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

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ABSTRACT (240 words)

Objective Exercise restriction is a non-pharmacological therapy of pericarditis that could reduce symptoms by slowing heart rate (HR). Beta-blockers could help to achieve 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.

Methods Retrospective review of consecutive cases with pericarditis referred to our centre. Beta-blockers were prescribed on top of standard anti-inflammatory therapy in symptomatic patients with rest HR>75bpm. The primary end-point was the persistence of pericardial pain at the first outpatient assessment. The secondary end-point was the occurrence of recurrent pericarditis. A clinical and echocardiographic follow-up was performed at 1, 3, 6 months and then every 12 months.

Results 347 patients (mean age 53 years, 58% females, 48% with a recurrence, 81% with idiopathic or viral aetiology) were included. Among them, 128 patients (36.9%) were treated with beta-blockers. Baseline features were similar in those with or without beta-blockers. Peak C-reactive protein values were correlated with heart rate on first observation ($r=0.351$, $p<0.001$). Patients treated with beta-blockers had a lower frequency of symptoms persistence at 2 weeks (respectively 3% vs. 15%; $p<0.001$) and recurrences at a median time of 26 months (respectively 27% vs. 42%; $p=0.006$).

Conclusions The use of beta-blockers on top of standard anti-inflammatory therapies was associated with improved symptoms control and reduced recurrences in patients with pericarditis. Additional studies are warranted to verify the efficacy of these drugs in this setting.

KEYWORDS: pericarditis; beta-blocker; therapy; recurrent pericarditis

KEY QUESTIONS

What is already known about this subject?

Persistence of pericardial pain is one of the most troublesome challenges in the management of pericarditis. Exercise restriction through heart rate control is recommended as a non-pharmacological therapy for pericarditis.

What does this study add?

In symptomatic patients with pericarditis and heart rate>75bpm, the empiric use of beta-blockers on top of anti-inflammatory therapies is associated with improved control of symptoms and reduced incidence of recurrences.

How might this impact on clinical practice?

Empiric use of beta-blockers could help to control pericardial pain in patients with persistent symptoms and increased rest heart rate. Additional prospective studies are warranted to confirm the efficacy of beta-blockers in this setting.

INTRODUCTION

Conventional therapy of pericarditis includes anti-inflammatory drugs (e.g. non-steroidal anti-inflammatory drugs, colchicine, corticosteroids) for pain control and relief.[1,2] Exercise restriction is a non-pharmacologic component of medical therapy and it is recommended by contemporary guidelines.[2,3] Pericardial pain is thought to be determined 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

Study design and population

Retrospective review of all patients referred to our centre for pericardial diseases with a diagnosis of acute or recurrent pericarditis from January 2017 to June 2020. Our centre is a referral centre 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 another NSAID and colchicine as first line therapy followed by corticosteroids at low to moderate doses and colchicine as a second line of therapy. In our centre patients with rest heart rate (HR) >75 bpm and symptoms despite anti-inflammatory therapy were treated with beta-blockers to achieve a rest HR <70 bpm. Pericardial pain was graded on a scale from 0 (absent) to 10 (highest intensity of symptom).

Clinical, laboratory testing, electrocardiographic and echocardiographic assessments were 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 the first outpatient assessment at 2 weeks. The secondary end-point was recurrent pericarditis. A clinical and echocardiographic follow-up was performed at 1, 3, 6, 12 months and then every 12 months.

According to 2015 ESC guidelines,[2] pericarditis was classified as recurrent in case of one or more relapses 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.

Statistical analysis

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. All analyses were performed using the SPSS version 18.0 (SPSS, Inc., Chicago, Illinois) and a two-sided significance level of <0.05 was considered statistically significant.

Patient and public involvement

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 a recurrence). The aetiology 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 (58% with bisoprolol, 9% with nadolol). Main baseline features were similar in those with or without beta-blockers (Table 1).

