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Review Article

Endothelin-1 in Pulmonary Artery Hypertension Secondary to Congenital Heart Disease

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ABSTRACT

Background: Congenital cardiac disease with increased pulmonary blood flow or increased pulmonary venous pressure is frequently accompanied by the development of pulmonary hypertension and its accompanying enhanced vascular reactivity. Breathlessness with worsening exercise tolerance is linked to the development of pulmonary arterial hypertension in congenital heart disease. The most prevalent symptom of pulmonary arterial hypertension and congenital heart disease (CHD) is dyspnea development, which was formerly believed to be brought on by deteriorating PAH but may also be brought on by inflammation and abnormalities in lung function. A sensitive non-invasive marker for vascular alterations in children with congestive heart failure is endothelin-1. **Conclusion:** Numerous investigations have suggested that the pulmonary vascular endothelium produces the 21-amino acid vasoactive polypeptide known as endothelin-1 (ET-1), which has strong vasoconstrictor effects and promotes the growth of vascular smooth muscle cells. The early vascular change diagnosis reduces comorbidities and enables early medical management and/or surgical repair.

Keywords: Congenital heart disease; Endothelin -1; Pulmonary artery hypertension.

INTRODUCTION

ET-1, a polypeptide including 21 amino acids, was discovered to be the most potent endogenous vasoconstrictor to date It was first identified in 1988 and generated by pulmonary and systemic vascular endothelial cells. It has since been shown that ET-1 has several physiologic features in the neurological, gastrointestinal, endocrine, pulmonary, renal, and cardiovascular systems, and they can be produced by a variety of cell types. These biologic characteristics include inflammation, fibrosis, cardiac and vascular hypertrophy, vascular smooth muscle proliferation, and control of vasomotor tone (Figure 1) [1].

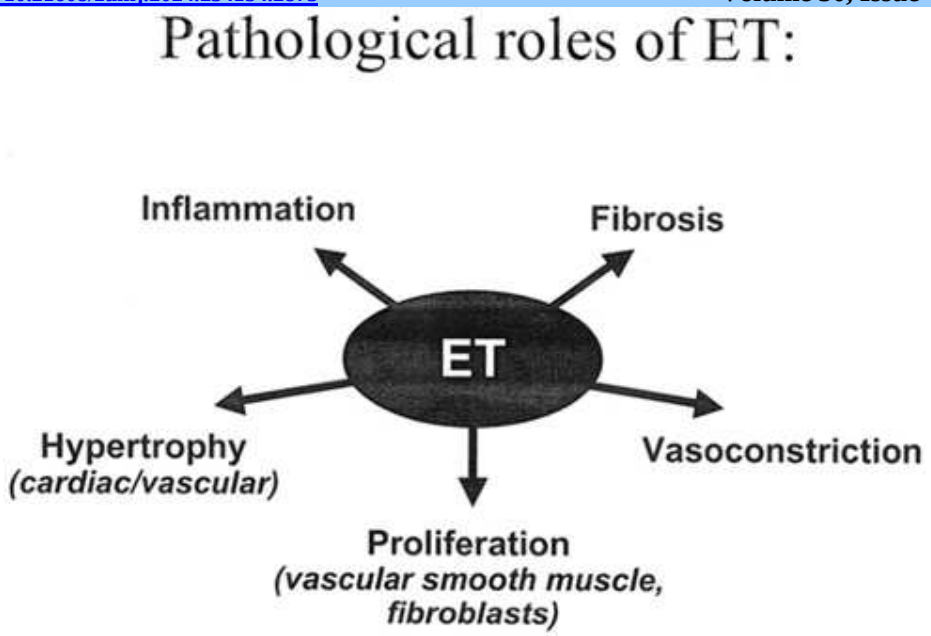

Figure 1: Endothelin-1 has been implicated in the pathology of several biological conditions beyond its very potent vasoconstricting effects. These include proliferation, hypertrophy, fibrosis, inflammation, and hypertrophy [2].

Furthermore, changes in Several illness conditions' pathophysiology have been connected to the ET-1 cascade such as pulmonary hypertension, bronchoconstriction, congestive heart failure, and fibrotic diseases. A growing body of research shows that changes in pulmonary blood flow are linked to modifications in newborns, infants, and children with congenital cardiac defects in ET-1 signaling [3].

