European Society of Cardiology
Working Group on
Myocardial & Pericardial Diseases

Newsletter

Issue 21 – February 2010

Editorial News

INSIDE THIS ISSUE:

Dear Members of the Working Group,

please find enclosed the 21th issue of our Newsletter.

In addition to the 'clinical case of the month' and the 'paper of the month' you will find within this issue the case resolution from the January case.

On the last page of the newsletter you will find some recommendations for further reading with a list a recently published papers in the field of our WG.....

Best wishes for all of you.

S. Pankuweit

The paper of the month:

Nonsteroidal anti-inflammatory drug treatment for postoperative pericardial effusion: a multicenter randomized, double-blind trial. Meurin P, Tabet JY, Thabut G, Cristofini P, Farrokhi T, Fischbach M, Pierre B, Driss AB, Renaud N, Iliou MC, Weber H; French Society of Cardiology. Ann Intern Med 2010 Feb 2;152(3):137-43.

Presented by **Arsen D. Ristić,** MD, PhD, FESC, Associate Professor of Internal Medicine – Cardiology, Department of Cardiology of the Clinical Center of Serbia, Belgrade University School of Medicine, Koste Todorovića 8, 11000 Belgrade, Serbia

Introduction

Post-cardiac injury syndrome develops within days to months after cardiac, pericardial injury or both. It resembles the post-myocardial infarction syndrome, both appearing to be variants of a common immunopathic process. Unlike post-myocardial infarction syndrome, post-cardiac injury syndrome acutely provokes a greater anti-heart antibody response (anti-sarcolemmal and anti-fibrillary), probably related to more extensive release of antigenic material [1]. Pericardial effusion after cardiac surgery is common and its size and site are related to the type of surgery, periprocedural medications, and individual response to surgical trauma. Cardiac tamponade after open heart surgery is more common following valve surgery (73%) than coronary artery bypass grafting (CABG) alone (24%) and may be related to the preoperative use of anticoagulants [2]. Most cases of cardiac tamponade occur more than 7 days after surgery, and may develop slowly, without clear-cut clinical signs [2,3]. This is a major concern because patients often have already been discharged from the hospital by that time. In the retrospective analysis of Ashikhmina et al [4] out of 21,416 patients that underwent cardiac surgery 327 (1.5%) had pericardial effusion. Clinical features of tamponade were documented in 138 patients (42%). Effusions were evacuated by echocardiography-guided pericardiocentesis (n = 169, 52%) or surgical drainage (n = 75, 23%). Effusion resolved after left thoracocentesis for pleural effusion in 3 patients (1%); 67 patients (20%) were treated conservatively. In 13 cases (4%), recurrent effusion required drainage after initial pericardiocentesis. Independent risk factors for effusion were larger body surface area, pulmonary thromboembolism, hypertension, immunosuppression, renal failure, urgency of operation, cardiac operation other than coronary artery bypass grafting, and prolonged cardiopulmonary bypass. Previous cardiac surgery is associated with lower risk of effusion.

Cardiac tamponade after cardiac surgery may also be caused by intrapericardial haematoma which most often spontaneously resolved but may also require urgent evacuation. Constrictive pericarditis may also occur after cardiac surgery. Warfarin administration in patients with early postoperative pericardial effusion imposes the greatest risk, particularly in those who did not undergo pericardiocentesis and drainage of the effusion [5].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to reduce the size of asymptomatic postoperative pericardial effusions (in 77% of the patients in one large study (3]). However, only one previous study [6] has shown the efficacy of NSAIDs for this condition and since patients who have recently had heart surgery are fragile, it is important to understand the balance of risks and benefits for this treatment. Although NSAIDs are usually given for only a short time to patients with pericardial effusions, they can cause serious adverse effects, such as upper gastrointestinal tract bleeding or perforation [7], but also myocardial infarction, acute heart failure, and acute renal failure [8].

