ORIGINAL ARTICLE

The complete reversal effect following angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and beta-blockers after the primary diagnosis of dilated cardiomyopathy

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Background: Whether combination administration of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and beta-blockers (BBs) has a "reversal" effect on cardiac structure and function for first-diagnosed idiopathic dilated cardiomyopathy (FSIDCM) patients with unclear etiologies and inducements is unknown. **Materials and Methods:** We studied the effect of the protocol on FSIDCM patients. The effect was investigated in 26 FSIDCM patients. The criteria of "complete reversal" included left ventricular end-diastolic diameter (LVEDD) ≤50 mm for females or ≤55 mm for males and left ventricular ejection fraction (LVEF) ≥45%; the criteria of "partial reversal" was the decreased rate of LVEDD (ΔLVEDD) >10% or the increase rate of LVEF (ΔLVEF) >10%; the criteria of "no reversal" included LVEDD >50 mm for females or >55 mm for males and ΔLVEDD <10%, and LVEF <45% and ΔLVEF <10%. **Results:** Within the follow-up period, nine patients showed "complete reversal," eight "partial reversal," and nine "no reversal." Improvements in echocardiogram parameters were the most significant in "complete reversal" patients ($P < 0.001$), followed by "partial reversal" and "no reversal" patients ($P < 0.05$). The QRS (Q wave, R wave, S wave) duration and symptoms duration in "complete reversal" patients were the shortest, followed by "partial reversal" and "no reversal" patients. **Conclusion:** ACEIs or ARBs and BBs have a "complete reversal" effect on the left ventricular size and function of some FSIDCM patients. Patients with a narrow QRS and short symptom duration may have a good response.

Key words: Angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, beta-blockers, dilated cardiomyopathy

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INTRODUCTION

Dilated cardiomyopathy (DCM) is characterized by enlargement of the left ventricle and systolic dysfunction. The main clinical manifestations include cardiac enlargement, heart failure, arrhythmia, thromboembolism, and sudden cardiac death. Heart failure occurs in 80% of DCM patients and sudden cardiac death occurs in 12%.[1] DCM is one of the most common causes of nonischemic heart failure and the most common reason for heart transplantation. The incidence is about 40 cases/100,000 people.[1]

The prognosis is conventionally poor with a 5-year survival rate of about 50%.[1] However, the prognosis of DCM has improved in the past 10–20 years with the combined administration of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers (BBs), and mechanical

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support therapy.[2,3] For some previously-diagnosed patients suffering from DCM without a definite etiology or inducement, ACEIs or ARBs and BBs treatment can improve prognosis and reduce mortality; however, it cannot reverse the structure and function of the heart. For other patients suffering from DCM with a definite etiology or inducement, left ventricular structure, and function could recover following ACEIs or ARBs and BBs, and removing the known etiology or inducement. However, it is unclear whether a combination administration of ACEIs or ARBs and BBs has the same reversal effect on first-diagnosed idiopathic DCM (FSIDCM) patients who are initially diagnosed with unknown etiology and inducement. Therefore, the present study aimed to observe the reversal effect following the above protocol in FSIDCM patients, and at the same time, the relevant influencing factors were further explored.

MATERIALS AND METHODS

Ethics

The study was an observational study approved by the ethics committee of Army Medical Center of PLA (No. 201856) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all parents.

Clinical registration

This study was registered in the *Chinese clinical trial registry* http://www.chictr.org.cn/index.aspx (No. ChiCTR2100041856).

Patients

The study included FSIDCM patients admitted to Daping Hospital hospital from December 31, 2012, to March 30, 2018. Referring to Chinese guidelines of DCM,[4] the inclusion criteria included: (1) echocardiogram showing a left ventricular end-diastolic diameter (LVEDD) >50 mm in females or >55 mm in males, and left ventricular ejection fraction (LVEF) <45% or left ventricular shortening fraction (FS) <25%, (2) chest X-ray showing an enlarged heart (cardiothoracic ratio [CTR] >0.5), and (3) no previous history of DCM, and the course of the disease and the etiologies were unclear through repeated medical history inquiry and various examinations at the first visit. The exclusion criteria included: (1) previous diagnosis of DCM, (2) reluctance to receive regular treatment or failure to complete follow-up, (3) coronary angiography (coronary computed tomography angiography [CTA]) showing coronary stenosis >50%, and (4) the presence of known etiologies or inducements that may lead to DCM, such as myocarditis, long-term drinking (>250 g/day), perinatal cardiomyopathy, history of radiotherapy and chemotherapy, hypertensive heart disease, diabetes mellitus, hyperthyroidism, hypothyroidism, rheumatic heart disease, pheochromocytoma, Cushing syndrome, or other systemic diseases.

