European Society of Cardiology
Working Group on
Myocardial & Pericardial Diseases

Newsletter

Issue 24 – May 2010

Editorial News

INSIDE THIS ISSUE:

Dear Members of the Working Group,

Please find enclosed the 24th issue of our Newsletter.

You may remember that 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 as the **the deadline for study Group submissions is extended to June 20th**

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 April case.

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

Best wishes for all of you.

S. Pankuweit

The paper of the month:

Clinical Features and Outcome of Hypertrophic Cardiomyopathy Associated With Triple Sarcomere Protein Gene Mutations

Francesca Girolami, BS, Carolyn Y. Ho, MD, Christopher Semsarian, MBBS, PHD, Massimo Baldi, MD, Melissa L. Will, BS, Katia Baldini, RN, Francesca Torricelli, BS, Laura Yeates, BSC, Franco Cecchi, MD, Michael J. Ackerman, MD, PHD, Iacopo Olivotto, MD† Florence, Italy; Boston, Massachusetts; Sydney, Australia; and Rochester, Minnesota. J Am Coll Cardiol. 2010;55:1444-53

Presented by **Elena Biagini, Massimiliano Lorenzini, Claudio Rapezzi**. Institute of Cardiology, University of Bologna, Italy

Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by unexplained left ventricular hypertrophy (LVH) that develops in the absence of predisposing cardiac conditions. More than 900 individual mutations of 12 genes (see Table 1) have so far been identified [Genomics of Cardiovascular Development, Adaptation, and Remodeling]. The clinical manifestations of HCM range from asymptomatic to progressive heart failure and vary even between individuals within the same family. So far, broad genotype-phenotype correlations have been attempted. Although in some cases the age of onset of hypertrophy may be associated with the underlying gene mutation, caution must be used in applying these generalizations to specific individuals and families as numerous exceptions have been noted (described). There are many other examples of rough genotype-phenotype correlations. MYH7 mutations have been associated with disease onset in the second decade of life; MYH7 mutation NP_000248.2:p.Arg403Gln (also known as NM_000257.2:c.1208G>A.) has been associated with an increased risk of sudden death; MYBPC mutations have been associated with a later onset, in the fourth or fifth decade of life (1); TNNT2 mutations have been associated with mild LVH and increased risk of sudden death in some families (2, 3). However, at present no strong and definite genotype-phenotype correlations, that may be used in directing the approach to genetic testing, have been found.

The long-standing paradigm has been that a single mutation in a single gene leads to familial HCM, hence the reference to familial HCM as a "monogenic" disorder, until recently when various authors described families with familial HCM in whom 2 disease-causing mutations had been identified (4, 5). The paper by Girolami et al. (6) taps in to this vein of research.

Summary of the paper

Girolami et al. (6) studied a total of 488 unrelated index HCM patients who underwent screening for myofilament gene mutations by direct deoxyribonucleic acid sequencing of 8 genes, including myosin binding protein C (MYBPC3), beta-myosin heavy chain (MYH7), regulatory and essential light chains (MYL2, MYL3), troponin-T (TNNT2), troponin-I (TNNI3), alphatropomyosin (TPM1), and actin (ACTC).

Of the 488 index patients, 4 (0.8%) harbored triple mutations, as follows: MYH7-R869H, MYBPC3-E258K and TNNI3-A86fs in a 32-year-old woman; MYH7-R723C, MYH7-E1455X and MYBPC3-E165D in a 46-year old man; MYH7-R869H, MYBPC3-K1065fs and MYBPC3-P371R in a 45-year old woman; and MYH7-R1079Q, MYBPC3- Q969X and MYBPC3-R668H in a 50-year old woman.

Table 1. Molecular Genetics of Hypertrophic Cardiomyopathy (HCM)

Locus Name	Gene Symbol	Protein Name	% of HCM Caused by Mutations in This Gene	Allelic Disorders [1]
CMH1	*MYH7*	Myosin heavy chain, cardiac muscle beta isoform	40%	DCM[2], Laing distal myopathy
CMH4	*MYBPC3*	Myosin-binding protein C, cardiac-type	40%	DCM
CMH2	*TNNT2*	Troponin T, cardiac muscle	5%	DCM
CMH7	*TNNI3*	Troponin I, cardiac muscle	5%	DCM, restrictive cardiomyopathy
CMH3	*TPM1*	Tropomyosin 1 alpha chain	2%	DCM
CMH10	*MYL2*	Myosin regulatory light chain 2, ventricular/cardiac muscle isoform	Unknown	
CMH8	*MYL3*	Myosin light polypeptide 3	1%	
	ACTC1	Actin, alpha cardiac muscle 1	Unknown	DCM
	CSRP3	Cysteine and glycine-rich protein 3, muscle LIM protein	Unknown	
CMH9	*TTN*	Titin		DCM, Udd distal myopathy
	MYH6	Myosin heavy chain, cardiac muscle alpha isoform		DCM
	TCAP	Telothonin		LGMD2G [3], DCM
Other genes implicated in HCM [4]				
	TNNC1	Troponin C, slow skeletal and cardiac muscles	Unknown	DCM

