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A retrospective study on the relationship between plasma β-hydroxybutyric acid levels and short-term prognosis of cardiac function in patients with acute myocardial infarction combined with heart failure

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Abstract

Background: Ketone body metabolism can improve cardiomyocytes metabolism and reduce myocardial oxygen consumption; however, its role in the short-term prognosis of patients with acute myocardial infarction combined with heart failure has not been clearly elucidated. The aim of this study was to investigate the effect of β-hydroxybutyric acid, the main component of ketone bodies, on the short-term prognosis of patients with acute myocardial infarction combined with heart failure.

Methods: This was a retrospective observational study that enrolled patients admitted to the Qilu Hospital of Shandong University for acute myocardial infarction combined with heart failure between January 1, 2019, and December 31, 2022. According to whether β-hydroxybutyric acid was elevated or not, subjects were divided into a β-hydroxybutyric acid elevated and nonelevated groups, to observe the difference in cardiac function improvement between the two groups.

Results: This study included a total of 260 patients, of which 170 exhibited elevated levels of β-hydroxybutyric acid. Compared to the patients in the nonelevated group, patients in the elevated β-hydroxybutyric acid group had higher plasma levels of creatine kinase myocardial band and greater Gensini scores. Multivariate logistic regression analysis indicated that an increase in β-hydroxybutyric acid levels (odds ratio: 3.076; 95% confidence intervals: 1.479–6.395; $P = 0.003$) is an independent protective factor affecting the prognosis of cardiac function in patients with acute myocardial infarction combined with heart failure.

Conclusion: In patients with acute myocardial infarction combined with heart failure, plasma β-hydroxybutyric acid serves as an independent protective factor for short-term improvement in cardiac function.

Keywords: Acute myocardial infarction, Energy metabolism, Heart failure, β-Hydroxybutyric acid

JW and DZ contributed equally to this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Introduction

Acute myocardial infarction (AMI) is a severe form of coronary atherosclerotic heart disease that commonly results from acute ischemic hypoxia caused by thrombotic obstruction or stenosis of the coronary artery, leading to myocardial damage. It often results in serious complications, such as heart failure, malignant arrhythmias, and cardiogenic shock.[1] Although myocardial blood supply can be restored through direct coronary intervention, intravenous thrombolysis, and other reperfusion therapies, heart failure caused by AMI still has high mortality and disability rates. Therefore, identifying methods to improve cardiac function after an infarction has become a focal point of research.

The primary pathological mechanism of acute myocardial infarction combined with heart failure is damage caused by myocardial ischemia and reperfusion injury. The pathological process leading to myocardial injury from ischemia involves the disruption of the balance between oxygen supply and myocardial demand, which ultimately culminates in hypoxic necrosis of cardiomyocytes. During ischemia-reperfusion injury, an imbalance between oxidative stress and antioxidants results in the excessive generation of reactive oxygen species (ROS).[2] These abundant ROS initially target mitochondria, leading to impaired mitochondrial function, decreased energy production, and loss of contractile function in cardiomyocytes. To combat myocardial damage caused by ROS, changes in energy metabolism within the mitochondria can play a role in mitigating myocardial injury.

Under normal conditions, the primary energy source for cardiomyocytes is derived from the oxidation of fatty acids.[3] However, when cardiomyocytes die because of ischemic hypoxia, their energy metabolism shifts from relying on fatty acid oxidation to carbohydrate metabolism, which includes substances such as glucose, lactate, and ketone bodies.[4] Cardiomyocytes are incapable of synthesizing ketone bodies under normoxic or hypoxic conditions and predominantly utilize ketone bodies produced by the liver. Following a myocardial infarction, ketone bodies, including acetoacetate, acetyl-CoA, and β-hydroxybutyric acid, are synthesized from fatty acids in the liver. Among these, β-hydroxybutyric acid is the most concentrated in the blood, with levels five times higher than those of acetoacetate and accounting for up to 85% of ketone bodies in the bloodstream. Ketone bodies are transported to the heart via monocarboxylate transporters in the blood, contributing to energy production. Consequently, β-hydroxybutyric acid is considered the main active component of ketone bodies, and many studies have focused on β-hydroxybutyric acid as a target for research on myocardial energy metabolism.[5–8]

