



# European Society of Cardiology Working Group on Myocardial & Pericardial Diseases

## Newsletter

Issue 16 - September 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' August
- 5** Recommendation for 'further reading'

Dear Members of the Working Group,

please find enclosed the 16<sup>th</sup> 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 august 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. Paukovt*

## The paper of the month:

**Titel: Circulating transforming growth factor- $\beta$  in Marfan syndrome. *Circulation*. 2009; 120: 526–532.** Matt P, Schoenhoff F, Habashi J, Holm T, Van Erp C, Loch D, Carlson OD, Griswold BF, Fu Q, De Backer J, Loeys B, Huso D, McDonnell NB, Van Eyk JE, Dietz HC; GenTAC consortium.

**Presented by** Andre Keren MD, Professor of Medicine (Cardiology), Department of Cardiology, Heart Failure and Heart Muscle Disease Center, Hadassah-Hebrew University Hospital, Jerusalem, Israel



**Background:** Marfan syndrome (MFS) is a genetic disorder transmitted by an autosomal dominant trait which affects the connective tissue leading to the well known cardiovascular, musculoskeletal, ocular and pulmonary manifestations of the disease. The pioneer work of Dietz H et al (1) revealed that the disease is caused by mutations in the *FBNI* gene which encodes fibrillin-1, an important component of the extracellular matrix. The original thought was that the pathogenetic mechanism of MFS can be explained solely by the structural abnormality of fibrillin-1. This belief was challenged by the same group of researchers who found initially in the mouse model of MFS (2) that fibrillin-1 has not only a structural role but interacts and regulates the transforming growth factor beta (TGFB) signaling which has recognized effects on cellular differentiation and proliferation. In the mouse model of MFS, the blunting of excessive TGFB by administration of neutralizing antibodies significantly reduced TGFB activity and either abolished or improved the pulmonary, valvular, aortic and other systemic manifestations of the disease (3-5). Moreover, administration in pediatric patients with MFS of angiotensin II type 1 receptor blockers known to decrease TGFB signaling, decreased aortic root dilatation (6).

**Summary:** In their recent publication, Matt P et al (7) probed a new frontier of the association of TGFB with MFS by evaluating both in the mouse model and in patients the hypothesis that the upregulation of TGFB in MFS might be reflected in *elevated circulating TGFB concentrations*. They also correlated the levels of circulating TGFB with the aortic root size and measured TGFB levels following the administration of Losartan, ACE inhibitors and beta blockers.

In the mouse model there was a significant age related increase in the circulating TGFB levels in the affected compared with the wild type mice. Administration of Losartan to the affected mice decreased significantly circulating TGFB, to control levels. In addition, a good correlation was found between the circulating TGFB levels and the size of the aortic root in treated and untreated animals. In humans, compared with 74 controls without MFS, the level of circulating TGFB level was significantly higher in the 53 untreated and also in the 144 treated patients with MFS. Patients with MFS who received therapy with Losartan, beta blockers or their combination had significantly lower circulating TGFB levels than untreated patients. In contrast with findings in the mouse model however, circulating TGFB levels remained elevated beyond control levels following therapy, and TGFB levels did not correlate with aortic root diameter. This lack of correlation can be perhaps explained by the fact that most patients with MFS in the study had relatively mild disease, by possible variability in circulating TGFB levels which can be influenced by unknown factors and by limitations of a snapshot examination as compared with serial follow up evaluations.

In this regard, Akimastos A et al (8) just reported a moderately strong correlation between plasma TGF $\beta$  as well as matrix metalloproteinase (MMP) levels and changes in aortic root diameters during 24 weeks follow up of 17 patients with MFS on standard beta blocker therapy randomized to receive either the ACE inhibitor Perindopril or placebo. Compared to placebo, Perindopril significantly reduced TGF $\beta$  and MMP levels (8).

Thus, currently available data are very encouraging, but clinical prospective studies will have to answer the important question whether we are going to cross the threshold of a clinically applicable biomarker for monitoring disease severity, progression and response to therapy in MFS. The potential usefulness of such a modality in management of patients with MFS and preventing complications like aortic dissection can not be overemphasized.

