

Improvement in quality of life of Chinese chronic heart failure patients with neuropsychiatric complications over 12-months post-treatment with metoprolol

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Abstract

Psychological disorders, such as depression and anxiety, are known to be associated with chronic heart failure (CHF). The present study was conducted to evaluate the effect of mental status on quality of life (QoL) in metoprolol treated CHF patients with depression, anxiety, and burn-out.

This single-center prospective study was conducted between February 2013 and April 2016, enrolled CHF patients (resting heart rate >80 bpm) with depression, anxiety, and burn out at baseline. Hospital anxiety and depression scale (HADS) and Copenhagen burnout inventory (CBI) were used to assess the depression–anxiety status and burn-out status, respectively. Change in QoL was evaluated as the endpoint at 1st, 3rd, 6th, and 12th month from baseline using Minnesota Living with Heart Failure Questionnaire (MLHFQ) and short form-8 (SF-8) scales. A student *t* test was used to determine the change and *P* value < .05 was considered statistically significant. One hundred fifty-four patients were enrolled (median age 66 years; 65.58% males) and divided into 8 groups based on the HADS and CBI scores at baseline. Overall, the mean SF8 score and MLHFQ scores in different mental status groups showed a significant improvement (*P* < .05) in QoL from baseline to 12th month, with no significant difference reported between the groups. With regard to the follow-up periods, there was a deterioration in QoL until 3rd month, after which there was a significant improvement (*P* < .05).

There was a significant improvement in QoL in metoprolol treated CHF patients with depression, anxiety, and burn-out.

Abbreviations: BB = beta blockers, CBI = Copenhagen burnout inventory, CHF = chronic heart failure, CVD = cardiovascular disorders, HADS = hospital anxiety and depression scale, MI = myocardial infarction, MLHFQ = Minnesota Living with Heart Failure Questionnaire, NYHA = New York Heart Association, QoL = quality of life, RHR = resting heart rate, SF-36 = short form-36, SF-8 = short form-8.

Keywords: anxiety, burn-out, chronic heart failure, depression, metoprolol, neuropsychiatric complications, quality of life

1. Introduction

Chronic heart failure (CHF) is a global health problem associated with high risk of mortality involving the stimulation of myocardial adrenergic receptors and activation of the adrenergic system leading to fibrosis and myocardial remodeling.^[1] Due to the inherent property of beta-blockers (BB) to protect the heart from these deleterious changes, they have remained a mainstay treatment for CHF, especially in cases of reduced ejection fraction.^[2,3] In 2007, revised guidelines for CHF was updated by

the Chinese Society of Cardiology and BBs were included among the 5 recommended drug classes for this condition.^[4]

Psychological disorders such as depression and anxiety are often associated with CHF with a reported prevalence of about 60% and 45%, respectively.^[5,6] Although depression is an independent risk factor with increased physical impairment and mortality, it remains undiagnosed in the majority of the cases.^[7] Furthermore, BBs are also known to cause neuropsychiatric adverse effects such as hallucinations, delirium, sleeping disorders, and nightmares.^[8,9] In addition, BBs are also rarely associated with increased depression and anxiety.^[10,11] Some studies have contrasting results with BBs having an anxiolytic effect^[12] and no increase in depressive symptoms.^[13] However, it is unknown whether the neuropsychiatric adverse events in CHF developed after administration of metoprolol or remained unnoticed by the treating physician during the start of therapy.

CHF patients have highly compromised the quality of life (QoL)^[14] and their therapeutic management usually aims at improving both clinical parameters and QoL,^[15,16] ultimately resulting in better survival.^[17,18] Although the influence of metoprolol on QoL have been studied in various cardiovascular diseases (CVD),^[19–22] there is little data reported in CHF^[23] and almost none in CHF with depressive disorders.^[24] Our previously published data has shown that though metoprolol treated CHF patients have significantly deteriorating symptoms of depression and burn-out, it provides a significant improvement in anxiety status (*P* < .0001).^[25] However, QoL in different mental status groups was not studied. Therefore, the present study was

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conducted to evaluate the impact of mental status on QoL in CHF patients with depression, anxiety, and burn-out disorders treated with metoprolol.