1. Allelic disorders = other phenotypes caused by mutation in the same gene
2. DCM = dilated cardiomyopathy
3. LGMD = limb-girdle muscular dystrophy
4. The consensus of the GeneReview authors is that additional confirmatory data supporting pathogenicity for this gene is necessary.

Modified from: Cirino AL, Ho C. Familial Hypertrophic Cardiomyopathy Overview. 2008 Aug 5 [updated 2009 May 26]. In: Pagon RA, Bird TC, Dolan CR, Stephens K, editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle

One patient had a history of resuscitated cardiac arrest, and 3 had significant risk factors for sudden cardiac death, prompting the insertion of an implantable cardioverter-defibrillator in all 4, with appropriate shocks in 2 patients. Moreover, 3 of the 4 patients presented a severe phenotype with progression to end-stage HCM by the fourth decade requiring cardiac transplantation (n = 1) or biventricular pacing (n = 2). The fourth patient, however, presented a clinically mild disease.
The authors concluded that HCM caused by triple sarcomere gene mutations was rare but conferred a remarkably increased risk of end-stage progression and ventricular arrhythmias, supporting an association between multiple sarcomere defects and adverse outcome. Comprehensive genetic testing might provide important insights to risk stratification and potentially indicate the need for differential surveillance strategies based on genotype.

Comment
These results strengthen previous observations and are a stimulus for further research in this direction. Multiple mutations have been found to occur in either the same gene (compound heterozygotes) or in different genes (double heterozygotes) in up to 5% of families with familial HCM. Importantly, individuals who carry 2 disease-causing familial HCM mutations have a more severe disease, including earlier onset, more severe left ventricular hypertrophy and heart failure and a higher rate of sudden death events (resuscitated cardiac arrest or sudden death). These preliminary observations suggest that the number of genes identified in an individual patient with familial HCM may be an important determinant of phenotype severity and clinical outcome of the disease. Tsoutsman et al. (7) developed, characterized and investigated the pathogenic mechanisms of double mutations in a double-mutant murine model of familial HCM. The mortality rate in TnI-203/MHC-403 mice was 100% by age 21 days. At age 14 days, TnI-203/MHC-403 mice developed a significantly increased of heart weight to body weight ratio, marked interstitial myocardial fibrosis, and increased expression of atrial natriuretic factor and brain natriuretic peptide compared to nontransgenic, TnI-203 and MHC-403 littermates. By age 16 to 18 days, TnI-203/MHC-403 mice rapidly developed a severe dilated cardiomyopathy and heart failure, with inducibility of ventricular arrhythmias, which led to death by the age of 21 days. The authors concluded that TnI-203/MHC-403 double-mutant mice developed a severe cardiac phenotype characterized by heart failure and early death.

It is noteworthy that 3 of the 4 patients (75%) with triple mutations in Girolami's series developed an end-stage phenotype with severe LV dysfunction. These 3 patients had originally presented with severe LV hypertrophy by the age of 25. In the next 10 to 20 years however, they developed marked cardiac remodelling characterized by restrictive physiology, atrial dilation, and systolic dysfunction associated with progressive LV wall thinning and fibrosis; 1 patient required cardiac transplantation. By comparison, only 29 of 488 patients or 6% of the overall genotyped population with HCM seen at the same centre developed end-stage disease, with a similar prevalence to that in other reports. This suggests that triple mutations confer a 14-fold increase in risk of developing end-stage disease. Furthermore, all 4 probands with triple mutations had significant ventricular arrhythmias, prompting the implantation of a defibrillator for primary or secondary prevention of sudden cardiac death. Notably, 1 patient had been resuscitated from cardiac arrest, and another received multiple appropriate interventions after ICD implantation. Overall, the clinical course of HCM patients with triple mutations strongly supports the concept that multiple sarcomere defects might be associated with a more severe clinical phenotype and disease course.

