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Review on Chamber-Specific Differences in Right and Left Heart Reactive Oxygen Species Handling

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Reactive oxygen species (ROS) exert signaling character (redox signaling), or damaging character (oxidative stress) on cardiac tissue depending on their concentration and/or reactivity. The steady state of ROS concentration is determined by the interplay between its production (mitochondrial, cytosolic, and sarcolemmal enzymes) and ROS defense enzymes (mitochondria, cytosol). Recent studies suggest that ROS regulation is different in the left and right ventricle of the heart, specifically by a different activity of superoxide dismutase (SOD). Mitochondrial ROS defense seems to be lower in right ventricular tissue compared to left ventricular tissue. In this review we summarize the current evidence for heart chamber specific differences in ROS regulation that may play a major role in an observed inability of the right ventricle to compensate for cardiac stress such as pulmonary hypertension. Based on the current knowledge regimes to increase ROS defense in right ventricular tissue should be in the focus for the development of future therapies concerning right heart failure.

Keywords: cardiac remodeling, heart failure, oxidative stress, pulmonary hypertension, uncoupling protein, MAO

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INTRODUCTION

Oxidative stress is defined as a condition by which an imbalance occurs between the production of reactive oxygen species (ROS) and the antioxidant defense system. The term ROS includes molecules that have one or more unpaired electrons (i.e., superoxide and hydroxyl) and non-radicals that are able to generate free radicals (i.e., hydrogen peroxide). Intracellular sources of ROS are the electron transport chain of the mitochondria, monoamine oxidase (MAO), p66shc (for review, see Di Lisa et al., 2017), xanthine oxidase (XO), uncoupling proteins (UCP, depending on the mitochondrial membrane potential; for review see Cadenas, 2018), uncoupled nitric oxide (NO) synthase (NOS), sodium-potassium ATPase (NKA), and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) (for review, see Egea et al., 2017). The defense system contains enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase, and coupled NOS. **Figures 1**, **2** give an overview about ROS sources and ROS defense systems in the heart. Whereas subtle changes in ROS act as intracellular signaling pathways (*redox signaling*) high levels of ROS can cause cell damage and dysfunction (*oxidative stress*) (for review, see Egea et al., 2017).

The following review article now summarizes our current understanding about similarities and differences in ROS handling between LV and RV. We searched the current literature (PubMed, MedLine data bank until July, 2018) using the terms "right heart and ROS," "pulmonary hypertension and ROS," "RV failure and ROS," "LV failure and ROS," "RV hypertrophy and ROS"