Therapeutic regime

Referring to Chinese guidelines of DCM,[4] all patients were treated with a combination administration of ACEIs or ARBs and BBs. The administration of ACEIs or ARBs started from 0.5 times the standard dose, BBs titration started from 0.25 times the standard dose, and gradually reaches the maximum tolerable dose depending on the patient's feedback and target heart rate (>60 bpm). Diuretics and aldosterone receptor antagonists were generally not taken unless the patients developed edema of the lower extremities and would be withdrawn when the edema of the lower extremities improved. The drugs are shown in Supplementary Table 1.

Living habits intervention

All patients were asked to maintain good living habits during the follow-up period, including good drug compliance, cold prevention, moderate exercise, adequate sleep, stress relief, and no smoking and alcohol withdrawal. Good drug compliance refers to taking medicine regularly without changing the type, dosage, or discontinuation of drugs at will. Measures to prevent colds include keeping warm and keeping cold medications available. Moderate exercise means that no obvious discomfort happened during exercise, and the increase in heart rate during exercise does not exceed 30% of the basic heart rate. Adequate sleep refers to not <8 h of sleep per day. Stress relief refers to keeping the spirit relaxed, forbidding heavy labor, and working no more than 8 h a day. The noncompliance of the treatment was adjusted by improving the awareness of patients and their families about the disease, through the supervision of patients by family members, and through more frequent telephone follow-up.

Transthoracic echocardiography and chest X-ray protocol

Transthoracic echocardiography was performed by experienced technologists at baseline and at follow-up. The follow-up parameters included LVEDD, LVEF, FS, left atrial diameter, right atrial diameter, left ventricular posterior wall thickness, interventricular septal thickness, and right ventricular diameter. LVEDD was assessed in the parasternal long-axis view. LVEF was assessed by biplane Simpson's method. The posterior-anterior chest X-ray was assessed by experienced radiologists. The follow-up parameter was CTR (CTR = T1/T + T2/T, T: the widest internal diameter of the thorax; T1: The widest diameter from the right margin of heart to the sternal line; T2: The widest diameter from the left margin of heart to the sternal line).

Clinical follow-up

At the first visit, a comprehensive clinical evaluation was performed by an experienced cardiologist, including

medical history inquiry and physical examination, electrocardiography, chest X-ray, echocardiography, coronary CTA, and clinical laboratory test. Then, ACEIs or ARBs and BBs were initiated immediately. The study population underwent a follow-up assessment after at least 3 months, including self-perception tests, New York Heart Association (NYHA) level, and echocardiography (chest X-ray). The endpoints were death and "complete reversal" of left ventricular structure and function. When the patient was alive and "complete reversal" did not happen, the endpoint was considered to be the recent follow-up visit.

Criteria of recovery

The definitions of "left ventricular reverse remodeling" were referred to in this study.[5-8] We defined "complete reversal" as follows: (1) LVEDD ≤50 mm for females and ≤55 mm for males and (2) a LVEF ≥45% or left ventricular shortening fraction (FS) ≥25%. We defined "partial reversal" as follows: ΔLVEDD (decrease) >10% or ΔLVEF (increase) >10%, but not meeting the criteria for "complete reversal." We defined "no reversal" as follows: (1) LVEDD >50 mm for females and >55 mm for males, and ΔLVEDD <10%, and (2) LVEF <45% and ΔLVEF <10%. Referring to NYHA level standards, we defined "symptom disappearance" as NYHA 1 level and no symptoms, "improvement of symptoms" as NYHA level improvement ≥1 level, and "no improvement of symptoms" as death or no improvement of NYHA level.

Statistical analysis

Data were analyzed using SPSS (version 20.0) software (IBM Corp., Armonk, NY, USA). Categorical variables were presented as percentages. Numerical variables were presented as mean ± standard deviation. When the difference of numerical variables before and after treatment conformed to the normal distribution, paired *t*-test was used for assessing the effect of treatment between baseline and the final phase; and when it did not conform to the normal distribution, Wilcoxon signed ranks test was used. When conforming to the normal distribution and variance being neat, the echocardiographic parameters, baseline characteristics, and maximum titration dose of medications in patients with different outcomes were compared using a one-way ANOVA. Otherwise, the Kruskal–Wallis's test was used. Since the sample size of this study was <40 (n <40), Fisher's exact test was used for the comparison of categorical variables such as living habits variables. Statistical significance was defined by a $P < 0.05$.

RESULTS

Population characteristics

A total of 26 FSIDCM patients were enrolled. The patients were aged 49.8 ± 10.6 years, and the mean symptoms duration was 1.5 ± 1.8 months. Twenty-three of the patients (88.5%) suffered dyspnea, pulmonary moist rales were found in nine patients (34.6%) and edema of lower extremities occurred in eight patients (30.8%). Initial echocardiography showed that the mean LVEDD was 64.3 ± 8.2 mm, the mean LVEF was 36.5 ± 9.7%, and the mean LVFS was 17.7 ± 5.6% [Supplementary Tables 2 and 3].

