

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

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

**This is a pre print version of the following article:**

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/1816262> since 2021-11-06T19:08:47Z

*Published version:*

DOI:10.1016/j.amjcard.2021.01.032

*Terms of use:*

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

## **Usefulness of beta-blockers to control symptoms in patients with pericarditis**

Massimo Imazio<sup>1</sup>, MD, FESC, Alessandro Andreis<sup>1</sup>, MD, Alessandra Agosti<sup>1</sup>, MD, Francesco Piroli<sup>1</sup>, MD, Stefano Avondo<sup>1</sup>, MD, Matteo Casula<sup>1</sup>, MD, Elena Paneva<sup>1</sup>, MD, Gabriele Barberi Squarotti<sup>1</sup>, Carla Giustetto<sup>1</sup>, MD, Gaetano Maria De Ferrari<sup>1</sup>, MD.

*<sup>1</sup> University Cardiology, A.O.U. Città della Salute e della Scienza di Torino, Turin, Italy*

Corresponding author

Massimo Imazio, MD, FESC

University Cardiology

AOU Città della Salute e della Scienza di Torino

Corso Bramante 88, 10126 Turin, Italy

E-mail: [massimo\\_imazio@yahoo.it](mailto:massimo_imazio@yahoo.it)

WORD COUNT: 2471 words (max 3000), 2 tables, 3 figures, and 8 references

## **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.<sup>1,2</sup> Exercise restriction is a non-pharmacologic component of medical therapy and it is recommended by contemporary guidelines.<sup>2,3</sup> 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.<sup>4</sup> 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<sup>2</sup> 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.<sup>2</sup>

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,<sup>2</sup> 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.

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in HEART editions and any other BMJPGGL products to exploit all subsidiary rights.

## 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.<sup>5-7</sup>

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,<sup>8</sup> 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.

**Twitter** @ImazioMassimo

#### **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.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**ORCID ID:** Massimo Imazio <http://orcid.org/0000-0002-5722-0245>

