European Society of Cardiology
Working Group on
Myocardial & Pericardial Diseases

Newsletter

Issue 23 – April 2010

Editorial News

INSIDE THIS ISSUE:

Dear Members of the Working Group,

please find enclosed the 23th 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 march 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:

Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. Proposed modification of the Task Force criteria

Marcus FI, McKenna WJ, Sherril D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MGPJ, Daubert JP, Fontaine G, Gear K, Hauer R, Nava A, Picard MH, Protonotarios N, Saffitz JE, Sanborn DMY, Steinberg JS, Tandri H, Thiene G, Towbin JA, Tsatsopoulou A, Wichter T, Zareba W. Circulation 2010 Feb 19 [Epub ahead of print], Eur Heart J. 2010 Feb 19 [Epub ahead of print]

Presented by Dr. Alison Muir and Dr. Perry M. Elliott, Inherited Cardiovascular Disease Unit, Department of Cardiology, The Heart Hospital, University College of London, London, UK.

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a disorder clinically characterised by ventricular arrhythmia, heart failure and sudden death and histologically by cardiomyocyte loss and replacement with fibrous or fibro-fatty tissue. The estimated prevalence of ARVC is 1 in 5000 of the population and it is an important cause of sudden cardiac deaths in athletes and in people under 35 years. In many individuals, the disease is caused by mutations in genes that encode different components of the intercalated disc of cardiomyocytes.

The diagnosis of ARVC is challenging due to the non-specific nature of clinical findings and the absence of a single diagnostic test. In an attempt to improve the accuracy of clinical diagnosis, a task force of international experts was convened in 1994 under the auspices of the Scientific Council of the International Society and Federation of Cardiology (ISFC) and the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Clinical and pathological features were grouped into 6 categories and assigned either major or minor status depending on the perceived specificity for the diagnosis. The presence of two major criteria from different categories, or one major and two minor, or four minor criteria, all from different categories was considered diagnostic of ARVC (1). From its inception, it was recognised that this approach had limitations, not least the lack of sensitivity of many of the criteria. This is particular true in families affected by ARVC where carriers of disease causing mutations often have very subtle findings that would not ordinarily lead to a diagnosis of ARVC in everyday clinical practice (2).

In this update, Marcus and colleagues propose modifications to the 1994 Task force criteria to increase sensitivity without losing specificity (3). The primary aims were to reduce reliance on subjective criteria for assessing ventricular structure and function and to incorporate data from cardiac magnetic resonance imaging and genetic analysis. The method was to compare data from 108 probands with newly diagnosed ARVC to those of normal subjects. Diagnostic criteria were selected after analysis of their sensitivity and specificity from receiver operator curves, with exclusion of proband test data if those data were crucial for the individual's diagnosis, to eliminate bias.

As in the original document, the diagnosis of ARVC is based on the identification of structural, histological, ECG, arrhythmic features and a family history. The sub-categorisation into major and minor criteria is also maintained. In the new system, patients are diagnosed with "definite" ARVC if they have 2 major, 1 major plus 2 minor, or 4 minor criteria from different categories, and "borderline" ARVC with 1 major and 1 minor, or 3 minor from different categories. The introduction of the novel term "borderline" ARVC enables the clinician to inform those individuals with minor abnormalities but not definite disease that they are at risk and require regular follow up.

Assessment of Structural Alterations

In the original criteria, structural abnormalities were defined as severe or mild and classified as major or minor criteria, respectively. This method relied heavily on subjective assessment of RV wall thinning and wall motion abnormalities and was thus subject to substantial inter-observer variability. The new criteria are based upon quantitative measurements of ventricular volumes and function using MRI and 2-D echo corrected for body surface area (3). The inclusion of quantitative parameters is clearly a major step forward, but there are important caveats. The authors recognise that the reference values for the normal subjects were determined from select populations and so the reference values quoted will not apply to all ethnic populations and may not apply to those under 12 years of age. Some subjectivity remains; for instance, major and minor echo criteria are defined by the presence of a regional wall motion abnormality (although hypokinesis is now excluded) which can be extremely difficult to assess using conventional 2-D echocardiography. Cardiac MRI theoretically reduces subjective bias as it not restricted by acoustic windows and can accurately assess RV wall motion abnormalities and volumes (4). However, significant degrees of inter-observer variability with regard to interpretation of wall thinning, localised functional abnormalities and fatty deposition are still a problem even with CMR (5) and so imaging should be performed in specialist centres using a dedicated protocol to analyse volumes, RV regional wall motion abnormalities and delayed enhancement imaging (6). The same is true of RV angiography, which although regarded as the gold standard imaging technique for ARVC in the past requires significant experience and should be reserved for specialised centres that frequently perform the technique (7,8).

