Curative effect of β-blocker on various ejection fractions of patients with atrial fibrillation

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Abstract. The aim of this study was to retrospectively deter-
mine the effects of metoprolol on patients presenting with
persistent atrial fibrillation (AF), but either with or without a
reduced ejection fraction (EF). All patients meeting the inclu-
sion criteria were treated for 2 years with metoprolol. Blood
pressure, heart rate and echocardiography parameters were
measured and analysed in patients before and after treatment.
The patients were divided into 2 cohorts as follows: Those
presenting with a low EF (<50%) and those with normal
EF values (≥50%). In total, 151 patients enrolled were 136;
however, of these 15 were lost to mortality during the follow-up
period, thus leaving a total of 136 patients. In total, 42 patients
presented EF values <50%, while the remaining 94 presented
with normal EF values. Treatment with metoprolol controlled
blood pressure (both diastolic and systolic) and heart rate in
patients with both low and normal EF values. EF values in
the low EF group significantly increased following treatment.
In addition, the echocardiography data revealed a statistically
significant decrease in left atrial and ventricular diameters
in the low EF group. On the whole, the findings of this study
demonstrate that patients with AF and low EF values who were
treated with metoprolol presented with improved cardiac func-
tion parameters. However, metoprolol should be contraindicated
for patients with high EF values (i.e., absence of heart failure)
as it seemed to increase their risk of heart failure based on the
N-terminal pro b-type natriuretic peptide (NT-pro BNP) results.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia
diagnosed in adults (1), with an increasing prevalence with
advancing age (2). Epidemiological studies have reported an
AF incidence rate of 0.77% in the Chinese population (2).
AF can lead to significant rates of morbidity [e.g., the devel-
opment of apoplexia, embolism and heart failure (HF)] and
mortality (3). Conversely, HF is also considered an etiological
factor contributing to and exacerbating AF (4). Chronic HF
is a group of syndromes which are characterised by cardiac
dystrophy and declining heart function (5). Clinically, chronic
HF is associated with ventricular filling disorder and a reduced
cardiac ejection fraction (EF) (6). The European Society of
Cardiology has characterised HF using left ventricular EF
as follows: When the EF value is ≥50%, patients are classi-
fied as having heart failure with preserved EF, whereas when
the EF value is <50%, patients are classified as having heart
failure with reduced EF (6). Patients with chronic HF and AF
have a greater risk of thromboembolic complications (e.g.,
cerebral stroke) (7). There are a number of pharmacological
treatments available for HF and AF, such as β-blockers (8),
angiotensin-converting enzyme inhibitors (9), angiotensin
receptor blockers (10) and mineralocorticoid receptor antago-
nists (11). Clinically, β-blockers are the most preferred for the
improvement of the prognosis, the prevention of arrhythmias,
the improvement of left ventricular EF, the control of heart rate
and the reduction of mortality of patients. Previous large-scale
clinical studies conducted on patients with or without AF have
confirmed the effectiveness of β-blockers for improving HF
in patients with preserved EF (11,12). However, the role of
metoprolol in patients with a reduced EF and persistent AF has
yet to be determined (13,14). Therefore, the aim of this study
was to retrospectively determine the effects of the sustained
administration of metoprolol on patients with chronic AF and
HF either with or without reduced EF.

Patients and methods

Patient information and follow-up. The Ethics Committee
of the First Affiliated Hospital of the University of Science
and Technology of China approved this retrospective
medical record review (approval no. NCT02309398). From
the history reports of the patients who were enrolled in this
study, all patients or patient carers signed informed consents.
Analyses were based on data from the Improving Care for
Cardiovascular Disease in China (CCC) project, which is
a collaborative project of the American Heart Association
(AHA) and the Chinese Society of Cardiology (CSC). Data

