

The Value of Myocardial Energy Expenditure in the Diagnosis of Cirrhotic Cardiomyopathy

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Objective: This study aimed to evaluate the diagnostic value of myocardial energy expenditure (MEE) in cirrhotic cardiomyopathy (CCM).

Methods: A cohort of 100 patients with cirrhosis were classified into a CCM group (34 cases) and a non-CMM group (66 cases) based on the 2020 CCM guidelines. Moreover, 30 healthy volunteers served as a control group. MEE and conventional echocardiographic parameters were measured, and intergroup differences were analyzed. MEE was measured by ultrasound and calculated by formula. Multivariate logistic regression was performed to determine the relationship between significant indicators and CCM. Receiver operating characteristic (ROC) curve analysis was conducted to assess the diagnostic performance of MEE, echocardiographic parameters, and their combination (MEE + echocardiography) in diagnosing CCM.

Results: (1) Significant differences were observed in the left atrial volume index (LAVI), left ventricular ejection fraction (LVEF), Tei index (TI), early/late peak diastolic flow rate (E/A) ratio, and MEE among the three groups ($P < 0.05$). (2) Both LVEF and MEE were substantially correlated with CCM and identified as independent predictors ($P < 0.05$). (3) The ROC analysis revealed areas under the curve (AUCs) of 0.834 and 0.929, respectively, with a combined diagnostic AUC of 0.965 for MEE + LVEF.

Conclusion: MEE and LVEF are reliable predictive markers for CCM, with their combined assessment offering superior diagnostic accuracy.

Keywords: liver cirrhosis, cirrhotic cardiomyopathy, echocardiography, myocardial energy expenditure

Introduction

Myocardial dysfunction is frequently observed in patients with cirrhosis. The clinical entity “cirrhotic cardiomyopathy” (CCM) was first defined in 1989 as cardiac dysfunction induced by cirrhosis, characterized by impaired cardiac systolic and diastolic functions alongside abnormal electrophysiological activities.¹ Although the prevalence of CCM in patients with cirrhosis remains uncertain, it is estimated that approximately 40%~50% of individuals with cirrhosis may develop CCM.² The condition of CCM is insidious, typically presenting without specific symptoms in its early stages. As the disease progresses to advanced stages, patients may experience heart failure characterized by clinical manifestations such as chest tightness, dyspnea, and peripheral edema, significantly increasing the risk of poor prognosis.³ Traditional ultrasonography lacks the comprehensiveness and sensitivity to detect the subtle myocardial systolic and diastolic dysfunctions associated with CCM, a predominantly subclinical condition.⁴ Consequently, identifying alternative diagnostic approaches that facilitate early detection is essential for determining effective treatment strategies and improving patient outcomes. Myocardial energy expenditure (MEE), assessed via echocardiography, is a parameter that evaluates myocardial energy metabolism and serves as a marker of early myocardial systolic and diastolic function. Unlike conventional parameters, MEE is calculated using a formula that integrates multiple parameters, providing a more holistic representation of myocardial bioenergetics and enabling a more precise assessment of cardiac function.⁵ Despite its potential, the application of MEE in diagnosing CCM remains underexplored, and its diagnostic value is yet to be established. Therefore, this study aimed to investigate the role of MEE and conventional echocardiographic parameters in the early diagnosis of CCM. Specifically, it evaluates the diagnostic effectiveness of combining MEE with echocardiography compared to echocardiography alone, emphasizing early detection and treatment to improve the prognosis of patients with CCM.

