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TOPIC HIGHLIGHT

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Contribution of oxidative stress to pulmonary arterial hypertension

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Abstract

Recent data implicate oxidative stress as a mediator of pulmonary hypertension (PH) and of the associated pathological changes to the pulmonary vasculature and right ventricle (RV). Increases in reactive oxygen species (ROS), altered redox state, and elevated oxidant stress have been demonstrated in the lungs and RV of several animal models of PH, including chronic hypoxia, monocrotaline toxicity, caveolin-1 knock-out mouse, and the transgenic Ren2 rat which overexpresses the mouse renin gene. Generation of ROS in these models is derived mostly from the activities of the nicotinamide adenine dinucleotide phosphate oxidases, xanthine oxidase, and uncoupled endothelial nitric oxide synthase. As disease progresses circulating monocytes and bone marrow-derived monocytic progenitor cells are attracted to and accumulate in the pulmonary vasculature. Once established, these inflammatory cells generate ROS and secrete mitogenic and fibrogenic cytokines that induce cell proliferation and fibrosis in the vascular wall resulting in progressive vascular remodeling. Deficiencies in antioxidant enzymes also contribute to pulmonary hypertensive states. Current therapies were developed to improve endothelial function, reduce pulmonary artery pressure, and slow the progression of vascular remodeling in the pulmonary vasculature by targeting deficiencies in either NO (PDE-type 5 inhibition) or PGI_2 (prostacyclin analogs), or excessive synthesis of ET-1 (ET receptor blockers) with the intent to improve patient clinical status and survival. New therapies may slow disease progression to some extent, but long term management has not been achieved and mortality is still high. Although little is known concerning the effects of current pulmonary arterial hypertension treatments on RV structure and function, interest in this area is increasing. Development of therapeutic strategies that simultaneously target pathology in the pulmonary vasculature and RV may be beneficial in reducing mortality associated with RV failure.

Key words: Pulmonary arterial hypertension; Rosuvastatin; Oxidative stress; Nicotinamide adenine dinucleotide phosphate oxidase; Statins

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INTRODUCTION

Pulmonary arterial hypertension (PAH), defined as mean pulmonary artery pressure (PAP) in excess of 25 mmHg at rest, is a rare and devastating disease that targets the endothelium of small pulmonary arteries resulting in vasoconstriction and profound vascular remodeling. Vasoconstriction results partly from endothelial dysfunction caused by an imbalance in bioavailability of dilators, such as nitric oxide (NO) and prostacyclin (PGI_2) *vs* excess in constrictors, such as, endothelin-1 (ET-1), thromboxane, serotonin, and angiotensin Ⅱ (Ang Ⅱ). The local imbalance in vasoactive mediators promotes proliferation, hypertrophy, and fibrosis within pulmonary arterioles. Early stages of vascular remodeling include medial hypertrophy and hyperplasia, whereas the arterioles of patients with advanced PAH are characterized by complex plexiform lesions resulting from intimal hyperplasia[1]. These changes eventually lead to luminal occlusion and arteriolar pruning. The progressive increase in PAH increases afterload on the right ventricle (RV) which promotes right ventricular hypertrophy (RVH). During an initial period of compensation the RV may exhibit enhanced contractility in response to the increased afterload. With progressive increases in afterload the RV decompensates which results in RV failure. RV failure is marked by diminished myocardial perfusion and ischemia, increased end diastolic volume, RV dilation, reduced stroke volume, and reduced cardiac output. The factors contributing to the hemodynamic and structural abnormalities of the decompensating RV are likely due to neurohormonal signaling (Ang Ⅱ, aldosterone, ET-1), natriuretic peptides, and adrenergic stimulation), oxidative stress (reactive oxygen and nitrogen species), inflammation (inflammatory cytokines), and myocardial cell death. One common cause of death in patients with PAH is right sided heart failure[2].

