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Effect of metoprolol in hypertrophic obstructive cardiomyopathy patients after alcohol septal ablation☆

Hana Hnátová *, Klára Fulínová, Barbora Řiháková, Jiří Bonaventura, Josef Veselka

Department of Cardiology, 2nd Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic

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ABSTRACT

Background: The use of beta-blockers in hypertrophic obstructive cardiomyopathy (HOCM) patients after alcohol septal ablation (ASA) lacks data support. We aimed to evaluate the effect of metoprolol on exercise capacity, hemodynamic and laboratory parameters, and quality of life in HOCM patients after ASA.

Methods: This was a prospective randomized single-center open-label crossover trial in 21 HOCM patients after ASA. Patients received metoprolol and no beta-blocker for two periods of three months. The endpoints were: peak oxygen uptake (pVO_2), maximal left ventricular outflow tract (LVOT) pressure gradient at peak exercise, a ratio of mitral peak velocity of the early filling (E) to early diastolic mitral annular velocity (e′) (E/e′) at rest, Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score, and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) plasmatic concentration.

Results: No significant association was found between the treatment and any of the endpoints in the assessed patients: 1) pVO_2 (19.5 ± 5.3 ml/kg/min vs. 19.4 ± 4.1 ml/kg/min, $p = 0.90$), 2) exercise-induced pressure gradient in LVOT 32 ± 37 mmHg vs. 32 ± 30 mmHg, $p = 0.84$, 3) E/e′ ratio at rest (11 ± 4 vs. 10 ± 4, $p = 0.23$), 4) KCCQ overall summary score (78 ± 11 vs. 77 te ± 15, $p = 0.56$), 5) NT-proBNP (215 pg/ml [121–333] vs. 153 pg/ml [102–228], $p = 0.19$).

Conclusions: In HOCM patients after successful ASA, metoprolol treatment did not improve exercise capacity, hemodynamic and laboratory parameters, or quality of life.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is a complex disease with a wide range of symptoms. Apart from dyspnea and chest pain, patients frequently develop arrhythmias and are at increased risk of sudden cardiac death [1]. One of the main factors affecting the severity of symptoms and prognosis is the presence and magnitude of pressure gradient in the left ventricular outflow tract (LVOT) [2]. Therefore, addressing significant LVOT obstruction (LVOTO) in symptomatic patients is the cornerstone of hypertrophic obstructive cardiomyopathy (HOCM) therapy. Currently, no data supporting the use of beta-blockers in asymptomatic patients with nonobstructive HCM, and no data related to the use of beta-blockers in patients who underwent alcohol septal ablation (ASA), with or without residual LVOTO are available.

This study aimed to evaluate the effect of metoprolol on exercise capacity, hemodynamic and laboratory parameters, and quality of life in patients with HOCM after ASA.

2. Methods

2.1. Patients

Between March 2020 and April 2022, a total of 216 adult patients with HOCM who previously underwent ASA were screened for eligibility. The inclusion criteria were age under 75, a resting maximal pressure gradient in LVOT less than 30 mmHg, and at least three months interval after ASA. Patients with a history of atrial fibrillation with fast ventricular response demanding bradycardic therapy, patients with severe dyspnea in New York Heart Association (NYHA) class III and IV, as well as patients with an implanted cardiac device requiring bradycardia treatment were excluded (Fig. 1). A total of 46 patients were randomized in a 1:1 fashion, of whom 21 completed the trial and were analyzed. The

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* Corresponding author at: Department of Cardiology, Motol University Hospital, V Úvalu 84, 150 06, Prague 5, Czech Republic.
E-mail address: hana.hnatova@fnmotol.cz (H. Hnátová).

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baseline demographic, clinical, and echocardiographic characteristics of the study population are summarized in Table 1.