Materials and Methods

Participants

This study included 100 patients with cirrhosis who were treated at Xingtai People's Hospital between January 2020 and March 2022. The diagnosis of CCM was based on the 2020 CCM guidelines.⁶ Patients with cirrhosis who had other known cardiac diseases or chronic cardiac dysfunction were excluded. CCM was defined by the presence of systolic dysfunction, diastolic dysfunction, or both, with or without electrocardiographic (ECG) abnormalities. Systolic dysfunction was identified if any of the following criteria were met: left ventricular ejection fraction (LVEF) $\leq 50\%$ or decreased global longitudinal strain of the left ventricle (absolute value $< 18\%$). Diastolic dysfunction was diagnosed if at least three of the following conditions were present: early mitral septal diastolic motion velocity (e') $< 7\text{cm/s}$, ratio of early diastolic mitral inflow to septal diastolic motion velocity (E/e') ≥ 15 , left atrial volume index (LAVI) $> 34\text{mL/m}^2$, or maximum tricuspid regurgitation flow velocity $> 2.8\text{m/s}$. Patients with cirrhosis were categorized into two groups: the CCM group, comprising 34 cases (18 men and 16 women, mean age of 53 ± 7 years), and the non-CCM group, consisting of 66 cases (36 men and 30 women, mean age of 53 ± 10 years). Exclusion criteria included alcoholic cirrhosis, hypertension, coronary atherosclerotic heart disease (CHD), diabetes, congenital or rheumatic heart disease, thyroid disorders, and poor imaging quality. Moreover, 30 healthy volunteers (18 men and 12 women, mean age: 52 ± 12 years) with no underlying diseases, who underwent routine physical examinations during the same period, were recruited as the control group. General clinical parameters, including age, sex, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure, and heart rate (HR), were collected. The study was conducted in accordance with the Helsinki Declaration (revised 2013).

Methodology

Echocardiographic assessments were performed using a Philips EPIQ 7C color Doppler ultrasound system (Model: EPIQ 7C, Royal Philips, Amsterdam, Netherlands), with patients positioned in the left lateral decubitus position and electrocardiograms recorded synchronously. A S5-1 ultrasonic probe was used to measure left atrial diameter (LAD), left ventricular end-diastolic dimension (LVDd), left ventricular end-systolic dimension (LVDs), interventricular septal thickness (IVST), and left ventricular posterior wall thickness (LVPWT). The LAVI was calculated, and spectral Doppler imaging was employed to determine the early peak diastolic flow rate (E) and late peak diastolic flow rate (A) at the mitral valve orifice, from which the E/A ratio was derived. Tissue Doppler imaging at the mitral valve annulus measured early diastolic velocity (e'), and the E/e' ratio was calculated. The LVEF was assessed using the biplane Simpson method. The MEE and TI were calculated based on established reference formulas: $TI = (ICT + IRT)/LVET$ (Note: ICT is the isovolumic contraction time of the ventricle, IRT is the isovolumic relaxation time of the ventricle, LVET is the left ventricular ejection time). The Tension-Time Index (TTI) represents the work done by the left ventricle during each contraction, equivalent to the left ventricular end-systolic tension multiplied by the left ventricular ejection time. According to research by Simone, Shimizu, and others, the left ventricular end-systolic stress is indicative of the left ventricular end-systolic tension,^{7,8} which means that the work done by the left ventricle during each contraction can be expressed as: Work done by the left ventricle during each contraction = circumferential end-systolic wall stress (cESS) x left ventricular ejection time (LVET). Furthermore, the work done by the left ventricle during each contraction multiplied by stroke volume (SV) can be converted into energy expenditure per contraction, represented as: $MEE = cESS \times LVET \times LSV$, where $MEE (\text{cal/min}) = MEE (\text{cal/systole}) \times HR (\text{systole/min})$.

Statistical Analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) statistical software (version 25.0, International Business Machines Corporation, New York, USA). The normality of measurement data was assessed, and results were expressed as mean \pm standard deviation ($\bar{x} \pm s$) for normally distributed data and as median (interquartile range) for skewed data. Group comparisons were performed using analysis of variance (ANOVA) or the Kruskal–Wallis *H*-test, depending on data distribution. Thirty patients were randomly selected from the collected images to evaluate measurement reproducibility. These images were remeasured and reanalyzed by the same observer

after 2 weeks, and independently assessed by a second observer. The intraclass correlation coefficient (ICC) with a 95% confidence interval (CI) was calculated to determine intra- and inter-observer reliability of ultrasound parameter measurements. Multivariate logistic regression analysis was employed to explore the associations between CCM and different clinical indicators. The receiver operating characteristic (ROC) curves were generated to evaluate the diagnostic performance of MEE, LVEF, and their combined use (MEE + LVEF) in the early diagnosis of CCM. The area under the curve (AUC) was calculated to compare the diagnostic efficacy.

