Reactive Oxygen Species and Antioxidants in Pulmonary Hypertension and Right Heart Failure

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Abstract

Pulmonary hypertension is a devastating condition, and currently available treatment options have not provided satisfactory results with regard to the prognosis of patients. Increased pulmonary arterial resistance stains the right heart, ultimately leading to right heart failure and death. Thus, new therapeutic strategies are needed. Evidence suggests that the mechanisms of the development of pulmonary hypertension, in particular pulmonary vascular remodeling, and the development of right heart remodeling involve reactive oxygen species.

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In animal models of pulmonary hypertension, various molecules with antioxidant properties have been shown to attenuate pulmonary vascular as well as right ventricular remodeling. Evidence for the benefit of antioxidant therapy in human pulmonary hypertension patients is, however, lacking. This chapter compiles information on cell, animal, and human studies that provide evidence for the role of reactive oxygen species and the beneficial effects of antioxidants in pulmonary hypertension and right heart failure.

Keywords

Antioxidants • Free radicals • Pulmonary hypertension • Pulmonary vascular remodeling • Right heart failure • Right ventricle • Reactive oxygen species

Abbreviations

Fe^{2+}	Ferrous ion
Fe^{3+}	Ferric ion
$HO^{\cdot}$	Hydroxyl radical
H_2O_2	Hydrogen peroxide
O_2	Molecular oxygen
$O_2^{\bullet-}$	Superoxide anion radical
PAH	Pulmonary arterial hypertension
ROS	Reactive oxygen species
RV	Right ventricle
SOD	Superoxide dismutase

Pulmonary Hypertension

Pulmonary hypertension is a clinical condition defined by the elevation of mean pulmonary arterial pressure $\geq$25 mmHg with normal pulmonary wedge pressure (PWP $\leq$ 15 mmHg). The term "pulmonary hypertension" represents a collection of various diseases with this hemodynamic definition (Galiè et al. 2009a; Chemla et al. 2002). Pulmonary arterial hypertension (PAH) (Group 1) includes idiopathic PAH, heritable PAH, PAH induced by drugs and toxins, persistent pulmonary hypertension of the newborn, and PAH associated with various diseases such as connective tissue diseases, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, and chronic hemolytic anemia. Pulmonary hypertension is also associated with hypoxic lung diseases such as chronic obstructive pulmonary disease and lung fibrosis (Group 3) and often worsens the prognosis of these primary diseases. Other classes of pulmonary hypertension include pulmonary hypertension due to left heart dysfunction (Group 2), chronic thromboembolic pulmonary hypertension (Group 4), pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis (Group 1), and diverse forms of pulmonary hypertension with unclear and/or multifactorial mechanisms (associated with myeloproliferative disorders, splenectomy, sarcoidosis, and other rare medical conditions) (Group 5) (Simonneau et al. 2004; Galiè et al. 2009a).

The increased pulmonary arterial pressure and resistance strain the right ventricle (RV), initially causing compensatory concentric RV hypertrophy, which in turn transitions to right-sided heart failure and death (Nauser and Stites 2003; Farber and Loscalzo 2004). The median survival for patients with PAH has been reported to be 2.8 years from the time of diagnosis without treatment (Runo and Loyd 2003). Even with currently available therapies, the prognosis remains poor, with a 3 year survival of PAH patients reported to be 58–75 % (Benza et al. 2010; Humbert et al. 2010; Thenappan et al. 2010).

Pulmonary hypertension is characterized by vasoconstriction within the pulmonary vasculature and histological abnormalities of the vascular wall, including medial hypertrophy, intimal proliferation, fibrosis, adventitial thickening, thrombotic lesions, and inflammatory infiltrates (Morrell et al. 2009; Humbert et al. 2004; Sweeney and Yuan 2000; Mandegar and Yuan 2002). In advanced stages of PAH, all of these characteristics are present in complex plexiform lesions.

Various biochemical pathways lead to vasoconstriction of pulmonary arteries and increased pulmonary vascular resistance, in part due to the abnormal production of vasoactive compounds. Increased vasoconstriction could also be due to abnormal expression and function of the potassium channels in pulmonary vascular smooth muscles cells (SMCs) (Burg et al. 2008). Endothelial dysfunction causes overexpression of vasoconstrictive and proliferative substances such as endothelin-1 and thromboxane A2 (Humbert et al. 2008). In addition, the levels of vasodilators and antiproliferative agents such as nitric oxide and prostacyclin are decreased. These abnormalities elevate the vascular tone and promote vascular thickening through the proliferation and hypertrophy of endothelial cells, SMCs, and fibroblasts. Inflammatory cells may also play an important role, since perivascular inflammatory infiltrates are present in lungs with pulmonary hypertension (Hassoun et al. 2009). However, the exact pathogenetic pathways that lead to these features are unknown.

Currently Available Therapy for Pulmonary Hypertension

Despite significant progress in treatment options in the last decade, pulmonary hypertension remains a serious lethal condition. Currently used drugs reduce symptoms, but mortality due to pulmonary hypertension remains high (Galiè et al. 2009b). Several groups of vasodilators are used as treatment strategies for pulmonary hypertension. Calcium channel blockers are the first group used in the therapy; however, only a small number of patients respond to this treatment (Sitbon et al. 2005). Three classes of drugs have been specifically approved to treat PAH (Group I). Among them, prostanoids are the most potent drugs in the treatment of PAH (Galiè et al. 2003; Safdar 2011). This class of agents, however, is not stable, and therefore, they often need to be applied continuously through an intravenous route. Prostanoids have also been used clinically and can be administered subcutaneously and through inhalation as well. However, the oral prostanoid, beraprost, does not provide a significant hemodynamic benefit (Galiè et al. 2002;

Barst et al. 2003). Endothelin-1 receptor antagonists and phosphodiesterase-5 inhibitors are oral vasodilators used in PAH (Galiè et al. 2004; Ghofrani et al. 2004). There is still a need for new efficient therapies that reverse the features associated with advanced stages of this disease and decrease the mortality associated with PAH. Therapies to prevent and/or treat other forms of pulmonary hypertension are also needed. In addition, there are currently no specific therapies available to prevent and/or treat right heart failure.

In this chapter, evidence for the role of free radicals and the beneficial effects of antioxidants in pulmonary hypertension and right heart failure is presented.

Reactive Oxygen Species (ROS) and Antioxidants

Sequential electron reduction of molecular oxygen (O_2) produces ROS. One-electron reduction produces superoxide anion radical ($O_2^{\bullet -}$), two-electron reduction produces hydrogen peroxide (H_2O_2), and three-electron reduction results in the formation of hydroxyl radical ($HO^{\cdot}$). $O_2^{\bullet -}$ is formed through various means in the biological system including enzymes such as xanthine oxidase and NADPH oxidase, which perform one-electron reduction of O_2 to form $O_2^{\bullet -}$. H_2O_2 is often formed through the dismutation reaction, in which two molecules of $O_2^{\bullet -}$ interact with each other to donate/accept an electron. In this reaction, the $O_2^{\bullet -}$ molecule, which receives an electron, becomes H_2O_2. In the biological system, the source of the electron that reduces H_2O_2 to $HO^{\cdot}$ includes reduced metal irons and in particular iron ions in the Fenton reaction. Iron ions are normally present in the cytosol in oxidized form as ferric ion (Fe^{3+}). Thus, reduction of ferric to ferrous ion (Fe^{2+}) is required to elicit the Fenton reaction and $HO^{\cdot}$ formation (Freeman and Crapo 1982; Halliwell and Gutteridge 1985; Suzuki and Ford 1994).