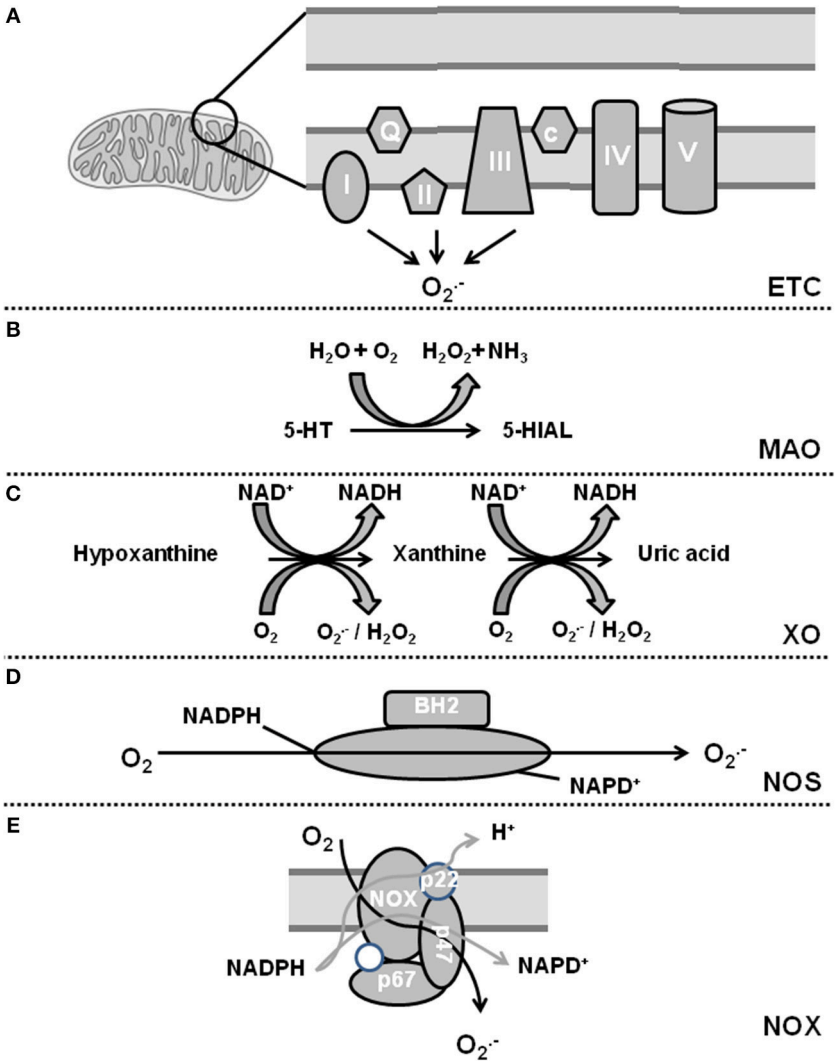

FIGURE 1 | Sources of reactive oxygen species in cardiomyocytes. **(A)** Complex I and III of the electron transport chain (ETC) constitutively release $O_2^{\cdot-}$ and complex II can be activated by NOX-dependent ROS. **(B)** Monoamine oxidase (MAO) generates H_2O_2. **(C)** Xanthine oxidase (XO) catalyzes a two-step reaction leading to additional release of H_2O_2. **(D)** Uncoupling of nitric oxide synthase (NOS) leads to generation of $O_2^{\cdot-}$. **(E)** NADPH oxidase (NOX) generates also $O_2^{\cdot-}$ upon activation.

and "LV hypertrophy and ROS." Most studies dealing with ROS and RV hypertrophy used models of pulmonary hypertension induced by banding, monocrotaline injection or chronic hypoxia. In these models ROS contribute to pulmonary hypertension and RV remodeling. In many studies, effects of ROS reduction on RV hypertrophy were secondary to reduced pulmonary pressure (reviewed by Wong et al., 2013). In the current review we therefore focus on studies directly assessing ROS and ROS-dependent effects in RV tissue and compare these results to established concepts generated from the LV.

OXIDATIVE STRESS IN THE HEART

Oxidative stress in cardiomyocytes occurs during chronic pressure or volume overload of the heart (Gladden et al., 2013; Hansen et al., 2016), cardiac ischemia/reperfusion (Riba et al., 2017), cardiomyopathy (Ishikawa et al., 2005), diabetes (Guido et al., 2017), chemotherapy-induced heart failure in the left (Mouli et al., 2015; Li et al., 2018), and right ventricle (Anghel et al., 2018), poison such as cigarette smoke (Talukder et al., 2011), chronic kidney disease (Duni et al., 2017), or aging (Chang et al., 2017), or as a response to congenital heart failure (Iacobazzi et al., 2016). Within the heart other sources of ROS are cells adjacent to cardiomyocytes such as inflammatory cells (Xu et al., 2011; Hernandez-Resendiz et al., 2018), endothelial cells (Burger et al., 2011), stem cells (Mandraffino et al., 2017), and cardiac fibroblasts (Ciulla et al., 2011). Redox signaling contributes to cardiac hypertrophy and even more important oxidative stress contributes to the transition of adaptive to maladaptive cardiac hypertrophy,

