European Society of Cardiology
Working Group on
Myocardial & Pericardial Diseases

Newsletter

Issue 31 – January 2011

Myocardial and Pericardial Diseases
ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®

INSIDE THIS ISSUE:



# Editorial News

Dear Members of the Working Group,

Please find enclosed the 31st issue of our Newsletter including the answer to the previous ´case of the month´.

Best wishes for all of you,

Tiina Heliö

Web Editor

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# Message from the Chairman

Dear Colleagues,

I sincerely hope that you have had a very good Christmas. As we now look forward to challenging year, I am pleased to inform you about the activities that we have planned for the year. We have successfully developed 3 study groups dedicated to the subjects of myocarditis, genetic cardiomyopathies and pericardial disease. The co-ordinators, study group leaders and members of the myocarditis and pericardial study groups are as follows:

| **Myocarditis** | | **Pericardial Disease** | |
|---|---|---|---|
| Nucleus Co-ordinator | Alida Caforio | Nucleus Co-ordinator | Arsen Ristic |
| Study Group Leader | Sabine Pankuweit | Study Group Leader | Massimo Imazio |
| Members | Cristina Basso (Padova, IT)<br>Karin Klingel (Tübingen, DE)<br>Ali Yilmaz (Stuttgart, DE)<br>Stephan B Felix (Greifswald, DE)<br>Michael Fu (Gothenburg, SE)<br>Roland Jahns (Würzburg, DE)<br>Stephane Heymans (Maastricht, NL) | Members | Bernhard Maisch (Marburg, DE)<br>Jaume Sagristà-Sauleda (Barcelona, ES)<br>Antonio Brucato (Bergamo, IT)<br>Petar M. Seferovic (Belgrade, RS)<br>Yehuda Adler (Tel Hashomer, IL)<br>Witold Z. Tomkowski (Warsaw, PL) |

The co-ordinators and study group leader for **Genetic Cardiomyopathies** are:

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|---|---|
| Nucleus Co-ordinator | Jens Mogensen (Aarhus, DK) |
| Study Group Leader | Pascal McKeown (Belfast, Northern Ireland, UK) |

The membership of this will depend on discussions with other organisations and so I hope to able to announce the team next month.

Each of these study groups will be working on a number of projects over the next two years. These include position statements on myocarditis and the management of cardiac tamponade, a textbook on pericardial disease, a teaching course for management of pericardial diseases and a training programme for inherited cardiovascular disease. I am also pleased to announce that we will be working with the ESC on a proposal for European Registry of Cardiomyopathies.

In addition to this challenging agenda we will also be working on proposals to improve participation by the Nucleus members in the life of the Working Group. We will announce these proposals in forthcoming newsletters.

Finally, I would like to remind you about the Working Group Annual Meeting which will be taking place between 13-15 October 2011 in Lisbon. We are indebted to Professor Hugo Madeira for taking on the enormous task of organising this meeting. We will be announcing the programme for the meeting later in the year.
On behalf of the whole Nucleus I wish you all a Happy New Year.

Yours sincerely,

Perry ELLIOTT
Chairman, FESC

# The paper of the month:

## Virus serology in patients with suspected myocarditis: utility or futility?

Authors: Felix Mahfoud, Barbara Gärtner, Michael Kindermann, Christian Ukena, Katharina Gadomski, Karin Klingel, Reinhard Kandolf, Michael Böhm, and Ingrid Kindermann.

European Heart Journal. doi:10.1093/eurheartj/ehq493.

***Presented by*** Dr. Tiina Heliö, Department of Cardiology, Helsinki University Central Hospital, Helsinki, Finland

**Summary**

Inflammatory heart diseases can be classified according to clinical, clinicopathological and immunohistological criteria. In North America and Europe myocarditis is most often caused by viral infections. The clinical presentation and course of myocarditis may be quite variable. The diagnosis of myocarditis is based on histopathological and immunohistochemical findings of endomyocardial biopsies (EMBs). The detection and quantification of the viral genome in the heart can be performed by using molecular pathological techniques such as PCR or *in situ* hybridization. The immunohistochemically detected inflammation has been reported to associate with poor outcome. Viral infections have also been estimated to trigger 35-50% of inflammatory dilated cardiomyopathy (DCMi) and early diagnosis and treatment of viral myocarditis aims to prevent it. However, the availability of EMB and molecular pathological analyses is limited and in clinical practice virus serology is still used for the diagnosis of myocarditis, although not recommended in international guidelines. The authors determined prospectively the diagnostic value of virus serology as compared to EMB and viral genome detection and immunohistochemistry in patients with clinically suspected myocarditis.