Patients treated with beta-blockers had a lower frequency of symptoms persistence at 2 weeks (respectively 3% vs. 15%; $p<0.001$; see Table 2 and Figure 1). After a median time of 26 months, the occurrence of complicated pericarditis (pericarditis with recurrences or incessant course, or cardiac tamponade or constrictive pericarditis) was less common in patients treated with beta-blockers (respectively 31% vs. 43%; $p=0.030$). Patients treated with beta-blockers had also a lower incidence of recurrences (respectively 27% vs. 42%; $p=0.006$; see table 2 and figure 2). Peak C-reactive protein values were correlated with heart rate on first observation ($r=0.351$, $p<0.001$; 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.

In our sample of patients with acute and recurrent pericarditis, patients treated with beta-blockers had less persistence of pericardial symptoms and a reduced incidence of

complicated pericarditis mainly due to a reduction of the recurrences (Table 2 and Figure 1,2).

Exercise restriction is recognized as an essential component of non-pharmacological 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 to 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.[5-7]

In our institution, beta-blockers were used for pericarditis to reduce heart rate in patients with persistence of symptoms despite appropriate anti-inflammatory therapy and rest heart rate>75bpm.

This study has limitations, especially related to its retrospective design not allowing a randomization of patients. Nevertheless we recorded a higher rest heart rate in patients with higher levels of C-reactive protein (Figure 3) suggesting the relationship between heart rate and inflammation,[8] probably triggered by enhanced friction of pericardial layers with higher cardiac frequencies.

Despite the limitations of the study, this observation may be helpful to design a specific trial to randomize patients with pericarditis and rest heart rate>75 bpm 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 and reduced recurrences in patients with

pericarditis. Additional studies are warranted to verify the efficacy of these drugs in this setting.

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Contributors

Massimo IMAZIO: study design and conception, data collection, interpretation and analysis, article drafting, critical revision and approval of the final version, responsible for the overall content as guarantor.

Alessandro ANDREIS: study design and conception, data collection, interpretation and analysis, article drafting, critical revision and approval of the final version, responsible for the overall content as guarantor.

All other authors contributed to the critical revision and approval of the final version.

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Competing interests None declared.

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FIGURE LEGENDS

Figure 1 – Freedom from symptoms of pericarditis in patients with or without pericarditis.

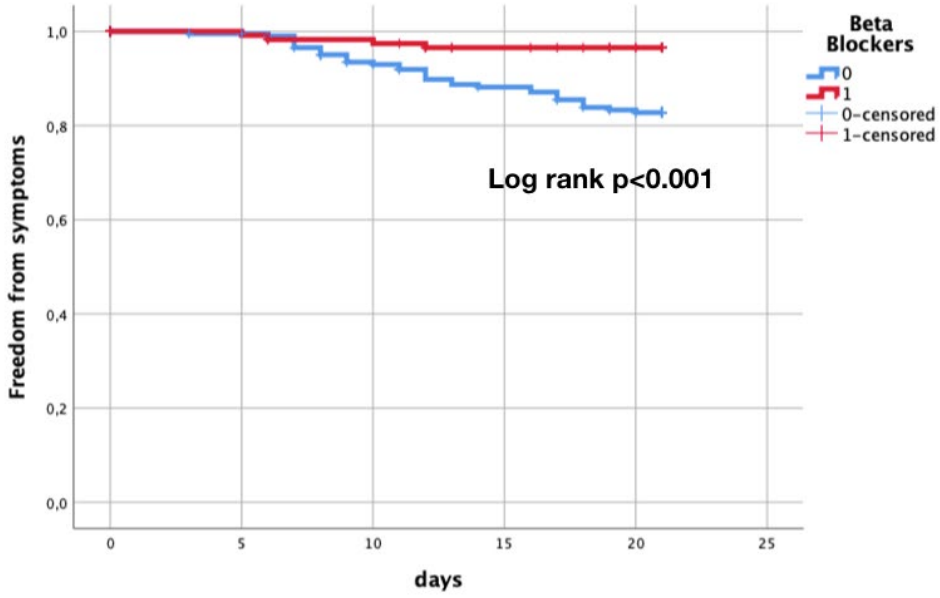


Figure 2 – Occurrence of complicated pericarditis in patients with or without beta-blockers.

