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Sex-dependent changes in physical, mental, and quality of life outcomes in metoprolol-treated Chinese chronic heart failure patients

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Abstract

This study assessed sex differences in cardiac and motor functions, quality of life (QoL), and mental status in Chinese chronic heart failure (CHF) patients after metoprolol treatment.

This single-center prospective study, conducted from February 2013 to April 2016, included CHF patients (men and women) with resting heart rate (HR) >80 beats/min using metoprolol continuous release tablets. Metoprolol-induced changes in cardiac and motor functions, QoL, and mental status at 1, 3, 6, 9, and 12 months from baseline, within and between the sexes, were analyzed. Descriptive data were represented as counts, percentages, and mean ± standard deviation. Differences at various follow-up periods were compared using repeated measures one-way analysis of variance, followed by post hoc Dunnett's multiple comparison test. Statistical significance was considered at $P < .05$.

Compared with men, women reported significantly higher systolic blood pressure (SBP) (122.28 ± 6.76 vs 125.47 ± 6.67 mm Hg, $P < .05$) and Veterans Specific Activity Questionnaire score (8.16 ± 0.98 vs 8.47 ± 0.89, $P = .05$) at 12 months. Men reported higher Hospital Anxiety and Depression Scale scores for depression than women at 1 month (10.27 vs 8.83, $P < .05$) and for anxiety at 12 months (8.4 vs 7.72, $P < .05$). Metoprolol significantly decreased HR and Minnesota Living with Heart Failure Questionnaire score in men (64.5 ± 3.13 and 53.7 ± 8.00) and women (65.38 ± 3.32 and 53.85 ± 8.42, respectively). Ejection fraction (%, men: 50.00 ± 4.45, women: 50.72 ± 4.09), cardiac index (L/min/m^2, men: 2.70 ± 0.25, women: 2.78 ± 0.23), 6-minute walk test distance (m, men: 414.41 ± 20.84, women: 420.34 ± 20.35), and short form-8 questionnaire scores (men: 52.05 ± 1.94, women: 52.19 ± 2.58) increased significantly in both the sexes ($P < .001$ for all) at 12 months. Copenhagen Burnout Inventory score significantly increased in men (mean score 62.43, $P < .05$).

Metoprolol treatment improves cardiac and motor functions, QoL, and anxiety scores but causes greater depression and burnout in men and women. Sex was seen to affect mental status of CHF patients the most.

Abbreviations: 6MWT = 6-minute walk test, BP = blood pressure, CBI = Copenhagen Burnout Inventory, CHF = chronic heart failure, CI = cardiac index, CVD = cardiovascular diseases, EF = ejection fraction, HADS = Hospital Anxiety and Depression Scale, HR = heart rate, MLHFQ = Minnesota Living with Heart Failure Questionnaire, NYHA = New York Heart Association, QOL = quality of life, SBP = systolic blood pressure, SD = standard deviation, SF-8 = short form-8 questionnaire, VSAQ = Veterans Specific Activity Questionnaire.

Keywords: sex, heart failure, metoprolol, quality of life

1. Introduction

The prevalence of cardiovascular diseases (CVDs) is increasing in China because of rapid changes in lifestyle and urbanization.[1] Heart failure (HF) affects approximately 4.5 million people in China,[2] with the majority of these patients being at New York Heart Association (NYHA) functional classification criteria level III to IV (84.7%).[1] The chronic condition of HF results in a huge economic burden on healthcare systems as it is associated with lower quality of life (QoL),[3,4] impairment in performing daily activities,[5] and loss of work productivity.[6] Indeed, the cost burden of HF in China for the year 2012 was estimated to be $5.416 billion.[7] β-Blockers are commonly used to treat HF as they counteract the sympathetic activity that occurs after left ventricular dysfunction and reduce heart rate (HR) and blood pressure (BP),[8] thus reducing mortality rate and enhancing the QoL.[9] Metoprolol is a β-blocker used to treat HF and is widely known to decrease the risk of death[10] and improve QoL and mobility.[11–13]