Result

General data

No significant differences were observed in age, sex, BMI, SBP, DBP, pulse pressure, or HR among the three groups ($P > 0.05$) (Table 1).

MEE and Conventional Ultrasound Indicators

Substantial differences were found in LAVI, LVEF, TI, early diastolic transmitral flow/mitral annular velocity (E/e'), and MEE across the three groups ($P < 0.05$), while E/A was insignificant ($P > 0.05$). Compared to the control group, LAVI, TI, E/e' , and MEE were elevated in the non-CCM and CCM groups, while LVEF was reduced only in the CCM group. No significant differences in LVEF were observed between the non-CCM and control groups ($P > 0.05$). Within the CCM group, LAVI, TI, E/e' , and MEE were considerably higher than in the non-CCM group, whereas LVEF was significantly lower (Table 2).

Analysis of Consistency

Both intra-observer and inter-observer measurements demonstrated excellent consistency ($ICC > 0.9$, $P > 0.05$).

Multivariate Logistic Regression Analysis

Indicators that showed significant differences between the non-CCM and CCM groups were subjected to multivariate logistic regression analysis. The results identified LVEF and MEE as substantial independent factors associated with CCM ($P < 0.05$) (Table 3).

Diagnostic Performance of LVEF, MEE, and Combined Parameters for CCM

The ROC analysis revealed that the AUC for MEE was 0.834 ($P < 0.001$), demonstrating its utility as a predictor for early CCM ($P < 0.05$). The AUC for LVEF in diagnosing early CCM was 0.929 ($P < 0.001$), indicating its effectiveness as a predictor. The combination of LVEF and MEE yielded the highest diagnostic accuracy, with an AUC significantly surpassing those of MEE and LVEF alone. The combined parameters achieved a sensitivity of 92.5% and a specificity of 96.2% for the early detection of CCM (Table 4 and Figure 1).

Table 1 Comparison of General Characteristics Across the Three Groups

Index	Control Group (n=30)	Non-CCM Group (n=66)	CCM Group (n=34)	F/H/ χ^2 value	P value
Age (years)	52±12	53±7	53±10	0.018	0.982
Gender/(n/%)					
Male	18/60.0	36/54.5	18/52.9	0.162	0.964
Female	12/40.0	30/45.5	16/47.1		
BMI (kg/m ²)	24.24±2.53	23.00±3.03	24.06±4.06	2.622	0.076
SBP (mmHg)	126.5±5.97	126.8±5.93	123.8±5.65	2.662	0.073
DBP (mmHg)	85.20±2.71	84.93±2.74	84.97±2.97	0.32	0.711
Pulse pressure (mmHg)	40.00(2.00)	42.00(12.00)	43.00(7.00)	5.872	0.053
HR (bpm)	68.00(6.00)	70.00(9.00)	72.00(8.00)	5.374	0.068

Abbreviations: CCM, cirrhotic cardiomyopathy; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Table 2 Comparison of MEE and Conventional Ultrasound Parameters Among the Groups

Index	Control Group (n=30)	Non-CCM Group (n=66)	CCM Group (n=34)	F/H value	P value
LAVI (g/m ²)	15.41±3.10	25.40±9.72 ^a	27.44±5.63 ^{ab}	36.035	<0.001
LVEF (%)	61.88±3.69	55.32±4.76	45.64±4.41 ^{ab}	11.373	<0.001
TI	0.37±0.05	0.44±0.06 ^a	0.52±0.09 ^{ab}	10.953	<0.001
E/e'	11.40(4.96)	9.44(3.04) ^a	8.16(2.51) ^{ab}	117.989	<0.001
MEE (cal/min)	78.09±31.37	114.24±49.08 ^a	154.95±63.42 ^{ab}	51.758	<0.001
E/A	1.00(0.26)	0.86(0.36)	1.11(0.40)	6.272	0.432

Note: ^aP value: Comparison with the control group; ^bP value: Comparison with the non-CMM group. Early diastolic transmitral flow/mitral annular velocity (E/e').

