



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

Newsletter

Issue 19 - December 09



## Editorial News

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Dear Members of the Working Group,

please find enclosed the 19<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 November 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**.....

Last but not least I would like to send my best wishes for a delightful Christmas season and a Happy New Year to all of you.....

*S. Panhavi*

## The paper of the month:

### **Systemic Cardiac Amyloidoses. Disease Profiles and Clinical Courses of the 3 Main Types**

Claudio Rapezzi, MD;<sup>1</sup> Giampaolo Merlini, MD;<sup>2</sup> Candida C. Quarta, MD;<sup>1</sup> Letizia Riva, MD;<sup>1</sup> Simone Longhi, MD;<sup>1</sup> Ornella Leone, MD;<sup>3</sup> Fabrizio Salvi, MD;<sup>4</sup> Paolo Ciliberti, MD;<sup>1</sup> Francesca Pastorelli, MD;<sup>4</sup> Elena Biagini, MD;<sup>1</sup> Fabio Coccolo, MD;<sup>1</sup> Robin M.T. Cooke, MA;<sup>1</sup> Letizia Bacchi-Reggiani, MSc MStat;<sup>1</sup> Diego Sangiorgi, MStat;<sup>1</sup> Alessandra Ferlini, MD;<sup>5</sup> Michele Cavo, MD;<sup>6</sup> Elena Zamagni, MD;<sup>6</sup> Maria Luisa Fonte, MD;<sup>2</sup> Giovanni Palladini, MD;<sup>2</sup> Francesco Salinaro, MD;<sup>2</sup> Francesco Musca, MD;<sup>2</sup> Laura Obici, MD;<sup>2</sup> Angelo Branzi, MD;<sup>1</sup> Stefano Perlini, MD.<sup>2</sup> *Circulation* 2009;120:1203-12.

**Presented by Candida C. Quarta and Luigi Tavazzi.** Institute of Cardiology, University of Bologna and S.Orsola-Malpighi Hospital, Bologna, Italy and GVM Hospitals of Care and Research, Villa Maria Cecilia Hospital, Cotignola, Italy

### **Background**

The term amyloidoses describes a group of diseases characterized by extracellular accumulation of fibrillary proteins, leading to loss of normal tissue architecture. Amyloidosis may be systemic or localized, and is currently classified according to the type of precursor protein. The three most frequent and clinically challenging types of systemic amyloidosis are: 1) acquired monoclonal immunoglobulin light-chain amyloidosis (AL), characterized by clonal plasma cells in the bone marrow which produce the immunoglobulin lights chains of the fibrillary deposits; 2) the hereditary, transthyretin-related form (ATTRm), which can be caused by over 100 mutations of transthyretin (TTR), a transport protein mainly synthesized by the liver; 3) wild-type (non-mutant) transthyretin-related amyloidosis (ATTRwt) or systemic “senile” amyloidosis, which mainly affects the hearts of elderly men. In all three forms, myocardial involvement is frequent and has major clinical implications. Despite the intrinsic, etiologic heterogeneity of cardiac amyloidosis, most available clinical/instrumental studies address the disease as a single entity. In this study, the Authors compare the diagnostic and clinical profiles of these three types of systemic cardiac amyloidosis in search of clinical and instrumental aspects specific for the three etiologies, beyond the shared anatomical substrate.

### **Summary**

The paper presents a multicenter longitudinal study of 233 consecutive patients with clear-cut diagnosis by type of the three main forms of cardiac amyloidosis, seen at 2 large Italian centers (Bologna and Pavia) providing coordinated amyloidosis diagnosis/management facilities since 1990. The study enrolled 157 patients with (AL), 61 patients with ATTRm, 15 patients ATTRwt. The three groups of patients were compared in terms of clinical and instrumental (echocardiographic and electrocardiographic) profiles at baseline and in term of clinical outcome. In about 40% of study population hemodynamic data and endomyocardial biopsy data were also available for comparisons. Diagnosis of amyloidosis was defined by histological documentation of Congo Red staining and apple-green birefringence under cross-polarized light in at least 1 involved organ. Amyloidotic cardiomyopathy was defined echocardiographically as end-diastolic thickness of the interventricular septum >1.2 cm in the absence of any other cause of ventricular hypertrophy. Clear-cut distinction between TTR-related and AL amyloidosis was based on genotyping and/or immunohistochemistry.

