European Society of Cardiology
Working Group on
Myocardial & Pericardial Diseases

Newsletter

Issue 15 - August 09

Editorial News

INSIDE THIS ISSUE:

1 Editorial News

2 The 'paper of the month'

3 The 'clinical case of the month'

4 Answer to the 'case of the month' July

5 Announcement of the Annual WG meeting

Dear Members of the Working Group,

please find enclosed the 15th 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 July case.

Best wishes for all of you.

S. Pankuweit

The paper of the month:

A new diagnostic test for arrhythmogenic right ventricular cardiomyopathy. Asimaki A, Tandri H, Huang H, Halushka MK, Gautam S, Basso C, Thiene G, Tsatsopoulou A, Protonotarios N, McKenna WJ, Calkins H, Saffitz JE. N Engl J Med 2009: 360:1075-84

Presented by: Dr. Lorenzo Montserrat, Cardiology Service. Instituto de Investigación Biomédica A Coruña. A Coruña. Spain ***Dr. Martín Ortiz,*** Fundación Carolina/BBVA. Cardiology Service. Instituto de Investigación Biomédica A Coruña. A Coruña. Spain.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a myocardial disorder characterized by fibro-fatty replacement of cardiac myocytes and special predilection by right ventricle[1]. Main complications are ventricular arrhythmias, heart failure and sudden cardiac death[2]. Natural history of ARVC usually include progressive phases, since concealed phase, characterized by absence or minor signs and symptoms, but during which sudden death could be the first manifestation[3]; till final stage of biventricular failure[4]. Diagnosis of ARVC is based on presence of major and minor criteria that include structural, histological, electrocardiographic, arrhythmic, and familial factors[5]. These recognized diagnostic criteria are specific but may lack sensitivity in those cases with mild phenotype and borderline abnormalities that overlap with normality. Thus, diagnosis of ARVC at its early stages remains a clinical challenge[4]. Moreover, endomyocardial biopsy is not always useful because of patchy cardiac muscle affection and preservation of subendocardial layers[6]. Genetic background of the disease includes mutations in desmosomal protein genes, which could be detected in almost 50% of cases. Desmosomal proteins (plakoglobin, plakophilin-2, desmoplakin, desmoglein-2 and desmocollin-2) are components of the cardiac desmosome that have important role in the pathogenesis of ARVC. Desmosomes have an important role in supporting structural stability through cell-cell adhesion, regulating transcription of genes involved in adipogenesis and apoptosis, and maintaining proper electrical conductivity through regulation of gap junctions and calcium homeostasis[7].

Asimaki et al.[8], in the March issue of The New England Journal of Medicine, presented a new diagnostic test for arrhythmogenic right ventricular cardiomyopathy. They analyzed samples obtained on autopsy or endomyocardial biopsy of 11 subjects who were known to have ARVC and 30 blinded heart-biopsy samples from subjects who had been evaluated in the John Hopkins ARVC registry, 11 of whom fulfilled clinical criteria of ARVC. Then they stained each sample with antibodies against plakoglobin, desmoplakin, plakophilin-2, N-cadherin and connexin-43, and compared to a panel of controls using immunohistochemical analysis. Results showed reduced immunoreactive signal levels for plakoglobin at intercalated discs in ARVC patients compared to controls, even in those samples taken from uncommon target disease regions (left ventricle and septum). Signal levels of plakopillin-2 and desmoplakin varied in the ARVC samples whereas connexin-43 showed marked reduction. To determine whether reduced signal levels for plakoglobin and connexin-43 at intercalated discs were specific for ARVC, authors analyzed samples from the native hearts of subjects who had undergone cardiac transplantation for end-stage heart disease (hypertrophic cardiomyopathy, dilated cardiomyopathy and ischemic heart disease).

