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**Is branched-chain amino acid nutritional supplementation beneficial or detrimental in heart failure?**

Narita K *et al*. Branched-chain amino acid in heart failure

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**Abstract**

Sarcopenia or cachexia is often complicated in heart failure. Nutritional support, particularly branched-chain amino acid (BCAA) supplementation, is a candidate treatment for improving sarcopenia or cachexia in elderly patients. However, the efficacy of BCAA supplementation in patients with heart failure has not been established, and the issue is comparatively more complex. Indeed, there are conflicting reports on the efficacy of BCAA supplementation. The evidence for including BCAA supplementation in treating patients with heart failure was reviewed, and the complexity of the issue was discussed.

**Key Words:** Branched-chain amino acid; Heart failure; Sarcopenia; Cachexia; Nutrition; Branched-chain a-ketoacids

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**Core Tip:** The pros and cons of branched-chain amino acid (BCAA) supplementation can vary depending on the patient and their specific conditions. Particularly, BCAA supplementation for patients with cardiac dysfunction, who could easily be presumed to have metabolic dysfunction, should be carefully considered.

**INTRODUCTION**

Sarcopenia or cachexia is often complicated in heart failure, which aggravates the clinical course of the disease. Sarcopenia and cachexia were reported to be present in approximately 20% of patients with heart failure; however, there were differences in their percentages among different studies[1]. Also, both of them sometimes coexist in approximately 10% of patients with heart failure[2]. Low physical performance and reduced cardiopulmonary capacity influence sarcopenia and cachexia[3]. These comorbidities are independent predictors of the clinical course of patients with heart failure[4]. Therefore, the therapeutic strategy for sarcopenia or cachexia is a critical issue in managing heart failure. However, there is no standard management strategy at this time.

Nutritional support might be one candidate treatment for the improvement of sarcopenia or cachexia. Amino acid supplementation was effective for sarcopenia in elderly patients. Rondanelli *et al*[5] demonstrated nutritional supplementation with whey protein, essential amino acids, and vitamin D for twelve weeks, significantly increasing fat-free mass and muscle strength. Among several amino acid supplementation types, branched-chain amino acids (BCAAs) were beneficial in forming skeletal muscles because they account for a large part of the essential amino acids that form these skeletal muscles[6]. Ottestad *et al*[7] reported that BCAA levels decreased by 10% in sarcopenic adults, whereas nonessential amino acid levels did not change, suggesting the importance of BCAAs in skeletal muscle maintenance.

**Beneficial effect of BCAA in patients with heart failure**

Several reports about BCAA’s effect on cardiopulmonary performance in other populations exist (Table 1). Chang *et al*[8] demonstrated that BCAA and arginine supplementation improved performance in intermittent sprints by reducing perceived exertion. Other reports on experimental and clinical conditions, according to the effect of improvement in exercise capacity by BCAA supplementation, were also presented[9-11]. Additionally, BCAA supplementation also reduced the muscle damage associated with endurance exercise[12]. Therefore, BCAA supplementation might have favorable effects on improving and maintaining exercise capacity, which might help patients with heart failure and reduced exercise capacity. Furthermore, several reports about the efficacy of BCAA supplementation for the improvement of sarcopenia also exist. Ko *et al*[13] demonstrated that BCAA administration for five weeks improved several parameters, including bioelectrical-impedance-analysis-derived skeletal mass index by approximately 10% and grip strength by about 10%. BCAA supplementation before and after exercise has shown beneficial effects in decreasing exercise-induced muscle damage and promoting muscle-protein synthesis[14]. Leucine supplementation also enhances myofibrillar protein synthesis, leading to increased muscle strength[15,16]. These effects could be partly explained by the shift to anabolic signaling of the skeletal muscle through the mammalian target of rapamycin complex 1 pathway[17]. Indeed, the anabolic pathway decreased because of alterations in the insulin-like growth factor 1/growth hormone axis and increased catabolism, induced by proinflammatory cytokines, in the presence of heart failure with sarcopenia[18]. There were several reports of the impact of BCAA on the treatment of sarcopenia.

