

# Serum Connective Tissue Growth Factor in Children with Pulmonary Arterial Hypertension Associated with Congenital Heart Disease: Review Article

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## ABSTRACT

**Background:** The significant pulmonary vascular resistance can result in right-sided heart failure, elevated pulmonary vascular resistance, and even mortality, a progressive condition known as pulmonary arterial hypertension (PAH), which also has a high mortality and morbidity rate.

**Objectives:** we aimed investigate plasma connective tissue growth factor (CTGF) levels in pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) (PAH-CHD) in children and the relationships of CTGF with hemodynamic parameters.

**Material and methods:** A review of MEDLINE, Cochrane Library, ClinicalTrials.gov, indexed through 31 October 2022, utilizing the following searches: connective tissue growth factor OR/AND one of the following: Biomarker; Children; Congenital heart disease; Pulmonary arterial hypertension [MESH], was conducted. Additional studies were identified through review of references. English-language epidemiological studies, clinical studies, and case reports/series of connective tissue growth factor was included. The authors reached consensus regarding study inclusion after full-text review. The body of literature was assessed for bias qualitatively.

**Conclusion:** Children with PAH-CHD had considerably higher serum connective tissue growth factor (CTGF) levels, which were inversely linked with oxygen saturation. The parameters of the echocardiograph and CTGF did not correlate. A possible diagnostic biomarker for PAH-CHD in children may be found in serum CTGF levels.

**Keywords:** Children's serum CTGF, Pulmonary arterial hypertension, heart disease.

## INTRODUCTION

The severe pulmonary arterial hypertension (PAH) condition has a high mortality and morbidity rate. It can cause right-sided heart failure, increased pulmonary vascular resistance, and even death<sup>(1)</sup>.

Congenital heart disease (CHD) with left-to-right shunts causes increased pulmonary blood flow that harms endothelial cells, triggers apoptosis, and raises pulmonary arterial pressure. All of which lead to the eventual development of neointima and pulmonary vascular remodelling. Children with CHD are hence more susceptible to PAH development<sup>(2)</sup>.

Even if several PAH-targeting medications have increased life expectancy and quality of life by avoiding pulmonary vascular remodelling<sup>(3)</sup>. The prognosis for PAH in children with CHD was not good<sup>(4)</sup>. Blood biomarkers for PAH have been used for diagnosis and prognosis over the years, but none of them have proven to be very successful. These include NT-proBNP (B-type natriuretic peptide), N-terminal pro B-type natriuretic peptide (BNP), endothelin-1 and growth differentiation factor<sup>(5)</sup>.

CCN2, or connective tissue growth factor, is a cysteine-rich matricellular protein that controls a number of illnesses, including the formation of tumours and tissue fibrosis, as well as biological processes like cell proliferation, differentiation, adhesion, and angiogenesis<sup>(6)</sup>.

## Congenital heart disease

Individuals with grown-up congenital heart disease (GUCH) are those patients who have reached

adulthood. The costs for supporting those individuals with long-term, competent medical care are significant. As a result, the burden of CHD on world health grows rapidly<sup>(7)</sup>. Additionally, there is expanding acknowledgement of neuro-developmental issues in adolescent among CHD survivors<sup>(8)</sup>.

CHD, inborn heart defects is defined as the structural malformation(s) of one or more heart chambers and/or deformities of the major intra-thoracic blood vessels and the ensuing deformities that occurs during embryonic development<sup>(9)</sup>.

## Incidence of CHD:

The frequency of CHD is estimated to be 40/1000 if the bicuspid aortic valve is taken into account. The incidence is approximately 4-6/1000 live births<sup>(10)</sup>. Approximately 33% to 50% of these abnormalities are serious and necessitate treatment during the first year of life<sup>(11)</sup>.

## Pulmonary hypertension of newborn

The failure of the typical circulatory transition that takes place after birth is referred to as hypertension of the newborn (PAH). It is a sickness that is defined by severe pulmonary hypertension that results in hypoxemia and decrease of blood flow from the right side of the heart to the left side<sup>(12)</sup>.

Since a patent foramen ovale and patent ductus arteriosus are frequently present at a young age, extrapulmonary blood shunting in newborns is brought on by the increased pulmonary vascular resistance. As a result, there is severe hypoxemia, which could last

forever. Refractory hypoxemia, respiratory distress, and acidosis are more likely to occur in newborn patients with inadequate pulmonary perfusion<sup>(13)</sup>. PPHN is most frequently discovered in term or near-term neonates when it comes to clinical diagnosis, but it can also—though infrequently—occur in premature infants<sup>(14)</sup>. **Harman and Baschat**<sup>(15)</sup> found that under conditions of foetal stress, it is possible to assess changes in flow distribution of umbilical venous return to the liver and the ductus venosus by using Doppler ultrasound techniques to track flow patterns and velocity profiles in the intra-abdominal portion of the umbilical vein and in the ductus venosus.

