventilation in PAH was due to ventilatory inefficiency caused by obstruction of the small pulmonary vessels and subsequent ventilation/perfusion inequalities [74, 75, 99]. However, this is unlikely to be the predominant mechanism, as ventilation/perfusion studies in PAH do not demonstrate marked ventilation/perfusion mismatch, at rest or on exercise [70, 100]. Furthermore, in PAH it is well established that $PaCO_2$ is reduced at rest and on exercise [40, 71]. If ventilatory inefficiency was the sole cause of an elevated $\dot{V}E/\dot{V}CO_2$, $PaCO_2$ would be normal. An increased ventilatory drive, rather than ventilatory inefficiency, is likely to be reflected in an elevated $\dot{V}E/\dot{V}CO_2$ in the presence of a reduced $PaCO_2$, as seen in PAH. This hypothesis warrants further investigation.

There is evidence that the elevated ventilatory response associated with PAH is related to central haemodynamic abnormalities. The $\dot{V}E/\dot{V}CO_2$ at rest has been shown to correlate with PVR, and both $\dot{V}E/\dot{V}CO_2$ and PVR decrease in response to treatment with an intravenous prostacyclin analogue [101]. The $\dot{V}E/\dot{V}CO_2$ correlates with PAP [75]. Arterial carbon dioxide tension has been shown to correlate with cardiac index and changes in cardiac index associated with disease progression and increasing PVR are reflected by changes in both $\dot{V}E/\dot{V}CO_2$ and $PaCO_2$ [71]. The $\dot{V}E/\dot{V}CO_2$ reflects disease severity and has been shown to correlate with NYHA functional class [35]. Furthermore, the $\dot{V}E/\dot{V}CO_2$ [38], and $PaCO_2$ are both prognostic markers in PAH [71].

In LHF, RV workload, indirectly determined by measurement of RV oxidative metabolism [102, 103] and PVR [53, 104], correlates with $\dot{V}E/\dot{V}CO_2$. Furthermore, in this condition, a significant negative relationship exists between RV ejection fraction and $\dot{V}E/\dot{V}CO_2$ [104]. Changes in exercise PVR following treatment with the phosphodiesterase inhibitor, sildenafil, also correlate significantly with changes in $\dot{V}E/\dot{V}CO_2$ [105] although there is no correlation between left ventricular function at peak exercise and $\dot{V}E/\dot{V}CO_2$ [104]. Furthermore, the increase in $\dot{V}E/\dot{V}CO_2$ reflects the degree in elevation of PAP [106] supporting a relationship between RV work, ventilatory response, and symptoms in this condition.

A distinct pattern of change in end-tidal carbon dioxide tension ($PetCO_2$) during exercise is evident in individuals with PAH. In severe PAH, $PetCO_2$ is low at rest and falls progressively throughout an incremental exercise test [31, 107, 108], most likely reflecting a low and falling $PaCO_2$ at rest and on exercise, respectively. During recovery $PetCO_2$ rises, reflecting slowed gas exchange kinetics and delayed recovery [31]. In moderate PAH the rise in $PetCO_2$ from rest to the anaerobic threshold (AT) is minimal, or absent, and in mild PAH the rise in $PetCO_2$ from rest to the AT is attenuated [108]. This particular pattern of $PetCO_2$ response distinguishes PAH from other conditions [107].

7. Evidence of RV Dysfunction on a Cardiopulmonary Exercise Test (CPET) in Individuals with PAH

In PAH, the incremental CPET consistently identifies reduced peak oxygen consumption and reduced VO_2 at the AT [31, 35, 38, 99, 109], reduced oxygen (O_2) pulse

[35, 38, 110], and slowed VO_2 kinetics [31]. The relationship between CO and oxygen consumption is very strong in healthy individuals, such that VO_2 is considered a surrogate of CO and VO_2/HR, or O_2 pulse has been used as a surrogate of SV [111]. Reduced VO_2 at peak exercise and AT, reduced O_2 pulse, and slowed VO_2 kinetics during and following exercise reflect RV dysfunction, reduced CO, and an oxygen deficit during exercise [31, 111]. Oxygen desaturation reflects reduced mixed venous oxygen saturation (along with reduced O_2 uptake in the lungs), further reflecting reduced CO and inadequate O_2 delivery [69]. The well-described elevation in $\dot{V}E/\dot{V}CO_2$ [17, 31, 35, 75, 99, 101, 108, 109] and the relationship between $\dot{V}E/\dot{V}CO_2$ and cardiac function described in PAH suggest that high values of $\dot{V}E/\dot{V}CO_2$ reflect high levels of RV pressure and workload [75, 101]. Low and falling $PetCO_2$ at rest and during exercise reflect low levels of $PaCO_2$ [71] associated with a ventilatory drive that is disconnected from carbon dioxide production. Low $PetCO_2$ is also suggestive of hyperventilation related to elevated RV pressure and workload.

8. Exercise Abnormalities and the Functional Consequences of Exercise-Induced PAH

Invasive evaluation of central hemodynamics during exercise identifies individuals who do not meet the diagnostic criteria for PAH but who have an elevated pulmonary artery pressure and reduced CO at peak exercise (exercise-induced PAH (EIPAH)) [112, 113]. These individuals demonstrate abnormalities during exercise which are characteristic of the changes seen in PAH, albeit of a milder severity [114]. In comparison to a healthy control group, individuals with EIPAH have reduced peak VO_2, reduced VO_2 at AT [112, 113], reduced O_2 pulse (Fowler et al., unpublished data), and a tendency towards arterial desaturation [113]. Individuals with EIPAH also demonstrate elevated $\dot{V}E/\dot{V}CO_2$, reduced $PetCO_2$ at the AT, and an attenuated rise in $PetCO_2$ from rest to the AT [113]. A higher proportion of these individuals terminate exercise because of dyspnea, compared with matched healthy controls (41% versus 5%, resp.) [113]. Furthermore, individuals with EIPAH are in NYHA functional class II or III and have reduced 6MWD [115] and QoL [113] and lower limb muscle strength compared with healthy individuals [116]. While it is uncertain whether EIPAH is a progressive pulmonary vasculopathy similar to PAH, it is apparent that exercise abnormalities identified during formal exercise testing reflect a similar mechanism of exercise limitation, signs consistent with impaired RV function during exercise, and possibly early systemic sequelae of a pulmonary vasculopathy (including muscle dysfunction), as described in PAH.

9. The Relationship between Ventilation and Dyspnoea

The relationship between ventilation and dyspnea is well established, from studies of healthy individuals during exercise and in individuals with disease. Afferent neural input relays details of ventilation from respiratory muscle spindles to the respiratory centre in the medulla [117]. Ventilation during rest and light exercise occurs with little or no awareness of breathing [118]. However, an increase in motor command to ventilatory muscles is perceived as a sensation of respiratory work/effort, or dyspnea [78], and the increase in ventilation required to perform moderate or intense exercise is accompanied by an increasing awareness of breathing to a point where breathlessness is described, even in healthy subjects [118]. An individual with PAH has a greater ventilatory demand and minute ventilation throughout submaximal exercise and registers an awareness of breathing during lower levels of exercise than a healthy individual [35]. This describes an association between elevated ventilation and dyspnea in PAH.

