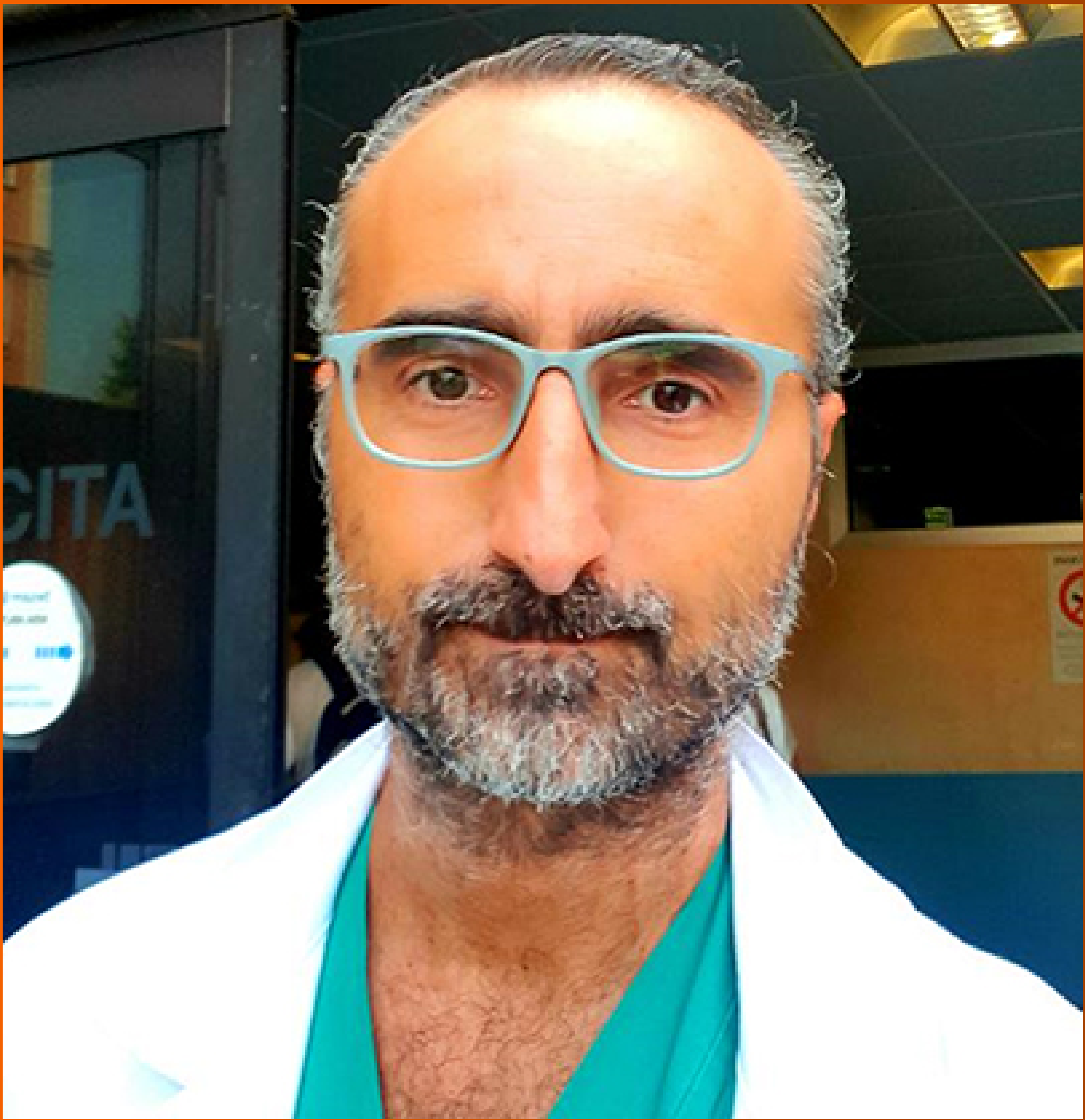
ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2021 June 26; 13(6): 155-182



Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 13 Number 6 June 26, 2021

World Journal of Cardiology

Contents Monthly Volume 13 Number 6 June 26, 2021

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RESPONSIBLE EDITORS FOR THIS ISSUE

