Usefulness of Beta-Blockers to Control Symptoms in Patients With Pericarditis

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Exercise restriction is a nonpharmacological treatment of pericarditis that could reduce symptoms by slowing heart rate (HR). Beta-blockers allow pharmacological control of HR. Aim of this paper is to explore the possible efficacy of beta-blockers to improve control of symptoms in patients with pericarditis. We analyzed consecutive cases with pericarditis referred to our center. Beta-blockers were prescribed on top of standard anti-inflammatory therapy in symptomatic patients (chest pain and palpitations) with rest HR>75 beats/min. The primary end point was the persistence of pericardial pain at 3 weeks. The secondary end point was the occurrence of recurrent pericarditis at 18 months. Propensity score matching was used to generate 2 cohorts of 101 patients with and without beta-blockers with balanced baseline features. A clinical and echocardiographic follow-up was performed at 3 weeks, 1, 3, 6 months and then every 12 months. A total of 347 patients (mean age 53 years, 58% females, 48% with a recurrence, 81% with idiopathic/viral etiology) were included. Among them, 128 patients (36.9%) were treated with beta-blockers. Peak C-reactive protein values were correlated with heart rate on first observation (r=0.48, p<0.001). Using propensity-score matched cohorts, patients treated with beta-blockers had a lower frequency of symptoms persistence at 3 weeks (respectively 4% vs. 14%; p = 0.024) and a trend towards a reduction of recurrences at 18 months (p = 0.069). In conclusion the use of beta-blockers on top of standard anti-inflammatory therapies was associated with improved symptom control. **(Am J Cardiol 2021;146:115−119)**

Conventional therapy of pericarditis includes anti-inflammatory drugs (e.g. nonsteroidal anti-inflammatory drugs, colchicine, corticosteroids) for pain control and relief.[1,2] Exercise restriction is a nonpharmacologic component of medical therapy and it is recommended by contemporary guidelines.[2,3] Pericardial pain is triggered and worsened by friction of inflamed pericardial layers. A plausible hypothesis is that a reduction of heart rate could be helpful to achieve a better control of symptoms in pericarditis by reducing the friction of inflamed pericardial layers, and thus mechanical inflammation.[4] However the use of beta-blockers in pericarditis is poorly known. On this basis, the aim of this paper is to explore the possible efficacy of beta-blockers to achieve a better control of symptoms in patients with pericarditis.

Methods

This observational study considered all patients referred to our center for pericardial diseases with a diagnosis of acute or recurrent pericarditis and without concomitant myocarditis from January 2017 to June 2020. Our center is a referral center for pericardial diseases in North-West of Italy (AOU Città della Salute e della Scienza di Torino, Torino, Italy). The observational study on medical therapy of pericarditis was approved by the institutional Ethics Committee and all patients provided written informed consent.

Patients were treated according to 2015 ESC guidelines for the management of pericardial diseases[2] with aspirin or a NSAID and colchicine as first line therapy followed by corticosteroids at low to moderate doses and colchicine as a second line of therapy. Patients with corticosteroid-dependent, colchicine-resistant pericarditis were treated with anti-interleukin 1 agents (anakinra or rilonacept).

In our center, patients with rest heart rate (HR) >75 beats/min and symptoms despite anti-inflammatory therapy (pericarditis chest pain and palpitations) were treated with beta-blockers to achieve a target rest HR <70 beats/min in the absence of contraindications. If betablockers were contraindicated, we used ivabradine in order to achieve control of HR. HR treatment was maintained till complete symptom resolution and remission of pericarditis. Chest pain was assessed using an analogic pain scale from 1 to 10. Zero represented 'no pain at all' whereas the upper limit represented 'the worst pain ever possible'.

Clinical, laboratory testing, electrocardiographic and echocardiographic assessments were routinely performed in all patients at the time of diagnosis, according to local practice and in accordance with guidelines.[2]

The primary end point was the persistence of pericardial pain at 3 weeks. The secondary end point was recurrent

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pericarditis at 18 months (this time was chosen since all recurrences after an episode of pericarditis occurred within 18 months from the index attack[5] and this was also the main end point in previous trials with colchicine).[6-10]

A clinical and echocardiographic follow-up was performed at 3 weeks, 1, 3, 6, 12 months and then every 12 months.