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In addition to age and race, sex is a variable that can affect drug response. Differences in parameters such as gastric and hepatic enzyme concentration, transporter protein concentration, body fat composition, cardiac output, and glomerular filtration rate influence drug pharmacokinetics, whereas variations in receptor number, receptor binding, and the consequent signal transduction pathways can affect drug pharmacodynamics.[14] Metoprolol is known to reduce the HR in women more than in men because of pharmacokinetic differences that result in greater drug exposure in the former.[15] Moreover, using pharmacokinetic modeling and simulations, this difference in exposure was shown to be associated with a 50% dose reduction in women. Clinically, this would implicate that a 100-mg dose in men would be on par with a 50-mg dose in women.[16]

Although previous research elucidates metoprolol's effects on cardiac performance, motor function, and QoL in Chinese patients with HF,[12] this effect has not been studied with respect to sex. Because metoprolol-mediated HR reduction varies according to sex,[15] it is possible that the aforementioned parameters are affected differently in men and women. Therefore, this study was conducted to compare the effect of metoprolol treatment on cardiac and motor functions, QoL, and mental status in men and women.

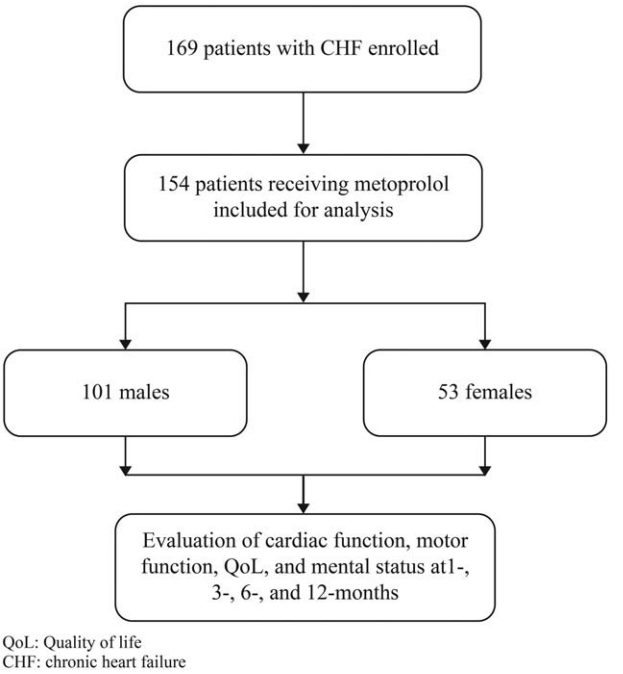

Figure 1. Study flow chart.

2. Methods

2.1. Ethical approval

The study protocol was approved by the Institutional Review Board of the Second Affiliated Hospital of Kunming Medical University and conforms to the Declaration of Helsinki and its subsequent revisions. An informed consent was obtained from all patients before enrolling in the study.

2.2. Study design and patient population

This single-center, prospectively designed study was conducted from February 2013 to April 2016 and included patients with chronic heart failure (CHF) (HR >80 beats/min) with or without neuropsychiatric disorders treated at the Second Affiliated Hospital of Kunming Medical University (Fig. 1). The exclusion criteria were resting HR <60 beats/min; systolic blood pressure (SBP) <90 mm Hg; metoprolol usage in the last 3 months; <6 months of expected survival; pacemaker dependency; traditional contraindication to β-blockers such as peripheral vascular diseases, diabetes mellitus, chronic obstructive pulmonary disease, and asthma; usage of class I or III antiarrhythmic agents, tricyclic antidepressants, anxiolytics, or other central nervous system medications; coronary bypass surgery; and a recent heart attack.

2.3. Sample size calculation

With a power of 80% and 5% 2-sided significance level, a total of 142 patients were required to observe a significant difference before and after metoprolol treatment. Thus, to account for any unseen attrition due to various reasons, we enrolled 169 patients.

2.4. Treatment intervention and follow-up

Patients were treated with daily oral doses of 23.75 or 47.5 mg metoprolol continuous release tablets with a dose escalation of 23.75 mg every 7 days until the target HR level (60–70 beats/min) was attained during follow-up.