In every case, these transplanted hearts showed high plakoglobin signal levels at intercalated discs, indistinguishable for control samples, whereas they had clearly diminished expression of connexin-43. Taken together, these results suggested that diminished signal level for plakoglobin is a consistent feature of ARVC but not of other forms of severe heart disease. Furthermore, reduced signal levels for the major ventricular gap-junction protein, connexin-43, indicate that the remodeling of gap-junctions is a fundamental feature of ARVC as well as of others ischemic and non-ischemic heart diseases. This new test, using an immunohistochemical technique to measure plakoglobin signal level in conventional biopsy samples, appears to be a highly sensitive (91%) and specific (82%) diagnostic test for ARVC.

Main important finding of this paper is the development of a new, simple and cost reliable test to diagnose ARVC, even in early and concealed phases of the disease. It is also remarkable the finding of a common pathogenic mechanism for the development of ARVC secondary to the presence of mutations in different desmosomal genes. In these cases, immunohistochemical analysis could be useful as all these different mutations would cause a loss of the normal plakoglobin binding to desmosomes. One theory coming from recent functional studies suggests that this could cause a migration of plakoglobin to the nucleus, where it would induce signaling pathways related to cell death and adipogenesis[9].

One of the most interesting applications of this novel technique is that it could become a gold standard method for the evaluation of the pathogenicity of desmosomal mutations. In some cases available clinical data is sufficient to decide if a specific genetic variant is causative or not, but this matter is usually difficult, especially with novel mutations or mutations with limited previous information. However, Asimaki et al.[8] only tested the diagnostic accuracy of the test for a limited number of mutations (eight) in four different genes, and we cannot assume that these results are applicable to other mutations in the same or different genes (like desmocollin-2).
Another advantage of this technique is that it may enhance the diagnostic accuracy of conventional endomyocardial biopsy or autopsy samples. Endomyocardial biopsies samples, for reasons of safety, are usually taken from septum, a region uncommonly involved by ARVC[6]. Asimaki et al.[8] demonstrated the presence of reduced plakoglobin signal levels even in regions appeared to be structurally normal.

Finally, the fact that reduction in the signal level of plakoglobin is present in structural and histologically normal regions, suggests that remodeling of desmosomes and gap junctions could start years before that histological changes appear. It is also possible that fibro-fatty replacement would not be necessary to induce conduction abnormalities that promote arrhythmias in ARVC. In this way, it would be important to consider the possibility of ARVC in cases of sudden death in structurally normal hearts.

The paper by Asimaki et al.[8] opens a completely new perspective for the diagnosis and understanding of ARVC. An accurate and early diagnosis of ARVC is the clue for the prevention of sudden death associated with this disease, which is presently a challenge for clinicians, both in cardiology and in sport medicine. However we have to be cautious with the generalization of paper conclusions. The authors demonstrated high degree of sensitivity and specificity for this method in a very limited number of patients and mutations. In order to confirm these results, newest studies in larger series will be necessary. If these results are confirmed, this work could probably be considered not only the paper of the month, but the paper of the year.

References

1. Fontaine G, Guiraudon G, Frank R, Tereau Y, Fillette F, Marcus FI, Chomette G, Grosgogeat Y. Dysplasie ventriculaire droite arythmogene et maladie de Uhl. Arch Mal Coeur. 1982;75:361–375.

2. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med. 1988 Jan 21;318(3):129-33.

3. Furlanello F, Bertoldi A, Dallago M, Furlanello C, Fernando F, Inama G, et al. Cardiac arrest and sudden death in competitive athletes with arrhythmogenic right ventricular dysplasia. Pacing Clin Electrophysiol 1998;21:331-5.

4. Corrado D, Fontaine G, Marcus FI, McKenna WJ, Nava A, Thiene G, Wichter T. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: need for an international registry. European Society of Cardiology and the Scientific Council on Cardiomyopathies of the World Heart Federation. J Cardiovasc Electrophysiol. 2000 Jul;11(7):827-32.

5. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G, Camerini F. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. Br Heart J. 1994;71(3):215-8.
6. Angelini A, Basso C, Nava A, Thiene G. Endomyocardial biopsy in arrhythmogenic right ventricular cardiomyopathy. Am Heart J. 1996; 132:203–206.

7. Awad MM, Calkins H, Judge DP. Mechanisms of disease: molecular genetics of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Nat Clin Pract Cardiovasc Med. 2008 May;5(5):258-67.

8. Asimaki A, Tandri H, Huang H, Halushka MK, Gautam S, Basso C, Thiene G, Tsatsopoulou A, Protonotarios N, McKenna WJ, Calkins H, Saffitz JE. A new diagnostic test for arrhythmogenic right ventricular cardiomyopathy. N Engl J Med. 2009 Mar 12;360(11):1075-84.

9. Garcia-Gras E, Lombardi R, Giocondo MJ, Willerson JT, Schneider MD, Khoury DS, Marian AJ. Suppression of canonical Wnt/beta-catenin signaling by nuclear plakoglobin recapitulates phenotype of arrhythmogenic right ventricular cardiomyopathy. J Clin Invest. 2006 Jul;116(7):2012-21

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 F.I. Gambarin, A. Serio, M. Pasotti, L. Tavazzi*, E. Arbustini
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Familial hypertrophic cardiomyopathy: malignant and variable phenotypes. A "Two-step" case of the month.

Personal history:
The proband (IV:5) is a 38-year-old female who had the first diagnosis of hypertrophic cardiomyopathy at the age of 10 years. She has been asymptomatic for more than 20 years.

Arrhythmic phase of the disease
Few years after the diagnosis, she was given Verapamil therapy to prevent further worsening of the hypertrophy and development of symptoms. In September 2003 she suffered the first episode of atrial flutter that was successfully treated with external cardioversion. Further episodes of atrial fibrillation and flutter recurred in the following years all repeatedly treated with external cardioversion. Amiodarone treatment was started after one of the several arrhythmias episodes and withdrawn due to hyatrogenic hyperthyroidism. After atrial ablation in 2006 and an ICD implantation, the atrial flutter recurred in February 2007. Since then, the atrial arrhythmia was chronic.

Heart failure phase
The onset of mild dyspnoea on efforts and asthenia dates first month of 2007; in January 2008 the patient complained about thoracic pain: she underwent coronary angiography that showed normal coronary arteries.

She was first addressed to our Centre in June 2008. She was in functional NYHA class III-IV. We performed cardiologic evaluation, ECG registration, Holter monitoring, echocardiogram and genetic counselling and blood sample collection for molecular analysis.

CARDIOLOGIC VISIT:
Arrhythmic heart sounds, apical systolic murmur. Fine crepitations on pulmonary bases, bilaterally. Hepatomegaly. Absence of leg swelling; presence of jugular turgor.

ECG (**Figure 1 see next page**):
atrial flutter with variable conduction to ventricles; mean ventricular rate of 60 beats/min; normal QRS axis; absence of indices of myocardial hypertrophy (negative Cornell and Sokolow-Lyon criteria).