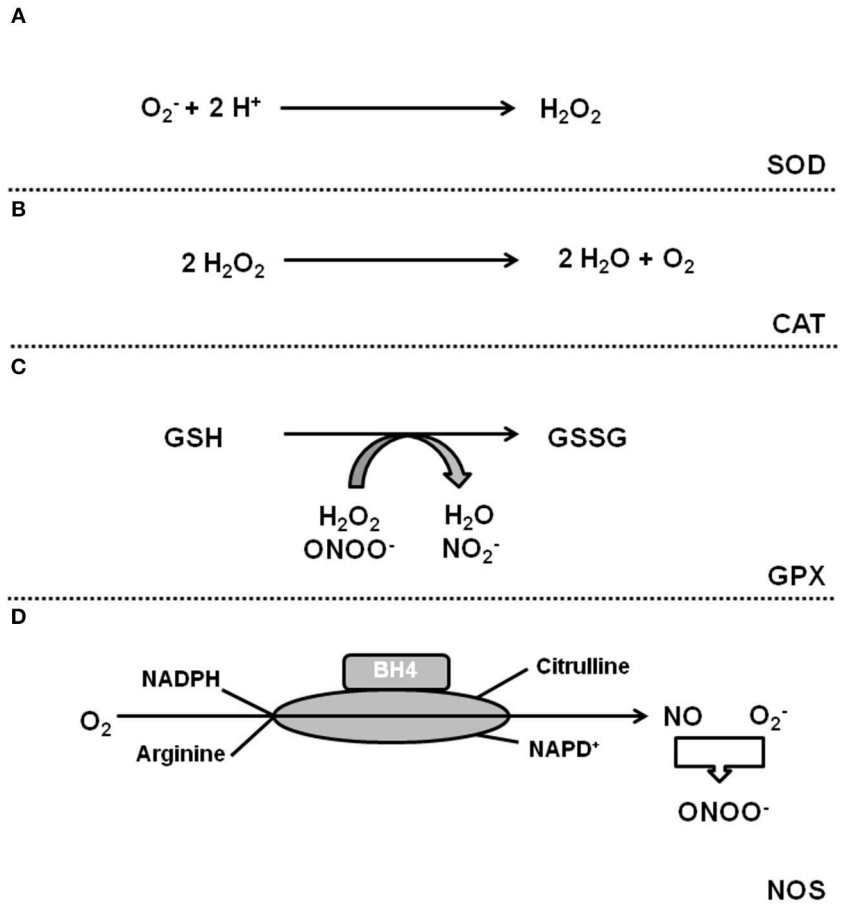

FIGURE 2 | ROS defense systems in cardiomyocytes. **(A)** Superoxide dismutases catalyze the formation of H_2O_2 that can be detoxificated by catalase **(B)**. **(C)** Gluatathione peroxidase (GPX) reduces H_2O_2. **(D)** Coupled NOS generates NO that neutralizes $O_2^{\cdot-}$.

named maladaptive remodeling. Oxidative stress can damage cells by growth factor-independent activation of cardiac growth regulation (Calamaras et al., 2015), can inactivate NO leading to loss of myocyte-specific NO function (Rassaf et al., 2006; Lüneburg et al., 2016), can directly reduce cardiomyocyte function by oxidative modification of sarcomere proteins such as tropomyosin (Heusch et al., 2010b; Canton et al., 2011) or sarcoplasmatic reticulum proteins (i.e., SERCA; Qin et al., 2017), can induce a calcium desensitization of myofibrils (Wang et al., 2008), can activate the Na-K-ATPase (Wang et al., 2017a), can damage mitochondrial function (Ide et al., 2001; Sverdlov et al., 2016), or can induce cell death (apoptosis, necrosis; Redza-Dutordoir and Averill-Bates, 2016). Therefore, ROS defense strategies of the cells are necessary for cell survival and functional stabilization in both ventricles.

DIFFERENCES BETWEEN RIGHT AND LEFT VENTRICLE

The different chambers of the heart are derived from different embryonic origin, namely the first (left ventricle, LV) and second heart field (right ventricle, RV). In rodent hearts, cardiomyocytes isolated from the LV or RV differ in size, number of mononucleated cells, cellular adaptation to culture conditions, and cell shortening (Schlüter, 2016; summarized in **Figure 3**). This gives raise to speculations that the LV and RV may differentially respond to cardiac stresses. Pressure overload is associated with adaptations performed on the transcriptional level. Many of them are similar between the RV and LV. However, some genes are upregulated in the pressure-overloaded RV only, including genes involved in Wnt signaling (Dickkopf 3, Sfrp2, and Wif1), annexin A7, clusterin/apolipoprotein J, neuroblastoma suppression of tumorigenicity 1 (Nbl1), formin-binding protein (Fnbp4), and the lectin-like oxidized low-density lipoprotein (oxLDL) receptor (LOX; Reddy and Bernstein, 2015). Differences occur also on the level of miRNA (Reddy and Bernstein, 2015). Considering the high impact of ROS for cardiac adaptation to pressure overload, it is also important to understand such differences with respect to ROS formation, ROS defense, and ROS-dependent cellular responses. Indeed, mitochondria isolated from the LV or RV of rat hearts generates different amounts of ROS (Schreckenberg et al., 2015; summarized in **Figure 3**). Treatment of isolated perfused rat hearts with serotonin, a substrate for MAO, results