A plausible explanation of the adverse consequences of complex genotypes is that multiple abnormal myofilament proteins might result in more profound derangement of sarcomere mechanics, myocardial energetics, and cardiomyocyte dysfunction. In addition, as the authors remark, to other pathophysiological mechanisms that might intervene, such as greater impairment of microvascular function due to adverse remodeling of the coronary arterioles, leading to recurrent myocardial ischemia and replacement fibrosis. Two of the patients reported with triple mutations had evidence of severe microvascular dysfunction and blunted myocardial perfusion preceding the development of LV wall thinning and systolic dysfunction, which is consistent with this hypothesis.
The TNNI3-203/MHC-403 double-mutant mouse model recently reported by Tsoutsman et al. (7), buttresses the concept of a gene dosage effect resulting in more severe clinical phenotypes. In this model, although each mutation by itself was linked to a hypertrophic phenotype, the presence of both mutations rapidly led to LV dilation, severe heart failure, and premature death. Additionally, downregulation of mRNA levels of key regulators of Ca^2 homeostasis in TnI-203/MHC-403 mice was observed. Increased levels of phosphorylated STAT3 were observed in TnI-203/MHC-403 mice and corresponded with the onset of disease, which suggests a possible cardioprotective response.

Mutations in sarcomeric genes lead to activation of intracellular signaling mechanisms, cardiac remodeling, and changes in contractile function. Signaling through the latent transcription factor signal transducer and activator of transcription (STAT) 3 has been implicated in linking cardiac myocyte remodeling with various extrinsic and intrinsic stimuli. Specifically, STAT3 activation, characterized by phosphorylation on a specific tyrosine residue (Y705), promotes cardiac myocyte hypertrophy both in cell culture systems and in animal models. Previous studies in murine models have indicated a role for STAT3 in cardiac protection, specifically with transgenic cardiac-specific STAT3 over-expression transducing a protective signal against cardiomyopathy after treatment with the antitumor drug doxorubicin in vivo and enhancing vascular formation in the heart in vivo to mediate additional cardiac adaptation under conditions of stress. Consistent with this role of STAT3 in cardiac protection, the cardiac-specific knockout of STAT3 enhanced susceptibility to cardiac injury after myocardial ischemia, with reduced cardiac function and increased mortality and resulted in higher sensitivity to inflammation, cardiac fibrosis, and heart failure with advanced age. In human hearts with end-stage dilated cardiomyopathy, altered STAT3 levels and activation have also been observed. Taken together, the results of these studies suggest that STAT3 may be an important mediator in the development of cardiac hypertrophy and, through its modulation of cardiac cell death, the subsequent progression to heart failure.
The pedigrees reported in the study by Girolami et al. highlight the complexity inherent to the HCM disease process and challenge conventional wisdom regarding the real clinical impact of single sarcomere gene mutations. For example, although most of their patients with triple mutations exhibited a severe phenotype and progressive disease, Patient #4 had modest LV hypertrophy and mild symptoms at age 50 years. Furthermore, several relatives of the index patients had an adult expression of the disease, despite carrying double mutations themselves. Such a discrepancy suggests that certain DNA variants might not be capable of causing disease in isolation but potentially exert modifying effects on disease expression, in combination with other mutations. The demonstration of such a hypothesis is hindered by the objective difficulty, inherent to all genetic studies in HCM, of proving which of the identified sequence variants are truly pathogenic and to what extent. However, the striking phenotypic expression and markedly

increased prevalence of end-stage remodelling observed in this cohort study indicate that the multiplicity of variants importantly contributed to disease pathogenesis and clinical outcome.

On the basis of the present findings, a comprehensive sarcomere mutational screening might provide important clues for risk stratification and potentially indicate the need for differential surveillance strategies based on genotype. Screening should probably not be stopped after the identification of one mutation, especially in families with a particularly severe phenotype, but should be continued on the same gene and at least on the 2 major genes. Additionally, due to the fact that the age at onset, the degree of hypertrophy, and the prognosis was related to the number of mutations in the families reported, before establishing phenotype-genotype correlations it seems necessary to check for a complex genetic status to better understand the broad expressivity of the disease and give these families better genetic counselling.

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

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

Presented by Dr. Giuseppe Limongelli[1] and Dr. Perry M. Elliott[2]. [1]Department of Cardiology, Monaldi Hospital, Second University of Naples, Naples, Italy. [2]Inherited Cardiovascular Disease Unit, Department of Cardiology, The Heart Hospital, University College of London, London, UK.

