European Society of Cardiology
Working Group on
Myocardial & Pericardial Diseases

Newsletter

Issue 22 – March 2010

Myocardial and Pericardial Diseases
ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®

INSIDE THIS ISSUE:



# Editorial News

Dear Members of the Working Group (WG),

The WG has started the process to create **three Study Groups** dedicated to promote and support scientific interests of the WG: **Genetic cardiomyopathies**, **Inflammatory and infective heart muscle disease** and **Pericardial diseases/interventional pericardiology.**
The recruitment of three Study Groups leaders to manage those study Groups is on-going. All members are invited to apply (see page1).

Also; In 2007, the WG proposed a new classification scheme for cardiomyopathies. The aim was to resolve ambiguities in the existing classification system and to incorporate knowledge from recent advances in molecular genetics.
**In 2010-11 the WG will produce a follow-on position statement outlining a clinically oriented approach to diagnosis for each of the major sub-groups of cardiomyopathy.**

Recent advances in the diagnosis and management of people with inherited cardiovascular disease have the potential to improve the health of affected individuals and their families, but pose new challenges for diagnosis and clinical management. The WG has prepared a **position statement on genetic counseling and testing in cardiomyopathies** that describes the common clinical dilemmas faced by clinicians and the methods by which these can be resolved (submitted for publication 2010).

As usual, you will find the case resolution from the February case in addition to the 'clinical case of the month' and the 'paper of the month'. Some recommendations for further reading and the announcement of this year' **annual working group meeting** in A Coruna are also included

Best wishes for all of you.

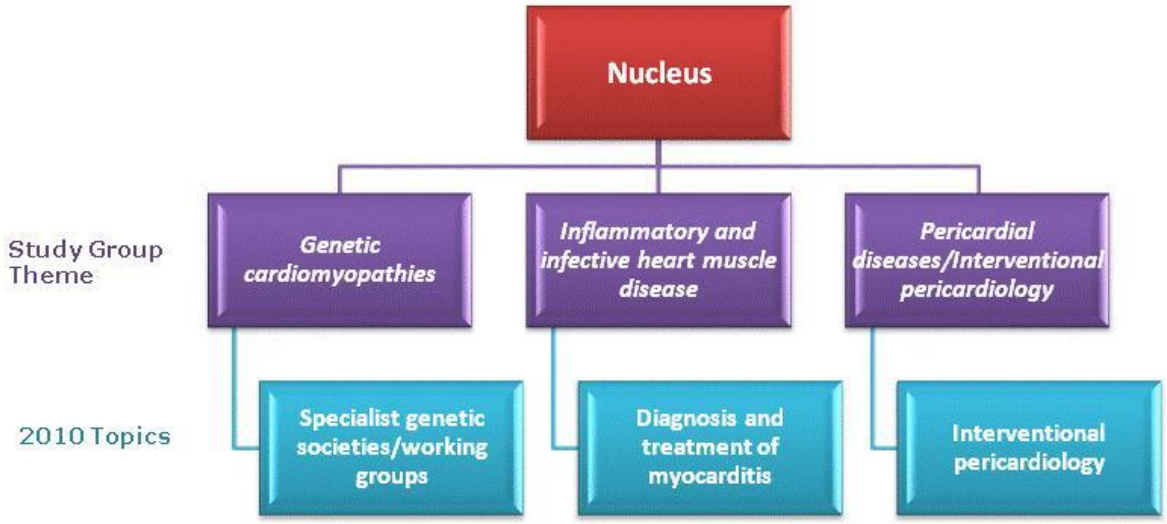
S. Pankuweit

# Three Study Groups and three topics of interest:

1. Study Group on Genetic cardiomyopathies ( Philippe Charron )
   Topic: Development of a joint advisory group with specialist genetic societies/working groups.

2. Study Group on Inflammatory and infective heart muscle disease ( Sabine Pankuweit )
   Topic: Development of supporting documentation for a possible future position statement on the diagnosis and treatment of myocarditis.