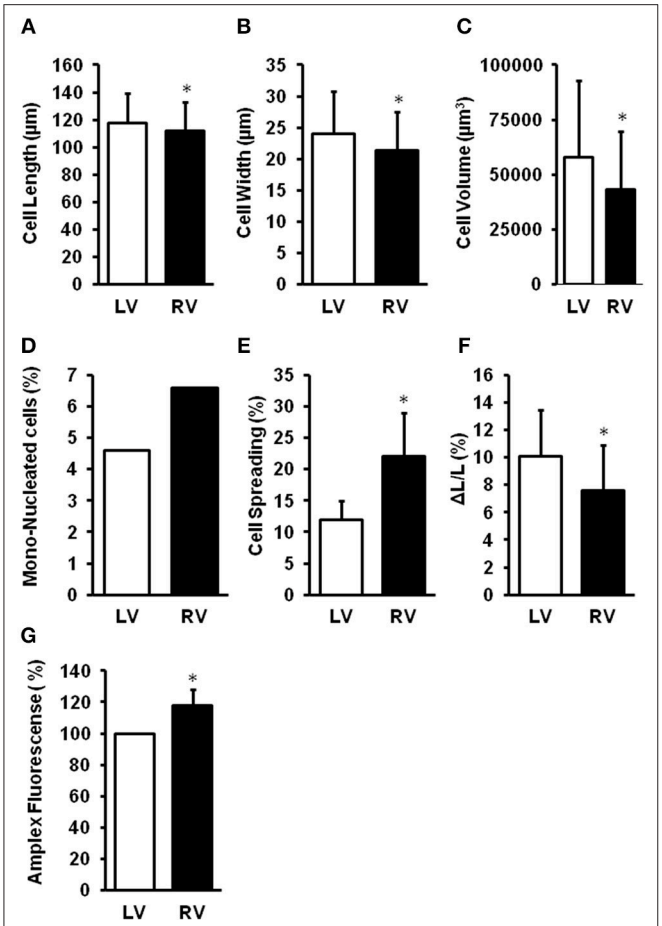

FIGURE 3 | Differences between right (RV) and left (LV) ventricular cardiomyocytes. LV cardiomyocytes are longer **(A)**, wider **(B)**, larger **(C)**, less mono-nucleated **(D)**, have a reduced cell spreading **(E)** as adaptation to culture conditions, and a stronger load-free cell shortening **(F)**. Furthermore, mitochondria from RV generate more ROS **(G)**. Data depicted from Schreckenberg et al. (2015) and Schlüter (2016). *$p < 0.05$ vs. LV.

in the promotion of protein carbonylation as evidenced by increased ROS formation, specifically in the RV but not the LV. Interestingly, no differences between RV and LV antioxidant enzymes and serotonin receptors/transporter are detected (Liu et al., 2008).

ROS IN RIGHT HEART HYPERTROPHY AND FAILURE: CYTOSOLIC ROS

Pressure overload induces the NOX subunit gp91 (Li et al., 2002; Byrne et al., 2003; Tanaka et al., 2005; Grieve et al., 2006; Liu et al., 2006, 2010; Guggilam et al., 2007; DeMarco et al., 2008; Nisbet et al., 2009; Chemaly et al., 2011; Xu et al., 2011; Ogura et al., 2013; Frazziano et al., 2014; Matsuda et al., 2015; Ma et al., 2016; Sirker et al., 2016; Zhu et al., 2017). In human right and left heart failure the p47phox subunit of NOX also translocates to the sarcrolemma (Nediani et al., 2007). Increased NOX expression is associated with increased formation of superoxide anions (Nediani et al., 2007; Ogura et al., 2013; Dos Santos Lacerda et al., 2017; Türck et al., 2018). Furthermore, hypoxia, leading to pulmonary hypertension, and RV hypertrophy, increases RV expression of NOX2/4 (Liu et al., 2014; Ye et al., 2016; Zhu et al., 2017). In the monocrotaline-induced pulmonary hypertension rat model, Nox4 expression is induced in cardiomyocytes but also in the intercellular area (mainly co-localizing with fibroblasts) (He et al., 2017). In the RV, NOX4 is also regulated by the α_{1A}-receptor (Cowley et al., 2017); stimulation of this receptor decreases NOX4 expression during pulmonary hypertension. NOX-dependent ROS modifies mitochondrial function by increased release of ROS from complex II of the mitochondria during the transition from RV hypertrophy to failure (Redout et al., 2007) (ROS induced ROS release). There are differences between the RV and LV ventricles in the primary source of ROS production. In the RV, NOX, and mitochondrial complex II activity both increase during the transition to heart failure, whereas, in the LV, NOX appears to be the primary source of ROS generation (Redout et al., 2010).