2. Methods

2.1. Study design, patients, treatment, and follow up

The current prospective study was conducted from February 2013 to April 2016. CHF patients, defined as impaired systolic function with resting heart rate (RHR) >80 bpm and incident neuropsychiatric disorders such as depression and anxiety using the hospital anxiety and depression scale (HADS) questionnaire and high burnout status using Copenhagen burnout inventory (CBI) scores at the Second Affiliated Hospital of Kunming Medical University were included in the study.

Patients with:

- (1) RHR < 60 bpm;
- (2) systolic blood pressure < 90 mm Hg;
- (3) metoprolol usage in past 3 months;
- (4) contraindication to BBs;
- (5) administered class I or class III antiarrhythmic agents;
- (6) <6 months expected survival;
- (7) pacemaker;
- (8) history of coronary bypass surgery and recent heart attack were excluded.

Dosing of metoprolol continuous release tablets (Betaloc ZOK, AstraZeneca, Sweden) and follow-up (at 1st, 3rd, 6th, and 12th month) schedule are presented elsewhere.^[25]

After evaluating patients' symptoms of mental status (anxiety/depression), the psychiatrist with close consultation with study investigator considered that drug intervention (antidepressants and anxiolytics) was not necessary. The symptoms were therefore managed with nonpharmacological therapy including psychological counseling, lifestyle modifications such as physical activity and so on.

The study protocol was approved by the institutional review board of The Second Affiliated Hospital of Kunming Medical University. Good clinical practices (E6) guidelines, declaration of Helsinki and its subsequent revisions were compiled for conducting this study. A written consent was taken from all patients at enrolment.

2.2. Study outcome and assessment tools

QoL was evaluated as the primary outcome using 2 QoL assessment tools for CHF: Minnesota Living with Heart Failure Questionnaire (MLHFQ) and short form-8 (SF-8).^[26] MLHFQ is a disease-specific QoL containing 21-item questionnaire, with each question rated from 0 (nil) to 5 (maximum negative effect). Total sum (0–105) of the psychological, physical, and social functioning limitation score has an inverse relation with the QoL, such that the highest score of 105 corresponds to worst QoL.^[26] SF-8, a generic QoL scale, is a compatible version of SF-36 with a revised set of 8 questions related to physical and mental health. Higher scores on SF-8 scale denote improved QoL.^[26]

2.3. Depression, anxiety, and burn-out measures

Depression and anxiety were measured using HADS^[27] which contains a set of 7 questions each for anxiety and depression. Individual questions are scored from 0 (no depression/anxiety) to 3 (maximum), with a HADS score of >7 indicating diagnoses of

depression (A) and anxiety (B).^[27] Burn-out status was assessed by CBI which evaluates personal burn-out (6 questions), work burn-out (7 questions), and client-related burn-out (6 questions).^[28] In the current study, only personal burn-out was evaluated and the score ranged from 0 (no burn-out) to 100 (maximum). An average score of >50 was diagnosed with positive burn out (C) status.^[28] The patients were asked to take the questionnaires at baseline to measure the extent of depression, anxiety, and burn-out, based on which they were further categorized.

2.4. Statistical analyses

Descriptive statistics were used to present baseline characteristics. Continuous variables were expressed as mean \pm standard deviation and median (range). Student *t* test was used to compare the means of 2 independent samples. A *P*-value < .05 was considered statistically significant. All analysis was performed using R version 3.4.1.

3. Results

3.1. Baseline characteristics

Of the 169 patients screened for enrolment, 15 were excluded either due to intolerance to metoprolol dose increments or were lost during follow-up. The final study population included 154 patients (median age 66 years; 65.58% males). As the same patient population was assessed previously for evaluating the change in mental status in metoprolol treated CHF patients, study flow diagram has been included elsewhere.^[25] The most common comorbidity among the enrolled population was stroke ($n=137$; 88.96%) and the majority of patients ($n=145$; 94.15%) belonged to New York Heart Association (NYHA) functional class III-IV. At baseline, patients displayed a mean ejection fraction (%) of 37.62 ± 5.95 and cardiac index ($L/min \cdot m^2$) was 1.78 ± 0.22 . Other baseline characteristics have been summarized in Table 1.