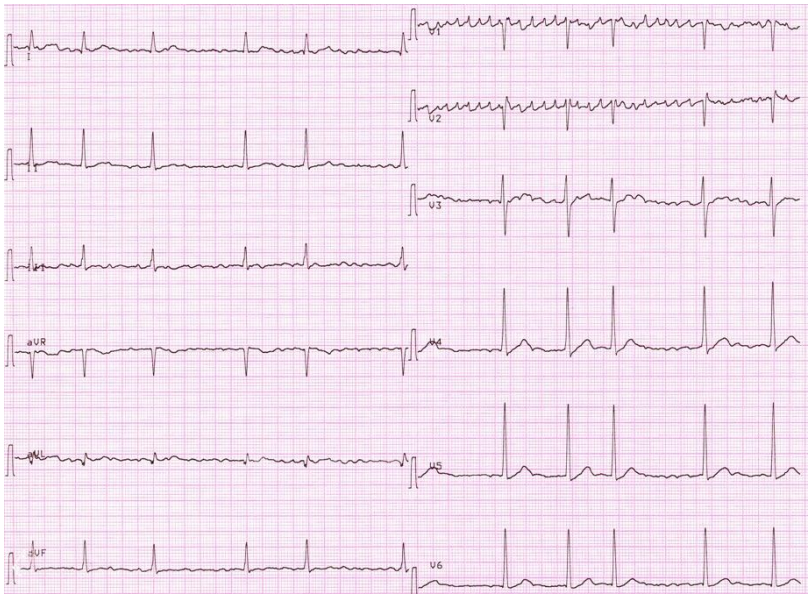

Figure 1. Atrial flutter with variable conduction to ventricles.

HOLTER MONITORING*:*
atrial fibrillation/flutter over the 24 hours of recording. Single recording of 13 consecutive beats of aberrant conduction to ventricles. Absence of pauses; few PM interventions. In the report the patient described dyspnoea and fatigue which corresponded to the recording of increased heart rate.

ECHOCARDIOGRAM (Figure 2):

- basal segments: interventricular septum thickness 10 mm; posterior wall 14 mm; inferior wall 15 mm;
- distal segments: inferior and posterior wall thickness, 26 mm;
- increased thickness of the right ventricular free wall;
- ejection fraction: 45-50%; decreased end-diastolic left ventricular volume (32 ml)
- biatral enlargement; presence of restrictive mitral inflow pattern (E/A 2,78, deceleration time 120 msec);
- Estimated pulmonary arterial pressure in systole: 35-40 mmHg;
- Hepatic veins and inferior vena cava: congested.

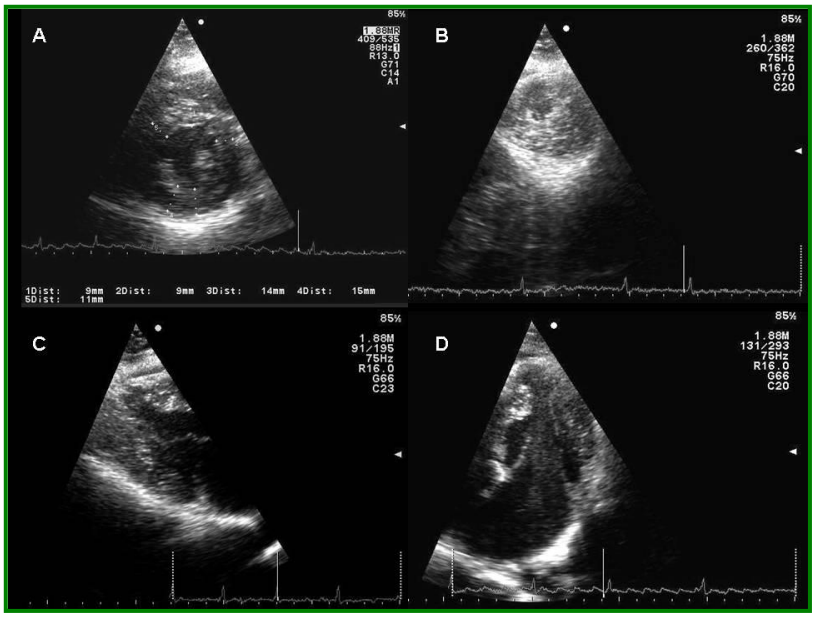

Figure 2.
Panel A and B: short axis views, basal and distal segments respectively. Worth noticing is the mild hypertrophy in the basal inferior and posterior segments, whereas in the apical segments the hypertrophy is much more evident. Panel C: long-axis view of the left ventricle. The severe hypertrophy of the posterior wall begins after the papillary muscles. Panel D: apical view showing the hypertrophy of distal segments and evidence of spontaneous *smoke* effect in the ventricle.

