Summary

Oxidative stress arises when the concentration of reactive oxygen species (ROS) increases in such a manner that it cannot be countered sufficiently by the cellular antioxidant defense, thereby damaging biomolecules, including DNA, lipids and proteins. The interest in oxidative stress comes from the fact that it has been implicated in the etiology of a wide variety of diseases, including atherosclerosis, hypertension, ischemia-reperfusion injury, cancer, type-2 diabetes, Parkinson’s and Alzheimer’s disease. Furthermore, it has also been implicated in the progression of ventricular hypertrophy to heart failure. This thesis focused on the role of ROS in compensatory right ventricular (RV) hypertrophy and RV failure. We investigated the sources of ROS production, ROS-mediated signaling pathways as well as its contribution to RV failure, in response to increased afterload.

In Chapter 1, a general overview is given concerning: normal RV function; pulmonary arterial hypertension, a disease which affects normal RV function; oxidative stress and its proposed sources in heart failure; and antioxidant defense mechanisms. In the final part of this chapter the monocrotaline (MCT) model of compensatory RV hypertrophy and failure is discussed and the aims of the study are outlined.

The characteristics that distinguish compensatory RV hypertrophy from RV failure were investigated in Chapter 2. In this chapter we compared a hypertrophic (HYP) and a failing (CHF) phenotype in parallel at day 19 and 25 after MCT treatment. At day 19 neither group showed signs of failure, while at day 25 only the CHF group showed RV failure. We report that mitochondrial biogenesis is an important distinguishing factor between HYP and CHF. Already at day 19 divergent expression of the transcription factors, NRF-1, NRF-2, PGC-1α and TFAM were detected between HYP and CHF, preceding the differences in mitochondrial biogenesis between both groups. Furthermore, we showed that antioxidant defense already decreases at day 19 in CHF, implicating oxidative stress in the decompensation of the myocardium. Another distinguishing factor between HYP and CHF is the extent of pro-apoptotic signaling. We showed that in HYP the expression of the anti-apoptotic factor ARC was increased. This was accompanied by unaltered Bax translocation to mitochondria, whereas in CHF there was an increased Bax translocation, implying the presence of increased pro-apoptotic signaling.

In Chapter 3, we showed that ROS levels were indeed increased in RV failure. In addition to the reduction in antioxidant defense we identified two sources
of increased ROS production in RV failure, which are, NADPH oxidase and mitochondria. Furthermore, we demonstrated that the increased mitochondrial ROS production was mediated by Complex II and released at Complex III. We also showed the presence of cellular hypoxia and an increased reduction state of mitochondrial coenzyme Q in RV failure. Finally we showed that the increased ROS production by NADPH oxidase and mitochondria resulted in myocardial oxidative stress.

To investigate causality between oxidative stress and RV failure, we treated rats developing RV failure with an antioxidant, EUK 134. The results from this experiment are presented in Chapter 4. In this chapter we showed that treatment with an antioxidant attenuates RV failure. We used both cardiac Magnetic Resonance Imaging (cMRI) and echocardiography to assess RV function. EUK 134 treatment of the CHF group attenuated cardiomyocyte hypertrophy and related changes in mRNA expression of MHCβ and type 3 deiodinase. It also reduced RV oxidative stress and pro-apoptotic signaling, preventing interstitial fibrosis. cMRI showed that ROS scavenging by EUK 134 significantly improved systolic function in the CHF group. Here we showed an important role of ROS in RV cardiomyocyte hypertrophy and contractile dysfunction, as well as the potential of EUK-class antioxidants as a therapeutic in the treatment of RV failure.

In Chapter 5, the results obtained in this thesis regarding the role of ROS in compensatory RV hypertrophy and RV failure are discussed with respect to oxidative stress in hypertrophy and heart failure in general. Furthermore, suggestions for future investigations are proposed, advocating more clinical research to be conducted in the application of antioxidants in the treatment of human RV failure.