Based on the baseline HADS and CBI scores, study population was divided into 8 groups:

- (1) Depression (A+ B- C-; $n=25$);
- (2) Anxiety (A- B+ C-; $n=15$);
- (3) Burn-out (A- B- C+ ; $n=16$);
- (4) Depression + anxiety (A+ B+ C-; $n=17$);
- (5) Anxiety + burn-out (A- B+ C+; $n=21$);
- (6) Depression + burn-out (A+ B- C+; $n=15$);
- (7) Depression + anxiety + burn-out (A+ B+ C+; $n=25$);
- (8) Control (A-B-C-; $n=20$).

3.2. Mental status and QoL

Table 2 presents the comparison of SF-8 scores in each of group with the control group. SF8 scores in the control group were higher when compared with all other groups. Control group showed a significantly higher scores compared with depression + anxiety group (45.65 ± 2.91 vs 43.11 ± 1.96 , $P=.004$).

Comparison of SF-8 score between the control group and all other groups did not show significant difference at all the time points, except at 1-month, between control and anxiety group (A- B+ C-) (40.46 ± 1.06 vs 39.55 ± 1.19 , $P=.02$), Table 2. Overall, the mean SF-8 score within different mental status groups showed a significant improvement in QoL from baseline to 12th month ($P < .05$). SF-8 score in all groups decreased at 1st

Table 1**Baseline characteristics.**

Patient characteristics (n=154)	N (%)
Age in years, median (range)	66 (54–78)
Gender	
Males	101 (65.58)
Females	53 (34.41)
Comorbidities	
Hypertension	115 (74.67)
Diabetes mellitus	101 (65.58)
Coronary artery disease	99 (64.28)
Stroke	137 (88.96)
Familial history of cardiac disease	54 (35.06)
History of MI	59 (38.31)
Personal history	
Smoking	111 (72.07)
Alcohol	86 (55.84)
BMI in kg/m ² , mean ± SD	23.85 ± 3.62
NYHA class III-IV	145 (94.15)
Cardiac function, mean ± SD	
Ejection fraction (%)	37.62 ± 5.95
Cardiac index (L/min*m ²)	1.78 ± 0.22
QoL, mean ± SD	
SF-8	44.02 ± 2.71
MLHFQ	74.16 ± 3.78
Mental health, mean ± SD	
HADS depression	8.82 ± 2.78
HADS anxiety	8.23 ± 2.05
CBI score	360.23 ± 6.51

BMI=body mass index, CBI=Copenhagen burnout inventory, HADS=hospital anxiety and depression scale, MI=myocardial infarction, MLHFQ=Minnesota Living with Heart Failure Questionnaire, NYHA=New York Heart Association, QoL=quality of life, SF-8=short form-8.

month follow-up compared with the baseline. Burnout group ($P=.00572$), burnout + anxiety group ($P=.012$), depression + burnout group ($P=.00991$) and control group ($P=.00019$) had significantly lower SF8 scores at 3rd month when compared with the baseline. Post 3rd month, the SF8 scores increased significantly in all groups. Comparison of specific with subsequent follow up points is presented in Table 1, Supplementary content, <http://links.lww.com/MD/C772>.

Similarly, except for the significant difference in MLHFQ scores between control versus the burnout group ($P=.03$) and depression + anxiety groups ($P=.05$) at baseline, the MLHFQ scores in all groups at each time points were similar to the control group Table 3. In terms of MLHFQ improvement within different neuropsychiatric groups, overall improvement in QoL

was reported at the end of the 12-month follow-up period. However, a significant elevation in MLHFQ scores was observed from baseline till 1st-month followed by a subsequent decline till 12th-month. QoL was significantly poorer at 3-months from baseline in all groups, thereafter the QoL improved significantly, Table 1, Supplementary content, <http://links.lww.com/MD/C772>.

