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Working Group on
Myocardial & Pericardial Diseases

Newsletter

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Myocardial and Pericardial Diseases
ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®

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Editorial News

Dear Members of the Working Group,

please find enclosed the 28th issue of our Newsletter.

First of all, on the next page you will find a short letter of the new chairman of our WG, Dr Perry Elliott, who was introduced during the WG assembly in Stockholm, ESC meeting.

As always, you will find within this issue the 'clinical case of the month' and the 'paper of the month' together with 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.

We would like to direct your attention to the recently published position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases with regard to genetic counselling and testing in cardiomyopathies, which we think is a great achievement of the whole WG, the nucleus members and Philippe Charron as first author and expert leader in this field.

Best wishes for all of you.

S. Pankuweit

Dear Colleagues,

It is a great pleasure to write my first letter to you as chairman of our working group. This is a great honour and responsibility, but I am looking forward to working with you over the next two years to promote our common goal of improving the outlook for patients with diseases of the myocardium and pericardium. I would like to thank my predecessor, Professor Luigi Tavazzi, for his calm and effective stewardship of the nucleus and express my gratitude to the outgoing members of our nucleus who have worked tirelessly over the past four years to raise the profile of our working group. The past few years have seen much progress, including our recent position statement on genetic testing in cardiomyopathies published in the European Heart Journal. This work provides the new nucleus with a solid foundation on which to build in the future.

I look forward to seeing you all at our annual meeting in A Coruna Spain.

Yours sincerely

Perry Elliott

The paper of the month:



Rare variant mutations in pregnancy-associated or peripartum cardiomyopathy

Morales A, Painter T, Li R, Siegfried JD, Li D, Norton N, Hershberger RE. Circulation. 2010 May 25;121(20):2176-82. Epub 2010 May 10.

Presented by Michal Saj[1], M. Sc, Assoc. Prof. Rafal Ploski[2], M.D. PhD**,** and Assoc. Prof. Zofia T. Bilinska[3], M.D. PhD,

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[2] Department of Medical Genetics, Centre of Biostructure, Medical University of Warsaw and
[3] Unit for Screening Studies in Inherited Cardiovascular Diseases, Institute of Cardiology Warsaw, Poland

Background

Peripartum cardiomyopathy (PPCM) is recognized as a distinct form of heart failure, with highly variable clinical course. Recently published [1] position statement from the Heart Failure Association of the ESC WG on peripartum cardiomyopathy provides new definition of PPCM as "an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular (LV) systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found". Therefore, the diagnosis of PPCM is 'the diagnosis of exclusion'. The LV may not be dilated but the LVEF is nearly always reduced below 45%". Sliwa et al. [1] also emphasized that the time frame (development of the disease during the last month of pregnancy or within 5 months of delivery) recognized as important part of definition of PPCM is arbitrary and may lead to under-diagnosis of PPCM. Of note, in 2005 Elkayam et al. published 23 cases of early pregnancy-associated heart failure (PACM) with the onset of idiopathic heart failure as early as in week 17 and found them to be clinically indistinguishable from classic PPCM [2]. Obviously, these two are undistinguishable from dilated cardiomyopathy (DCM).

Though PPCM may be reversible and spontaneous recovery is often reported, rapid hemodynamic compromise leading to the requirement of ventricular assist devices within days or urgent heart transplantation may occur. PPCM constitutes the most frequent factor contributing to pregnancy-related death. Risk factors include: maternal age over 30 years, multiple gestation, multiparity, preeclampsia and toxemia of pregnancy [3, 4]. Whereas cause(s) of PPCM are not known, the role of higher cardiac demand, immune system dysfunction/autoimmune response, myocarditis, dietary deficiencies, oxidative stress and genetic origin were all suggested [4, 5]. Recently, a major focus has been placed on the role of prolactin, which, as a result of aberrant proteolytic cleavage probably caused by an unbalanced oxidative stress, is the source of pathogenic anti-angiogenic, pro-apoptotic and pro-inflammatory 16-kDa subform [6]. This hypothesis has direct clinical relevance pointing to blockade of prolactin by bromocriptine as a therapeutic option, which indeed appeared successful in pilot trials [7]. Given this background the results of Morales et al. [8], which bring up the issue of genetic causes of PPCM, are worth commenting.

Summary

The authors hypothesized that mutations in genes linked with DCM may also account for some PPCM/PACM cases and employed their DCM patient database to test this. The database comprised 4110 women with idiopathic cardiomyopathy from 520 families.