Abbreviations: CCM, cirrhotic cardiomyopathy; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; TI, Tei index; MEE, myocardial energy expenditure.

Table 3 Multivariate Logistic Regression Analysis

Variables	B	SE	Wald	P value	OR	95% CI	
						Lower Limit	Upper Limit
LAVI (g/m ²)	0.203	0.129	2.488	0.115	1.225	0.952	1.578
LVEF (%)	-6.991	2.094	11.143	0.001	0.001	0.001	0.056
TI	0.066	0.203	0.105	0.746	0.936	0.629	1.395
E/e'	0.073	0.251	0.085	0.771	1.076	0.658	1.759
MEE (cal/min)	0.084	0.033	6.454	0.011	1.087	1.019	1.16
Constant	0.314	5.846	0.003	0.957	1.368		

Note: Early diastolic transmitral flow/mitral annular velocity (E/e').

Abbreviations: LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; TI, Tei index; MEE, myocardial energy expenditure; SE, standard error; OR, odds ratio; CI, confidence intervals.

Table 4 ROC Analysis of MEE, LVEF, and Combined MEE+LVEF for CCM Diagnosis

Variables	AUC	SE	P value	95% CI		Cut-off Value	Sensitivity	Specificity
				Lower Limit	Upper Limit			
MEE (cal/min)	0.834	0.050	<0.001	0.735	0.933	0.933	81.1%	80.8%
LVEF (%)	0.929	0.027	<0.001	0.877	0.982	1.245	83.0%	88.5%
LVEF+MEE	0.965	0.020	<0.001	0.927	0.999	0.684	92.5%	96.2%

Abbreviations: ROC, receiver operating characteristic; MEE, myocardial energy expenditure; LVEF, left ventricular ejection fraction; SE, standard error; AUC, area under the curve; CI, confidence intervals.

Discussion

Cirrhosis is a chronic and progressive liver disease characterized by sustained impairment of liver function. Persistent high-output circulation and abdominal fluid accumulation that compress the pulmonary circulation disrupts β -adrenergic receptor activity and calcium ion signaling pathways. These alterations contribute to cardiac electrophysiological abnormalities, diminishing the myocardium's responsiveness to contractile stimulation and progressively increasing cardiac workload, ultimately culminating in cardiovascular damage.⁹ Cirrhotic cardiomyopathy (CCM), a significant complication of liver cirrhosis, is characterized by myocardial contractile and diastolic dysfunction in the absence of pre-existing heart disease. This progressive decline in cardiac function can ultimately result in heart failure.¹⁰ Relevant