Nichols *et al*[19] performed a systematic review of the effect of amino acid supplementation in heart failure. They demonstrated that essential amino acid supplementation could improve important outcome measures related to sarcopenia. For instance, amino acid supplementation increased the six-minute walk test distance by approximately 20%. In contrast, few reports demonstrated BCAA efficacy in the improvement of heart failure[20,21]. Oral intake of AAs is presumed to improve exercise capacities through its beneficial effect on the skeletal muscle in patients with heart failure. Furthermore, BCAA treatment decreased the heart rate, preserved cardiac function, and prolonged survival in heart failure with reduced ejection fraction model rats[20]. Uchino *et al*[21] reported that in-hospital heart failure patients with hypoalbuminemia showed increased serum albumin, decreased cardiothoracic ratio (CTR), and increased cholinesterase after BCAA supplementation. Another beneficial effect of BCAA is that it activates rapamycin’s mammalian target (mTOR), promoting albumin synthesis[22]. The increase in serum albumin might favorably affect the clinical course of heart failure. The improvement in CTR could be due to decongestion efficiently induced by BCAA administration.

**Detrimental effect of BCAA in patients with heart failure**

A clinical trial on the efficacy of BCAA supplementation in cardiac rehabilitation was conducted[23]. However, the issue might be more complex. Conversely, there are reports of BCAA’s pathological role in heart failure. In clinical studies, several reports about the link between the high level of circulating BCAA and the risk of cardiovascular diseases, including heart failure, are present[24-27]. For instance, in the study of type 2 diabetes patients free of cardiovascular and renal diseases, patients with incident heart failure had 5.6% higher serum BCAAs than those without heart failure (HF). Serum BCAAs had a positive linear association with incident HF, adjusting for age, sex, and duration of diabetes. They demonstrated that high levels of BCAA corresponded to the increased event risk of atherosclerotic diseases and heart failure. Recent studies reported that BCAA catabolism is impaired in a failing heart, downregulating catabolic enzyme expression[28,29]. This catabolic derangement increases the levels of BCAAs and branched-chain a-ketoacids (BCKAs), which reportedly have a direct effect on cardiac remodeling and dysfunction through mTOR activation and reactive oxygen production (Figure 1)[30]. In basic experiments, incubation with BCKAs led to decreased cell survival and increased apoptosis in primary cardiomyocytes[31]. Moreover, increased BCAA concentration in the heart was shown to suppress glucose metabolism, enhancing ischemia-reperfusion injury by enhancing the GCN2/ATF6/PPAR-α pathway[32]. BCKA dehydrogenase (BCKD) activity, a critical step in BCAA catabolism, is regulated by the phosphorylation of regulatory subunit E1a. BCKD kinase (BCKDK) phosphorylates E1a to inhibit BCKA dehydrogenase activity, increasing BCKDK expression in defective hearts[33]. From these findings, the additional increase of BCAA through BCAA supplementation might exacerbate BCAA metabolites’ burden in a failed heart, worsening the clinical course further in heart failure.

By contrast, some hopeful hints about the BCAA metabolic pathway in heart failure therapy might exist. In BCKDK regulation, 3,6-dichlorobenzo[b]thiophene-2-carboxylic acid (BT2), a small-molecule BCKDK inhibitor, blocks BCKD phosphorylation, leading to increased BCAA catabolism[34]. Moreover, BT2 might alleviate oxidative stress by reducing BCKA or mTOR complex 1 activity by lowering BCAA concentrations, thereby improving cardiac function[35]. A study of BT2 administration to mice suggested that BT2 treatment improved cardiac function and led to remodeling without apparent toxicity[34].

The transcriptional factor Kruppel-like factor 15 (KLF15) also has a critical role in cardiac BCAA catabolic regulation[28]. KLF15-deficient hearts displayed reduced BCAT2 expression, another critical step in BCAA catabolism, whereas intramyocardial BCKA levels were elevated in KLF15-null hearts. KLF15 is reportedly a direct transcriptional activator of BCAT2[36]. KLF15 expression is lower in human cardiomyopathy. Therefore, the loss of KLF15 is a critical molecular mechanism underlying stress-induced BCAA catabolic defects in the diseased heart[37,38]. The modification of the KLF15 pathway could help the diseased heart in the BCAA metabolic pathway; however, its overexpression evoked arrhythmia due to its regulatory role in the potassium channel[39].