Xanthine oxidoreductase (XO) activity remains unaltered in the monocrotaline-induced RV hypertrophy model but its activity increases with the transition to RV failure. XO is mainly localized in $CD68^+$ inflammatory cells based on studies with an affinity-purified polyclonal antibody (de Jong et al., 2000). In another rat model of pulmonary hypertension-induced RV failure, metabolomics analysis revealed an increase in xanthine, and uric acid in the hypertrophied RV, suggesting the production of ROS by XO. Furthermore, the RV level of α-tocopherol nicotinate declined, consistent with oxidative stress decreasing antioxidants (Wang et al., 2017). XO also contributes to ROS formation in LV (Moris et al., 2017).

Uncoupled NOS is another protein involved in the generation of oxidative stress in the LV secondary to pressure overload (Takimoto et al., 2005). In the RV, uncoupled NOS contributes to ROS generation, too. In caveolin-1 (Cav-1) knockout mice subjected to chronic hypoxia the transition from RV hypertrophy to failure is accelerated compared to wild-type mice and caused by uncoupling of RV endothelial NOS and increased protein tyrosine nitration; all changes are prevented by re-expressing an endothelial-specific Cav-1 transgene (avoiding NOS uncoupling) or by NOS inhibition without modifying the extent of pulmonary hypertension (Cruz et al., 2012). Also, in a pharmacological model of hypertension chronic administration of L-NAME leads to uncoupling of NOS in RV (Schreckenberg et al., 2015).

Uncoupling of NOS can be caused by reduced substrate (arginine) for NOS. Reasons for substrate limitation can be an induction of arginase that leads to substrate limitation (Heusch et al., 2010; Schreckenberg et al., 2015), increased plasma concentrations of asymmetric dimethyl arginine (ADMA), a natural circulating inhibitor of NOS (Lüneburg et al., 2016), or depletion of NOS with tetrahydrobiopterin (BH_4, Shimizu et al., 2013).

ROS IN RIGHT HEART HYPERTROPHY AND FAILURE: MITOCHONDRIAL ROS

A proteomic analysis of the normal rabbit and porcine RV and LV free walls shows equivalent cellular aerobic capacity, volume

of mitochondria, mitochondrial enzyme content (cytochrome c oxidase, respiratory complexes 1 and 3–5, aconitase, SOD), and mitochondrial enzyme activities (Phillips et al., 2011). Interestingly, mitochondrial membrane potential, a surrogate of overall mitochondrial function, is lower in the resting RV compared to the LV (Nagendran et al., 2008), while—at least in rats—ROS formation in mitochondria isolated from the RV is slightly higher than in LV mitochondria (Schreckenberg et al., 2015). At last in part, the latter might be the consequence of a reduced ROS defense capacity (Borchi et al., 2010; Manni et al., 2016). Comparing mitochondria from hypertrophic RV with those of non-hypertrophic LV revealed differences in electrone transport chain activity and ATP generating enzyme expression Gupto et al., 2016.

While the mitochondrial protein profiles of the RV and LV are quite similar at rest, they diverge when subjected to an increased afterload (Phillips et al., 2011), and mitochondrial membrane potential increases with RV hypertrophy (Nagendran et al., 2008). This hyperpolarization of mitochondria, indicating reduced oxidative phosphorylation, is related to an activation of the nuclear factor of activated T cells (NFAT) pathway and is reversed by dichloroacetate, an inhibitor of pyruvate dehydrogenase kinases (PDK) (Nagendran et al., 2008). Thus, an increase in PDK activity in RV hypertrophy contributes to the decreased oxidation of pyruvate in mitochondria and an increased conversion of pyruvate to lactate in the cytosol. An increase in glycolytic hexokinase and lactate dehydrogenase activities occurs following monocrotaline-induced pulmonary hypertension at the stage of compensated RV hypertrophy (Balestra et al., 2015), further supporting the concept of a metabolic switch from mitochondrial oxidative phosphorylation to glycolysis in the compensated phase of RV hypertrophy (Paulin and Michelakis, 2014; Sutendra and Michelakis, 2014). Indeed, a decreased mitochondrial oxygen usage and an increased anaerobic glycolysis has been described in patients with pulmonary hypertension (Wong et al., 2011) (for a detailed review, see Freund-Michel et al., 2014), and the decrease in mitochondrial oxidative phosphorylation during the development of RV hypertrophy has been suggested to decrease mitochondrial ROS formation (for review, see Paulin and Michelakis, 2014).