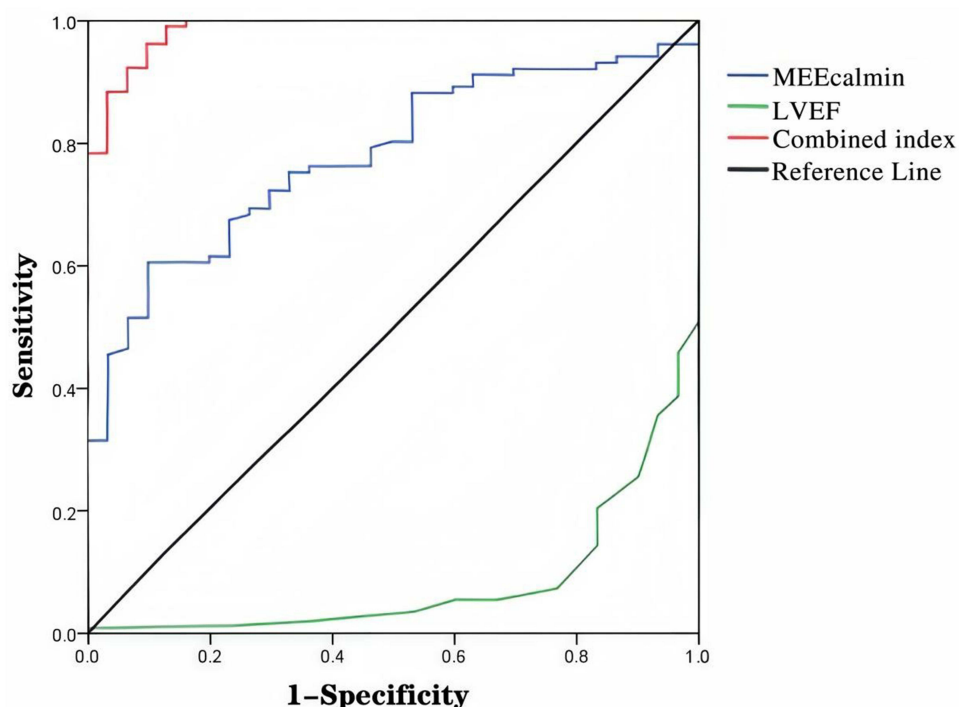


Figure 1 Receiver Operating Characteristic (ROC) curves for MEE, LVEF, and combined MEE+ LVEF in diagnosing CCM.

studies highlight a strong correlation between CCM and complications of cirrhosis, including ascites and hepatorenal syndrome. Moreover, whether or not patients undergo liver transplantation, CCM significantly worsens their prognosis.¹¹

In 2005, the Montreal World Congress of Gastroenterology proposed preliminary diagnostic criteria for CCM.¹² Systolic dysfunction was defined as LVEF <55%, while diastolic dysfunction was diagnosed based on one or more of the following: deceleration time (DT) >200 ms, IRT >80 ms, or E/A ratio <1. Conversely, the updated 2020 CCM guidelines introduced revised criteria. Systolic dysfunction required LVEF ≤50% or an absolute global longitudinal strain (GLS) <18%. Diastolic dysfunction required all of the following: E <7 cm/s; LAVI >34 mL/m²; E/e' >15; and tricuspid regurgitation velocity >2.8 m/s.

The adoption of different diagnostic criteria for CCM can lead to variations in disease prevalence, surgical complications, cardiac events, and mortality rates. Accurate diagnosis is critical for improving the long-term prognosis of individuals with liver cirrhosis.

Echocardiography serves as a critical diagnostic tool for CCM due to its non-invasive nature, real-time imaging capabilities, and high accuracy.¹³ In early-stage liver cirrhosis, patients present with an elevated heart rate, and reduced systolic and diastolic blood pressure. As the disease progresses, structural changes occur, including left ventricular wall thickening and enlargement of the left and right atria end-diastolic diameter.¹⁴ The TI and LVEF are commonly used echocardiographic parameters for assessing cardiac function.¹⁵ Studies utilizing the TI derived from echocardiographic flow velocity curves have reported reduced left ventricular function in patients with liver cirrhosis compared to healthy individuals.¹⁶ The TI alone is inadequate for comprehensively assessing the progression of cardiac diastolic dysfunction and cannot accurately indicate its severity.¹⁷ Similarly, LVEF, commonly used to evaluate left ventricular systolic function, is influenced by cardiac vascular bed dilation, reduced preload, and increased heart rate in patients with CCM, potentially compromising its accuracy.^{18,19} Although the latest CCM diagnostic criteria incorporate speckle-tracking imaging technology for the first time, they remain imperfect.²⁰ Consequently, relying solely on cardiac structural changes or a single echocardiographic parameter makes early and accurate CCM diagnosis challenging.