Additionally, the mitochondrial matrix-targeted 2C-type ser/thr protein phosphatase 2C family member (PP2Cm) is the endogenous phosphatase of the BCKD and functions as a key regulator of BCAA catabolism and homeostasis. The PP2Cm expression in the heart is dynamically regulated in the failing heart[40]. A study on PP2Cm-deficient mice revealed that PP2Cm deficiency led to heart failure signs, including weight gain, reduced left ventricular ejection fraction (LVEF), and chamber dilation[30]. The study findings suggested the impact of BCAA metabolism on the pathogenesis of heart failure. Furthermore, BT2 overturned the dysfunction induced in PP2Cm-knockout mice, significantly preserved LVEF, and reduced chamber dilation. The efficacy of BT2 treatment for the reinforcement of the BCAA metabolic pathway might be more than expected for the dysfunctional heart[41]. These basic findings would present some hints for treating heart failure, which is associated with the BCAA pathway.

**CONCLUSION**

Studies have shown that BCAAs are beneficial in heart failure. Conversely, BCAAs could act as exacerbators of heart failure. Nevertheless, improving BCAA metabolism might lead to an effective treatment strategy for the disease. In conclusion, the pros and cons of BCAA supplementation could vary depending on the patient and their specific conditions. Particularly, BCAA supplementation for patients with cardiac dysfunction, who could easily be presumed to have metabolic dysfunction, should be carefully considered.

**REFERENCES**

1 **Christensen HM**, Kistorp C, Schou M, Keller N, Zerahn B, Frystyk J, Schwarz P, Faber J. Prevalence of cachexia in chronic heart failure and characteristics of body composition and metabolic status. *Endocrine* 2013; **43**: 626-634 [PMID: 23179776 DOI: 10.1007/s12020-012-9836-3]

2 **Emami A**, Saitoh M, Valentova M, Sandek A, Evertz R, Ebner N, Loncar G, Springer J, Doehner W, Lainscak M, Hasenfuß G, Anker SD, von Haehling S. Comparison of sarcopenia and cachexia in men with chronic heart failure: results from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). *Eur J Heart Fail* 2018; **20**: 1580-1587 [PMID: 30160804 DOI: 10.1002/ejhf.1304]

3 **Curcio F**, Testa G, Liguori I, Papillo M, Flocco V, Panicara V, Galizia G, Della-Morte D, Gargiulo G, Cacciatore F, Bonaduce D, Landi F, Abete P. Sarcopenia and Heart Failure. *Nutrients* 2020; **12** [PMID: 31947528 DOI: 10.3390/nu12010211]

4 **von Haehling S**, Garfias Macedo T, Valentova M, Anker MS, Ebner N, Bekfani T, Haarmann H, Schefold JC, Lainscak M, Cleland JGF, Doehner W, Hasenfuss G, Anker SD. Muscle wasting as an independent predictor of survival in patients with chronic heart failure. *J Cachexia Sarcopenia Muscle* 2020; **11**: 1242-1249 [PMID: 32767518 DOI: 10.1002/jcsm.12603]

5 **Rondanelli M**, Klersy C, Terracol G, Talluri J, Maugeri R, Guido D, Faliva MA, Solerte BS, Fioravanti M, Lukaski H, Perna S. Whey protein, amino acids, and vitamin D supplementation with physical activity increases fat-free mass and strength, functionality, and quality of life and decreases inflammation in sarcopenic elderly. *Am J Clin Nutr* 2016; **103**: 830-840 [PMID: 26864356 DOI: 10.3945/ajcn.115.113357]

6 **Shimomura Y**, Yamamoto Y, Bajotto G, Sato J, Murakami T, Shimomura N, Kobayashi H, Mawatari K. Nutraceutical effects of branched-chain amino acids on skeletal muscle. *J Nutr* 2006; **136**: 529S-532S [PMID: 16424141 DOI: 10.1093/jn/136.2.529S]

7 **Ottestad I**, Ulven SM, Øyri LKL, Sandvei KS, Gjevestad GO, Bye A, Sheikh NA, Biong AS, Andersen LF, Holven KB. Reduced plasma concentration of branched-chain amino acids in sarcopenic older subjects: a cross-sectional study. *Br J Nutr* 2018; **120**: 445-453 [PMID: 29909813 DOI: 10.1017/S0007114518001307]