A case of DCM in a young person

Case Presentation:

A 21-year-old woman was referred for clinical management of idiopathic dilated cardiomyopathy. She complained of cough, associated with progressive dyspnoea for almost a week. After few days, she was admitted to the intensive care unit of her local hospital because of congestive heart failure, with moderate bilateral pleural effusion and mild pericardial effusion. She had no previous medical history of note. She denied drug and alcohol abuse. Her maternal uncle had died suddenly at 42 years of age for a suspected myocardial infaction. No family history of cardiomyopathy was reported. Her blood pressure on admission was145/90mmHg. Blood tests showed the following: leucocytosis; mildly increased CRP (14mg/L); mild increase of Troponin I (0.04 ng/ml); and normal CK (135U/I). ECG showed ventricular bigeminy. A chest radiograph demonstrated small bilateral pleural effusions. Echocardiography demonstrated a mildly dilated left ventricle with an ejection fraction of 25% and a pericardial effusion. She was initially treated with furosemide, ASA, enoxaparin, levofloxacin, and pantoprazol and was transferred for further evaluation.

Physical examination revealed the following: weight 59 kg; height 165 cm; absence of dysmorphic facial features; BP 130/80 mmHg; HR 72 bpm; 2/6 systolic murmur at the apex. Blood tests were all normal, except for NT proBNP 1366 pg/ml and CRP 8.4 mg/dl. Her electrocardiogram showed sinus rhythm, PR 120 msec, left atrial anomalies; left axis deviation and repolarisation anomalies. Echocardiography demonstrated: left ventricular dilatation (58 mm) with global left ventricular hypokinesia (EF 35%); mild left atrial enlargement (42 mm; 30ml/m2); type I diastolic dysfunction; E/Ea 9; normal right ventricular dimensions (27mm) and contractility (TAPSE: 20mm); small pericardial effusion. A cardiac MRI showed no oedema, mild LV dilation (56mm), EF 35%, absence of myocardial fibrotic scars (Figure 1 A and B).

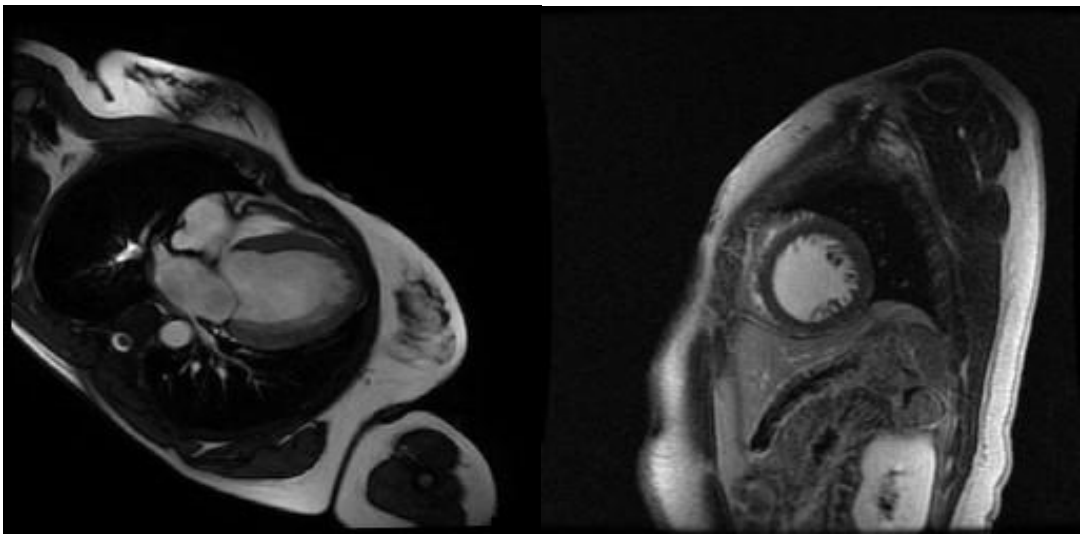

Figure 1 (A and B). Cardiac magnetic resonance imaging (cMRI) with late gadolinium enhancement (LGE), showing a dilated left ventricle, without evidence of tissue abnormalities (scars, patchy fibrosis).