#### References

1. Dietz HC, Cutting GR, Pyeritz RE, Maslen CL, Sakai LY, Corson CM, Puffenberger EG, Hamosh A, Nanthakumar EJ, Curristin SM, Stetten G, Meyers DA, Francamano CA. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. *Nature*. 1991; 352: 337–339.
2. Dietz HC, Mecham RP. Mouse models of genetic disease resulting from mutations in elastic fiber proteins. *Matrix Biol*. 2000;19:481-488.
3. Neptune ER, Frischmeyer PA, Arking DE, Myers L, Bunton TE, Gayraud B, Ramirez F, Sakai LY, Dietz HC. Dysregulation of TGF-beta activation contributes to pathogenesis in Marfan syndrome. *Nat Genet*. 2003; 33: 407–411.
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5. Habashi JP, Judge DP, Holm TM, Cohn RD, Loeys BL, Cooper TK, Myers L, Klein EC, Liu G, Calvi C, Podowski M, Neptune ER, Halushka MK, Bedja D, Gabrielson K, Rifkin DB, Carta L, Ramirez F, Huso DL, Dietz HC. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science*. 2006; 312: 117–121.
6. Brooke BS, Habashi JP, Judge DP, Patel N, Loeys B, Dietz HC III. Angiotensin II blockade and aortic-root dilation in Marfan's syndrome. *N Engl J Med*. 2008; 358: 2787–2795.
7. Matt P, Schoenhoff F, Habashi J, Holm T, Van Erp C, Loch D, Carlson OD, Griswold BF, Fu Q, De Backer J, Loeys B, Huso D, McDonnell NB, Van Eyk JE, Dietz HC; GenTAC consortium. Circulating transforming growth factor- $\beta$  in Marfan syndrome. *Circulation*. 2009; 120: 526–532.
8. Akimastos AA, Aggarwal A, Savarirayan R, Dart AM, Kingwell BA. A role for plasma transforming growth factor and matrix metalloproteinases in aortic aneurysm surveillance in Marfan syndrome? *Atherosclerosis*, in press [epub ahead of print, August 8, 2009], doi:10.1016/j.atherosclerosis.2009.08.003

## The clinical case of the month: *What is your diagnosis?*

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

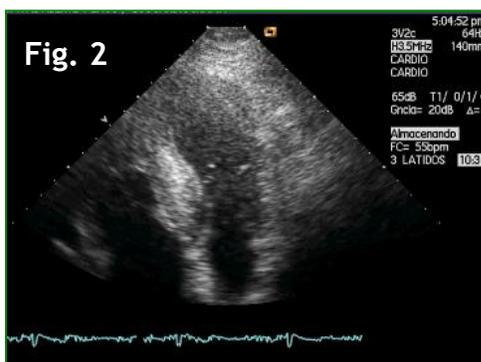
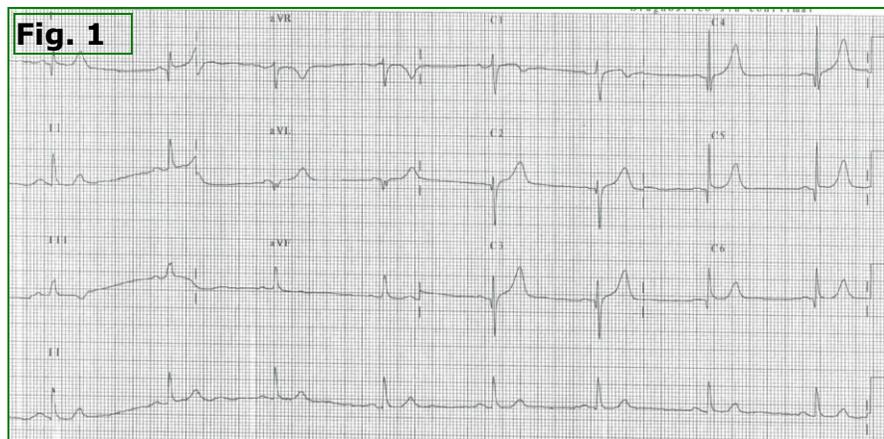
**Presented by Dr. Martín Ortiz.** Fundación Carolina/BBVA. Cardiology Service. Instituto de Investigación Biomédica A Coruña. A Coruña. Spain. **Dr. Roberto Barriales-Villa.** Cardiology Service. Instituto de Investigación Biomédica A Coruña. A Coruña. Spain. **Dr. Lorenzo Monserrat.** Cardiology Service. Instituto de Investigación Biomédica A Coruña. A Coruña. Spain.