The increase in glucose uptake and the mitochondrial hyperpolarization are lost with the progression of RV hypertrophy to failure (Nagendran et al., 2008). For the LV, ROS sensors revealed increased mitochondrial ROS in resting and contracting cardiomyocytes during the progression to heart failure. Pathway analysis of mitochondrial ROS-sensitive networks indicated that increased mitochondrial ROS in failing cardiomyocytes disrupts the normal coupling between cytosolic signals and nuclear gene programs driving mitochondrial function, calcium handling, action potential repolarization, and antioxidant enzymes (Dey et al., 2018). Indeed, in the RV, during the transition from RV hypertrophy to RV failure, mitochondrial ROS defense system (SOD-2) is down-regulated (Redout et al., 2007).

Another key regulator that is decreased during RV failure is the peroxisome proliferator-activated receptor gamma coactivator (PGC) 1α, leading to impaired fatty acid oxidation, decreased mitochondrial mass and number, and reduced oxidative capacity, potentially contributing to increased ROS production (Karamanlidis et al., 2011; Gomez-Arroyo et al., 2013). In an animal model of pulmonary hypertension-induced RV failure, fatty acid oxidation decreases secondary to the failure of palmitoylcarnitine to stimulate oxygen consumption. In humans with pulmonary hypertension, RV long-chain fatty acids and triglyceride contents are increased and ceramide, a mediator of lipotoxicity, accumulates (Brittain et al., 2016).

ROS DEFENSE SYSTEMS IN RV

In rats treated with monocrotaline to increase pulmonary artery pressure without inducing RV hypertrophy, RV hydrogen peroxide increases but SOD, catalase, and glutathione peroxidase activities are also enhanced (Siqueira et al., 2018).

During pressure overload–induced LV hypertrophy, antioxidant enzymes are activated in the compensated stage but their activity decreases during the onset of LV failure. In contrast, only the antioxidant enzyme catalase becomes activated in some (Ecarnot-Laubriet et al., 2003) but not all studies (Pichardo et al., 1999) while SOD and glutathione peroxidase are not activated at all in the compensated stage of RV hypertrophy secondary to pulmonary hypertension, predisposing the RV to ROS induced damage at an earlier stage than in the LV (Pichardo et al., 1999; Ecarnot-Laubriet et al., 2003; Schreckenberg et al., 2015). With a progression of from RV hypertrophy to failure, down-regulation of antioxidant enzymes, and increased ROS production occurs in a mice model of pulmonary hypertension (Aziz et al., 2015; Reddy and Bernstein, 2015), although in one model of monocrotaline-induced RV failure, glutathione peroxidase increases while catalase, and SOD activities are similar to sham animals (Türck et al., 2018).

Despite some controversial results the general view, however, remains that increased ROS formation and decreased ROS defense leads to increased oxidative stress driving the progression from RV hypertrophy to RV failure.

DOWNSTREAM SIGNALING

(Patho)physiological conditions known to activate p38 mitogen activated protein (MAP) kinase are often associated with increased ROS formation (Wenzel et al., 2001, 2006, 2007). Indeed, p38 MAP kinase is activated by oxidative stress (Redout et al., 2007). An activation of p38 MAP kinase pathways is linked to cardiac hypertrophy and dysfunction and in RV and LV of end-stage failing human hearts, p38 MAP kinase and extracellular-signal regulated kinase (ERK), but not c-Jun N-terminal kinases (JNK), are activated; a significant correlation between protein kinase activities is observed between LV and RV from the same heart (Nediani et al., 2007).

Increased ROS subsequently modifies tropomyosin, induces matrix metalloproteases (MMPs 2, 9, and 13), sensitizes β-adrenoceptors (via induction of protein kinase C-ε), and causes endothelial dysfunction in the right ventricle (Cheng et al., 2009; Lu et al., 2011; Cau et al., 2013; Schreckenberg et al., 2015).

In LV tissue, ROS is associated with an induction of $p90^{rsk}$ and the sodium-proton-exchanger (NHE) and furthermore, via ROS-dependent formation of lipid peroxidation-derived aldehydes (Cingolani et al., 2011). Furthermore, ROS activates the mammalian target of rapamycin (mTOR)-$p70^{s6k}$ pathway (Calamaras et al., 2015). Both pathways (NHE and mTOR-$p70^{s6k}$) are also involved in growth factor-dependent acceleration of protein synthesis (Simm et al., 1998; Schäfer et al., 2002). Commonly ROS and growth factors activate also the ERK pathway but the latter is not directly linked to the regulation of protein synthesis (Pönicke et al., 2001; Calamaras et al., 2015).

