REVIEW

Management of pericarditis and myocarditis: Could heart-rate-reducing drugs hold a promise?

Prise en charge des péricardites et myocardites: les médicaments bradycardisants sont-ils prometteurs?

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Summary Rest is usually recommended in acute pericarditis and acute myocarditis. Given that myocarditis often leads to hospitalization, this task seems easy to carry out in hospital practice; however, it could be a real challenge at home in daily life. Heart rate-lowering treatments (mainly beta-blockers) are usually recommended in case of acute myocarditis, especially in case of heart failure or arrhythmias, but level of proof remains weak. Calcium channel inhibitors and digoxin are sometimes proposed, albeit in limited situations. It is possible that rest or even heart rate-lowering treatments could help to manage these patients by preventing heart failure as well as by limiting “mechanical inflammation” and controlling arrhythmias.

KEYWORDS
Pericarditis; Myocarditis; Beta-blockers; Inflammation; Heart rate

Abbreviations: CRP, C-reactive protein; ESC, European Society of Cardiology; HF, heart failure; HR, heart rate; LV, left ventricular; NSAID, non-steroidal anti-inflammatory drug; PROBE, prospective randomized open blinded endpoint.

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Introduction

Acute pericarditis and acute myocarditis are often difficult to distinguish; they constitute a continuum, with frontier forms named "myopericarditis". Acute pericarditis is diagnosed in case of two of the following elements: typical chest pain or pericardial rub; typical electrocardiogram; pericardial effusion (often on echocardiography); and biological inflammatory syndrome. On the other hand, acute myocarditis involves myocardium with biomarker elevation (mainly troponin) and left ventricular (LV) dysfunction.

Acute pericarditis is rather frequent with an annual incidence estimated at 27.7 new cases per 100,000 inhabitants in Europe [1]. About 5% of all patients with non-ischaemic chest pain who are admitted to emergency departments could have pericarditis [2]. The causes of pericarditis vary, with most common causes including viral or bacterial infections of the pericardium [3]. Most patients are young, with a heavy cost to society, especially due to hospitalizations.

Myocarditis is less common than pericarditis. The main difficulty in the assessment of this condition is the wide spectrum of possible clinical presentations, ranging from acute fulminant forms to late dilated cardiomyopathies. A broad range of pathological processes are involved and many classifications have been proposed [4,5]. Epidemiological studies are lacking and real incidences and prevalences are not well established [6]. Prospective post-mortem data suggested that myocarditis could be implicated in the sudden death of young adults at rates of 8.6–12% [7,8]. Up to 15% of pericarditis could be considered as myopericarditis, including cardiac enzyme elevation, wall motion abnormalities, arrhythmias and conduction disturbance [9]. The introduction of hypersensitive dosages of cardiac enzymes, such as high-sensitivity troponin, should increase the prevalence of this diagnosis; the value of these sorts of biomarkers in these clinical settings has to be investigated.

Main guidelines for acute pericarditis were published by the European Society of Cardiology (ESC), in 2004 [3]. Diagnosis is consensually defined. Hospitalizations are recommended in the worst cases and treatments include non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, other anti-inflammatory drugs and colchicine. Although rest is highly recommended, this is difficult to obtain in this young population and the means of achieving it are lacking. Importantly, there are many problems associated with the management of this disease, including different procedures in different centres (despite guidelines), hospitalization, choice of drugs and duration of treatment. Relief of symptoms is the immediate goal for the physician, but the high risk of recurrences and even the aim of controlling the inflammatory process deserve to be considered. Guidelines for the management of myocarditis are patchier, especially for heart rate (HR)-controlling treatments.

However, HR-controlling treatments may exert several beneficial effects. HR is a well-established risk-marker for various cardiovascular diseases [10,11], including coronary artery disease [12,13] and heart failure (HF) [14,15]. Sinus tachycardia is almost invariably observed in myopericarditis [3,16], even in the absence of other contributing

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factors, such as fever or haemodynamic compromise [17]. Nevertheless, data are scarce and sinus tachycardia is often considered as linked to pain or associated with complications of pericarditis or myocarditis, such as tamponade or acute HF, respectively. In the case of HF, suitable beta-blockers are indicated as HR-controlling treatments; however, these drugs have to be introduced after the initial phase. In other cases, the place of beta-blockers and other HR-reducing therapies has to be clarified. In this article, we review the literature, including recent results from our group suggesting a possible link between HR and pericardial inflammation, paving the way for more studies on this topic. Controlling HR could then be a new endpoint to treat pericardial inflammation and improve the symptoms (pain). Rest and a few pharmacological strategies are available to achieve this goal.