2.5. Study outcomes

The study objective was to compare cardiac and motor functions, QoL, and mental status at 1, 3, 6, and 12 months from baseline in men and women. The methods used to determine resting HR (beats/min), SBP (mm Hg), ejection fraction (EF, [%]), cardiac index (CI, [L/min/m^2]), and exercise capacity and motor function (6-minute walk test [6MWT]) and information of Veterans Specific Activity Questionnaire (VSAQ), QoL short form-8 questionnaire (SF-8), and the Minnesota Living with Heart Failure Questionnaire (MLHFQ) are elaborated elsewhere.[12] Mental and burnout status at baseline and each follow-up was analyzed using the Hospital Anxiety and Depression Scale (HADS) questionnaire and the Copenhagen Burnout Inventory (CBI), respectively. The HADS is a simple, easy to use, and a quick self-assessment scale comprising 14 questions (7 each for anxiety and depression), each scored from 0 to 21, with a mean score >7 denoting the presence of anxiety or depression.[17] The CBI is a 19-item questionnaire that assesses the level of exhaustion using 3 subdimensions: personal burnout (6 questions), work-related burnout (7 questions), and client-related burnout (6 questions). Each question can be rated from 0 to 100, with 100 indicating total burnout.[18] This study used only the personal burnout subscale which had responses on a 5-point Likert scale: "never," "seldom," "sometimes," "often," and "always."

2.6. Statistical analysis

The statistical software R (version 3.2.2, R core team, R Foundation for Statistical Computing, Vienna, Austria) was used to perform all the analyses. The baseline characteristics were reported as descriptive data with counts, percentages, and mean ± standard deviation (SD). Differences in HR, SBP, EF, CI, and 6MWT and

Table 1

Baseline sociodemographic characteristics of the patients.

Patient characteristics (n = 154)	N (%)
Age, median years	66.39
Men	101 (65.58)
Women	53 (34.41)
Comorbidities	
Hypertension	115 (74.67)
Diabetes mellitus	101 (65.58)
Coronary artery disease	99 (64.28)
Stroke	137 (88.96)
Cardiac disease family history	54 (35.06)
Smoking	111 (72.07)
Alcohol	86 (55.84)
History of MI	59 (38.31)
BMI, kg/m^2	23.85 ± 3.62
GFR, mL/min/1.73 m^2	73.9 ± 26.8
NYHA class III–IV	145 (94.15)
Concomitant medications at baseline	
ACEIs/ARBs	150 (97.40)
Diuretics	145 (94.15)
Digoxin	114 (74.02)
Antithrombotic agents	146 (94.80)

Values are expressed as n (%) and mean ± SDs.
ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, BMI = body mass index, GFR = glomerular filtration rate, MI = myocardial infarction, NYHA = New York Heart Association.

VSAQ, SF-8, MLHFQ, HADS, and CBI scores at the various follow-up periods were compared with the baseline using repeated measures one-way analysis of variance (ANOVA), followed by post hoc Dunnett's multiple comparison test. A $P<.05$ was considered to be statistically significant for all the analyses.

3. Results

3.1. Sociodemographic characteristics

Of the 169 patients included in the study, 11 were excluded because of intolerance to metoprolol dose increments and 4 patients were lost to follow-up. Complete data were obtained for 154 patients (median age: 66.39 years; men [n = 101] and women [n = 53]; Table 1). The mean body mass index was 23.85 ± 3.62 kg/m^2, with a greater proportion of patients being smokers (72.07%) or consumed alcohol (55.84%). The patients were predominantly NYHA class III/IV (94.15%); suffered from comorbidities such as stroke (88.96%) and hypertension (74.67%); and were on concomitant medications such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (97.40%), antithrombotic agents (94.80%), or diuretics (94.15%).

3.2. Change in cardiac function postmetoprolol treatment

An average metoprolol dose of 99.75 mg was required to reach the target HR. As measured by resting electrocardiogram, a significant decrease in mean resting HR was seen postmetoprolol treatment compared with baseline in men and women at 12 months (83.16 ± 6.47 and 81.89 ± 7.21 beats/min, $t = -1.07$ vs 64.59 ± 3.13 and 65.38 ± 3.32 beats/min, $t = 1.43$, respectively; $P < .001$). However, the difference in HR between the sexes was nonsignificant ($P = .15$). Women had a higher SBP than men at all times (136.92 ± 2.17 vs 121.39 ± 14.09 mm Hg; $t = 10.9$, $P < .001$ at baseline and 125.47 ± 6.67 vs 122.28 ± 6.76 mm Hg; $t = 2.8$, $P < .05$ at 12 months). Baseline SBP of 136.92 ± 2.17 mm Hg significantly decreased to 125.47 ± 6.67 mm Hg in women at 12 months ($P < .001$; Table 2). However, a significant increase in SBP was reported in men at 12 months.