In about 65% of cases, amyloidotic cardiomyopathy was detected at routine echocardiographic screening after diagnosis of systemic amyloidosis. In <2% of cases (2 AL; 1 ATTRwt) diagnosis of cardiac systemic amyloidosis was incidental. In the remaining 34% of cases, patients were initially diagnosed as having hypertrophic cardiomyopathy, heart failure, or arrhythmia at a secondary or tertiary cardiologic center.

At presentation, the 3 groups of patients showed some expected clinical differences, including high prevalence of neurological impairment and carpal tunnel syndrome in ATTRm, kidney involvement in AL, and heart failure in both AL and ATTRwt (a disease thought to be confined to elderly men).

Regarding ECG, at univariate analysis left bundle branch block was more frequent in ATTRwt; ATTRm patients less often displayed low QRS voltage (25% versus 60% in AL;  $P < 0.0001$ ) or low voltage-to-mass ratio ( $1.1 \pm 0.5$  versus  $0.9 \pm 0.5$ ;  $P < 0.0001$ ). At multivariate analysis low QRS voltages were negatively associated with ATTRm.

Highly significant differences were apparent for most echocardiographic morphological and functional descriptors: morphologically, ATTRwt group showed the highest average values, with 3 to 4 mm greater mean LV wall thickness (diastolic interventricular septum thickness  $19.7 \pm 4$  mm) than in ATTRm ( $16.6 \pm 3.8$  mm) or AL ( $15.8 \pm 2.8$  mm),  $p < 0.0001$ ; LV ejection fraction values varied considerably, tending to be normal in ATTRm ( $58 \pm 13\%$ ), around lower normal limits in AL ( $52.5 \pm 13\%$ ), and abnormally low in ATTRwt ( $44.2 \pm 15.4$ ,  $p < 0.0001$ ).

The different etiologies showed relevant hemodynamic differences, with AL patients most often displaying abnormal values in the different measures of diastolic function.

With regard to clinical outcome, in terms of both overall and MACE-free survival, the group with the least morphological impairment—AL—had a rather aggressive clinical course; the group that showed the greatest LV wall thickness—ATTRwt—showed a less aggressive course **despite the patients' higher average age. On multivariate analysis, ATTRm was a strongly favorable predictor of survival, and ATTRwt predicted freedom from major cardiac events.**

### Comment

The paper regards the largest available follow-up study of cardiac amyloidosis and represents a relevant contribution at different levels ranging from disease classification to diagnosis and clinical management.

**From a nosographic point of view**, this study supports the concept that cardiomyopathies due to AL, ATTRm and ATTRwt should be considered three different cardiac diseases with different pathophysiologic substrates and clinical courses. Cardiac amyloidosis is commonly considered a form of restrictive cardiomyopathy (i.e., a myocardial disease with increased parietal stiffness, causing precipitous rises in ventricular pressure accompanied by only small increases in volume). Nevertheless, as many as one-fifth of the hemodynamically evaluated patients did not display any abnormal finding, and the majority of the overall patients did not display restrictive filling pattern, which is traditionally considered the key non-invasive marker of restrictive pathophysiology. Sub analysis of baseline hemodynamic data highlights the differences among the three etiologic forms, with only AL patients displaying abnormal values in the different measures of diastolic function in the vast majority of cases. The higher frequency of hemodynamic impairment in the AL patients contrasts with their lesser morphological involvement. So, within a group of infiltrative cardiomyopathies that are traditionally considered “restrictive”, the degree of infiltration (assessed by increased wall thickness) does not seem to be associated with the severity of restrictive hemodynamic impairment. This mismatch could plausibly be attributed to the well-documented direct toxicity of the immunoglobulin circulating immunoglobulin light-chains in AL, along with other plausible contributory factors.

For instance, it is reasonable to hypothesize that a higher frequency of vascular localization of amyloid deposition in AL could be responsible for myocardial ischemia, contributing to ventricular dysfunction. Furthermore, gradual deposition in the TTR-related forms might allow the organism time to develop local compensatory mechanisms (a rather less likely scenario in the rapidly developing amyloidotic cardiomyopathy of AL patients). Different types of amyloid substance could also lead to different degrees of myocardial damage (unfortunately, the study did not explore this aspect). Taken together, these observations may also explain why the clinical outcome of the three groups of patients, in terms of both overall and MACE-free survival, appeared to contrast with the degree of morphological involvement, where the group with the least morphological derangement (AL) had a rather aggressive clinical course. In contrast, the group that showed the greatest LV wall thickness values (ATTRwt) seemed to have a less aggressive course.