10. Factors That Contribute to Fatigue in PAH

A sensation of fatigue is commonly reported in LHF, COPD, and PAH and is described as the limiting factor during exercise testing in up to half of individuals with these conditions [35, 119]. In LHF, muscle fatigue and early termination of exercise have been shown to be directly associated with reduced CO and leg blood flow and increased arterial lactate concentrations [120]. Through these mechanisms, reduced CO is considered to influence the sensation of general fatigue in individuals with LHF. It has been proposed that slowed VO_2 kinetics and oxygen deficit in individuals with PAH are associated with similar depletion of high-energy compounds in the muscle as in LHF [31].

A change in muscle fibre proportion, with a reduction in type I and an increase in type II muscle fibres [93], results in reduced aerobic capacity, early anaerobic metabolism, and an increased propensity for fatigue in the muscles in PAH. Similar changes in muscle morphology and function in LHF and COPD are believed to be important factors contributing to the sensation of fatigue during exercise and reduced exercise capacity, in these conditions [121]. The skeletal muscle abnormalities identified in PAH [93] are also likely to contribute to the sensation of fatigue associated with this condition.

11. Summary and Conclusions

An acute increase in PAP and RV workload, in association with reduced oxygen delivery during exercise, and the longer term systemic and peripheral sequelae of PAH contribute to increased ventilation during exercise in individuals with PAH. The sensation of dyspnea reflects elevated ventilation during exercise and represents a limited capacity for increasing CO to meet the elevated metabolic demands of physical activity. While longer-term sequelae of reduced CO and tissue oxygenation contribute to fatigue in PAH, in the short term, fatigue signifies inadequate tissue oxygen delivery related to an attenuated rise in CO during exercise.

The symptoms of dyspnea and fatigue associated with PAH reflect both acute and chronic RV dysfunction, influence functional class, and, indirectly, predict survival. The level of these symptoms on exertion is used by clinicians

to grade disease severity and prognosis in individuals with PAH. Clinicians are encouraged to also use these symptoms to guide and monitor the response to physical activities and exercise training in individuals with PAH. Severe dyspnea and fatigue are likely to reflect high levels of RV work, which exceed RV capacity, and which potentially contribute to RV ischemia, inflammation and progressive RV failure in individuals in whom there is active disease progression.

A CPET identifies findings consistent with RV dysfunction during exercise in individuals with PAH. A CPET also identifies a pulmonary vasculopathy and impaired RV function during exercise in symptomatic individuals who do not meet the diagnostic criteria for PAH. The CPET is encouraged as a tool to identify the functional consequences of PAH, to stratify symptomatic individuals for invasive evaluation, and for longitudinal followup in individuals who do not have PAH on initial assessment but who are at increased risk for developing PAH.

The evidence from exercise training studies, to date, suggests that, at least in the short term, exercise training at moderate intensity is associated with improved exercise capacity, without adverse outcomes, in individuals who are stable on PAH-specific therapy. For individuals with PAH who intend to undertake an exercise training program, wherever possible, a prior CPET is encouraged. A CPET allows the opportunity to screen individuals for risks associated with exercise (e.g., an abnormal blood pressure or heart rate response) and allows accurate determination of exercise intensity. The exercise intensity employed during training should be prescribed according to the individuals' CPET results, including the maximum heart rate response (especially in light of chronotropic impairment in PAH) and symptomatic responses at submaximal and maximal exercise. Clinicians are strongly encouraged to utilize symptoms to monitor and guide exercise workload and physical activity levels. Increasing or severe fatigue and/or severe dyspnea during exercise suggest a high level of RV work, which may have a detrimental impact on RV function.

12. Future Research

While there are data which describe exercise limitation and provide insights into the likely origin and symptoms associated with PAH, further research is required to confirm and expand these findings. This research might include studies to clarify the role of central hemodynamics and the RV in the origin of symptoms and exercise limitation in this population. Invasive measures of RV function during exercise are feasible, can be performed without adverse events and offer insights into the hemodynamic responses associated with exercise. Evaluation of the role of the central ventilatory drive, chronic muscle acidosis, the ergoreflex, and muscle dysfunction (including the role of deconditioning) would also be of value.

Complementary studies exploring the mechanisms by which exercise training improves symptoms, exercise capacity, and QoL are also required. Further studies are needed to determine the optimal intensity for exercise training and the appropriate level of symptoms during physical activity for individuals with PAH. These studies should include randomised controlled trials directed at determining the longer-term outcomes of exercise training on central hemodynamics, RV function, disease progression, exercise capacity, and QoL. Trial endpoints might include measures of RV function (ideally using magnetic resonance imaging, invasive hemodynamics or echocardiography), the association between symptoms and RV function, biomarkers such as brain natriuretic peptide, QoL, longer-term changes in physical function and usual activity levels, peripheral endothelial function, muscle strength, endurance and morphology (according to the exercise modality studied), and the ventilatory response during submaximal and maximal exercise testing.

Previous work in animal models of PAH suggests that exercise training trials in animal models are feasible and useful. The findings suggest that studies of exercise training in animal models may allow exploration of histological consequences of training, and exploration of exercise intensities that are currently considered potentially unsafe in human studies. Further exploration of the utility of ventilatory response during exercise as a surrogate for RV function would also be of value in animal, and human, studies.

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Clinical Study

Persistent Pulmonary Hypertension of Non Cardiac Cause in a Neonatal Intensive Care Unit

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Parenchymal lung diseases are the main cause of persistent pulmonary hypertension of the newborn (PPHN). We aimed to assess the non cardiac conditions associated to PPHN in the newborn and the survival rate over the last 15 years, at our center. A retrospective chart review of the neonates admitted for PPHN from 1996 to 2010 was performed. New therapies were introduced in 2003, and the survival rates between two periods (1996–2002 and 2003–2010) were compared. Out of 6750 newborns, 78 (1.1%) had the diagnosis of PPHN of non cardiac cause. The most prevalent causes were associated to pulmonary hypoplasia (30.7%), infection (24.3%), and aspiration syndromes (15.3%). Many other causes were identified in 33.3%. The overall survival rate was 68%. There was a significant difference on survival rates between the two periods (1996–2002 = 63.8% and 2003–2010 = 71.4%, $P = 0.04$). Our study showed a myriad of non cardiac aetiologies for PPHN of the newborn, most of them related to lung disease or lung hypoplasia. We observed an improvement in survival rate since 2003, which was associated to the use of new therapies.

1. Introduction

From the first clinical classification of pulmonary hypertension (PH), in Evian (France) in 1973, the knowledge about the disease significantly improved and recently, in 2008, that classification was updated at Dana Point (USA) [1]. This classification tries to include all possible causes of PH in children and adults; nevertheless, it is not a specific classification for PH presenting in the newborn.

PH presenting in the neonatal period may result from a myriad of causes [2]. Most commonly, it presents immediately after birth, a condition referred to as persistent pulmonary hypertension of the newborn (PPHN), when pulmonary vascular resistance fails to decrease at birth. This disease is recognized as arterial PH in the Dana Point classification of PH. Most cases of PPHN are associated with lung parenchymal diseases, such as meconium aspiration syndrome, and respiratory distress syndrome; however, some present without known lung disease as primary PPHN. Some infants who have PPHN have lethal causes of respiratory failure, such as alveolar-capillary dysplasia [3], genetic defects in surfactant synthesis [4], or severe lung hypoplasia secondary to oligohydramnios or congenital anomalies. Congenital heart diseases are also a possible cause of PH, but usually the prognosis and outcome are more related to the heart disease than to the pulmonary vascular involvement during the first weeks of life. In a new group of newborns, PH presents without known heart or lung disease, as primary PPHN.

