

## The Role of Branched Chain Amino Acids for Heart Failure in Children

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### ABSTRACT

Heart failure is an abnormality of the heart's structure or function, causing impairment in oxygen delivery to peripheral tissue. The most common causes of heart failure in children are congenital heart disease and cardiomyopathies. Impairment in cardiac function will affect nutritional status such as higher metabolic demands, lower intake, nutrients malabsorption, and failure to thrive. About 86% children with chronic heart failure had malnutrition. Branched chain amino acids (BCAAs) are essential amino acids that involved in protein synthesis, muscle atrophy prevention, and regulating biogenesis of mitochondrial for cardiac energy formation. This review elucidates current findings on BCAAs supplementation for children with heart failure.

**Keywords:** BCAA; Heart Failure; Congenital Heart Disease; Nutritional Status

### INTRODUCTION

Heart failure (HF) is an abnormality of heart's structure and function causing oxygen disbalance in peripheral tissue.[1] The most common causes of HF in children are congenital heart disease (CHD) and cardiomyopathies. CHD occurs in 8 out of 1000 live births and responsible for 20% of chronic HF. About 10-14 thousand children are admitted to hospital each year due to heart failure, and 27% of them had cardiac muscle abnormalities.[2]

Malnutrition is common among children with chronic HF. About 86% of HF patients had their weight/height below -2 SD of the Z-score. Cardiac dysfunction results in higher metabolic demand, lower nutritional intake, malabsorption, and failure to thrive. As consequence, muscle atrophy, decreasing functional status and immunity could occur, along with longer intra-hospital treatment and higher morbidity-mortality rate.[3]

Branched chain amino acids (BCAAs) are essential amino acids consisting of Leucine, Isoleucine, and Valine. BCAAs are not synthesized in the body, hence adequate and balanced diet is crucial. BCAAs are involved in protein synthesis and have metabolic function.[4] Subsequently, most catabolism process of BCAAs occurs in non-hepatic tissue such as cardiac muscle, neurons, and kidney tissue.[5] Previous studies reported positive effect of BCAAs supplementation for heart disease. This review aims to explore current findings of BCAAs supplementation for HF in children.

### Heart Failure in Children

Heart failure in children is a progressive clinical syndrome due to cardiovascular or non-cardiovascular abnormalities.

Signs and symptoms of HF include edema, dyspnea or respiratory distress, failure to thrive, exercise limitation, circulation and neuro-hormonal impairment.[6] Pathophysiology of HF in children is divided into two major groups, over-circulation and pump failure.

Over-circulation occurs if there is a volume overload in the heart chamber and hypercontractility of the left ventricle, followed with pulmonary hypertension. Following conditions are the cause of over-circulation in children: left-to-right shunt (atrium septal defect, ventricle septal defect, and patent ductus arteriosus), mixed-blood circulation (truncus arteriosus and single chamber heart), parallel circulation in transposition of the great arteries, and conditions which increase the cardiac output (anemia, valve regurgitation, rheumatic heart disease, and endocarditis).

Meanwhile, pump failure is indicated by dysfunction of the left ventricular caused by congenital or acquired disease. Most of these patients will develop pulmonary hypertension. Causes of pump failure include congenital disease (aortic stenosis, coarctation of the aorta, right atrium obstruction), inflammation, arrhythmias, and dilatated cardiomyopathy.[7]

New York Heart Association (NYHA) classification is commonly used for heart failure classification in adults. However, this classification is not applicable for pediatrics. Ross classification is a modified NYHA classification and applicable for pediatrics. Similar to NYHA, Ross also classifies HF into four class (Table 1.) [7]

**TABLE 1:** Ross classification for HF in children.[7]

<b>Class I:</b> Asymptomatic
<b>Class II:</b> Mild tachypnea or diaphoresis with feeding in infants, dyspnea on exertion in older children
<b>Class III:</b> Marked tachypnea or diaphoresis with feeding in infants, marked dyspnea on exertion, prolonged feeding times with growth failure
<b>Class IV:</b> Symptoms such as tachypnea, retractions, grunting, or diaphoresis at rest

### Cardiac Energy Metabolism and Its Implication

Alteration of cardiac energy metabolism is one cause of HF. The heart beats around 100 thousand times a day and consumes large amount of energy (about 6000 grams of ATP). Therefore, energy deficiency impacts cardiac performance and mechanical impairments. The heart utilizes glucose and fatty acid as energy source.

In dysfunctional heart, there are several changes in energy metabolism components. Studies in animal models demonstrated a relative change in fatty acid (60-90%) and glucose (10-40%) contribution in ATP synthesis resulted in lower substrate uptake, higher oxidation process, or both. At the early stage of HF, there is little or no changes in fatty acid contribution. However, at the advanced stage, the contribution is very limited. In addition, during this stage glucose utilization is also limited.[8]

At molecular level, there are changes of cardiac mitochondrial structure and function. As consequences, electron transport complex activity and ATP production are suppressed, resulting in lower energy production and oxygen consumption. At advanced stage of HF, the ATP level is dropped by 30-40%. This condition leads to decrease energy supply to cardiac muscle cells and suppressed cardiac contractility.[8]

Disbalance of energy metabolism is the cause of malnutrition in HF. Children with HF experienced hypermetabolic state, lower intake, nutritional loss, inefficient energy metabolism, and malabsorption. Previous study reported that children with CHD had low weight/age of Z-score during first three months of life.[9] Decreasing fat mass together with inadequate energy intake leads to negative energy balance. [10]