2.2. Trial design

This was a prospective randomized single-center open-label crossover trial. At enrollment, previously prescribed beta-blockers and non-dihydropyridine calcium channel blockers were discontinued in all patients, and a washout period of one month was provided. None of the patients used disopyramide since it is unavailable in our country. Patients were then randomly assigned into two treatment sequences – arms. Trial arm A received oral metoprolol succinate (metoprolol) for three months (on-treatment period); trial arm B remained with no beta-blocker treatment for the first three months (off-treatment period). Subsequently, the patients crossed over to the opposite treatment strategy for another three months. The treatment periods were separated by one month-long washout period. In all patients appointed to metoprolol treatment, the initial dose was 50 mg daily. Based on their home blood pressure monitoring, the dose was down-titrated in case of symptoms of hypotension or bradycardia. When an increase of self-measured blood pressure over 135/85 mmHg was detected, other antihypertensive drugs were initiated and up-titrated for better blood pressure control. Patients were evaluated at the baseline and at the end of each treatment period. All three visits consisted of a blood sample collection to determine the plasmatic concentration of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (Atellica analyzer, Siemens), resting 12-lead electrocardiogram, resting blood pressure measurement, resting transthoracic echocardiography, symptom-limited cardiopulmonary exercise test with echocardiographic measurement of maximal LVOT pressure gradient at peak exercise and evaluation of symptoms via the overall summary score of the Kansas City Cardiomyopathy Questionnaire (KCCQ), the 23-item version. The protocol was approved by the hospital ethics committee, and the trial was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. The trial was registered at ClinicalTrials.gov. (NCT04133532).

2.3. Resting transthoracic echocardiography

All dimensions were measured in the parasternal long axis view, the left ventricular ejection fraction was estimated from the parasternal long axis and apical four- and two-chamber view, and left atrial volume was calculated from the apical biplane views using the Simpson method. Mitral inflow and lateral mitral annular velocities were measured. Maximum flow velocity in LVOT was measured from a five-chamber view with continuous wave Doppler, and the maximal pressure gradient was automatically calculated using the simplified Bernoulli formula. The presence of mitral valve regurgitation was assessed semi-quantitatively in both parasternal and apical views.

2.4. Cardiopulmonary exercise test with peak exercise LVOT gradient measurement

The cardiopulmonary exercise test was performed on an upright bicycle ergometer (eBike III Comfort Ergometer, General Electric). The work rate started at 50 W and was increased by 25 W every two minutes to a symptom-limited maximum. Patients were instructed to maintain a pedalling speed of around 60 rounds per minute. Gas exchange was assessed using a breath-by-breath analysis (Omnia version 2.2, COSMED), and the peak oxygen uptake (pVO_2) was determined. An