Summary of the paper

In the February issue of the Annals of Internal Medicine, Meurin and the colleagues from the French Society of Cardiology [9] have published results of their randomized trial on the NSAIDs Treatment for Postoperative Pericardial Effusion, performed in 5 French postoperative cardiac rehabilitation centres. They evaluated 196 patients at high risk for tamponade because of moderate to large persistent pericardial effusion (grade 2, 3, or 4 on a scale of 0 to 4, as measured by echocardiography) more than 7 days after cardiac surgery. The patients were randomly assigned at each site in blocks of 4 to diclofenac, 50 mg, or placebo twice daily for 14 days. The main end point was change in effusion grade after 14 days of treatment. Secondary end points included frequency of late cardiac tamponade. The initial mean pericardial effusion grade was 2.58 (SD, 0.73) for the placebo group and 2.75 (SD, 0.81) for the diclofenac group. The 2 groups showed similar mean decreases from baseline after treatment (-1.08 grades [SD, 1.20] for the placebo group vs. -1.36 (SD, 1.25) for the diclofenac group). The mean difference between groups was -0.28 grade (95% CI, -0.63 to 0.06 grade; P=0.105). Eleven cases of late cardiac tamponade occurred in the placebo group and 9 in the diclofenac group (P=0.64). These differences persisted after adjustment for grade of pericardial effusion at baseline, treatment site, and type of surgery. Therefore, in this trial, the use of diclofenac, 100 mg/d, did not significantly reduce the size of pericardial effusions or the risk for late cardiac tamponade. Moreover, this study confirms that moderate to large pericardial effusion (grade 2, 3, or 4) occurring 7 to 30 days after cardiac surgery is a severe condition because 10.2% of these patients required pericardiocentesis in the 14 days after they enrolled in the study.

Discussion

Therapy with NSAIDs has been previously considered useful for postoperative pericardial effusions that persist after the first postoperative week. Pericardial effusions and tamponade that occur early after surgery are usually related to surgical bleeding; however, late effusions and tamponade (which are much more frequent) have multiple causal mechanisms, and inflammation seems to play an important role. Postpericardiotomy syndrome may include fever, friction rubs, chest pain, pleuritis, and pericardial effusion. Therefore, use of an NSAID to treat late postoperative pericardial effusions seems logical, and it is common in daily practice (up to 77% of patients in several surveys [2,3,10]). However, patients who have valvular surgery routinely receive oral anticoagulants, and the combination of these agents with an NSAID could provoke gastrointestinal haemorrhage. In addition, use of an NSAID after CABG could promote atherothrombotic complications. Diclofenac was selected for this study because it is widely used and seems not to antagonize the irreversible platelet inhibition induced by aspirin [11], which is usually prescribed for these patients. However, the main limitation of the study is that it was underpowered to detect small beneficial effects from diclofenac or to evaluate adverse clinical events from the drug, because only 95 patients received the drug.

Although postoperative pericardial effusion is frequent and potentially severe, few randomized, controlled trials have examined treatment for this condition. Recommendation given in the ESC Guidelines to treat postoperative pericardial effusion with NSAIDs was based on the results of the double-blind, placebo-controlled, randomized study by Horneffer et al. [6] applying a 10-day course of ibuprofen or indomethacin. Of 1019 adult patients undergoing cardiac operations during a 14-month period, a diagnosis of postpericardiotomy syndrome was made in 187, and 149 were enrolled in the study. Diagnosis was based on the presence of at least two of the following: fever, anterior chest pain, and friction rub. Drug efficacy was defined as the resolution of at least two of these criteria within 48 hours of drug initiation. Ibuprofen and indomethacin were 90.2% and 88.7% effective, respectively, and both were significantly more effective than placebo (62.5%, p = 0.003).

The occurrence of side effects, including nausea, vomiting, renal failure, and fluid retention, was low in all groups (13.1% for ibuprofen, 16.1% for indomethacin, and 16.7% for placebo [p = not significant). Length of hospital stay, incidence of ischemic events, and accumulation of significant pericardial effusions were similar in all groups. The results of this study suggested that both ibuprofen and indomethacin provide safe and effective symptomatic treatment for postpericardiotomy syndrome.