Apart from NOX, activation of the renin-angiotensin-system is apparent in the RV during pressure overload (for review, see Ameri et al., 2016). Compared to normal hearts, however, angiotensin II binding is diminished in the failing RV of pulmonary artery hypertension patients due to angiotensin II type 1 receptor down-regulation, despite RV myocardial angiotensin converting enzyme (ACE) activity being increased (Zisman et al., 1998). Interestingly, the ACE DD genotype, associated with an increased myocardial ACE activity, is more frequent in patients with pulmonary hypertension than in healthy individuals, but it is also associated with preserved RV function in pulmonary hypertension patients (Abraham et al., 2003).

A specific role for LOX-1 in RV hypertrophy and failure has been suggested. First, oxLDL receptors cross react with NOX (Ogura et al., 2013). Furthermore, ventricular expression of oxLDL receptors is induced under hypoxia leading to pulmonary hypertension and RV hypertrophy (Zhu et al., 2017). Cross-reactivity of oxLDL receptors with angiotensin II receptors type 1 has also been reported. In all these cases, NOX is subsequently activated favoring oxidative stress. It seems that this mechanism plays an important role in right heart failure.

THERAPEUTIC IMPLICATIONS

In general, attenuation of mitochondrial-derived oxidative stress is a reasonable therapeutic concept to attenuate RV hypertrophy and transition to RV failure (for review, see Maarman et al., 2017).

As expected from the findings that ROS is increased in RV hypertrophy and transition to RV failure, trapping molecules targeting mitochondrial ROS (mitoTEMPO), folic acid, EUK-134, a synthetic antioxidant mimicking the activity of SOD, attenuate RV hypertrophy (Redout et al., 2010; Qipshidze et al., 2012; Datta et al., 2015).

Regulation of SOD, in particular SOD-1 (located in the cytosol), and SOD-2 (located in mitochondria), has been proven to attenuate hypertrophy and even more important transition to heart failure. In a pharmacological rat model of hypertension (L-NAME induced hypertension) SOD-2 was induced in the LV but not in the RV (Schreckenberg et al., 2015). Up-regulation of SOD-2 in the LV was associated with less oxidative stress and preserved function in the presence of hypertrophy. Similarly, induction of SOD-2 activity has repeatedly reported to improve cardiac

TABLE 2 | Differences between LV and RV in ROS handling leading to hypertrophy and failure.

(A) ROS formation		
NOX gp91	LV ↑	RV ↑
NOX p47phox	LV ↑	RV ↑
NOX2/4		RV ↑
NOX-dependent ROS	LV ↑	
NOX-dependent Complex II		RV ↑
XO		RV ↑
NOS uncoupling	LV ↑	RV ↑
PDK		RV ↑
(B) ROS defense		
α-tocopherol nicotinate		RV ↓
Non-oxidative glucose metabolism		RV ↑
SOD-2	LV ↑	RV ↓
PGC-1α		RV ↓
Catalase	LV ↑	
Glutathione peroxidase	LV ↑	
(C) ROS-associated remodeling		
AT-1 receptor		RV ↓
ACE		RV ↑
LOX-1		RV↑

↑, *activated or induced during hypertrophy and/or transition to failure.*
↓, *deactivated or reduced during hypertrophy and/or transition to failure.*

TABLE 1 | Treatment of the angiotensin-NOX-ROS axis and effects on hypertrophy.

Drug	Species	Tissue	Target	Read-out	References
Isoflavone	Mice	LV	Ang-II-dependent	Hypertrophy	Chen et al., 2014
Taxofilin	Mice	LV	Ang-II-dependent	Hypertrophy	Guo et al., 2015
Spironolacton	Rats	LV	Renin-dependent	Hypertrophy	Habibi et al., 2011
Amlodipine/Atorvastatin	Rats	LV	Hypertension	Hypertrophy	Lu et al., 2009
Green Tea	Rats	LV	Ang-II-dependent	Hypertrophy	Papparella et al., 2008
AT1/ACE-I	Rats	LV	SHR	Hypertrophy	Tanaka et al., 2005
ACE inhibition	Rats	LV	Salt-induced BP	Cardiac function	Tsutsui et al., 2001
Atorvastatin	Rats	LV	Pressure overload	Hypertrophy	Li et al., 2013
Apocynin	Rats	LV	Pressure overload	Hypertrophy	Liu et al., 2010