The patient group comprised 124 patients (age 40 $\pm$ 15 years) with clinically suspected myocarditis. Patients were included if they had a febrile infection of the bronchial tree, the gut, or the urinary tract within the last 6 months and at least one of the following: impaired global or regional left ventricular systolic function, increased serum concentrations of myocardial necrosis markers, pericardial effusion of unclear reason, VT or NS-VT, or VF of unknown origin. Subjects with familial cardiomyopathy were excluded. Samples for virus serology were collected before EMBs and in 30 patients second samples were drawn 7-28 days after the initial sample. Acute viral infection with enterovirus, adenovirus, parvovirus B19, cytomegalovirus, human herpesvirus, and Epstein-Barr virus was diagnosed by demonstrating IgM or IgA in the initial samples or IgG seroconversion during the follow-up. Before EMB each individual underwent left heart catheterization with coronary angiography. Cardiac MRI and echocardiography were performed before EMB to choose the optimal biopsy site. Histopathological and immunohistochemical analyzed were carried out in paraffin –embedded tissue sections. Molecular detection of viral genomes in the tissue was performed using PCR-based techniques. A biopsy was considered positive for viral infection if the viral genome could be demonstrated by PCR and specificity was confirmed by DNA sequencing of viral amplification products.

The authors report viral genome in the myocardium of 58 patients (47%) while acute viral infection was diagnosed in 20 patients (16%) by serology. Moreover, only in 5 out of 124 individuals (4%) serology was compatible with the same virus which was found by EMB. Sensitivity and specificity of virus serology were 9 and 77%, the positive predictive value 25% and the negative predictive value 49%. The authors point

out that determination of viral antibody titers with follow-up samples is time-consuming and expensive. Often there is a considerable delay between the onset of the infection and clinical myocarditis, which diminishes the possibilities of using serology. The time when various antibodies appear, is also variable. Most viruses involved in the pathogenesis of myocarditis are also prevalent in the population and these facts complicate the interpretation of serological results. On the other hand, the disadvantages of using EMB include lack of specificity, risk of complications and the possibility of sampling errors. The authors emphasize that EMB still may provide important prognostic information since immunohistochemical signs of inflammation relate to poor outcome. They conclude that serological examinations should no longer be used as standard tool when myocarditis is suspected whereas EMB would offer the possiblity for exact diagnosis.

**Comments**

With a wide range of symptoms from mild chest pain to severe arrhythmias or sudden cardiac death, myocarditis presents a clinical challenge. Myocarditis may also lead to inflammatory DCM and heart failure. Viral infections are important causes of myocarditis but in clinical practice the ethiology of myocarditis quite often remains unclear. Recently, the use of viral genomic analyses in endomyocardial biopsies has been assessed for diagnostic purposes. Although the methods are highly sensitive for detection of viral pathogenes in EMBs, the number of specialized centers with extensive experience is limited. The role of antiviral or immunosuppressive treatment will probably be clarified in the future. According to current guidelines endomyocardial biopsy should be performed usually at least in patients with new-onset heart failure < 2 weeks' duration associated with a normal sized or dilated left ventricle in addition to hemodynamic compromise or in the setting of unexplained new-onset heart failure of 2 weeks' to 3 months' duration associated with a dilated left ventricle and new ventricular arrhythmias, Mobitz type II second- or third-degree atrioventricular (AV) heart block, or failure to respond to usual care within 1 to 2 weeks.

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6. Mason JW, O'Connell JB, Herskowitz A et al. Myocarditis Treatment Trial Investigators. A clinical trial of immunosuppressive therapy for myocarditis. N Engl J Med. 1995; 333:269-275.

# 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 Tiina Heliö**
Department of Cardiology, Helsinki University Central Hospital, Helsinki, Finland

## A previously healthy 41-year old woman resuscitated from ventricular fibrillation

The patient had been previously quite healthy, with no regular medication.
One evening in November 2008 when she was in the kitchen, she suddenly dropped on the floor unconscious and convulsed. The patient was resuscitated, the ambulance was called and the patient was defibrillated from ventricular defibrillation (Fig 1.). The return of spontaneous circulation -time was 24 minutes. The patient was transferred to the hospital for intensive care.

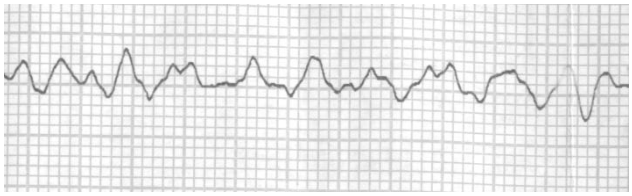

*Fig. 1. ECG showing the ventricular arrhythmia before defibrillation*

At the arrival at the hospital there was stable sinus rhythm (100/min), with prolonged QT-interval (Fig 2.). The patient was acidotic and hypokalemic.