Traditionally, ROS have been thought to nonspecifically and indiscriminately react with biological molecules and cause damage to biologic events (Halliwell and Gutteridge 1985). However, during the early 1990s, it was observed that (1) ligand-receptor interactions produce ROS, (2) antioxidants block signal transduction, and (3) ROS can stimulate signaling events; therefore, ROS have been proposed to serve as second messengers (Schreck et al. 1991; Suzuki and Ford 1992; Sen and Packer 1996; Wolin 1996; Suzuki et al. 1997). Notably, Schreck et al. (1991) proposed that H_2O_2 was a second messenger for the activation of NF-κB transcription factor in T cells. In vascular smooth muscle cells of systemic circulation, Rao and Berk (1992) demonstrated that ROS promote cell growth. Subsequently, ROS were reported to mediate signal transduction induced by angiotensin II in these cells (Griendling et al. 1994) and platelet-derived growth factor (Sundaresan et al. 1995) through NADPH oxidase. The concept of the role of ROS in cell signal transduction has been supported by a large number of studies and is now widely accepted (Sen and Packer 1996; Wolin 1996; Suzuki et al. 1997; Rhee et al. 2000; Forman et al. 2010).

The term "antioxidant" can be broadly defined as any molecule that can inhibit the formation and actions of ROS. These molecules could (1) inhibit the production

of ROS (e.g., inhibitors of oxidases), (2) directly scavenge ROS, (3) scavenge other reactive substances that may be produced in response to the actions and reactions of ROS, (4) chelate metal ions such as iron to inhibit Fenton reaction, and (5) promote the expression of antioxidant proteins.

Oxidative Stress and Antioxidant Status in Human Pulmonary Hypertension

In humans, several reports have provided evidence for increased oxidation in pulmonary hypertension. Patients with pulmonary hypertension were found to have increased lipid peroxidation compared to healthy control subjects as indicated by the gas chromatography/mass spectrometry measurements of urine isoprostane levels (Cracowski et al. 2001) and plasma malondialdehyde (Irodova et al. 2002). Bowers et al. (2004) reported that lungs from idiopathic PAH patients had increased DNA oxidation levels based on measurements of 8-hydroxyl guanosine levels as well as increased nitrotyrosine levels. Our laboratory has shown that plasma from patients with idiopathic PAH has increased protein carbonyl content (Wong et al. 2012) and reduced levels of lipophilic antioxidants, including alpha-tocopherol and beta-carotene (Preston et al. 2005), compared to control subjects. Plasma from idiopathic PAH patients was also found to contain malondialdehyde-modified albumin (Odhiambo et al. 2007). In lung tissues, superoxide dismutase 2 expression is lower in patients with PAH compared to control subjects (Bowers et al. 2004; Archer et al. 2010).

Role of ROS and the Effects of Antioxidants in Animal Models of Pulmonary Hypertension

Gillespie and coworkers in piglets provided early evidence for the role of ROS and the effectiveness of antioxidant molecules in pulmonary hypertension. Pulmonary hypertension induced by group B streptococcus was attenuated by a $HO^{\cdot}$ scavenger dimethylthiourea (Pauly et al. 1988; Bowdy et al. 1990) and bilirubin (Pauly et al. 1991). Dimethylthiourea also reversed sepsis-induced pulmonary hypertension (Shook et al. 1990). In rats, pulmonary hypertension was found to be inhibited by compounds thought to have reactive oxygen scavenging activities including dimethylthiourea (Langleben et al. 1989; Lai et al. 1998), probucol (Irukayama-Tomobe et al. 2000), N-acetylcysteine (Hoshikawa et al. 2001; Lachmanová et al. 2005), tempol (Elmedal et al. 2004; Jankov et al. 2008), erdosteine (Uzun et al. 2006), allicin (Sun and Ku 2006), pyrrolidine dithiocarbamate (Sawada et al. 2007; Huang et al. 2008), sulfur dioxide (Jin et al. 2008), resveratrol (Csiszar et al. 2009; Yang et al. 2010), and EUK-134 (Redout et al. 2010). However, many of these antioxidants are weak and nonspecific.

More specific antioxidant enzymes, particularly superoxide dismutase (SOD), have also been shown to be effective as well. Abman and coworkers

(Kinsella et al. 2005) demonstrated that SOD improves hemodynamics. Steinhorn and coworkers reported that SOD improves oxygenation and reduces oxidation (Lakshminrusimha et al. 2006), restores eNOS expression and function (Farrow et al. 2008), and normalizes phosphodiesterase 5 (Farrow et al. 2010) in neonatal lambs with persistent pulmonary hypertension. Gene transfer of extracellular SOD has also been shown to reduce pulmonary hypertension in rats (Kamezaki et al. 2008).

The inhibitors of the production of ROS are also effective in ameliorating pulmonary hypertension. Jankov et al. (2008) showed that a xanthine oxidase inhibitor, allopurinol, inhibits chronic hypoxic pulmonary hypertension in neonatal rats. In fetal lambs, the roles of uncoupled nitric oxide synthase-generated ROS in pulmonary hypertension were also documented (Konduri et al. 2007; Lakshminrusimha et al. 2007).

Accumulating evidence suggests that NADPH oxidase has a role in the development of pulmonary hypertension, and thus the inhibitors of NADPH oxidase may be promising as therapeutic agents. Black and coworkers (Brennan et al. 2003; Grobe et al. 2006) first proposed the role of NADPH oxidase in fetal lambs with pulmonary hypertension. Foltz and coworkers (Liu et al. 2006) reported that chronic hypoxia-induced pulmonary hypertension was inhibited in $gp91^{phox}$ knockout mice. The involvement of NADPH oxidase in pulmonary hypertension was also observed in newborn piglets (Dennis et al. 2009) and mice (Nisbet et al. 2009). More recently, NOX4 has specifically emerged as an important mediator of ROS generation and the development of various forms of pulmonary hypertension (Sturrock et al. 2006; Mittal et al. 2007; Gosemann et al. 2013; Wedgwood et al. 2013). In cultured pulmonary vascular cells, the NOX4 inhibitor GKT137831 attenuated hypoxia-induced cell proliferation (Green et al. 2012).