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were collected prospectively for an investigator-initiated single centre study at The First Affiliated Hospital of the University of Science and Technology of China (UTSC). Chinese patients (aged >40 years) with persistent AF between 2015 and 2016 were treated with a single 47.5 mg dose of metoprolol once per day for 2 years were selected for study. The inclusion criteria were as follows: i) Patients classified as Class II, III, or IV according to the New York Heart Association Functional Classification system (15); ii) diagnosed with persistent AF and HF presenting with either a reduced EF (<50%) or preserved EF (≥50%). The exclusion criteria were as follows: i) incomplete β-blocker administration data; ii) had contraindication for β-blockers; iii) had their β-blockers discontinued. The total number of enrolled patients was 151, of which 47 presented with a reduced EF and 104 presented with a preserved EF. However, 15 patients were lost due to mortality during the follow-up period (5 in the reduced EF group and 10 in the preserved EF group). During the follow-up period, patient heart rates were brought to <110 beats per min according to the European Society of Cardiology Guidelines (7), using doses of metoprolol specifically determined for each individual patient by outpatient doctors or through telephone counselling. The following indicators were examined using echocardiography: Left ventricular EF, left ventricular end diastolic diameter and left atrial diameter. N-terminal pro b-type natriuretic peptide (NT-pro BNP) and 6-min walk tests (6MWT) were also performed during follow-up. 6MWTs were carried out according to the American Thoracic Society (ATS) guidelines (16). Briefly, patients were instructed to walk as far as possible up and down a 30-meter corridor for 6 min under the supervision of a physiotherapist. The physiotherapist encouraged the subject with standardised statements, such as 'you are doing well' and 'keep up the good work' and was asked to refrain from using other phrases. The patient or the physiotherapist could interrupt the 6MWT if the following symptoms appeared: Chest pain, intolerable dyspnoea, leg cramps, staggering, diaphoresis, or a pale or ashen appearance. All 6MWTs were administered by the same individual. The measurements included the following: A 6-min walking distance. Echocardiography and blood pressure measurements were performed before and after treatment using standard techniques by trained and experienced personnel.

Statistical analysis. Statistical analyses were performed using IBM SPSS Statistics 23 software (IBM Corp.). The approximate normal distribution of data was assessed by visual (histograms and normal Q-Q plots) and numerical investigative means (z-value of skewness and kurtosis; P-value of Shapiro-Wilk test). The analyses of patient characteristics and cardiac parameters between the cohorts was performed using Chi-square tests and independent sample t-tests. The analyses of cardiac parameters at baseline and after 2 years of metoprolol treatment were performed using paired sample t-tests. All tests were two-sided, with P-values <0.05 considered to indicate statistically significant differences.

Results

In total, 136 patients completed this 2-year study (151 original enrolments with 15 lost to mortality during the follow-up period). Of these, 42 had EF values <50% and 94 presented with preserved EF values (≥50%). No significant demographic or physical characteristic differences were observed between these 2 groups (Table I).

As measured by echocardiography, atrial and ventricular enlargement are characteristics of AF and HF, respectively (Table II). In the low EF group, the patient baseline cardiac parameters prior to metoprolol treatment exhibited a statistically significant elevation in diastolic blood pressure, as well as statistically significant elevations in left ventricular and left atrial diameter compared to the preserved EF group. Additionally, the NT-pro BNP values were greater in the patients in the low EF group compared to the preserved EF group, and the 6MWT results were diminished in the low EF group compared to the patients with preserved EF function. The difference between the EF values between the 2 study groups was also statistically significant.

Following 2 years of treatment with metoprolol, patients with reduced EF values <50% (Table III) exhibited significantly reduced systolic and diastolic blood pressures and heart rate compared to the baseline levels. These findings are typical of the effects observed following the administration of β-blockers. Notably, left ventricular diameter decreased, the EF value increased, and 6MWT results improved following treatment.

As regard patients presenting with preserved EF (≥50%) (Table IV) during baseline examinations, treatment with metoprolol significantly reduced the systolic and diastolic blood pressures and heart rate, as expected following β-blocker administration. However, the left ventricular and atrial diameters increased, the NT-pro BNP values increased, EF decreased, and the 6MWT results decreased.

Cardiac parameters of patients at the 2-year follow-up following metoprolol treatment, with comparisons between the two cohorts (EF <50% and EF ≥50%) being performed (Table V). At the 2-year follow-up the patients with preserved EF exhibited cardia parameters which were statistically significantly superior to those of the the reduced EF group for all ultrasonic-derived cardiac parameters (e.g., left ventricle and atrial diameters, EF) NT-proBNP and the 6-min walk test.

Discussion

The aim of this study was to determine the role of metoprolol in adult Chinese patients with persistent AF, but with either reduced or preserved EF. β-blockers are widely used for the treatment and management of cardiac disorders (e.g., arrhythmia, reduced left ventricular EF, cardiac rate abnormalities, hypertension and HF) (17). β-blockers are preferred due to their inhibitory effects on the sympathetic nervous system, which translates into a beneficial effect for cardiac disorders, including HF (18-21). However, the long term effects of β-blockers on HF remain controversial (22-24).

The SENIORS trial noted that adult patients with HF and differing degrees of EF treated with nebivolol (a β1 receptor blocker with nitric oxide-potentiating vasodilatory effects) failed to report any significant effect onmortality and cardiovascular hospital admission (25). In a pilot study, Mittal *et al* performed an investigator-initiated, randomised, double-blind, placebo-controlled, 14-week pilot study with

Table I. Demographic and physical characteristics of the study subjects.