Myocardial energetics, a field exploring the dynamics of energy metabolism, oxygen supply-demand balance, and the relationship between cardiac workload and myocardial function, provides insights into this challenge. Research suggests

that both myocardial contraction and relaxation and basal metabolic processes depend on metabolic energy derived from adenosine triphosphate (ATP) to perform biomechanical work. The primary substrates for ATP synthesis are free fatty acids and glucose.²¹ Any disruptions in energy substrate utilization or mitochondrial function can precipitate mechanical contraction impairment, diastolic dysfunction, induce ventricular remodeling, and cardiomyocyte damage.²²

In liver cirrhosis, myocardial ischemia and hypoxia contribute to reductions in mitochondrial number and structural integrity. These alterations impair fatty acid metabolism, and ATP synthesis and secretion while reducing energy utilization efficiency. As a consequence, myocardial dysfunction occurs, disrupting normal myocardial energy metabolism and exacerbating cardiac complications. Prolonged myocardial energy overload results in persistent cardiac function and significantly elevates the risk of heart failure.²³

Considering these factors, evaluating myocardial energy metabolism alongside cardiac systolic and diastolic functions could be a viable approach to determining the presence of CCM in patients with cirrhosis. The MEE is an indicator of myocardial energy consumption. Elevated MEE levels are an independent predictor of sudden cardiac death in patients with heart failure, particularly in chronic heart failure patients with reduced LVEF.^{24,25} It has been documented that elevated MEE is related to LVEF. Elevated levels of MEE and lower adipose mass have been reported to be more effectively to predict cardiac death than LVEF.²⁶ In the present study, LVEF and MEE significantly correlated with CCM. The ROC curve analysis demonstrated the diagnostic performance of MEE and LVEF in identifying CCM. The AUC values for MEE, LVEF, and their combination were 0.834, 0.929, and 0.965, respectively. The combined diagnostic approach exhibited the highest AUC, significantly outperforming the individual parameters. In this study, MEE and conventional echocardiography are combined to evaluate their diagnostic efficiency for CCM; this can improve the diagnostic accuracy, sensitivity and specificity for CCM, conjoint analysis can provide more comprehensive information, which can help doctors to better develop personalized treatment strategies, monitor the treatment effect, and improve the diagnosis of heart failure, and timely adjust treatment programs and to improve the prognosis of patients.

Limitations

First, the study's retrospective nature and small sample size limit the generalizability of findings. Furthermore, cirrhosis caused by different factors may show different clinical features and myocardial lesions. Patients with cirrhosis are often accompanied by a variety of complications, such as ascites and hepatic encephalopathy, these complications may also have an impact on cardiac function; therefore MEE combined with echocardiography should take these different etiologies and complications into account when diagnosing CCM. Lastly, limitations of echocardiography include limited visibility of certain areas of the heart, such as the apex, and relatively weak ability to detect subtle abnormalities in the myocardium. In addition, due to the varying experience and technical level of doctors, their subjectivity is strong, leading to differing results.

In the future, multimodality integration of the MEE with echocardiography and other imaging techniques (such as cardiac MRI and CT) could improve the diagnostic accuracy and comprehensiveness of CCM. The comprehensive application of different imaging techniques can obtain more detailed information of cardiac structure and function, and further improve the diagnostic efficiency. It can also utilize artificial intelligence technology to automatically analyze and interpret image data such as MEE and echocardiography, which can improve the accuracy and consistency of diagnosis, these methods provide more reliable support for the diagnosis and evaluation of CCM.

Conclusion

Integrating MEE with echocardiography offers notable clinical value in diagnosing CCM, with the combined approach achieving superior diagnostic efficacy. Incorporating MEE into the diagnostic criteria for CCM could enhance diagnostic precision, facilitate timely intervention, and improve prognosis.

Ethical Statement

The study was conducted in accordance with the Declaration of Helsinki (2013 revision) and was approved by the Ethics Committee of Xingtai People's Hospital. Written informed consent was obtained from all participants.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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