ROS in Endothelin-1 Signaling

Endothelin-1, a peptide composed of 21 amino acids, is a potent vasoconstrictor originally identified in vascular endothelial cells (Yanagisawa et al. 1988). Plasma endothelin-1 is elevated in patients with idiopathic PAH (Stewart et al. 1991; Giaid et al. 1993). Histological studies of lung tissues from patients with pulmonary hypertension demonstrated excess endothelin-1 production and increased expression of prepro-endothelin-1 (Giaid et al. 1993). Similarly, increased endothelin-1 expression was found in the lungs of fawn-hooded rats with pulmonary hypertension (Zamora et al. 1996). In secondary pulmonary hypertension, plasma levels of endothelin-1 are positively correlated with the severity of the disease and negatively correlated with prognosis (Yoshibayashi et al. 1991; Cody et al. 1992). In various animal models of secondary pulmonary hypertension, endothelin-receptor antagonists have been shown to block the progression of the disease (Miyauchi et al. 1993; Bonvallet et al. 1994; Okada et al. 1995; Eddahibi et al. 1995; Sakai et al. 1996; Ueno et al. 2000). Human studies have shown that an endothelin-receptor antagonist bosentan increased exercise capacity and improved hemodynamics in patients with pulmonary hypertension (Channick et al. 2001; Rubin et al. 2002).

Bosentan has been approved for the treatment of human PAH, indicating the importance of understanding endothelin-1 signaling to develop better therapeutic agents to treat pulmonary hypertension. Other endothelin-receptor antagonists with different receptor specificities were also approved later and show similar treatment efficacy (Barst et al. 2004, 2006; Galiè et al. 2005).

Endothelin-1 is a mitogen of pulmonary artery SMCs (Hirata et al. 1989; Hassoun et al. 1992; Janakidevi et al. 1992). Activation of either ET_A or ET_B receptor can induce proliferation of human pulmonary artery SMCs (Davie et al. 2002). Endothelin-1 has also been shown to promote cell survival (antiapoptotic) signaling in pulmonary artery SMCs (Suzuki et al. 2007).

Wedgwood et al. (2001) reported that endothelin-1 induces the production of ROS in pulmonary artery SMCs of fetal sheep through NADPH oxidase and antioxidants block endothelin-1-induced cell proliferation. Our laboratory found that, in bovine and human pulmonary artery SMCs, endothelin-1, serotonin, and PDGF promote protein carbonylation, which may mediate oxidant signaling (Wong et al. 2008; Wong et al. 2012). Proteomic analysis revealed that one protein that is carbonylated in response to endothelin-1 is annexin A1 (Wong et al. 2008). This protein possesses antiproliferative and apoptotic activities and, upon oxidative modifications, is degraded by proteasomes. The loss of annexin A1 results in increased cell growth and survival (Fig. 74.1).

ROS in Serotonin Signaling

Serotonin (5-hydroxytryptamine) is a potent vasoconstrictor and a mitogen of pulmonary artery SMCs. Evidence for the role of serotonin in the development of pulmonary hypertension was first recognized in fawn-hooded rats, in which a genetic deficit in serotonin platelet storage and high plasma levels of serotonin were associated with the development of pulmonary hypertension (Sato et al. 1992). Further studies showed that a continuous intravenous infusion of serotonin during the exposure of rats to hypoxia potentiated pulmonary hypertension (Eddahibi et al. 1997). Serotonin transporter-deficient mice also have been shown to develop less hypoxic pulmonary hypertension and vascular remodeling due to the inability of serotonin to promote SMC growth (Eddahibi et al. 2000). In patients with idiopathic PAH, high levels of plasma serotonin were detected (Herve et al. 1995). Eddahibi et al. (2001) reported that pulmonary artery SMCs from patients with pulmonary hypertension grow faster than cells from control subjects in response to serotonin. The mechanism of pulmonary artery SMC growth has been reported to involve both serotonin transporter (Lee et al. 1994) and serotonin receptors (Liu et al. 2004).

In bovine pulmonary artery SMCs, Fanburg and coworkers reported that serotonin uptake by serotonin transporter activates NADPH oxidase and the production of $O_2^{\bullet -}$ (Lee et al. 1998, 1999) and H_2O_2 (Lee et al. 2001). They proposed that ROS are involved in serotonin-induced growth of pulmonary artery smooth muscle cells by activating the MEK/ERK pathway (Fig. 74.2). We have shown that the GATA4

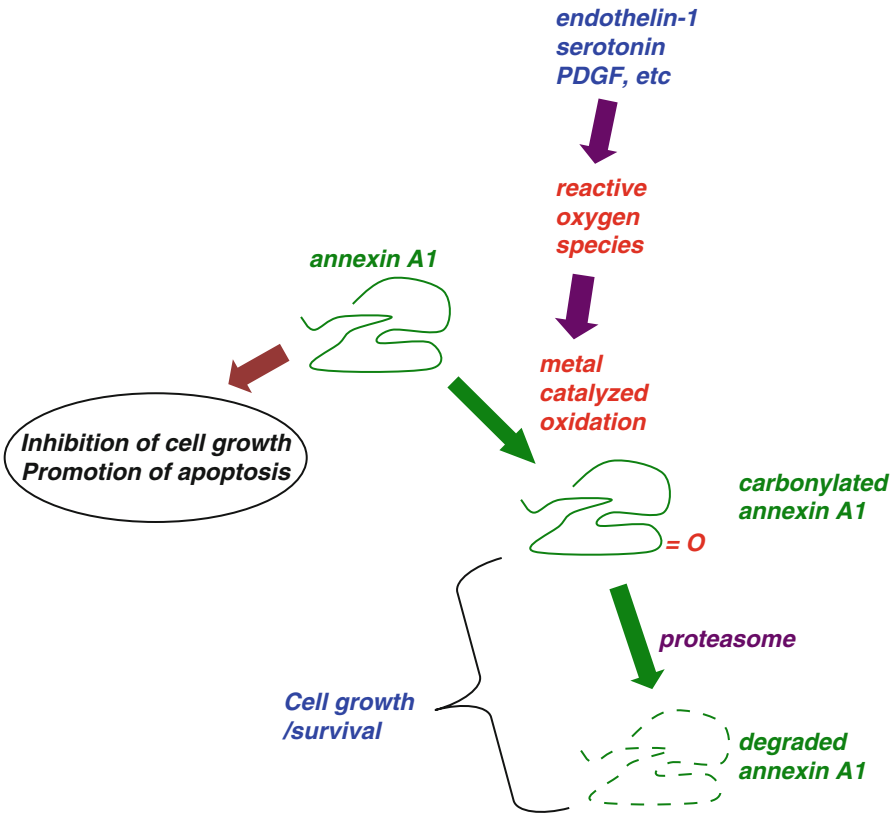

Fig. 74.1 Protein carbonylation-dependent mechanism of ROS signaling in pulmonary artery smooth muscle cells proposed by Suzuki and coworkers. Mediators of pulmonary vascular remodeling such as endothelin-1, serotonin, and PDGF promote the production of reactive oxygen species. Metal-catalyzed production of hydroxyl radicals results in carbonylation of annexin A1, which normally functions as an antiproliferative and apoptotic protein. Carbonylated annexin A1 gets degraded by the proteasome, resulting in increased cell growth and survival

transcription factor plays an important role in pulmonary artery SMC growth regulation and antioxidants inhibit serotonin-induced GATA4 activation (Suzuki et al. 2003). In human pulmonary artery SMCs, Lawrie et al. (2005) found that serotonin activates GATA4 through ROS produced by monoamine oxidase A.