### Different phenotypes in the same family: how genetic studies can help us

#### Case Presentation:

A 50 year old man was admitted due to atypical chest pain not effort related, beginning four days before. He did not have coronary risk factors. Mild systolic murmur was heard on physical examination. ECG showed sinus rhythm, pathologic Q waves in DI, aVL and V3 to V6, with normal repolarisation pattern (fig. 1). Coronary angiography was normal. His echocardiogram showed asymmetrical septal hypertrophy (maximum 17 mm at basal and medium septum), elongated mitral leaflets and cordal system without SAM; left ventricular ejection fraction was normal and pseudonormal pattern was present on diastolic function assessment (Fig. 2). Cardiac MRI confirmed hypertrophic cardiomyopathy diagnosis, showing maximum wall thickness of 19 mm at basal infero-septal segment (Fig. 3).



Stress test and 24-hour Holter ECG were normal. He was treated with beta-blockers and remained asymptomatic. After informed consent, blood sample was taken for genetic test. A heterozygous frameshift mutation was detected in myosin binding protein C gene (MYBPC3): K600fs, Del A 12413. This mutation has been previously associated with hypertrophic cardiomyopathy. It was detected in only one patient from a French cohort of 197 unrelated index cases. Authors did not provide familial data. Mutated residue was conserved among species and isoforms. Moreover, this genetic variant was absent in 100 healthy adult controls<sup>1</sup>.

Clinical and genetic screening was performed on first degree relatives. (Fig. 4. Pedigree)