Biphasic responses were observed in EF and CI for both men and women, although the intersex differences were nonsignificant. EF in men and women, respectively, decreased significantly from baseline (37.60 ± 5.91% and 37.64 ± 6.10%) to 35.24 ± 6.15% and 34.79 ± 6.24% at 1 month ($P < .05$) and then increased to 50.00 ± 4.45% and 50.72 ± 4.09% at 12 months ($P < .001$). At 1-month follow-up, CI decreased significantly from baseline in men (1.78 ± 0.22 vs 1.71 ± 0.29 L/min/m^2, respectively; $P < .05$) but not in women (1.79 ± 0.21 vs 1.75 ± 0.24 L/min/m^2, respectively). However, from 2 months onward, the increase in CI during at all other follow-ups was significant both in men and women ($P < .001$; Table 2).

3.3. Changes in motor function and QoL outcomes postmetoprolol treatment

Distance walked in the 6MWT by men and women, respectively, decreased significantly from 368.42 ± 33.82 m and 369.57 ±

Table 2

Effect of metoprolol therapy on cardiac function.

	HR, beats/min			SBP, mm Hg		
Time	Men (M)	Women (W)	*P* value (M vsW)	Men (M)	Women (W)	*P* (M vs W)
Baseline	83.16 ± 6.47	81.89 ± 7.21	.2844	121.39 ± 14.09	136.92 ± 2.17	<.001
Month 1	82.72 ± 6.74	82.73 ± 6.77	.1934	126.73 ± 13.65	126.74 ± 13.72	.1402
Month 3	82.72 ± 6.74	82.73 ± 6.77	.1934	126.73 ± 13.65	126.74 ± 13.72	.1402
Month 6	82.72 ± 6.74	82.73 ± 6.77	.1934	126.73 ± 13.65	126.74 ± 13.72	.1402
Month 12	64.59 ± 3.13	65.38 ± 3.32	.1597	122.28 ± 6.76	125.47 ± 6.67	<.05

	EF, %			CI, L/min/m^2		
Time	Men (M)	Women (W)	*P* value (M vs W)	Men (M)	Women (W)	*P* (M vs W)
Baseline	37.60 ± 5.91	37.64 ± 6.10	.9708	1.78 ± 0.22	1.79 ± 0.21	.7955
Month 1	35.24 ± 6.15	34.79 ± 6.24	.6733	1.71 ± 0.29	1.75 ± 0.24	.2815
Month 3	35.9 ± 5.27	35.36 ± 4.75	.5184	2.26 ± 0.21	2.26 ± 0.18	.9797
Month 6	48.13 ± 4.56	47.32 ± 4.36	.2846	2.61 ± 0.19	2.60 ± 0.18	.7494
Month 12	50.00 ± 4.45	50.72 ± 4.09	.3182	2.70 ± 0.25	2.78 ± 0.23	.0668

Values are expresses as mean ± SD.
CI = cardiac index, EF = ejection fraction, HR = heart rate, SBP = systolic blood pressure.