Aspirin [12] and diclofenac [13] were tested in clinical trials that examined prevention of the postcardiotomy syndrome (not treatment), but these trials included rather limited number of patients. A prospective, randomized, double-blind on primary prevention of postpericardiotomy syndrome was performed by Finkelstein et al [14] in 163 patients who underwent cardiac surgery in two centres in Israel between. On the 3rd postoperative day, the patients were randomly assigned to receive colchicine (1.5 mg/day) or placebo for 1 month. All were evaluated monthly for the first 3 postoperative months for development of postpericardiotomy syndrome. Of the 111 patients who completed the study, 47 (42.3%) received colchicine and 64 (57.7%) placebo. There was no statistically significant difference between the groups in clinical or surgical characteristics. The postpericardiotomy syndrome was diagnosed in 19 patients (17.1%), 5/47 cases (10.6%) in the colchicine group and 14/64 (21.9%) in the placebo group. However the study was underpowered and the difference showed only a trend toward statistical significance ($p < 0.135$). Therefore, colchicine is further being tested in an ongoing prevention trial of prevention (COPPS) [15].

In conclusion, the study of Meuring et al. is one step further in introduction of evidence-based medicine in the management of pericardial diseases and suggests that, until we have further data, clinicians should avoid the routine use of NSAIDs [9]. This is most probably especially true, in the absence of evidence of inflammation, such as elevated C-reactive protein levels or other symptoms. Furthermore, in the postoperative setting, corticosteroids plus colchicine may be the favoured choice to avoid negative interactions between NSAID and oral anticoagulant therapy [16]. However, careful monitoring of postoperative pericardial effusions is warranted, especially for large effusions. Redo surgery and pericardiectomy are very rarely needed. Primary prevention of postperiocardiotomy syndrome using short-term perioperative steroid treatment, intrapericardial treatment or colchicine should be also further evaluated.

References Part I

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References Part II

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9. Meurin P, Tabet JY, Thabut G, Cristofini P, Farrokhi T, Fischbach M, Pierre B, Driss AB, Renaud N, Iliou MC, Weber H; French Society of Cardiology. Nonsteroidal anti-inflammatory drug treatment for postoperative pericardial effusion: a multicenter randomized, double-blind trial. Ann Intern Med 2010;152(3):137-43.
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The clinical case of the month: *What is your diagnosis?*

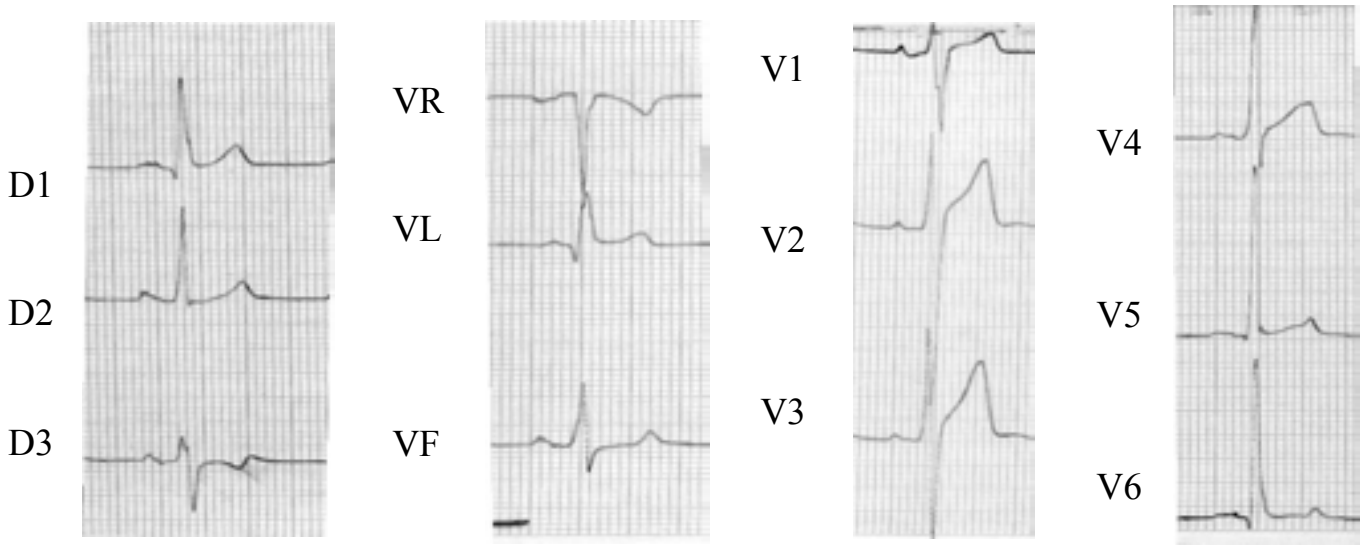
Answers will be given in the next newsletter and on the web site