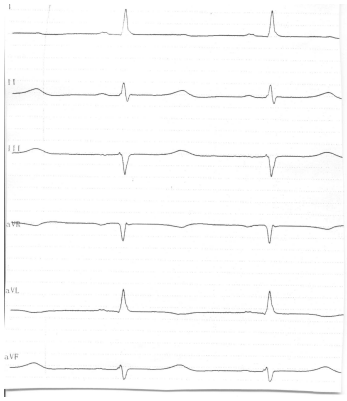

*Fig. 2. ECG taken after resuscitation at the hospital demonstrating sinus rhythm, normal atrioventricular conduction and prolonged QT-interval.*

Thorax X-ray was non-remarkable with some atelectasis. Plasma CK-MBm concentration was 14 ug/l (normal range 0-7 ug/l) and that of troponin T was 0.04 ug/l (normal range < 0.03 ug/l). CRP was negative.

Bed-side echocardiography showed a slightly increased left ventricular end-diastolic diameter (61mm), diminished ejection fraction and normal ventricular walls (Fig 3). There was mild tricuspid valve regurgitation with a systolic gradient of 25 mmHg.

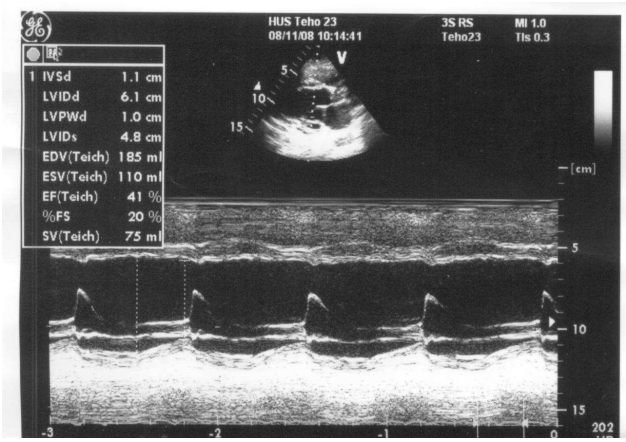


*Fig. 3. In echocardiography there was septal hypokinesia and diminished left ventricular contractility. No pericardial effusion could be observed.*

ECG monitoring demonstrated some episodes of non-sustained ventricular tachycardia (Fig. 4).
The patient told that six months earlier she had experienced a tachycardia lasting for about half an hour but it had subsided spontaneously before an ECG could be taken at the local health center.

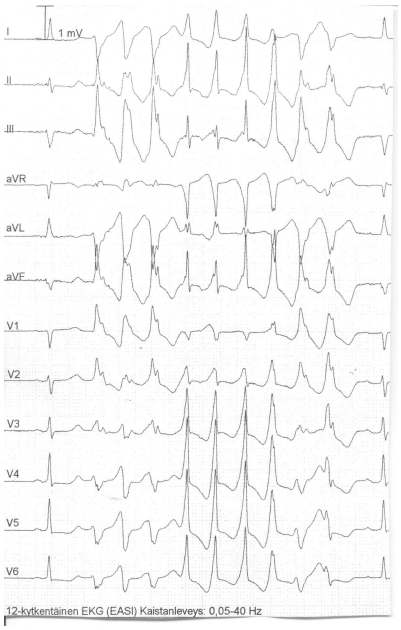


*Fig. 4. After the resuscitation, the patient had episodes of non-sustained ventricular tachycardias.*

The laboratory results remained negative for infections caused by common viruses, mycoplasma or toxoplasma. There was no evidence of a connective tissue disease (serum ANCA, ENA, PR3AB, MPOAB, ANA titers remained negative). The serum concentrations of lysozyme and calcium and the serum ACE activity were normal as well as the levels of ACTH, aldosterone, renin and cortisol. Cardiac MRI showed a dilated left ventricle with diminished systolic function (LVEF 43%). There was late enhancement in the basal area of the left ventricle anteroseptally, anteriorly and inferoseptally. On the contrary, the right ventricular size and function were normal and there was no late enhancement.

## QUESTIONS

- **What is your hypothesis?**
- **Which examinations would you recommend?**

## Answer for the previous "Clinical case of the month" presented in December issue.

### *"Cardiomyopathy due to a lamin A/C gene mutation and familial inquest"*

**By Dr. Philippe Charron**, Department of Cardiology, Pitié-Salpêtrière Hospital and Paris 6 University, Paris, France.

### Case resolution and discussion

**1/ Which cardiac examination do you recommend in the family members?**

The pedigree indicates an autosomal dominant disease (male-to-male transmission) and the risk of transmitting the disease is therefore 50% in first-degree relatives. Before the results of genetic testing are available, cardiac examination is recommended in all first-degree relatives with ECG and Echocardiography (no Holter ECG required at that stage as no significant abnormal conduction defect identified in the family). A specific information letter was given to the proband to facilitate the information transmission within the family. First cardiac examination should be performed at least at 10 years of age, and can be performed earlier (reference 1). Because of common age-related cardiac expression of DCM, regular examination can be performed every 1-3 years before 10 years of age, every 1-2 years between 10 and 20 years of age and every 2-5 years between 20 and 50-60 years of age (1).