Current therapies were developed to improve endothelial function, reduce PAP, and slow the progression of vascular remodeling in the pulmonary vasculature by targeting deficiencies in either NO (PDE-type 5 inhibition) or PGI_2 (prostacyclin analogs), or excessive synthesis of ET-1 (ET receptor blockers) with the intent to improve patient clinical status and survival[3]. Although little is known concerning the effects of current PAH treatments on RV structure and function interest in this area is increasing[4]. Important clinically relevant questions are raised in this regard because the simultaneous goals of reducing pulmonary vascular resistance and improving RV function may be challenging. Current therapies may reduce proliferation and increase apoptosis in cells in the pulmonary vascular wall and these same effects may be detrimental to cardiomyocytes in a decompensating RV. ET-1 receptor blockade may reduce PAP and slow pulmonary vascular remodeling, yet the negative inotropic effects could be beneficial in some patients with compensated RVH and detrimental in patients with a decompensated RV. Therapeutic strategies that could be potentially beneficial to both the pulmonary vasculature and the RV would be those that reduce reactive oxygen species (ROS), reactive nitrogen species (RNS), inflammation, and fibrosis[4].

The underlying causes of PAH are still largely unknown but, like many diseases, are likely to involve an interaction between genetic and environmental factors. Diagnosis usually occurs in patients with established disease because symptoms at presentation, such as dizziness, dyspnea, and syncope, are generally nonspecific. Despite modest therapeutic advancements in the last 15 years, PAH still results in high morbidity and mortality[5]. Clearly, there is a critical need for further research to identify novel targets for treatment of PAH. Herein, we will review the contribution of oxidant stress to PAH and RV failure derived from several animal models of PH and the potential role of alternative strategies such as HMG co-A reductase class of drugs, referred to as statins, as adjunctive therapy.

OXIDATIVE STRESS IN THE VASCULAR WALL

Physiologically active levels of ROS, which can be generated in healthy endothelial, smooth muscle, and adventitial cells in the pulmonary and systemic vasculatures, are involved in the routine regulation of physiologic and cellular processes[6-8]. ROS refer collectively to both unstable free radicals, such as superoxide anion ($O_2^{\bullet-}$), nitric oxide (NO), hydroxyl moiety ($^{\bullet}OH$), hypochlorite (ClO^-), and peroxynitrite ($ONOO^-$), and stable oxidants such as hydrogen peroxide (H_2O_2). Free radicals are short lived because they are highly reactive and are scavenged by a series of anti-oxidant moieties and enzymes. Oxidative stress occurs when there are repeated external insults that provoke excess ROS formation which overwhelms antioxidant systems, thus creating an imbalance in the redox state of the cell favoring oxidation. Excess synthesis of ROS can result in cell and tissue damage due to oxidation of a number of cell constituents such as proteins, lipids, carbohydrates, and DNA. Oxidative stress can contribute significantly to the pathogenesis of atherosclerosis[9], heart failure[10], ventricular hypertrophy[11], respiratory distress[12], ischemia-reperfusion injury[13], and pulmonary and systemic hypertension[14]. Oxidative stress *via* peroxynitrite-induced tyrosine nitration can damage endothelial nitric oxide synthase (eNOS) and prostacyclin synthase (PGIS) which impairs vasodilation by diminishing the capacity of vessels to synthesize the vasodilators, NO and PGI_2[15]. Moreover peroxynitrite damage to eNOS redirects the synthase activity from NO to superoxide generation and superoxide synthesized in this manner has been implicated in eNOS-dependent tyrosine nitration of prostacyclin synthase[16].