Over the last decades, a timely referral to a tertiary centre, the use of new techniques of mechanical ventilation, extracorporeal membrane oxygenation, a better support therapy, the use of inhaled nitric oxide (iNO), and new pharmacological pulmonary vasodilators have ameliorated the prognosis of this clinical condition allowing a survival rate of about 90% in several referral centres [5].

The aims of this study were to review the non cardiac conditions associated to PPHN in the newborn and the survival rate of the affected patients over the last 15 years, at our centre.

2. Material and Methods

Neonates with the diagnosis of PPHN of non cardiac cause, admitted between 1996 and 2010, were identified from the database of our neonatal intensive care unit (NICU), a tertiary referral center for neonatal cardiac and pediatric surgery in the north of Portugal. Gestational data, demographic data, the cause of PPHN, treatment, days of NICU stay, neonatal outcome, and necropsy findings of the deceased neonates were retrieved from the clinical charts and retrospectively reviewed.

The diagnosis of PPHN was made on clinical grounds, chest X-ray, arterial blood gases analysis, and 2D-echocardiograhic findings. Pulmonary artery pressure estimation was based on the gradient between right ventricle and atrium, through tricuspid regurgitation, assuming the right atrium pressure as 15 mmHg (estimated pulmonary systolic artery pressure (PSAP) = right ventricle to right atrium gradient + 15 mmHg).

The diagnosis of PPHN was made on clinical grounds, chest X-ray, arterial blood gases analysis, and 2D-echocardiograhic findings. Pulmonary artery pressure estimation was based on the gradient between right ventricle and atrium, through tricuspid regurgitation, assuming the right atrium pressure as 10 mmHg (estimated pulmonary systolic artery pressure (PSAP) = right ventricle to right atrium gradient + 15 mmHg). Pulmonary hypertension was stratified as mild if estimated PSAP was less than 40 mmHg, moderate if between 40 and 60 mmHg, and severe if higher than 60 mmHg. Additionally, other parameters were evaluated to help in definition of the severity of PH: (i) shunt direction at ductus arteriosus or foramen ovale (left-to-right shunt was considered normal, bidireccional shunt was considered sign of mild to moderate PH and right to left shunt was considered sign of severe PH); (ii) orientation of ventricular septum (the normal orientation was considered left to right, septum rectification was indicative of mild-to-moderate PH, and when the septum budge from right-to-left a severe PH was likely), and (iii) systolic function of the left ventricle, through the left ventricular ejection fraction (in cases of moderate PH it was expected a hipercontractil left ventricle whilst in severe PH usually we found a decrease on left ventricle ejection fraction). All the parameters were evaluated routinely. Echocardiographic evaluation was also used to exclude or confirm any congenital heart disease.

Inhaled nitric oxide (iNO) (usually starting with 20 ppm) has been routinely used since 2003 after echocardiographic definition of severe PH and an oxygenation index (mean airway pressure × fraction of inspired oxygen × 100/partial arterial pressure of oxygen) over 20. Sildenafil has been used in infants with persistent pulmonary hypertension refractory to iNO. Since iNO and sildenafil have been used since 2003, a comparison of the survival rates between two epochs was made (1996–2002 and 2003–2010).

Since 2003, we have also routinely used a total daily water intake of 80 mL/kg (until start enteral feeds) along with a perfusion of dopamine 5 mcg/kg/min, in order to keep a systemic blood pressure over 40 mmHg, and a hematocrit of about 45% (haemoglobin ≥15 g/dL). A perfusion of dobutamine (5 mcg/kg/min) is started if signs of myocardial dysfunction are present at echocardiographic evaluation. Higher doses of dopamine and dobutamine or epinephrine perfusion are used according to clinical criteria. Minimal stimulation as well as sedation and analgesia is usually performed with a perfusion of morphine (or fentanyl in the case of hypotension) and midazolam. Paralyzing agents as vecuronium are usually avoided; it is only used in selected cases as a rescue ventilation adjunt therapy. When mechanical ventilation is need, conventional ventilation is preferred to high-frequency oscillation ventilation, which is mainly used as rescue ventilation. The goals of mechanical ventilation are to maintain a PaO_2 of 60–90 mmHg and a $PaCO_2$ >30 mmHg (usually 35–50 mmHg), in order to avoid oxidative stress and hypocapnia.

ECMO treatment was not achievable in our country until 2010. Our centre, recently, started ECMO support to neonates and children.

Categorical variables were compared through Chi-square or the exact Fisher's test. The Mann-Whitney test was used to compare two independent samples.

This study has been approved by the ethics committee board of our institution.

Table 1: Demographics ($n = 78$).

Gestational age (weeks), median (min–max)	39 (30–41)
Preterm (<37 weeks gestation)	16 (20.5%)
Birthweight (grams), median (min–max)	3080 (1450–4170)
Intrauterine growth restriction	4 (5%)
Gender	
male	53 (67.9%)
female	25 (32.1%)
C-section	51 (65.3%)
Outborn	34 (43.5%)

3. Results

In the last 15 years, 6750 newborns were admitted to our unit. Seventy-eight (1.1%) had the diagnosis of PPHN of non cardiac cause. The demographics of the studied population are reported in Table 1, and the causes of PPHN are reported in Table 2. Twenty-five (32.0%) were deceased (13 males; 12 females). The median of death day was 7 (1–114). There were 34 outborns that were referred to our centre. Mortality rate in the outborn group was 32.3% (11/34), not different from the inborn group that was 31.8% (14/44) ($P = 0.967$). Pulmonary hypertension was classified as mild in 14 (17.9%) patients, moderate in 24 (30.7%), and severe in 40 (51.2%). Treatment aspects are reported in Table 3. The normalization of pulmonary hypertension occurred by day eight of life (2–160) in the survivors. The median of days of stay in the NICU was 12 days (1–167). The overall survival rate was 68%. There was a significant difference on survival rates between two periods (1996–2002 = 63.8% and 2003–2010 = 71.4%) ($P = 0.04$); see Table 4. Along with this increase in survival, days of NICU stay and of normalization of PH in the survivors accordingly increased.

Table 2: Causes of PPHN ($n = 78$).

Aspiration of bloody amniotic fluid, *n* (%)	1 (1.2)
Aspiration of blood from upper airways (traumatic intubation), *n* (%)	1 (1.2)
Meconium aspiration syndrome, *n* (%)	10 (12.8) (2†)
Congenital pneumonia and sepsis, *n* (%)	19 (24.3) (4†)
Severe hyaline membrane disease, *n* (%)	3 (3.8) (1†)
Transient tachypnea of the newborn, *n* (%)	4 (5.1)
Intrauterine ductus arteriosus closure (indomethacin), *n* (%)	2 (2.5)
Congenital diaphragmatic hernia, *n* (%)	17 (21.7) (10†)
Potter syndrome, *n* (%)	1 (1.2) (1†)
Nephrourological malformation with oligoamnios, *n* (%)	1 (1.2)
Idiopathic hypoplastic lung, *n* (%)	2 (2.5) (1†)
Idiopathic pulmonary arteriolar calcification, *n* (%)	1 (1.2) (1†)
Pulmonary "arteriopathy", *n* (%)	1 (1.2) (1†)
Arterial pulmonary thrombosis, *n* (%)	1 (1.2) (1†)
Fetal tachyarrhythmia, *n* (%)	1 (1.2)
Maternal diabetes, *n* (%)	1 (1.2) (1†)
Malformation of vein of Galeno, *n* (%)	2 (2.5) (2†)
Perinatal asphyxia, *n* (%)	4 (5.1)
Unknown aetiology, *n* (%)	6 (7.6)

†: deceased.