Under physiological conditions, circulating levels of β-hydroxybutyric acid are quite low, with concentrations between 0.1 and 0.25 mmol/L.[9] Recent studies have reported a significant elevation in the levels of β-hydroxybutyric acid levels in the peripheral circulation of patients with cardiovascular diseases. For instance, in comparison with healthy subjects, patients with AMI have been found to have a concentration of β-hydroxybutyric acid in their blood around 0.6 mmol/L, which is more than three times higher than normal; patients with heart failure with reduced ejection fraction have plasma β-hydroxybutyric acid concentrations around 0.4 mmol/L, demonstrating an increase of more than 1.6 times compared to the normal range. Furthermore, there is a clear negative correlation between plasma β-hydroxybutyric acid levels and both cardiac function and prognosis.[5,10,11] These findings suggest that β-hydroxybutyric acid has the potential to serve as a biomarker reflecting the severity of myocardial injury and predicting outcomes. This study aimed to investigate the impact of β-hydroxybutyric acid on the short-term prognosis of patients with acute myocardial infarction combined with heart failure.

Materials and Methods

Study Design

In this retrospective study, we examined patients admitted to the Qilu Hospital of Shandong University for acute myocardial infarction combined with heart failure, covering the period from January 1, 2019, to December 31, 2022. This study included 398 patients. Following application of the inclusion and exclusion criteria, the final dataset comprised 260 patients. The patient selection and inclusion processes are depicted in Fig. 1. According to the best cutoff value of β-hydroxybutyric acid for predicting cardiac functional outcome obtained by ROC curve analysis, the patients were divided into β-hydroxybutyric acid elevated group and nonelevated group. This study was approved by the ethics committee of Qilu Hospital of Shandong University.

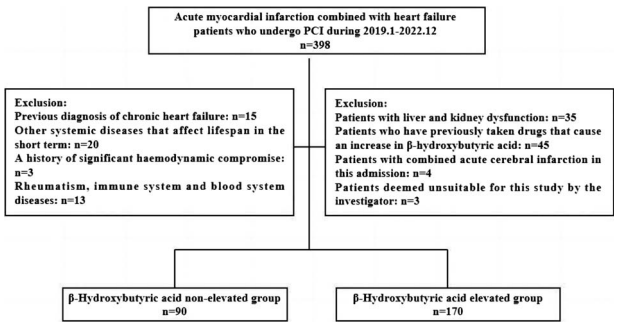

Figure 1. Process of selecting the study subjects. PCI, percutaneous coronary intervention.

Study endpoint

Our study's primary endpoint was an improvement in cardiac function, defined as a reduction of ≥30% in plasma N-terminal pro b-type natriuretic peptide (NT-proBNP) levels during the hospital stay. The NT-proBNP reduction rate was calculated using the following formula: (plasma NT-proBNP concentration at admission - plasma NT-proBNP concentration at discharge) ÷ plasma NT-proBNP concentration at admission.

Sample Size Calculation

In the pre-experimental data, the effective rate of the experimental group (*P*1) was 83.3%, and the effective rate of the control group (*P*2) was 50%. Class I error α = 0.05, Class II error β = 0.2, and the sample size ratio (k) of experimental group and control group was 1:1. Based on the sample size calculation formula:

$$n_2 = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 [p_1(1-p_1) + p_2(1-p_2)]}{(p_1 - p_2)^2}, n_1 = n_2, z_{1-\alpha/2} = 1.96, z_{1-\beta} = 0.84$$

The sample size of experimental group was 28, and that of control group was 28. Assuming a 20% loss-to-follow-up rate, a minimum sample size of 35 would be required for the test group and 35 for the control group.

Data Collection

We harnessed data from the hospital's digital electronic medical record system to compile the following patient information:

The demographic characteristics included age, sex, and vital statistics such as weight, height, and body mass index (BMI).

Risk factors for disease: We considered histories of hypertension, diabetes, smoking, alcohol consumption, and cerebrovascular accidents, such as stroke.

Surgical and procedural indices: This entailed an assessment of coronary artery disease status, Gensini score, number of stents placed, postprocedural TIMI flow grade, and ejection fraction (EF), as observed on cardiac echocardiograms.

Laboratory indices: We evaluated fasting plasma glucose (FPG), NT-proBNP concentrations, and plasma β-hydroxybutyric acid levels. Liver function was gauged using indices such as alanine aminotransferase and aspartate aminotransferase and lipid profiles encompassing triglycerides, total cholesterol, and low-density lipoprotein. Myocardial injury is indicated by biomarkers such as creatine kinase myocardial band (CKMB) and high-sensitivity cardiac troponin I (cTnI).