To simplify the discussion, pericarditis and myocarditis are schematically distinguished in the manuscript, even if a continuum binds the diseases. Only diseases without LV dysfunction will be extensively discussed here, as the question seems solved in that case, with strong evidence for beta-blockers. In this article, we aim to summarize the available data on HR control and the management of patients with acute pericarditis or myocarditis. Rest, beta-blockers and new HR-reducers are reviewed, and further directions are discussed.

Methods

An exhaustive review of the literature was performed, using the PubMed platform, with the following keywords: "bradycardia"; "beta-blockers"; "calcium channel inhibitors"; "pericarditis"; "myocarditis"; "myopericarditis"; "rest"; and "guidelines". Combining two keywords, as appropriate, a total of 786 articles were initially screened and 103 were further analysed. Original data were considered as a higher level of pertinent information, including experimental data. Review articles were considered as secondary level information and are rarely cited in this manuscript. The available guidelines on the topic were screened with particular attention.

Prognostic factors: is heart rate a prognostic factor in myopericardial diseases?

Many prognostic factors have been proposed for acute pericarditis. According to a literature review [18–21], several clinical features are usually considered to be more frequently associated with an increased risk of short-term complications or a specific diagnosis: fever > 38 °C [22]; subacute onset (symptoms developed over a period of several days or weeks) [23]; immunodepression [23]; trauma [24]; oral anticoagulant therapy [25]; myopericarditis (pericarditis with clinical or serological evidence of myocardial involvement) [26–28]; large pericardial effusion (effusion with a diastolic echo-free space > 20 mm wide) or cardiac tamponade [29,30]; lack of initial response to aspirin or NSAIDs within 1 week [18]; and corticosteroid use [31].

Some clinical features (fever > 38 °C, subacute course, large effusion or tamponade and aspirin or NSAID failure) have also been proposed as prognostic factors for higher risk of specific causal conditions and complications [32,33], and help with risk stratification when deciding about hospitalization. More recently, biological markers were proposed to stratify the risk, especially troponin, even if mildly elevated [34], and C-reactive protein (CRP) [35]. Some clinical conditions may favour a higher probability of autoimmune disease, especially female sex [32]. Although sinus tachycardia is frequently observed in patients with pericarditis [16], tachycardia was not clearly identified as a prognostic marker. Recently, our group identified a link between HR and CRP [36] (Fig. 1). In this retrospective study of 73 patients (median age, 38 years; interquartiles 28–51), median HR was 88.0 beats per minute on admission (interquartiles 76.0–100.0) and 72.0 beats per minute on discharge (65.0–80.0). HR on admission was significantly correlated with CRP peak (p < 0.001), independent of temperature on admission, hospitalization duration and age. HR on hospital discharge was correlated with recurrence, independent of age. In acute pericarditis, HR on admission seemed to be independently correlated with CRP concentrations and HR on discharge seemed to be independently correlated with recurrence. This may suggest a link between HR and pericardial inflammation.

For acute myocarditis, clinical markers, advanced New York Heart Association functional class and lack of beta-blocker therapy have been associated with poor outcome [37]. Immunohistological signs of inflammation, but not histology (positive Dallas criteria) or viral genome detection, were also related to poor outcome [37]. Although troponin elevation was proposed as a marker to distinguish pericarditis from myopericarditis [34], troponin elevation did not seem to predict outcome in myocarditis [38]. Electrocardiography might provide additional information, especially in the presence of prolonged QRS duration [39]. More recently, magnetic resonance imaging was proposed as the best predictor, showing that late gadolinium enhancement could be
better than clinical or echocardiographical markers for predicting outcome [40].

Rest: guideline recommendations

Rest is recommended in case of acute pericarditis [3,24] but can be rarely obtained. Rest may help to achieve pain cessation, lower HR and decrease pericardial inflammation. Surprisingly, the effects of rest have not been evaluated in this pathology, to our knowledge. Furthermore, there is no study assessing the effects of beta-blockers or other drugs that could induce bradycardia. Several studies [41] have assessed or are currently evaluating the role of aspirin and other anti-inflammatory drugs [42,43], corticosteroids [44–46] and, more recently, colchicine [31,47–50] (for comprehensive review, see Algararrondo et al. [51]).

The ESC guidelines on pericardial diseases, published in 2003 [3], are the most cited. Symptomatic management relies on exercise restriction and although rest is mentioned, no study has explored its potential beneficial effects. The value of bradycardia is not discussed and beta-blockers are not mentioned. Anyway, many of these recommendations were based on expert opinion because of the lack of specific studies [21]. This is true for most of the therapeutic strategies presented here, including general recommendations, such as the value of rest.