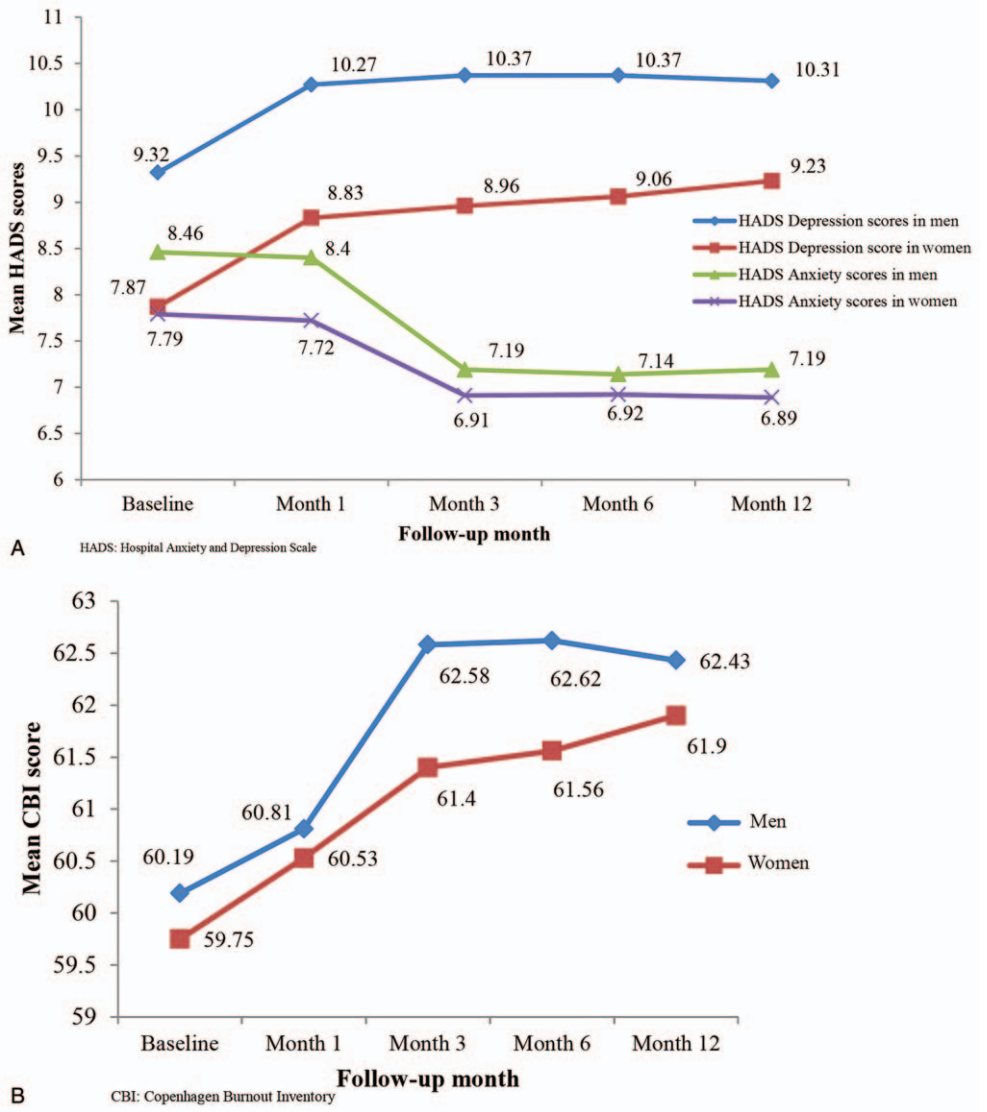

Figure 2. (A) HADS depression scores between and within sex posttreatment. (B) CBI score between and within sex posttreatment.

34.51 m to 341.58 ± 32.45 m and 340.94 ± 33.09 m at 1 month ($P < .001$), but later increased significantly to 414.41 ± 20.84 m and 420.34 ± 20.35 m at last follow-up ($P < .001$; Table 3). Although the VSAQ scores followed a similar trend, the upward curve observed started at different follow-up points for men and women. In men, the score decreased significantly from 6.41 ± 1.03 at baseline to 4.86 ± 0.87 at 1 month ($P < .001$), but increased significantly thereafter to 8.16 ± 0.98 at 12 months ($P < .001$). On the contrary, in women the lowest VSAQ score compared with the baseline was reported in at 3 months (5.62 ± 1.15; $P < .001$), after which a significant increase was observed till 12 months (8.47 ± 0.89; $P < .001$).

QoL, evaluated using the SF-8, in men and women, respectively, decreased significantly from baseline (44.00 ± 2.59 and 44.06 ± 2.95) to 39.22 ± 1.69 and 39.70 ± 1.55 at 1 month ($P < .001$) and thereafter increased significantly till the last follow-up (52.05 ± 1.94 and 52.19 ± 2.58; $P < .001$). The MLHFQ scores in men and women, respectively, increased significantly from baseline (74.36 ± 3.68 and 73.77 ± 3.95) to 88.67 ± 4.36 and 89.06 ± 4.40 at 1 month ($P < .001$) but decreased significantly thereafter to 53.74 ± 8.00 and 53.85 ± 8.42 by 12 months ($P < .001$; Table 3).