Table 3: Treatment ($n = 78$).

Inhaled nitric oxide, *n* (%)	19 (24.3%)
Surfactant, *n* (%)	24 (30.7%)
Dopamine, *n* (%)	57 (73%)
Dobutamine, *n* (%)	35 (44.8%)
Epinephrine, *n* (%)	3 (3.8%)
Sildenafil, *n* (%)	12 (15.3%)
Diuretics, *n* (%)	33 (42.3%)
Sedation, *n* (%)	71 (91%)
Oxygen, *n* (%)	78 (100%)
Days of oxygen, median (min–max)	6 (1–114)
Mechanical ventilation, *n* (%)	71 (91%)
Days of mechanical ventilation, median (min–max)	7 (1–114)
Extracorporeal membrane oxygenation (ECMO), *n* (%)	1 (1.2%)
Days of ECMO	17

4. Discussion

Persistence of pulmonary hypertension leading to respiratory failure in the neonate has been recognized for 40 years since its original description by Gersony and colleagues in 1969 [6]. During the development of the pulmonary vasculature in the fetus, many structural and functional changes occur to prepare the lung for the transition to air breathing. The development of the pulmonary circulation is genetically controlled by an array of mitogenic factors in a temporospatial order. With advancing gestation, pulmonary vessels acquire increased vasoreactivity. The fetal pulmonary vasculature is exposed to a low oxygen tension environment that promotes high intrinsic myogenic tone and high vasocontractility. At birth, a dramatic reduction in pulmonary arterial pressure and resistance occurs with an increase in oxygen tension and blood flow. The striking hemodynamic differences in the pulmonary circulation of the fetus and newborn are regulated by various factors and vasoactive agents. Among them, nitric oxide, endothelin-1, and prostaglandin I(2) are mainly derived from endothelial cells and exert their effects via cGMP, cAMP, and Rho kinase signalling pathways. Alterations in these signalling pathways may lead to vascular remodelling, high vasocontractility, and PPHN [7, 8].

In this study we were able to document PPHN in 16 preterm neonates, including one with 30 weeks of gestational age with a congenital sepsis and pneumonia. It is already known that the mechanisms that could lead to PH are already present in the human fetus by 31 weeks of gestation [5, 9, 10]. In our patients we observed a high number of C-sections that are related to prenatal diagnosis of pulmonary hypoplasia, as congenital diaphragmatic hernias, Potter syndrome, or meconium-stained amniotic fluid.

The most common cause of PPHN in this study was pulmonary hypoplasia. Congenital diaphragmatic hernia was the most prevalent cause of pulmonary hypoplasia. Congenital diaphragmatic hernia and oligohydramnios secondary to renal anomalies or premature rupture of membranes leads to pulmonary hypoplasia. Pulmonary hypertension often occurs as a complication because of the decreased number of blood vessels and increased reactivity of the vessels in the hypoplastic lungs. PPHN is usually more chronic and less responsive to vasodilator therapy in these infants and their outcome is related to the degree of lung hypoplasia, associated anomalies, as well as lengt of pulmonary hypertension [11]. The outcome for neonates who have congenital diaphragmatic hernia has improved since gentle ventilation and permissive hypercapnia have been incorporated into the management, with many centers reporting 75% survival in recent years [11, 12]. The survival of patients with congenital diaphragmatic hernia has improved in our center since 2003, and is nowadays over 61% [13].

The second cause of PPHN in this study was congenital pneumonia and sepsis. PPHN can be a complication of pneumonia or sepsis secondary to common neonatal pathogens [14]. Bacterial endotoxin causes pulmonary hypertension from several mechanisms, including the release of thromboxane, endothelin, and several cytokines [15, 16]. Sepsis also leads to systemic hypotension from activation of inducible nitric oxide synthase with excess nitric oxide release in the systemic vascular beds, impaired myocardial function, and multiorgan failure. Addressing PH should be a component of the overall management of septic shock and prevention of multiorgan failure in the affected neonates.

Another significant group of causes of PPHN were the aspiration syndromes, mainly meconium aspiration syndrome, representing 12.8% of PPHN in this series. Although meconium staining of amniotic fluid occurs in 10% to 15% of pregnancies, meconium aspiration syndrome

Table 4: Survival rates between two periods.

	1996–2002 $n = 36$	2003–2010 $n = 42$	P
Gestational age, weeks, median (min–max)	41 (30–41)	39 (32–41)	**0.032**§
Preterm (<37 weeks of gestation), *n* (%)	8 (22)	8 (19)	0.081*
Birthweigt, g, median (min–max)	3100 (1450–4170)	3040 (1800–4070)	0.354§
Gender			
Male, *n* (%)	23 (64)	30 (71)	
Female, *n* (%)	13 (36)	12 (29)	0.456*
C-section, *n* (%)	23 (64)	28 (67)	0.657*
Outborn, *n* (%)	18 (50)	16 (38)	0.071*
NICU stay	10 (1–67)	16 (1–167)	**0.034**§
Time to normalization of PH	5 (2–25)	9 (2–160)	**0.0391**§
Survival, *n* (%)	23 (63.8)%	30 (71.4)	**0.040****

§: Mann-Whitney test; *: Chi-Squared test; **: Fisher Exact test; NICU: neonatal intensive care unit; PH; pulmonary hypertension.

occurs infrequently, in up to 5% of neonates born through meconium stained fluid. The incidence of meconium aspiration syndrome has declined in recent years [17] with decreasing postterm pregnancies. This observation suggests that meconium aspiration syndrome is often a result of in utero stress with aspiration of meconium by a compromised fetus. Meconium can cause respiratory failure from several mechanisms. Meconium can cause mechanical obstruction to the airways, particularly during exhalation, resulting in air trapping, hyperinflation, and increased risk for pneumothorax. Meconium components also inactivate surfactant, [18] trigger an inflammatory response with release of cytokines, and increase the production of the vasoconstritors endothelin and thromboxane [19]. Recent advances in the management of PPHN have resulted in an excellent outcome for neonates who have meconium aspiration syndrome [20].

In this study PPHN occurred as a complication of hyaline membrane disease and transient tachypnea of the preterm newborn, often delivered by C-section, at 34–37 week's of gestation. The increasing reactivity of pulmonary arteries at this gestation period predisposes these neonates to PH when gas exchange is impaired because of surfactant deficiency [21].

The association of PPHN with maternal intake of nonsteroid anti-inflammatory drugs as indomethacin has been recognized in case reports since 1970 [22, 23]. A strong causal association is also suggested by the consistent reproduction of hemodynamic and structural features of PPHN by fetal ductal constriction [24, 25].