Characteristics	EF <50% (n=42)	EF ≥50% (n=94)	P-value
Sex, male, n (%)	24 (57.1)	47 (50.0)	0.441
Age (years)	72.9±9.9	71.1±8.3	0.297
Weight (kg)	66.2±13.3	64.9±10.5	0.531
Height (cm)	165.0±8.0	165.1±8.3	0.915
Hypertension, n (%)	29 (69.0)	55 (58.5)	0.243
Diabetes, n (%)	7 (16.7)	15 (16.0)	0.917
Ischemic cardiomyopathy, n (%)	1 (4.2)	2 (2.1)	0.926
Coronary heart disease, n (%)	11 (26.2)	15 (16.0)	0.161
Congestive heart failure, n (%)	14 (23.0)	17 (18.7)	0.050

Comparisons between the 2 cohorts (EF <50% and EF ≥50%) were made using Chi-square tests and independent samples t-tests. All discrete data are expressed as n (% of total) and all continuous data are expressed as the means ± SD. EF, ejection fraction.

Table II. Patient baseline cardiac parameters before metoprolol treatment.

Baseline parameters (pre-treatment)	EF <50% (n=42)	EF ≥50% (n=94)	P-value
Systolic pressure (mmHg)	136.2±23.5	135.5±20.2	0.860
Diastolic pressure (mmHg)	85.6±15.5	79.4±13.8	0.022
Heart rate (beats/min)	90.3±23.0	84.3±18.7	0.112
Left ventricle diameter (mm)	66.4±7.6	55.0±6.3	<0.001
Left atrium diameter (mm)	51.5±6.1	47.3±6.4	0.001
Ejection fraction (%)	39.6±7.1	62.7±7.5	<0.001
NT-proBNP (pg/ml)	3,454.7±1,254.6	633.5±519.7	<0.001
6-min walk test distance (m)	201.9±86.7	322.3±112.6	<0.001

Comparisons between the 2 groups (EF <50% and EF ≥50%) were performed using independent-samples t-tests. All data are expressed as the means ± SD. EF, ejection fraction; NT-proBNP, N-terminal pro b-type natriuretic peptide.

Table III. Cardiac parameters before and after metoprolol treatment for patients with a reduced EF.

Parameters for EF <50% (n=42)	At baseline	At 2-year follow-up	P-value
Systolic pressure (mmHg)	136.2±23.5	127.6±13.4	<0.001
Diastolic pressure (mmHg)	85.6±15.5	76.6±10.0	<0.001
Heart rate (beats/min)	90.3±23.0	77.8±10.5	<0.001
Left ventricular diameter (mm)	66.4±7.6	65.0±7.5	0.001
Left atrial diameter (mm)	51.5±6.1	52.0±5.2	0.264
EF (%)	39.6±7.1	43.7±7.8	<0.001
NT-proBNP (pg/ml)	3,454.7±1,254.6	3,350±2,452.7	0.790
6-min walk test distance (m)	201.9±86.7	238.5±89.7	0.008

Comparisons between the time points was performed using paired samples t-tests. All data are expressed as the means ± SD. EF, ejection fraction; NT-proBNP, N-terminal pro b-type natriuretic peptide.

metoprolol succinate as a study drug for patients with heart failure with preserved EF. The results of the pilot study revealed that metoprolol administration yielded some benefits for patients with HF with preserved EFs, as reflected by improvements in echocardiographic and biochemical parameters (26). A meta-analysis was published to clarify whether any β-blocker was superior in patients with HF and reduced EF. This analysis included 21 trials and found that

Table IV. Cardiac parameters before and after metoprolol treatment for patients with preserved ejection fraction.

Parameters for EF ≥50% (n=94)	At baseline	At 2-year follow-up	P-value
Systolic pressure (mm Hg)	135.5±20.2	127.1±12.7	<0.001
Diastolic pressure (mm Hg)	79.4±13.8	74.0±9.2	<0.001
Heart rate (beats/min)	84.3±18.7	75.8±9.9	<0.001
Left ventricular diameter (mm)	55.0±6.3	57.1±5.4	<0.001
Left atrial diameter (mm)	47.3±6.4	50.0±7.1	<0.001
EF (%)	62.7±7.5	54.3±5.2	<0.001
NT-proBNP (pg/ml)	633.5±519.7	1,998.7±1,242.7	<0.001
6-min walk test distance (m)	322.3±112.6	304.6±109.1	0.038

Comparisons between the time points was performed using paired samples t-tests. All data are expressed as the means ± SD. EF, ejection fraction; NT-proBNP, N-terminal pro b-type natriuretic peptide.