ROS and Right Heart Failure

In addition to the role of ROS in the pulmonary vasculature, these species may also mediate the development of RV hypertrophy and right heart failure. Thus, antioxidant-based therapies to prevent and/or treat pulmonary hypertension-induced heart

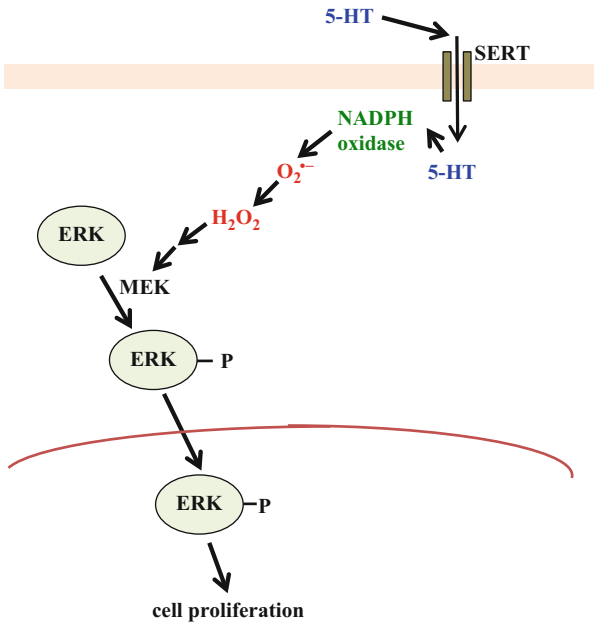

Fig. 74.2 The mechanism of serotonin signaling for the proliferation of pulmonary artery smooth muscle cells proposed by Fanburg and coworkers. Serotonin (*5-HT*) uptake by the serotonin transporter (*SERT*) activates *NADPH* oxidase and produces reactive oxygen species, which activate the *MEK*/*ERK* pathway for cell proliferation

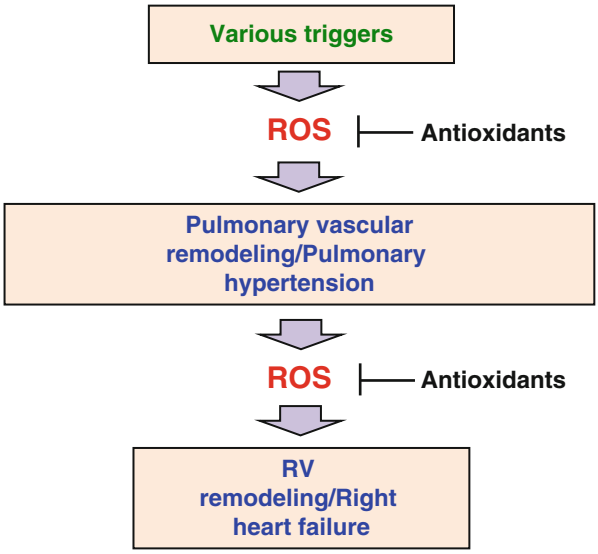

Fig. 74.3 A simplistic view of the proposed roles of ROS and the effects of antioxidants. Various triggers promote the pathogenesis of pulmonary hypertension. These triggers activate the generation of ROS, which in turn contribute to the development of pulmonary vascular remodeling and pulmonary hypertension. Increased pulmonary vascular pressure also promotes the production of ROS, which contribute to RV remodeling and subsequent right heart failure

failure may be possible. During the transition to heart failure, ROS are produced but RV is not able to activate antioxidant defenses (Ecarnot-Laubriet et al. 2003). RV antioxidant enzymes are increased during hypertrophy and decreased during right heart failure in rats (Farahmand et al. 2004). Redout et al. (2007, 2010) have shown

that right heart failure due to monocrotaline-induced pulmonary hypertension increased the ROS production in rats and treatment with the antioxidant EUK-134 attenuated right heart failure. In the SU5416/hypoxia model of pulmonary hypertension and right heart failure in rats, Protandim, which is a plant extract that induces Nrf2-dependent promotion of endogenous antioxidant defenses, has been shown to prevent fibrosis and capillary loss in the RV and preserved RV function (Bogaard et al. 2009).

Our laboratory reported that ROS activate the CBF/NF-Y transcription factor, thereby triggering a right heart-specific activation of hypertrophic responses (Park et al. 2010). In addition, treating perfused isolated rat hearts with serotonin promoted protein carbonylation, specifically in the RV, but not in the left ventricle (Liu et al. 2008). These differential responses to serotonin between RV and left ventricle may be defined by the low expression of monoamine oxidase A in the RV compared to the left ventricle, which may preserve the cytosolic level of serotonin and the ability of serotonin to produce $O_2^{\bullet -}$ through NADPH oxidase (Liu et al. 2008). These results suggest that ROS signaling regulates pulmonary hypertension-induced RV hypertrophy and right heart failure.

Conclusions

Evidence suggests that the production of ROS plays an important role in the pathogenesis of pulmonary hypertension as well as right heart failure. As described above, studies using various animal models have shown that compounds with antioxidant properties are effective in inhibiting pulmonary hypertension. Evidence for the benefit of antioxidant therapy in human pulmonary hypertension is, however, lacking. Since currently available treatment options for pulmonary hypertension do not bring satisfactory results on the prognosis of patients, new therapeutic strategies are needed. Many antioxidants have been proven to be safe in humans. Based on results from animal studies, effects of antioxidants in the treatment of pulmonary hypertension should be explored in humans. Since animal data show that antioxidants have antiproliferative actions on remodeled pulmonary arteries, the antioxidant therapy may inhibit the progression of the disease and possibly reverse pulmonary vascular remodeling. In addition, antioxidants may prevent the transition from compensatory RV hypertrophy to heart failure. Thus, the use of antioxidants may be a new reinforcement in the complex therapy for pulmonary hypertension that could improve the prognosis of patients (Fig. 74.3). Thus, further understanding of the mechanisms of ROS involvement in the pulmonary circulation and the right heart should guide more effective human clinical trials.

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References

Archer SL, Marsboom G, Kim GH, Zhang HJ, Toth PT, Svensson EC, Dyck JR, Gomberg-Maitland M, Thébaud B, Husain AN, Cipriani N, Rehman J (2010) Epigenetic attenuation of mitochondrial superoxide dismutase 2 in pulmonary arterial hypertension: a basis for excessive cell proliferation and a new therapeutic target. Circulation 121:2661–2671

Barst RJ, McGoon M, McLaughlin V, Tapson V, Rich S, Rubin L, Wasserman K, Oudiz R, Shapiro S, Robbins IM, Channick R, Badesch D, Rayburn BK, Flinchbaugh R, Sigman J, Arneson C, Jeffs R, Beraprost Study Group (2003) Beraprost therapy for pulmonary arterial hypertension. J Am Coll Cardiol 41:2119–2125

Barst RJ, Langleben D, Frost A, Horn EM, Oudiz R, Shapiro S, McLaughlin V, Hill N, Tapson VF, Robbins IM, Zwicke D, Duncan B, Dixon RA, Frumkin LR, STRIDE-1 Study Group (2004) Sitaxsentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med 169:441–447