Medical therapy

All patients were treated with a combined administration of ACEIs or ARBs and BBs. The maximum titration dose of ACEIs or ARBs was 1.5 ± 0.6 times the standard dose, and the maximum titration dose of BBS was 1.2 ± 0.6 times the standard dose. A total of eight patients took diuretics and aldosterone receptor antagonists intermittently.

The response of first-diagnosed idiopathic dilated cardiomyopathy patients to medications

During a follow-up period of 2.4 ± 1.7 years, nine (34.6%) patients showed "complete reversal," eight (30.8%) patients showed "partial reversal," and nine (34.6%) patients showed "no reversal" [Supplementary Figure 1a]. Sixteen (61.5%) showed "symptom disappearance," four (15.4%) "improvement of symptoms," six (23.1%) "no improvement of symptoms" [Supplementary Figure 1b].

The changes in the cardiac structure and function between the baseline and the endpoint are shown in Figure 1a-c. At the endpoint, left ventricular size and systolic function returned to normal in "complete reversal" patients ($P < 0.05$) [Figure 1a-c], which occurred in most patients within 2 years [Supplementary Figure 2]. Chest X-ray shows the size of the cardiac shadow decreased [Supplementary Figure 3] and CTR decreased from 0.66 ± 0.6 to 0.56 ± 0.02 [Supplementary Figure 4] in "complete reversal" patients. The decrease in LVEDD and increase in LVEF and FS were the highest in "complete reversal" patients ($P < 0.05$) [Figure 1d]. In "partial reversal" patients, there was no significant change in the left ventricular size ($P < 0.05$, ΔLVEDD <10%), but the left ventricular function improved ($P < 0.05$, ΔLVEF >10%, ΔFS >10%) [Figure 1d]. In "no reversal" patients, no significant changes in the left ventricular size occurred ($P > 0.05$, ΔLVEDD <10%), and the left ventricular function deteriorated ($P > 0.05$, ΔLVEF >-10%, ΔFS >-10%) [Figure 1d].

The patients with "symptom disappearance" and "symptom improvement" showed improvements in NYHA level ($P < 0.05$, ΔNYHA ≥1). The NYHA level of patients with "no improvement of symptoms" was worse than that before medical therapy ($P < 0.05$). Improvements in NYHA level were the most significant in "symptom disappearance" patients ($P < 0.001$), and improvements were more pronounced in "symptom

improvement" patients than in "no improvement of symptoms" patients ($P < 0.05$) [Supplementary Figure 5].

The influence of basic conditions and titration dose of drugs on the response

The effects of clinical parameters, laboratory parameters, echocardiogram parameters, electrocardiogram parameters, and maximum titration dose of drugs on the response were analyzed in this study [Table 1 and Supplementary Table 4]. It was found that QRS duration, age and symptoms duration had a significant impact on the treatment effect. The narrower the QRS duration, the younger the age, and the shorter the duration of the symptoms at the first diagnosis, the better the therapeutic response [Table 1 and Supplementary Figure 6]. Meanwhile, the maximum titration dose of drugs seemed to have an impact on the treatment effect. The higher titration dose of ACEIs or ARBs and BBs, the better the therapeutic response tended to be [Supplementary Table 4]. However, the short-term administration of diuretics and aldosterone receptor antagonists had no impact on the response ($P > 0.05$) [Supplementary Table 4].

The influence of living habits on the response

Medication compliance and prevention of colds had a significant impact on the treatment effect in this study. Those who sticked to regular medication and the prevention of colds had a better treatment response ($P < 0.05$). Despite no statistical difference, physical exercise, stress relief, and adequate sleep were also helpful for the treatment [Table 2].

Relapse

Of "complete reversal" patients, three patients had a relapse which was defined as a decrease of more than 10% in LVEF or an increase of more than 10% in LVEDD based on "complete reversal" [Supplementary Table 5]. One patient relapsed after withdrawal, one patient had recurrent colds before relapse and another had long-term sleep deprivation before relapse. However, two patients maintained normal measurements after 7 and 5 months of medication withdrawal, respectively.