Therapeutic interventions: The use of various medications was recorded, including SGLT-2 receptor antagonist, angiotensin converting enzyme inhibitors, diuretics, β-adrenergic receptor-blocking agent, inotropic agents, and recombinant human brain natriuretic peptides (rh-BNP).

Prognostic Information: To assess whether cardiac function improved, we collected plasma NT-proBNP concentration at discharge.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (SPSS Inc, Chicago, Illinois, IL, USA).

Table 1

Baseline Characteristics

Characteristics	β-Hydroxybutyric Acid Nonelevated Group (n = 90)	β-Hydroxybutyric Acid Elevated Group (n = 170)	*P*
Age, y	67 (55–71)	65 (57–73)	0.990
Male	64 (71.111)	109 (64.118)	0.256
BMI, kg/m^2	25.950 (24.220–29.200)	25.370 (22.335–27.680)	0.050
Smoking	50 (55.556)	76 (44.706)	0.968
Alcohol intake	30 (33.333)	64 (37.647)	0.492
Hypertension	58 (53.333)	96 (56.471)	0.708
Diabetes	24 (26.667)	38 (22.353)	0.438
Cerebral infarction	9 (10.00)	16 (9.412)	0.879
Killip level III	84 (93.333)	165 (97.000)	0.156
Coronary artery lesions			0.267
Single-vessel lesion	25 (27.778)	48 (28.235)	
Double-vessel lesions	28 (31.111)	70 (41.176)	
Triple-vessel lesions	37 (41.111)	52 (30.588)	
EF, %	48.000 (43.000–51.000)	45.000 (40.000–51.000)	0.900
Postoperative TIMI grade 3	82 (91.111)	160 (94.118)	0.365
Gensini score	60.000 (44.000–80.000)	66.500 (51.250–83.000)	0.019
SGLT-2 receptor antagonist	22 (24.444)	34 (20.000)	0.408
Angiotensin-converting enzyme inhibitors	38 (24.444)	81 (47.647)	0.404
Cardiotonic	9 (10.000)	25 (14.706)	0.285
Diuretic	14 (37.778)	88 (51.765)	0.032
β-Adrenergic receptor-blocking agent	71 (78.889)	138 (81.176)	0.659
rh-BNP	10 (11.111)	47 (37.903)	<0.001
FPG, mmol/L	5.120 (4.230–5.370)	5.040 (4.230–5.605)	0.967
CKMB, ng/mL	19.000 (5.600–41.800)	47.400 (7.125–127.800)	<0.001
cTnI, μg/L	1851.400 (742.725–5476.000)	2912.500 (890.250–8330.750)	0.381
NT-proBNP, pg/mL	1497.000 (1059.000–2769.750)	1748.500 (1199.250–2777.750)	0.414

Data are n (%) or median (IQR).

BMI, body mass index; CKMB, creatine kinase myocardial band; cTnI, cardiac troponin I; EF, ejection fraction; FPG, fasting plasma glucose; IQR, interquartile range; rh-BNP, recombinant human brain natriuretic peptide.

Continuous variables were expressed as median (interquartile range), while categorical variables were presented as frequencies (percentages). Continuous variables were tested for normal distribution using the Shapiro-Wilk test; those conforming to normal distribution were analyzed using the *t* test, whereas those not conforming were assessed using the nonparametric Mann-Whitney *U* test. For categorical variables, the chi-square test was used. *P* values <0.05 were considered to be different between the 2 groups. To investigate the extent to which each variable had a prognostic impact on short-term cardiac function, a rate of decrease in NT-proBNP of ≥30% was taken as an improvement in short-term cardiac function. Univariate analysis was performed first, and variables with a *P* value <0.10 from univariate analysis and factors previously considered to have a significant impact were included in a multivariate logistic regression model, and stepwise regression was used to screen the independent variables for analysis, with odds ratio (OR) and its 95% confidence interval (CI) used as a measure of outcome as an indicator, and the difference was considered statistically significant with a *P* value <0.05.