Forty two unrelated cases of PPCM/PACM (23 with familial clustering) were identified. Nineteen patients were screened for mutations by sequencing of exon and exon-intron boundaries in 14 DCM genes. Six (32%) non-synonymous mutations all located in different genes were found. Five of them (in *MYH7*, *TNNT2*, *MYH6*, *SCN5A* and *PSEN2* genes) were associated with PPCM, while one (in *MYBPC3*) was present in a PACM subject. Three patients with PPCM and one patient with PACM inherited their mutations. The pathogenicity was validated by excluding the presence of mutations among 246-413 control subjects.

Discussion

In the same issue of Circulation van Spaendonck-Zwarts et al. [9] performed the search for PPCM cases in their database of 90 families with DCM. Five families had members with PPCM (6%). Further, 10 independent PPCM cases were also studied including 3 patients who did not fully recover. Their first-degree family members, previously undiagnosed, were examined and DCM was found within all 3 of these families. Moreover, one mutation (in the *TNNC1* gene) segregating with disease was found in a DCM family with a PPCM patient.

Thus, the studies by Morales et al. and van Spaendonck-Zwarts et al. both describe an association of genetic factors with PPCM. It appears that the same mutations which are responsible for DCM may play, at least in a subset of patients, a pathogenic role in PPCM.

An important clinical message from these results is that family history in PPCM may be revealing and should be elicited [4], and evidence for the genetic causation should be sought in PPCM with the aim of early diagnosis of affected relatives similarly as it is done in DCM. This, as the Morales et al. [8] advise, should include analysis of 3- to 4-generation family pedigrees along with thorough clinical examination of first-degree family members. Although general genetic testing is not recommended as routine [1], it can be performed as part of research projects. DCM genetic background is highly heterogeneous, and PPCM has several unique features, therefore variants in genes not known in DCM may underlie disease activation. However, performing genome wide and candidate gene association studies with modern high-throughput techniques like high-density arrays may bring us closer to understanding the genetic factors behind this condition [10].

The studies by Morales et al. [8] and van Spaendonck-Zwarts et al. [9] raise interesting questions regarding pathogenesis and treatment of PPCM. In the context of emerging central role of 16-kDa cleavage product of prolactin in PPCM with antiangiogenic and proapoptotic activities [6] it would be interesting to know whether there are any differences in outcome between groups of patients with identified variants associated with development of PPCM and other groups with unknown etiology of the disease. It could well be speculated that the disease development in patients with genetic defect(s) depends mainly on factors like volume overload rather than prolactin, which could make bromocriptine treatment ineffective.

The high incidence of PPCM in certain communities is suggestive of distinct environmental factors playing a major role in the development of PPCM. This is supported by earlier studies showing myocarditis [11, 12] and abnormal immune response [13, 14] in PPCM. Ultrastructural differences might also exist. Recently, our group analyzed myocardium of PPCM patient and 3 other patients with fulminant heart failure not related to PPCM serving as a control group - two with myocarditis and one with DCM. PPCM subject's myocardial tissue demonstrated endothelial cell apoptosis as well as remodelling of small capillaries leading to impairment of microcirculation, whereas no such alterations were present in the control group suggesting pathogenic uniqueness of PPCM [15]. In the context of discussed findings [8, 9] it would clearly be interesting to compare the role of these factors in PPCM/PACM with and without DCM associated genetic defects. Finally, it should also be noted that the discussed studies had some limitations, the most obvious being the relatively small number of women with DCM and/or PPCM/PACM.

In particular, Morales et al. spent 15 years building their DCM patient database and ended up with only 42 unrelated cases of PPCM/PACM, of which 19 were screened for mutations in 14 DCM genes. Also, the screening performed could be regarded as incomplete since only 14 out of more than 30 known DCM genes were selected for analysis and even those were not screened in all patients. However, this may suggest that many more mutations are still to be detected in this cohort.

In conclusion, the findings of Morales et al. [8] and van Spaendonck-Zwarts et al. [9] provide an interesting new perspective on PPCM/PACM with implications for both the basic research and clinical practice.

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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 Tiina Heliö [1] and Sari Aaltonen [2],

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A previously healthy young woman with a rapidly developed dyspnoea and thick-walled left ventricle

The patient is a 25-year old previously healthy woman who had studied building branch and worked at construction sites until March 2009 when she became unemployed. Her only regular medication comprised contraceptive pills (desogestrel and ethinylestradiol). She had been thin all her life (169,5cm/ 49 kg, BMI 17.1 kg/m^2) with a blood pressure of 105/50 mmHg in February 2009. She did not smoke or use drugs neither had alcohol abuse. Her mother had rheumatoid artrhitis and her father had died accidentally. Neither of them was diagnosed with any cardiac disease. The patient was the only child.