DISCUSSION

The changes in left ventricular structure and function in FSIDCM patients with unknown etiologies and inducements during a period of ACEIs or ARBs and BBs treatment were observed in this study. In previous studies, about 12%–34% of diagnosed DCM patients experienced "reversal" of left ventricular structure and function during ACEIs or ARBs and BBs treatment.[8-12] However, the inclusion and exclusion criteria of the subjects varied from the studies. Some studies included DCM patients with known etiologies or inducements, such as atrial fibrillation[8-10,12] and severe hypertension,[9,10,12] which may have complicated the results. Merlo *et al*. excluded patients with persistent supraventricular arrhythmias and blood pressure >160/100 mmHg.[11] However, the course of previous treatment was not clear, ACEIs or ARBs were taken by only 45% of patients, and BBs were taken by only 16% of patients.[11] In this study, we tried to rule out known etiologies or inducements that may cause cardiac enlargement, and all patients were treated with ACEIs or ARBs and BBs at the first diagnosis. Finally, we observed that 34.6% of FSIDCM patients achieved "complete reversal" during a follow-up period of 2.4 ± 1.7 years. Although this proportion was close to that in other

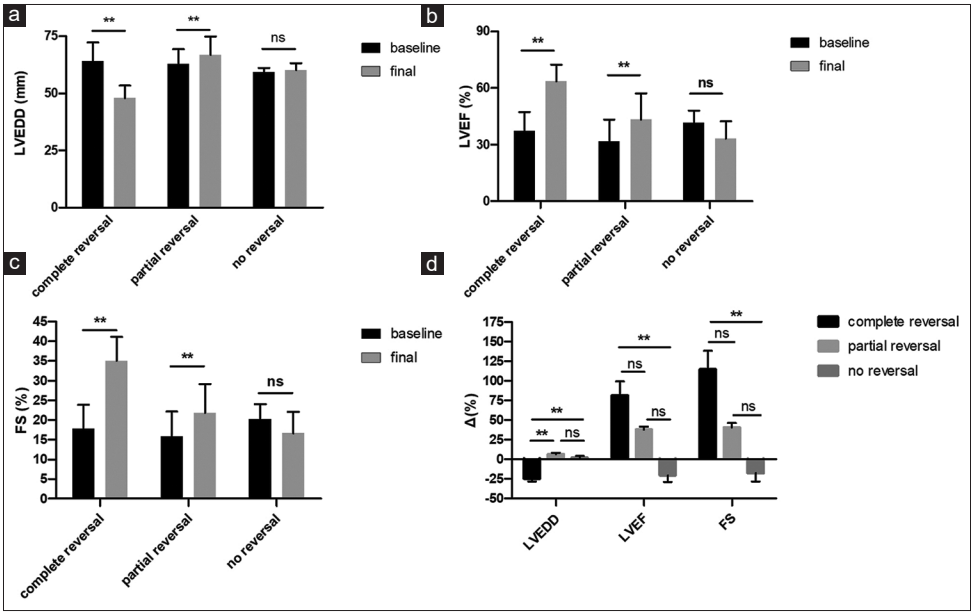

Figure 1: Changes in echocardiographic parameters in patients with different outcomes. (a) LVEDD, (b) LVEF, (c) FS and (d) comparison of the proportion of changes in LVEDD, LVEF, and FS. LVEDD: Left ventricular end-diastolic diameter, LVEF: Left ventricular ejection fraction, FS: Fractional shortening

Table 1: The influence of patient's basic state on the treatment (*n*=26)

Variable	Complete reversal (*n*=9)	Partial reversal (*n*=8)	No reversal (*n*=9)	*P*
Age (years)	45.4±8.6	58.1±12.6	46.9±6.3	0.022*
Male, *n* (%)	8 (88.9)	8 (100)	8 (88.9)	1.0
BMI (kg/m^2)	23.5±2.1 (*n*=8)	24.4±5.6 (*n*=8)	25.9±2.1 (*n*=7)	0.472
Symptoms duration (months)	0.8±0.3	1.3±1.5	2.3±2.6	0.940
Heart rate (bpm)	92.8±15.6 (*n*=8)	100.6±13.1	93.0±17.1	0.515
Systolic BP (mmHg)	122.9±20.5 (*n*=8)	124.3±10.2	121.3±17.1	0.691
Diastolic BP (mmHg)	87.6±19.0 (*n*=8)	85.3±5.7	80.7±15.9	0.575
NYHA class	2.8±0.4	2.6±0.5	2.8±0.7	0.736
AST (U/L)	35.1±20.9 (*n*=8)	42.3±22.9	39.4±26.4	0.644
ALT (U/L)	65.1±54.2 (*n*=8)	50.4±47.9	59.5±49.3	0.577
Serum creatinine (umol/L)	95. 8±17.0 (*n*=8)	79. 0±11.7	78.9±17.4	0.063
FT3 (pmol/L)	5.1±0.5 (*n*=7)	4.5±0.8	4.5±0.6 (*n*=8)	0.190
FT4 (pmol/L)	13.2±1.9 (*n*=7)	12.6±2.4	14.3±3.0 (*n*=8)	0.412
hTSH (IU/mL)	2.1±1.1 (*n*=7)	2.0±1.4	1.7±1.0 (*n*=8)	0.736
Serum potassium (g/L)	4.1±0.5 (*n*=8)	4.2±0.4	4.0±0.3	0.544
Erythrocyte (×10^{12}/L)	5.0±0.5 (*n*=8)	4.7±0.5	4.9±0.4	0.340
Hemoglobin (g/L)	151.3±12.0 (*n*=8)	141.1±12.5	142.1±21.1	0.390
QRS duration (ms)	94.8±7.3 (*n*=8)	107.8±27.6	120.0±38.7	0.298
LA (mm)	43.9±6.3	46.9±4.4	47.9±6.5	0.343
LVEDD (mm)	64.2±8.1	62.9±6.5	65.7±10.1	0.895
RA (mm)	39.9±3.4	44.0±5.5	43.1±7.1	0.289
RV (mm)	25.4±4.2 (*n*=8)	27.1±4.9 (*n*=7)	27.1±7.4 (*n*=9)	0.785
IVS (mm)	10.7±2.0	10.0±0.9	10.0±0.9	0.980
LVPW (mm)	10.4±2.5	9.4±1.1	10.0±0.9	0.431
FS (%)	17.8±6.1	15.8±6.4	19.3±4.4	0.441
LVEF (%)	37.3±10.0	31.6±11.6	39.9±6.4	0.212