8 **Chang CK**, Chang Chien KM, Chang JH, Huang MH, Liang YC, Liu TH. Branched-chain amino acids and arginine improve performance in two consecutive days of simulated handball games in male and female athletes: a randomized trial. *PLoS One* 2015; **10**: e0121866 [PMID: 25803783 DOI: 10.1371/journal.pone.0121866]

9 **Calders P**, Pannier JL, Matthys DM, Lacroix EM. Pre-exercise branched-chain amino acid administration increases endurance performance in rats. *Med Sci Sports Exerc* 1997; **29**: 1182-1186 [PMID: 9309629 DOI: 10.1097/00005768-199709000-00010]

10 **Calders P**, Matthys D, Derave W, Pannier JL. Effect of branched-chain amino acids (BCAA), glucose, and glucose plus BCAA on endurance performance in rats. *Med Sci Sports Exerc* 1999; **31**: 583-587 [PMID: 10211856 DOI: 10.1097/00005768-199904000-00015]

11 **Watson P**, Shirreffs SM, Maughan RJ. The effect of acute branched-chain amino acid supplementation on prolonged exercise capacity in a warm environment. *Eur J Appl Physiol* 2004; **93**: 306-314 [PMID: 15349784 DOI: 10.1007/s00421-004-1206-2]

12 **Coombes JS**, McNaughton LR. Effects of branched-chain amino acid supplementation on serum creatine kinase and lactate dehydrogenase after prolonged exercise. *J Sports Med Phys Fitness* 2000; **40**: 240-246 [PMID: 11125767]

13 **Ko CH**, Wu SJ, Wang ST, Chang YF, Chang CS, Kuan TS, Chuang HY, Chang CM, Chou W, Wu CH. Effects of enriched branched-chain amino acid supplementation on sarcopenia. *Aging (Albany NY)* 2020; **12**: 15091-15103 [PMID: 32712600 DOI: 10.18632/aging.103576]

14 **Shimomura Y**, Murakami T, Nakai N, Nagasaki M, Harris RA. Exercise promotes BCAA catabolism: effects of BCAA supplementation on skeletal muscle during exercise. *J Nutr* 2004; **134**: 1583S-1587S [PMID: 15173434 DOI: 10.1093/jn/134.6.1583S]

15 **Komar B**, Schwingshackl L, Hoffmann G. Effects of leucine-rich protein supplements on anthropometric parameter and muscle strength in the elderly: a systematic review and meta-analysis. *J Nutr Health Aging* 2015; **19**: 437-446 [PMID: 25809808 DOI: 10.1007/s12603-014-0559-4]

16 **Murphy CH**, Saddler NI, Devries MC, McGlory C, Baker SK, Phillips SM. Leucine supplementation enhances integrative myofibrillar protein synthesis in free-living older men consuming lower- and higher-protein diets: a parallel-group crossover study. *Am J Clin Nutr* 2016; **104**: 1594-1606 [PMID: 27935521 DOI: 10.3945/ajcn.116.136424]

17 **Glynn EL**, Fry CS, Drummond MJ, Timmerman KL, Dhanani S, Volpi E, Rasmussen BB. Excess leucine intake enhances muscle anabolic signaling but not net protein anabolism in young men and women. *J Nutr* 2010; **140**: 1970-1976 [PMID: 20844186 DOI: 10.3945/jn.110.127647]

18 **Anker SD**, Chua TP, Ponikowski P, Harrington D, Swan JW, Kox WJ, Poole-Wilson PA, Coats AJ. Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. *Circulation* 1997; **96**: 526-534 [PMID: 9244221 DOI: 10.1161/01.cir.96.2.526]

19 **Nichols S**, McGregor G, Al-Mohammad A, Ali AN, Tew G, O'Doherty AF. The effect of protein and essential amino acid supplementation on muscle strength and performance in patients with chronic heart failure: a systematic review. *Eur J Nutr* 2020; **59**: 1785-1801 [PMID: 31659450 DOI: 10.1007/s00394-019-02108-z]

20 **Tanada Y**, Shioi T, Kato T, Kawamoto A, Okuda J, Kimura T. Branched-chain amino acids ameliorate heart failure with cardiac cachexia in rats. *Life Sci* 2015; **137**: 20-27 [PMID: 26141987 DOI: 10.1016/j.lfs.2015.06.021]