According to 2015 ESC guidelines,[2] pericarditis was classified as recurrent in case of relapse after a documented first episode, with a minimum symptom-free interval of 4-6 weeks. This cohort study followed the recommendations of the STROBE statement.

Continuous variables, presented as means and standard deviations or medians and interquartile range, were compared by non-parametric tests: Mann-Whitney's test was used for independent data. Categorical variables, presented as counts and percentages, were compared using the chi-square test with Yates' correction or Fisher's exact test as appropriate. The survival probability and the freedom from symptoms were evaluated with the Kaplan-Meier curves. A propensity score for use of beta-blockers was created to adjust for baseline differences between patients treated with or without beta-blockers. A logistic regression model with use of beta-blockers as the outcome was used to generate propensity scores for all subjects. Variables included for the propensity score were age, etiology (idiopathic and post-cardiac injury syndrome), use of colchicine and use of corticosteroids.

All analyses were performed using MedCalc Statistical Software version 19.6 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020) and a 2-sided significance level of <0.05 was considered statistically significant.

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Results

We included 347 patients with pericarditis (mean age 53 years, 58% females, 48% with recurrent pericarditis). The etiology was idiopathic or viral in 81% of cases with detailed causes reported in Table 1. Among them, 128 patients (36.9%) were treated with beta-blockers (63% with bisoprolol, 23% with metoprolol, and 13% with nadolol). Main baseline features were similar in those with or without beta-blockers, but an older age, a lower frequency of idiopathic pericarditis, and a greater use of

Table 1
Baseline characteristics of the overall studied population

Variable	Population	Beta blockers		p
	(n = 347)	Yes (n = 128)	No (n = 219)	
Age (years)	53 ± 19	60 ± 19	48 ± 18	<0.001
Women	201 (58%)	67 (52%)	134 (61%)	0.116
Recurrent pericarditis	165 (48%)	65 (51%)	100 (46%)	0.374
Etiology:				
Idiopathic/viral	281 (81%)	95 (74%)	186 (85%)	0.016
*Post cardiac injury syndrome**	23 (7%)	14 (11%)	9 (4%)	0.023
Autoimmune	17 (5%)	9 (7%)	8 (3.7%)	0.198
Neoplastic	12 (3%)	4 (3%)	8 (4%)	0.999
Radiation	4 (1%)	3 (2%)	1 (0.5%)	0.144
Tuberculous	3 (1%)	1 (1%)	2 (1%)	0.999
Trauma	3 (1%)	0 (0%)	3 (1%)	0.300
Uremia	3 (1%)	2 (2%)	1 (1%)	0.557
Clinical Presentation:				
Fever	123 (36%)	42 (33%)	81 (37%)	0.485
ECG abnormalities	84 (27%)	30 (26%)	54 (27%)	0.895
Pericardial effusion	191 (57%)	70 (57%)	121 (57%)	0.999
Increased inflammatory markers (WBC or CRP or ESR)	158 (70%)	60 (76%)	98 (66%)	0.172
HR on presentation (bpm)	83 ± 14	89 ± 11	78 ± 15	<0.001
HR at subsequent visit (bpm)	72 ± 13	73 ± 13	70 ± 12	0.159
Relative variation (%)	−12 ± 18	−21 ± 15	−4 ± 17	<0.001
Absolute variation (bpm)	−11 ± 16	−19 ± 15	−5 ± 14	<0.001
Drug Therapy:				
Colchicine	254 (73%)	86 (67%)	168 (77%)	0.060
Prednisone	109 (31%)	60 (47%)	49 (22%)	<0.001
Anti IL-1 (anakinra, rilonacept)	33 (10%)	12 (9%)	21 (10%)	0.999
Beta-blocker				
Bisoprolol		81 (63%)		
Metoprolol		30 (23%)		
Nebivolol		17 (13%)		

* Post cardiac injury syndrome including cases related to cardiac surgery or percutaneous procedures. bpm = beats per minute, CRP = C-reactive protein, ECG = electrocardiogram, ESR = erythrocyte sedimentation rate, HR = heart rate, IL = interleukin, WBC = white blood cells.