Results

General characteristics of patients

This study included 260 patients admitted with acute myocardial infarction combined with heart failure within 12 hours of receiving percutaneous coronary intervention (PCI) treatment. According to ROC curve analysis, the best cutoff value of β-hydroxybutyric acid for predicting cardiac function outcome was 0.255 μmol/L. Among these patients, 170 exhibited elevated levels of β-hydroxybutyric acid (β-hydroxybutyric acid ≥0.255 umol/L), while the remaining 90 had nonelevated levels of β-hydroxybutyric acid (β-hydroxybutyric acid <0.255 umol/L). The group with elevated β-hydroxybutyric acid levels presented higher levels of CKMB, and Gensini scores, as well as higher usage rates of diuretics and rh-BNP compared to the nonelevated group ($P < 0.05$). No statistically significant differences were observed in the distribution of other indicators between the two groups (Table 1). Notably, myocardial injury biomarkers were significantly elevated in the group with higher β-hydroxybutyric acid levels.

Characteristics of outcome indicators according to various states of cardiac function improvement in patients.

In this study, which included 260 patients with acute myocardial infarction combined with heart failure, those who experienced improvement in cardiac function were younger, had more coronary single-vessel lesions, and had a higher rates of rh-BNP use ($P < 0.05$) than those with no improvement in cardiac function. Additionally, a greater proportion of patients with improved cardiac function had elevated levels of β-hydroxybutyric acid ($P < 0.05$). There were no significant differences in the remaining indicators between the improvement and nonimprovement groups (Table 2).

Univariate analysis of factors influencing cardiac function prognosis following acute myocardial infarction.

Based on the criterion that a reduction of NT-proBNP levels by more than 30% from admission to discharge serves as an indicator for short-term improvement in cardiac function among patients with acute myocardial infarction combined with heart failure, a univariate analysis was conducted to identify factors possibly influencing the achievement of an NT-proBNP reduction rate of ≥30%. The results and variables used in the analysis are listed in Table 3. Factors including age (crude OR: 0.963; 95% CI: 0.941–0.986; $P = 0.001$), double-vessel lesions (crude OR: 0.253; 95% CI: 0.113–0.570; $P = 0.001$), triple-vessel lesions (crude OR: 0.180; 95% CI: 0.080–0.407; $P < 0.001$), elevated levels of β-hydroxybutyric acid (crude OR: 2.753; 95%

Table 2

Comparison of Clinical Characteristics Among Patients at Different Stages of Cardiac Function Improvement

Characteristics	Unimproved Cardiac Function (n = 83)	Improved Cardiac Function (n = 177)	*P*
Male	57 (68.675)	116 (65.537)	0.617
Age, y	68.000 (63.000–75.000)	63.000 (54.000–72.000)	0.002
Smoking	34 (40.964)	82 (46.328)	0.417
Alcohol intake	32 (38.554)	62 (35.028)	0.581
Hypertension	47 (56.627)	102 (57.627)	0.879
Diabetes	15 (18.072)	47 (26.554)	0.135
Cerebral infarction	12 (14.458)	13 (7.345)	0.070
Killip level III	81 (97.590)	168 (94.915)	0.318
Coronary artery lesions			<0.001
Single-vessel lesion	9 (10.843)	64 (36.158)	
Double-vessel lesions	35 (42.169)	63 (35.593)	
Triple-vessel lesions	39 (46.988)	50 (28.249)	
EF, %	45.000 (42.000–50.000)	48.000 (41.000–51.000)	0.312
Gensini score	65.000 (48.000–83.000)	63.000 (46.000–82.000)	0.427
Postoperative TIMI grade 3	76 (91.566)	166 (93.785)	0.511
SGLT-2 receptor antagonist	12 (14.458)	44 (24.859)	0.057
Angiotensin-converting enzyme inhibitors	35 (42.169)	84 (47.458)	0.425
Cardiotonic	7 (8.434)	27 (15.254)	0.128
Diuretic	35 (42.169)	87 (49.153)	0.293
β-Adrenergic receptor-blocking agent	64 (77.108)	145 (81.921)	0.362
rh-BNP	12 (17.647)	45 (30.822)	0.045
Elevated β-hydroxybutyric acid	41 (49.396)	129 (72.881)	<0.001
FPG, mmol/L	4.860 (4.230–5.370)	5.200 (4.230–5.370)	0.325
CKMB, ng/mL	26.850 (6.350–82.100)	33.600 (5.950–99.100)	0.413
cTnI, μg/L	2196.000 (1232.000–5551.000)	3011.780 (696.000–8297.000)	0.656
NT-proBNP level at admission, pg/mL	1614.000 (1203.000–2580.000)	1732.000 (1080.000–2940.000)	0.999

Data are presented as n (%) or median (IQR).