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BIOCHEMISTRY:

	Result:	Normal range:
- B-type Natriuretic Peptide	367 pg/ml	0-50
- Lactic Dehydrogenase	622 U/L	230-460
- Sodium	131 mEq/L	135-153
- Troponin I	0.123 ng/ml	0-0.04

Other biochemical parameters were normal (total serum CPK and CK-MB, creatinine, Lactic Acid, Myoglobin, haemochrome, C-reactive Proteine, ErytroSedimentation Rate).

The patient was admitted to the hospital August 2008 to optimize pharmacological treatment and to restore hemodynamics. She was put on the waiting list for heart transplantation. Heart transplantation was performed on 30th December 2008.

Family History and Screening (Figure 3):

The first step of the family screening study included the family nucleus from III:7 (within the blue line area. We traced medical records of the deceased maternal grand-mother (II:2), documenting that she was affected but reported data were descriptive only

The proband is the fourth offspring of non-consanguineous parents, with unaffected father and proven, affected mother. The proband (IV:5) is the fourth of six sibs. A younger brother died suddenly at the age of 28 years (IV:3); an older sister underwent heart transplantation for HCM at the age of 56 years (IV:2); one younger brother is affected by HCM (IV:7). Two sibs (IV:4, IV:6) are unaffected.

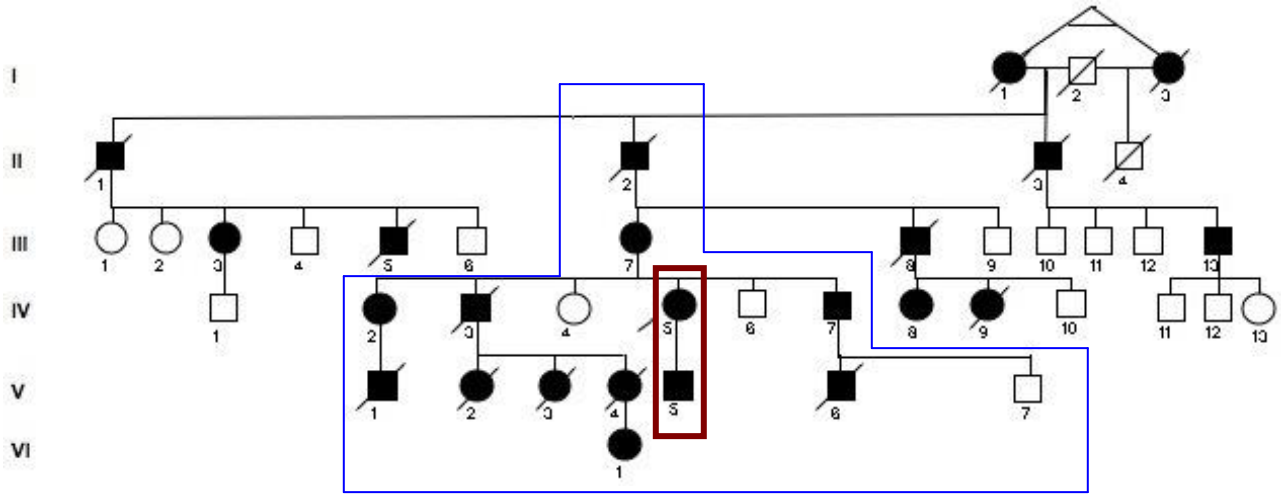


Figure 3. Family tree. The arrow indicates the proband.

□ ○ = **Healthy male and healthy female respectively**

■ ● = **Affected male and affected female respectively**

⊠ ⊘ = **Deceased male and deceased female respectively**

The proband is mother of a 9-year-old boy (V:5) who is affected by HCM (z score of the left ventricular wall thickness 4,05 with the exception of distal posterior wall that showed z score of 8,74) with normal mitral inflow pattern (**Figure 4**). The ECG of the boy (**Figure 5**) showed abnormal T waves (negative T waves in the inferior leads) but no left ventricular hypertrophy.