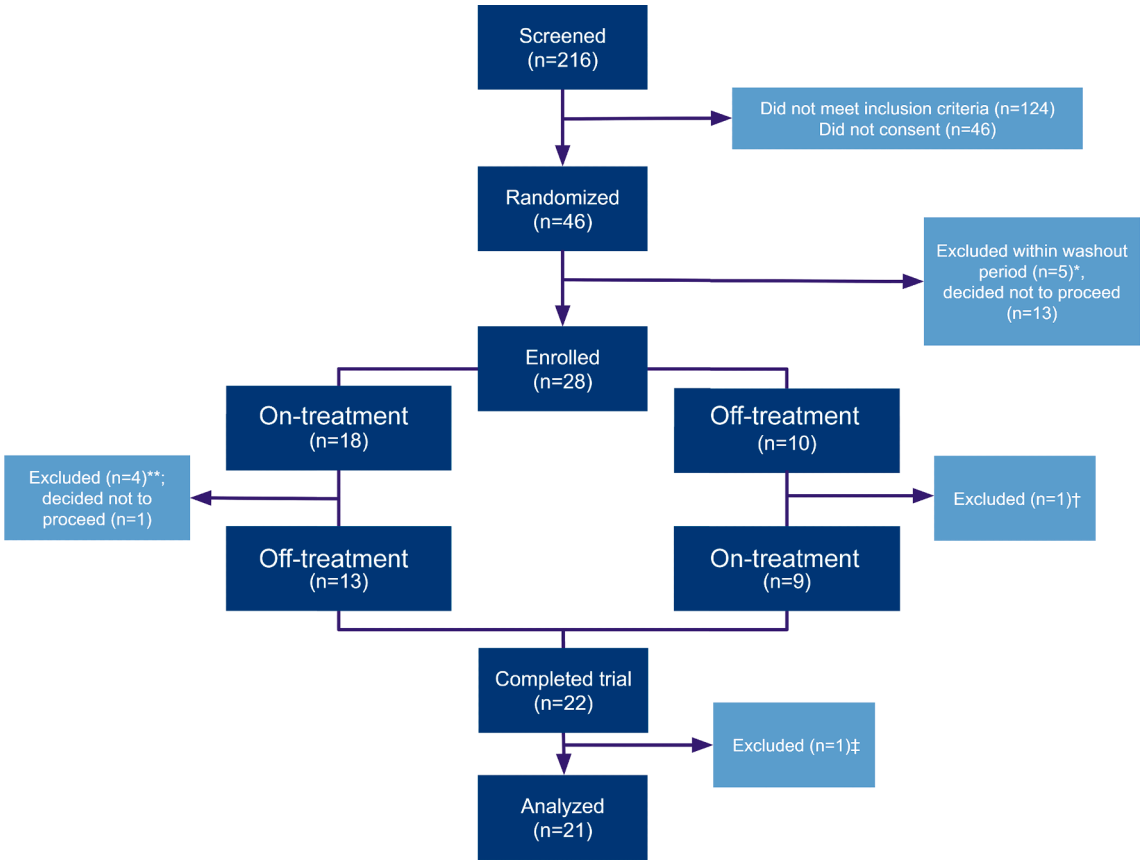

Fig. 1. CONSORT Diagram, * 4 patients excluded due to atrial fibrillation with fast ventricular response, 1 patient due to pacemaker implantation, ** 2 patients excluded due to atrial fibrillation with fast ventricular response, 2 due to intolerance of beta-blockers (bradycardia, diarrhea), † Excluded due to intolerance of beta-blocker withdrawal, ‡ Excluded due to noncompliance with the protocol, CONSORT = Consolidated Standards of Reporting Trials.

Table 1
Baseline characteristics (n = 21).

Demographic characteristics		
age, years	61	± 8
men	14	67 %
time from ASA to inclusion, months	61	(35–89)
Hemodynamics value		
heart rate at rest, beats/min	73	± 14
systolic blood pressure at rest, mm Hg	127	± 20
diastolic blood pressure at rest, mm Hg	73	± 9
Symptoms		
Dyspnea		
NYHA class I	9	43 %
NYHA class II	12	57 %
NYHA class III/IV	0	0 %
Angina		
no angina	16	76 %
CCS class I	1	5 %
CCS class II	4	19 %
CCS class III/IV	0	0 %
Quality of life		
KCCQ	76	± 18
Laboratory parameter		
NTproBNP, ng/l	309	± 385
Baseline pharmacological therapy		
beta-blocker	15	71 %
non-dihydropyridine calcium channel blocker	3	14 %
disopyramide	0	0 %
Echocardiographic characteristics		
LVEF, %	64	± 4
maximal pressure gradient in LVOT, mm Hg	11	± 5
E/A	0,82	± 0,29
E/e′	10	± 5
the E wave deceleration time, ms	288	± 88
left atrial diameter, mm	43	± 6
left atrial volume, ml	66	± 18
any mitral regurgitation	10	45 %
mitral regurgitation more than mild	0	0 %
indexed left ventricular mass, g/m^2	121	± 21
Exercise		
peak VO_2, ml/kg/min	18	± 5
maximal pressure gradient in LVOT at 0 W, mm Hg	10	± 5
maximal pressure gradient in LVOT at maximal work rate, mm Hg	14	± 9
maximal work rate during the exercise test, watts	129	± 27

Footnote: Values are mean ± SD, n (%), or median (interquartile range). CCS - Canadian Cardiovascular Society, E/A - mitral peak E/A wave velocity ratio, E/e′ - ratio of mitral peak velocity of early filling (E) to early diastolic lateral mitral annular velocity, KCCQ - Kansas City Cardiomyopathy Questionnaire Overall Summary Score, LVEF - left ventricular ejection fraction, NT-proBNP - N-terminal pro–B-type natriuretic peptide, NYHA - New York Heart Association, peak VO_2 - peak oxygen consumption.

echocardiographic assessment of the maximal pressure gradient in LVOT using continuous wave Doppler was performed immediately after the termination of the exercise test while the patient was still sitting on the ergometer.