CKMB, creatine kinase myocardial band; cTnI, cardiac troponin I; EF, ejection fraction; FPG, fasting plasma glucose; IQR, interquartile range; rh-BNP, recombinant human brain natriuretic peptide.

CI: 1.599–4.739; $P < 0.001$), and the use of rh-BNP (crude OR: 2.079; 95% CI: 1.016–4.253; $P = 0.045$) were identified as potentially correlated with the improvement of cardiac function following acute myocardial infarction.

Multivariate analysis of factors affecting cardiac function prognosis after acute myocardial infarction. Based on the results of the univariate analysis, variables with $P < 0.10$ were included in a multivariate logistic regression analysis. The results and variables used in the analysis are listed in Table 3. Factors such as age (OR: 0.964; 95% CI: 0.936–0.992; $P = 0.013$), double-vessel lesions (OR: 0.353; 95% CI: 0.143–0.873; $P = 0.024$), and triple-vessel lesions (OR: 0.366; 95% CI: 0.146–0.915; $P = 0.032$) emerged as independent risk factors impeding cardiac function recovery in patients. Conversely, elevated levels of β-hydroxybutyric acid (OR: 3.076; 95% CI: 1.479–6.395; $P = 0.003$) were identified as an independent protective factor aiding the recovery of cardiac function in these patients.

Discussion

The results of this study revealed that patients with elevated levels of β-hydroxybutyric acid exhibited higher values of CKMB, higher Gensini scores, and increased usage rates of diuretics and rh-BNP compared to those in the nonelevated group ($P < 0.05$). Univariate and multivariate analyses further highlighted that elevated β-hydroxybutyric acid (OR: 3.076; 95% CI: 1.479–6.395; $P = 0.003$) is an independent protective factor for the recovery of cardiac function in patients with acute myocardial infarction combined with heart failure.

An article published by the team of Academician Ge Junbo demonstrated that in patients with acute myocardial infarction, the level of β-hydroxybutyric acid in the plasma was negatively correlated with ejection fraction ($r = 0.6032$; $P < 0.01$) and positively correlated with NT-proBNP levels ($r = 0.3908$; $P < 0.05$). These findings were validated in a mouse model of myocardial infarction. However, the study did not conduct further analysis of the correlated factors and did not employ linear regression to exclude potential confounding factors.[12] In 2021, an article by Marie-Sophie LY de Koning published in the Journal of the American College of Cardiology mentioned that the area of myocardial infarction within 24 hours was positively proportional to the levels of β-hydroxybutyric acid.[13] Taking this into consideration, researchers believe that the elevation of β-hydroxybutyric acid is associated with the extent of myocardial injury.

β-Hydroxybutyric acid, synthesized in the liver, serves as a product of energy metabolism for critical organs such as the heart and brain. Studies suggest that the elevation of β-hydroxybutyric acid following acute myocardial infarction is a result of cardiomyocytes adapting to the body's nutritional status and hemodynamics. Since 2016, researchers like Aubert have conducted foundational and clinical research to discover that in heart failure with reduced ejection fraction, as induced by stress loads and AMI, and in heart failure with preserved ejection fraction, there is an elevation in plasma levels of β-hydroxybutyric acid. This elevation is accompanied by increased expression of myocardial β-hydroxybutyric acid oxidative metabolism enzymes and raised levels of ketone derivatives, suggesting a significantly enhanced capacity for myocardial utilization of β-hydroxybutyric acid for energy supply.[14] This indicated a shift in the energy metabolism mode of cardiomyocytes. A decline in the ability to oxidize fatty acids results in increased concentrations of fatty acids in plasma. Hence, the liver compensatively synthesizes β-hydroxybutyric acid to mitigate the adverse effects associated with the oxidation of free fatty acids.

