European Society of Cardiology
Working Group on
Myocardial & Pericardial Diseases

Newsletter

Issue 17 - October 09

Myocardial and Pericardial Diseases
ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®

Editorial News

INSIDE THIS ISSUE:

Dear Members of the Working Group,

please find enclosed the 17th 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 September 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. Pankuweit

The paper of the month:

Diagnostic synergy of non-invasive cardiovascular magnetic resonance and invasive endomyocardial biopsy in troponin-positive patients without coronary artery disease.
Baccouche H, Mahrholdt H, Meinhardt G, Merher R, Voehringer M, Hill S, Klingel K, Kandolf R, Sechtem U, Yilmaz A. Eur Heart J, August 20, 2009 epub ahead of print

Presented by Lukasz A. Malek, M.D. PhD[1,2], Assoc. Prof. Zofia T. Bilinska, M.D. PhD[1],
[1]1st Department of Cardiology and [2]Cardiovascular Magnetic Resonance Unit Institute of Cardiology, Warsaw, Poland

Summary
The paper presents a retrospective study on a group of 82 patients with TnI-positive acute chest pain and no evidence of significant CAD who underwent late gadolinium enhancement cardiac magnetic resonance imaging (LGE-CMR) and CMR-guided endomyocardial biopsy (EMB) in the process of the diagnostic work-up. Each of the procedures alone enabled the final diagnosis with similar frequency (80% and 88%, respectively) while the combined approach had the highest diagnostic accuracy (95%). Overall, both procedures had a substantial match of diagnoses (kappa=0.70). Myocarditis was the most common diagnosis by either LGE-CMR or EMB, but it was more readily disclosed with EMB (58 vs. 81%, $p<0.001$). Among 16 LGE-CMR failed diagnoses, there was 1 diagnosis of active myocarditis and 10 of borderline myocarditis by EMB. On the other hand, of 10 EMB failed diagnoses, myocarditis was found in 5 patients by LGE-CMR. The problem of sampling error inherent to EMB may be avoided with CMR, but borderline myocarditis detected by EMB may be missed by LGE-CMR alone, possibly due to the limited spatial resolution. To summarize, LGE-CMR and EMB have a good diagnostic performance in patients with TnI-positive acute chest pain and absence of significant CAD. Combining these methods helps to overcome some limitations of the techniques applied individually.

Comments
Baccouche et al. address a common problem of patients admitted to hospital because of biomarker-positive acute chest pain, who have no evidence of critical stenoses on coronary angiography. In this setting, in the TACTICS-TIMI18 trial the rate of death or reinfarction at six months was 3.1% [1]. The article strengthens the role of LGE-CMR as a noninvasive tool in the differential diagnosis of patients with TnI-positive acute chest pain and non-significant CAD. The method is safe, reproducible, and is becoming widely available. Arguably the most important feature of CMR is late gadolinium enhancement [2]. Different patterns of LGE distribution within the myocardium help to differentiate between ischaemic and non-ichaemic causes of the disease and in many cases provide information on the etiology of non-ischaemic myocardial injury (i.e. myocarditis, hypertrophic or dilated cardiomyopathy, amyloidosis, etc.). The pattern of LGE distribution can be especially useful in the evaluation of myocarditis and myocardial infarction [3].

Endomyocardial biopsy has been a gold-standard technique in the diagnosis of myocarditis for years [4]. Current recommendations for endomyocardial biopsy do not involve patients with troponin positive ACS and normal coronary arteries on coronary angiography, especially when they respond to conventional treatment, have no dysrrhythmia and deteriorating LV function [5]. The majority of patients with myocarditis, presenting with a mask of MI have excellent long-term prognosis [4]. However, late sudden deaths have been reported [1,4,6] and some of the patients have progression to dilated cardiomyopathy with time [7]. That is why, identifying the cause of the disease, explaining its pathogenesis, learning more about the myocardial tissue disease process may be helpful in defining patients' prognosis [8]. On the other hand, endomyocardial biopsy is an invasive procedure, although safe in experienced hands, but with a small percentage of complications related to the procedure [4]. Death and cardiac tamponade have been reported, although no complications were observed in the presented paper. Other inherent limitations of endomyocardial biopsy are sampling error that may lead to a negative diagnosis with smoldering, patchy process of myocarditis. Interobserver variability in the interpretation of data is another issue.