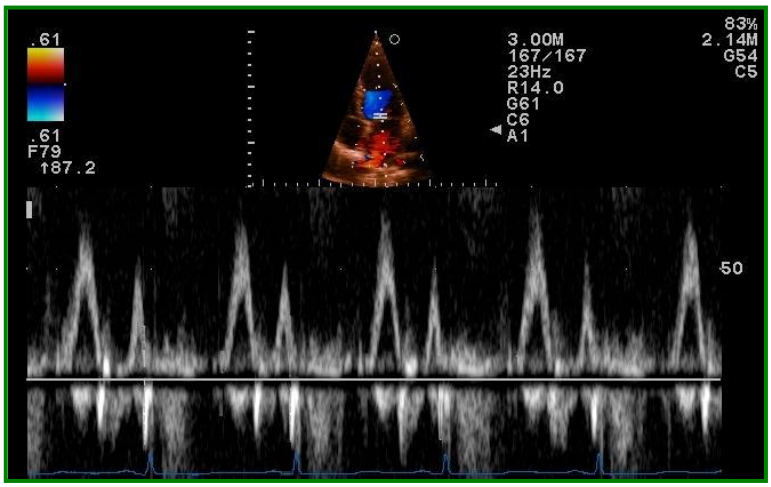


Figure 4.
Normal mitral inflow pattern in the 9-year-old boy (V:5) with hypertrophic cardiomyopathy.

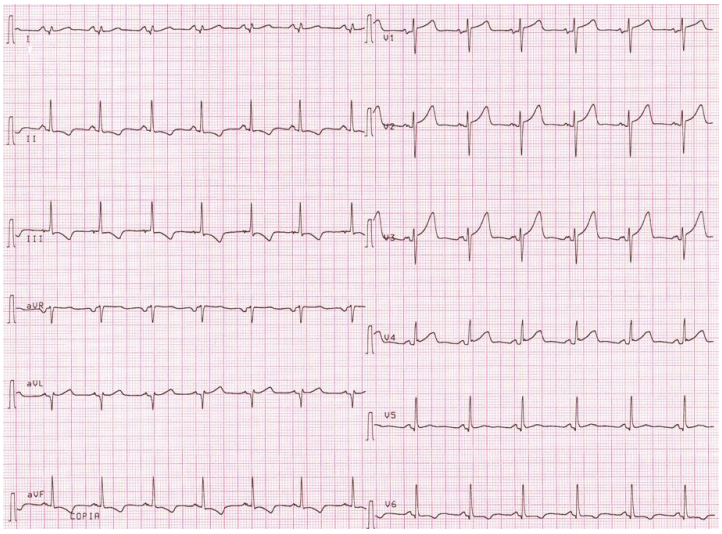


Figure 5.
Electrocardiographic examination of the 9-year-old son of the proband. No ECG criteria (Sokolow-Lyon and Cornell) for left ventricular hypertrophy. Negative T waves in inferior and lateral leads. Early repolarization on precordial leads (C2 to C4).

The whole family includes 41 relatives (excluding healthy siblings of healthy members), of which 23 are affected. Among affected relatives, 14 died prematurely: of these, 12 died suddenly (aged between 8 and 63 years), one died of heart failure at the age of 56 years and one woman died at childbirth at the age of 25. One patient underwent ICD implantation after syncope at the age of 16 years.

Questions:

1) ***Could you hypothesise what is the causative gene of the disease in this family or indicate genes that should be screened with priority??***
2) ***Figure 1: suppose you see this ECG without having the ECHO data: would you suspect an HCM? If yes, why?***

(The story of an additional family member will be provided next month along with the case resolution).