In the other hand, HF also exacerbates malnutrition. Chronic HF impacts the autonomic nervous system by chronically stimulates sympathetic nervous system and Renin-Angiotensin-Aldosterone system (RAAs), Angiotensin II is a potent vasoconstrictor and decreases muscle mass via oxidative stress, protein degradation, cytokine activation, loss of appetite, and muscle regeneration suppression. Children with HF undergo chronic catabolism state which results in loss of body weight and homeostasis disruption. Veins obstruction causes chronic hypoxia and intestinal edema, disrupting the intestinal absorption.[11] Subsequently, activation of neuro-hormonal and proinflammatory cytokine (TNF- $\alpha$  and interleukins) worsens HF outcomes.[3]

### Branched Chain Amino Acid and Its Metabolism

Leucine, Valine, and Isoleucine are three essential amino acids with branch or BCAAs. About 35% of essential amino acids are BCAAs.[4] These BCAAs are involved in muscle protein synthesis, insulin secretion, and energy generation through its catabolism process. [12,13] BCAAs provide major components, namely carbon and nitrogen, for synthesis of protein, sterol, ketone bodies, and glucose. Leucine is involved in cell signaling pathway through target of rapamycin (mTOR) regulation. Therefore, BCAAs are crucial in maintaining cell physiologic function and growth.[12]

The serum BCAAs homeostasis are very stable and dependent to balance of protein degradation and catabolism. The catabolism of BCAAs is important to eliminate amino acid excess and energy generation. All of catabolism process occur in mitochondria of muscle and other tissues.[14] BCAAs are not directly degraded in the liver, yet majorly in the muscle and other tissues. The process begins with BCAAs transformation into branched chain alpha keto-acids (BCKAs) by branched chain amino-transferase (BCAT). The amino groups are released and transforming Leucine into  $\alpha$ -ketoisocaproate, Valine into  $\alpha$ -ketoisovalerate, and Isoleucine into  $\alpha$ -keto- $\beta$ -methylvalerate. Then, these BCKAs undergo decarboxylation by branched chain alpha keto-acids dehydrogenase (BCKD), followed by other enzymatic and produce Acetyl-CoA and Succinyl-CoA. Finally, these products enter the Krebs cycle in mitochondrial respiration.[4]

Dietary reference intake for average BCAAs supplementation for school age children is 99 mg/kgBW/day. This intake is estimated for children's growth. One study reported that BCAAs supplementation for school age children should be higher than its reference, around 147-192 mg/kgBB/day.[15]

BCAAs supplementation is safe if consumed as indicated. Several side effects of BCAAs include fatigue and loss of coordination. BCAAs supplementation should be used cautiously before and during activities involving motoric coordination. BCAAs supplementation is safe for children for short-term duration up to 6 months.

### Branched Chain Amino Acid for Heart Failure

Current evidence of BCAAs supplementation for HF is scarce. Studies in animal model and in vitro reported beneficial effects of BCAAs supplementation for HF. Early study of BCAAs supplementation in isolated mice' heart showed that BCAAs protected the heart from ischemic injury, negative ATP balance, and improved the hemodynamics after the injury.[16] Another study in Dahl HF rats reported that BCAAs administration of 1.5 mg/gBB/day for 10 weeks had following benefits: improving cardiac function by decreasing heart rate, preventing left ventricular dimension in the diastolic phase, intraventricular septal thickness, and fractional shortening; maintaining body weight by preventing muscle mass loss and enhancing nutritional intake; and decreasing mortality rate.[13]

The catabolism of BCAAs might have protective effects on structural and functional deterioration among HF model.[17] Administration of high dose Leucine was associated with hypertrophy compensation after infarction, fibrosis-apoptosis suppression, and oxidative metabolism regulation to preserve structure and function of the heart. Subsequently, Leucine enhance mTOR activity in the cardiac mitochondria and ATP production. The activation of mTOR is associated with lower cardiac remodeling, higher energy balance, and regulation of oxygen in the cells.[18] BCAAs also improved mitochondrial biogenesis in the cardiac muscle tissue.

The level of mitochondrial DNA (mtDNA) and PGC-1 $\alpha$  level in cardiomyocytes is elevated after administration of BCAAs. PGC-1 $\alpha$  is involved in oxidative phosphorylation and related to expression of reactive oxidative species system such as copper/zinc superoxide dismutase (SOD1), manganese superoxide dismutase (SOD2), catalase, and glutathione peroxidase (GPx1). Activation of mRNA encoding PGC-1 $\alpha$ , nuclear respiratory factor-1 (NRF-1), mtDNA transcription factor A (Tfam), and  $\beta$ -subunit of the mitochondrial H<sup>+</sup>-ATP synthase ( $\beta$ -F1-ATPase) is responsible for this condition.[19] Currently, only one study explored association between BCAAs and HF. The study reported that patients with low BMI had worse outcome than high BMI which low level of BCAAs among low BMI patients is associated with higher repeated hospitalization.[20] Therefore, it is plausible to conclude low BCAAs is associated with worse prognosis in HF patients.

### CONCLUSION

BCAAs are involved in protein synthesis, muscle atrophy prevention, and regulating biogenesis of mitochondrial for cardiac energy formation. Current evidence in animal model demonstrated beneficial cardiac outcome. Studies in human should be conducted to confirm these benefits.

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