3.4. Changes in mental and burnout status postmetoprolol treatment

HADS depression score significantly increased at 1-month follow-up after metoprolol treatment compared to baseline (from 9.32 ± 2.95 and 7.87 ± 2.15 to 10.27 ± 2.82 and 8.83 ± 2.67 in men and women, respectively; $P < .05$). However, the scores were comparable thereafter until the last follow-up (Fig. 2A). Although men had a significantly higher baseline score than women ($P < .05$), during subsequent follow-ups, the score significantly decreased: 1 month ($P < .05$), 3 months ($P < .05$), 6 months ($P < .05$), and 12 months ($P = .02$). Metoprolol significantly decreased the HADS anxiety score from 8.46 ± 2.04 and 7.79 ± 2.01 at baseline to 7.19 ± 1.17 and 6.91 ± 0.90 at 3 months in men ($P < .001$) and women ($P < .05$),

Table 3

Effect of metoprolol therapy on motor functions and QoL outcomes.

	6MWT, m			VSAQ (score)		
Time	Men (M)	Women (W)	*P* (M vsW)	Men (M)	Women (W)	*P* (M vsW)
Baseline	368.42 ± 33.82	369.57 ± 34.51	.8435	6.41 ± 1.03	6.73 ± 1.15	.0963
Month 1	341.58 ± 32.45	340.94 ± 33.09	.9087	4.86 ± 0.87	5.95 ± 0.92	.2141
Month 3	349.71 ± 34.04	352.74 ± 31.46	.5830	5.48 ± 0.97	5.62 ± 1.15	.4424
Month 6	398.40 ± 21.18	398.72 ± 22.52	.9318	7.89 ± 1.07	7.79 ± 1.00	.5713
Month 12	414.41 ± 20.84	420.34 ± 20.35	.0911	8.16 ± 0.98	8.47 ± 0.89	.0473
	SF-8 (score)			MLHFQ (score)		
Time	Men (M)	Women (W)	*P* (M vs W)	Men (M)	Women (W)	*P* (M vs W)
Baseline	44.00 ± 2.59	44.06 ± 2.95	.9064	74.36 ± 3.68	73.77 ± 3.95	.3759
Month 1	39.22 ± 1.69	39.70 ± 1.55	.0795	88.67 ± 4.36	89.06 ± 4.40	.6076
Month 3	42.26 ± 2.51	42.57 ± 3.07	.5301	86.55 ± 5.00	87.58 ± 5.14	.2357
Month 6	48.83 ± 1.18	48.94 ± 1.28	.5982	64.36 ± 3.48	64.79 ± 4.52	.5413
Month 12	52.05 ± 1.94	52.19 ± 2.58	.7309	53.74 ± 8.00	53.85 ± 8.42	.9397

Values are expressed as mean ± SD.

6MWT = 6-minute walk test, MLHFQ = Minnesota Living with Heart Failure Questionnaire, SF-8 = short form-8 questionnaire, VSAQ = Veterans Specific Activity Questionnaire.

respectively, following which the scores remained stable until the last follow-up (Fig. 2A). Although men had a HADS higher score, the difference was significant only at the 12th month of follow-up (mean score: 10.31, $P < .05$). The CBI score was significantly higher in men at 3 months compared with the baseline (62.58 ± 8.92 vs 60.19 ± 6.50; $P < .05$) and remained stable thereon (Fig. 2B). Although there was an increasing trend in women, metoprolol treatment resulted in no significant increment in the CBI score at any follow-up. Moreover, both the sexes had similar scores throughout the study period.

4. Discussion

The effect of metoprolol treatment on cardiac, motor, and QoL outcomes in patients with CHF was investigated previously.[12] However, there is limited data on the sex-specific effect of metoprolol on the aforementioned outcomes.

In the present study, a significant reduction in HR in both the sexes from baseline to 12 months due to the β_1-selective blocking action of metoprolol was observed.[19] In agreement, studies on the effects of β-blockers have also shown time-dependent improvements in ventricular structure and function in addition to the beneficial actions of β-blockers such as reduction in heart rate and blood pressure and their antiischemic effects.[19–21] Although HR is generally higher in women,[22] in our study HR was similar between sexes, which was consistent with previous findings.[23] On the contrary, we observed higher SBP in women at all timepoints. However, metoprolol decreased SBP during the last follow-up in women but not in men. It is possible that because SBP in men was already almost normal (120 mm Hg), the usage of metoprolol was not as effective in men as in women because of the compensatory mechanisms that increased SBP.