21 **Uchino Y**, Watanabe M, Takata M, Amiya E, Tsushima K, Adachi T, Hiroi Y, Funazaki T, Komuro I. Effect of Oral Branched-Chain Amino Acids on Serum Albumin Concentration in Heart Failure Patients with Hypoalbuminemia: Results of a Preliminary Study. *Am J Cardiovasc Drugs* 2018; **18**: 327-332 [PMID: 29511994 DOI: 10.1007/s40256-018-0269-0]

22 **Gopal DM**, Kalogeropoulos AP, Georgiopoulou VV, Tang WW, Methvin A, Smith AL, Bauer DC, Newman AB, Kim L, Harris TB, Kritchevsky SB, Butler J; Health ABC Study. Serum albumin concentration and heart failure risk The Health, Aging, and Body Composition Study. *Am Heart J* 2010; **160**: 279-285 [PMID: 20691833 DOI: 10.1016/j.ahj.2010.05.022]

23 **Takata M**, Amiya E, Watanabe M, Hosoya Y, Nakayama A, Fujiwara T, Taya M, Oguri G, Hyodo K, Takayama N, Takano N, Mashiko T, Uemura Y, Komuro I. An exploratory study on the efficacy and safety of a BCAA preparation used in combination with cardiac rehabilitation for patients with chronic heart failure. *BMC Cardiovasc Disord* 2017; **17**: 205 [PMID: 28750610 DOI: 10.1186/s12872-017-0639-6]

24 **Du X**, Li Y, Wang Y, You H, Hui P, Zheng Y, Du J. Increased branched-chain amino acid levels are associated with long-term adverse cardiovascular events in patients with STEMI and acute heart failure. *Life Sci* 2018; **209**: 167-172 [PMID: 30092297 DOI: 10.1016/j.lfs.2018.08.011]

25 **Paynter NP**, Balasubramanian R, Giulianini F, Wang DD, Tinker LF, Gopal S, Deik AA, Bullock K, Pierce KA, Scott J, Martínez-González MA, Estruch R, Manson JE, Cook NR, Albert CM, Clish CB, Rexrode KM. Metabolic Predictors of Incident Coronary Heart Disease in Women. *Circulation* 2018; **137**: 841-853 [PMID: 29459470 DOI: 10.1161/CIRCULATIONAHA.117.029468]

26 **Fan Y**, Li Y, Chen Y, Zhao YJ, Liu LW, Li J, Wang SL, Alolga RN, Yin Y, Wang XM, Zhao DS, Shen JH, Meng FQ, Zhou X, Xu H, He GP, Lai MD, Li P, Zhu W, Qi LW. Comprehensive Metabolomic Characterization of Coronary Artery Diseases. *J Am Coll Cardiol* 2016; **68**: 1281-1293 [PMID: 27634119 DOI: 10.1016/j.jacc.2016.06.044]

27 **Lim LL**, Lau ESH, Fung E, Lee HM, Ma RCW, Tam CHT, Wong WKK, Ng ACW, Chow E, Luk AOY, Jenkins A, Chan JCN, Kong APS. Circulating branched-chain amino acids and incident heart failure in type 2 diabetes: The Hong Kong Diabetes Register. *Diabetes Metab Res Rev* 2020; **36**: e3253 [PMID: 31957226 DOI: 10.1002/dmrr.3253]

28 **Peterson MB**, Mead RJ, Welty JD. Free amino acids in congestive heart failure. *J Mol Cell Cardiol* 1973; **5**: 139-147 [PMID: 4704669 DOI: 10.1016/0022-2828(73)90047-3]

29 **Li R**, He H, Fang S, Hua Y, Yang X, Yuan Y, Liang S, Liu P, Tian Y, Xu F, Zhang Z, Huang Y. Time Series Characteristics of Serum Branched-Chain Amino Acids for Early Diagnosis of Chronic Heart Failure. *J Proteome Res* 2019; **18**: 2121-2128 [PMID: 30895791 DOI: 10.1021/acs.jproteome.9b00002]