In this paper, the authors used immunohistological criteria, developed initially for the diagnosis of a chronic inflammatory process in the setting of a clinically acute disease. The immunohistological criteria of active myocarditis applied by Baccouche et al. define the inflammatory infiltrate as ≥14 leukocytes/mm^2 (CD3+ T lymphocytes and/or CD68+ macrophages) with additional myocardial damage, while borderline myocarditis – without myocardial damage/necrosis [9]. In order to assess chronic myocardial inflammation, other authors used the criterion of ≥7 leukocytes/mm^2 (CD3+ cells) [10,11]. There are few reports on the results of endomyocardial biopsy in the setting of MI-mimicking myocarditis [4,12].

True acurate diagnosis of myocarditis may be life-saving, especially in the setting of rare forms of myocarditis, like giant-cell, eosinophilic myocarditis [13,14]. CMR is by no means helpful in defining the type of inflammatory infiltrate in the myocardium, and this knowledge influences on the way of treatment.

Kuhl et al. identified genomes of Parvovirus B19 in the myocardial tissues of patients presenting with ACS and normal coronary angiography [12]. Parvovirus B19 is known to infect endothelial cells and to cause obstruction of microcirculation, in this way leading to ischemia, micro-areas of necrosis, and elevation of necrotic enzymes [15]. Of interest, Mahrholdt et al. demonstrated that each of two most common agents causing viral myocarditis [parvovirus B19 (PVB19) and human herpesvirus 6 (HHV6)] can lead to a different pattern of myocardial damage and clinical course as demonstrated with LGE-CMR [16]. The identification of viral genome in the myocardium has prognostic implications [12,17].

In the presented paper, endomyocardial biopsy was shown to be superior to LGE-CMR in identifing myocarditis mostly due to its ability to reveal minor forms of the disease (borderline myocarditis). There are at least two causes which could have influenced this finding. First, endomyocardial biopsies performed in the presented study were all CMR-guided, which most likely improved the diagnostic accuracy of this procedure. Secondly, limitations of CMR protocol to cine and LGE-CMR could have underestimated the diagnostic potential of CMR in myocarditis. The study by Abdel-Aty et al. demonstrated that the diagnostic accuracy of CMR in myocarditis increased with the extension of LGE-CMR protocol by addition of two other sequences: T2W triple inversion recovery (to assess myocardial oedema) and T1W spin echo early after gadolinium injection (reflecting increased hyperemia and capillary leak) [18]. The best diagnostic accuracy was achieved with any two positive out of three sequencies yielding 85% diagnostic accuracy.

That study and also others led to the recent development of standardized CMR protocol and diagnostic criteria for myocarditis known as Lake Louise Consensus Criteria [19]. According to those criteria the presence of at least two out of three findings consistent with myocardial inflammation (regional or global myocardial oedema on T2W imaging, global hyperemia and capillary leak on T1W imaging early after gadolinium administration or at least 1 focal lesion with a nonischaemic pattern of necrosis/fibrosis on inversion recovery prepared T1W images late after gadolinium administration) in a patient with clinical suspicion of myocarditis are diagnostic of the disease. The presence of left ventricular dysfunction or pericardial effusion are also supportive [19]. If there is strong clinical evidence of myocardial inflammation and the onset of symptoms has been very recent but none of the criteria are present or if only one of the criteria is present, a repeat CMR study between 1 and 2 weeks after the initial one is recommended [19].

To sum up, as suggested by the authors of the paper CMR should become the first line method in the diagnosis of unknown causes of TnI-positive acute chest pain without the evidence of CAD, with EMB limited to cases of unknown or uncertain diagnosis after CMR study and clinically important indications, e.g. deteriorating LV function, new atrio-ventricular blocks, complex ventricular arrhythmias. An appropriate use of these methods may help to overcome some limitations of individually applied techniques.

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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 Tiina Heliö and Dr Maija Kaartinen,
Helsinki University Central Hospital, Helsinki, Finland.