Maldevelopment of pulmonary arteries (pulmonary "arteriopathy" and idiopathic pulmonary arteriolar calcification) and thrombosis of pulmonary arteries (probably associated to coagulation disorders that were not assessed) were necropsy findings in three patients without any evident cause for the PH on clinical grounds. Maladaptation of the pulmonary vascular bed in asphyxia, maternal diabetes, and fetal tachyarrhythmia were also identified in this study, as well as in two patients with malformation of vein of Galeno and PPHN associated to high cardiac output failure from large arteriovenous malformations. These causes of PPHN have already been described [26]. The cases of PPHN of unknown aetiology in this series were transient forms with a good outcome, suggesting transient maladaptation to extrauterine life.

Neonates who have PPHN require supportive care tailored to the degree of hypoxemia and physiologic instability. Oxygen is a potent vasodilator and was used in all patients, once hypoxemia is usually present. Mechanical ventilation facilitates alveolar recruitment and lung expansion, potentially improving the ventilation/perfusion (V/Q) match. In this study, mechanical ventilation was used in all, except in four cases of transient tachypnea of the newborn and three cases of PPHN of unknown aetiology with mild pulmonary hypertension. Surfactant has been shown to decrease the need for ECMO in full-term neonates with severe respiratory failure [27]. The beneficial effect of surfactant in this study was seen particularly in babies who had meconium aspiration syndrome and sepsis. Sedatives, although widely used to minimize fluctuations in oxygenation and facilitate ventilation, have not been tested in randomized trials [5]. We have used sedatives in all ventilated patients to ameliorate oxygenation and to decrease discomfort. We do not use for routine skeletal muscle relaxants. Inotropic and vasopressor support with dopamine, dobutamine, and epinephrine is used to optimize cardiac function, stabilize systemic blood pressure, and decrease right-to-left shunt. From 2003 we have used iNO and sildenafil, in selected cases of severe PPHN, mainly in congenital diaphragmatic hernia. Both the survival rate of congenital diaphragmatic hernia and all cases of PPHN showed a significant increase since 2003. ECMO has significantly improved the survival of neonates with severe but reversible lung disease [28, 29], but we do not have experience on that. We tried ECMO in a poor prognosis for of bilateral congenital diaphragmatic hernia with severe pulmonary hypoplasia and pulmonary hypertension, but the patient did not survive.

The overall survival rate described in the literature, including all causes of PPHN, is over 70–75% [30]. Our results are now according to these figures. There is, however, a marked difference depending on the underlying disease. There are also significant differences in long-term outcome according to the cause of PPHN.

This study is limited by the fact of being a single center retrospective analysis, including a small sample of some rare pulmonary disorders causing PH. Prospective studies with the objective of evaluating the different therapies in the various groups of underlying diseases, including a significant number of patients, will give much more information regarding therapeutic efficacy and survival.

Future research must address the different causes of PPHN and therapies separately, in large multicenter studies.

In conclusion, our study shows a myriad of non cardiac aetiologies for PPHN, most of them related to lung disease or lung hypoplasia. We observed an improvement in survival rate since 2003, and we believe that this is related to the use of new therapies. We hope that ECMO will offer additional advantages at our NICU for selected infants in the near future.

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Clinical Study

Intravascular Talcosis due to Intravenous Drug Use Is an Underrecognized Cause of Pulmonary Hypertension

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Intravenous injection of illegal drugs or medications meant for oral administration can cause granulomatous disease of the lung. This intravascular talcosis results in pulmonary fibrosis and pulmonary hypertension. Nine cases of histologically confirmed intravascular talcosis were reviewed with specific attention given to the clinical histories in these patients. Five autopsy cases were included in this series with detailed investigation in the anatomic features associated with intravascular talcosis and pulmonary hypertension. All nine patients showed perivascular and/or intravascular deposition of polarizable foreign material in their lungs. Intravascular talcosis as a result of previous intravenous drug use was not clinically suspected in any patient despite clinically diagnosed pulmonary hypertension in five. All patients showed dilatation of the right and left heart, but none had dilatation of the aortic valve. Congestive heart failure with hepatosplenomegaly was also common. We conclude that intravascular talcosis is an underdiagnosed cause of pulmonary hypertension in patients with known history of intravenous drug use.

1. Introduction

Pulmonary disease as a result of talc exposure has been well documented and can have multiple etiologies [1]. Inhalational talc exposure causes talc pneumoconiosis, while intravenous talc exposure causes intravascular talcosis. The disease symptoms and gross anatomic findings in these two different etiologies are essentially identical, and the histology of these two forms of talc-related lung diseases are also quite similar. Pulmonary deposition of insoluble microscopic foreign material results in a foreign body giant cell reaction within the lung parenchyma. Over time and continued exposure this process results in pulmonary fibrosis, in some cases extensively. The differentiating feature between these two diseases is the location of the foreign material. Inhalational talc pneumoconiosis results in an alveolar distribution, and intravascular talcosis leads to a perivascular pattern of deposition. In acute settings it is also possible to identify polarizable foreign material within intravascular spaces.

The source of foreign material in intravascular talcosis is through the intravenous injection of drugs. Illegal street drugs commonly contain an adulterant to increase the mass, and this adulterant commonly contains microscopic insoluble material. Another common source is the injection of prescription medications meant for oral use. In these medications which are ground for intravenous injection, there are fillers and binders added to the medications. In fact the term intravascular talcosis is a misnomer as talc is only one of several possible materials used as excipients that also include methylcellulose and crospovidone [2]. Special stains have been shown to have the ability to differentiate the composition of intravascular foreign material in diagnostically difficult situations [3].

With the intravenous injection of foreign material, the lungs represent the first capillary bed to serve as a filter to remove this material. Due to the size of much of this material it usually becomes lodged in the pulmonary vasculature. This results in acute small embolization of vessels. Over time the foreign material is deposited in perivascular tissues, and foreign body giant cell reaction occurs with associated fibrosis. This fibrosis of the lung parenchyma in turn results in the development of pulmonary hypertension in some patients.

Intravascular talcosis as a cause of pulmonary hypertension has been well documented since the early description of this disease in the 1960s although the term intravascular talcosis has not been commonly used in the past [4, 5].

The diagnosis of intravascular talcosis has important social and medical treatment implications but is not commonly suspected in many patients even in the presence of known intravenous drug abuse [6]. Here we present nine cases of intravascular talcosis on biopsy and autopsy cases that were not clinically suspected. We give a detailed review of the patient histories. In five autopsy cases we also include detailed analysis of the pulmonary and cardiac disease relating to intravascular talcosis. The goal of this study is to increase awareness of intravascular talcosis as a cause for pulmonary hypertension and to present clinical and anatomic features that can suggest the diagnosis.

2. Materials and Methods

Cases of intravascular talcosis were identified through a natural language search for "talc" in our electronic laboratory information system over an eleven-year-period spanning 1/2000–12/2010. Surgical specimens and autopsy cases were included in the search. Final diagnoses were reviewed to select cases of intravascular talcosis, and slides were reviewed by the authors to confirm the diagnosis. Cases were excluded if slides or blocks were not available for review or the diagnosis was not confirmed. In autopsy cases, all slides were pulled and examined for the presence of polarizable foreign material in association with histocytic infiltration. The clinical histories of patients with confirmed intravascular talcosis were abstracted for relevant clinical data. This study was approved by the UPMC Institutional Review Board (IRB no. PRO11020060).