In September 2009 she had initially some fever, then prolonged cough and symptoms of a common cold. Sinuitis was suspected whereafter antibiotics and a combination drug containing ASA 350mg per tablet (which she took up to four tablets a day) were prescribed. However, she had to be admitted to the hospital in November 2009 due to progressive dyspnoea. On the previous day, her blood pressure was 120/65 mmHg and pulse rate 110/min. She reported also some difficulties in swallowing and before admission to the hospital she had inadvertently lost weight about four kilograms.

At the hospital emergency her respiratory frequency was 29/min, oxygen saturation 80%, blood pressure was 245/157mmHg and she had sinus tachycardia 107/min. Blood gas analyses demonstrated metabolic alcalosis. Serum creatinine concentration was increased (216 umol/l, normal range 50-90 umol/l). There was hematuria, mild proteinuria, hyponatremia (117 mmol/l, normal range 137-145 mmol/l) and mild anemia. Blood thrombocyte count was normal. Plasma potassium concentration was repeatedly normal. Crp was 7 mg/l and erythrocyte sedimentation rate 13 mm/h. The concentration of plasma natriuretic peptide was high (34 568 ng/l, normal range <155 ng/l) whereas the concentrations of plasma CK, CKMBm and lactate were normal. ECG showed LVH (Fig.1).

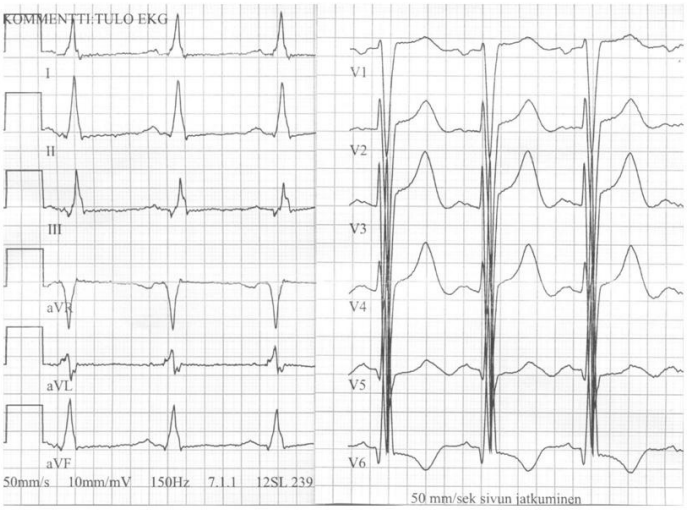

Figure 1.

The first ECG showed sinustachycardia, LVH and negative p-waves in V1, suggestive of left atrial abnormality

According to hospital records, in initial bed-side echocardiography the maximal left ventricular wall thickness measured up to 18 mm. In addition the left ventricular contractility was diminished (Fig. 2). The E/A relation was inversed and there were mild aortic and mitral valve regurgitations (not shown). Thorax X-ray demonstrated enlarged heart, pulmonary oedema and moderate bilateral pleural effusions. Medical treatment for hypertension and alveolar oedema was promptly initiated.

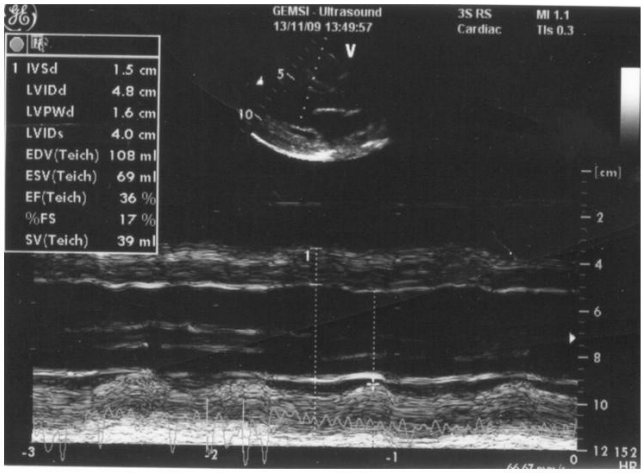

Figure 2.

The main findings of the bedside echocardiography at the emergency were thickened left ventricular walls and diminished left ventricular contractility (EF 36%).