Forty year old man with a rapidly developed severe dyspnea preceded by bronchitis for two weeks

Case Presentation:

A 40- year old Finnish man from the capital area was admitted to the hospital emergency because of severe dyspnea following two weeks of bronchitis.
The patient had been previously healthy. He was a smoker but was not diagnosed with any pulmonary disease. He did not have any regular medication.
He had initially symptoms of an upper respiratory tract infection. As the symptoms persisted, bronchitis was suspected and he was prescribed roxithromycin at the health center.

Four days later he was admitted to the hospital emergency because he could hardly walk 100 meters because of severe dyspnea. There was no chest pain. In physical examination, the patient was febrile and his respiratory frequency was 40/min. His blood pressure was 130/78 mmHg, he had sinus tachycardia 144/min, and oxygen saturation was 94% with oxygen mask. In auscultation, rales could be heard from the lungs. ECG is shown in Figure 1. Laboratory analyses demonstrated leucocytosis (23.9 10^9/l) and high CRP (277 mg/l). During episodes of dyspnea, he became hypotensive and oxygen saturation dropped down to 90% and CPAP treatment was started. Thorax-X-ray is shown in Figure 2.

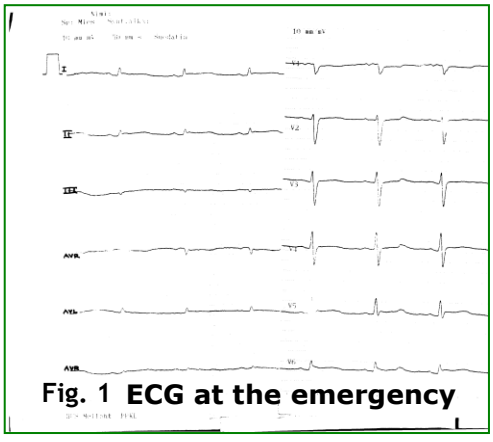

Fig. 1 ECG at the emergency

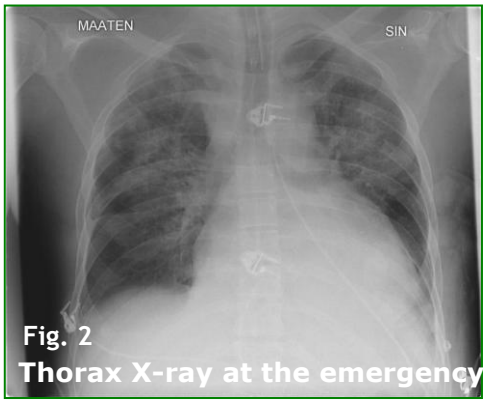

Fig. 2
Thorax X-ray at the emergency

Clinical diagnosis was pneumonia and sepsis. Intravenous inotropes, cefuroxim and levofloxacin were initiated. However, the patient 's condition continued deteriorating twenty four hours after he had arrived at the hospital. Despite noradrenalin infusion, fluid resuscitation, antibiotics and CPAP mask, respiratory difficulties grew and the patient had to be intubated and put to respirator. The next day blood bacterial cultures revealed a pneumococcus resistant to macrolide antibiotics. The patient was still hypotensive, BP dropped to 80/50 mmHg and had sinustachycardia 126/min and CRP remained high (201 mg/l).

What would you have done and why?

Answer for the previous" Clinical case of the month" presented in the September newsletter

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

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.

1. What is your interpretation about K600fs mutation behaviour in this family? Is K600fs mutation the real genetic cause of the disease?

Our answer: K600fs should be considered the cause of the disease in the affected carriers.
Besides the patient with HCM associated with this mutation described in the literature, our group has additional clinical data of 8 families with the K600fs mutation in the MYBPC3 gene. All those families come from Pontevedra, a province of Galicia in the northwest of Spain. The mutation cosegregates with the disease in the 8 families. There are 21 carriers of the mutation and penetrance is nearly 90% in subjects older than 30 years old. Average maximal wall thickness is 20 mm and only two cases have more than 30 mm (one of them with a second mutation). Most carriers are in NYHA functional class II. Left atrial enlargement and atrial fibrillation were common, especially in those carriers who had been practice competitive sports. Consequently, two mutation carriers younger than 55 year old suffered ischemic strokes.
We used BLAST program to assess predicted functional consequences of K600fs mutation. This analysis predicted a stop codon that leads to protein C truncation on amino acid 601 with the consequent lost of C4 and successive domains. Moreover, this mutation was absent in 323 healthy adult controls (100 from the literature[1] and 223 from our own investigation).
This information strongly supports the association of the K600fs mutation with the development of hypertrophic cardiomyopathy.