**2/ Which additional management can you propose to the family members?**

Genetic counselling should be offered to the family members, and predictive genetic testing can be proposed to optimize the cardiac management of the relatives according to the results (no follow-up required if no mutation, specific cardiac FU in the presence of the mutation). In children, age at genetic testing should not be too early (because of possible adverse psychological effect and no significant medical benefit as no cardiac complications have been reported before 10 years of age in laminopathies) and can be reasonably proposed at 10 years of age or after. Information letter was given to the proband to transmit the information and the offer to the family members (no direct contact between our medical team and the relatives is authorized in France and in many European countries, because of ethical reasons).

**3/ Which cardiac management do you propose now to the sister?**

The cardiac examination performed in the sister who carries the mutation was normal, except holter-ECG with the presence of one run of non-sustained ventricular tachycardia. This finding illustrates the difficulties we may be facing to in the context of a lamin A/C mutation in an apparently healthy relative. Available data about management of apparently healthy relatives are particularly limited (2-4). However, systematic prophylactic ICD implantation was performed in a small population of 17 patients with LMNA mutation and an indication for pace paker (significant conduction defect or sinus dysfunction (2). Appropriate ICD therapy was observed in 8 patients (42%), most of them without LV systolic dysfunction. This study suggests the possible occurrence of early ventricular arrhythmia in patients with LMNA

mutation and suggests the possible indication for prophylactic ICD at an early stage, at least when significant conduction defect are present. However the precise risk in relatives without conduction defect and normal echocardiography is unknown. Preliminary data from a European registry (275 patients with LMNA mutation) was however recently presented at the 2010 AHA congress (5) identifying four independent factors associated with of life-threatening ventricular arrhythmias (VA): male gender, non-sustained VT, LV EF <45%, truncation mutations. VA occurred only in the presence of 2 or more of these factors. In the present case of the sister, she carried only one risk factor. We decided to propose first a medical treatment with beta-blockers and to monitor Holter ECG. In case of recurrent nsVT however, we plan to discuss ICD implantation.

**References**

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5. I.A.W. van Rijsingen, E Arbustini, PM. Elliott, J Mogensen, JF. H van Ast, AJ. van der Kooi, J. P van Tintelen, MP van den Berg, A Pilotto, M Pasotti, S Jenkins, C Rowland, U Aslam, A.A.M. Wilde, A Perrot, S Pankuweit, A.H. Zwinderman, P Charron, Y.M. Pinto. Risk Stratification for Life-threatening Ventricular Arrhythmias in Lamin A/C Mutation Carriers, Results of an European Registry. American Heart Association congress 2010.

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

1) **International collaborative systematic review of controlled clinical trials on pharmacological treatments for acute pericarditis and its recurrences.**
Lotriionte M, Biondi-Zoccai G, Imazio M et al. American Heart Journal. 2010; 160(4):662-670.

2) **Non-invasive evaluation of myocardial fibrosis: implications for the clinician.**
Leong DP, Madsen PL, Selvanayagam JB. Heart. 2010; 96: 2016-2024.

3) **Amyloid diseases of the heart: assessment, diagnosis, and referral.**
Dubrey SW, Hawkins PN and Falk RH. Heart. 2011; 97:75-84.

4) **The right ventricle in Fabry disease: natural history and impact of enzyme replacement therapy.**
Niemann M, Breunig F, Beer M, Herrmann S, Strotmann J, Hu K, Emmert A, Voelker W, Ertl G, Wanner C and Weidemann F. Heart. 2010; 96: 1915-1919.

5) **Is genotype clinically useful in predicting prognosis in hypertrophic cardiomyopathy? Genetics and clinical destiny: improving care in hypertrophic cardiomyopathy.**
Ho CY. Circulation. 2010; 122: 2430-2440.

6) **Is genotype clinically useful in predicting prognosis in hypertrophic cardiomyopathy? Mutation type is not clinically useful in predicting prognosis in hypertrophic cardiomyopathy.**
Landstrom AP and Ackerman MJ. Circulation. 2010; 122: 2441-2450.

7) **Mutations in the mitochondrial thioredoxin reductase gene TXNRD2 cause dilated cardiomyopathy.**
Sibbing D, Pfeufer A, Perisic T et al. European Heart Journal. doi:10.1093/eurheartj/ehq507