The ESC guidelines do not refer to myocarditis. The Japanese Society guidelines on myocarditis, published in 2009 [52], proposed that “patients with asymptomatic or mildly symptomatic myocarditis with cardiac signs and symptoms should be admitted to the hospital, kept at bed rest, and monitored carefully”. Although treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers to protect the myocardium is recommended, beta-blockers are not mentioned. Indeed, the Heart Failure Society guidelines do not even detail treatment of HF [53], as they focus on immunosuppression. Canadian guidelines on myocardial diseases [54] advocate, irrespective of clinical presentation, that patients with myocarditis and HF should be treated with typical measures (e.g. angiotensin-converting enzyme inhibitors, beta-blockers and diuretics if necessary).

More recently, an update was proposed in a comprehensive review [16], which underlined the lack of clinical trials supporting the ESC guidelines of 2004. The first-line situation of colchicine is underlined and other drugs failing to show value, such as statins, are discussed in a comprehensive review on therapeutic avenues [55], but beta-blockers and other HR-lowering agents are not mentioned.

Beta-blockers improve myocarditis clinical outcome

In case of myocarditis, there are no available clinical data on this topic, to our knowledge. Importantly, beta-blockers are not “pure” HR-reducers, as they act on blood pressure and, last but not least, on adrenergic stimulation, which may explain, at least in part, their positive impact in case of myocarditis and support their hypothetical value in acute pericarditis.

In case of myocarditis, lack of beta-blockers seems to be associated with poor clinical outcome [37,56]. Kindermann et al. [37] identified three independent predictors for poor clinical outcome: New York Heart Association class III or IV at entry (hazard ratio 3.20; 95% confidence interval 1.36–7.57; p = 0.008); immunohistological evidence of inflammatory infiltrates in the myocardium (hazard ratio 3.46; 95% confidence interval 1.39–8.62; p = 0.008); and, above all, lack of beta-blocker therapy (hazard ratio 0.43; 95% confidence interval 0.21–0.91; p = 0.027).

Beta-blockers could be involved in clinical settings in several ways. They remain contraindicated at an early stage in case of acute HF. Nevertheless, they could provide acute haemodynamic benefit, probably by prolonging diastole [57]. In the case of myocarditis, beta-blockers could have an effect on arrhythmias at an early stage and long-term benefits in terms of HF. Hence, beta-blockers are highly recommended in case of HF, including LV dysfunction or clinical HF.

USA guidelines recommend using “beta-adrenergic blocking agents in all patients admitted for acute myocarditis and HF” in case of myocarditis, because of the high incidence of LV dysfunction and, by analogy, with other causes of LV dysfunction. Evidence-based HF therapy should be mandatory, even though there is no clinical trial of HF therapy available in patients [58].

Models of viral myocarditis have been developed in rodents. Beta-adrenergic receptors are upregulated by the disease [59], underlining the value of beta-blockers in the management of this disease. All beta-blockers should provide beneficial haemodynamic effects; however, certain differences are seen between the available beta-blockers. Experimental evidence strongly suggests that carvedilol, but not metoprolol, can protect against viral myocarditis [60]. The superior cardioprotective effect of carvedilol might result from its ability to upregulate the production of anti-inflammatory cytokines [61] while downregulating the production of proinflammatory cytokines, to promote antioxidative effects [62,63] and suppress matrix metalloproteinase production as well as positive immunomodulatory effects [64–66]. Whether metoprolol [67], betaxolol [68] and NO-metoprolol [69] can also mediate all the effects of carvedilol remains to be investigated.

Obviously, the use of beta-blockers should only be debated in case of myocarditis without LV dysfunction; otherwise, LV dysfunction indicates their use to prevent pathological remodelling.

Other heart rate-lowering treatments

Calcium inhibitors have been proposed to inhibit the activation of inflammatory pathways and oxygen stress in animal models, but not independently of HR [70,71]. As calcium inhibitors remain contraindicated in case of HF, they should be avoided in cases of myocarditis and pericarditis, and seem to be difficult to assess in potential clinical trials.

As digoxin—a purified cardiac glycoside—is not yet recommended in severe HF, it is used less and less in clinical settings. In experimental models, it has been shown to promote activation of inflammatory pathways [72], thereby
preventing its use in further studies in pericarditis or myocarditis.