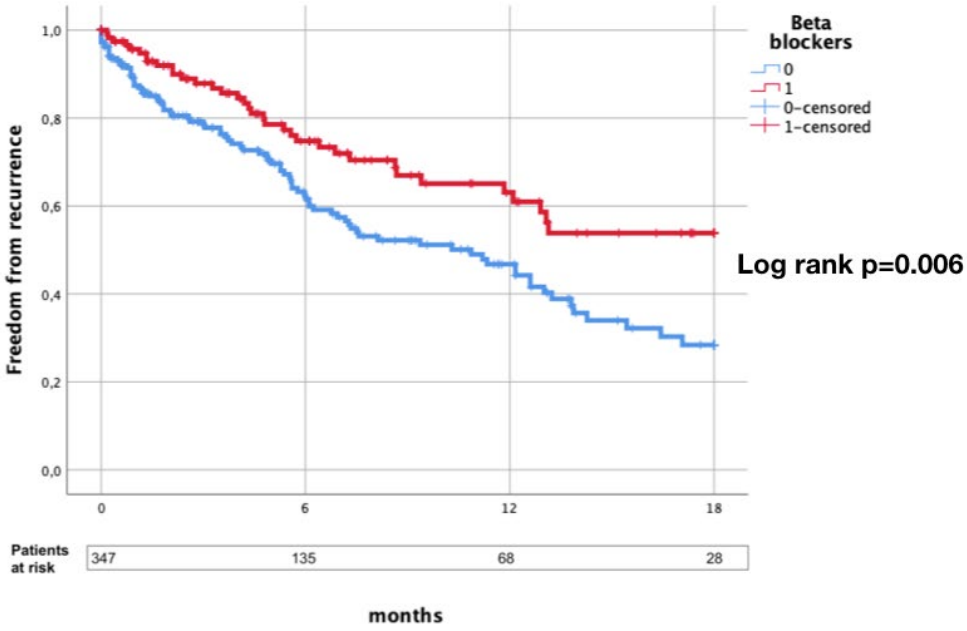
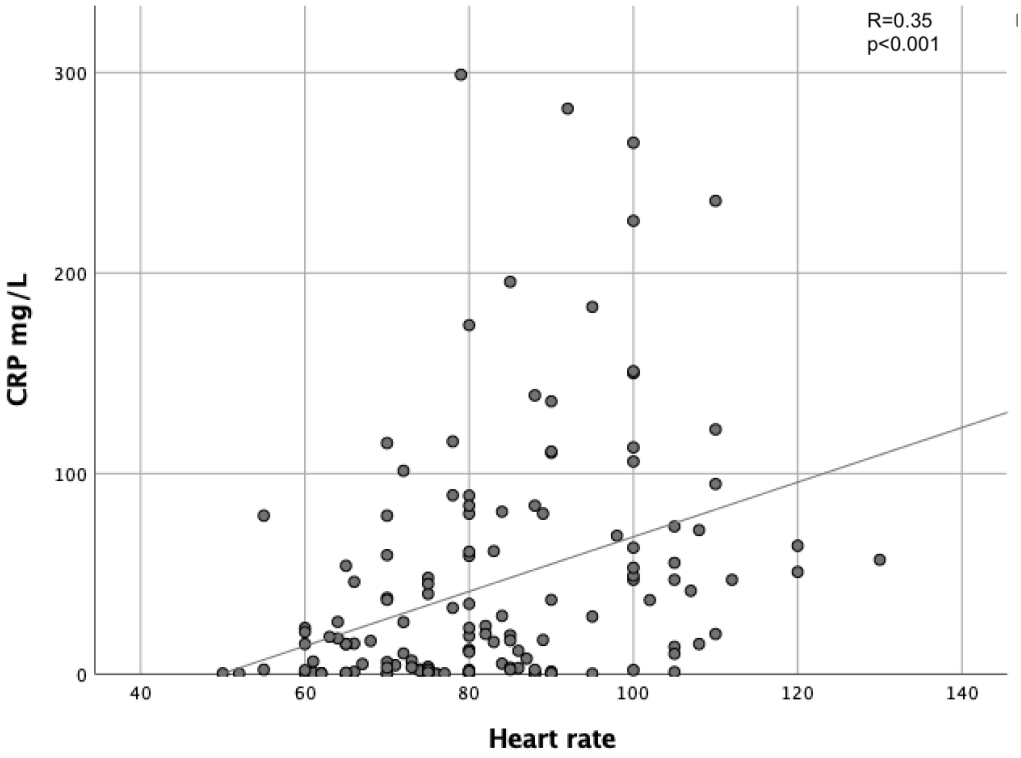