30 **Sun H**, Olson KC, Gao C, Prosdocimo DA, Zhou M, Wang Z, Jeyaraj D, Youn JY, Ren S, Liu Y, Rau CD, Shah S, Ilkayeva O, Gui WJ, William NS, Wynn RM, Newgard CB, Cai H, Xiao X, Chuang DT, Schulze PC, Lynch C, Jain MK, Wang Y. Catabolic Defect of Branched-Chain Amino Acids Promotes Heart Failure. *Circulation* 2016; **133**: 2038-2049 [PMID: 27059949 DOI: 10.1161/CIRCULATIONAHA.115.020226]

31 **Guo X**, Huang C, Lian K, Wang S, Zhao H, Yan F, Zhang X, Zhang J, Xie H, An R, Tao L. BCKA down-regulates mTORC2-Akt signal and enhances apoptosis susceptibility in cardiomyocytes. *Biochem Biophys Res Commun* 2016; **480**: 106-113 [PMID: 27697526 DOI: 10.1016/j.bbrc.2016.09.162]

32 **Li Y**, Xiong Z, Yan W, Gao E, Cheng H, Wu G, Liu Y, Zhang L, Li C, Wang S, Fan M, Zhao H, Zhang F, Tao L. Branched chain amino acids exacerbate myocardial ischemia/reperfusion vulnerability *via* enhancing GCN2/ATF6/PPAR-α pathway-dependent fatty acid oxidation. *Theranostics* 2020; **10**: 5623-5640 [PMID: 32373236 DOI: 10.7150/thno.44836]

33 **Wang W**, Zhang F, Xia Y, Zhao S, Yan W, Wang H, Lee Y, Li C, Zhang L, Lian K, Gao E, Cheng H, Tao L. Defective branched chain amino acid catabolism contributes to cardiac dysfunction and remodeling following myocardial infarction. *Am J Physiol Heart Circ Physiol* 2016; **311**: H1160-H1169 [PMID: 27542406 DOI: 10.1152/ajpheart.00114.2016]

34 **Chen M**, Gao C, Yu J, Ren S, Wang M, Wynn RM, Chuang DT, Wang Y, Sun H. Therapeutic Effect of Targeting Branched-Chain Amino Acid Catabolic Flux in Pressure-Overload Induced Heart Failure. *J Am Heart Assoc* 2019; **8**: e011625 [PMID: 31433721 DOI: 10.1161/JAHA.118.011625]

35 **Uddin GM**, Zhang L, Shah S, Fukushima A, Wagg CS, Gopal K, Al Batran R, Pherwani S, Ho KL, Boisvenue J, Karwi QG, Altamimi T, Wishart DS, Dyck JRB, Ussher JR, Oudit GY, Lopaschuk GD. Impaired branched chain amino acid oxidation contributes to cardiac insulin resistance in heart failure. *Cardiovasc Diabetol* 2019; **18**: 86 [PMID: 31277657 DOI: 10.1186/s12933-019-0892-3]

36 **Liu Y**, Dong W, Shao J, Wang Y, Zhou M, Sun H. Branched-Chain Amino Acid Negatively Regulates KLF15 Expression *via* PI3K-AKT Pathway. *Front Physiol* 2017; **8**: 853 [PMID: 29118722 DOI: 10.3389/fphys.2017.00853]

37 **Fisch S**, Gray S, Heymans S, Haldar SM, Wang B, Pfister O, Cui L, Kumar A, Lin Z, Sen-Banerjee S, Das H, Petersen CA, Mende U, Burleigh BA, Zhu Y, Pinto YM, Liao R, Jain MK. Kruppel-like factor 15 is a regulator of cardiomyocyte hypertrophy. *Proc Natl Acad Sci U S A* 2007; **104**: 7074-7079 [PMID: 17438289 DOI: 10.1073/pnas.0701981104]

38 **Leenders JJ**, Wijnen WJ, Hiller M, van der Made I, Lentink V, van Leeuwen RE, Herias V, Pokharel S, Heymans S, de Windt LJ, Høydal MA, Pinto YM, Creemers EE. Regulation of cardiac gene expression by KLF15, a repressor of myocardin activity. *J Biol Chem* 2010; **285**: 27449-27456 [PMID: 20566642 DOI: 10.1074/jbc.M110.107292]