Presented by Dr Philippe Charron, Centre de référence Maladies cardiaques héréditaires, Hôpital Pitié-Salpêtrière & Université Paris 6, France.

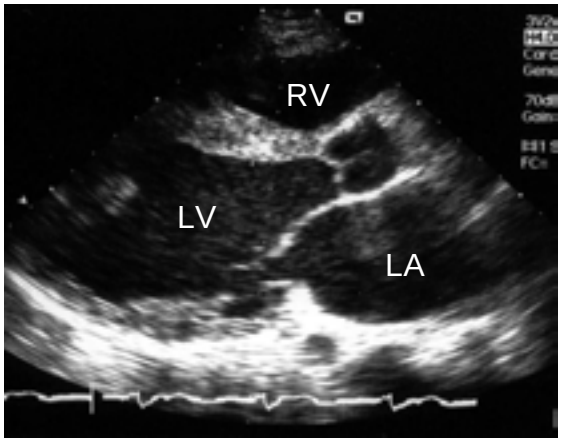
Titel

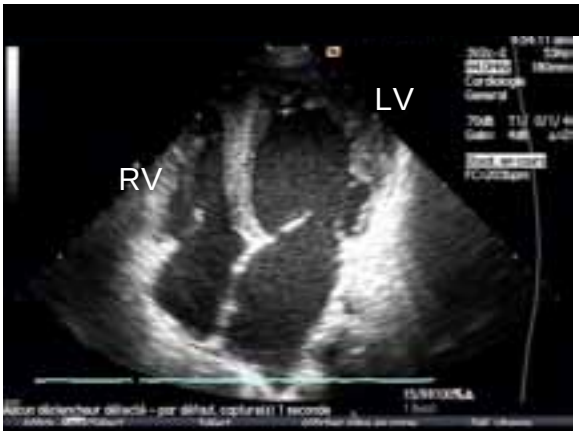
Case Presentation:

A 22-year-old man was addressed to the emergency department because of congestive heart failure. At clinical examination, left and right congestive heart failure was present. Transcient atrial fibrillation was observed. ECG was performed during sinus rhythm (see Figure).