#### **Fetal pulmonary hypertension:**

For the developing foetus, pulmonary hypertension is a typical and necessary condition. Because the placenta rather than the lungs functions as the organ of gas exchange, only 5 to 10% of the total ventricular output is transferred to the pulmonary vascular bed. The rest of right ventricular output passes through the ductus arteriosus and into the aorta<sup>(16)</sup>. It seems that numerous pathways cooperate before birth to keep the pulmonary vascular tone high. Endothelin-1, low oxygen tension, and leukotrienes are pulmonary vasoconstrictors in a healthy foetus. Low baseline synthesis of vasodilators such prostacyclin and nitric oxide (NO) also contributes to vasoconstriction<sup>(17)</sup>.

**FDA Drug Safety Communication**<sup>(18)</sup> has examined the findings of a more recent study and come to the opinion that it is premature to draw any conclusions about a potential connection between SSRI usage during pregnancy and persistent pulmonary hypertension (PPHN) given the contradictory findings from several studies. The FDA is recommending medical practitioners to continue treating depression during pregnancy as they now do and to report any negative side effects to the FDA Med Watch programme.

PPHN continues to be a major contributor to prenatal morbidity and mortality. Early detection of risk factors for PPHN is crucial due to the inability to effectively prevent or cure the disease. Although there is understanding on factors that may raise the risk of PPHN, it is still insufficient. Currently, giving birth by caesarean section without first going through labour appears to have the single highest risk of a newborn developing PPH<sup>(13)</sup>.

#### **Connective tissue growth factor**

Body fluids include various CTGF domains that are vulnerable to protease cleavage. The carboxy-terminal domain-containing portions bind to the cell surface, whereas the N-terminal domain builds up in body fluids before being internalised and ejected.

The same route is used to mediate TGF- $\beta$ , platelet-derived growth factor, and nerve growth factor dimerization<sup>(19)</sup>.

#### **Biological function of CTGF/CCN2**

CCN2's precise biological role is still a mystery. In vitro, the development of granulation tissue, fibroblast proliferation, matrix synthesis, and angiogenesis are all enhanced by CTGF, which has negligible independent activity. For instance, CTGF stimulates matrix production and FGF-mediated cell proliferation<sup>(20)</sup>. It has also been demonstrated that iodinated CTGF interacts with the low-density lipoprotein receptor. Although the contact is involved in CTGF internalisation and endosomal degradation, it has not yet been demonstrated that it causes a CTGF-mediated signalling event. Generally speaking, in order to help extracellular proteins attach to their cell surface receptors, CCN2 may act as an adapter molecule. Iodinated CTGF exhibits this ability by directly binding fibronectin. In actuality, endogenous CTGF forms a complex with integrins  $\alpha 5\beta 1$  and  $\alpha 4\beta 1$  and syndecan 4 in fibroblasts. As a result of fibronectin, Ctgf/mouse embryonic fibroblasts (MEFs) exhibit noticeably less sticky signalling. In contrast to the brief fibrotic response that CTGF or TGF- $\beta$  administration induces in vivo, Injecting TGF- $\beta$  and CTGF into the same area of the skin causes a prolonged fibrotic response that persists for at least a week after the ligand administration has stopped<sup>(21)</sup>.

In a recent study, it has been demonstrated that by interacting with TGF- $\beta$  through a binding site in the amino-terminal von-Willebrand factor domain, CCN2 assisted in transporting TGF- $\beta$  to the high-affinity TGF- $\beta$  type II receptor. They exhibit insufficient TGF- $\beta$ -induced adhesion signalling and are unable to produce a number of pro-fibrotic mRNAs and proteins, such as type I collagen and  $\alpha$ -SMA. Even in the absence of CTGF, embryonic fibroblasts still react to TGF- $\beta$  via the Smad pathway. CCN2 may generally regulate the activity of specific receptor/ligand interactions. By boosting cell adhesion, amplifying the signalling mediated by other receptors, and serving as a chemical connector to assist integrate external and intracellular signalling networks, CCN2 may thus play a number of roles in signal transduction<sup>(22)</sup>.

#### **CONCLUSION**

Children with PAH-CHD had considerably higher serum CTGF levels, which were inversely linked with oxygen saturation. The parameters of the echocardiogram and CTGF did not correlate. A possible diagnostic biomarker for PAH-CHD in children may be found in serum CTGF levels.

#### **Declarations:**

**Consent for Publication:** I certify that all writers have given their consent to submit the work.

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