Increased sympathetic nervous system activity can also stimulate the production of β-hydroxybutyric acid production in the liver. During acute myocardial infarction, the initiation of sympathetic nervous

Table 3

Univariate and Multivariate Analyses of Factors Influencing Cardiac Function Improvement

Characteristics	Univariate Analysis OR (95% CI)	*P*	Multivariate Analysis OR (95% CI)	*P*
Age	0.963 (0.941–0.986)	0.001	0.964 (0.936–0.992)	0.013
Male	0.867 (0.497–1.515)	0.617		
BMI	1.022 (0.960–1.087)	0.499		
Smoking	1.244 (0.734–2.109)	0.418		
Alcohol intake	0.859 (0.501–1.473)	0.581		
Hypertension	1.042 (0.615–1.764)	0.879		
Diabetes	1.639 (0.855–3.143)	0.137		
Cerebral infarction	0.469 (0.204–1.078)	0.075	0.800 (0.273–2.347)	0.685
Killip level III	0.461 (0.097–2.182)	0.329		
FPG	1.089 (0.877–1.351)	0.440		
CKMB	1.003 (1.000–1.006)	0.072	1.000 (0.996–1.004)	0.953
cTnI	1.000 (1.000–1.000)	0.570		
Elevated β-hydroxybutyric acid	2.753 (1.599–4.739)	<0.001	3.076 (1.479–6.395)	0.003
NT-proBNP level at admission	1.000 (1.000–1.000)	0.832		
EF	2.761 (0.110–69.413)	0.537		
Gensini Score	0.994 (0.982–1.006)	0.344		
Number of stents inserted	0.628 (0.357–1.106)	0.107		
Coronary artery lesions				
Single-vessel lesion	Ref			
Double-vessel lesions	0.253 (0.113–0.570)	0.001	0.353 (0.143–0.873)	0.024
Triple-vessel lesions	0.180 (0.080–0.407)	<0.001	0.366 (0.146–0.915)	0.032
Postoperative TIMI grade 3	1.390 (0.519–3.725)	0.513		
SGLT-2 receptor antagonist	1.957 (0.972–3.943)	0.060	2.147 (0.911–5.062)	0.081
Angiotensin converting enzyme inhibitors	1.239 (0.732–2.096)	0.425		
Cardiotonic	1.954 (0.814–4.692)	0.134		
Diuretic	1.326 (0.783–2.243)	0.293		
β-Adrenergic receptor-blocking agent	1.345 (0.710–2.549)	0.363		
rh-BNP	2.079 (1.016–4.253)	0.045	1.763 (0.763–4.074)	0.185

Ref means single-vessel lesion is a reference comparing the risk of double-vessel lesions and triple-vessel lesions.

BMI, body mass index; CKMB, creatine kinase myocardial band; cTnI, cardiac troponin I; EF, ejection fraction; FPG, fasting plasma glucose; IQR, interquartile range; OR, odds ratio; rh-BNP, recombinant human brain natriuretic peptide.

stress leads to a surge in circulating catecholamine levels and the release of free fatty acids, both of which stimulate the liver to synthesize β-hydroxybutyric acid. Studies have shown that the concentration of β-hydroxybutyric acid correspondingly decreases after administration of a β-adrenergic receptor-blocking agent.[15] The insulin/glucagon ratio in the blood also plays a role in the elevation of β-hydroxybutyric acid levels. When the proportion of insulin decreases, free fatty acids are released into the bloodstream, and as glucagon levels rise, the liver accelerates the breakdown and oxidation of lipids to increase blood sugar. In the process of lipid metabolism and breakdown in the liver, the level of β-hydroxybutyric acid also increases.

Synthesizing the aforementioned perspectives, in patients with acute myocardial infarction combined with heart failure, cardiomyocytes experience an increase in blood levels of β-hydroxybutyric acid due to ischemia-induced stress and disturbances in the blood hormone ratios. Under these pathological conditions, cardiomyocytes enhance the oxidation and metabolism of β-hydroxybutyric acid to improve adaptability and cardiac energy metabolism. Additionally, β-hydroxybutyric acid exerts a salvaging effect on myocardial damage through anti-inflammatory and antioxidative mechanisms. Therefore, patients with acute myocardial infarction combined with heart failure, who exhibit elevated levels of β-hydroxybutyric acid in the plasma, tend to have a better short-term cardiac functional prognosis.

The outcome measure studied in this article is cardiac function improvement, defined as a decrease in NT-proBNP levels by ≥30% during the hospital stay of patients. This indicator has been used as a basis for improved cardiac function in numerous studies,[16] and some studies have considered plasma NT-proBNP levels to be the gold standard for prognostic assessment within 180 days after myocardial infarction.[17] Consequently, this study utilized the rate of decrease in plasma NT-proBNP as an index for gauging the improvement in cardiac function. In a univariate analysis investigating factors that influence the recovery of cardiac function, researchers observed that the status of coronary artery lesions, elevated β-hydroxybutyric acid levels, age, and whether rh-BNP was used, all impacted the short-term recovery of cardiac function after acute myocardial infarction. In the multivariate logistic regression analysis, β-hydroxybutyric acid demonstrated a significant impact on short-term prognosis for patients with acute myocardial infarction, with a $P = 0.003$, an OR of 3.076, and a 95% CI ranging from 1.479 to 6.395. The findings suggest that β-hydroxybutyric acid plays a meaningful role in the short-term recovery of cardiac function in patients with acute myocardial infarction combined with heart failure.