function. Interestingly, at least for the LV multiple strategies to improve SOD activity work, such as the natural product Sheng-Mai-San (Chai et al., 2016), inhibition of the renin-angiotensin-system (Tanaka et al., 2005), calcium antagonists (Umemoto et al., 2004), or resveratrol (Danz et al., 2009). Whether any of these mechanisms is sufficient to increase SOD activity in RV remains unclear. As mentioned above, SOD is induced during hypertrophy in LV tissue (Date et al., 2002; Lu et al., 2010; Qiao et al., 2014; Aziz et al., 2015; Schreckenberg et al., 2015). Failure to increase SOD as an adaptive mechanism to rescue mitochondrial and cytosolic ROS is associated with heart failure (Redout et al., 2007; Koga et al., 2013). In a model of bronchopulmonary dysplasia, SOD-2 expression but not activity is induced leaving ROS formation unchanged. This underlines the importance of SOD-2 activity for protection against ROS-derived damage. Failure of the RV to up-regulate SOD-2 expression and activity might be a key step for right heart failure.

Other treatment using secoisolariciresinol diglucoside (Puukila et al., 2017), dehydroepiandrosterone (Alzoubi et al., 2013; Rawat et al., 2014), trimethoxystilbene (Liu et al., 2014), pterostilbene (Dos Santos Lacerda et al., 2017), trapidil (Türck et al., 2018), and α_{1A}-adrenoceptor stimulation with A61603 (Cowley et al., 2017) and finally fenofibrate (Galhotra et al., 2018) attenuate both RV hypertrophy and dysfunction and decreases RV ROS levels at the same time; however, a causality between changes in ROS and preservation of RV morphology and/or function could not be proven.

In contrast to the pharmacological approaches, neither the genetic deletion of sirtuin 3 (Waypa et al., 2013) nor the up-regulation of thioredoxin 2 (Adesina et al., 2017) affected RV hypertrophy during pulmonary hypertension. Sirtuin-3 is a nicotinamide adenine dinucleotide–dependent deacetylase that activates forkhead box O3a (FOXO3)-dependent up-regulation of SOD-2 (Sundaresan et al., 2009). Thioredoxin 2 is a mitochondrial located protein involved in ROS defense of the organelle (Dunn et al., 2010).

β-Blockers may also considered as a therapeutic option in right heart failure. β-Adrencoeptor signaling is sensitized by ROS. At least in the left ventricle carvedilol, a β-blocker with antioxidative properties, was able to attenuate the hypertrophic response to anthracylines (Arozal et al., 2011). In rats with monocrotaline-induced pulmonary hypertension bucindolol treatment decreases RV necrosis, fibrosis, and infiltration of inflammatory cells and improves RV systolic function. In addition, bucindolol promotes a decrease in the cardiac sympathovagal balance by reducing sympathetic drive and increasing parasympathetic drive (Lima-Seolin et al., 2017). Changes in ROS were not measured. In a model of hypertension (two-kidney one-clip), β-blockers attenuated ROS and MMP2, a ROS-dependent regulated MMP, independent of its antioxidative property suggesting that direct stimulation of β-adrenoceptors increases ROS in ventricular tissue (Rizzi et al., 2014).

There are multiple reports that treatment regimes affecting the angiotensin-NOX-ROS axis attenuate hypertrophy and heart failure, but also few examples showing no effects (**Table 1**).

CONCLUSION

A coupling between ROS, cardiac hypertrophy and heart failure has been established for the LV. Concerning the RV only few data are available that directly analyzes right heart hypertrophy in the context of ROS signaling. As it stands there is consensus that RV tissue has a reduced oxidative defense capacity thereby favoring oxidative stress especially during the transition from RV hypertrophy to failure. Whether ROS targets in the RV include those proteins that are directly linked to cardiac growth is unclear and questionable. In contrast, oxidative modification of proteins leading to failure seems to be similar between both ventricles. **Table 2** highlights the findings on ROS formation, defense, and targets in RV in comparison to LV.

AUTHOR CONTRIBUTIONS

K-DS and RaS wrote the manuscript, performed literature search, and work on the conception. HK and CH provided data to **Figure 3** and read and improved the manuscript. RoS read and added conceptional ideas and data to the chapter defense system.

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