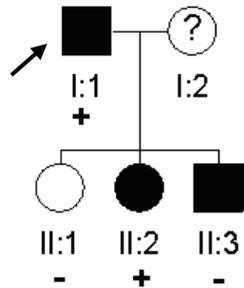
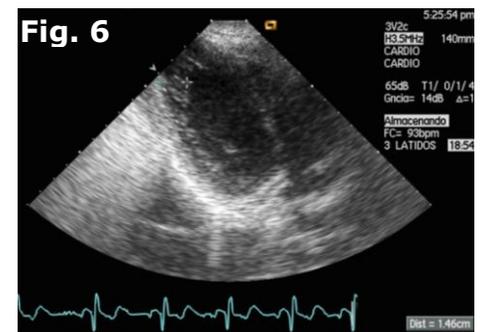
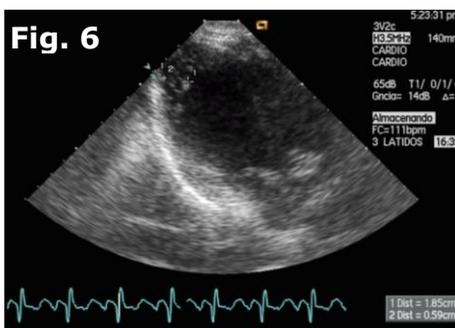
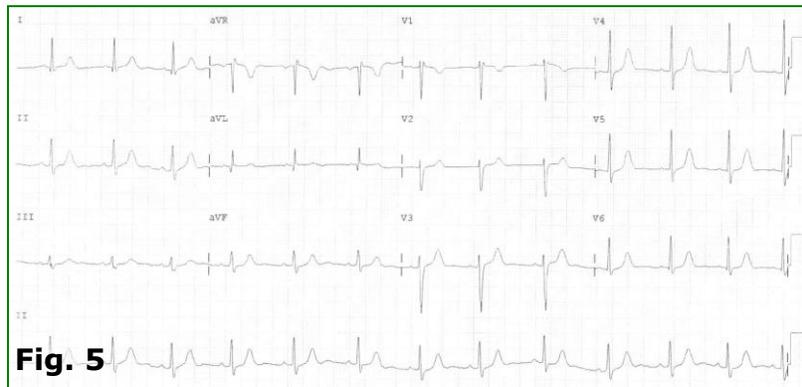
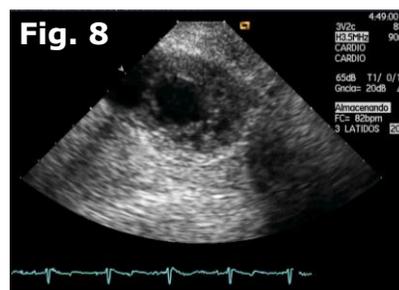
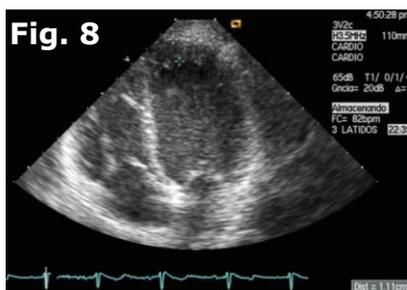
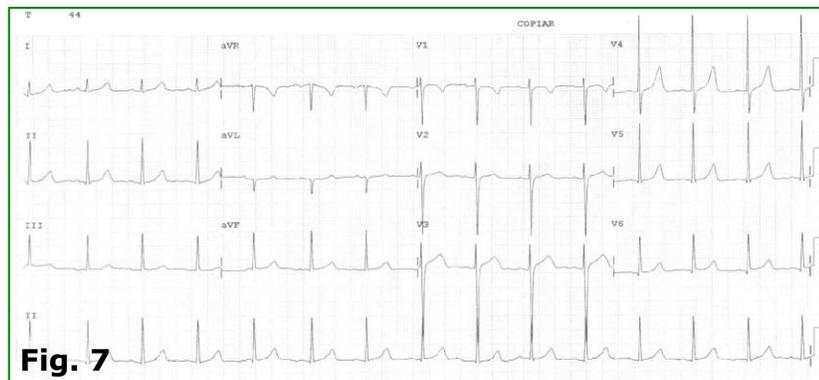


Fig. 4. Black symbols: phenotypic affected subject. White symbols: healthy subjects. ?: subject without clinical and genetic study. +: mutation carrier. -: no mutation carrier. Arrow indicates index case.

His 15 year old daughter (subject II:2) had a normal ECG (Fig. 5) and her echocardiogram showed apical and posterior hypertrabeculation areas that met left ventricular non compaction cardiomyopathy criteria (Fig. 6). Genetic analysis demonstrated that she was also K600fs mutation carrier.



Then we examined the other two siblings. Ten year old son (II:3) had left ventricular hypertrophy criteria on ECG (Fig. 7) and his echocardiogram showed apical and posterior hypertrabeculation areas too (Fig. 8). However he was not carrier of K600fs mutation. Twenty-four year old daughter neither was genetically affected, her echocardiogram was normal and ECG was suggestive but not diagnostic of left ventricular hypertrophy (Fig. 9).



Question with regard to this case:

1. What is your interpretation about K600fs mutation behaviour in this family? Is K600fs mutation the real genetic cause of the disease?
2. Could K600fs mutation have a heterogeneous phenotypic manifestation in the two carriers?
3. Apparently, this mutation does not cosegregate in some family members. Could genetic test have a false negative result in the clinically affected son?
4. What would be your next attitude?