2.1. Definition of Normal Metrics. Left ventricular hypertrophy was defined as wall thickness greater than 1.5 cm and right ventricular hypertrophy as wall thickness greater than 0.5 cm. Mitral valve dilation was defined as valve circumference greater than 9.9 cm in males and 9.1 cm in females, aortic valve dilation as valve circumference greater than 8.5 cm in males and 7.9 cm in females, tricuspid valve dilation as valve circumference greater than 11.8 cm in males and 11.1 cm in females, and pulmonic valve dilation as valve circumference greater than 7.5 cm in males and 7.4 cm in females [7]. Cardiomegaly was determined as a function of sex and body mass using the report by Kitzman et al. [7]. Splenomegaly was defined as spleen weight greater than 245 grams in males and greater than 190 grams in females. Hepatomegaly was defined as liver weight greater than 2000 grams in males and greater than 1800 grams in females. Increased lung weight was defined as combined lung weight greater than 1050 grams.

3. Results

3.1. Clinical Features of Intravascular Talcosis. A total of nine cases of intravascular talcosis are included in this study—five autopsy cases and four lung biopsy cases. Demographics for these patients are summarized in Table 1. The average age for all patients was 44 years. Three cases were diagnosed in patients with admitted drug use that was not recent, and these patients had a higher average age at 56 years. There was a predominance of males with only one female in the nine patients.

The clinical histories of the patients were variable and are briefly described herein. Case 1 had a history of intravenous drug use and IgA nephropathy and was admitted for dyspnea and chest pain. Case 2 had a history of intravenous drug use and coronary artery disease and presented with acute chest pain. Case 3 had a history of remote intravenous drug use and history of stroke and was found unresponsive at his skilled nursing facility. Case 4 had a history of remote intravenous drug use, chronic obstructive pulmonary disease, and multiple pneumothoraces and was admitted for new pneumothorax and possible lung transplant evaluation. Case 5 had a history of intravenous drug use, chronic obstructive pulmonary disease, and chronic back pain requiring multiple surgeries and presented with a new episode of severe back pain. Case 6 had a history of remote intravenous drug use and right lung transplantation for talcosis and presented with increased work of breathing. Case 7 presented in the trauma suite with multiple traumatic penetrating chest injuries; a pneumonectomy was performed, but the patient did not survive. No history is available for this patient. Case 8 had a history of deteriorating lung function due to severe emphysema and presented for double lung transplantation. Case 9 had a history of multiple spine surgeries and presented with an enlarged periaortic lymph node and pulmonary infiltrate. While the majority of patients (6 of 8) with histologically confirmed intravascular talcosis had admitted intravenous drug abuse, two denied intravenous drug use. Other common clinical features were hepatitis C seropositivity (7 of 8 tested) and tobacco use (6 of 8 with history).

Pulmonary hypertension was clinically diagnosed in five of the nine patients based on clinical features, cardiac catheterization, and echocardiography. Four patients had cardiac catheterization data available for review with all having elevated peak pulmonary artery pressures with an average of 43 mmHg (range 37–50 mmHg). End diastolic pulmonary artery pressures were increased in only two patients (average 15.25 mmHg, range 4–22 mmHg). Mean pulmonary artery pressures reported were elevated in two patients (average 25.25 mmHg, range 20–32 mmHg). Echocardiography (either transthoracic or transesophageal) studies were performed in six patients. Two patients had completely normal studies. Four patients had abnormal findings: mild right atrial dilatation (2), moderate-to-severe right ventricular dilatation (3), moderate pulmonary artery dilatation (2), moderate pulmonary hypertension (3; peak pulmonary systolic pressures 52–70 mmHg), moderate left atrial dilatation (2), mild left ventricular hypertrophy (1), severe left ventricular hypertrophy (1), and mildly decreased left ventricular ejection fraction (3).

Five patients had chest computed tomography performed prior to pathological examination. Three showed emphysematous changes, one showed centrilobular and interstitial nodules, and one showed bibasilar atelectasis versus

Table 1: Demographics for cases of talc granulomatosis.

Case	Specimen	Sex	Age (years)	Admitted IVDU	Hep C	Tobacco smoking	Pulmonary symptoms/diagnoses
1	Autopsy	M	37	Yes	Negative	no	Dyspnea Pulmonary HTN
2	Autopsy	M	40	Yes	Positive	yes	
3	Autopsy	M	62	Yes, remote	Positive	no	
4	Autopsy	M	55	Yes, remote	Positive	yes	IPF Pulmonary HTN Recurrent pneumothoraces
5	Autopsy	F	44	Yes	Positive	yes	COPD
6	Transbronchial biopsy	M	51	Yes, remote	Positive	yes	Dyspnea Pulmonary HTN s/p R lung transplant for talc exposure*
7	Pneumonectomy due to trauma	M	20	NA	NA	NA	
8	Double lung transplant native lungs	M	53	No	Positive	yes	Dyspnea Mild pulmonary HTN
9	Wedge resection	M	31	No	NA	yes	Dyspnea Pleuritic chest pain Pulmonary HTN

* Initially diagnosed with talc pneumoconiosis.
Abbreviations: HTN: hypertension, IPF: idiopathic pulmonary fibrosis, COPD: chronic obstructive pulmonary disease, s/p: status post, NA: not available.

pneumonia. In one patient with severe panlobular emphysema, diffuse fibrosis was also evident.

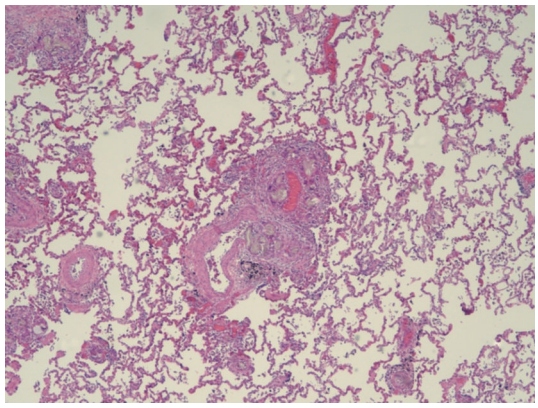
Pulmonary function testing was performed in four patients, and the following parameters were noted to be abnormal: forced vital capacity (FVC) (4 patients; 26–72% of predicted), forced expiratory volume in 1 second (FEV1) (4; 22–65% of predicted), diffusing capacity of the lung for carbon monoxide (DLCO) (4 patients; 1 with 62% of predicted and 3 others that were unattainable due to low lung volumes), and vital capacity (VC) (4 patients; 36 and 73% of predicted in 2 patients, and unattainable in 2 patients).

Regarding relevant medical comorbidities, seven out of eight patients with known baseline status had a past medica l history significant for hypertension that required medical management. Three patients had a history of chronic renal insufficiency (one of whom had IgA nephropathy and eventually required hemodialysis), and one patient developed acute renal failure prior to death.