2.5. Endpoints

The primary endpoint was the value of peak oxygen uptake (pVO_2). Secondary endpoints were the value of maximal pressure gradient in LVOT at peak exercise, the ratio of mitral peak velocity of the early filling (E) to early diastolic mitral annular velocity (e′) (E/e′) at rest, the overall summary score of the KCCQ, and the plasmatic NT-proBNP concentration.

2.6. Statistical analysis

Normally distributed data are presented as mean ± SD, non-normally distributed data as median with interquartile range, and categorical data as numbers with percentages (%). The two trial arms were compared by the paired Student's *t*-test and the Wilcoxon signed rank test, as appropriate. All analyses were done in all randomly assigned patients completing both treatment periods, as presented in Table 2. All statistical tests were conducted at a 2-sided $p < 0.05$ level of significance. No imputation was made for missing data.

3. Results

We assessed the effect of metoprolol on exercise capacity, hemodynamic, and laboratory parameters and reported quality of life in 21 HOCM patients after successful ASA. All of the endpoints and other measured parameters are summarized in Table 2.

None of the measured parameters (except for resting heart rate – 75

Table 2
Trial endpoints (n = 21).

	On–treatment	**Off-treatment**	**Difference (95 % CI)**	***p-value***
Hemodynamics				
heart rate at rest, beats/min	75 ± 13	82 ± 10	7 (2 to 12)	0.01
systolic blood pressure at rest, mm Hg	135 ± 21	135 ± 13	−1 (−9 to 8)	0.84
diastolic blood pressure at rest, mm Hg	82 ± 12	80 ± 9	−1 (−6 to 4)	0.61
Symptoms				
Dyspnea				
NYHA class I	12 (57)	12 (57)	–	1
NYHA class II	9 (43)	8 (38)	–	0.56
NYHA class III/IV	0 (0)	1 (5)	–	0.06
Angina				
no angina	19 (90)	19 (90)	–	1
CCS class I	1 (5)	1 (5)	–	1
CCS class II	1 (5)	1 (5)	–	1
CCS class III/IV	0 (0)	0 (0)	–	1
Quality of life				
KCCQ	78 ± 11	77 ± 15	−1 (−5 to 3)	0.56
Laboratory parameter				
NTproBNP, ng/l	215 (121–333)	153 (102–228)	–	0.19
Echocardiographic charasteristics				
LVEF, %	65 ± 3	63 ± 3	−1 (−3 to 0)	0.08
maximal pressure gradient in LVOT, mm Hg	11 ± 8	13 ± 8	2 (0 to 5)	0.07
E/A	0.9 ± 0.3	0.8 ± 0.4	−0.1 (−0.3 to 0.1)	0.44
E/e′	11 ± 4	10 ± 4	−1 (−3 to 1)	0.23
the E wave deceleration time, ms	308 ± 91	278 ± 69	−30 (−75 to 15)	0.19
left atrial diameter, mm	43 ± 5	44 ± 6	1 (−1 to 3)	0.55
left atrial volume, ml	64 ± 17	64 ± 17	0 (−4 to 4)	0.97
any mitral regurgitation	9 (43)	7 (33)	–	0.19
mitral regurgitation more than mild	0 (0)	0 (0)	–	1
Exercise				
peak VO_2, ml/kg/min	19.5 ± 5.3	19.4 ± 4.1	−0.1 (−1.9 to 1.7)	0.90
maximal pressure gradient in LVOT at 0 W, mm Hg	11 ± 8	13 ± 8	2 (0 to 4)	0.07
maximal pressure gradient in LVOT at maximal work rate, mm Hg	32 ± 37	32 ± 30	1 (−6 to 7)	0.84
maximal work rate during the exercise test, watts	120 ± 32	125 ± 28	4 (−6 to 15)	0.41

Footnote: Values are mean ± SD, n (%), or median (interquartile range). CCS - Canadian Cardiovascular Society, E/A - mitral peak E/A wave velocity ratio, E/e′ - ratio of mitral peak velocity of early filling (E) to early diastolic lateral mitral annular velocity, KCCQ - Kansas City Cardiomyopathy Questionnaire Overall Summary Score, LVEF - left ventricular ejection fraction, NT-proBNP - N-terminal pro–B-type natriuretic peptide, NYHA - New York Heart Association, peak VO_2 - peak oxygen consumption.

± 13 beats per minute vs. 82 ± 10 beats per minute, $p = 0.01$) showed statistically significant differences in on-treatment and off-treatment periods.