#### Reference

Richard P, Charron P, Carrier L, Ledeuil C, Cheav T, Pichereau C, et al. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. *Circulation* 2003;107:2227-2232

**Answer for the previous “Clinical case of the month” presented in the august newsletter**

**“Familial hypertrophic cardiomyopathy: malignant and variable phenotypes. Second step and resolution of the case of the month”**

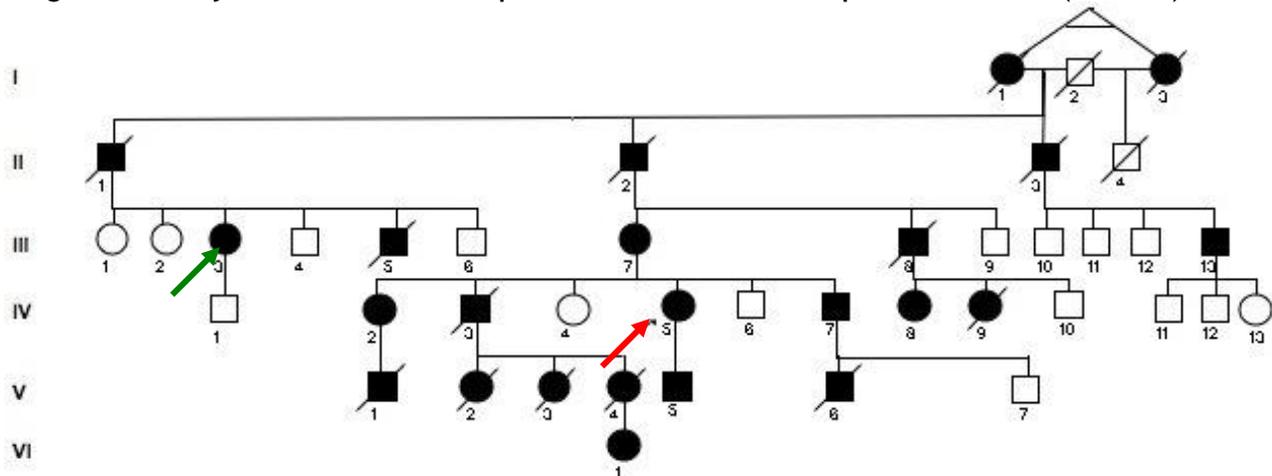
by **F.I. Gambarin, A. Serio, M. Pasotti, L. Tavazzi\*, E. Arbustini**, Centre for Inherited Cardiovascular Diseases, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, \*Research Unit, GVM Care and Research, Cotignola, Italy

(This material is original; it has not previously published and is part of a research on Hypertrophic Cardiomyopathies supported by funds from Cariplo Foundation and Health Ministry granted to EA).

**Further family investigation:**

The maternal cousin (relative III:3) of the proband (IV:5) was contributory for the final diagnosis (Figure 1, green arrow).

Figure 1. Family tree. Red arrow: the proband. Green arrow: the proband’s cousin (see text)



This patient came to our attention at the age of 56 years with the following history and clinical records:

- RCM diagnosis – age: 46 years;
- atrial flutter – age: 47 years
- ICD implantation – age 48 years (no appropriate ICD interventions documented during a 10-year follow-up).

*Serial echocardiography studies (up to 2008): normal wall thickness (septum, z score -1.0 to 0,75), biatrial dilation, restrictive LV filling pattern.*

On more recent examinations:

Severe intraventricular and intra-atrial spontaneous smoke (low flow due to the increased ventricular filling pressures) (Figure 2).

**Symptoms**

In the last two years she complained frequent episodes of congestive heart failure with hepatomegaly, pleural effusion, peritoneal effusion mild leg oedema.

### Endomyocardial biopsy (EMB)

Interstitial and perivascular fibrosis; myocyte disarray; both normal and hypertrophic cardiomyocytes.

The patient underwent heart transplantation at the age of 57 years.