Figure 3. Correlation between heart rate on first observation and C-reactive protein.



TABLES

Table I – Baseline characteristics of the studied population.

	Population (n=347)	Beta blocker + (n=128)	Beta blocker – (n=219)	P
Age, years	53 ± 19	60 ± 19	48 ± 18	**<0.001**
Female gender	201 (58%)	67 (52%)	134 (61%)	0.116
Recurrent pericarditis	165 (48%)	65 (51%)	100 (46%)	0.374
Already on beta-blockers	99 (31%)	99 (79%)	-	**<0.001**
AETIOLOGY				
Idiopathic/viral	281 (81%)	95 (74%)	186 (85%)	**0.016**
Tubercular	3 (1%)	1 (1%)	2 (1%)	0.999
Post cardiac injury syndrome (cardiac surgery or percutaneous procedures)	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
Trauma	3 (1%)	-	3 (1%)	0.300
Uraemia	3 (1%)	2 (2%)	1 (1%)	0.557
Tubercular	3 (1%)	1 (1%)	2 (1%)	0.999
Radiation	4 (1%)	3 (2%)	1 (0.5%)	0.144
CLINICAL PRESENTATION				
Pericarditic chest pain	252 (74%)	81 (64%)	171 (79%)	**0.005**
Dyspnoea	75 (22%)	33 (26%)	42 (19%)	0.175
Palpitations	15 (4%)	7 (6%)	8 (4%)	0.421
Asthenia	95 (28%)	39 (31%)	56 (26%)	0.316
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
Pericardial rubs	9 (3%)	-	9 (4%)	**0.030**
Increased inflammatory markers (WBC or CRP or ESR)	158 (70%)	60 (76%)	98 (66%)	0.172
Heart rate on presentation	79 ± 16	81 ± 18	78 ± 15	0.192
TREATMENT				
NSAIDs or aspirin	186 (54%)	43 (34%)	143 (65%)	**<0.001**
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		72 (58%)		
Metoprolol		24 (19%)		
Nebivolol		11 (9%)		
Nadolol		4 (3%)		
Carvedilol		2 (2%)		
Propranolol		1 (1%)		

Table II. Outcomes

	Population (n=347)	Beta blocker + (n=128)	Beta blocker – (n=219)	P
Symptoms persistence at 2 weeks	37 (11%)	4 (3%)	33 (15%)	**<0.001**
Complicated pericarditis	135 (39%)	40 (31%)	95 (43%)	**0.030**
Recurrent pericarditis	128 (37%)	35 (27%)	93 (42%)	**0.006**
Cardiac tamponade	2 (0.6%)	2 (1.6%)	0	0.135
Pericardial constriction	13 (3.7%)	7 (5.5%)	6 (2.7%)	0.244

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