3. Study Group 3: Study Group on Pericardial diseases/interventional pericardiology ( Arsen Ristic )
   Topic: Development of an advisory group on current clinical needs and available procedures on interventional pericardiology.




**Recruitement of Three Study Grousp leaders:**

- Each study group leader will cooperate with a Study Group coordinator (mentioned above) named among the members of the nucleus.
- Each study group leader will serve for one year, with the possibility of extension for one additional year.
- Each study group leader will be expected to produce a report and will have the opportunity to report their group's progress at the Annual General Meeting.

**Learn more and apply from our web site: [www.escardio.org/cmp](http://www.escardio.org/cmp) - section "NEWS"**

# The paper of the month:

**Disease penetrance and risk stratification for sudden cardiac death in asymptomatic hypertrophic cardiomyopathy mutation carriers.** Michels M, Soliman OII, Phefferkorn J, Hoedemaekers YM, Kofflard MJ, Dooijes D, Majoor-Krakauer D and Ten Cate FJ. European Heart Journal;30(21):2593-8, 2009

***Presented by Tiina Heliö,*** Helsinki University Central Hospital, Helsinki, Finland.

**Introduction**

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disorder and sudden cardiac death (SCD) probably the most feared complication of HCM. SCD occurs in about 1% of HCM patients per year. Algorithms for assessing risk for SCD in HCM patients have been developed to identify high risk individuals who would benefit from preventive measures, especially from implantable cardioverter defibrillator (ICD) therapy. The increasing availability of DNA tests for HCM –causing gene defects has facilitated diagnostic testing of HCM patients. Alongside, predictive genetic testing of asymptomatic individuals has become common. In their recent article, Michels et al. demonstrate that some asymptomatic mutation carriers without HCM have SCD risk factors. The authors point out that follow-up studies are needed to evaluate the risk stratification for SCD in these individuals.

**Summary of the paper**

Michels et al. describe the outcome of cardiac evaluation and the risk stratification for sudden cardiac death (SCD) in asymptomatic hypertrophic cardiomyopathy (HCM) mutation carriers.

Cardiac evaluation was performed to 76 individuals from 32 families. The subjects had been tested predictively and they were shown to be HCM mutation carriers. Cardiac assessment comprised medical history, examination, electrocardiography (ECG), Doppler echocardiography, exercise testing and 24h Holter monitoring. HCM in adult members of these families was diagnosed according to previously published criteria by McKenna et al.

The SCD risk stratification was carried out in accordance with guidelines. A syncope was defined as unexplained loss of consciousness. Three different definitions for a positive family history of SCD were used: 1) SCD in one or more relatives, not depending on the age or degree of relatedness, 2) SCD in a first-degree relative less than 40 year or 3) SCD in more than one first-degree relative less than 40 year. An abnormal blood pressure response in exercise test was defined as a failure to increase systolic pressure over 20mmHg or a fall in blood pressure during upright testing. Non-sustained ventricular tachycardia (NS-VT) was defined as three or more consecutive beats at a rate 120/min or over, lasting less than 30 s. A maximal wall thickness of >/= 30 mm or over in echocardiography was considered as a risk factor.

Index patients (n=32) had a mean age of 35 $\pm$ 14 years at diagnosis. SCD was the first presentation in almost one third of the cases. Twenty-six index patients (81%) had some myosin binding protein C gene (*MYBPC3*) mutation (one patients was a compound heterozygote), four (13%) a cardiac beta-myosin heavy chain gene (*MYH7*)mutation, one a mutation in cardiac troponin T gene (*TNNT2*) and one in tropomyosin gene (*TPM1*).

Seventy-six asymptomatic HCM mutation carriers (thirty-three men and 43 women with an age range of 16-79 years and a mean age of 40 years), were identified and referred to cardiac evaluation and risk stratification. HCM was diagnosed in 31 (41%) asymptomatic subjects. Men had more often HCM than women (p=0,04). However, there was no significant difference in age between affected men and women.