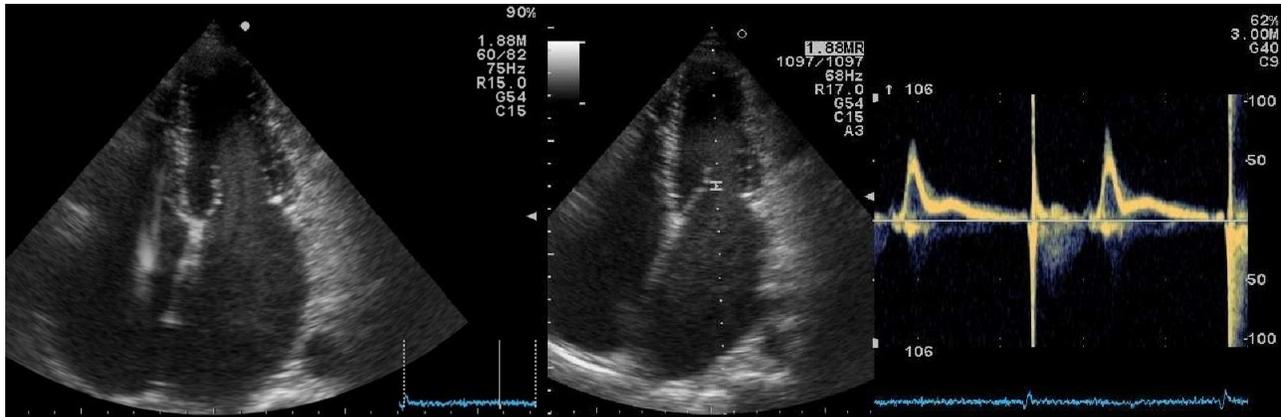


Figure 2. Panel A: evidence of spontaneous intra-cardiac smoke in restrictive cardiomyopathy pattern (biatrial dilation, normal ventricular chamber size, normal ventricular wall thickness). Panel B: Pulsed Wave Doppler shows restrictive mitral inflow pattern.

### Considerations on the genetic basis of RCM

Restrictive cardiomyopathy is a rare cardiomyopathy clinically characterized by impaired relaxation and abnormal left ventricular filling, dilation of both atria and absence of significant left ventricular hypertrophy [1-3]. The genetic basis of primary restrictive cardiomyopathy includes mutations of the following genes: *alpha cardiac actin* [4], *desmin* [5,6] *Troponin I* [3,4] and *Troponin T* [4,7].

### Results of genetic testing

The molecular analysis identified the p.Leu144Gln mutation of the *Troponin I* gene in the proband, her son, and the cousin who also underwent heart transplantation. The extension of genetic testing to live patients of the family confirmed the segregation of the mutation with the phenotype. Other sarcomeric genes tested negative.

### TNNI3-associated phenotypes

*TNNI3* patients may show pure RCM and HCM with or without restrictive pattern. Different phenotypes may coexist in the same family [4,8,9]. In the present family, as in other families observed in our centre with *TNNI3*-related cardiomyopathy, only the presence of a pure RCM without conduction disease in at least one member of the family seems to predict mutations of this gene. Differential clinical diagnosis includes pure restrictive phenotype caused by mutations of the *Desmin* gene, which are however characterized by the presence of atrioventricular block preceding the onset of restrictive haemodynamics and in some case, of clinically overt myopathy or increased sCPK. [6].

### Conclusion:

Although genetic testing was performed only in living members of the family, the clinical records of deceased relatives documented HCM or SD due to cardiomyopathy. The phenotypes associated with *Troponin I* gene defects (RCM, HCM with or without restriction pattern) seem to

be rather malignant as shown by the family history: 12 affected relatives died suddenly, one patient underwent ICD implantation and three underwent heart transplantation.

Three phenotypes may coexist in families with cardiomyopathy caused by *Troponin I* gene mutations:

1. hypertrophic cardiomyopathy with impaired diastolic filling without evolution through restrictive haemodynamics over 10 years (the impairment of diastolic function could appear later on in the course of the natural history of the disease);
2. hypertrophic cardiomyopathy with restrictive haemodynamics;
3. pure restrictive phenotype with normal wall thickness, severe biatrial enlargement, normal ventricular dimension, restrictive mitral inflow pattern.