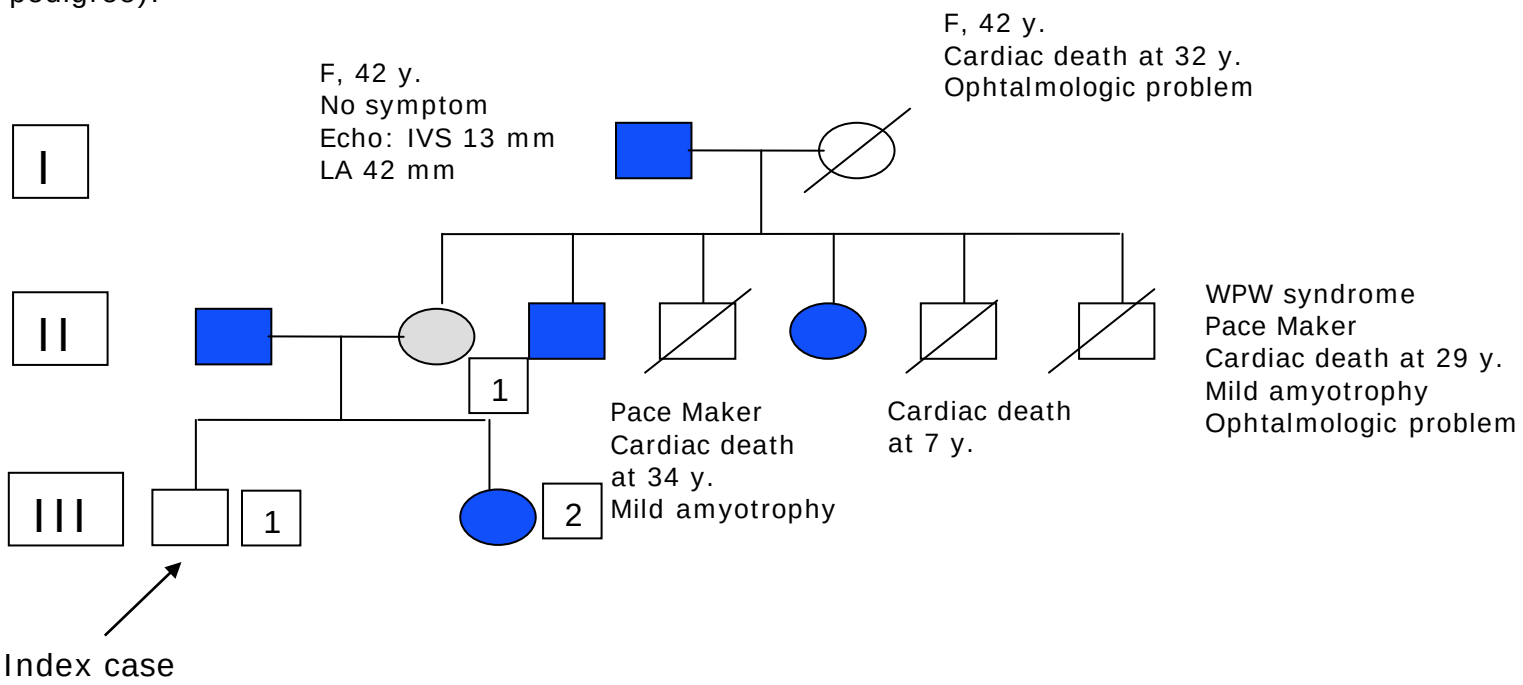


Echocardiography exhibited enlarged left ventricle (LVEDD: 61 mm), increased wall thickness (MWTd: 15 mm), depressed systolic dysfunction (LVEF: 25%), enlarged left atrium (LA: 49 mm), mild mitral regurgitation (MR: 2/4) and elevation of systolic pulmonary artery pressure (sPAP: 65 mmHg).





The evolution during the first days of medical treatment was simple with heart failure resolution.
Past history of the patient was characterized by a diagnosis of hypertrophic cardiomyopathy at 16 years of age (wall thickness on echocardiography: : IVS 12 mm, LW 16 mm, PW 20 mm) and normal LVEF (65%). The patient also has ophtalmologic problem with choriocapillary atrophy.
Few weeks after hospital discharge, lipothymia occurred and atrio-ventricular block grade 2 was observed, alterning with atrial tachycardia. Pace maker was implanted.
Persistant elevation of CPK was also observed (2-5 fold normal values), without muscular force defect at clinical examination.
Family history was characterised by several relatives with cardiac or non cardiac problems (see pedigree).



What do you think about the diagnosis of this patient ?
Which further investigation would you perform?