39 **Jeyaraj D**, Haldar SM, Wan X, McCauley MD, Ripperger JA, Hu K, Lu Y, Eapen BL, Sharma N, Ficker E, Cutler MJ, Gulick J, Sanbe A, Robbins J, Demolombe S, Kondratov RV, Shea SA, Albrecht U, Wehrens XH, Rosenbaum DS, Jain MK. Circadian rhythms govern cardiac repolarization and arrhythmogenesis. *Nature* 2012; **483**: 96-99 [PMID: 22367544 DOI: 10.1038/nature10852]

40 **Lu G**, Ren S, Korge P, Choi J, Dong Y, Weiss J, Koehler C, Chen JN, Wang Y. A novel mitochondrial matrix serine/threonine protein phosphatase regulates the mitochondria permeability transition pore and is essential for cellular survival and development. *Genes Dev* 2007; **21**: 784-796 [PMID: 17374715 DOI: 10.1101/gad.1499107]

41 **Sun H**, Lu G, Ren S, Chen J, Wang Y. Catabolism of branched-chain amino acids in heart failure: insights from genetic models. *Pediatr Cardiol* 2011; **32**: 305-310 [PMID: 21210099 DOI: 10.1007/s00246-010-9856-9]

**Footnotes**

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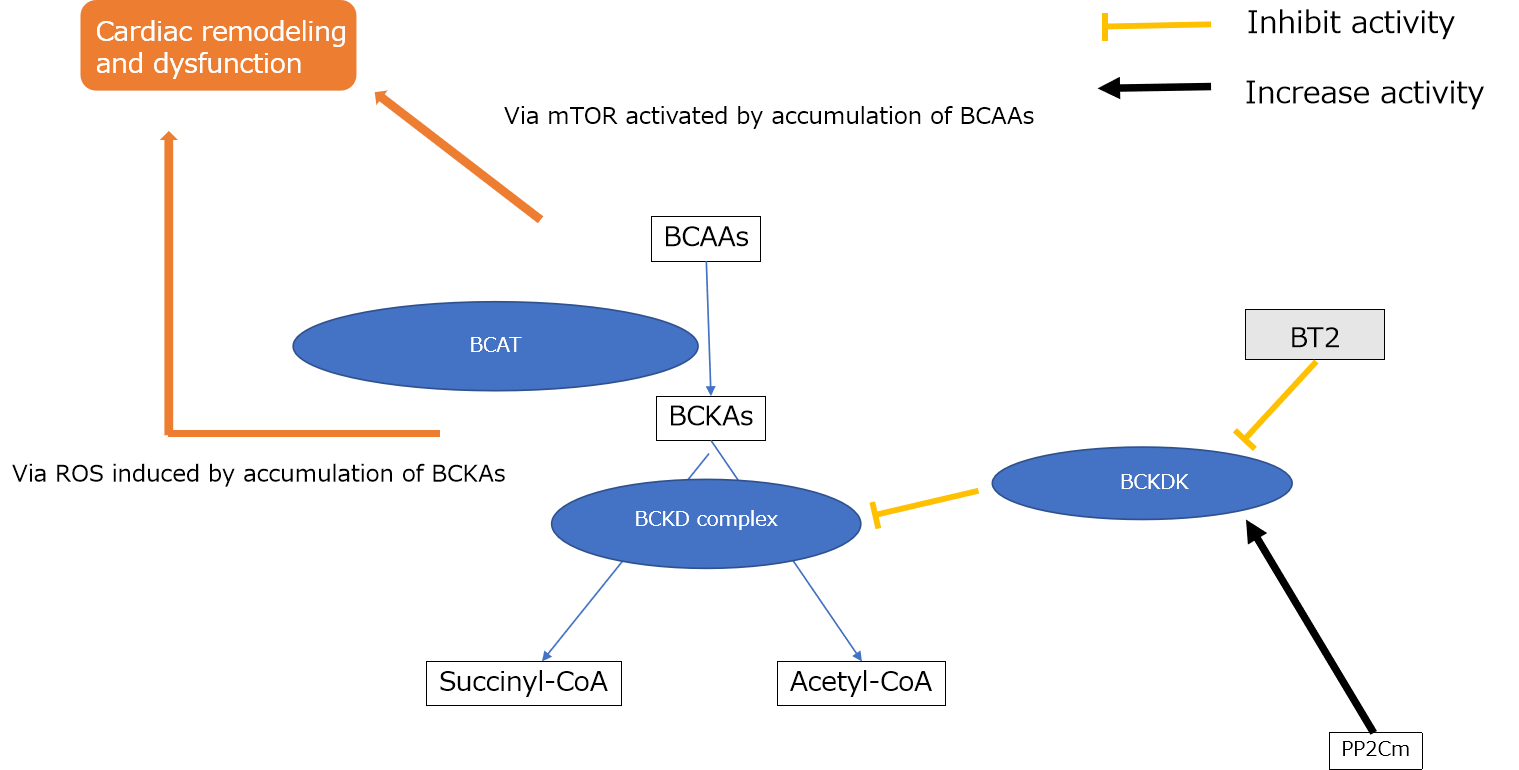
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**Figure Legends**