There are multiple enzymatic and metabolic sources known to generate superoxide within cells in the vascular wall[17,18]. They include the nicotinamide adenine dinucleotide phosphate (NADPH) oxidases[19], the mitochondrial electron transport chain complexes, xanthine oxidase (XO)[20,21], cytochrome P450, cyclooxygenase[22], and uncoupled nitric oxide synthase[23,24]. In mitochondria ROS are normally produced as byproducts of aerobic metabolism by the electron transport complexes, with 1%-2% of oxygen (O_2) being converted to $O_2\bullet^-$ at any given time. Normally, the activities of most oxidases are below a level that could influence signaling pathways, but the NADPH oxidases and mitochondria generate sufficient superoxide under basal conditions to activate signaling related to control of soluble guanylate cyclase and ion channels[17]. In disease states such as hypertension the NADPH oxidases[25], XO[26], and nitric oxide synthases become major sources of ROS, especially in the vasculature and are activated by hormones, growth factors, cytokines, and shear stress[27]. With disease mitochondria electron transport complexes can be disrupted and become a source of ROS that promote cellular senescence, necrosis, or apoptosis[17]. Despite these varied sources of ROS, the consensus is that the NADPH oxidases are not only the principle generator of $O_2\bullet^-$ in the vasculature during disease[9,28-30], but their activities regulate the activities of other ROS-generating oxidases such as, XO[26] and eNOS, and are important in recruitment of ROS-generating phagocytic cells.

EVIDENCE OF OXIDATIVE STRESS IN THE PULMONARY HYPERTENSIVE LUNG

Most of the available animal models of pulmonary hypertension (PH) exhibit the two principal pathological features in the pulmonary vasculature common to most forms of PH, which include excessive vasoconstriction and remodeling of the pulmonary arteriolar wall, primarily by a mechanism of smooth muscle proliferation within the medial layer[14,31,32]. Because ROS may promote vasoconstriction, smooth muscle cell proliferation, and vascular remodeling, they are likely to play a critical role in many forms of PH.

Ren2 model of PAH

We recently reported a new model of PAH and pulmonary vascular remodeling in the male TG(mRen2)27 rat[14,33]. The Ren2 is a derivative of the Sprague-Dawley (SD) rat that expresses the mouse renin gene in renal and extrarenal sites resulting in increased tissue synthesis of Ang Ⅱ *via* the local RAS, Ang Ⅱ-dependent hypertension, and end organ damage. Thus, we investigated the possibility that an activated intrapulmonary RAS would result in PAH in the Ren2 due in part to oxidative stress. We based this notion on the well documented fact that Ang Ⅱ stimulates NADPH oxidase-generated ROS in the vasculature (Ang Ⅱ)[27,34,35]. Ang Ⅱ causes rapid induction of NADPH oxidase-dependent superoxide synthesis *via* protein kinase C (PKC)[36] and more prolonged stimulation *via* transactivation of growth factors[37,38]. Ang Ⅱ also causes redox-sensitive XO activation and eNOS uncoupling leading to increases in superoxide levels in vascular tissue[18,22]. In 8-9 wk old male Ren2 rats, we reported that the lung expresses mouse renin and other RAS components. We also showed increases in intrapulmonary NADPH oxidase activity, superoxide, right ventricular systolic pressure, and medial layer thickening of pulmonary resistance arterioles[14]. Additionally, we found that the superoxide dismutase/catalase mimetic, tempol, reverses PAH and pulmonary vascular remodeling. Lastly, we showed that PAH developed prior to the onset of LV dysfunction and was not due to hypoxemia[33]. Data from these studies in the Ren2 rat support the concept that PAH can occur as a consequence of NADPH oxidase-induced oxidative stress induced by activation of the local renin-angiotensin system (RAS) within the pulmonary vasculature and lung parenchyma. In support of this concept, other laboratories recently demonstrated the potential efficacy of gene therapy targeting the RAS for treatment of PAH[39,40]. It is likely that therapies specifically targeting the RAS will reduce Ang Ⅱ-induced activation of NADPH oxidases thereby limiting oxidative stress in the pulmonary vasculature, as well as in the RV.