*MYBPC3* mutations were involved in 23 (74%) relatives with HCM and mutations in *MYH7* were present in six (19%) relatives with HCM. *MYH7* gene mutation carriers were affected at an significantly earlier age at onset than those with mutations in *MYBPC3* (p=0.01). Both relatives carrying a mutation in the *TNNT2* and the *TPM1* genes were affected.

The HCM diagnosis was based in about half of the carriers both on echocardiographic and ECG criteria. Twelve (39%) carriers fulfilled only ECG criteria, 9% of the carriers only echocardiographic criteria. Two carriers had significant left ventricular outflow tract obstruction. In 33 mutation carriers (43%) ECG or echocardiography did not reveal any minor or major criteria compatible with HCM. These subjects were significantly younger and more often female than mutation carriers presenting the HCM phenotype. The majority of subjects without HCM (88%) carried a mutation in *MYBPC3.*
In risk stratification for SCD, four (5%) carriers had one first-degree relative that experienced SCD below 40 years, two with and two without HCM. Fifty-six (74%) carriers had a relative who had died suddenly not depending on the degree of the relationship or the age or the deceased relative. NS-VT was observed during 24h ECG monitoring in three subjects (4%), one without HCM. During upright exercise test an abnormal blood pressure response was observed in four (5%) carriers, one without HCM.

## Discussion, comments

The authors reported HCM in 41% of asymptomatic carriers. The younger age of mutation carriers without ECG or echocardiographic criteria was compatible with age-dependent penetrance, warranting repeated cardiac evaluation up to advanced age. In regard to genotype-phenotype relations, the founder mutations were concluded to have mild effects during first three decades of life although some mutation carriers would later develop a severe disease. The *MYH7* mutation carriers were affected at a younger age than *MYBPC3* carriers, but the clinical expression of the mutations was variable suggesting that environmental or epigenetic factors could affect the development of HCM. These findings emphasize the variability of the clinical picture associated with HCM mutations.

The annual rate of SCD among HCM carriers varies between 0,5-1,5% The risk stratification in HCM patients aims at identifying patients in high risk for SCD, who might benefit from an ICD. So far, the algorithms have been based on HCM patients, not asymptomatic mutation carriers. Even in this group, positive predictive value has been low and additional new criteria have been sought.
In this study Michels et al. describe the results of conventional risk stratification for SCD in asymptomatic HCM mutation carriers with and without HCM. They point out that the value of traditional risk factors needs to be evaluated also in this specific population.

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5. Maron BJ. et al. Sudden cardiac arrest in hypertrophic cardiomyopathy in the absence of conventional criteria for high risk status. Am J Cardiol 2008; 101:544-547.

# 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 Arsen D. RISTIĆ, Ivan MILINKOVIĆ, Petar M. SEFEROVIĆ, Department of Cardiology, Clinical Centre of Serbia and Belgrade University School of Medicine, Belgrade, Serbia**

## ACUTE PERICARDITIS WITH CARDIAC TAMPONADE IN A YOUNG PATIENT: RARE ETIOLOGICAL BACKGROUND WITH A PROLONGED, LIFE TREATENING COURSE

### Case Presentation:

A 20 years old female student of cinematography was admitted to our department with clinical and echocardiography signs of cardiac tamponade. The disease started one month prior admission, with fever up to 38°C, followed by dry cough. She had no signs of arthritis, no skin rash, and she did not take any medication before symptoms occurred. She had no previous medical history, was physically active and a non-smoker. However, she was exposed to the intensive and prolonged emotional stress due to the disagreement with her family regarding the topic of her studies and the selection of Belgrade University instead of Toronto where her parents live.