3.1. Exercise capacity and hemodynamic parameters

The patients exercise capacity was assessed by a symptom-limited cardiopulmonary exercise test and no in-between the group difference in pVO_2 was observed (19.5 ± 5.3 ml/kg/min vs. 19.4 ± 4.1 ml/kg/min, $p = 0.90$). The maximal work rate during the exercise test was comparable between on-treatment and off-treatment periods (120 ± 32 vs. 125 ± 28, $p = 0.41$). Metoprolol affected neither the resting maximal LVOTO measured in a sitting position (11 ± 8 on-treatment vs. 13 ± 8 off-treatment, $p = 0.07$) nor the exercise-induced maximal LVOTO (32 ± 37 mmHg vs. 32 ± 30 mmHg, $p = 0.84$). E/e′ ratio at rest was 11 ± 4 on-treatment and 10 ± 4 off-treatment and did not differ significantly ($p = 0.23$). The proportion of patients with any mitral regurgitation remained unaffected (43 % vs. 33 %, $p = 0.19$); none of the patients had more than mild mitral regurgitation. Systolic and diastolic blood pressure did not differ between on-treatment and off-treatment periods (135 ± 21 vs. 135 ± 13, $p = 0.84$ and 82 ± 12 vs. 80 ± 9, $p = 0.61$).

3.2. Laboratory parameter

Treatment with metoprolol was not associated with a statistically significant difference in plasmatic concentration of NT-proBNP (215 pg/ml [121–333] on-treatment vs. 153 pg/ml [102–228] off-treatment, $p = 0.19$).

3.3. Quality of life

Treatment with metoprolol did not affect the KCCQ overall summary score (78 ± 11 vs 77 ± 15, $p = 0.56$). The proportion of patients in NYHA class I-IV remained unchanged in the on-treatment and off-treatment periods, equally as the percentage of patients with no