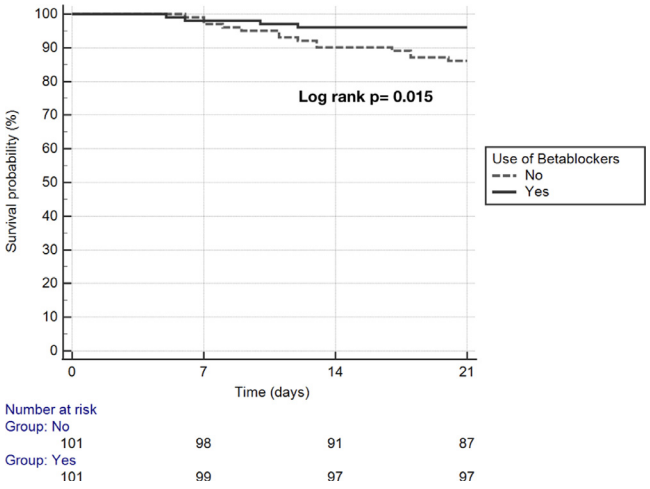

Figure 1. Freedom from symptoms of pericarditis at 3 weeks in patients with or without beta-blockers (log rank p = 0.015).

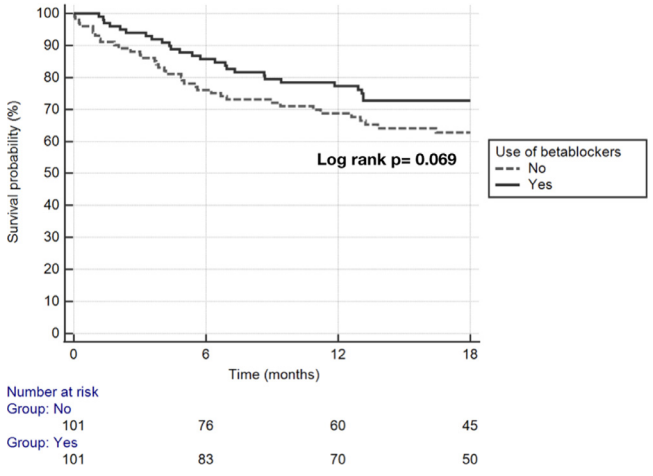

Figure 2. Occurrence of recurrences at 18 months in patients with or without beta-blockers (Log rank p = 0.069).

corticosteroids in patients treated with beta-blockers (Table 1). Propensity score-matched populations were generated to adjust baseline differences and are reported in Table 2 with outcomes.

Patients treated with beta-blockers showed a marked reduction of basal heart rate compared with other patients (−21% vs −7%, p <0.001, Table 2) and a lower frequency of symptoms persistence at 3 weeks (respectively 4% vs 14%; p = 0.024; see Table 2 and Figure 1). Patients treated with beta-blockers had also a trend towards a lower incidence of recurrences at 18 months (Log rank p = 0.069; Figure 2). In the general population, peak C-reactive protein values were correlated with heart rate on first observation (r = 0.48, p <0.001; see Figure 3).

Discussion

This observational study reports for the first time the use of beta-blockers to achieve a better control of pericardial chest pain through a reduction of heart rate.

Table 2
Comparison of propensity-matched populations with or without beta-blockers (baseline and outcomes data)