QUESTIONS

1. What is your working hypothesis and differential diagnoses?

2. Which further evaluations would you suggest?

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

"A 46 year-old man with right ventricular dilatation"

by Diego A. García and Lorenzo Monserrat, Cardiology Department. Instituto de Investigación Biomédica and Complejo Hospitalario, Universitario de A Coruña. Spain

Differential diagnosis and diagnostic strategy

Our case, a 46-year-old male patient, presented with exertional dyspnea and palpitations, a severe right ventricular and atrial dilatation, monomorphic ventricular extrasystolia, mild left ventricular dilatation, systolic dysfunction (EF 45%) and a family history of DCM (father). Causes of right chambers dilatation include pressure overload, volume overload, and myocardial dysfunction, which may be secondary to ischemic heart disease or to primary cardiomyopathies (mainly ARVC) (1). Several possible aetiologies such as ischemic heart disease, right side valvulopathies, atrial septal defect, proximal vascular abnormalities, pulmonary thromboembolism and congenital causes had been acceptably discarded by 2D, Doppler and stress echocardiography, Computerized Tomographic Pulmonary Angiography and a thoracic CT. The presence of mild left ventricular enlargement and dysfunction (LV end diastolic diameter was increased by 11% above the maximum predicted by the Henry´s formula) would not explain the severity of the right chambers compromise. However, the left ventricular involvement and the family history of DCM would suggest the presence of a primary cardiomyopathy with biventricular compromise.
Although ARVC would be the cardiomyopathy that best fit with the patient's characteristics (severe right ventricular dilatation with left ventricle involvement), our patient did not fulfil the current ARVC diagnostic criteria (2). The possibility of an extracardiac shunt should also be considered, even thought it would not explain the left ventricular involvement. This hypothesis was also supported by the finding of a repletion defect in the superior vena cava that might be produced by a "vascular steal" phenomenon.

With the hypothesis of a familial cardiomyopathy with biventricular involvement we performed a genetic study of the main ARVC disease-causing genes (desmosomal genes: PKP2, DSP, DSG2 and DSC2). We also performed a MRI, which is the procedure of choice to study extracardiac shunts (3) and could help to evaluate the structural and functional characteristic of the right ventricle, reducing subjective bias associated with echocardiography (4).

Genetic analysis informed the presence of four genetic variants (Table1): DSG2 variant I85N (g42507C>G or Ile85Asn) has not been previously described either in patients or in healthy controls thus, taking in account the thousands of samples analysed so far, it was considered a mutation. At functional level, this variant affects a residue slightly conserved (I85) producing an amino acid change from a nonpolar (isoleucine, I) to another uncharged polar aminoacid (asparagine, N). This may produce important physicochemical changes in the mass, the hydrophobicity and polarity (Grantham distance: 149 [0-215]). We performed an in silico analysis to predict the effect of amino acid substitution at residue 85 (I to N) using two softwares: Polyphen (= Polymorphism phenotyping) and Sorting Intolerant From Tolerant (SIFT). Polyphen predicted that the change may affect the function of the protein and SIFT was not conclusive. This data, however, was insufficient to ascertain the pathogeniciy of I85N.
DSP variant A2294G (g42507C>G or Ala2294Gly) has been identified in three families (Dr van der Zwaag, personal communication).

Only one has been partially published and appeared in a database of mutations and benign variants related to dysplasia / arrhythmogenic right ventricular cardiomyopathy (ARVC). In this family, the variant was the only one found in the proband diagnosed with ARVC (5 genes related to this phenotype were analyzed), but showed no cosegregation with the disease as the proband's mother, who also presented this phenotype, did not present this variant. In the second family, the proband (currently 72 years old) carried a second confirmed pathogenic mutation in desmoplakin (DSP). In the last family, this variant was identified in the father of a male patient who died suddenly at the age of 25, although the latter patient did not carry the variant. Both, however, were carriers of a confirmed pathogenic mutation in another gene. Finally, Polyphen software predicted that this variant may not affect the protein function. With this data, we considered A2294G as a probably non pathogenic variant.

The other genetic variants found in the plakophilin (PKP2) gene, L366P and the intronic IVS12+(13-14)insC were polymorphism frequently identified in healthy controls.

Gene	Genetic variant	Result	Pathogenicity
DSG2	**I85N** g42507C>G	**Heterozygous**	**Mutation of uncertain pathogenicity**
DSP	**A2294G** g42507C>G	**Heterozygous**	**Genetic variant probably non pathogenic**
PKP2	L366P g27847T>C	Homozygous	Polymorphism not associated with disease
	IVS12+(13-14)insC g100751-2insC	Homozygous	Polymorphism not associated with disease
DSC2	-	No mutation	-

Table1.