*P<0.05. Data are presented as mean±SD or *n* (%). BMI=Body mass index; BP=Blood pressure; NYHA=New York Heart Association; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; FT3=Free triiodothyronine; FT4=Free thyroxine; hTSH=Hypersensitive thyroid-stimulating hormone; QRS=Q wave, R wave, S wave; LA=Left atrium; LVEDD=Left ventricular end-diastolic diameter; RA=Right atrium; RV=Right ventricle; IVS=Interventricular septum; LVPW=Left ventricular posterior wall; FS=Fractional shortening; LVEF=Left ventricular ejection fraction; SD=Standard deviation

Table 2: The influence of living habits on the treatment (*n*=26)

Variable	Complete reversal (*n*=9), *n* (%)	Partial reversal (*n*=8), *n* (%)	No reversal (*n*=9), *n* (%)	*P*
Medication compliance	9 (100)	2 (25)	7 (77.8)	0.002*
Tobacco use	4 (44.4)	3 (37.5)	2 (22.2)	0.684
Excessive drinking	2 (22.2)	2 (25)	0	0.415
Lack of sleep	2 (22.2)	2 (25)	0	0.415
Heavy stress	1 (11.1)	4 (50)	4 (44.4)	0.210
Recurrent colds	0	5 (62.5)	3 (33.3)	0.017*
Physical exercise	4 (44.4)	1 (12.5)	1 (11.1)	0.291

*P<0.05. Data are presented as *n* (%)

studies,[9,12] the follow-up period in this study was shorter, and the inclusion and exclusion criteria in this study varied from the other studies.

There was no significant difference in LVEDD at baseline among FSIDCM patients with different outcomes in this study. Those with atrial fibrillation were excluded. Therefore, we could not reach the conclusion that smaller LVEDD and atrial fibrillation at baseline could predict the occurrence of "reversal."[10] Kawai *et al*. found that higher systolic pressure and lower pulmonary capillary wedge pressure at baseline could predict "reversal."[8] However, pulmonary capillary wedge pressure was not measured in our study because of its invasive nature. In contrast to the conclusions of Kawai *et al*.,[8] there was no significant difference in systolic blood pressure at baseline in this study (P > 0.05) [Table 1]. Therefore, for FSIDCM patients, higher baseline systolic blood pressure does not necessarily predict a better response. Gupta *et al*. found that the recovery of LVEF in patients with nonischemic DCM was associated with short QRS duration at baseline.[13] In this study, it was found that the shorter the QRS duration, the better the response [Supplementary Figure 6a]. Therefore, a short QRS duration at baseline may also be associated with a good response in FSIDCM patients. Arad *et al*. found that a short symptom duration was an independent predictor of

left ventricular remodeling reversal.[6] In this study, it was found that the shorter the duration of the symptoms, the better the response tended to be [Supplementary Figure 6b], which may be due to the fact that patients with shorter symptom duration have milder myocardial damage. In addition, age may also be an important factor affecting the response. Table 1 showed that patients with younger ages had a better response ($P < 0.05$). However, "no reversal" patients betrayed this law due to longer symptom duration. Nagatomo *et al*. found that anemia can weaken the response to BBs in patients with HF with reduced ejection fraction.[14] In this study, the baseline hemoglobin level in "complete reversal" patients tended to be higher than in other patients [Table 1], suggesting that the "complete reversal" patients might respond better to BBs. In this study, all patients were told to break bad habits including smoking, excessive drinking, inadequate sleep, heavy stress, physical inactivity, repeated colds, and irregular medication administration, but some patients failed, especially "partial reversal" patients and "no reversal" patients, where the proportion of irregular medication administration and recurrent colds was higher [Table 2]. Therefore, the response might also be affected by medication compliance and recurrent colds. However, it was noteworthy that "partial reversal" patients with worse medication compliance had a better response than "no reversal" patients, which might be related to symptom duration. In "partial reversal" patients, symptom duration might play a greater role than drug compliance.