**From a clinical point of view**, a particularly important observation of the study regards standard ECG. Although the presence of low QRS voltages is considered a key player to orient diagnostic suspicion of cardiac amyloidosis, the prevalence of low QRS voltages at the time of diagnosis was lower than in other reports (~45% overall) and particularly low in the ATTRm subset (25%), despite a greater myocardial infiltration (as indicated by mean ventricular wall thickness values). A possible explanation for this finding could be greater myocardial cellular damage (regardless of wall thickness) induced by light-chain toxicity in AL. Interestingly the occurrence of left bundle-branch block was relatively frequent in ATTRwt type (up to 40% of cases). Appropriately, the study underscores the importance of not excluding a diagnosis of amyloidotic cardiomyopathy (especially of TTR-related forms) on the grounds of normal QRS voltage or left bundle-branch block.

To sum up, the paper underscores the profound differences between the three most frequent etiological types of cardiac amyloidosis in terms of disease profile and long-term outcome. Awareness of this heterogeneity may help orient aspects of the diagnostic workup of patients with suspected cardiac amyloidosis and subsequent clinical management.

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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 Massimiliano Lorenzini, Claudio Rapezzi  
University of Bologna and S.Orsola-Malpighi Hospital, Bologna, Italy**

### A case of “bright myocardium” (not all that glitters is gold)

#### Case Presentation:

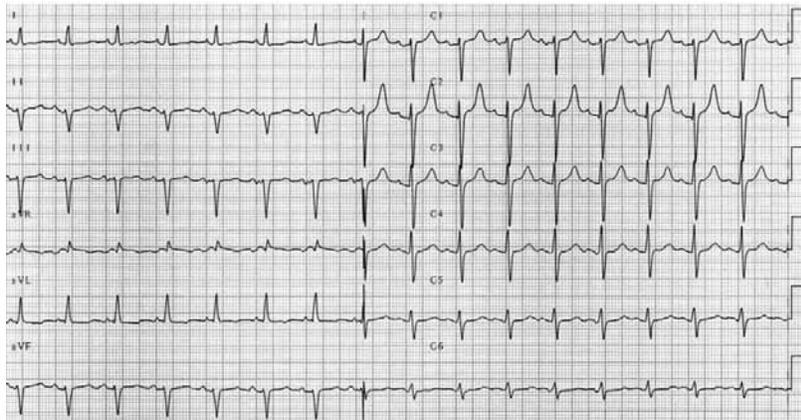
A 37 year old man, who received a renal transplant aged 35, is admitted to a nephrology ward for worsening renal failure associated with heart failure.

The patient had a history of recurrent, bilateral, renal colics with calculi expulsion from a young age. Aged 33 the patient started hemodialytic treatment for end-stage renal failure (aetiology was not fully investigated). One month after starting dialysis he underwent bilateral nephrectomy for an acute post-dialytic hematoma of the left kidney.

After two years of three-weekly dialysis regime, the patient underwent a renal transplant from a living donor (wife).

About a year from the transplantation he suffered repeated renal colics associated with a progressive worsening of renal function leading to his current hospitalization.

On admission, blood pressure was 140/80 mmHg, heart rate was 100 bpm and pitting ankle oedema was present. Cardiac and abdominal examinations were normal while chest examination revealed bilateral basal pulmonary crepitations. The ECG (Figure 1) showed sinus tachycardia (heart rate, 106 bpm), left anterior hemiblock and non-specific alterations of the ventricular repolarization. The chest X-ray showed bilateral congestion of the pulmonary bases without signs of pleural effusion.