### References

1. Elliott P, Andersson B, Arbustini E, *et al.* Classification of the cardiomyopathies: a position statement from the European society of cardiology working group on myocardial and pericardial diseases. *Eur Heart J* 2008;29:270-6
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4. Kaski JP, Syrris P, Burch M, *et al.* Idiopathic Restrictive Cardiomyopathy in Children is Caused by Mutations in Cardiac Sarcomere Protein Genes. *Heart*. 2008 *in press* (PMID: 18467357)
5. Arbustini E, Morbini P, Grasso M, *et al.* Restrictive cardiomyopathy, atrioventricular block and mild to subclinical myopathy in patients with desmin-immunoreactive material deposits. *J Am Coll Cardiol*. 1998;31:645-53
6. Arbustini E, Pasotti M, Pilotto A, *et al.* Desmin accumulation restrictive cardiomyopathy and atrioventricular block associated with desmin gene defects. *Eur J Heart Fail*. 2006;8:477-83
7. Menon S, Michels V, Pellikka P, *et al.* Cardiac troponin T mutation in familial cardiomyopathy with variable remodeling and restrictive physiology. *Clin Genet*. 2008 *in press* (PMID: 18651846)
8. Mogensen J, Kubo T, Duque M, *et al.* Idiopathic restrictive cardiomyopathy is part of the clinical expression of cardiac troponin I mutations. *J Clin Invest*. 2003;111:209-16. Erratum in: *J Clin Invest*. 2003;111:925
9. Mogensen J, Arbustini E. Restrictive cardiomyopathy. *Curr Opin Cardiol*. 2009;24:214-20.

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

- 1) Left ventricular remodelling and torsional dynamics in dilated cardiomyopathy: reversed apical rotation as a marker of disease severity.  
Popescu BA, Beladan CC, Calin A, Muraru D, Deleanu D, Rosca M, Gingham C.  
Eur J Heart Fail. 2009 Oct;11(10):945-51
- 2) Severe Hypertrophic Cardiomyopathy in an Infant with a Novel PRKAG2 Gene Mutation: Potential Differences Between Infantile and Adult Onset Presentation.  
Kelly BP, Russell MW, Hennessy JR, Ensing GJ.  
Pediatr Cardiol. 2009 Sep 29. [Epub ahead of print]
- 3) Clinical profile and predictors of complications in peripartum cardiomyopathy.  
Goland S, Modi K, Bitar F, Janmohamed M, Mirocha JM, Czer LS, Illum S, Hatamizadeh P, Elkayam U.  
J Card Fail. 2009 Oct;15(8):645-50. Epub 2009 Jul 16.
- 4) Activating autoantibodies to the beta-1 adrenergic and m2 muscarinic receptors facilitate atrial fibrillation in patients with Graves' hyperthyroidism.  
Stavrakis S, Yu X, Patterson E, Huang S, Hamlett SR, Chalmers L, Pappy R, Cunningham MW, Morshed SA, Davies TF, Lazzara R, Kem DC.  
J Am Coll Cardiol. 2009 Sep 29;54(14):1309-16.
- 5) Myeloid Differentiation Factor-88/Interleukin-1 Signaling Controls Cardiac Fibrosis and Heart Failure Progression in Inflammatory Dilated Cardiomyopathy.  
Blyszczuk P, Kania G, Dieterle T, Marty RR, Valaperti A, Berthonneche C, Pedrazzini T, Berger CT, Dirnhofer S, Matter CM, Penninger JM, Lüscher TF, Eriksson U.  
Circ Res. 2009 Sep 17. [Epub ahead of print]
- 6) Humoral anti-proteasomal autoimmunity in dilated cardiomyopathy.  
Voigt A, Bartel K, Egerer K, Trimpert C, Feist E, Gericke C, Kandolf R, Klingel K, Kuckelkorn U, Stangl K, Felix SB, Baumann G, Kloetzel PM, Staudt A.  
Basic Res Cardiol. 2009 Sep 17. [Epub ahead of print]
- 7) Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types.  
Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, Salvi F, Ciliberti P, Pastorelli F, Biagini E, Coccolo F, Cooke RM, Bacchi-Reggiani L, Sangiorgi D, Ferlini A, Cavo M, Zamagni E, Fonte ML, Palladini G, Salinaro F, Musca F, Obici L, Branzi A, Perlini S.  
Circulation. 2009 Sep 29;120(13):1203-12. Epub 2009 Sep 14