In a foundational experiment, mice were fed a ketogenic diet and underwent ligation of the left anterior descending artery. It was observed that those mice on the ketogenic diet displayed a slowed recovery in myocardial function, along with an increase in the area of myocardial infarction.[18] However, increasing ketone body concentrations have a protective effect on the ischemic myocardium.[19] In another study, researchers found that supplementation with β-hydroxybutyric acid could prevent reperfusion injuries.[20] A clinical controlled study published in the journal Circulation demonstrated that with exogenous supplementation of β-hydroxybutyric acid, there was an approximate increase in cardiac output by 40%, an 8% improvement in ejection fraction, and a roughly 30% decrease in systemic vascular resistance. The above research validates the impact

of β-hydroxybutyric acid on the short-term recovery of cardiac function following a myocardial infarction. These findings are consistent with the results observed in this article, where patients with acute myocardial infarction combined with heart failure, who had elevated levels of plasma β-hydroxybutyric acid, showed a better short-term prognosis.

Drawing from previous research, the mechanisms by which β-hydroxybutyric acid plays a role in the recovery of cardiac function following myocardial infarction can be briefly summarized as follows: β-hydroxybutyric acid, as an energy substrate with a low oxygen demand, is increasingly utilized during myocardial infarction, thus leading to reduced myocardial oxygen consumption, while also enhancing the function of marginal zone cardiac myocytes to facilitate cardiac recovery after infarction.[6] β-Hydroxybutyric acid mediates the inhibition of histone acetylation and suppresses pyroptosis led by Caspase-1,[7] thereby alleviating the damage caused by myocardial ischemia-reperfusion. Additionally, it can modulate the activation of the NLRP3 inflammasome and inhibit the downstream secretion of inflammatory cytokines such as interleukin-1β by macrophages, hence curtailing the inflammatory cytokine storm that occurs during acute myocardial infarction and mitigating myocardial damage in the process.[8,9] Beyond these mechanisms, research equally reveals that β-hydroxybutyric acid plays a role in endoplasmic reticulum stress response and the regulation of mitochondrial function.[10] β-Hydroxybutyric acid, possibly through the mechanisms mentioned above, may improve the development of heart failure postacute myocardial infarction. This might also elucidate how elevated plasma levels of β-hydroxybutyric acid can enhance the short-term prognosis of cardiac function in patients suffering from acute myocardial infarction combined with heart failure.

Limitations

Our study had some limitations. First, this study was retrospective and relied on the use of medical record systems for the collection of clinical data, which carries a risk of information bias. Second, β-hydroxybutyric acid is not a mandatory test for patients with acute myocardial infarction combined with heart failure, and the majority of patients did not select this test for laboratory testing at the time of their first medical contact, which caused some difficulty in selecting patients for this study. Third, this study was only able to establish associations between independent influencing factors and dependent variables. To ensure the accuracy of the findings, there is a need for validation through large-scale randomized controlled trials.

Conclusion

Our study reveals that, among patients suffering from acute myocardial infarction combined with heart failure, plasma β-hydroxybutyric acid emerges as an independent protective factor for the short-term amelioration of cardiac function.

Conflict of interest statement

Yuguo Chen, Editor-in-Chief of *Emergency and Critical Care Medicine*, confirms no involvement in any stage of this article's peer-review process, ensuring unbiased editorial decision-making. The authors declare no conflict of interest.

Author contributions

All authors participated in the conception and design of the study, provision of study materials and patients, collection and assembly of data, data analysis and interpretation, and writing of the manuscript.

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Ethical approval of studies and informed consent

The study followed the principles of the Declaration of Helsinki as revised in 2013. The study protocol was approved by the ethics committee of the Qilu Hospital of Shandong University (KYLL-202011-204; December 28, 2020). The data has been anonymized to protect patient privacy. Written informed consent was waived by the ethics committee of Qilu Hospital of Shandong University, owing to the anonymized retrospective nature of the analysis.

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