Initially, she was treated with Ciprofloxacin and Ceftriaxone after the chest X-ray showed signs of pneumonia and bilateral pleural effusions. Since the therapy had no effect, she was admitted to pulmonology department, sub-febrile and with progressive pleural effusions. Laboratory analyses revealed high sedimentation rate ranging 88-94 mm/h, C-reactive protein (CRP) 107-131 mg/l, fibrinogen 8.8 μmol/L, leukocytes $9.6x10^9$/l, platelets $528-613x10^9$/l, D-dimer 2050-3079 U/l, aspartate aminotransferase (AST) 112 U/l, alanine aminotransferase (ALT) 109 U/l, alkaline phosphatase 171 U/l, gamma glutamyl transferase 163 U/l, she was HIV, HBsAg, HCV negative, with positive IgG antibodies on Mycoplasma pneumoniae (175.6, IgM 0.33). Among the tumour markers she had mildly elevated Ca 125 (526), but normal Ca 72-4 and CEA. Diagnostic puncture of pleural effusion revealed 50 ml of serous pleural effusion (sterile exudate with negative direct microscopy on acid-fast stain). MRI of the pelvis and abdomen as well as gynaecology examination were unremarkable. MSCT of the thorax showed small bilateral pleural effusion and discretely enlarged lymph glands (11-14 mm) retrosternaly, around the thoracic aorta and in subcarinal region with small amount of pericardial effusion. Pleural puncture was performed once again with the pleural biopsy, this time 500 ml of sero-haemorrhagic fluid was obtained. The microbiology examination of the pleural effusion samples was again BK and Löwenstein negative and no malignant infiltration was detected in both cytology examination of the fluid and the biopsy samples. Although pericardial effusion was rather small, due to the fast accumulation our patient became progressively hypotensive, tachycardic, and orthodyspnoic and subsequently an emergency pericardiocentesis had to be performed in the sitting position providing an immediate clinical relief although only 400 ml of serous exudate was evacuated ***(Figure 1).***

During further hospitalisation she was haemodynamically stable with no recurrence of tamponade but continuously moderately febrile with peeks up to 38.6°C (with high sedimentation rate and parameters of inflammation, high leucocytes with relative lymphopenia, thrombocytosis, low urea and cholesterol and anaemia of chronic disease). She felt exhausted with occasional chest pain. Except minor but persistent bilateral pleural effusion other clinical findings were unremarkable.

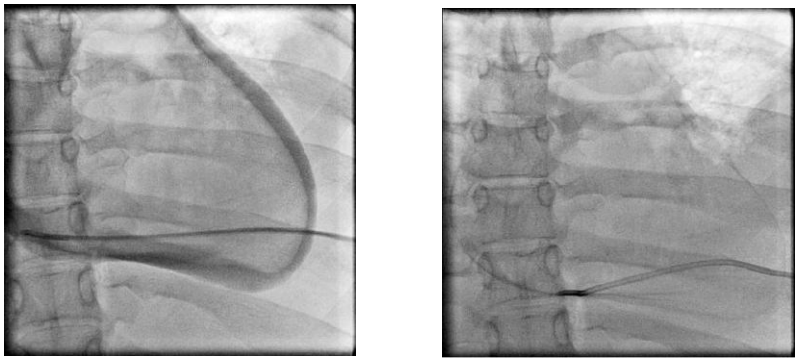


**Figure 1.** Rapidly evolving, small pericardial effusion causing acute cardiac tamponade with a dramatic clinical presentation. Left-sided figure demonstates a circulary pericardial effusion in the anterior-posterior view after evacuation of 100 ml of effusion and injection of 30 ml of angiographic contrast media intrapericardially using the intercostally placed 7F catheter. Right-sided figure reveals a normal heart shadow after evacuation of 400 ml of serous effusion.

Drainage of pericardial effusion lasted for 5 days, during which she received Cephtriaxone intravenously. She had no recurrences of pericardial effusion for about a month, when a 5-6 mm small pericardial effusion was again detected with signs of organisation. Immediately after pericardiocentesis Colchicine (0.5 mg BID) with Cephtriaxone and Gentamycin were administered. With this therapy she was not febrile for three days, but then developed diarrheic syndrome. Vancomycin, Ciprofloxacin, Metronidazole, and Nystatin were given and after diarrhoeas stopped Vancomycin was switched to Teicoplanin. No test to Clostridium difficile came back positive. In the meantime an extensive diagnostic work-up was preformed (***Tables 1-3 on the following pages***).