Table V. Cardiac parameters of patients at 2-year follow-up following metoprolol treatment.

Parameters at 2-year follow-up	EF <50% (n=42)	EF ≥50% (n=94)	P-value
Systolic pressure (mm Hg)	127.6±13.4	127.1±12.7	0.823
Diastolic pressure (mm Hg)	76.6±10.0	74.0±9.2	0.144
Heart rate (beats/min)	77.8±10.5	75.8±9.9	0.293
Left ventricle diameter, (mm)	65.0±7.5	57.1±5.4	<0.001
Left atrial diameter, (mm)	52.0±5.2	50.0±7.1	0.106
Ejection fraction, (%)	43.7±7.8	54.3±5.2	<0.001
NT-proBNP (pg/ml)	3,350±2,452.7	1,998.7±1,242.7	<0.001
6-min walk test distance (m)	238.5±89.7	304.6±109.1	0.001

Comparisons were made between the two cohorts (EF <50% and EF ≥50%) using independent samples t-tests. All data are expressed as the means ± SD.

the benefit of β-blockers in patients with HF and a reduced EF was primarily due to a class effect, as no statistical evidence supported the superiority of any single drug over the others (22). Published research has also focused on the effects of β-blockers on patients with HF with preserved EF and AF. Indeed, it has been shown that metoprolol is beneficial for all patients, even in patients with a reduced EF. Selective β-blockers inhibit the sinus node, ultimately leading to the control of the atrioventricular node, which is responsible for AF. Hence, the selective inhibition of β1 receptors helps preserve cardiac function in HF (21).

BNP or NT-pro BNP are biomarkers detected by tests used to aid in the detection, diagnosis and the evaluation of the severity of HF. The NT-pro BNP levels were measured in this study; due to high variability in the reduced EF group, no statistically significant difference was found between the baseline and post-treatment time points. In the preserved EF group, however, a statistically significant increase in NT-pro BNP was observed after 2 years of treatment, which was consistent with the worsening HF in this patient cohort, as indicated by other cardiac parameters (e.g., enlarged left ventricle/atria and reduced EF). When comparing the patients with preserved and reduced EF at the 2 year follow-up, the patients with preserved EF exhibited values which were

statistically significant superior for all ultrasonic derived cardiac parameters, NT-pro BNP and the 6MWT than the reduced EF group.

Previous studies including meta-analyses on the use of β-blockers have not reported a reduced mortality rate of patients with HF with preserved EF (12,25,27). The present study highlights the importance of efficient metoprolol treatment in adult patients with chronic AF and reduced EF, as well as the beneficial effects on cardiac parameters resulting from such a treatment. Left ventricular enlargement leads to increased end diastolic and systolic volumes and a reduced cardiac output. A reduction in diastolic blood pressure favours protection against left ventricular enlargement, while a decrease in systolic pressure may increase the pumping efficiency of the heart. This study confirmed that metoprolol treatment resulted in a desired negative chronotropic effect that is essential for reducing the workload of the failing heart. Metoprolol treatment significantly reduced left atrial and left ventricular diameters, indicating that metoprolol reverses some of the pathophysiological changes observed in patients with AF and HF. However, metoprolol treatment in patients with preserved EF did not present the same effects; indeed, several important cardiac parameters worsened, including EF, which diminished. It is not clear whether these findings are

due to the cardiac function natural histories in these patients presenting with AF and preserved EF, or whether the drug itself had a deleterious or non-protective effect, as this study lacked an untreated control group for a statistical comparison. Beyond this, this study was also hampered by the small sample size. Nonetheless, the sample size was still sufficient for the identification of statistically significant associations using paired-sample t-tests.

In conclusion, this study demonstrated a beneficial effect for long-term sustained-release metoprolol treatment in adult Chinese patients with persistent AF and reduced EF. Large-scale clinical trials with patients with HF presenting with AF and varying degrees of EF are still required to determine whether the mortality rate is also reduced.

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Availability of data and materials

All data generated or analysed during this study are included in this published article or are available from the corresponding author on reasonable request.

Authors' contributions

WC and LM conceived and designed the study, provided study materials or patients and were responsible for the collection and assembly of the data, data analysis and interpretation. WC was involved in the writing of the manuscript. LM was involved in the editing of the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China approved this retrospective medical record review (approval no. NCT02309398). From the history reports of the patients who were enrolled in this study, all patients or patient carers signed informed consents. Please kindly check this situation with the Regional Ethics Committee of our hospital if it is necessary.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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