**Fig. 1:**

Standard ECG, showing left anterior hemiblock and non-specific alterations of the ventricular repolarization

The laboratory exams documented: leucocytes  $10.17 \times 10^3/\mu\text{L}$  (n.v.  $4.80-8.50 \times 10^3/\mu\text{L}$ ), haemoglobin 9,9 g/dl (n.v. 13,0-16,5 g/dl), haematocrit 30.8 % (n.v. 40.0-54.0%), platelets  $220 \times 10^3/\mu\text{L}$  ( $150-400 \times 10^3/\mu\text{L}$ ), urea 1,45 g/L (n.v. 0,15-0,50 g/L), creatinine 4.30 mg/dl (n.v. 0.50-1.20 mg/dl), total proteins 5.7 g/dl (n.v. 6.0-8.0 g/dl), alkaline phosphatase 477 U/L (n.v. 98-220 U/L), sodium 137 mEq/L (135-146 mEq/L), potassium 4.5 mEq/L (3.5-5.3 mEq/L). Urine test: incolor, limpid, PH 5.5 (n.v. 5.5-6.5), specific gravity 1.010 (n.v. 1.014-1.028), proteins: 69 mg/dL (n.v. <20 mg/dL), red blood cells 19/ul (n.v. 0-15), leucocytes 33/ul (n.v. 0-18/ul), bacteria 10.000/ul (n.v. 0-8000/ul), crystals 734/ul.

Due to the coexistence of heart failure, a cardiological consultation and an echocardiogram were requested. The echocardiogram (Figures 2) showed: a hyperechogenic appearance of the myocardium of the “granular sparkling” type, a slight concentric hypertrophy of the left ventricle (interventricular septum 12 mm, posterior wall 13 mm), an increase of ventricular volumes (end-diastolic/end-systolic 136/63 ml), a slight hypokinesia of the inferior wall, a left ventricular ejection fraction within the normal limits (55%), a slight dilation of the left atrium (longitudinal M-mode diameter 45 mm), minimal mitral regurgitation, slight anterior and posterior pericardial effusion.

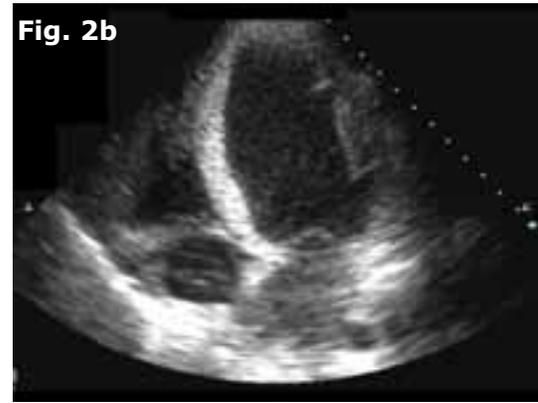


Fig 1.: Two-dimensional echocardiogram. A) parasternal, longitudinal view and B) 4-chamber view. The myocardium appears hyperechogenic. A slight concentric hypertrophy of the left ventricle is present (interventricular septum 12 mm, posterior wall 13 mm) as well as increase of ventricular volumes (end-diastolic/end-systolic 136/63 ml),

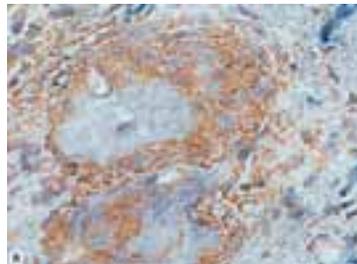
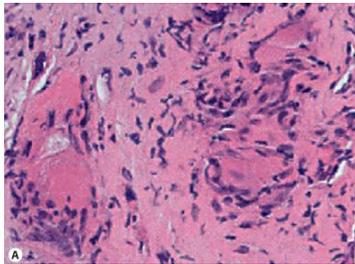
**In the light of the patient’s history, examination and tests, what do you think is the correct diagnosis and what further investigations should be performed?**

**Answer for the previous “Clinical case of the month” presented in November****“Onset of congestive heart failure and subsequent life-threatening ventricular tachyarrhythmias”**

by **Dr. Sabine Pankuweit**, University Hospital Marburg, Department of Cardiology, Marburg, Germany

**Diagnosis, case resolution and treatment**

The patient underwent a second coronary angiography in which endomyocardial biopsies from the interventricular septum and the left ventricle were taken. The biopsies showed histopathological evidence of cardiac sarcoidosis ( fig. 1a ). Nonnecrotizing granulomas were composed of epithelioid cells, moderate numbers of multinucleated giant cells containing asteroid bodies and scattered lymphocytes. The florid granulomas appeared to replace and destroy cardiac myofibrils and were surrounded by abundant fibrous tissue. Immunohistochemically, T cells were detected as an intense rim-like staining of CD3-positive cells localized around the center of the granulomas ( fig. 1b). Negative results were obtained from polymerase chain reactions in cardiac tissue for genomic sequences of entero-, parvo B19, influenza, herpes, adeno- and Epstein-Barr viruses and for Chlamydia pneumoniae, Borrelia burgdorferi and Mycobacterium tuberculosis. Special stainings for infectious organisms were negative.