The endothelin cascade

Proendothelin-1 is produced by cleaving preproET-1, a 203-amino acid peptide precursor that is translated from the human ET-1 gene, which is located on chromosome 6. Endothelin Converting Enzyme-1 (ECE-1) is a membrane-bound metalloprotein converting enzyme that cleaves proendothelin, large ET-1, into its functional form. ETA and ETB are at least two distinct receptor populations that have varying densities based on factors like age, species, pathological condition, and vascular bed under study—mediating the physiological effects of ET-1 [4].

ETA receptors are present in vascular smooth muscle cells which activate phospholipase, hydrolyze phosphoinositol to diacylglycerol, and release inositol 1,4,5-triphosphate after that Ca2+ to cause vasoconstriction. Additionally, ETA receptors are involved in inflammation, and fibrosis, affecting the growth of smooth muscle cells. ETB receptors are present in endothelial cells, which release NO and activate potassium channels to cause vasodilation. Additionally, ETB receptors mediate the pulmonary elimination of circulating ET-1 [5].

A second, less well-studied class of ETB receptors is present in smooth muscle cells that mediate comparable functions to those of ETA receptors on smooth muscle cells. Exogenous ET-1 was shown to primarily cause hemodynamic effects through ETB receptor-mediated vasodilation in the youthful, healthy pulmonary circulation; as one age, this transitions to ETA receptor-mediated vasoconstriction [6].

Apart from endothelial cells, several other cell types in the lung have also been shown to

produce ET-1, such as airway epithelial cells, and vascular and smooth muscle cells. Last but not least, the myocardium produces ET-1, which may have a significant impact on the development and functionality of the heart. On the part of ET-1 in the myocardial changes linked to CHD, however, data are incredibly scarce [7].

Endothelin-1 and pulmonary hypertension secondary to CHD

Higher pulmonary blood flow or higher pulmonary venous pressure are frequently observed alongside congestive heart failure (CHD) in the onset of pulmonary hypertension and the heightened vascular reactivity that goes along with it. Early vascular alterations are reversible following surgical repair; more severe abnormalities, however, are gradual and irreversible. Pulmonary vascular disease has become less common due to early surgical correction of CHD. However, during the perioperative and postoperative periods, even children with reversible vascular abnormalities may face notable morbidity and mortality due to both transient and persistent elevations in pulmonary vascular resistance (PVR) [8].

Furthermore, modest increases in PVR in infants with single ventricle physiology might rule out several possible surgical options (such as Fontan treatments and caval-pulmonary anastomosis). As a result, the pulmonary vasculature's condition frequently determines both the viability of surgical treatment and its clinical outcome [9].

Growing data points to the involvement of endothelial dysfunction in the development of pulmonary hypertension, its maintenance, and the increased vascular reactivity that accompany it, as a result of the changed mechanical pressures linked to congestive heart failure (CHD). The data on ET-1 in particular is strong. For instance, multiple human investigations show that children with congestive heart failure (CHD) have significantly higher plasma ET-1 levels and enhanced pulmonary blood flow. Less frequently, research has shown that the amount of ET-1 and pulmonary hypertension severity are positively correlated, and other research has shown that there is a generalized increase in lung ET-1 levels, indicating that patients with pulmonary hypertension produce ET-1 [10].

It was shown that there was a relationship in children with normal pulmonary function between mean pulmonary arterial pressure and plasma ET-1 levels of vascular resistance, but not with pulmonary blood flow. These findings, along with initial in vitro results, indicate that pressure—rather than flow—is the main mechanical force that increases ET-1. It is intriguing to consider a potential function for ET-1 in the increased prevalence of pulmonary hypertension resulting from congenital heart defects with high pressure and high flow (ventricular septal defects) in contrast to anomalies characterized by high flow and low pressure (atrial septal defects) [11].

Patients undergoing transplantation with advanced pulmonary vascular disease provide further human data. For instance, it has been shown that individuals a subgroup of those with advanced secondary pulmonary hypertension is attributable to congestive heart failure have higher levels of preproET-1 gene expression [9].