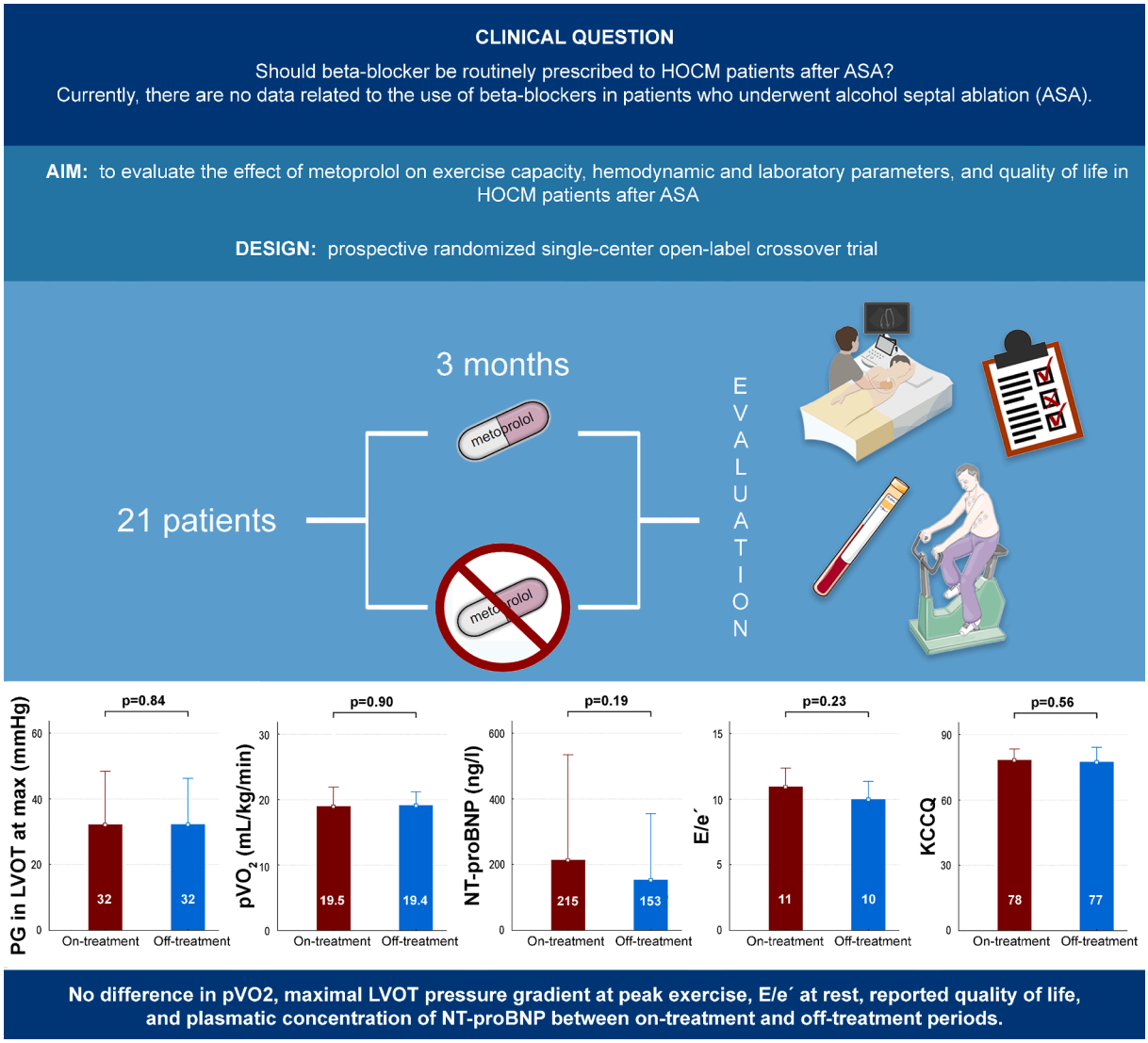

Fig. 2. Effect of Metoprolol in Hypertrophic Obstructive Cardiomyopathy Patients After Alcohol Septal Ablation. In this prospective randomized single-center open-label crossover trial we aimed to evaluate the effect of metoprolol on exercise capacity, hemodynamic and laboratory parameters, and quality of life in patients with HOCM after ASA. In random order, patients received metoprolol and no beta-blocker for two successive three-month periods (on-treatment and off-treatment period). No significant association was found between the treatment and any of the endpoints.
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angina pectoris and angina in Canadian Cardiovascular Society (CCS) class I-IV.

4. Discussion

To the best of our knowledge, this is the first trial assessing the effect of metoprolol treatment in HOCM patients post-ASA. The principal findings of this study are as follows: no significant association was found between metoprolol treatment and pVO_2, exercise-induced LVOTO, E/e′, symptoms assessed by the KCCQ overall summary score and NT-proBNP plasmatic concentration (Fig. 2).

In patients with HOCM, the LVOTO is accountable for a significant portion of symptoms. Pharmacotherapy – non-vasodilating beta-blockers titrated to maximum tolerated dose – is recommended as first-line therapy to improve symptoms in patients with resting or provoked LVOTO [3]. The support for the use of beta-blockers in HOCM is lacking large randomized trials. Small cohort studies that have been conducted suggest the effect of propranolol and nadolol on the reduction of resting and provoked LVOTO as well as symptom alleviation [4–6]. The recommendation has been recently supported by a double-blinded, placebo-controlled, randomized cross-over trial, which demonstrated that metoprolol reduced LVOTO and improved symptoms and quality of life in patients with HOCM [7]. However, diastolic filling pressures left atrial volume and plasmatic concentration of NT-proBNP remained unaffected by the metoprolol treatment [7].

An important question remaining to be answered is whether patients without significant resting LVOTO benefit from beta-blocker treatment. Symptoms in patients without significant LVOTO (including patients after ASA) can be related to the residual LVOTO, a possible dynamic component of LVOTO, the increased left ventricular filling pressures related to diastolic dysfunction, increased myocardial oxygen demand and myocardial ischemia. Therefore, the therapy objective in this cohort is assumed to target the above-mentioned factors [8,9].

Both the 2023 European Society of Cardiology guidelines and the 2020 American College of Cardiology/American Heart Association guidelines recommend beta-blockers, verapamil, or diltiazem to reduce symptoms in HCM patients with a normal ejection fraction of the left ventricle without significant LVOTO [3,9] despite the lack of large-scale data. Trials from the 1980 s analyzing small mixed cohorts of mostly up to 30 patients with and without LVOTO supported the use of verapamil or diltiazem to reduce chest pain and improve exercise tolerance [10–12] and indicated an effect of beta-blocker on improving left ventricular diastolic function. [13,14] The guideline recommendations are based mostly on a presumption of a positive effect due to known mechanism of action, clinical experience, and extrapolation of its effect in patients with HOCM. Notably, no specific recommendations are provided for patients after septal reduction therapy.