Tissue Characterisation

This category previously only had one major criterion, which was met if fibrofatty replacement could be demonstrated on endomyocardial biopsy. It has now been subclassified into major and minor criteria dependent on the percentage of observed residual myocytes in an endomyocardial biopsy with observed fibrous replacement, with or without fatty replacement (3). The conventional endomyocardial biopsy however lacks sufficient sensitivity due to the segmental nature of the disease. Studies show that biopsy guided by electroanatomic voltage mapping to areas of low voltage, may increase the diagnostic accuracy of biopsy (9). A role for endomyocardial biopsy and immunohistochemical testing has emerged recently. A reduced immunoreactive signal for plakoglobin at intercalated discs was a consistent feature of ARVC and not other forms of diseases and this approach represents an exciting potential new diagnostic test for ARVC but is appropriately not included in the proposed revised criteria as it requires confirmation in larger series before being adopted as a reliable diagnostic technique (10).

Assessment of ECG Abnormalities

ECG changes in ARVC are reported in up to 98% of cases (11). The most common repolarisation abnormality is T wave inversion in the right praecordial leads (V1-V3) in the absence of right bundle branch block (RBBB), which has been reported in 54%-85% of probands (12,13). These repolarisation abnormalities were previously considered as minor diagnostic criteria due to their lack of specificity and because T wave inversions are more likely to represent cases with severe dysfunction (14). Complete and incomplete RBBB are commonly observed in affected patients but are also common among normal subjects and were therefore excluded from the original diagnostic criteria (15). In the revised criteria T wave inversion in the right praecordial leads (V1-V3) or beyond in individuals >14 years of age in the absence of complete RBBB has been upgraded to a major criterion. Justification for this change comes from data showing that this ECG abnormality is observed in only 4% and 1% of normal women and men, respectively (15).

The new criteria also include a minor criterion for those individuals with more limited T wave inversion (V1-V2) or those with T wave inversion in the setting of complete RBBB as T wave inversion in V1-V4 in the setting of RBBB is uncommon in those who do not have ARVC and is frequently observed in those with the disease.

Depolarisation abnormalities associated with ARVC are due to the pathological changes seen in ARVC which result in delayed conduction in the RV free wall. In the original 1994 Task Force criteria, the presence of a post excitation epsilon wave (a distinct wave of small amplitude occupying the ST segment in the right precordial leads (16)) reflecting delayed right ventricular activation was considered a major diagnostic criterion (1). These have been reported in around 30% of cases (17) but the sensitivity can be significantly increased by using a highly amplified, modified recording technique. In one series, the incidence of epsilon waves increased from 23% to 77% with this change in recording technique (18) which has led to this remaining a major criterion in the proposed revised criteria (3).
Localised prolongation (>110ms) of the QRS complex in the right precordial leads (V1-V3), has been removed in the new criteria. In contrast "prolonged S wave upstroke" in V1-V3 of ≥55msec is included as a new minor criterion in the revised diagnostic criteria (17). This criterion has a high sensitivity on the standard ECG, reported in 84-95% of ARVC patients without RBBB (17,18), and has been correlated with disease severity.
The signal-averaged ECG (SAECG) is used to assess for evidence of late potentials, a sign of delayed depolarisation. This was previously considered abnormal when two or more of the following parameters were met: QRS duration >114msec; low amplitude signal duration <40μV (LAS) is >38msec or the root mean square voltage in the last 40msec of the QRS (RMS40) <20μV (19). This criterion was found to be abnormal in 58% of index cases and 45% of affected relatives (17,19). The proposed criteria now include any one of the three SAECG parameters as positive for late potentials because analysis of the sensitivity and specificity of any one criterion was similar to that of any two or three of these criteria (3).

Assessment of Arrhythmias
Early studies reported ventricular arrhythmias in 42-64% of patients (19), but these did not constitute a major criterion in the original Task Force criteria. In the revised criteria, ventricular tachycardia of LBBB morphology with superior axis is reclassified as a major criterion, while LBBB VT with inferior axis is a minor criterion. This is because LBBB VT with an inferior axis is typical of RVOT tachycardia and not specific to ARVC (20).
The presence of >1000 extrasystoles in a 24 hour period was a second minor diagnostic criterion which has been reported in 22-42% (17,19). However, the cut of 1000 extrasystoles was arbitrary. The revised proposed criteria lower the volume of ventricular ectopy representing a minor criterion to >500/24 hours but again, this cut off requires further validation in prospective studies.