4. Discussion

The present study was performed to evaluate the impact of mental status on QoL in metoprolol treated CHF patients with depression, anxiety, and burn-out disorders. To the best of our understanding, this is the first study of its kind, which reported significant overall improvement in the QoL scores from baseline to 12th month, although a deterioration in QoL was observed until 3rd month. The change in QoL was significant within majority of the time intervals ($P<.05$).

Studies have evaluated QoL in metoprolol treated CVD in the past. A randomized study with 154 myocardial infarction (MI) patients reported an improvement in QoL ($P=.03$) along with an increase in life expectancy by 1 month after treatment with metoprolol for 3 years.^[20] Furthermore, a significant improvement ($P<.05$) was also observed in the physical activity, life satisfaction, and total QoL parameters when patients with cardiomyopathy were subjected to HF questionnaire during 18 months after metoprolol treatment.^[22] In contrast, a double-blinded randomized pilot study, Randomized evaluation of strategies for left ventricular dysfunction showed no significant change ($P<.05$) in QoL with metoprolol treated ischemic and dilated cardiomyopathy.^[19] Sheldon et al evaluated the effect of metoprolol on QoL in vasovagal syncope patients using the short-form 36 (SF36) and Euroqol EQ-5D questionnaires at baseline, 6th and 12th month, with both the questionnaires showing no improvement ($P<.05$) in QoL during the 6-months and 1-year observatory period.^[21] However, limited studies have shown the effect of HF on QoL scores.^[23,24,29] Management of CHF using amino-terminal pro-B type natriuretic peptide-guided therapy reported significant improvement ($P<.05$) in the QoL with a lower MLHFQ score during the end of 10th month follow up.^[23,29] In terms of improvement in MLHFQ scores at the end of 12th month, our study findings concurred with previous findings.

Although physiologic and behavioral pathways are proposed for connecting mental status to CHF, the mechanism linking depression and anxiety with CHF and their outcomes are poorly understood.^[30,31] Further, the mechanism for BBs related neuropsychiatric adverse reactions are also not fully

Table 2**SF8 score in different mental status groups.**

Mental status	No of patients (N=154)	SF8 score, mean ± SD (P value; compared to control group)				
		Baseline	M1	M3	M6	M12
A+ B- C-	25	43.4 ± 2.57 (.08)	39.16 ± 1.93 (.41)	42.24 ± 3.1 (.39)	49.2 ± 1.32 (.2)	51.96 ± 2.47 (.43)
A- B+ C-	15	44.07 ± 2.81 (.11)	40.46 ± 1.06 (.02)	42.93 ± 3.3 (.95)	49 ± 1.2 (.48)	51.8 ± 2.24 (.36)
A- B- C+	16	43.68 ± 3.05 (.06)	39.63 ± 1.71 (.88)	41.5 ± 2 (.06)	48.75 ± 1.24 (.91)	51.81 ± 2.43 (.38)
A+ B+ C-	17	43.11 ± 1.96 (.004)	39.35 ± 1.27 (.63)	42.70 ± 2.64 (.74)	48.94 ± 1.25 (.56)	52.18 ± 1.85 (.62)
A- B+ C+	21	44.1 ± 2.6 (.08)	39.42 ± 1.4 (.76)	42.47 ± 2.52 (.53)	49.14 ± 1.28 (.27)	52.33 ± 2.08 (.8)
A+ B- C+	15	43.93 ± 2.69 (.08)	39.26 ± 2.28 (.67)	41.73 ± 2.31 (.14)	48.66 ± 1.11 (.93)	51.67 ± 2.61 (.32)
A+ B+ C+	25	44.12 ± 2.71 (.08)	38.72 ± 1.74 (.07)	42.24 ± 2.82 (.36)	48.52 ± 1.05 (.61)	52.28 ± 1.86 (.72)
A- B- C-	20	45.65 ± 2.91	39.55 ± 1.19	43 ± 2.71	48.7 ± 1.26	52.5 ± 2.12

A=depression, B=anxiety, C=burn-out, M=month, SD=standard deviation, SF-8=short form-8.