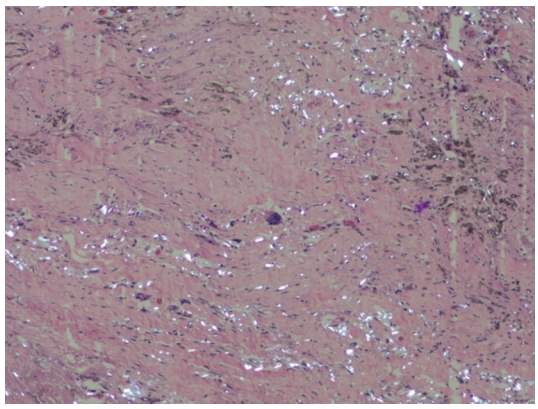
At the time of initial pathological diagnosis, no patients were clinically suspected of having intravascular talcosis. One patient had previously been diagnosed with inhalational talc pneumoconiosis at an outside institution based on biopsy. Following this diagnosis the patient had a single-sided lung transplant, and a later biopsy at our institution of the nontransplanted native lung was diagnostic of intravascular talcosis. This patient had a history of remote intravenous drug use. Another patient experienced multiple bilateral spontaneous pneumothoraces and was diagnosed with idiopathic pulmonary fibrosis; however, histological examination of the patient's lungs at autopsy demonstrated intravascular talcosis as a cause for his pulmonary fibrosis.

3.2. Histologic Features of Intravascular Talcosis. The low power microscopic appearance in histologic sections of the lungs varied from focal areas of foreign body reaction and fibrosis to cases with extensive areas of fibrosis (Figure 1). The common finding in all cases was the diagnostic feature of a perivascular localization of foreign material deposition and fibrosis (Figure 2). In cases with extensive fibrosis the perivascular deposition could still be seen in areas with residual alveolated lung. The morphology of the foreign material itself varied with some showing more plate-like material and others more needle-like material (Figures 3(a) and 3(b)). Occasional asteroid bodies were found in some cases (Figure 3(c)). The histologic sections from autopsy cases and two of the four surgical pathology specimens showed some classical features associated with pulmonary hypertension [8]. Many medium caliber arteries showed hypertrophy of the muscular walls and larger arteries, when seen on sections, showed intimal proliferation similar to that seen in atherosclerosis. Many of the smaller caliber vessels failed to show these changes, and no plexiform vascular lesions were seen.

3.3. Anatomic Findings in Intravascular Talcosis Seen at Autopsy. Anatomic findings in the five patients having autopsy can be seen in Table 2. Causes of death included cardiac failure with pulmonary edema, cardiac arrhythmia secondary to pulmonary thromboembolus, multisystem organ failure secondary to sepsis, pulmonary fibrosis, and cardiopulmonary decompensation from pulmonary hypertension. All five patients had increased lung weights with an average of 1,894 grams. Cardiomegaly was present in three

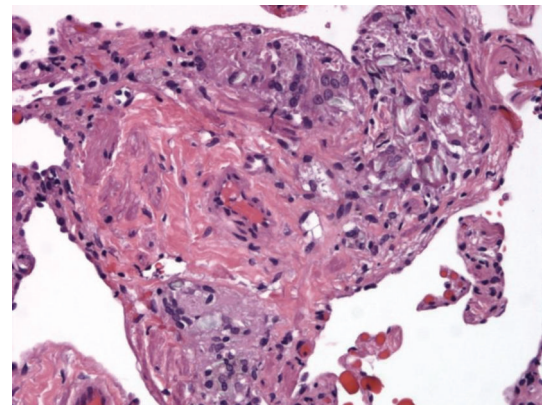


(a)

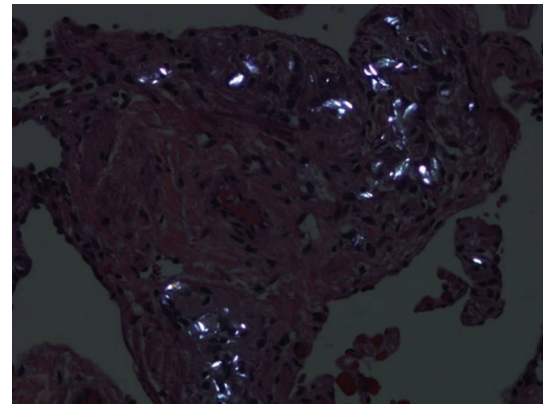


(b)

Figure 1: Low-power magnification of two cases of intravascular talcosis. The degree of fibrosis ranged from focal fibrosis in perivascular areas (a) to diffuse areas of fibrosis (b). Foreign material can be seen within areas of fibrosis associated with a foreign body giant cell reaction. Polarization of the material is evident in (b).



(a)



(b)

Figure 2: Higher magnification view of perivascular deposition of foreign material with foreign body giant cell reaction and fibrosis (a). The foreign material is highlighted under polarization (b).

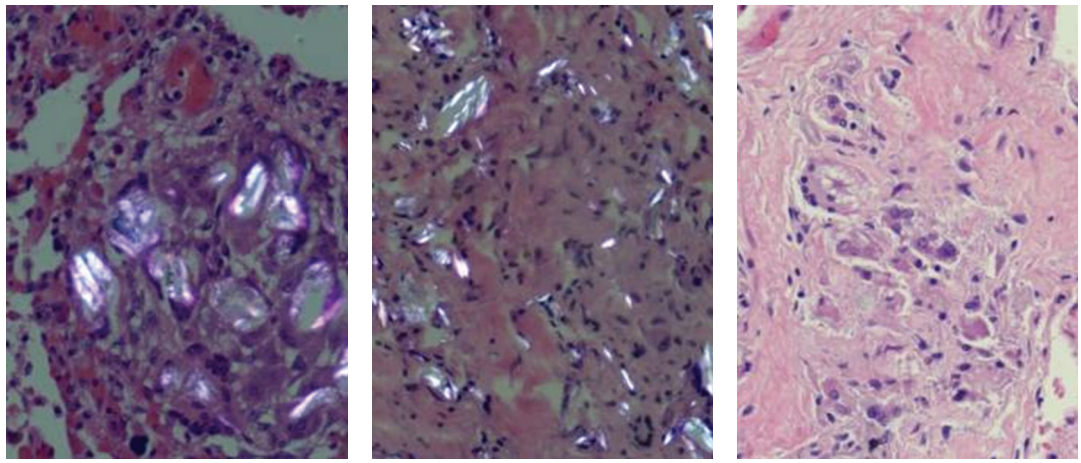
Table 2: Anatomic features of intravascular talcosis.

Average organ weights (grams)		[range]
Lungs	(1894)	1490–2490
Heart	(600)	350–1030
Liver	(2421)	1300–4110
Spleen	(437)	80–860
Average heart valve circumference (cm)		
Mitral	(10.9)	10.5–11.5
Aortic	(7.2)	6.5–8
Tricuspid	(13.5)	12–15.5
Pulmonic	(8.5)	7–10

of five patients with an average heart weight of 600.4 grams. All five patients showed dilation of both right and left heart. The mitral and tricuspid valves were dilated in all 5 patients, average circumference of 10.9 cm and 13.5 cm, respectively. The pulmonic valve was dilated in 4 of 5 with an average circumference of 8.5 cm. None of the 5 patients had dilation of the aortic valve, average circumference 7.2 cm. Hepatomegaly was present in three of five and splenomegaly in four of five patients. The presence of polarizable foreign material was also present in extrapulmonary tissues in each of the five patients—bone marrow (3), lymph nodes (2), kidneys (2), spleen (2), liver (2), myocardium (2), thyroid (1), venous thrombus (1), and right ventricular thrombus (1) (Figure 4). One patient that is not deceased had prior biopsies of the liver and retina which showed similar polarizable foreign material. In each of the extrapulmonary tissues, the foreign material was intra-or perivascular, showed smaller particles than in the lungs, and lacked significant giant cell reaction. In one patient with transbronchial lung biopsy, previous biopsies of the retina and liver were reported to show polarizable foreign material. Four patients had evidence of moderate-to-severe coronary artery atherosclerosis, and three had histologic evidence of subendocardial and/or myometrial ischemia.