It was proposed that an increase in ET-1 levels associated with increased pulmonary blood flow is the result of an up-regulation of ECE-1 following exposure to these relevant mechanical stresses [12]. These new results point to a growing ETA and ETB receptors play a part in the etiology of pulmonary hypertension associated with congestive heart failure. These results are consistent with a previous publication [13] showing that individuals with severe pulmonary hypertension due to thromboembolic illness have an increased expression of the ETB receptor gene in smooth muscle cells.

When considered collectively, these findings point to a critical the ET-1 cascade's involvement in the pulmonary hypertension associated with congestive heart failure More research is needed to determine whether the ETA or ETB receptor may play a role in this illness. This is especially important during the first few days of life, when there hasn't been enough research done to compare the possible advantages of the endothelium The diseases of the smooth muscle cell ETB receptor (vasoconstriction and smooth muscle cell

proliferation) vs the ETB receptor (vasodilation) [14].

Endothelin-1 after cardiac surgery for CHD

Generally, cardiopulmonary bypass is a surgical procedure used to treat CHD Generalized endothelial cell injury is the outcome of cardiopulmonary bypass and related harm from ischemia reperfusion. Following ischemia-reperfusion, abnormalities of the Numerous organs, including the heart, lung, brain, liver, kidneys, colon, and pulmonary and systemic vascular smooth muscle, have well-reported histologic and functional endothelial cells [15, 16].

Strong evidence suggests that ET-1 contributes significantly to the pathophysiology of ischemia-reperfusion damage. Specifically, across a range of types of ischemia-reperfusion damage, which encompasses hypothermic CPB (CPB), ET-1 levels are markedly elevated in both people and animals. It has been demonstrated that during ischemia-reperfusion, ET-1 becomes dominant while NO generation is inhibited; this imbalance leads to damage from ischemia-reperfusion. Moreover, CPB raises the expression of ET receptors, especially in the respiratory system, as well as the synthesis of ET-1 [17].

Damage to the heart caused by ischemia-reperfusion during CPB is well-established and is thought to be a primary factor in post-bypass reduced cardiac output syndrome. After CPB, there is unmistakable evidence of both systolic and diastolic heart failure in both adults and kids. The etiology is complex and multifaceted involving damage to endothelial and cardiac cells. Apoptosis, necrosis, and interstitial and cellular edema are all visible in cardiac histology. Coronary vascular endothelial cells exhibit swelling and necrosis as revealed by endothelial cell imaging, while functional tests show a decrease in ET-1 secretion and endothelium-dependent relaxation. Decreased microcirculatory coronary blood flow and reserve, as well as impaired myocardial function, are the outcomes of these alterations [18].

Strong coronary vasoconstriction is produced by both endogenous and exogenous ET-1. Furthermore, it has been demonstrated that ET-1 positively inotropically affects isolated ventricular myocytes. The pro-arrhythmic impact of ET-1 may be explained by the inotropic effect, which is linked to the prolonging of the ventricular myocardium's action potential. However, because of its strong coronary vasoconstricting effects, ET-1 treatment reduces myocardial function and output due to myocardial ischemia, even if it has a direct positive inotropic impact on myocytes [19].

Heart failure, myocardial ischemia, and atherosclerosis are just a few of the cardiovascular conditions that have been linked to elevated myocardial ET-1 levels and plasma. Better coronary constrictor response to ET-1 and increased myocardial synthesis and release of ET-1 have been observed during myocardial ischemia-reperfusion damage. Furthermore, the bulk of research with endothelin receptor antagonists has demonstrated a decrease in myocardial injury caused by ischemia-reperfusion [20].

While several studies have shown elevated plasma ET-1 levels both during and following cardiopulmonary bypass implantation, relatively few have explicitly examined the relationship between ET-1 and myocardial dysfunction following cardiopulmonary bypass. When aortopulmonary vascular grafts are placed in utero and provide increased pulmonary blood flow, the usual decline in cardiac output that occurs after hypothermic CPB is entirely mitigated by antagonists that target both dual and specific endothelin receptors [21].

Furthermore, pretreatment with the oral dual endothelin receptor antagonist bosentan reduced Myocardial injury and cardiac cell death caused by leukocytes while also improving left and right ventricular performance. All things considered, our findings point to the pathophysiological significance of endogenous ET-1 in the diminished cardiac function that follows CPB and the potential benefit of endothelin receptor antagonists in reducing the damage and enhancing post-bypass myocardial function [22].