Table 3**MLHFQ score in different mental status groups.**

Mental status	No of patients (N=154)	MLHFQ score, mean±SD (P value; compared to control group)				
		Baseline	M1	M3	M6	M12
A+ B- C-	25	73.16±4.09 (.96)	88.72±3.85 (.87)	87.24±4.83 (.77)	64.76±3.81 (.93)	54.76±9.78 (.2)
A- B+ C-	15	74.06±4.3 (.48)	89.4±3.68 (.68)	86.73±4.42 (.97)	63.47±3.62 (.42)	52.2±3.76 (.87)
A- B- C+	16	75.75±3.36 (.03)	87.63±5.38 (.41)	85.31±4.84 (.38)	64.06±3.38 (.67)	54.25±7.92 (.30)
A+ B+ C-	17	75.47±3.69 (.05)	88.18±5.14 (.62)	86.29±5.88 (.78)	64.52±3.39 (.93)	53.17±3.99 (.35)
A- B+ C+	21	74±4.21 (.46)	87.95±4.6 (.45)	86.95±4.28 (.92)	64.14±3.53 (.71)	55.80±13.48 (.22)
A+ B- C+	15	74.27±3.56 (.34)	90.93±3.95 (.12)	88.53±5.7 (.36)	65.8±5.03 (.5)	55.26±11.88 (.32)
A+ B+ C+	25	74.2±3.28 (.28)	89.08±4.8 (.88)	87.2±5.6 (.8)	64.56±3.47 (.94)	52.68±3.36 (.51)
A- B- C-	20	73.1±3.46	88.9±3.21	86.8±5.16	64.65±4.88	52±3.43

A=depression, B=anxiety, C=burn-out, M=month, MLHFQ=Minnesota Living with Heart Failure Questionnaire, SD=standard deviation.

understood;^[32] however, lipophilic BBs (such as metoprolol) are believed to cross the blood brain-barrier unlike hydrophilic BBs (such as atenolol) and induce the neuropsychiatric adverse reactions by blocking the central beta-2 and/or 5-hydroxytryptamine receptors.^[33] MI patients are frequently diagnosed with mental stress or anxiety which might be reduced by the use of BBs, especially metoprolol. Assessment of patients who survived 5 years post MI showed an improvement, not only in terms cardiac functions, but also in the anxiety status and QoL when treated with metoprolol.^[34] A study conducted by Vologdina et al recruited 78 CHF patients with Class III NYHA functional classification and suffering from depressive disorders. During a 3 month follow up period, the mental status was improved along with a significant improvement ($P < .001$) in QoL measured by MLHFQ and SF36.^[24] Our previous published study also showed an improvement in the anxiety status with metoprolol treated CHF patients.^[25] In the present study, QoL showed a significant improvement with both, SF-8 and MLHFQ, from baseline to 12th month in all groups of mental status. Furthermore, significant change and increase in the QoL scores were observed after 3rd month of follow up in all the 8 categories.

Our study has certain strengths. This is a first study conducted worldwide to evaluate the impact of depression, anxiety and burn-out on QoL from baseline to 12th month in metoprolol treated CHF patients. Additionally, this was the first study to assess the impact of burn-out on QoL. The results showed a significant improvement in QoL among all categories of patients with different mental status and within the majority of follow up intervals. However, the single treatment design is a limitation and may not be sufficient to draw conclusions. Therefore, a larger randomized study with better sample size, a longer follow up duration and control group would be helpful to validate and strengthen the results obtained after metoprolol treatment.

5. Conclusion

A significant improvement in QoL in metoprolol treated CHF patients diagnosed with depression, anxiety and burn-out from baseline to 12th-month follow-up. Although there was deterioration in QoL until 3rd month, there was a significant improvement after 3rd month until the 12th month.

Author contributions

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