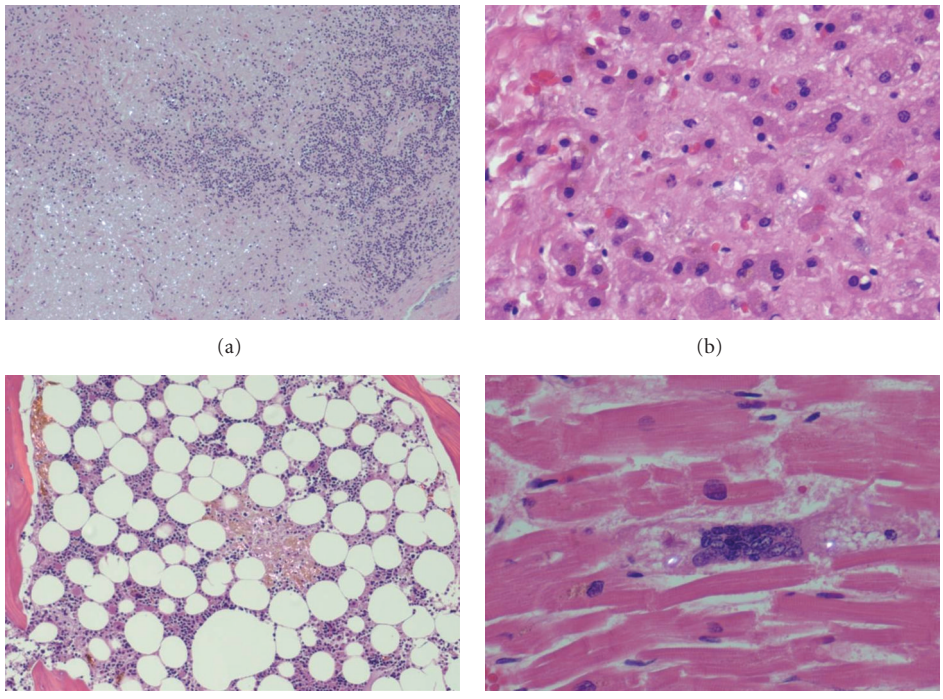
4. Discussion

The finding of perivascular or intravascular polarizable foreign material in the lungs is essentially diagnostic of intravascular talcosis due to intravenous injection of illegal drugs. The most important differential to establish is



(a) (b) (c)

Figure 3: The foreign material deposits of intravascular talcosis have varying morphologies. Some cases showed more plate-like polarizable material (a) while other cases showed more needle-like morphology (b). Asteroid bodies are a common finding in intravascular talcosis (c).



(a) (b) (c) (d)

Figure 4: Systemic sites of foreign material are an important feature seen in intravascular talcosis. This material is smaller than seen in the lungs and only rarely incites a foreign body giant cell reaction. Representative figures show deposition in lymph node (a), liver (b), bone marrow (c), and heart (d).

between intravascular talcosis and talc pneumoconiosis due to inhalation of microscopic dust. The differentiation of these two etiologies in foreign material associated granulomatous lung disease can be challenging as perivascular location in some ways includes the entire lung parenchyma.

In this paper we searched for and selected cases of intravascular talcosis based on the histological location of the polarizable foreign material in perivascular or intravascular locations. Our findings show that none of the nine patients included in this study were clinically suspected of having intravascular talcosis due to intravenous drug abuse. This is despite the fact that five had clinically diagnosed pulmonary hypertension and six had admitted history of intravenous drug abuse.

While the effects of intravascularly injected talc had an adverse impact on these patients' hemodynamic profiles as

described in the current study, it is interesting to note that many of the histologic specimens demonstrated talc that was found to be distributed in the perivascular area and not intravascularly. While a definitive answer to explain this is elusive, one plausible hypothesis is that small talc particles are extravasated from the vascular space over time by the hydrostatic pressure within the vessels. The fact that a majority of patients in the current analysis had systemic hypertension would also facilitate this movement. With time, macrophages (and resulting giant cells) may also contribute to the movement of this foreign material farther from the intravascular space. Ultimately, fibrosis of this milieu of talc, immune cells, and perivascular stroma around the pulmonary vessels would, in addition to any remaining intravascular talc, contribute to the increased pulmonary artery pressures.

Fibrosis and occlusion of small vessels within the lungs of these patients due to the intravascular and/or perivascular deposition of insoluble foreign material is the most probable cause of pulmonary hypertension in light of the clinical history and anatomic findings; however, contributions from other aspects of the patients' comorbidities, such as emphysema and fibrosis of other etiologies, cannot be completely excluded. The anatomic findings in the five patients undergoing autopsy were all likely related to the pulmonary hypertension in these patients. While the phenomenon of pulmonary hypertension in patients with intravenous drug use is well documented this is the first report to our knowledge to carefully examine the changes to the heart related to the disease. In the cases presented here all patients had dilatation of the left and right heart as determined by enlarged valve circumference. Cardiomegaly was also common being seen in three of five patients. Despite this finding none showed dilatation of the aortic valve. The reason for this is not known. Features of left sided congestive heart failure with hepatomegaly and splenomegaly were also common.

The additional evidence to support the diagnosis in these patients was the common finding of fine birefringent material in systemic locations in these patients. This feature has been previously reported in patient with intravascular talcosis [9]. This finding should suggest the diagnosis of intravascular talcosis rather than talc pneumoconiosis in patients with pulmonary granulomas as inhalation of talc and related material should not result in systemic deposition. The smaller size of the material in the systemic sites compared to the lung parenchyma suggests that this material was small enough to escape the pulmonary capillary bed.

Our analysis yielded findings from non-invasive testing which may increase suspicion for this disease in high risk individuals. Right-sided cardiac dilatation and pulmonary artery dilatation/hypertension were each found in at least half of patients that underwent echocardiography. Additionally, all patients (4/4) who underwent pulmonary function testing had decreased FVC and FEV1, along with either decreased or unattainable (due to low lung volumes) VC and DLCO.

In the current study, hypertension requiring medical treatment was present in 7 out of 8 patients that were assessed. Only three patients had chronic kidney insufficiency (an additional patient had acute renal failure prior to death), and one of these required hemodialysis. Additionally, autopsy findings demonstrated either moderate-to-severe atherosclerotic disease or cardiac ischemia. These relevant cardiac and renal co-morbidities may have contributed to the observed cardiac findings, and while intravascular talcosis and its hemodynamic impacts may have exacerbated these conditions, their definitive relationship to intravascular talcosis is unknown.

Intravascular talcosis as a result of intravenous injection of drugs is not an uncommon finding but is not universally seen in all intravenous drug users, and the finding of pulmonary hypertension has been previously reported in these patients [5]. The current study demonstrates that intravascular talcosis is an underrecognized cause of pulmonary hypertension despite the combination of pulmonary hypertension and a history of intravenous drug use in many of our patients. Patients with risk factors and findings identified herein may benefit from further clinical evaluation for intravascular talcosis.

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