Barst RJ, Langleben D, Badesch D, Frost A, Lawrence EC, Shapiro S, Naeije R, Galiè N (2006) Treatment of pulmonary arterial hypertension with the selective endothelin-a receptor antagonist sitaxsentan. J Am Coll Cardiol 47:2049–2056

Benza RL, Miller DP, Frost A, Barst RJ, Krichman AM, McGoon MD (2010) Analysis of the lung allocation score estimation of risk of death in patients with pulmonary arterial hypertension using data from the REVEAL registry. Transplantation 90:298–305

Bogaard HJ, Natarajan R, Henderson SC, Long CS, Kraskauskas D, Smithson L, Ockaili R, McCord JM, Voelkel NF (2009) Chronic pulmonary artery pressure elevation is insufficient to explain right heart failure. Circulation 120:1951–1960

Bonvallet ST, Zamora MR, Hasunuma K, Sato K, Hanasato N, Anderson D, Sato K, Stelzner TJ (1994) BQ123, an ETA-receptor antagonist, attenuates hypoxic pulmonary hypertension in rats. Am J Physiol 266:H1327–H1331

Bowdy BD, Marple SL, Pauly TH, Coonrod JD, Gillespie MN (1990) Oxygen radical-dependent bacterial killing and pulmonary hypertension in piglets infected with group B streptococci. Am Rev Respir Dis 141:648–653

Bowers R, Cool C, Murphy RC, Tuder RM, Hopken MW, Flores SC, Voelkel NF (2004) Oxidative stress in severe pulmonary hypertension. Am J Respir Crit Care Med 169:764–769

Brennan LA, Steinhorn RH, Wedgwood S, Mata-Greenwood E, Roark EA, Russell JA, Black SM (2003) Increased superoxide generation is associated with pulmonary hypertension in fetal lambs: a role for NADPH oxidase. Circ Res 92:683–691

Burg ED, Remillard CV, Yuan JX (2008) Potassium channels in the regulation of pulmonary artery smooth muscle cell proliferation and apoptosis: pharmacotherapeutic implications. Br J Pharmacol 153(Suppl 1):S99–S111

Channick RN, Simonneau G, Sitbon O, Robbins IM, Frost A, Tapson VF, Badesch DB, Roux S, Rainisio M, Bodin F, Rubin LJ (2001) Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet 358:1119–1123

Chemla D, Castelain V, Herve P, Lecarpentier Y, Brimioulle S (2002) Haemodynamic evaluation of pulmonary hypertension. Eur Respir J 20:1314–1331

Cody RJ, Haas GJ, Binkley PF, Capers Q, Kelley R (1992) Plasma endothelin correlates with the extent of pulmonary hypertension in patients with chronic congestive heart failure. Circulation 85:504–509

Cracowski JL, Cracowski C, Bessard G, Pepin JL, Bessard J, Schwebel C, Stanke-Labesque F, Pison C (2001) Increased lipid peroxidation in patients with pulmonary hypertension. Am J Respir Crit Care Med 164:1038–1042

Csiszar A, Labinskyy N, Olson S, Pinto JT, Gupte S, Wu JM, Hu F, Ballabh P, Podlutsky A, Losonczy G, de Cabo R, Mathew R, Wolin MS, Ungvari Z (2009) Resveratrol prevents monocrotaline-induced pulmonary hypertension in rats. Hypertension 54:668–675

Davie N, Haleen SJ, Upton PD, Polak JM, Yacoub MH, Morrell NW, Wharton J (2002) ET_A and ET_B receptors modulate the proliferation of human pulmonary artery smooth muscle cells. Am J Respir Crit Care Med 165:398–405

Dennis KE, Aschner JL, Milatovic D, Schmidt JW, Aschner M, Kaplowitz MR, Zhang Y, Fike CD (2009) NADPH oxidases and reactive oxygen species at different stages of chronic hypoxia-induced pulmonary hypertension in newborn piglets. Am J Physiol Lung Cell Mol Physiol 297: L596–L607

Ecarnot-Laubriet A, Rochette L, Vergely C, Sicard P, Teyssier JR (2003) The activation pattern of the antioxidant enzymes in the right ventricle of rat in response to pressure overload is of heart failure type. Heart Dis 5:308–312

Eddahibi S, Raffestin B, Clozel M, Levame M, Adnot S (1995) Protection from pulmonary hypertension with an orally active endothelin receptor antagonist in hypoxic rats. Am J Physiol 268:H828–H835

Eddahibi S, Raffestin B, Pham I, Launay JM, Aegerter P, Sitbon M, Adnot S (1997) Treatment with 5-HT potentiates development of pulmonary hypertension in chronically hypoxic rats. Am J Physiol 272:H1173–H1181

Eddahibi S, Hanoun N, Lanfumey L, Lesch KP, Raffestin B, Hamon M, Adnot S (2000) Attenuated hypoxic pulmonary hypertension in mice lacking the 5-hydroxytryptamine transporter gene. J Clin Invest 105:1555–1562

Eddahibi S, Humbert M, Fadel E, Raffestin B, Darmon M, Capron F, Simonneau G, Dartevelle P, Hamon M, Adnot S (2001) Serotonin transporter overexpression is responsible for pulmonary artery smooth muscle hyperplasia in primary pulmonary hypertension. J Clin Invest 198:1141–1150

Elmedal B, de Dam MY, Mulvany MJ, Simonsen U (2004) The superoxide dismutase mimetic, tempol, blunts right ventricular hypertrophy in chronic hypoxic rats. Br J Pharmacol 141:105–113

Farahmand F, Hill MF, Singal PK (2004) Antioxidant and oxidative stress changes in experimental cor pulmonale. Mol Cell Biochem 260:21–29

Farber HW, Loscalzo J (2004) Pulmonary arterial hypertension. N Engl J Med 351:1655–1665

Farrow KN, Lakshminrusimha S, Reda WJ, Wedgwood S, Czech L, Gugino SF, Davis JM, Russell JA, Steinhorn RH (2008) Superoxide dismutase restores eNOS expression and function in resistance pulmonary arteries from neonatal lambs with persistent pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol 295:L979–L987

Farrow KN, Lakshminrusimha S, Czech L, Groh BS, Gugino SF, Davis JM, Russell JA, Steinhorn RH (2010) SOD and inhaled nitric oxide normalize phosphodiesterase 5 expression and activity in neonatal lambs with persistent pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol 299:L109–L116

Forman HJ, Maiorino M, Ursini F (2010) Signaling functions of reactive oxygen species. Biochemistry 49:835–842

Freeman BA, Crapo JD (1982) Biology of disease: free radicals and tissue injury. Lab Invest 47:412–426

Galiè N, Humbert M, Vachiery JL, Vizza CD, Kneussl M, Manes A, Sitbon O, Torbicki A, Delcroix M, Naeije R, Hoeper M, Chaouat A, Morand S, Besse B, Simonneau G (2002) Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind placebo-controlled trial. J Am Coll Cardiol 39:1496–1502

Galiè N, Manes A, Branzi A (2003) Prostanoids for pulmonary arterial hypertension. Am J Respir Med 2:123–137

Galiè N, Manes A, Branzi A (2004) The endothelin system in pulmonary arterial hypertension. Cardiovasc Res 61:227–237