Answer for the previous" Clinical case of the month" presented in January

"Misleading phenotype or biased cardiologists?"

by Michele Pasotti, Fabiana Isabella Gambarin, Alessandra Serio, Luigi Tavazzi*, Eloisa Arbustini
Centre for Inherited Cardiovascular Diseases, Fondazione IRCCS Policlinico San Matteo, Pavia and *GVM Care and Research, Cotignola (Ravenna), Italy.

Diagnosis, case resolution and treatment

Examination of the paternal clinical reports.

The paternal medical records reported that one month before dying suddenly the father had undergone pacemaker implantation for brady-tachy syndrome and the echocardiographic study had shown mild left ventricular dilation and dysfunction (LVEDD = 60 mm; LVEF = 40%). The coronary angiography was not performed. The discharge diagnosis was early DCM associated with chronic AF.

Considerations and diagnostic resolution

When we had to decide how to progress with the diagnostic work-up, the key data were:

1. the severe paternal family history of sudden cardiac death
2. the paternal conduction disease and dilated cardiomyopathy
3. the paternal SD despite PM
4. the documented short episodes of NSVT
5. the mild delay of subhissian conduction recorded at the EP study.
6.

We proposed the analysis of *LMNA* that tested positive.

ICD implantation

In the post-test counselling, we informed the patient about our current knowledge on clinical phenotypes associated with *LMNA* gene mutations, the family and personal data as warning indicators of a potential risk of events, and explained the possible treatments, both medical and ICD. In particular, we suggested the ICD implantation for primary prevention. The patient refused the proposal of the ICD (he signed the refusal form) and accepted medical treatment with bisoprolol 5mg/day.

The patient regularly come to our attention twice a year and is asymptomatic four years after onset of symptoms. Serial ECG Holter monitoring did not show further episodes of NSVT and AF. The echocardiographic parameters are stable.

Despite the clinical stability and wellness of the patient, the data reported in the literature about the risk of sudden death in *LMNA* mutation carriers, independently on LV dysfunction and dilatation (1-4) and the malignant family history raise the question on to whether the patient is really protected from life-threatening ventricular arrhythmias. Should we further encourage ICD implantation?

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List of recently published papers in the field of our WG recommended for further reading:

1) Constrictive pericarditis as a late sequela of streptococcal pneumonia: diagnostic role of cardiovascular magnetic resonance. Foley PW, Ratib K, Graham TR, Leyva F. J Cardiovasc Med (Hagerstown). 2010 Feb 11.

2) Fulminant Myocarditis Associated With Pandemic H1N1 Influenza A Virus in Children. Bratincsák A, El-Said HG, Bradley JS, Shayan K, Grossfeld PD, Cannavino CR. J Am Coll Cardiol. 2010 Jan 26. [Epub ahead of print]

3) Tumor necrosis factor-alpha promotes myocarditis in female mice infected with coxsackievirus B3 through upregulation of CD1d on hematopoietic cells. Huber S. Viral Immunol. 2010 Feb;23(1):79-86

4) Ginsenoside-Rb1 Attenuates Dilated Cardiomyopathy in cTnT(R141W) Transgenic Mouse. Zhao H, Lv D, Zhang W, Dong W, Feng J, Xiang Z, Huang L, Qin C, Zhang L. J Pharmacol Sci. 2010;112(2):214-22.

5) Replacement and reactive myocardial fibrosis in idiopathic dilated cardiomyopathy: comparison of magnetic resonance imaging with right ventricular biopsy. Schalla S, Bekkers SC, Dennert R, van Suylen RJ, Waltenberger J, Leiner T, Wildberger J, Crijns HJ, Heymans S. Eur J Heart Fail. 2010 Mar;12(3):227-31.

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7) Amyloidogenic light chains induce cardiomyocyte contractile dysfunction and apoptosis via a non-canonical p38□ MAPK pathway. Shi J, Guan J, Jiang B, Brenner DA, Del Monte F, Ward JE, Connors LH, Sawyer DB, Semigran MJ, Macgillivray TE, Seldin DC, Falk R, Liao R. Proc Natl Acad Sci U S A. 2010 Feb 11.