2. Could K600fs mutation have a heterogeneous phenotypic manifestation in the two carriers of the presented family?

Our answer: It could be, but there may be other explanations.
The index patient has asymmetric septal hypertrophy comparable to the phenotype that we have identified in multiple carriers from other families. However, the phenotype of the second carrier (one of his daughters) is different, without left ventricular hypertrophy but with apical hypertrabeculation. The absence of the typical hypertrophy may be explained by the age of the patient and delayed onset of the disease expression. The presence of apical trabeculation may have three explanations: a) It is a normal variant, b) Is a different phenotypic manifestation of the K600fs mutation, c) It has a different cause, which may be a second mutation in the family. We do not think that it is within the normal spectrum for a Caucasian young woman.

3. Apparently, this mutation does not cosegregate in some family members. Could genetic test have a false negative result in the clinically affected son?

This question is connected with the previous. We initially considered that the son of the index was clinically affected because of the presence of apical trabeculation, but he did not have hypertrophy in other segments. We confirmed that he did not carry the K600fs mutation. As in his father, apical trabeculation was not present in other carriers of the K600fs mutation from 8 different families. Thus we suspected that there are two different phenotypes in this family: HCM and apical trabeculation. The absence of the mutation in the son that did not have hypertrophy does not exclude the cosegregation of the K600fs with HCM in the family. K600fs did not cosegregate with the apical hypertrabeculation.

4. What would be your next attitude?

Our answer: See the mother!

We suspected the presence of two different phenotypes in the family explained by the presence of other genetic factor associated with the development of apical hypertrabeculation. Proband's wife clinical assessment was done (subject I:2). Her physical exam and ECG (Fig. 1) were normal. The echocardiogram showed normal wall thickness in the basal and mid-left ventricular segments but prominent trabeculations in the apical posterior, inferior and lateral walls were detected (Fig. 2 and 3).