Genetic variants identified in the proband. The variants are name by aminoacid code and below by nucleotide code. See text for description.

Next, we performed the familial study, for which the I85N and A2294G variants were tested on the affected proband's father but he did not carry any of them (as in consequence neither did the affected grandfather, figure 2). The proband's mother could not be genotyped but despite she could be an obligate carrier of at least one variant, she was clinically unaffected. Hence, we could not demonstrate cosegregation of these variant with disease.

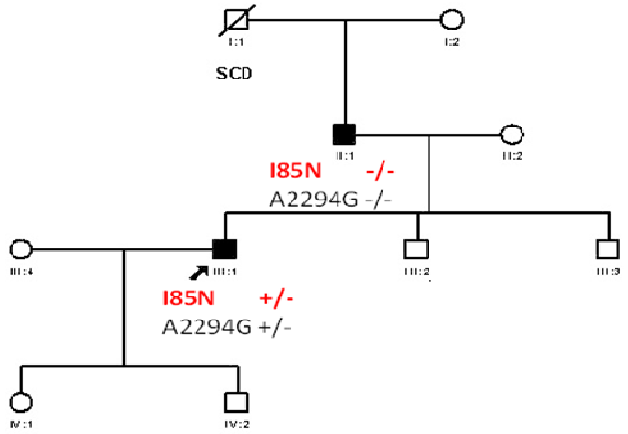

Figure 2.

Familiar pedigree. Genetic study was available only for patients II.1 and III.1 (proband). Filled symbols means clinical affected individuals. Genetic test result is drawn below each symbol. +/- means heterozygous for the mutation and -/- means wild type.

The cardiac MRI (Fig. 1a and 1b) confirmed the presence of a dilatation of both right chambers with a mild depressed right ventricular function (ventricular end diastolic diameter: 60mm, end diastolic volume: 356ml; right atrium diameter 64 mm and ejection fraction of 47%). It also showed the dilatation and functional impairment of the left ventricle (end diastolic diameter: 60mm, end diastolic volume: 243ml and ejection fraction decreased by 40%). No regional structural or functional right ventricle abnormalities were observed. However, the most relevant finding was the demonstration (by Angio MRI, 3D shaded surface display) of a partial anomalous pulmonary venous return (PAPVR), producing a shunt from the right superior pulmonary lobe to the superior vena cava (white arrow, Fig. 1c). This explained the right high cardiac output of 8 l/m calculated by MRI.