Chest computed tomography (CT), including high-resolution images, showed no typical features of pulmonary sarcoid. Transbronchial biopsies showed no signs of lung involvement, and the ratio of CD4/CD8 cells in bronchoalveolar fluid was normal (0.5, normal range 0.4–1.8). Investigation of other organs revealed an absence of systemic involvement including lymphadenopathy and ocular, neurological and cutaneous lesions. Sonography of the right kidney showed a loss of parenchyma due to recurrent episodes of chronic pyelonephritis in the past. The activity of angiotensin-converting enzyme was 22 U/l (normal range 18–55), and the serum creatinine level was slightly increased (1.1 mg/ml, normal range 0.4–1.0). Serum troponin T levels were normal.

Sequencing of the patient's *btn12* gene revealed a homozygous G - A transition in exon 5 constituting the sarcoidosis-associated risk variant rs2076530 ( fig. 2).

G A A G G T G G T A A G T A G A A T T C

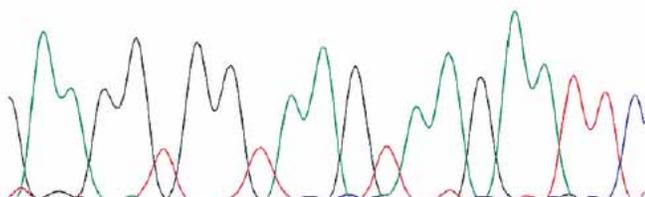


Fig 2: Electropherogram showing a homozygous G ] A transition (underlined) in exon 5 of the patient's *btn12* gene. The mutated gene codes for a splice variant which lacks the carboxy-terminal immunoglobulin-like constant domain and the transmembrane helix. The truncating splice site mutation (rs2076530) has been identified as a risk factor for sarcoidosis.

With regard to the arrhythmias, loading with amiodarone was efficient to suppress the tachyarrhythmias, and the patient became hemodynamically stable within the next days. Weaning from the respirator proceeded without complications. When extubated, the patient was fully orientated but suffered from a minor form of retrograde amnesia.

Immediately after diagnosing cardiac sarcoidosis, the patient was administered high doses of oral corticosteroids (initially prednisolone at 250 mg per day). The DDD pacemaker device was upgraded to a biventricular resynchronization system including an implanted cardioverter defibrillator. Under treatment with amiodarone and steroids, no further episodes of ventricular tachycardia occurred.

## Discussion

Isolated cardiac sarcoidosis has been described in a few case reports, but is extremely rare and usually preceded future involvement of other organs [1, 3, 5]. Sarcoid heart disease without evidence of systemic manifestation is a diagnostic challenge for the treating physician, because most of the noninvasive diagnostic procedures performed are unable to detect granulomatous infiltrates in the myocardium. Routine imaging techniques such as echocardiography allow the assessment of global or segmental left ventricular dysfunction, but frequently fail to reveal signs of myocardial inflammation. Recently, cardiac magnetic resonance imaging (MRI) has been suggested as a promising and comprehensive investigation for the early diagnosis of cardiac sarcoidosis [9, 10]. Although MRI provides a reliable estimation of the extent of cardiac involvement, data on how accurate the technique differs between sarcoid lesions and other forms of inflammatory heart diseases are not available. Moreover, not for all patients, such as in our case, is MRI a suitable diagnostic procedure. Laboratory tests for elevated serum levels of angiotensin-converting enzyme, although a common finding in sarcoidosis, are difficult to interpret in heart failure patients who are commonly on medication with angiotensin-converting enzyme inhibitors [11]. Measuring troponin levels does not add further strength to the differential diagnosis of sarcoidosis, since they are usually normal, as also seen in our patient [12]. As in our case, endomyocardial biopsy is very useful in diagnosing isolated cardiac manifestation of the disease. However, a negative biopsy does not rule out sarcoid heart disease due to a patchy or focal distribution of granulomas and the limited diagnostic sensitivity of the procedure [7, 13, 14].