In recent years, myosin inhibitor mavacamten has been proven beneficial in the HOCM cohort, [15,16] and a phase II study indicating safety and tolerability in non-obstructive HCM patients has been published. [17] Given the lack of other pharmacotherapy options supported by robust data [18] beta-blockers and verapamil are being used as first-line therapy in symptomatic patients without significant LVOTO.

We aimed to assess whether a beta-blocker treatment has a positive effect on exercise capacity, hemodynamic and laboratory parameters, and quality of life of a specific cohort of patients without significant LVOTO – in patients after successful ASA, without significant residual LVOTO. No prior HCM trial was limited to patients post-septal reduction therapy. Moreover, the previous trials almost always included both patients with HOCM and non-obstructive forms of HCM. [10–14] Therefore, it is not possible to comprehensively compare our data to any prior results.

The negative results of our trial question the effect of metoprolol in patients with HOCM after elimination or significant reduction of LVOTO following successful ASA. It can be assumed that the demonstrated positive effect of beta-blockers in patients with HCM in preceding trials [13,14,4–7] was driven by the alleviation of LVOTO and hence does not occur in patients post-ASA patients without residual LVOTO.

Peak oxygen uptake (pVO_2) did not differ on– and off-treatment, indicating that the inherent reduction in heart rate caused by beta-blocker is not overbalanced by the theoretical improvement of diastolic filling. In line with this finding, the E/e′ remained unaltered by the beta-blocker medication. Dybro et al. assessed the effect of metoprolol in patients with HOCM and also found no difference in pVO_2 and filling pressures on– and off-treatment, although beta-blocker reduced resting and exercise-induced gradient [7].

Unlike in HOCM patients, [7] despite some increase of maximal pressure gradient in the LVOT at peak exercise, there was no significant change in exercise-induced maximal pressure gradient in LVOT on– and off-treatment in our cohort. That might indicate the limited role of metoprolol in reducing the residual dynamic component of LVOTO in patients after successful ASA.

In our trial, including patients without significant resting gradient, the treatment does not seem to affect symptoms assessed by the KCCQ overall summary score, in contrast with the effect of beta-blockers in HOCM patients. [7] This is probably due to the fact that most symptom alleviation is facilitated by the reduction of resting and exercise-induced LVOTO, as shown by Dybro et al. [7] The plasmatic concentration of NT-proBNP remained unchanged, in agreement with it being the marker of the increased hemodynamic stress of cardiac chambers, caused either by increased filling pressures or LVOTO, both of which showed no difference on– and off-treatment in our trial.

5. Limitations

Our study has several limitations. First, a relatively small number of patients have been enrolled and finished the trial. The reasons include a considerably high prevalence of atrial fibrillation demanding uninterrupted use of beta-blockers in patients post-ASA, corresponding to rather advanced disease. Therefore, we cannot exclude selection bias in our study. Second, there are some inherent limitations of the unblinded study. Third, data presented in this study are not able to assess the possible positive effect of metoprolol treatment in post-ASA HOCM patients with no significant resting LVOTO but exercise-induced LVOTO. Our cohort included few of these patients, and the small overall group size does not enable meaningful subanalysis. A potential future trial designed to assess this effect would yield important information. Last, we cannot rule out the contribution of a beta-blocker as a measure of prevention of atrial or ventricular arrhythmia. A history of atrial fibrillation with fast ventricular response demanding bradycardic therapy was an exclusion criterion in our present study and considering a relatively short follow-up, our trial was not designed to evaluate an antiarrhythmic effect of beta-blocker on lowering the possible higher risk of ventricular arrhythmias in patients after ASA reported by some authors [19] and rebutted by others. [20].

6. Conclusions

In this prospective randomized single-centre open-label crossover trial in HOCM patients after successful ASA, metoprolol treatment did not improve exercise capacity, hemodynamic and laboratory parameters, or reported quality of life.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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