During her hospital stay, she was treated with bisoprolol (progressively increased to 10mg), ramipril (progressively increased to 10mg), spironolactone (25mg), furosemide (25mg), and pantoprazol (40mg). She complained of nausea and dyspepsia and ASA (600mg x 3) was discontinued. Her six minute walking test was 360 meters. An ambulatory electrocardiogram demonstrated sinus rhythm (mean 89; range 49-160), 8865 ventricular ectopic beats, frequent ventricular bigeminy, 353 polymorphic ventricular couplets, and a 4 beat polymorphic run of ventricular tachycardia (160 bpm); a second ECG Holter (after bisoprolol increase to 10mg) demonstrated frequent AV-node (junctional) rhythm with episodes of AV dissociation. Serum antibodies and a nasopharyngeal swab (to analyse DNA/RNA by PCR amplification) were obtained for Influenza A and B, parainfluenza, respiratory syncitial virus, parvovirus, adenovirus, HIV, HCV, HBV, CMV, EBV, Toxoplasma, Mycoplasma, Chlamydia, Legionella, Rickettsia, Bartonella and Borrelia. ANA, ANCA, antiDNA, ENA, Vidal-Wright, VDRL, and Tine test were also performed. The patient had a mild serological positivity for Rickettsia (ELISA) and was commenced on doxycyclin 50mg x2/die.

QUESTIONS

What is the differential diagnosis in this patient ?
What further investigations (if any) would you perform?
Should any additional therapy be started?

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

"A Young Patient with Restrictive Cardiomyopathy and Severe Pulmonary Hypertension"

by Łukasz Mazurkiewicz[1] and Zofia T. Bilińska[1] [1]Dept. of Coronary Heart Disease and Structural Heart Diseases, [2]Unit for Screening Studies in Inherited Cardiovascular Diseases. Institute of Cardiology, Warsaw

Diagnosis, case resolution and treatment

Question 1:

What other examinations could have been performed in the patient?

The patient could have had endomyocardial biopsy performed. According to the guidelines (1), EMB is reasonable in the setting of heart failure associated with restrictive cardiomyopathy (Class of Recommendation IIa, Level of Evidence C). The first indication would have been to exclude systemic infiltrative disorders or storage diseases that could not be diagnosed otherwise, namely with the examination of extracardiac tissues, fluids. In our patient, there was neither Fabry disease, nor hemochromatosis, nor systemic diseases. There was no thickening of the myocardial walls, rendering infiltrative disorders rather unlikely. The use of both MRI and CT limited the significance of endomyocardial biopsy as a helpful tool to exclude pericardial diseases. In addition, there was no late enhancement after gadolinium injection showing lack of any evidence of structural damage of the myocardium. CPK was normal, thus rendering significant associated myopathy less possible.

Other important issues in restrictive cardiomyopathy are genetic studies (2-6). Thanks to the courtesy of Prof. Eloisa Arbustini, in the Pavia Centre for Inherited Cardiovascular Diseases, mutations in the following genes were excluded in the patient: MYH7, MYBPC3, TNNT2, TNNI3. Mutations in genes coding for other proteins like, desmin (DES) and alpha cardiac actin (ACTC) have also been associated with restrictive cardiomyopathy (5-6).

Question 2 and 3: Would you have referred the patient for heart transplantation at the time, knowing the criteria for disqualification from the procedure?

Current guidelines state that heart transplantation should be considered in patients with the end-stage heart failure, with no serious co-morbidity and no alternative treatment options (7). Contraindications include irreversible high pulmonary vascular resistance (6-8 Wood units) and TG > 15 mmHg. There is no guideline how to approach patients who develop contraindications for heart transplantation first and indications for the procedure significantly later. This renders them ineligible for cardiac transplantation. A vasodilator challenge should be made when the pulmonary artery systolic pressure is ≥50 mmHg and either TG is ≥15 mmHg or PVR is >3 Wood units. In our patient, TG dropped from 19 to 14 mmHg, however PASP remained high >60 mmHg. ISHLT guidelines for listing patients for heart transplantation as relative contraindications show PAS exceeding 60 mmHg in conjunction with one of the three parameters (PVR> 5 Wood units, PVRI >6 or TG exceeding 16-20 mmHg) as important factors increasing the risk for early right heart failure and early death (8).

Therefore, we decided to try oral vasodilator, however due to most probably normal systemic vascular resistance – the attempt in the patient failed. Our patient was disqualified from HTX. Our cardiac surgeons considered him as being at too high a risk for developing right heart failure directly after HTX. A young doctor (LM) advised the patient to take Magnesium 2 x 0.5g in addition to his medication that was constant for the previous year apart from slight modifications of diuretics dosage, amiodarone according to QTc interval and serum concentration, acenocoumarol according to INR and kalium dosage).