Currently, there are no published clinical data available on the newest class of HR-lowering treatments, such as ivabradine. Rare data seem to indicate that resynchronization could be of value in case of myocarditis with poor LV ejection fraction, suggesting a role for such treatments, particularly in case of intolerance or contraindication of beta-blockers. In one basic study comparing carvedilol with ivabradine in murine viral myocarditis, both drugs were able to reduce HR and inhibit proinflammatory cytokine production [73,74]. Both ivabradine and carvedilol similarly attenuated myocardial lesions and fibrosis, inhibited nitric oxide synthesis by inducible nitric oxide synthase and decreased the production of two of the main pro-inflammatory cytokines—tumour necrosis factor alpha and interleukin 6.

**Perspectives and future directions**

Prospective studies on pericarditis or myocarditis remain rare. For ethical reasons, it is difficult to propose randomized studies on rest or beta-blockers in case of myocarditis.

The duration of treatment for pericarditis or myocarditis is not well established and clinical habits vary considerably. How long should rest or even avoidance of sport be respected? For athletes, competition should be avoided for at least 6 months [75] and probably definitely in case of incomplete recovery.

**Pericarditis**

Research in this domain is hampered because animal models were developed in large animals [76–78], which, often through postsurgical interventions, limited their utilization. Besides, studies have been conducted with goals other than the pericarditis itself. The first step should be to develop pericarditis models in rodents, which are essential for understanding and dissecting the mechanisms involved in the disease pathology and response to treatment.

The effect of rest could be explored through observational studies, such as registries with anonymous self-questionnaires. The hypothetical link between HR and pericardial inflammation is schematically presented in Figs. 2 and 3, suggesting that rest could lower HR and decrease mechanical inflammation. Obviously, blood pressure, cardiac work, etc. are also reduced. Beta-blockers could be studied through post-hoc analyses of large studies in patients with pericarditis; however, given that few patients are treated with beta-blockers, such an approach might have reduced power. We propose that "pharmacologically-induced rest" could potentially mimic the benefits of rest. Pharmacological candidates (e.g. ivabradine) have shown good tolerance [79] and are efficient in various clinical settings, especially in HF [14,79] and coronary disease [12,80,81], as recently reviewed [10]. We further suggested that HR could be at least partly associated with inflammation, providing a vicious circle, supporting the value of HR-lowering drugs for controlling symptoms linked to tachycardia and, above all, inflammation worsened by tachycardia [36]. Bradycardia obtained with ivabradine could be sufficient to obtain "pharmacological rest" and could achieve the goal without over-limiting the HR, especially in daily life. HR reduction should be about 10 beats per minute. By contrast, beta-blockers and other poorly tolerated drugs seem difficult to propose as the

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disease is most often benign. These medications have many adverse effects that might not be well tolerated, especially in this young population.

Myocarditis

The effect of beta-blockers could be studied through nation-wide myocarditis registries. More efficient designs could involve a prospective randomized open blinded endpoint (PROBE) study design. In addition to its lower cost, the PROBE design offers other advantages compared with the double-blind prospective trial; for example, the great similarity between a PROBE study and regular clinical practice should make the results obtained in a PROBE trial much more applicable to the practical management of patients. This scheme might be rational as the disease can be often life-threatening, justifying drugs such as beta-blockers, even if not well-tolerated in young people. Preliminary data reinforce this hypothesis [37]. More specifically tailored treatment could be proposed prospectively, taking into account clinical, biological, histological, immunohistological and magnetic resonance imaging prognostic factors.

Conclusions

Available data on HR-lowering treatments for acute pericarditis and myocarditis are surprisingly sparse. Level of proof for rest remains very low, with beta-blockers being largely recommended for myocarditis only. Local clinical habits are rarely questioned, but vary widely, indicating the need for systematic guidelines in these areas. Further clinical trials are also required.

The HR hypothesis in the pathophysiology of pericarditis and myocarditis could be beneficial in terms of improving understanding of the potential link between HR and inflammation and proposing new therapeutic targets. This hypothesis deserves a larger prospective study: is there a link between HR and pericardial or myocardial inflammation or pathological remodelling leading to clinical events in these pathologies? Ideally, the therapeutic approach could be combined to reinforce the interpretation. New HR treatments would then be of interest. New biomarkers, including adipokines, are currently being discussed or even studied to provide new tools to accurately assess the activity of diseases such as pericarditis, the diagnosis of which is not always easy [82]. When these new biological tools are available and well established, they should facilitate clinical trials on this subject, as well as new imaging modalities [83, 84].

Disclosure of interest

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