Chronic hypoxia-induced PH

The rodent model of chronic hypoxia-induced PH (CH-PH) is one of the most frequently used animal models to study PH. Although clinical classification schemes categorize CH-PH separately from forms of PAH, both CH-PH and PAH share many pathophysiological features in common, including elevated PAP, medial thickening of pulmonary arterioles, and RVH. To induce CH-PH typically mice or rats are exposed 10% oxygen under normobaric or hypobaric conditions. CH-PH is reversible if animals are returned to normoxia. Hypoxia induces an immediate increase in PAP, initiates an inflammatory response within the first few hours of exposure[41], and sustains the inflammatory response over time[42]. There is a paradoxical increase in ROS during hypoxia which is likely due in part to the increase in numbers of inflammatory cells within the lung vasculature and parenchyma. Alveolar epithelial cells exposed to hypoxic gas signal vascular endothelial cells to release cytokines and chemokines that attract circulating macrophages. Hypoxia also induces the release of bone marrow-derived monocytic progenitor cells that are then attracted to and accumulate in the pulmonary vasculature. Once established, monocytes secrete mitogenic and fibrogenic cytokines that induce cell proliferation and fibrosis in the vascular wall resulting in progressive vascular remodeling.

As indicated above there is an increase in ROS in CH-PH. For instance, in a mouse model of CH-PH, intrapulmonary artery $O_2\bullet^-$ levels are elevated[43-45]. Moreover, the pathological changes associated with exposure to chronic hypoxia, i.e. increased intrapulmonary artery superoxide, increased PAP, RVH, and pulmonary vascular remodeling,

are abolished by administration of the antioxidant, N-acetylcysteine or the XO inhibitor, allopurinol. Xanthine oxidase levels and enzyme activities of pulmonary artery endothelial cells can be dramatically increased by exposure to hypoxia resulting in significant $O_2\bullet^-$ generation[20]. This implicates ROS, including ROS generated by the activity of XO, as important mediators of pathophysiological changes that occur in this model. Nox2 knockout mice fail to develop CH-PH which suggests a critical role for $O_2\bullet^-$ generated by Nox2 containing NADPH oxidases[44]. It is possible that an activated intrapulmonary RAS induces NADPH oxidase and XO induced oxidative stress in CH-PH rodents. Angiotensin converting enzyme (ACE) levels are selectively increased in the wall of newly muscularized arterioles, but not in whole lung homogenates of CH-PH rats[46]. Treatment of CH-PH rats with ACE inhibitors or AT_1R blockers prevent development of disease. Like the affected areas of the pulmonary vasculature, ACE expression is selectively elevated in affected areas of the RV, especially areas with pronounced fibrosis and treatment with ACE inhibitors or AT_1R blockers reduce development of RVH and fibrosis[47]. This suggests that hypoxia induces local ACE activity which generates Ang Ⅱ and that the remodeling in the pulmonary resistance arterioles and RV is mediated by local AT_1R signaling which induces several oxidant generating pathways.

Monocrotaline-induced PAH

Perhaps the most frequently used rodent model of PH is the rat monocrotaline model of PAH (MCT-PAH). MCT-PAH is often used to model the progression of RV failure[10,48,49]. MCT is a pyrrolizidine alkaloid that is administered by one time IP injection, usually at a dose of 60 mg/kg. Although the precise mechanism of action of MCT is unknown there are several published longitudinal studies describing the details of the progression of PAH and RVH[50-53]. Like CH-PH, rats injected with MCT experience a rapid intrapulmonary inflammatory response[51] with notable increases in inflammatory monocytes in the adventitia of pulmonary resistance arterioles within 8-16 h after injection. Muscularization of nonmuscularized and muscularized arterioles leading to increased medial layer thickness is detectable as early as 3 and 7 d post injection, respectively and reaches significance by 10 and 14 d, respectively[50]. A decrease in the normalized ratio of number of small arterioles to alveoli number is apparent by 21 d indicating arterial pruning. RVH is apparent by 21 d and becomes progressively more severe. A radiotelemetric monitoring study in conscious male Wistar rats showed that systolic PAP, which is normally around 35 mmHg, begins to increase by 12 d post MCT injection and rises progressively to 60-65 mmHg by 28 d[52]. Consistent with earlier studies, RVH begins to become apparent by 21 d. If rats are left untreated mortality begins to occur due to RV failure beginning around 4 wk post injection and few rats survive beyond the 5th wk following MCT injection.