**What would be your diagnosis and suggestion for treatment?**

**Table 1.** Extensive laboratory evaluation of a young patient with prolonged febrile condition after acute cardiac tamponade

| Material | Type of the analysis | Result |
|---|---|---|
| Blood | ELISA for HIV, HSV, EBV, Hepatitis A, B i C, Mycoplasma pneumoniae, Salmonella, Brucella, T. gondi | Negative |
| | ELISA for Candida i Aspergilus | IgM + |
| | ELISA for Toxocara | Negative |
| | ELISA for H. pylori | Negative |
| | ELISA for Borellia burgdoferi | IgG 1:40 |
| | ELISA for CMV | IgG 1:640 |
| | Paul-Bunell reaction | Positive, IgG 1:40 |
| | ELISA for Coxsackie virus | IgG 1:80, IgM - |
| | Haemoculutures | Sterile |
| | Endocrinological analyses | Cortisol 354.2 nmol/l, ACTH 19.1 pmol/l, chromogranin A 183.6 U/l, calcitonin 1.7 ng/l |
| Pericardial effusion | Cytology | Nonspecific inflammation |
| | Culture | Sterile |
| Pleural effusion | Cytology | No acid-fast bacilli, rare lympho-cytes, eosinophilic leukocytes, anucleated ceratinocytes |
| | PCR for Mycobacterium tuberculosis | Negative |
| | Culture | Sterile |
| Pleural biopsy | Histology | Nonspecific inflammation |
| Ascites | Cytology | Nonspecific inflammation |
| | Culture | Sterile |
| | Biochemical analyses | glucose 5.5 mmol/l, total bilirubin 9.1 mmol/l, direct bilirubin 2.9 mmol/l, total proteins 49 g/l, albumin 28 g/l, cholesterol 2.35 mmol/l, triglicerydes 0.42 mmol/l, ALP 62 mmol/l, amylase 61 mmol/l, LDH 365 mmol/l |
| Vaginal secretion | Smear | Normal flora |
| Urine | Culture | Negative |
| | Microscopy | Candida 2000 Cfu/ml |
| | Biochemistry | Normal |
| Feces | Coproculture | Enterococcus spp., E. Colli, Proteus spp., Citrobacter spp. |

**Table 2.** Results of the immunology tests performed as a part of aetiological valuation of a young patient with prolonged febrile condition after acute cardiac tamponade.

| Parameters | One month period | | | | | | |
|---|---|---|---|---|---|---|---|
| IgA (U/l) | | 1.71 | | | | | |
| IgM (U/l) | | 1.5 | | | | | |
| IgG (U/l) | | 13.2 | | | | | |
| C3 complement (g/l) | | 2.01 | | | | | |
| RF (U/ml) | | | | | Ø (<9.7) | | |
| Cryoglobulins | | | | | Ø | | |
| Immune complexes (U/l) | | | | | 0.26 | | |
| ANA (titre) | Negative | | Spotty 1:20 | | Spotty 1:160 | Spotty 1:40 | Spotty 1:160 |
| ANCA (g/l) | | | Ø | | | Ø | 2 |
| Anti CCP At | | | | | | | 5 |
| Anti ds DNA (IgG) Ab | 1:10 | | Ø | | 0.2 | Ø | 5 |
| Anti-LKM1 (IgG) Ab | Ø | | | | | | Ø |
| Anti Ro SS-A Ab | 4 | | | | 0.3 | 7.7 | Ø |
| Anti La SS-B Ab | | | | | Ø | | Ø |
| Anti RNP-70 Ab | 1.5 | | | | Ø | 2 | Ø |
| Anti Sm Ab | | | | | | 0.5 | |
| AntiJo-1 Ab | | | | | | | Ø |
| Antineutrophyl Ab | | | | | Ø | | |
| Antimitochondrial Ab | | | Ø | | | Ø | |
| Anti-smooth muscles Ab | 1.3 | | Ø | | | | |
| Anticardiolipin Ab IgM | | | | 0.7 neg | | | |
| Anticardiolipin Ab IgG | | | | 2.2 neg | | | |
| Antiphospholipid Ab IgM | | | | 0.4 neg | | | |
| Antiphospholipid Ab IgG | | | | 0.6 neg | | | |