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NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Ramdas G Pai, Dimitrios Tousoulis, Marco Matteo Ciccone

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https://www.wjgnet.com/1949-8462/editorialboard.htm

PUBLICATION DATE
June 26, 2021

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https://www.wjgnet.com/bpg/gerinfo/242

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Cardiology

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World J Cardiol 2021 June 26; 13(6): 163-169

DOI: 10.4330/wjc.v13.i6.163

ISSN 1949-8462 (online)

MINIREVIEWS

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

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Author contributions: Amiya E contributed to the conception and design of the research; Narita K contributed to the acquisition and analysis of the data; Narita K and Amiya E contributed to the interpretation of the data; and Narita K and Amiya E drafted the manuscript; all authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Conflict-of-interest statement: Amiya E belongs to the Department of Therapeutic Strategy for Heart Failure, Graduate School of Medicine, University of Tokyo, which is endowed by Actelion Pharmaceuticals Japan Ltd., Otsuka Pharmaceutical, NIPRO CORPORATION, Terumo Corp., Senko Medical Instrument Mfg., Century Medical Inc., Kinetic Concepts Inc., and St. Jude Medical. The other author has no conflicts of interest to disclose.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external

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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

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.

Citation: Narita K, Amiya E. Is branched-chain amino acid nutritional supplementation beneficial or detrimental in heart failure? *World J Cardiol* 2021; 13(6): 163-169
URL: https://www.wjgnet.com/1949-8462/full/v13/i6/163.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i6.163

Manuscript source: Invited manuscript

Specialty type: Cardiac and cardiovascular systems

Country/Territory of origin: Japan

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 5, 2021
Peer-review started: February 5, 2021
First decision: February 28, 2021
Revised: March 12, 2021
Accepted: May 22, 2021
Article in press: May 22, 2021
Published online: June 26, 2021

P-Reviewer: Kharlamov AN
S-Editor: Liu M
L-Editor: A
P-Editor: Yuan YY

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.

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
Coombes and 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/m^2) 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.

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

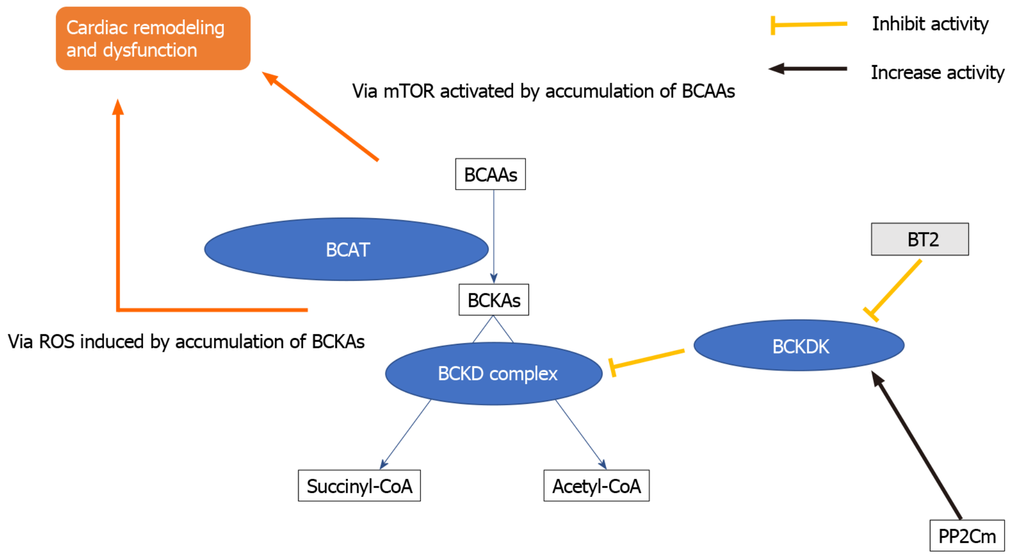

Figure 1 Branched-chain amino acid and its catabolic pathway in patients with heart failure. Branched-chain amino acid (BCAA) are degraded into their final products of acetyl-CoA and succinyl-CoA, however the decrease of branched-chain keto acid (BCKA) dehydrogenase leads to the increase of BCKA. The 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.

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.

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