Assessment of Family History
The original 1994 criteria defined the presence of confirmed ARVC at necropsy or surgery as a major criterion, but a family history of sudden cardiac death due to presumed ARVC or a family member meeting 1994 diagnostic criteria for the disease were only minor criteria. Since 1994, understanding of the pathophysiology of this disease has vastly expanded with the identification of numerous mutations in components of the desmosome. The revised criteria have been updated to include this genetic information.

As well as a first degree relative meeting the new Task Force criteria or a having confirmed disease at necropsy or surgery, positive genetic results in the patient under evaluation now constitute major criteria. A pathogenic mutation is categorised as associated or probably associated with ARVC if it alters or is expected to alter the encoded protein, alters or is predicted to alter the structure or function of that protein, is un-observed in large non ARVC/D control populations, or has demonstrated linkage to the disease phenotype in a conclusive pedigree. The difficulty with this criterion is that many mutations identified are novel and it can be difficult to predict the functional implication of these mutations. Minor criteria in the family history category remain a sudden cardiac death in a first-degree relative at less than 35years due to suspected ARVC or first-degree relative with a clinical diagnosis in whom the Task force criteria cannot be applied to determine if they are met or not. For the first time, a diagnosis of ARVC either clinically or pathologically in a second degree relative is also included as a minor criterion recognising that in large families where individuals are affected, small abnormalities that previously did not meet Task Force criteria could represent disease burden.

Implications of the new criteria

The fundamental problem with ARVC is that unlike most other cardiomyopathies, there is no simple gold standard on which to base the diagnosis. Hypertrophic and dilated cardiomyopathies, for example, are defined respectively by an increased wall thickness or ventricular dilatation with impaired systolic function, whereas the contemporary concept of ARVC is based on a triad of histopathological, clinical and genetic abnormalities that require multiple clinical and molecular tools to define them.

The aim of this new diagnostic algorithm is to enhance the definition of each of these specific components of the ARVC paradigm in order to increase the sensitivity of the previous diagnostic criteria. It is probable that this goal will be achieved with respect to patients that have right ventricular disease caused by desmosomal protein gene mutations, not least because of the prominence given to a genetic diagnosis and family history in the new scheme. However, it will also highlight the many pitfalls inherent in the techniques used to make a diagnosis. For example, assessment of right ventricular dimensions and function requires a systematic approach and a degree of experience in order to avoid misinterpretation of normal variants. Similarly, sampling error in endomyocardial biopsy can result in both false positive and false negative findings. Perhaps, the greatest danger, however, is an over reliance on genetic analysis to make a diagnosis. Emerging data are showing that some sequence variants in desmosomal protein genes are relatively common in normal controls and in patients with other cardiomyopathies. Thus, due caution should be applied when a novel sequence variant of uncertain pathogenicity is found in a patient with borderline clinical features.

It is very likely that the new criteria, if carefully and thoughtfully applied, will be more specific for the diagnosis of patients and relatives with classical right ventricular fibrofatty replacement caused by mutations in desmosomal protein genes. However, we strongly suspect that this increased specificity will probably reflect the enhanced familial and genetic criteria rather than the more detailed assessment of right ventricular size and function. The underlying assumption of the new criteria is that the histopathological, clinical and genetic concepts of the disease are highly concordant. It is important to remember, however, that in everyday clinical practice much of the information required for a "definite" diagnosis may be difficult to acquire or interpret. For example, sampling error in endomyocardial biopsy or the presence of a novel sequence variant in a desmosomal protein gene.

Moreover, the ARVC phenotype can be caused by other genetic and acquired disorders that if overlooked or misdiagnosed could result in inappropriate treatment and incorrect advice to families. In conclusion, the authors deserve praise for their thoughtful reappraisal of the 1994 criteria, but it is critically important that clinicians recognise the limitations of even the most modern diagnostic tools and always interpret the results of tests in the light of the patients presentation, family pedigree and signs and symptoms.