Role of β-blockers in increasing the EF, along with modulating the hemodynamics and remodeling the dilated left ventricle, is well documented.[24] Similarly, both the sexes in our study demonstrated a biphasic response for EF and CI, with an initial decrease at 1 month and gradual increment till the 12th month. This response, as reported earlier,[12,25] occurs because of larger ventricular volume following initial therapy, which subsequently stabilizes with time.[25] The EF and CI in this study were similar between the sexes. This observation about EF, but not CI, was consistent with findings from an earlier Chinese study.[26] Li et al[26] reported that women had a greater CI than men (3.5 ± 0.4 vs 3.3 ± 0.4 L/min/m^2; $P < .05$). The variation in CI could possibly be due to the different study population (elderly with HF vs healthy middle-aged participants) and the method used for measurement (echocardiography vs 3 Tesla MRI). Moreover, the minimum CI value observed for both the sexes in the present study is comparable to that of healthy individuals aged 40 to 65 years (3.2 L/min/m^2) and our previous results for the elderly (1.79 L/min/m^2) (unpublished results). CI has been reported to increase by 0.1 to 0.3 L/min/m^{2}after 3 months.[20,27] The magnitude of change in CI in the current study was 0.92 L/min/m^2 in men and 0.99 L/min/m^2 in women after 12 months. However, the change observed after 3 months of therapy (0.48 L/min/m^{2}in men and 0.47 L min^{-1} m^{-2}in women) is closer to the values reported earlier.

We also found that metoprolol significantly increased the distance walked in both men and women using 6MWT, a reliable tool for evaluating functional capacity and providing prognostic information.[28,29] This beneficial change can counteract the abnormalities in skeletal musculature caused due to CHF because of various functional, morphologic, and metabolic changes,[30] leading to deterioration of motor function. It is also plausible to hypothesize that CHF deteriorates the locomotor function and exercise tolerance in patients and affects the therapeutic efficacy of metoprolol by reducing the patients' performance compared with placebo[31] or patients' baseline values[32] which is contrary to our observations. The baseline VSAQ scores in the present study (men: 6.41 ± 1.03 and women: 6.73 ± 1.15) are higher than those in other patients with HF (3.37 ± 1.41),[33] indicating a vast ethnic variation and that Chinese patients with HF fare better in terms of functional capacity and mortality risk than their counterparts.

Similarly, we observed a biphasic response for both the QoL scales, similar to the motor function results. It has been reported that patients with HF have markedly impaired QoL because the disease affects motor functions limiting daily activities, social relationships owing to consistent need for support, economic status due to work impairment, and self-care.[34] Metoprolol has been reported to improve QoL assessed by various questionnaires in multiple countries.[12,35–37] However, results not in favor of

metoprolol have also been reported.[11,38,39] A recent randomized clinical trial showed that although patients in the metoprolol group experienced significant improvement in general health and role limitations due to the "emotional problems" subscale of the SF-36 compared with baseline, these effects were nonsignificant when compared with placebo, indicating the presence of a placebo effect.[13] A major point to note for the differences in metoprolol's effect on QoL is the study duration. QoL was measured after at least 12 months in the studies that report a favorable result for metoprolol, whereas the ones that do not report favorable results evaluated QoL after 3 or 6 months. An exception to this is a Russian study which assessed QoL after a maximum of 3 months.[37] In the present study too, QoL scores improved compared with baseline only at 6 months. Moreover, although not analyzed in the present study, QoL improvement has been associated with positive clinical changes.[36]

In contrast to the general notion about women being more anxious and depressed than men,[40,41] we found men to score higher in the HADS scale for both depression and anxiety. It was seen that metoprolol treatment increased the HADS depression score but reduced the HADS anxiety score in both the sexes. These results are consistent with previous data,[42] although metoprolol has been reported to decrease the depression score, as measured by the self-management support program and Hamilton scale.[37] Depression and anxiety are known to cause pathophysiological modifications through neurohormonal dysregulation causing cardiac abnormalities.[43,44] However, symptoms related to depression and anxiety usually go unrecognized,[45] often resulting in disease progression and mortality.[44,46] The antianxiety effect of metoprolol could be attributed to inhibition of β_1-receptors in the amygdala,[47] although this is yet to be evaluated in humans. Metoprolol significantly increased burnout in men compared to baseline. However, the burnout scores were similar among the sexes. Although the CBI score increased by >2 points in both the sexes, it is possible that the change in women was not significant due to the inadequate sample size.