It is unclear whether FSIDCM patients could stop taking drugs after "complete reversal." The withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF) study found that approximately 40% of the recovered DCM patients relapsed and approximately 50% did not following pharmacological treatment withdrawal.[15] However, the TRED-HF study included those with known etiologies or inducements, such as alcoholic cardiomyopathy, perinatal cardiomyopathy, toxic cardiomyopathy, hyperthyroid cardiomyopathy, and arrhythmic cardiomyopathy, and those receiving mechanical support therapy. The DCM patients with known etiologies or inducements may recover spontaneously after removing the etiologies or inducements[16,17] and mechanical support therapy itself can induce "reversal."[18-20] In addition, the effect of living habits on medication treatment was not observed in the TRED-HF study. In this study, the DCM patients with known etiologies or inducements, and those who received mechanical support therapy were excluded, and the effect of living habits on medication treatment was observed. Of "complete reversal" patients, one patient relapsed after medication withdrawal, one patient had recurrent colds before relapse and another had long-term sleep deprivation before relapse. Therefore, "complete reversal" does not mean that the patient is cured. Medication withdrawal, recurrent colds, and sleep deprivation may still aggravate the disease to recur. However, among the "complete reversal" patients, two patients remained normal measurements after 7 and 5 months of medication withdrawal, respectively.

The inclusion criteria of this study are very strict, and those patients who had been diagnosed and treated in the subordinate hospitals were excluded because of the unclear treatment course, resulting in a small sample size and the inability to build a clinical predictive model. Some clinical data of individual patients in this study could not be obtained. Hence, the findings and conclusions in the study are limited and cannot be applied broadly. In addition, this study is not able to identify which patients can safely stop taking the drugs after "complete reversal;" thus, this question remains for future study.

CONCLUSIONS

ACEIs or ARBs and BBs can have a "complete reversal" effect on some FSIDCM patients. At the first diagnosis, patients with narrow QRS and short symptom duration may have a good response. Good living habits may be helpful to treatment effect during the treatment period.

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Conflicts of interest

There are no conflicts of interest.

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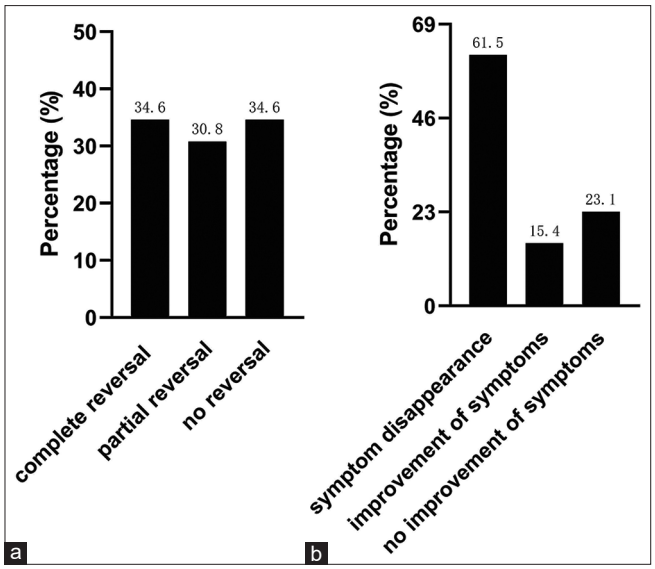
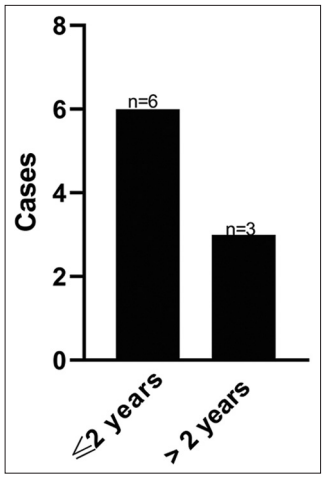
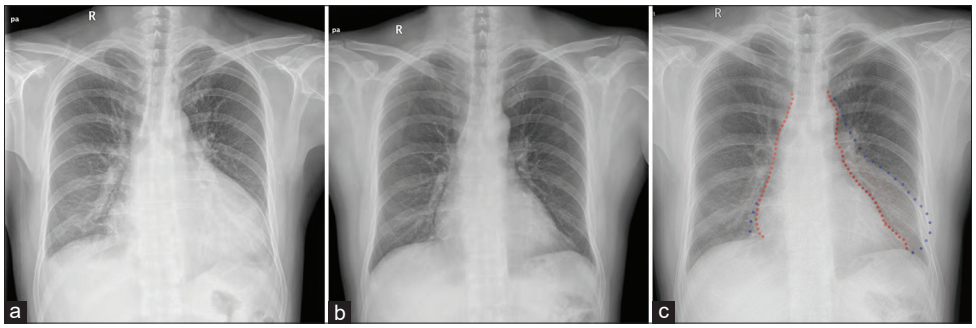