The MCT-PAH model is also characterized by elevated intrapulmonary and RV superoxide levels[48,49,54-56] while there is a notable absence of oxidative stress in the LV[11]. Moreover, antioxidant therapy can attenuate development of MCT-PAH and RVH. For instance, intratracheal delivery of adenovirus containing the gene for human extracellular SOD acts as an antioxidant and ameliorates development of MCT-PAH[54]. Intraperitoneal administration of EUK-134, an SOD/catalase mimetic, also reduces oxidative stress, interstitial fibrosis, and proapoptotic signaling in the RV and improves RV function[11]. More recently it was reported that the antioxidant, resveratrol, decreased leukocyte infiltration into the pulmonary vasculature, pulmonary artery smooth muscle cell proliferation, NADPH oxidase-induced oxidative stress, and prevented the development of MCT-PAH and RVH[56]. Thus, it appears that multiple antioxidant therapies are effective at reducing progression of MCT-PAH.

Caveolin-1 Knock Out (cav-1 ko) Mouse Model of PH

eNOS is abundant in caveoli and forms a heteromeric complex with cav-1. Cav-1 bound to eNOS is a negative regulator of eNOS activity in endothelial cells while binding of Ca^{2+}-calmodulin to eNOS disrupts the eNOS-cav-1 complex resulting in eNOS activation and NO synthesis[57]. Disruption of cav-1 gene expression in cav-1 knockout mice (cav-1 ko) leads to global loss of caveoli resulting in hyperactive eNOS and excessive synthesis of NO[58]. In the lung, endothelial cells and type I pneumocytes are rich in caveoli and several studies demonstrate that the loss of appropriate eNOS regulation by cav-1 ko causes multiple complications in the pulmonary vasculature and alveolar space. Cav-1 ko mice exhibit PH, endothelial cell proliferation, endothelial dysfunction, lung fibrosis, and biventricular hypertrophy[58-60]. eNOS hyperactivation in pulmonary arterioles is marked by increased activation of Akt and eNOS leading to elevated cGMP and enhanced relaxation, as well as hyperactivation of the p42/p44ERK-MAPK pathways leading to cell proliferation and fibrosis. These fibrotic and proliferative responses are pronounced in alveolar septa and result in impaired gas exchange, arterial hypoxemia, and PH with RVH. Pulmonary defects can be reversed with either NOS blockade or targeted reexpression of cav-1 in endothelial cells[61,62]. This animal model demonstrates the critical nature of the cav-1/eNOS interaction for normal lung and myocardial function, as well as the deleterious consequences to the lung of disruption of NOS function that leads to excessive synthesis of the free radical, NO.

Neonatal models of PAH

In two lamb models of persistent PH of the newborn caused by either prenatal placement of an aortopulmonary shunt[24] or ductal ligation[63], superoxide levels become elevated in pulmonary arterioles. Superoxide is the primary oxidant responsible for oxidative stress in these models and is derived mainly from NADPH oxidase and secondarily from uncoupled eNOS. Thus, it is increasingly apparent that activation of intrapulmonary superoxide generating systems, especially the NADPH oxidases, plays

a key role in development of diverse animal models of PH.