Sex-based differences in metoprolol's pharmacokinetics is well known.[14] Metoprolol is metabolized by the cytochrome P450 2D6 (CYP2D6) enzyme, which has been speculated to undergo induction during pregnancy,[48] leading to increased oral clearance.[49] In the absence of pregnancy, women experience greater metoprolol exposure than men because of lower total body clearance, leading to greater reduction in exercise HR than in men.[15] Furthermore, a recent analysis of extensive and poor CYP2D6 metabolism in men and women has revealed that women in general experience greater HR reduction than men and that metoprolol dosage should be adjusted according to body weight, especially for women.[50] Despite all the factors affecting the pharmacokinetics of metoprolol, a dose equivalence study by Eugene[16] showed that a 50% dose reduction in men is equivalent to metoprolol exposure as compared to women. Therefore, sex-based prescription of metoprolol and dose adjustments are required to avoid any unnecessary systemic exposure to the drug. Even the present study findings should be interpreted in correlation with the aforementioned observations in delineating sex-specific differences seen in SBP, VSAQ score, and HADS depression and anxiety scores.

It is noteworthy to mention that the inclusion of patients with smoking and alcohol consumption could have also affected the current findings. It has been reported that smoking can have an adverse effect on the efficacy of β-blockers wherein they were less effective in fighting elevated BP and HR in 2 large epidemiological studies.[49,50] However, as the present study did not aim at assessing the role of smoking or alcohol consumption on metoprolol's efficacy, their role in modifying the drug's action cannot be ruled out. In addition, the interference of other concomitant medication used by our patients (ACEIs, digoxin, etc.) on metoprolol cannot be eliminated.

Sex-based assessment and comparison of multiple cardiac, functional, and mental effects of metoprolol treatment in patients with CHF is the prime strength of this study. However, there are a few limitations as well: clinical trials involving β-blockers frequently involve more men than women.[51,52] Therefore, the efficacy of these drugs is directly proportional to the male population of the study.[53] In the present study too, the difference seen in the sex proportion could be attributed to the fact that the prevalence of HF is more in men as per the real-world data.[54] In future, more number of real-world, prospective studies with larger sample size are required to validate our study findings. Because the study included patients from a single center, the study findings cannot be extrapolated to other population elsewhere and limits the heterogeneity of sample considered. Lack of controls could have induced a possible overlooking of certain observations. Having a control population would have enabled a better understanding of metoprolol's efficacy. As most of the parameters were assessed using self-administered and self-reported questionnaires, this might have led to either over- or under-reporting of results. However, adequate assistance was provided by healthcare professionals to limit this. As HADS depression and CBI scores increased after treatment, it would be beneficial to extend the follow-up time in future trials to understand the change mediated by long-term metoprolol treatment. As the study was not designed mechanistically to explore metoprolol-induced changes in cardiac and motor functions, most of the results remain hypothetical. Finally, the outcomes can possibly vary in young or adolescent patients to some extent compared with the current elderly population. It should also be noted that changes observed in our study could be attributed to various factors such as time, patients' lifestyle modification, and so on and cannot be solely pointed to metoprolol's role. In conclusion, men and women suffering from CHF exhibited significant improvement in cardiac performance, functional capacity, QoL, and anxiety after treatment with metoprolol. However, depression and burnout were aggravated by metoprolol.

5. Conclusion

Sex-related differences were observed the most in mental status, indicating that psychologically men and women respond differently to metoprolol. It would be beneficial to assess the psychological impact of long-term metoprolol usage in patients with CHF. In addition, future mechanistic studies to understand metoprolol-elicited sex differences in cardiac and motor functions are needed.

Author contributions

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