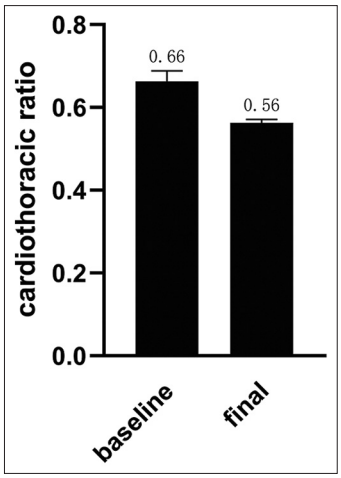
Supplementary Figure 1: Clinical outcomes of 26 FSIDCM patients during follow-up. DCM, dilated cardiomyopathy. (a) Reversion of left ventricular size and function, (b) Symptom improvement. FSIDCM: First-diagnosed idiopathic dilated cardiomyopathy, DCM: Dilated cardiomyopathy



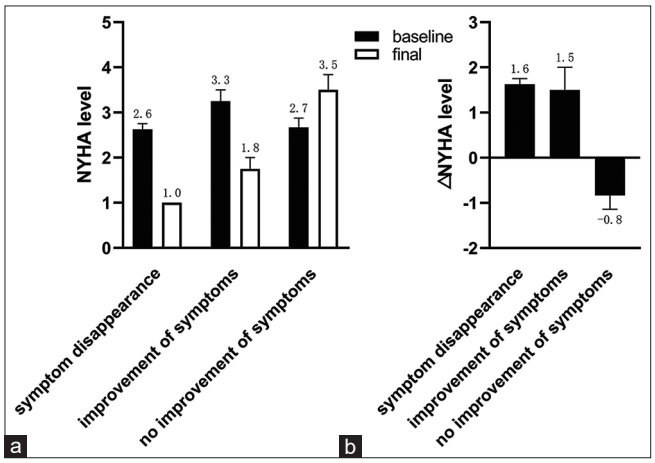
Supplementary Figure 2: Time distribution of left ventricular size and functional recovery in "complete reversal" patients



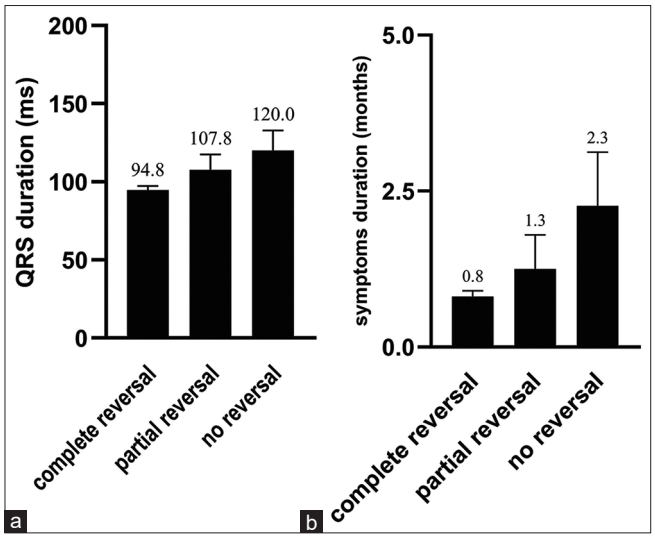
Supplementary Figure 3: The heart shadow size in "complete reversal" patients. (a) At baseline, (b) at the endpoint and (c) the reduction of cardiac shadow size between baseline and endpoint



Supplementary Figure 4: The changes of cardiothoracic ratio in "complete reversal" patients before and after treatment



Supplementary Figure 5: Changes of NYHA level in patients with different degrees of symptom improvement before and after treatment. (a) The NYHA level before and after treatment, (b) The magnitude of changes of NYHA level before and after treatment. NYHA: New York Heart Association



Supplementary Figure 6: The influence of QRS duration (a) and symptoms duration, (b) on treatment effect. QRS: Q wave, R wave, S wave

Supplementary Table 1: Therapeutic drugs

Drugs	Specifications (mg)	Standard dose (mg)	Initial dose (mg)
ACEIs			
Perindopril tert-butylamine tablets	4	4	2
Benazepril hydrochloride tablets	5	5	2.5
Imidapril hydrochloride tablets	5	5	2.5
Ramipril tablets	5	5	2.5
ARBs			
Candesartan cilexetil tablets	4	4	2
Losartan potassium tablets	50	50	25
Valsartan dispersible tablets	80	80	40
Irbesartan tablets	75	75	37.5
BBs			
Metoprolol succinate sustained-release tablets	47.5	47.5	11.875
Metoprolol tartrate tablets	25	25	6.25
Bisoprolol fumarate tablets	5	5	1.25
Diuretics			
Furosemide tablets	20	20	20
MRAs			
Spironolactone tablets	20	20	20

