INTRODUCTION
CHAPTER 1

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Cardiopulmonary circulation is a high flow, low pressure and low resistance (10% of systemic vascular resistance) system. It is a complex system and differs both functionally and structurally from systemic circulation. Pulmonary circulation serves several functions like gas exchange, filtering of particles and the chemical processing of the blood. The gas exchange between blood and inspired air requires optimal conditions like low pulmonary artery pressure (PAP). The normal mean pulmonary artery pressure (mPAP) is around 15 mm Hg [1]. In certain lung disorders, like pulmonary hypertension (PH) mPAP increases >25 mm Hg at rest. PH is a progressive, debilitating disease and is characterized by an increase in pulmonary arterial resistance which further increase afterload of right ventricle (RV) subsequently resulting in RV hypertrophy(RVH), right heart failure and death [2].

PH is a complex disease of various origins, with poor prognosis and affects more than 100 million people worldwide and has an annual incidence of 50 cases per million [1]. PH can be idiopathic, heritable and associated with a number of diseases (connective tissue disease, congenital left-to-right shunt, hemoglobinopathies, HIV disease, schistosomiasis and liver disease) as secondary disorder [1]. A strong female predominance (at least three-times more frequent than men) of several types of PH has been well demonstrated. Idiopathic PH (IPH) has an annual incidence of 1-2 cases per million people in the US and Europe and is 2-4 times as common in women as in men [3, 4]. It is likely that IPH accounts for at least 40% of cases of PH, while Associated PH (APH) accounts for the majority of the remaining cases as the prevalence of PH in certain at-risk groups is substantially higher for example in chronic obstructive pulmonary disease (90%)[5], chronic heart disease (75%), hemoglobinopathies (10%) [6], HIV infection (0.5%) [7], systemic sclerosis (10-20%) [8], and sickle cell disease (25%) [9]. PH is also associated with the
newborn and is known as persistent pulmonary hypertension of the newborn (PPHN) which arises when the normal decrease in pulmonary vascular tone does not occur after birth and has been estimated to occur in 0.2% of live-born term infants, and some degree of PH complicates the course of more than 10% of all neonates with respiratory failure [10].

In PH, there is persistent hypoxemia, vasoconstriction, inflammation, thrombosis and excessive migration, proliferation, apoptosis-resistance in pulmonary arterial smooth muscle cells (PASMC), endothelial cells (EC), adventitial cells and abnormal accumulation of extracellular matrix proteins resulting in remodelling of pulmonary arteries [2, 11]. RVH is a secondary complication in PH (which occurs due to increased workload by right heart) as a consequence of increased vascular resistance in pulmonary arteries [2]. However, sustained pathologic RVH is deleterious and may lead to right heart decompensation, dilatation and ultimately right ventricle failure (RVF) which is the most frequent cause of death in patients suffering from PH [12, 13].

Various approaches like endothelin receptor antagonists, phosphodiesterase-5 inhibitors, calcium channel blockers are being used as therapy in PH but they only ameliorate the prognosis of the disease and are able to increase the lifespan only up to 3-5 years. Heart and lung transplantation remains the only definitive treatment for patients with advanced PH. Considering this, there is a need to elucidate the exact mechanism of PH and find new therapeutic targets.

There is an important role of oxidative stress in PH [14]. Oxidative stress leads to DNA damage and in return activates a number of DNA repairing enzymes. One of these enzymes is poly (ADP-ribose) polymerase-1(PARP-1) which functions as a DNA damage sensor and repairs DNA by binding to DNA breaks. It is also involved in other multiple physiological cellular functions such as, gene transcription, cell cycle progression, chromatin function, genomic stability and cell death. Due to severe oxidative and nitrosative stress, extensive DNA damage occurs leading to overactivation of PARP-1 that results in
depletion of energy stores in the form of NAD and ATP thus, causing cellular
dysfunction and death. In the pathophysiology of a number of cardiovascular
disorders (Myocardial infarction, heart failure, etc), oxidative stress induced
DNA damage and PARP-1 overactivation has been reported [15-18].
Activation of PARP-1 in ECs has been shown to impair relaxation of the blood
vessels in response to vasodilators such as acetylcholine [19]. Moreover, it has
also been implicated as a central mediator of EC dysfunction in a variety of
induced dysfunction [22] and septic shock [23]. PARP inhibitors and genetic
PARP-1 deficiency has been proven to normalize the angiotensin II-induced
endothelial dysfunction in vivo [24].

PARP-1 plays a vital role in the evolution and progression of cardiac
hypertrophy and its expression and enzymatic activity increases gradually with
the degree of cardiac hypertrophy [25]. PARP-1 is also involved in events
related to cardiac growth, muscle gene regulation, and cell death [26]. In a
number of studies inhibition or genetic inactivation of PARP-1 protected against
cardiac hypertrophy and heart failure. There is also evidence for over expression
of PARP-1 in human subjects with heart failure [26]. PARP-1 activation also
plays a role in the development of heart failure induced by various forms of
circulatory shock (endotoxic, septicemic) [27, 28], as well as in the
cardiomyopathy associated with diabetes mellitus [29]. A beneficial effect of
PARP-1 inhibitors has been noticed in different experimental models of heart
failure [30]. Angiotensin II induced cardiac hypertrophy is absent in
homozygous PARP-1 deficient mice [31]. Again, in these protective effects,
either the PARP-mediated energetic mechanism, or PARP-mediated regulation
of gene expression, or the combination of the two mechanisms may be involved.

Thus, it is evident from above discussion that PARP-1 is involved in a
number of cardiovascular conditions. **However, the role of PARP-1 in PH has
not been established till date.**
REFERENCES


endothelial dysfunction associated with hypertension and aging'. *Int J Mol Med*, pp659-64.