Galiè N, Badesch D, Oudiz R, Simonneau G, McGoon MD, Keogh AM, Frost AE, Zwicke D, Naeije R, Shapiro S, Olschewski H, Rubin LJ (2005) Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol 46:529–535

Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G, ESC Committee for Practice Guidelines (CPG) (2009a) Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 30:2493–2537

Galiè N, Manes A, Negro L, Palazzini M, Bacchi-Reggiani ML, Branzi A (2009b) A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. Eur Heart J 30:394–403

Ghofrani HA, Voswinckel R, Reichenberger F, Olschewski H, Haredza P, Karadas B, Schermuly RT, Weissmann N, Seeger W, Grimminger F (2004) Differences in hemodynamic and oxygenation responses to three different phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension: a randomized prospective study. J Am Coll Cardiol 44:1488–1496

Giaid A, Yanagisawa M, Langleben D, Michel RP, Levy R, Shennib H, Kimura S, Masaki T, Duguid WP, Steward DJ (1993) Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med 328:1732–1739

Gosemann JH, Friedmacher F, Hunziker M, Alvarez L, Corcionivoschi N, Puri P (2013) Increased activation of NADPH oxidase 4 in the pulmonary vasculature in experimental diaphragmatic hernia. Pediatr Surg Int 29:3–8

Green DE, Murphy TC, Kang BY, Kleinhenz JM, Szyndralewiez C, Page P, Sutliff RL, Hart CM (2012) The Nox4 inhibitor GKT137831 attenuates hypoxia-induced pulmonary vascular cell proliferation. Am J Respir Cell Mol Biol 47:718–726

Griendling KK, Minieri CA, Ollerenshaw JD, Alexander RW (1994) Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. Circ Res 74:1141–1148

Grobe AC, Wells SM, Benavidez E, Oishi P, Azakie A, Fineman JR, Black SM (2006) Increased oxidative stress in lambs with increased pulmonary blood flow and pulmonary hypertension: role of NADPH oxidase and endothelial NO synthase. Am J Physiol Lung Cell Mol Physiol 290:L1069–L1077

Halliwell B, Gutteridge J (1985) Free radicals in biology and medicine. Oxford University Press, Oxford

Hassoun PM, Thappa V, Landman MJ, Fanburg BL (1992) Endothelin 1: mitogenic activity on pulmonary artery smooth muscle cells and release from hypoxic endothelial cells. Proc Soc Exp Biol Med 199:165–170

Hassoun PM, Mouthon L, Barbera JA, Eddahibi S, Flores SC, Grimminger F, Jones PL, Maitland ML, Michelakis ED, Morrell NW, Newman JH, Rabinovitch M, Schermuly R, Stenmark KR, Voelkel NF, Yuan JX, Humbert M (2009) Inflammation, growth factors, and pulmonary vascular remodeling. J Am Coll Cardiol 54:S10–S19

Herve P, Launay JM, Scrobohaci ML, Brenot F, Simonneau G, Petitpretz P, Poubeau P, Cerrina J, Duroux P, Drouet L (1995) Increased plasma serotonin in primary pulmonary hypertension. Am J Med 99:249–254

Hirata Y, Takagi Y, Fukuda Y, Marumo F (1989) Endothelin is a potent mitogen for rat vascular smooth muscle cells. Atherosclerosis 78:225–228

Hoshikawa Y, Ono S, Suzuki S, Tanita T, Chida M, Song C, Noda M, Tabata T, Voelkel NF, Fujimura S (2001) Generation of oxidative stress contributes to the development of pulmonary hypertension induced by hypoxia. J Appl Physiol 90:1299–1306

Huang J, Kaminski PM, Edwards JG, Yeh A, Wolin MS, Frishman WH, Gewitz MH, Mathew R (2008) Pyrrolidine dithiocarbamate restores endothelial cell membrane integrity and attenuates monocrotaline-induced pulmonary artery hypertension. Am J Physiol Lung Cell Mol Physiol 294:L1250–L1259

Humbert M, Morrell NW, Archer SL, Stenmark KR, MacLean MR, Lang IM, Christman BW, Weir EK, Eickelberg O, Voelkel NF, Rabinovitch M (2004) Cellular and molecular pathobiology of pulmonary arterial hypertension. J Am Coll Cardiol 43:S13–S24

Humbert M, Montani D, Perros F, Dorfmüller P, Adnot S, Eddahibi S (2008) Endothelial cell dysfunction and cross talk between endothelium and smooth muscle cells in pulmonary arterial hypertension. Vascul Pharmacol 49:113–118

Humbert M, Sitbon O, Yaïci A, Montani D, O'Callaghan DS, Jaïs X, Parent F, Savale L, Natali D, Günther S, Chaouat A, Chabot F, Cordier JF, Habib G, Gressin V, Jing ZC, Souza R, Simonneau G, French Pulmonary Arterial Hypertension Network (2010) Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. Eur Respir J 36:549–555

Irodova NL, Lankin VZ, Konovalova GK, Kochetov AG, Chazova IE (2002) Oxidative stress in patients with primary pulmonary hypertension. Bull Exp Biol Med 133:580–582

Irukayama-Tomobe Y, Sakai S, Miyauchi T (2000) Chronic treatment with probucol effectively inhibits progression of pulmonary hypertension in rats. Life Sci 67:2017–2023

Janakidevi K, Fisher MA, Del Vecchio PJ, Tiruppathi C, Figge J, Malik AB (1992) Endothelin-1 stimulates DNA synthesis and proliferation of pulmonary artery smooth muscle cells. Am J Physiol 263:C1295–C1301

Jankov RP, Kantores C, Pan J, Belik J (2008) Contribution of xanthine oxidase-derived superoxide to chronic hypoxic pulmonary hypertension in neonatal rats. Am J Physiol Lung Cell Mol Physiol 294:L233–L245

Jin HF, Du SX, Zhao X, Wei HL, Wang YF, Liang YF, Tang CS, Du JB (2008) Effects of endogenous sulfur dioxide on monocrotaline-induced pulmonary hypertension in rats. Acta Pharmacol Sin 29:1157–1166

Kamezaki F, Tasaki H, Yamashita K, Tsutsui M, Koide S, Nakata S, Tanimoto A, Okazaki M, Sasaguri Y, Adachi T, Otsuji Y (2008) Gene transfer of extracellular superoxide dismutase ameliorates pulmonary hypertension in rats. Am J Respir Crit Care Med 177:219–226

Kinsella JP, Parker TA, Davis JM, Abman SH (2005) Superoxide dismutase improves gas exchange and pulmonary hemodynamics in premature lambs. Am J Respir Crit Care Med 172:745–749

Konduri GG, Bakhutashvili I, Eis A, Pritchard K Jr (2007) Oxidant stress from uncoupled nitric oxide synthase impairs vasodilation in fetal lambs with persistent pulmonary hypertension. Am J Physiol Heart Circ Physiol 292:H1812–H1820

Lachmanová V, Hnilicková O, Povýsilová V, Hampl V, Herget J (2005) N-acetylcysteine inhibits hypoxic pulmonary hypertension most effectively in the initial phase of chronic hypoxia. Life Sci 77:175–182