In a recently published genetic study, sarcoidosis has been linked to a truncating splice variant in the *btnl2* gene [8]. The authors reported that a point mutation in the *btnl2* gene introduces a cryptic splice site located 4 base pairs upstream of the affected wild-type donor site that generated a mutant protein with a premature stop codon. The truncated BTNL2 protein lacks a membraneanchoring domain and exhibits disrupted membrane localization. BTNL2 is expressed in cells of the immune system and has been implicated as a receptor molecule involved in the control of T cell proliferation. Loss of membrane localization appears to impair the inhibitory immunoregulatory function of BTNL2. Thus, the altered intracellular distribution of mutant BTNL2 may account for the exaggerated cellular immune response and increased inflammatory activity of macrophages seen in sarcoidosis. In the study population from the German sarcoidosis consortium, the odds ratio of the susceptibility allele rs2076530 was 1.60 in heterozygotes and 2.75 in homozygotes, suggesting only a moderate influence on the individual risk level [8]. Nonetheless, identifying the risk-associated single nucleotide polymorphism may help to predict sarcoidosis as the underlying cause of heart failure. Particularly, younger patients, who are at a low risk of ischemic cardiomyopathy, may benefit from a refined diagnostic strategy that includes the routine testing of the *btnl2* haplotype.

## Summary

Early diagnosis of cardiac sarcoidosis is important, because the prevalence of ventricular tachycardia and a complete heart block is high among these patients. Sudden cardiac death due to ventricular fibrillation may be the first symptom of the disease and many cases of isolated heart involvement are only diagnosed postmortem. Other signs of cardiac involvement include left ventricular enlargement, wall motion abnormalities of localized or diffuse nature and diastolic stiffness of the ventricular wall, papillary muscle dysfunction and pericardial effusion. As in our case, endomyocardial biopsy is useful in diagnosing isolated cardiac manifestation of the disease. However, a negative biopsy does not rule out sarcoid heart disease due to a patchy or focal distribution of granulomas and the limited diagnostic sensitivity of the procedure [7, 13, 14]. Screening for the respective haplotype may help to identify patients with heart failure caused by sarcoid infiltration of the myocardium. Treatment with high doses of corticosteroids appears to prevent the remodeling of the myocardial tissue and improves left ventricular function [6, 15].

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

Effects of Mechanical Stress and Carvedilol in Lamin A/C-Deficient Dilated Cardiomyopathy. Chandar S, Yeo LS, Leimena C, Tan JC, Xiao XH, Nikolova-Krstevski V, Yasuoka Y, Gardiner-Garden M, Wu J, Kesteven S, Karlsdotter L, Natarajan S, Carlton A, Rainer S, Feneley MP, Fatkin D. *Circ Res*. 2009 Dec 17. [Epub ahead of print]

The yield of risk stratification for sudden cardiac death in hypertrophic cardiomyopathy myosin-binding protein C gene mutation carriers: focus on predictive screening. Christiaans I, Birnie E, van Langen IM, van Spaendonck-Zwarts KY, van Tintelen JP, van den Berg MP, Atsma DE, Helderma-van den Enden AT, Pinto YM, Hermans-van Ast JF, Bonsel GJ, Wilde AA. *Eur Heart J*. 2009 Dec 16. [Epub ahead of print]

Contrast echocardiography guidance for alcohol septal ablation of hypertrophic obstructive cardiomyopathy. Himbert D, Brochet E, Ducrocq G, Vahanian A. *Eur Heart J*. 2009 Dec 17. [Epub ahead of print]

Melusin gene (ITGB1BP2) nucleotide variations study in hypertensive and cardiopathic patients. Palumbo V, Segat L, Padovan L, Amoroso A, Trimarco B, Izzo R, Lembo G, Regiz Zagrosek V, Knoll R, Brancaccio M, Tarone G, Crovella S. *BMC Med Genet*. 2009 Dec 17; 10(1):140.

Cardiac Myosin Heavy Chain Isoform Exchange Alters the Phenotype of cTnT-Related Cardiomyopathies in Mouse Hearts. Rice R, Guinto P, Dowell-Martino C, He H, Hoyer K, Krenz M, Robbins J, Ingwall JS, Tardiff JC. *J Mol Cell Cardiol*. Dec 2009. [Epub ahead of print]