---

**FIGURE LEGENDS**

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

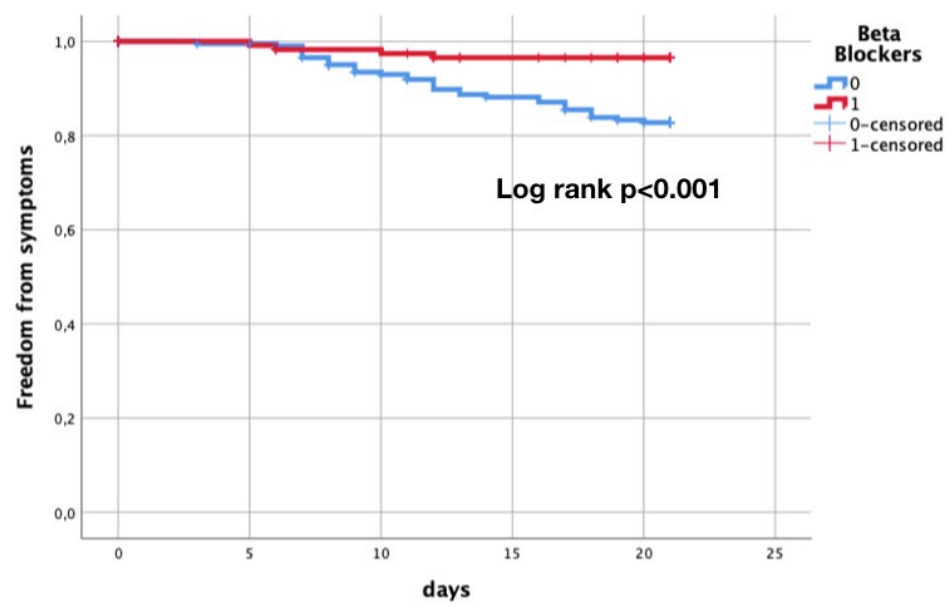
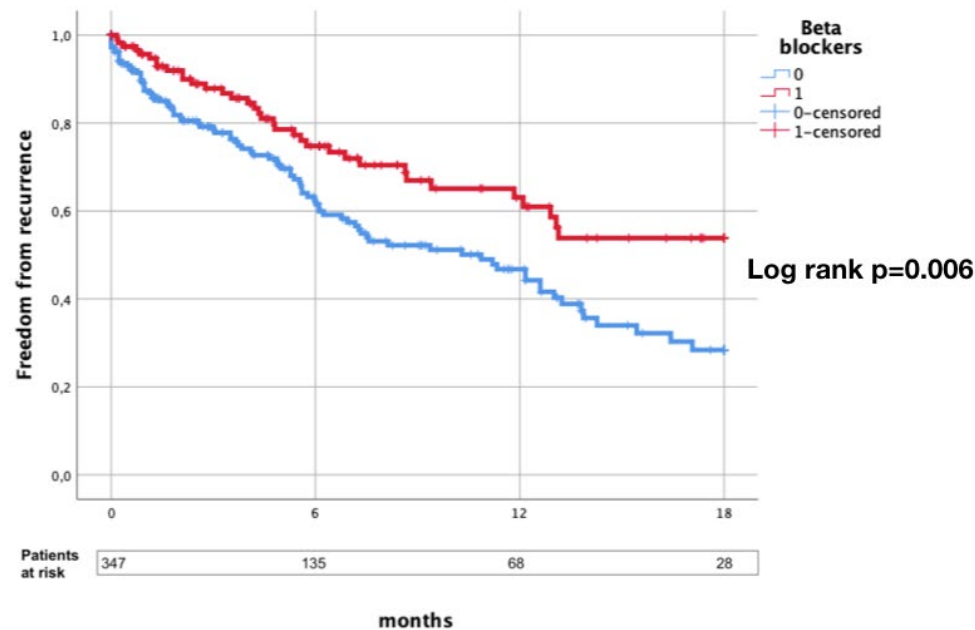
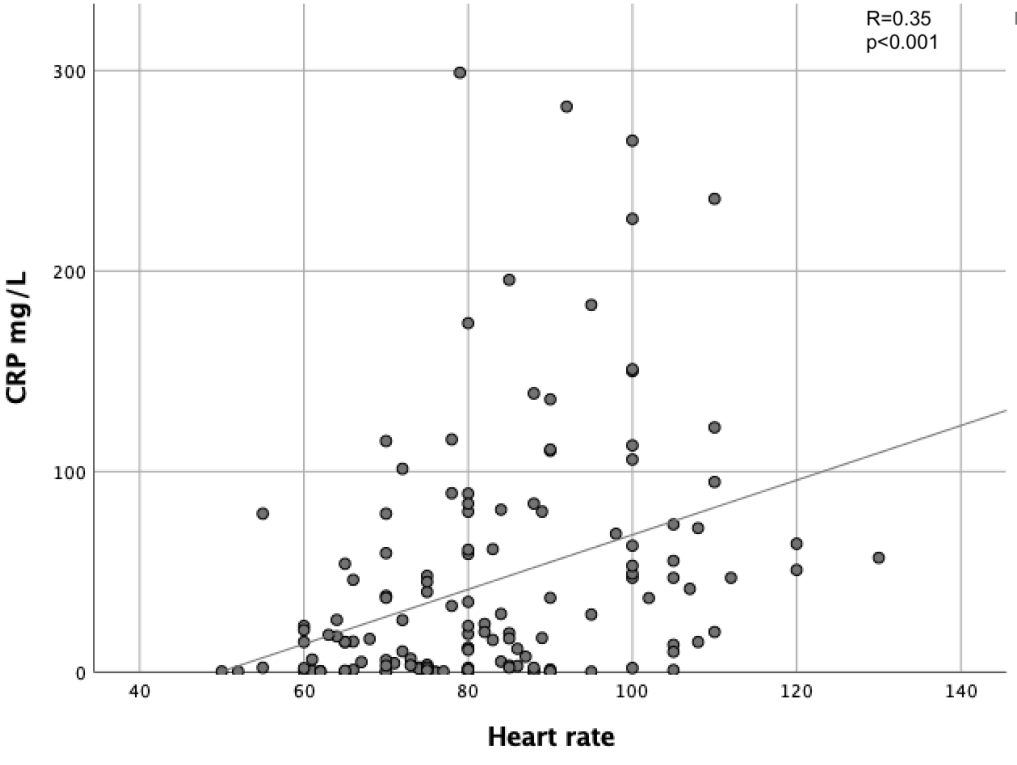


Figure 2 – Occurrence of complicated pericarditis in patients with or without beta-blockers.