ANA - antinuclear antibodies, ANCA – Anti-neutrophil cytoplasmic antibodies , Ab – antibodies, RF – rheumatoid factor

**Table 3**. Comprehensive diagnostic evaluation in an attempt to establish the aetiology of prolonged febrile illness after acute cardiac tamponade complicated by a pseudomembranous enterocolitis and the subacute pancreatitis.

| **Diagnostic procedure** | **Interpretation** |
|---|---|
| Examination of the breasts | Normal findings |
| Gynecological examination | Normal findings |
| Ophtalmology examination | Normal findings |
| MRI of the brain and selar region | Normal findings |
| Echosonography of the neck | Normal findings |
| Echosonography of the abdomen and pelvis | Polycystic ovaria with marginal microcysts and 17 mm of free fluid in the Douglas recessus. Few days after introduction of tuberculostatic drugs serous oedema of the pancreas without any cystic formation or collection were noted. |
| MRI of the abdomen | Minimal perisplenic ascites |
| Computed tomography of the abdomen | Signs of subacute pancreatitis. |
| Colonoscopy with retrograde ileoscopy | Normal endoscopy findings |
| Oesophagogastroduodenoscopy | Normal endoscopy findings |
| Pathohistology of biopsy samples of small intestine, and gastric mucosis | Nonspecific inflammation |
| MRI of the chest | Bilateral pleural effusion up to 5 cm with basal compressive subatelektasis. |
| Bone marrow biopsy | Normal findings |

**Answer for the previous" Clinical case of the month" presented in February**

## "Hypertrophic-hypokinetic left ventricle"

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

### Diagnosis, case resolution and treatment

The patient is characterized by the atypical association of hypertrophic cardiomyopathy rapidly evolving towards systolic dysfunction, supraventricular arrhythmia alterning with atrio-ventricular block, hyperCK elevation and visual loss due to choriocapillary atrophy.

The variable association of these clinical features prompted us to considere several possible underlying causes including mitochondrial disease, AMP-kinase gamma-2 disease (PRKAG2 gene), desminopathy, glycogen storage disease (such as Pompe's disease or Danon's diasease).

Skeletal muscle biopsy was performed in the patient because of CK elevation. Light microscopy demonstrated some sarcoplasmic clear vacuoles (see the figure on the next page), that were PAS-positive (periodic acid Schiff). Immunohistochemical study indicated the presence of dystrophin on vacuole membranes. In contrast, immunohistochemistry with antibodies against LAMP-2 protein failed to detect any material, demonstrating that LAMP-2 protein was absent in the skeletal muscles of the patients. All these features are typical of Danon's disease.