Variable	Beta blockers		p
	Yes (n=101)	No (n=101)	
Age (years)	57 ± 18	57 ± 17	0.822
Women	53 (52%)	59 (58%)	0.479
Recurrent pericarditis	49 (49%)	39 (39%)	0.201
Etiology:			
Idiopathic/viral or post-cardiac injury	91(90%)	91 (90%)	1.000
Clinical Presentation:			
Fever	33 (33%)	34 (34%)	1.000
ECG abnormalities	25 (25%)	21 (21%)	0.401
Pericardial effusion	58 (57%)	57 (56%)	1.000
Increased inflammatory markers (WBC or CRP or ESR)	49 (49%)	59 (58%)	0.514
HR on presentation (bpm)	89 ± 10	79 ± 14	<0.001
HR at subsequent visit (bpm)	70 ± 12	73 ± 13	0.290
Relative variation (%)	−21 ± 15	−7 ± 15	<0.001
Absolute variation (bpm)	−19 ± 14	−6 ± 13	<0.001
Drug Therapy:			
Colchicine	76 (75%)	76 (75%)	1.000
Prednisone	36 (36%)	36 (36%)	1.000
Anti IL-1 (anakinra, rilonacept)	12 (12%)	9 (9%)	0.501
Main outcomes:			
Follow-up (months)	24 ± 9	27 ± 13	0.093
Symptoms persistence at 3 weeks	4 (4%)	14 (14%)	0.024
Recurrent pericarditis at 18 months:	26 (26%)	38 (38%)	0.069*
Constrictive pericarditis	4 (4%)	5 (5%)	1.000
Cardiac Tamponade	1 (1%)	5 (5%)	0.212

* **Log-rank test.** *bpm = beats per minute, CRP = C-reactive protein, ECG = electrocardiogram, ESR = erythrocyte sedimentation rate, HR = heart rate, IL = interleukin, WBC = white blood cells.*

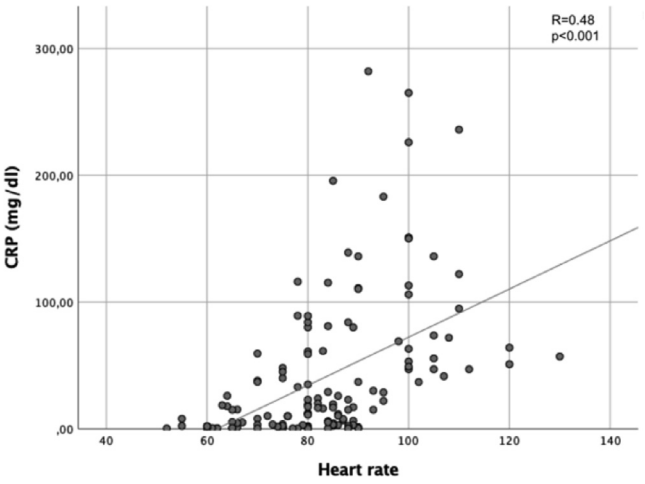

Figure 3. Correlation between heart rate on first observation and C-reactive protein (r = 0.48; p <0.001).

In our sample of patients with acute and recurrent pericarditis, patients treated with beta-blockers had less persistence of pericardial symptoms at 3 weeks.

Exercise restriction is recognized as an essential component of nonpharmacological therapy of pericarditis. It is also reported that early initiation of physical exercise could trigger pericardial symptoms and increase the risk of recurrences.

The presumed mechanism by which beta-blockers could help to mitigate symptoms and reduce recurrences is probably related to the reduction of pericardial layers friction by slowing heart rate, as also previously suggested. An additional effect of beta-blockers compared with other drugs acting on heart rate, such as digoxin and calcium channel blockers, is their capability to downregulate pro-inflammatory cytokines and promoting anti-oxidative effects, as shown in animal models of myocarditis.[11-14]

In our institution, beta-blockers were used for pericarditis to reduce heart rate in patients with persistence of symptoms (pericarditic chest pain and palpitations) despite appropriate anti-inflammatory therapy and rest heart rate>75beats/min.

This study has limitations, especially related to its retrospective design not allowing a randomization of patients. However, we used a propensity score matching in order to adjust for baseline differences between patients treated with or without beta-blockers.

Despite the limitations of the study, these observations may be helpful to design a specific trial to randomize patients with pericarditis and rest heart rate>75 beats/min to receive beta-blockers or placebo. Moreover, it can provide initial evidence to support the use of these drugs in persistently symptomatic patients on anti-inflammatory therapies and with increased basal heart rate.

In conclusion, the use of beta-blockers on top of standard anti-inflammatory therapies seems associated with improved symptoms control. Additional studies are warranted to verify the efficacy of these drugs in this setting.

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Authors Contribution Statement

MI designed the study. All authors contributed to the planning, conduct, drafting and reporting of the work. The manuscript was revised and approved by all authors.

Competing Interests

None declared.

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