ACEIs=Angiotensin converting enzyme inhibitor; ARBs=Angiotensin receptor blockers; BBs=Beta blockers; MRAs=Aldosterone receptor antagonists

Supplementary Table 2: Baseline data (*n*=26)

Variable	Value
Age (years)	49.8±10.6
Male (%)	24 (92.3)
BMI (kg/m^2)	24.5±3.7 (*n*=23)
Duration of symptoms (months)	1.5±1.8
Heart rate (bpm)	95.4±15.2 (*n*=25)
Systolic BP (mmHg)	122.8±15.8 (*n*=25)
Diastolic BP (mmHg)	84.4±14.4 (*n*=25)
NYHA class	2.7±0.5
AST (U/L)	39.0±22.8 (*n*=25)
ALT (U/L)	58.4±48.7 (*n*=25)
Serum creatinine (umol/L)	84.3±17.0 (*n*=25)
FT3 (pmol/L)	4.7±0.7 (*n*=23)
FT4 (pmol/L)	13.4±2.4 (*n*=23)
hTSH (IU/mL)	1.9±1.2 (*n*=23)
Serum potassium (g/L)	4.1±0.4 (*n*=25)
eGFR (mL/min)	115.4±25.6 (*n*=11)
Erythrocyte (×10^{12}/L)	4.0±0.5 (*n*=25)
Hemoglobin (g/L)	144.7±16.0 (*n*=25)
QRS duration (ms)	108.0±29.2 (*n*=25)
LA (mm)	46.2±5.9
LVEDD (mm)	64.3±8.2
RA (mm)	42.3±5.6
RV (mm)	26.5±5.6 (*n*=24)
IVS (mm)	10.2±1.3
LVPW (mm)	9.9±1.7
FS (%)	17. 7±5.6
LVEF (%)	36.5±9.7

Data are presented as mean±SD or *n* (%). BMI=Body mass index; BP=Blood pressure; NYHA=New York Heart Association; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; FT3=Free triiodothyronine; FT4=Free thyroxine; hTSH=Hypersensitive thyroid-stimulating hormone; QRS=Q wave, R wave, S wave; LA=Left atrium; LVEDD=Left ventricular end-diastolic diameter; RA=Right atrium; RV=Right ventricle; IVS=Interventricular septum; LVPW=Left ventricular posterior wall; FS=Fractional shortening; LVEF=Left ventricular ejection fraction; SD=Standard deviation; eGFR=Estimate glomerular filtration rate

Supplementary Table 3: Symptoms and physical signs at baseline (*n*=26)

Variable	Value, *n* (%)
Dyspnea	23 (88.5)
Exertional dyspnea	22 (84.6)
Paroxysmal nocturnal dyspnea	8 (30.8)
Orthopnea	7 (26.9)
Cough	14 (53.8)
Dizziness	3 (11.5)
Physical fatigue	15 (57.7)
Palpitation	8 (30.8)
Abdominal distension	2 (7.7)
Lung moist rales	9 (34.6)
Edema of lower extremities	8 (30.8)

Data are presented as *n* (%)

Supplementary Table 4: Drug treatment of patients with different outcomes

Drugs	Complete reversal	Partial reversal	No reversal	*P*
ACEIs (ARBs)	1.5±0.6	1.6±0.5	1.3±0.7	0.479
BBs	1.3±0.7	1.3±0.6	1.1±0.5	0.574
Furosemide (%)	2 (22.2)	2 (25)	4 (44.4%)	0.657
Spironolactone (%)	2 (22.2)	2 (25)	4 (44.4%)	0.657

ACEIs (ARBs) and BBs: Maximum administration dose (mg)/standard dose (mg). Kruskal–Wallis test is used for "ACEIs (ARBs)" and "BBs". Fisher's exact test is used for "Furosemide" and "Spironolactone". ACEIs=Angiotensin-converting enzyme inhibitor; ARBs=Angiotensin receptor blockers; BBs=Beta blockers

Supplementary Table 5: Changes of left ventricular size and function and the duration from complete reversal to recurrence in patients with recurrence

Patient	LVEDD (mm)			LVEF (%)			*T* (months)
	Complete reversal	Recurrence	Δ (%)	Complete reversal	Recurrence	Δ (%)	
Patient 1	52	58	11.5	46	21	−50	38
Patient 2	39	51	30.8	65	70	7.7	23
Patient 3	53	60	13.2	56	41	−26.8	39

T=The duration from complete reversal to recurrence; LVEDD=Left ventricular end-diastolic diameter; LVEF=Left ventricular ejection fraction