Two months later control Doppler echocardiographic study revealed that his pulmonary artery systolic pressure dropped down to 50-60mmHg. It was hard to believe in this, subsequent right heart catheterization confirmed the drop in pulmonary artery systolic pressure to 40mmHg, with elevated mean pulmonary wedge pressure of 24 mmHg. The patient's condition slightly improved, his MVO_2 increased up to 16.8 ml/kg/min. Another cardiac MRI revealed no significant changes with regard to both ventricles' size and function in comparison to previous study, apart from a decrease in diameter of the pulmonary artery (37 mm→33mm). Thus, as for now, our patient does not have luckily any contraindications for HTX, and for the time being, does not meet any criteria for HTX either.

It is difficult to explain the spectacular response of the pulmonary artery systolic pressure to, most probably, introducing Magnesium in our patient with restrictive cardiomyopathy. Lack of late gadolinium enhancement on his CMR shows that there is no irreversible damage of the myocardium. Serum magnesium level, while on supplementation 1.0g daily (in a patient treated with diuretics and spironolactone) was normal: 0.89 mmol/l (N: 0.7-1.05 mmol/l).

The role of magnesium in human heart includes: influences in the energetic metabolism, in the excitement–contraction coupling, the adrenergic nervous activation and the renin–angiotensin–aldosterone system activation, and modification of the effect of drugs. Magnesium therapy has been associated with significant hemodynamic effects. Hemodynamically, magnesium therapy has been shown to reduce systemic vascular resistance and mean arterial pressure in animals and humans, to improve cardiac indexes, to increase coronary artery blood flow, and to reduce coronary vascular resistance (9-10).

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

Cardiac {beta}1-adrenoceptor autoantibodies in human heart disease: rationale and design of the Etiology, Titre-Course, and Survival (ETiCS) Study. Deubner N, Berliner D, Schlipp A, Gelbrich G, Caforio AL, Felix SB, Fu M, Katus H, Angermann CE, Lohse MJ, Ertl G, Störk S, Jahns R; on behalf of the ETiCS-Study Group. Eur J Heart Fail. 2010 May 21.

A role for toll-like receptor 3 variants in host susceptibility to enteroviral myocarditis and dilated cardiomyopathy. Gorbea C, Makar KA, Pauschinger M, Pratt G, Bersola JL, Varela J, David RM, Banks L, Huang CH, Li H, Schultheiss HP, Towbin JA, Vallejo JG, Bowles NE. J Biol Chem. 2010 May 14. [Epub ahead of print]

Characterization of the arrhythmogenic substrate in ischemic and nonischemic cardiomyopathy implications for catheter ablation of hemodynamically unstable ventricular tachycardia. Nakahara S, Tung R, Ramirez RJ, Michowitz Y, Vaseghi M, Buch E, Gima J, Wiener I, Mahajan A, Boyle NG, Shivkumar K. J Am Coll Cardiol. 2010 May 25;55(21):2355-65.

Emotional Stress Triggers Symptoms in Hypertrophic Cardiomyopathy: A Survey of the Hypertrophic Cardiomyopathy Association. Lampert R, Salberg L, Burg M. Pacing Clin Electrophysiol. 2010 May 13. [Epub ahead of print]

Ventricular Tachyarrhythmia Associated with Hypertrophic Cardiomyopathy: Incidence, Prognosis, and Relation to Type of Hypertrophy. Furushima H, Chinushi M, Iijima K, Sanada A, Izumi D, Hosaka Y, Aizawa Y. J Cardiovasc Electrophysiol. 2010 May 3. [Epub ahead of print]

Beta-thalassemia cardiomyopathy: history, present considerations, and future perspectives. Kremastinos DT, Farmakis D, Aessopos A, Hahalis G, Hamodraka E, Tsiapras D, Keren A. Circ Heart Fail. 2010 May 1;3(3):451-8

Can genetic testing improve our aim in hypertrophic cardiomyopathy? Charitakis K, Basson CT. Circ Res. 2010 May 14;106(9):1446-8. No abstract available

Peripartum cardiomyopathy as a part of familial dilated cardiomyopathy. van Spaendonck-Zwarts KY, van Tintelen JP, van Veldhuisen DJ, van der Werf R, Jongbloed JD, Paulus WJ, Dooijes D, van den Berg MP. Circulation. 2010 May 25;121(20):2169-75. Epub 2010 May 10