It should be noted that most animal models of PH do not faithfully reproduce the pathophysiology observed in human PH especially in the advanced stages. Thus, extrapolating the contribution of oxidative stress in the etiology of PH in humans from animal models may be premature. Recently, a novel rodent model of PAH was developed that exhibits similar lesions in the pulmonary vasculature as occur in advanced human PAH. Upon autopsy, the pulmonary arterioles of rats given a one-time injection of a VEGF receptor blocker, exposed to hypoxia for 3 wk and returned to normoxia for 10-11 wk, exhibit concentric neointimal and plexiform lesions, similar to those observed in humans. This novel rodent model may represent the most human-like model of PAH developed to date and offer new opportunities to examine mechanisms leading to development of plexiform and other complex lesions in PAH.

Oxidative stress in humans with PH

There is evidence of oxidative stress in the lungs of patients with PH. Recently, it was shown that patients with idiopathic PAH have elevated XO activity compared to control patients and that XO activity can be reversed with treatment[64].

Immunohistochemical studies of lung biopsy samples of patients with severe PH demonstrate ubiquitous and profound elevation of 3-Nitrotyrosine. 3-Nitrotryosine is a widely used biomarker of oxidative damage caused by reaction of peroxynitrite with tyrosine residues on proteins. 3-Nitrotyrosine is also considered evidence for scavenging of NO by superoxide. Indeed, these patients have lower levels of exhaled NO than normal patients and this may be due, in part, to loss of NO that reacts with superoxide. 8-Hydroxyguanosine staining is present within the endothelial cells within plexiform and concentric lesions from patients with PAH and is absent in the pulmonary vascular endothelium of control patients[65]. 8-Hydroxyguanosine is a biomarker of oxidative damage caused by reaction of superoxide with guanine. In the lungs of the same PH patients the amount and activity of Mn-SOD was lower, indicating decreased capacity to scavenge superoxide. These data suggest that the lungs of patients with severe PH are under chronic oxidative stress[65].

Pleiotropic effects of statins could be beneficial for treatment of PAH and RVH

Since antioxidant therapy appears to be beneficial for treatment of PAH and cor pulmonale in animal models it seems reasonable to incorporate strategies that reduce the excessive activity of oxidant generating systems as adjunctive therapy. Of interest in this regard are the 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) inhibitors (statins), originally developed for their cholesterol lowering/antiatherogenic effects. Statins exhibit diverse beneficial effects in the vascular wall independent of effects on cholesterol synthesis[66,67]. Statins improve cardiovascular outcomes/risk by restoring endothelial and smooth muscle cell function, inhibiting smooth muscle cell proliferation, reducing oxidative stress and inflammation in the vascular wall, and decreasing platelet thrombogenic activity. Many of the therapeutic benefits of statins in the vasculature are the likely consequence of reduced synthesis of $O_2^{\bullet -}$ which could result in more positive regulation of cell proliferation, apoptosis, growth, migration, inflammation, extracellular matrix synthesis and degradation, differentiation and contraction[68]. Statins are associated with decreased expression of some of the NADPH oxidase subunit mRNAs and proteins, as well as increased expression of antioxidants, such as catalase[69] or heme-oxygenase-1[70]. Indeed, most statins increase lung heme-oxygenase activity in adult mice[70]. One way in which statins act to inhibit NADPH oxidase activity is by blocking Rac1 geranylation which reduces the ability of Rac1 to translocate to the membrane and interact with the NADPH oxidase complex and signal properly[71-73]. It has not been determined whether statins reduce oxidant stress in the pulmonary circulation or RV by blocking Rac1 geranylation.