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

"A case of unusual heart failure"

by *Dr. Michael Arad*, Leviev Heart Institute and Heart Failure Service and *Dr. Izhar Hardan*, Multiple Myeloma Service, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, Israel

Diagnosis, case resolution and treatment

Free light chains were measured in serum to find LAMBDA Free Light Chain (FLC) level of 263 mg/l (normal 6-26) with reduced F-KAPPA/F-LAMBDA ratio, compatible with Plasma Cell Dyscrasia. Bone marrow biopsy revealed 10% CD-138 positive plasma cells.

The echocardiographic features comprising a hypertrophic, non-dilated left ventricle with severe diastolic dysfunction and rapidly progressive contractile failure are compatible with an infiltrative disease. In the light of the above, the late gadolinium enhancement (LGE) pattern demonstrated on MRI is highly suggestive of cardiac amyloidosis. A diagnosis of amyloidosis was therefore established and the patient was referred to chemotherapy.

The gold standard for diagnosing cardiac amyloidosis still requires a positive Congo Red stain from endomyocardial biopsy or from another tissue in the presence of compatible cardiac morphology and physiology (1,2).
Except for certain geographic regions, the most common type of cardiac amyloidosis is AL, caused by deposition and toxicity of the amyloid in the myocardium. The introduction of a serological test for FLC greatly enhanced the work-up of patients suspected to suffer from amyloidosis. The association with plasma cell dyscrasia: either primary amyloidosis (the majority) or multiple myeloma (the minority) is obvious. FLCs are elevated in 80-90% of patients with cardiac amyloidosis (3). FLC may not be detectable in a minority with a low-level secretion who suffer from a more indolent but still lethal disease. On the other hand, the mere presence of monoclonal immunoglobulin or light chain elevation cannot be accepted as diagnostic of amyloidosis because of it presence in up to 1% of normal elderly population.
Bone marrow, subcutaneous fat pad or rectal biopsy is the preferred mode of tissue diagnosis, in particular when systemic involvement is suspected. However, Congo Red staining itself is not without limitations. Because amyloid deposits may have a patchy distribution, in particular in the initial stage, Congo Red stain of endomyocardial biopsy may be negative due to a sampling error. It also may be negative in the Light Chain Deposition Disease, in particular type KAPPA, where FLCs do not create the classical β-sheet layers. Typical extra cellular fibrillar deposits can be detected by an electron microscopic examination even when Congo Red is negative, and therefore a sample in glutaraldehyde should be a routine part of endomyocardial biopsy (1).
Cardiac MRI is a relatively new technique where a distinct pattern of diffuse LGE is found in up to 80% of cardiac amyloidosis patients but is rather rare in other cardiomyopathies (4,5). We therefore believe that a combination of echo-doppler suggestive of infiltrative cardiomyopathy, monoclonal FLC elevation along with typical MRI findings may be diagnostic of amyloidosis even when Congo Red stain is negative/non-available. In our case we considered endomyocardial biopsy to be risky because of advanced conduction disease (see ECG) but were completely confident in the diagnosis established by non-invasive criteria.

A patient with cardiac amyloidosis and heart failure should be treated with Melphalane/Steroids or Bortezomib to suppress the light chain production (6,7). Lenalidomide is an option; Thalidomide is usually poorly tolerated by amyloidosis patients with cardiac involvement (8). High dose chemotherapy and autologous bone marrow transplantation is reserved for younger patients without severe cardiac involvement (wall thickness < 15mm, preserved systolic function, no heart failure and no 'low voltage' on ECG). Its long-term advantage over conventional chemotherapy remains to be demonstrated (6,9). The issue of cardiac transplantation is highly controversial, but this option might be considered in isolated cardiac amyloidosis with no other organ involvement and when FLC levels may be reduced to normal with therapy and/or ensuing bone marrow transplantation (10).