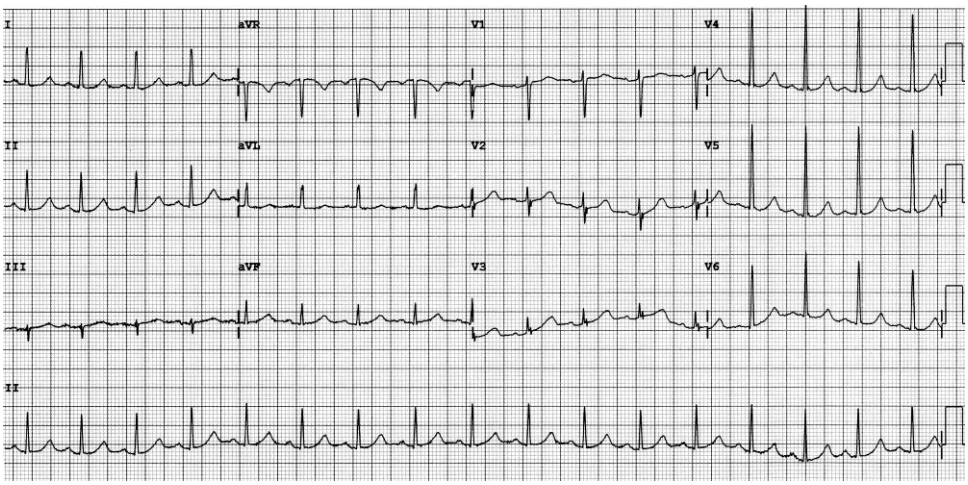

Fig. 1. ECG

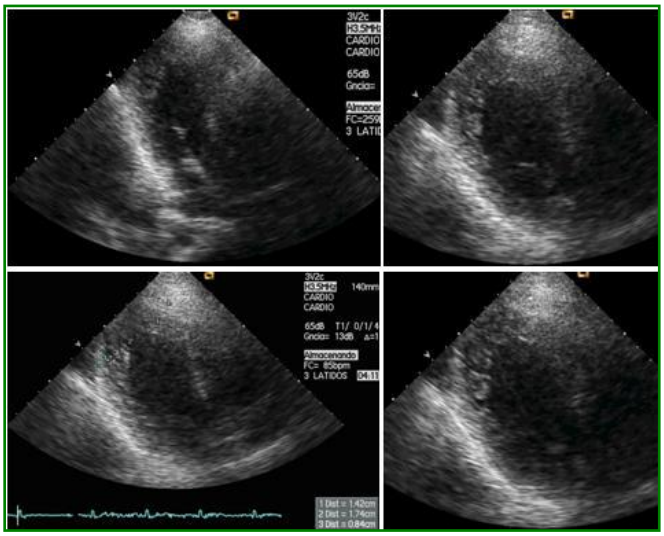

Fig. 2. Echocardiogram: three-chamber apical view

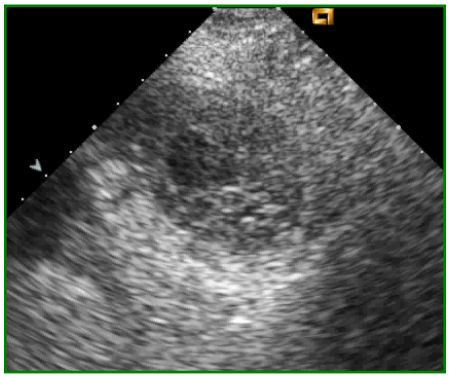

Fig. 3. Echocardiogram: parasternal short axis view (apical level)

So, two different phenotypes were present in the same family and siblings could inherit different combination forms (Fig. 4). To date, no mutation has been detected in subject I:2 (MYH7, MYBPC3, TNNT2, TNNI3 and TPM1 genes sequencing already performed).

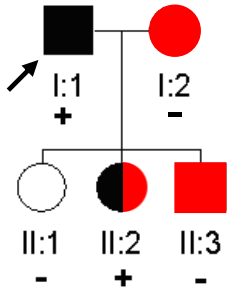

Fig. 4. New pedigree. White symbols: not affected subjects; black symbols: HCM affected subjects; red symbols: subjects affected with apical hypertrabeculation. Subject II:2: presented apical hypertrabeculation but she carried K600fs mutation associated with HCM and has the possibility of develop both phenotypes. + and – symbols represent presence or absence of K600fs mutation in MYBPC3 gene respectively.

Genetic test and complete clinical familial study allowed us to suspect this complex disease presentation: two different phenotypes converging in the same family. These data are also useful to reaffirm K600fs as a disease causing mutation.

Our conclusion in this family is that there are two different problems: hypertrophic cardiomyopathy caused by the K600fs mutation in MYBPC3 (I.1 affected, II:2 carrier that could develop the disease later in life) and apical hypertrabeculation that would be associated with a second (still unknown) genetic cause (I:2 affected, II:2 affected, II:3 affected). A relevant implication of this knowledge is that patient II:2 could have a different evolution and risk compared with other carriers of the K600fs mutation, because of the presence of a second genetic factor.

This case illustrates both the usefulness of the genetic testing for an appropriate interpretation of the clinical findings, and the importance of a detailed and full clinical study of the families for an appropriate interpretation of the genetic results.

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

1) Calcineurin Protects the Heart in a Murine Model of Dilated Cardiomyopathy. Heineke J, Wollert KC, Osinska H, Sargent MA, York AJ, Robbins J, Molkentin JD J Mol Cell Cardiol. 2009 Oct 22. [Epub ahead of print]

2) Myocardin is required for cardiomyocyte survival and maintenance of heart function. Huang J, Lu MM, Cheng L, Yuan LJ, Zhu X, Stout AL, Chen M, Li J, Parmacek MS. Proc Natl Acad Sci U S A. 2009 Oct 22. [Epub ahead of print]

3) New ECG criteria in arrhythmogenic right ventricular dysplasia/cardiomyopathy. Cox MG, van der Smagt JJ, Wilde AA, Wiesfeld AC, Atsma DE, Nelen MR, Rodriguez LM, Loh P, Cramer MJ, Doevendans PA, van Tintelen JP, de Bakker JM, Hauer RN. Circ Arrhythm Electrophysiol. 2009 Oct;2(5):524-30. Epub 2009 Jul 7.

4) Myocarditis: Infection Versus Autoimmunity. Rose NR .J Clin Immunol. 2009 Oct 14. [Epub ahead of print]