Lai YL, Wu HD, Chen CF (1998) Antioxidants attenuate chronic hypoxic pulmonary hypertension. J Cardiovasc Pharmacol 32:714–720

Lakshminrusimha S, Russell JA, Wedgwood S, Gugino SF, Kazzaz JA, Davis JM, Steinhorn RH (2006) Superoxide dismutase improves oxygenation and reduces oxidation in neonatal pulmonary hypertension. Am J Respir Crit Care Med 174:1370–1377

Lakshminrusimha S, Wiseman D, Black SM, Russell JA, Gugino SF, Oishi P, Steinhorn RH, Fineman JR (2007) The role of nitric oxide synthase-derived reactive oxygen species in the altered relaxation of pulmonary arteries from lambs with increased pulmonary blood flow. Am J Physiol Heart Circ Physiol 293:H1491–H1497

Langleben D, Fox RB, Jones RC, Reid LM (1989) Effects of dimethylthiourea on chronic hypoxia-induced pulmonary arterial remodelling and ventricular hypertrophy in rats. Clin Invest Med 12:235–240

Lawrie A, Spiekerkoetter E, Martinez EC, Ambartsumian N, Sheward WJ, MacLean MR, Harmar AJ, Schmidt AM, Lukanidin E, Rabinovitch M (2005) Interdependent serotonin transporter and receptor pathways regulate S100A4/Mts1, a gene associated with pulmonary vascular disease. Circ Res 97:227–235

Lee SL, Wang WW, Lanzillo JJ, Fanburg BL (1994) Serotonin produces both hyperplasia and hypertrophy of bovine pulmonary artery smooth muscle cells in culture. Am J Physiol 266: L46–L52

Lee SL, Wang WW, Fanburg BL (1998) Superoxide as an intermediate signal for serotonin-induced mitogenesis. Free Radic Biol Med 24:855–858

Lee SL, Wang WW, Finlay GA, Fanburg BL (1999) Serotonin stimulates mitogen-activated protein kinase activity through the formation of superoxide anion. Am J Physiol 277: L282–L291

Lee SL, Simon AR, Wang WW, Fanburg BL (2001) H_2O_2 signals 5-HT-induced ERK MAP kinase activation and mitogenesis of smooth muscle cells. Am J Physiol 281:L646–L652

Liu Y, Suzuki YJ, Day RM, Fanburg BL (2004) Rho kinase-induced nuclear translocation of ERK1/ERK2 in smooth muscle cell mitogenesis caused by serotonin. Circ Res 95:579–586

Liu JQ, Zelko IN, Erbynn EM, Sham JS, Folz RJ (2006) Hypoxic pulmonary hypertension: role of superoxide and NADPH oxidase (gp91phox). Am J Physiol Lung Cell Mol Physiol 290: L2–L10

Liu L, Marcocci L, Wong CM, Park AM, Suzuki YJ (2008) Serotonin-mediated protein carbonylation in the right heart. Free Radic Biol Med 45:847–854

Mandegar M, Yuan JX (2002) Role of K^+ channels in pulmonary hypertension. Vascul Pharmacol 38:25–33

Mittal M, Roth M, König P, Hofmann S, Dony E, Goyal P, Selbitz AC, Schermuly RT, Ghofrani HA, Kwapiszewska G, Kummer W, Klepetko W, Hoda MA, Fink L, Hänze J, Seeger W, Grimminger F, Schmidt HH, Weissmann N (2007) Hypoxia-dependent regulation of nonphagocytic NADPH oxidase subunit NOX4 in the pulmonary vasculature. Circ Res 101:258–267

Miyauchi T, Yorikane R, Sakai S, Sakurai T, Okada M, Nishikibe M, Yano M, Yamaguchi I, Sugishita Y, Goto K (1993) Contribution of endogenous endothelin-1 to the progression of cardiopulmonary alterations in rats with monocrotaline-induced pulmonary hypertension. Circ Res 73:887–897

Morrell NW, Adnot S, Archer SL, Dupuis J, Jones PL, MacLean MR, McMurtry IF, Stenmark KR, Thistlethwaite PA, Weissmann N, Yuan JX, Weir EK (2009) Cellular and molecular basis of pulmonary arterial hypertension. J Am Coll Cardiol 54:S20–S31

Nauser TD, Stites SW (2003) Pulmonary hypertension: new perspectives. Congest Heart Fail 9:155–162

Nisbet RE, Graves AS, Kleinhenz DJ, Rupnow HL, Reed AL, Fan TH, Mitchell PO, Sutliff RL, Hart CM (2009) The role of NADPH oxidase in chronic intermittent hypoxia-induced pulmonary hypertension in mice. Am J Respir Cell Mol Biol 40:601–609

Odhiambo A, Perlman DH, Huang H, Costello CE, Farber HW, Steinberg MH, McComb ME, Klings ES (2007) Identification of oxidative post-translational modification of serum albumin in patients with idiopathic pulmonary arterial hypertension and pulmonary hypertension of sickle cell anemia. Rapid Commun Mass Spectrom 21:2195–2203

Okada M, Yamashita C, Okada M, Okada K (1995) Endothelin receptor antagonists in a beagle model of pulmonary hypertension: contribution to possible potential therapy? J Am Coll Cardiol 25:1213–1217

Park AM, Wong CM, Jelinkova L, Liu L, Nagase H, Suzuki YJ (2010) Pulmonary hypertension-induced GATA4 activation in the right ventricle. Hypertension 56:1145–1151

Pauly TH, Bowdy BD, Haven CA, Barr SB, Gillespie MN (1988) Evidence for hydroxyl radical involvement in group B streptococcus-induced pulmonary hypertension and arterial hypoxemia in young piglets. Pediatr Res 24:735–739

Pauly TH, Smith M, Gillespie M (1991) Bilirubin as an antioxidant: effect on group B streptococci-induced pulmonary hypertension in infant piglets. Biol Neonate 60:320–326

Preston IR, Tang G, Tilan JU, Hill NS, Suzuki YJ (2005) Retinoids and pulmonary hypertension. Circulation 111:782–790

Rao GN, Berk BC (1992) Active oxygen species stimulate vascular smooth muscle cell growth and proto-oncogene expression. Circ Res 70:593–599

Redout EM, Wagner MJ, Zuidwijk MJ, Boer C, Musters RJ, van Hardeveld C, Paulus WJ, Simonides WS (2007) Right-ventricular failure is associated with increased mitochondrial complex II activity and production of reactive oxygen species. Cardiovasc Res 75:770–781

Redout EM, van der Toorn A, Zuidwijk MJ, van de Kolk CW, van Echteld CJ, Musters RJ, van Hardeveld C, Paulus WJ, Simonides WS (2010) Antioxidant treatment attenuates pulmonary arterial hypertension-induced heart failure. Am J Physiol Heart Circ Physiol 298: H1038–H1047

Rhee SG, Bae YS, Lee SR, Kwon J (2000) Hydrogen peroxide: a key messenger that modulates protein phosphorylation through cysteine oxidation. Sci STKE 2000:pe1

Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I, Landzberg M, Simonneau G (2002) Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 346:896–903