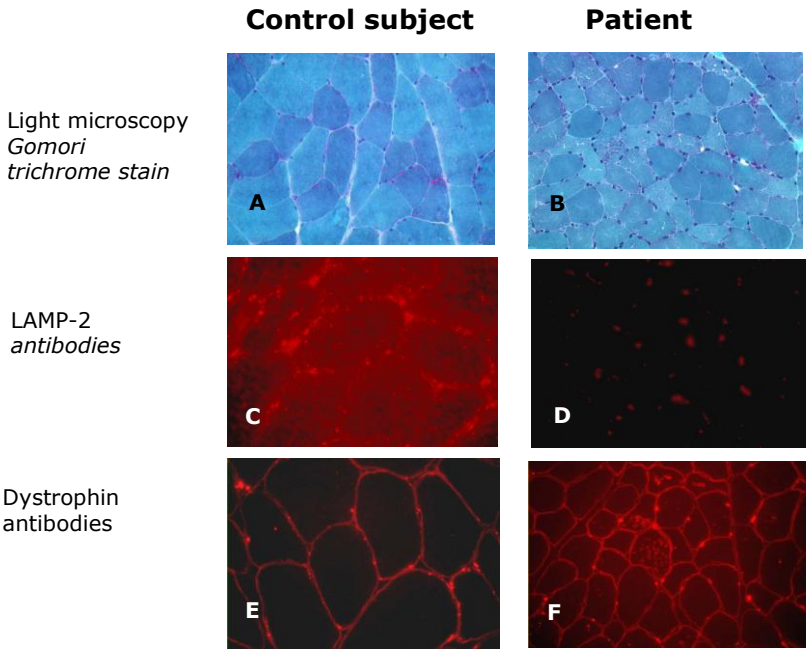
Sequencing of the LAMP-2 gene was performed in the patient and led to the identification of a hemizygous 7 pb deletion in exon 1 (173_179del, responsible for a premature stop codon) of the gene. The heterozygous mutation was also present in the mother.

Danon's disease is an X-linked lysosomal disease, with normal acid maltase, due to a primary deficiency of lysosome-associated membrane protein-2 (LAMP-2). The pathological hallmark of the disease is intracytoplasmic vacuoles containing autophagic material and glycogen in cardiac and skeletal muscle cells. The phenotype typically associated with mutations in the LAMP-2 gene is characterized by the triad of cardiomyopathy, skeletal myopathy, and mental retardation. In fact, skeletal myopathy is mild in most cases (85% in the largest studied population), but all male patients had elevated serum CK level, and mild mental retardation is observed in only 70%. In addition, Wolff-Parkinson-White syndrome, or preexcitation, is present in 35%, and ophtalmogic abnormalities with visual loss were reported in several patients. Women are typically less severely affected than males, with later-onset cardiomyopathy.

Mutations of the LAMP-2 gene usually lead to truncated proteins that are lacking the transmembrane domain, and can not function as a structural lysosomal membrane protein. Beyond the structural role of the protein, LAMP-2 may also have aditional role through autophagic vacuoles.

No specific treatment is currently available. The correct identification of Danon disease is however important, as the pathophysiology, clinical evolution, prognosis, mode of inheritance (X-linked), and therefore genetic counselling, are very different.

The natural history of Danon's disease is particularly important to consider as it is characterized in male patients by an early onset and a very poor prognosis. This was the case in our patient with recurrent heart failure. He died at 25 years while waiting for heart transplantation. In the largest population studied so far (20 male subjects with Danon disease), mean age at onset was before 20 years in all cases and all subjects except one died before 30 years. Deaths were related to LV dysfunction and congestive heart failure, or sudden death. This is in contrast with the natural history of HCM, where cardiac death is evaluated to be about 1-2% per year and evolution towards heart failure in only 10%. The severe cardiac evolution was underlined in another recent study (6 young boys, out of 7, developed cardiac death, aborted sudden death or heart transplantation over a mean follow-up of 8 years). These observations underscore the importance of timely diagnosis and early consideration of heart transplantation.




Results from the skeletal muscle biopsy: Normal sections are shown on A, C and E, and sections from patient on B, D and F. All sections were analyzed with a 60x oil objective, except image B with 40x.

Fig. A and B: Light microscopy (Gomori trichrome stain). Presence of multiple small vacuoles in some fibers.
Fig. C and D: Immunohistochemistry with LAM-2 antibodies.
Fig. E and F: Immunohistochemistry with dystrophin antibodies.