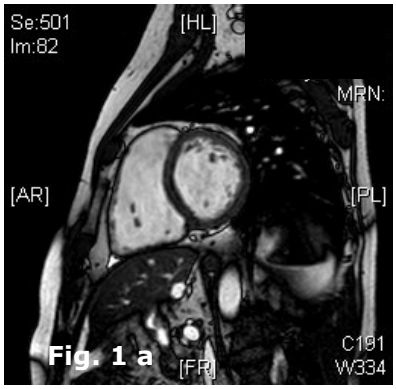

Fig. 1 a

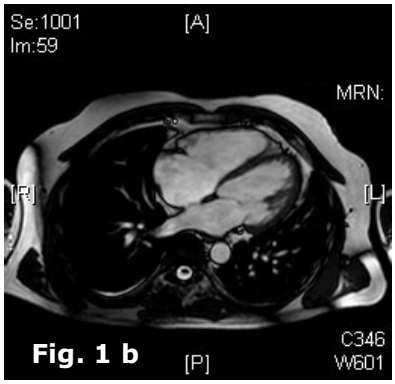

Fig. 1 b

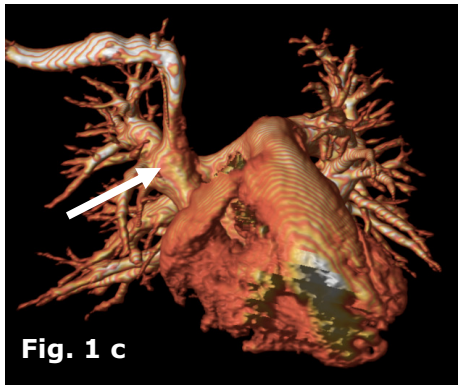
Fig. 1 c

In conclusion, we consider that the right chambers dilatation would be explained by the presence of an extracardiac shunt (PAPVR). We cannot exclude that the genetic variants identified in the DSG2 and DSP genes could contribute to the biventricular moderate dysfunction, but they could also be non-pathogenic. In any case, the familial antecedents of DCM would not be explained by the presence of these genetic variants. ARVC diagnosis was not supported by clinical criteria and we cannot confirm that the identified genetic variants are associated with the development of disease. The left ventricular compromise in the proband and in his father may have two different etiologies (in the case of the proband's father DCM could be secondary to hypertension and valvular disease), but it may also be possible that they have a familial DCM caused by other still unknown genetic cause. In the latter case the substantial differences in phenotypic manifestations would be due to the presence of PAPVR in the proband. We consider that this case is still open and we are evaluating other genes that have been associated with the development of familial DCM. For example, mutations in sarcomeric genes have already been associated with the development of congenital abnormalities, such as atrial septal defects.

Acknowledgements: We gratefully acknowledge the excellent technical assistance of Dr Rafaela Soler Fernandez, Dr. Esther Rodriguez and Dr. Cristina Mendez from the radiology service, Complejo Hospitalario, Universitario de A Coruña. Spain.

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

1) ***Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases.***
Charron P, Arad M, Arbustini E, Basso C, Bilinska Z, Elliott P, Helio T, Keren A, McKenna WJ, Monserrat L, Pankuweit S, Perrot A, Rapezzi C, Ristic A, Seggewiss H, van Langen I, Tavazzi L. Eur Heart J. 2010 Sep 7

2) ***Research priorities in hypertrophic cardiomyopathy: report of a working group of the national heart, lung, and blood institute.***
Force T, Bonow RO, Houser SR, Solaro RJ, Hershberger RE, Adhikari B, Anderson ME, Boineau R, Byrne BJ, Cappola TP, Kalluri R, Lewinter MM, Maron MS, Molkentin JD, Ommen SR, Regnier M, Tang WH, Tian R, Konstam MA, Maron BJ, Seidman CE. Circulation. 2010 Sep 14;122(11):1130-3.

3) ***Ventricular Remodeling and Survival are More Favorable for Myocarditis Than For Idiopathic Dilated Cardiomyopathy in Childhood: An Outcomes Study from the Pediatric Cardiomyopathy Registry.***
Foerster SR, Canter CE, Cinar A, Sleeper LA, Webber SA, Pahl E, Kantor PF, Alvarez JA, Colan SD, Jefferies JL, Lamour JM, Margossian R, Messere JE, Rusconi PG, Shaddy RE, Towbin JA, Wilkinson JD, Lipshultz SE. Circ Heart Fail. 2010 Sep 10.

4) ***De novo desmin mutation N116S is associated with arrhythmogenic right ventricular cardiomyopathy.***
Klauke B, Kossmann S, Gaertner A, Brand K, Stork I, Brodehl A, Dieding M, Walhorn V, Anselmetti D, Gerdes D, Bohms B, Schulz U, Zu Knyphausen E, Vorgerd M, Gummert J, Milting H. Hum Mol Genet. 2010 Sep 9.

5) ***Relationship between left ventricular stimulation characteristics at implantation and echocardiographic response after 6 months of cardiac resynchronization therapy.***
Deplagne A, Ploux S, Ritter P, Lafitte S, Reant P, Jais P, Haissaguerre M, Clementy J, Bordachar P. Europace. 2010 Sep 8.

6) ***Ventricular Remodeling and Survival are More Favorable for Myocarditis Than For Idiopathic Dilated Cardiomyopathy in Childhood: An Outcomes Study from the Pediatric Cardiomyopathy Registry.***
Foerster SR, Canter CE, Cinar A, Sleeper LA, Webber SA, Pahl E, Kantor PF, Alvarez JA, Colan SD, Jefferies JL, Lamour JM, Margossian R, Messere JE, Rusconi PG, Shaddy RE, Towbin JA, Wilkinson JD, Lipshultz SE. Circ Heart Fail. 2010 Sep 10.

7) ***Clinical cardiac involvement in idiopathic inflammatory myopathies: A systematic review.***
Gupta R, Wayangankar SA, Targoff IN, Hennebry TA. Int J Cardiol. 2010 Sep 6

8) ***Triage and management of pericardial effusion.***
Imazio M, Mayosi BM, Brucato A, Markel G, Trinchero R, Spodick DH, Adler Y. J Cardiovasc Med (Hagerstown). 2010 Sep 1.