Runo JR, Loyd JE (2003) Primary pulmonary hypertension. Lancet 361:1533–1544

Safdar Z (2011) Treatment of pulmonary arterial hypertension: the role of prostacyclin and prostaglandin analogs. Respir Med 105:818–827

Sakai S, Miyauchi T, Sakurai T, Yamaguchi I, Kobayashi M, Goto K, Sugishita Y (1996) Pulmonary hypertension caused by congestive heart failure is ameliorated by long-term application of an endothelin receptor antagonist. Increased expression of endothelin-1 messenger ribonucleic acid and endothelin-1-like immunoreactivity in the lung in congestive heart failure in rats. J Am Coll Cardiol 28:1580–1588

Sato K, Webb S, Tucker A, Rabinovitch M, Obrien RF, McMurtry IF, Stelzne TJ (1992) Factors influencing the idiopathic development of pulmonary hypertension in the fawn-hooded rat. Am Rev Respir Dis 145:793–797

Sawada H, Mitani Y, Maruyama J, Jiang BH, Ikeyama Y, Dida FA, Yamamoto H, Imanaka-Yoshida K, Shimpo H, Mizoguchi A, Maruyama K, Komada Y (2007) A nuclear factor-kappaB inhibitor pyrrolidine dithiocarbamate ameliorates pulmonary hypertension in rats. Chest 132:1265–1274

Schreck R, Rieber P, Baeuerle PA (1991) Reactive oxygen intermediates as apparently widely used messengers in the activation of the NF-kappa B transcription factor and HIV-1. EMBO J 10:2247–2258

Sen CK, Packer L (1996) Antioxidant and redox regulation of gene transcription. FASEB J 10:709–720

Shook LA, Pauly TH, Horstman SJ, Marple SL, Gillespie MN (1990) Dimethylthiourea reverses sepsis-induced pulmonary hypertension in piglets. Am J Med Sci 300:29–32

Simonneau G, Galie N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, Gibbs S, Lebrec D, Speich R, Beghetti M, Rich S, Fishman A (2004) Clinical classification of pulmonary hypertension. J Am Coll Cardiol 43:5S–12S

Sitbon O, Humbert M, Jais X, Ioos V, Hamid AM, Provencher S, Garcia G, Parent F, Herve P, Simonneau G (2005) Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 111:3105–3111

Stewart DJ, Levy RD, Cernacek P, Langleben D (1991) Increased plasma endothelin-1 in pulmonary hypertension: marker for mediator of disease? Ann Intern Med 114:464–469

Sturrock A, Cahill B, Norman K, Huecksteadt TP, Hill K, Sanders K, Karwande SV, Stringham JC, Bull DA, Gleich M, Kennedy TP, Hoidal JR (2006) Transforming growth factor-beta1 induces Nox4 NAD(P)H oxidase and reactive oxygen species-dependent proliferation in human pulmonary artery smooth muscle cells. Am J Physiol Lung Cell Mol Physiol 290: L661–L673

Sun X, Ku DD (2006) Allicin in garlic protects against coronary endothelial dysfunction and right heart hypertrophy in pulmonary hypertensive rats. Am J Physiol Heart Circ Physiol 291: H2431–H2438

Sundaresan M, Yu ZX, Ferrans VJ, Irani K, Finkel T (1995) Requirement for generation of H_2O_2 for platelet-derived growth factor signal transduction. Science 270:296–299

Suzuki YJ, Ford GD (1992) Superoxide stimulates IP_3-induced Ca^{2+} release from vascular smooth muscle sarcoplasmic reticulum. Am J Physiol 262:H114–H116

Suzuki YJ, Ford GD (1994) Mathematical model supporting the superoxide theory of oxygen toxicity. Free Radic Biol Med 16:63–72

Suzuki YJ, Forman HJ, Sevanian A (1997) Oxidants as stimulators of signal transduction. Free Radic Biol Med 22:269–285

Suzuki YJ, Day RM, Tan CC, Sandven TH, Liang Q, Molkentin JD, Fanburg BL (2003) Activation of GATA-4 by serotonin in pulmonary artery smooth muscle cells. J Biol Chem 278:17525–17531

Suzuki YJ, Nagase H, Wong CM, Vinod Kumar S, Jain V, Park AM, Day RM (2007) Regulation of Bcl-x_L expression in lung vascular smooth muscle. Am J Respir Cell Mol Biol 36:678–687

Sweeney M, Yuan JX (2000) Hypoxic pulmonary vasoconstriction: role of voltage-gated potassium channels. Respir Res 1:40–48

Thenappan T, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M (2010) Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. Eur Respir J 35:1079–1087

Ueno M, Miyauchi T, Sakai S, Goto K, Yamaguchi I (2000) Endothelin-a-receptor antagonist and oral prostacyclin analog are comparably effective in ameliorating pulmonary hypertension and right ventricular hypertrophy in rats. J Cardiovasc Pharmacol 36:S305–S310

Uzun O, Balbay O, Comunoğlu NU, Yavuz O, Nihat Annakkaya A, Güler S, Silan C, Erbaş M, Arbak P (2006) Hypobaric-hypoxia-induced pulmonary damage in rats ameliorated by antioxidant erdosteine. Acta Histochem 108:59–68

Wedgwood S, Dettman RW, Black SM (2001) ET-1 stimulates pulmonary arterial smooth muscle cell proliferation via induction of reactive oxygen species. Am J Physiol 281:L1058–L1067

Wedgwood S, Lakshminrusimha S, Czech L, Schumacker PT, Steinhorn RH (2013) Increased p22(phox)/Nox4 expression is involved in remodeling through hydrogen peroxide signaling in experimental persistent pulmonary hypertension of the newborn. Antioxid Redox Signal 18:1765–1776

Wolin MS (1996) Reactive oxygen species and vascular signal transduction mechanisms. Microcirculation 3:1–17

Wong CM, Cheema AK, Zhang L, Suzuki YJ (2008) Protein carbonylation as a novel mechanism in redox signaling. Circ Res 102:310–318

Wong CM, Preston IR, Hill NS, Suzuki YJ (2012) Iron chelation inhibits the development of pulmonary vascular remodeling. Free Radic Biol Med 53:1738–1747

Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, Yazaki Y, Goto K, Masaki T (1988) A novel potent vasoconstrictor peptide producing vascular endothelial cells. Nature 332:411–415

Yang DL, Zhang HG, Xu YL, Gao YH, Yang XJ, Hao XQ, Li XH (2010) Resveratrol inhibits right ventricular hypertrophy induced by monocrotaline in rats. Clin Exp Pharmacol Physiol 37:150–155

Yoshibayashi M, Nishioka K, Nakao K, Saito Y, Matsumura M, Ueda T, Temma S, Shirakami G, Imura H, Mikawa H (1991) Plasma endothelin concentrations in patients with pulmonary hypertension associated with congenital heart defects. Evidence for increased production of endothelin in pulmonary circulation. Circulation 84:2280–2285

Zamora MR, Stelzner TJ, Webb S, Panos RJ, Ruff LJ, Dempsey EC (1996) Overexpression of endothelin-1 and enhanced growth of pulmonary artery smooth muscle cells from fawn-hooded rats. Am J Physiol 270:L101–L109