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**Figure 1 Branched-chain amino acid and its catabolic pathway in patients with heart failure.** Branched-chain amino acid (BCAA) are degraded into their final products of acetyl-CoA and succinyl-CoA, however the decrease of branched-chain keto acid (BCKA) dehydrogenase leads to the increase of BCKA. The increases of BCAAs and BCKAs potentially exacerbate heart failure. mTOR: Mammalian target of rapamycin; BCAA: Branched-chain amino acid; BCKA: Branched-chain keto acid; BCAT: Branched chain aminotransferase; ROS: Reactive oxygen species; BCKD: Branched-chain keto acid dehydrogenase; BCKDK: Branched-chain keto acid dehydrogenase kinase; BT2: 3,6-dichlorobenzo[b]thiophene-2-carboxylic acid; PP2Cm: Protein phosphatase 2C in mitochondria.

**Table 1 Outcomes of branched-chain amino acid administration in clinical trials**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Study design** | **Sample size** | **Subjects** | **Dose** | **Length** | **Outcome** |
| Chang *et al*[8] | Double-blind, randomized | 22 | Well-trained handball players | 0.17 g/kg BCAA and 0.04 g/kg arginine together | 1 d | Improve the performance in intermittent sprint |
| Watson *et al*[11] | Double-blind, randomized | 8 | Healthy male | 12 g/L BCAA | Every 15 mins during exercise | Exercise capacity change observed between subjects in response to BCAA ingestion |
| Coombesand McNaughton [12] | Prospective, assigned to one of two groups | 16 | Males | 12 g/d BCAA | 14 d | Supplementary BCAA decreased serum concentrations of the intramuscular enzymes |
| Ko *et al* [13] | Quasi-experimental single-arm intervention | 33 | Middle-aged and elderly | Leucine 0.54 g, isoleucine 0.43 g, valine 0.36 g, glutamine 0.65 g, arginine 0.61 g and other amino acids 1.01 g | Twice daily for 5 wk | Short-term positive effects on sarcopenic parameters |
| Komar *et al*[15] | Systematic review and meta-analysis | 999 | - | Each reference | Each reference | Beneficial effects on body weight, body mass index, and lean body mass in older persons |
| Murphy *et al*[16] | Randomized, single-blind, parallel-group, placebo-controlled crossover study | 20 | Men, 65-85 yr of age, bmi (in kg/m2) from 20 to 35, nonsmokers, and generally healthy | Higher protein intake group (1.2 g/kg/d) or lower protein intake group (0.8 g/kg/d) | 9 d | Enhances the anabolic effect of resistance exercise |
| Glynn *et al*[17] | Prospective | 14 | Young participants (6 men, 8 women) | 10 g essential amino acids | 180 min post ingestion | Induce a maximal skeletal muscle protein anabolic response |
| Nichols *et al*[19] | Systematic review and meta-analysis | 167 | - | Each reference | Each reference | Increase lean body mass and 6-minute walk test distance in patients with heart failure |
| Uchino *et al*[21] | Randomized, controlled trial | 18 | In-hospital heart failure patients with serum albumin < 3.5 g/dL | One pack of BCAA granules containing 1144 mg of l-valine, 1904 mg of l-leucine, and 952 mg of l-isoleucine | 28 d, 3 time a day | Increased serum albumin and decreased ctr in-hospital hf patients with hypoalbuminemia |

BCAA: Branched-chain amino acid.