References

1. Falk RH. Diagnosis and management of the cardiac amyloidoses. Circulation 2005;112:2047-60.
2. Selvanayagam JB, Hawkins PN, Paul B, Myerson SG, Neubauer S. Evaluation and management of the cardiac amyloidosis. J Am Coll Cardiol. 2007;50:2101-10
3. Bochtler T, Hegenbart U, Heiss C, et al., Evaluation of the serum-free light chain test in untreated patients with AL amyloidosis. Haematologica. 2008;93:459-62.
4. Maceira AM, Joshi J, Prasad SK, et al. Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation. 2005;111:186-93
5. Vogelsberg H, Mahrholdt H, Deluigi CC, et al. Cardiovascular magnetic resonance in clinically suspected cardiac amyloidosis: noninvasive imaging compared to endomyocardial biopsy. J Am Coll Cardiol. 2008;51:1022-30.
6. Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med. 2007;357:1083-93.
7. Kastritis E, Anagnostopoulos A, Roussou M, et al., Treatment of light chain (AL) amyloidosis with the combination of bortezomib and dexamethasone. Haematologica. 2007;92:1351-8.
8. Dispenzieri A, Lacy MQ, Zeldenrust SR, et al. The activity of lenalidomide with or without dexamethasone in patients with primary systemic amyloidosis. Blood. 2007;109:465-70.
9. Kristen AV, Perz JB, Schonland SO, et al., Non-invasive predictors of survival in cardiac amyloidosis. Eur J Heart Fail. 2007;9:617-24.
10. Sack FU, Kristen A, Goldschmidt H, Schnabel PA, Dengler T, Koch A, Karck M. Treatment options for severe cardiac amyloidosis: heart transplantation combined with chemotherapy and stem cell transplantation for patients with AL-amyloidosis and heart and liver transplantation for patients with ATTR-amyloidosis. Eur J Cardiothorac Surg. 2008;33:257-62.

Second Announcement

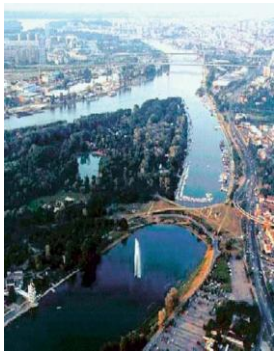
EUROPEAN SOCIETY OF CARDIOLOGY®

EUROPEAN CONFERENCE ON MYOCARDIAL AND PERICARDIAL DISEASE

The first 50 years of cardiomyopathies

October 9-10, 2009,
Serbian Academy of Sciences and Arts
Belgrade, Serbia





Annual Conference of the Working Group on Myocardial and Pericardial Diseases of the European Society of Cardiology

ORGANIZED IN COLLABORATION WITH

The Cardiology Society of Serbia

The Cardiology Section Serbian Medical Society

The Serbian Academy of Sciences and Arts

UNIVERSITY OF BELGRADE SCHOOL OF MEDICINE

On behalf of the Organizing Committee and the nucleus of the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases (WG21), it is our pleasure to cordially invite you to take part in the European Conference on Myocardial and Pericardial Diseases: The first 50 years of cardiomyopathies **that will be held in** Belgrade, Serbia, on October 9-10, 2009. **The Conference will be focused on inflammatory and viral heart disease, inherited heart muscle diseases, and pericardial diseases, with a special focus on the anniversary of 50 years of cardiomyopathies (preliminary program of the Conference can be downloaded from www.escardio.org). Six best abstracts of authors less than 40 years of age will be selected for oral presentations in the YOUNG INVESTIGATORS AWARD SESSION. The best contribution will be awarded with a diploma and participation at the Annual Conference of the ESC WG on Myocardial and Pericardial Diseases in 2010. Deadline for abstract submission (up to 250 words) is September 10, 2009. Abstracts should be sent as e-mail attachments to arsen.ristic@med.bg.ac.yu.**

Belgrade is one of the most exciting, rapidly developing European capitals, famous for its natural beauties, cultural events, and friendly, relaxed atmosphere. We are therefore looking forward to cordially welcoming you in Serbia in October 2009, hoping that we will have a very interesting and successful Conference.

PETAR M. SEFEROVIĆ
ARSEN D. RISTIĆ