References

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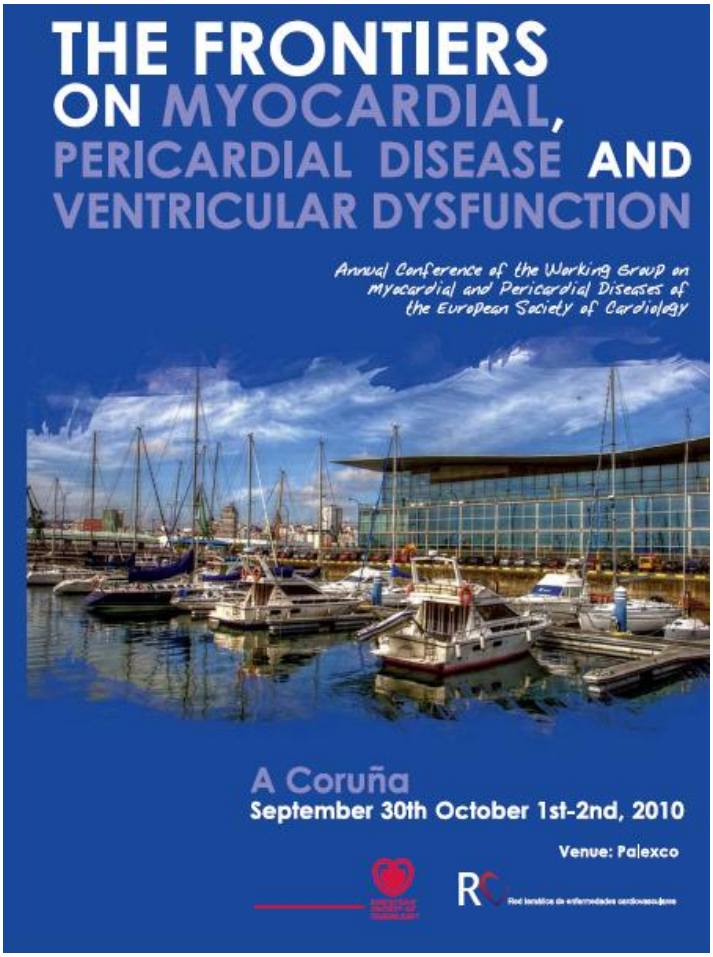
List of recently published papers in the field of our WG recommended for further reading:

Myeloid differentiation factor-88 contributes to TLR9-mediated modulation of acute coxsackievirus B3-induced myocarditis in vivo. Riad A, Westermann D, Escher F, Becher PM, Savvatis K, Lettau O, Heimesaat MM, Bereswill S, Volk HD, Schultheiss HP, Tschöpe C. Am J Physiol Heart Circ Physiol. 2010 Mar 12. [Epub ahead of print]

Human parvovirus B19-associated myocarditis. Bock CT, Klingel K, Kandolf R. N Engl J Med. 2010 Apr 1;362(13):1248-9.

Lack of evidence for a pathogenic role of proteasome-directed autoimmunity in dilated cardiomyopathy. Voigt A, Trimpert C, Bartel K, Egerer K, Kuckelkorn U, Feist E, Gericke C, Klingel K, Kandolf R, Felix SB, Baumann G, Kloetzel PM, Stangl K, Staudt A. Basic Res Cardiol. 2010 Mar 25.

## Announcement for the working group meeting 2010 in A Coruna




This is not the first time that a International Meeting on Myocardial and Pericardial diseases takes place in A Coruña. For many years, members of our Working Group have asked if we would continue "the tradition", remembering the extraordinary success of the previous meetings hold in our city: the first in 1993, the second in 1996 and the third in 1999.

This year the official annual meeting of the Working Group on Myocardial and Pericardial diseases of the European Society of Cardiology will gather in A Coruña most of the European experts in these fields.

The meeting will review from the basic aspects of these diseases, to the most recent clinical and research advances. The meeting will focus in practical issues, combining short presentations and the discussion of clinical cases.

**Further information, registration and accommodation**

**www.coruna2010.com**

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