**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	<b>&lt;0.001</b>
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%)	-	<b>&lt;0.001</b>
<b>AETIOLOGY</b>				
<i>Idiopathic/viral</i>	281 (81%)	95 (74%)	186 (85%)	<b>0.016</b>
<i>Tubercular</i>	3 (1%)	1 (1%)	2 (1%)	0.999
<i>Post cardiac injury syndrome (cardiac surgery or percutaneous procedures)</i>	23 (7%)	14 (11%)	9 (4%)	<b>0.023</b>
<i>Autoimmune</i>	17 (5%)	9 (7%)	8 (3.7%)	0.198
<i>Neoplastic</i>	12 (3%)	4 (3%)	8 (4%)	0.999
<i>Radiation</i>	4 (1%)	3 (2%)	1 (0.5%)	0.144
<i>Trauma</i>	3 (1%)	-	3 (1%)	0.300
<i>Uraemia</i>	3 (1%)	2 (2%)	1 (1%)	0.557
<i>Tubercular</i>	3 (1%)	1 (1%)	2 (1%)	0.999
<i>Radiation</i>	4 (1%)	3 (2%)	1 (0.5%)	0.144
<b>CLINICAL PRESENTATION</b>				
Pericarditic chest pain	252 (74%)	81 (64%)	171 (79%)	<b>0.005</b>
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%)	<b>0.030</b>
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
<b>TREATMENT</b>				
NSAIDs or aspirin	186 (54%)	43 (34%)	143 (65%)	<b>&lt;0.001</b>
Colchicine	254 (73%)	86 (67%)	168 (77%)	<b>&lt;0.060</b>
Prednisone	109 (31%)	60 (47%)	49 (22%)	<b>&lt;0.001</b>
Anti IL-1 (anakinra, rilonacept)	33 (10%)	12 (9%)	21 (10%)	0.999
Beta blocker				
<i>Bisoprolol</i>		72 (58%)		
<i>Metoprolol</i>		24 (19%)		
<i>Nebivolol</i>		11 (9%)		
<i>Nadolol</i>		4 (3%)		
<i>Carvedilol</i>		2 (2%)		
<i>Propranolol</i>		1 (1%)		

**Table II. Outcomes**

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

## REFERENCES

1. Lazaros G, Imazio M, Brucato A, Vlachopoulos C, Lazarou E, Vassilopoulos D, Tousoulis D. The Role of Colchicine in Pericardial Syndromes. *Curr Pharm Des.* 2018;24(6):702-709
2. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, Brucato A, Gueret P, Klingel K, Lionis C, Maisch B, Mayosi B, Pavié A, Ristic AD, Sabaté Tenas M, Seferovic P, Swedberg K, Tomkowski W, ESC Scientific Document Group. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2015;36:2921–2964.
3. Pelliccia A, Solberg EE, Papadakis M, Adami PE, Biffi A, Caselli S, La Gerche A, Niebauer J, Pressler A, Schmied CM, Serratos L, Halle M, Van Buuren F, Borjesson M, Carré F, Panhuyzen-Goedkoop NM, Heidbuchel H, Olivotto I, Corrado D, Sinagra G, Sharma S. Recommendations for participation in competitive and leisure time sport in athletes with cardiomyopathies, myocarditis, and pericarditis: position statement of the Sport Cardiology Section of the European Association of Preventive Cardiology (EAPC). *Eur Heart J.* 2019 Jan 1;40(1):19-33. doi: 10.1093/eurheartj/ehy730. PMID: 30561613.
4. Roubille F, Tournoux F, Roubille C, Merlet N, Davy JM, Rhéaume E, Busseuil D, Tardif JC. Management of pericarditis and myocarditis: could heart-rate-reducing drugs hold a promise? *Arch Cardiovasc Dis.* 2013 Dec;106(12):672-9
5. Guang-Yi C, Li-Sha G, Yue-Chun L. Role of Heart Rate Reduction in the Management of Myocarditis. *Curr Pharm Des.* 2018;24(3):365-378.
6. Yue-Chun L, Teng Z, Na-Dan Z, Li-Sha G, Qin L, Xue-Qiang G, Jia-Feng L. Comparison of effects of ivabradine versus carvedilol in murine model with the Coxsackievirus B3-induced viral myocarditis. *PLoS One.* 2012;7(6):e39394.
7. Skrzypiec-Spring M, Haczkiwicz K, Sapa A, Piasecki T, Kwiatkowska J, Ceremuga I, Wozniak M, Biczysko W, Kobierzycki C, Dziegiel P, Podhorska-Okolow M, Szlag A. Carvedilol Inhibits Matrix Metalloproteinase-2 Activation in Experimental Autoimmune Myocarditis: Possibilities of Cardioprotective Application. *J Cardiovasc Pharmacol Ther.* 2018 Jan;23(1):89-97.
8. Khoueiry Z, Roubille C, Nagot N, Lattuca B, Piot C, Leclercq F, Delseny D, Busseuil D, Gervasoni R, Davy JM, Pasquié JL, Cransac F, Sportouch-Dukhan C, Macia JC, Cung TT, Massin F, Cade S, Cristol JP, Barrère-Lemaire S, Roubille F. Could heart rate play a role in pericardial inflammation? *Med Hypotheses.* 2012 Oct;79(4):512-5.