Strong evidence points to the role of endothelial injury-related changes in the expression and location of the role of ET-1

and ET receptors in pulmonary arterial hypertension development and the heightened vascular reactivity that goes along with it. Increased production of ET-1 and pulmonary vascular endothelial dysfunction is induced during CPB by several events, including abnormal pulmonary blood flow, alveolar hypoxia, complement activation, neutrophil activation, surgical stress, and hypothermia [23].

Concentrations of plasma ET-1 rise steadily both during and after CPB. Increased endothelin receptors and gene expression were linked to this. A correlation in the plasma levels of ET-1 three hours after cardiopulmonary bypass (CPB) in a study of children with congenital cardiac disease suggests a role for ET-1 in the etiology of post-cardiopulmonary bypass pulmonary arterial hypertension [24].

It has been proposed that endothelin receptor antagonist therapy reduces the elevated pulmonary arterial pressure and associated changes in reactivity that result from cardiopulmonary bypass surgery. Therefore, with either dual or ETA-selective antagonists as a pretreatment, the increase in PVR following cardiopulmonary bypass was entirely stopped in lambs that already had pulmonary arterial hypertension from increased blood flow in the lungs. Furthermore, the endothelin receptor antagonist-pretreated lambs did not exhibit any of the potentially fatal acute increases in PVR that are caused by the heightened pulmonary vascular reactivity that follows CPB [25].

Similarly, blocking with bosentan reduced leukocyte-mediated lung damage and enhanced pulmonary function in addition to attenuating the increase in PVR after CPB. Finally, a 20-minute infusion of the ETA-selective antagonist BQ 123 decreased the infants' congenital heart disease-related pulmonary vascular resistance after surgery with CPB [26].

When considered collectively, the data point to ET-1's involvement in the development of pulmonary impairment following CPB. Additionally, these findings imply that endothelin receptor antagonist pretreatment will stop CPB-induced pulmonary dysfunction. Reduced PVR, enhanced right ventricular function, and a decline in the frequency of post-bypass The expected consequences of this are elevated pulmonary compliance and oxygenation, as well as episodes of pulmonary hypertension. A rise in oxygen supply accompanied by a decrease in the incidence of post-bypass poor cardiac output syndrome should be the outcome [27].

Following hypothermic CPB, damage to the brain, kidneys, and liver has been clearly shown in both children and adults. Each of these wounds significantly raises the patients' rates of co-morbidity and mortality. Specifically, children's long-term outcomes are significantly influenced by neurologic aftereffects of brain injury resulting from cardiopulmonary bypass, and ongoing research is primarily focused on identifying and preventing these aftereffects [28].

Furthermore, this organ damage causes metabolic disturbances that change cardiopulmonary function and pave the way for the emergence of low cardiac output syndrome. It is suggested by experimental models of organ injury that ischemia injury to the liver, kidneys, and brain results in elevated levels of ET-1. Studies using it have shown that endothelin receptor antagonists reduce ischemic injury, indicating that ET-1 may have a pathophysiological role in these injuries [29, 30].

In conclusion, strong evidence points to ET-1's involvement in the development of CHD-related pulmonary hypertension and in the alterations to pulmonary vascular tone and responsiveness following CPB usage. Furthermore, data points to ET-1's involvement in the pathogenesis of multiple organ ischemia-reperfusion injury linked to cardiopulmonary bypass. It is still unclear exactly what part Of these mechanisms, ETA and ETB receptors are involved. It is commonly known that smooth muscle ETB receptor cells are an inducible receptor that is upregulated in pathological circumstances [23, 31].

On the other hand, in pathological circumstances, the endothelium ETB receptor is down-regulated; as a result, the possible vasodilating impact of ETB may be inhibited and targeted towards vasoconstriction,

proliferation, and inflammation. Based on these findings, greater investigation into ET receptor antagonists for the management of both acute and chronic pulmonary hypertension is warranted resulting from congestive heart failure is necessary, given their recent discovery as possible therapeutic drugs [32].

While initial findings point to a potential role for dual receptor blockade, further research is needed to clarify the precise role that dual ET receptor antagonists versus selective ETA receptor antagonists should play in CPB ischemia-reperfusion damage and CHD, especially in the neonatal period [33].

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors are responsible for the content and writing of the paper.

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