Although statins display only minimal reductions in blood pressure in the hypertensive systemic circulation[74,75], recent evidence suggests that these agents may be efficacious in treating PAH. For instance, in rat models of PAH statins attenuate the development of PH, pulmonary vascular remodeling, and RVH[76-78] and in some reports reverse established PAH[79]. In rodents, statins may improve endothelial function by reversing lung eNOS dysfunction during hypoxia-induced PH[77,80] or increasing lung eNOS expression during monocrotaline-induced PAH[78,81]. We showed that rosuvastatin reverses PAH in the Ren2 rat by reducing NADPH oxidase-mediated oxidative stress in the lungs[33]. We also observed that the pulmonary arterioles of Ren2 rats have a thickened medial layer due to an increase in number, but not density, of smooth muscle cells. This raises the question whether rosuvastatin directly inhibits SMC proliferation in the pulmonary vasculature. Statins inhibit SMC proliferation through inhibiting RhoA activity by inhibiting isoprenylation of this protein which prevents translocation to the plasma membrane[82]. Rho kinase inhibitors ameliorate PAH[83]. Indeed, simvastatin reduces proliferation and increases apoptosis of neointimal and medial SMC in pulmonary arteries or rats with PAH[79]. An observational study of adjunctive simvastatin therapy in patients with severe PH suggests functional improvements in symptoms[84].

Statins are well known to improve cardiac function in animal models of heart disease[85,86], as well as in patients[87]. Although mechanistic studies suggest improved cardiac function following statin treatment is associated with improving NO signaling and reducing inflammatory mediators more recent interest focuses on a potential role for statins in promoting myocyte regeneration and myocardial repair. Statins are known to induce mobilization of endothelial progenitor cells (EPCs) which may, in part, explain their beneficial cardiovascular effects[88-90].

One recent study demonstrates that pravastatin dose-dependently increases circulating bone marrow derived progenitor cells which help to facilitate regenerating myocardium in diseased heart[90]. This is of importance because circulating bone marrow-derived EPCs are able to incorporate into the vascular wall where they may assist in repair of endothelial injury[91]. EPCs can also migrate into the myocardium where they are able to differentiate into functional cardiomyocytes[92]. Intravenous administration of syngeneic bone marrowed derived-EPCs can prevent the development of MCT-PAH in rats[93]. Delayed delivery of EPCs to rats with established MCT-PAH prevented further disease progression while disease was reversed in rats with established MCT-PAH that received EPCs transduced with eNOS. EPCs incorporated into the endothelial lining of distal pulmonary arterioles and restored microvascular structure and function. The efficacy of EPC delivery to the RV in MCT-PAH rats has not been examined. It seems reasonable to speculate that statin therapy may exhibit multiple beneficial effects in the RV that improve RV function and structure by reducing oxidative stress and promoting repair of the RV by mobilization of endothelial progenitor cells to the injured RV myocardium. Therefore, statins may be an attractive option for treatment of PAH and cor pulmonale because they may simultaneously prevent further tissue damage by decreasing oxidative stress and enhance repair to injured sites in both the pulmonary vasculature and RV.

A recent double-blind, randomized, placebo-controlled clinical trial of adjunctive simvastatin therapy in patients with PAH receiving conventional therapy demonstrated modest benefit in the form of a small and early reduction in RV mass and N-terminal pro-B-type natriuretic peptide levels, a marker of PAH; however, benefits were not sustained over a 12 mo period[94]. Whether the reduction in RV mass was secondary to a reduction in PVR is unknown as PVR was not measured in this study. The authors also noted the potential for drug interactions as conventional therapies such as sildenafil and bosentan, like statins, are substrates of CYP3A4. This raises the possibility that combination therapies could enhance or reduce the exposure to one or both drugs.

CONCLUSION

In summary, PAH is associated with a generalized state of enhanced oxidative stress. Current clinical approaches which targeted the endothelial dysfunction and vasoconstriction have not produced long-lasting mortality benefit. Thus, alternative approaches to treating this complex disease are needed. In this review, we put forward that oxidative stress plays a significant role in the pathogenesis of this disease. Some studies suggest that improvement in physiological and micrographic parameters can occur when animals are treated early with statins. For significant improvement in this patient population to occur, it is critical that early recognition of the condition be increased. In addition, clinical trials which evaluate approaches to preventing the deleterious effects of the oxidative stress which can lead to an irreversible state of pulmonary artery hypertension and resultant right ventricular failure and subsequently death must be conducted.

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