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

A Young Patient with Restrictive Cardiomyopathy and Severe Pulmonary Hypertension

Case Presentation:

A 24-year-old patient was first evaluated at our Institution 6 years ago because of 6-month history of paroxysmal atrial fibrillation and a suspicion of restrictive cardiomyopathy. The patient complained of decreased exercise tolerance and palpitations. Physical examination at the time revealed a tall man (179 cm, 84kg, BSA 2 m^2) with barrel chest. Accentuated pulmonary component of the second tone was found. The patient was in sinus rhythm, right axis deviation and left atrial enlargement were present in 12-lead standard ECG. Chest X-ray revealed increased heart silhouette, left atrial enlargement and mild congestion in the pulmonary circulation. In echocardiographic examination, the sizes of both ventricles and right atrium were normal, however there was a significant left atrial enlargement (62 mm x 48 mm in 4-chamber view). LV and RV systolic functions were normal. There was no endocardial thickening. A Doppler echocardiographic study revealed a mitral restrictive filling pattern (E/A=2.7) and increased RVSP – approximately 45 mmHg (tricuspid regurgitation was slight), pulmonary acceleration time was 90 ms. In TEE there were no heart defects as well, proximal parts of coronary arteries were normal. Subsequently cardiac MR and chest CT were performed without revealing any pericardial pathology. There was no evidence of any systemic disease in the patient. In 24-hour Holter monitoring, the mean heart rate was 77 bpm, there were no pauses, no arrhythmia. Alfa-galactosidase activity in serum and leukocytes was normal, CK activity was normal 82 U/l, serum ferrum concentration was 205 μg/dl. In an exercise stress test, the patient attained 10.9 METs with Bruce protocol, of note he had prolonged postexertional tachycardia, 5 minutes after the exercise his heart rate in sinus rhythm was 110-120 bpm.

Family history was negative with respect to heart failure, arrhythmias or cardiomyopathy. However, in clinical and noninvasive examinations, the patient's mother was found to be in atrial fibrillation with ventricular response 70-100 bpm. A subsequent echocardiographic study revealed enlargement of both atria (LA>RA), no indirect signs of pulmonary hypertension. Myocardial thickness and contractility were normal. She had a detectable troponin I (0.04 ng/ml). A beta-blocker (metoprolol succinate 50 mg) was introduced along with antithrombotic therapy to prevent thromboembolic complications. The patient's elder brother, although asymptomatic, was found to have mild left atrial enlargement in echocardiography.

Question 1: Based on the presented data, what other examinations could have been performed in the patient to clarify his condition?

For another 3 years, the patient suffered from recurrent episodes of paroxysmal atrial fibrillation with rapid ventricular response while on bisoprolol, uptitrated up to 10 mg and amiodarone were started. In addition, there was progression in his heart failure symptoms, the patient dropped out of his university studies (computer science).

Physically, jugular venous distention appeared, especially during effort, and the patient's head became oedematous at faster walk. In addition, mild hepatomegaly was present, there was neither ascites, nor ankle edema. Since then, to control congestive symptoms, the patient required 2 diuretics (frusemide and hydrochlorothiazide), spironolactone 25-50 mg. Bisoprolol at 10 mg and amiodarone were continued. Standard 12-lead ECG revealed: sinus rhythm 72 bpm, minor right axis deviation, left atrial enlargement, incomplete right bundle branch block RSR' in V1, tall R waves in RV leads suggestive of right ventricular hypertrophy. In echocardiography, a further increase in LA size (29 cm^2), restrictive filling pattern, RV systolic pressure from slight TR was 100 mmHg. A cardiopulmonary study in this young man showed MVO_2 of 22.3 ml/kg/min (50% of reference) and MVO_2 at AT was 16.7ml/kg/min, there was a drop in systemic pressure from 170 to 150 mmHg during maximal exercise, and his maximum METs was 6.4. At that time (in 2006), a first approach was made to define contraindications for HTX better, and right heart pressures were as follows: PCWP 43/43/42 mmHg, PA 71/41/53 mmHg, thus the transpulmonary gradient (TG) was 11 mmHg, RA: 12/8/8 mmHg, RV: 71/5-13 mmHg and LV: 100/24-34mmHg. CO – 5.8l/min, PAR 1.88 Wood units, and SVR – 13.7 Wood units. His coronary angiography was normal. The decision was to repeat right heart catheterization in 6-12 months. In 2007, more pronounced limitation of exercise capacity (swelling of his head at mild exercise), NYHA III, a drop in MVO_2 -20.5 ml/kg/min, MVO_2 at AT 13.3 ml/kg/min, PAP 57/23/37 mmHg, increased TG of 15 mmHg and PVR – 2.6 Wood units.

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

The patient was not entirely convinced to have cardiac transplant since he still could cycle on the level surface slowly for 1-2 hours. After a long discussion with the patient and his parents, we accepted the decision. Soon, the patient developed thyreotoxicosis due to amiodarone treatment that had to be controlled with thyreostatics. At the time, the patient was in atrial fibrillation, amiodarone was continued to control rapid ventricular response, he was hospitalized 3 times due to worsening of heart failure. Once the patient returned to euthyreosis, he spontaneously converted into sinus rhythm (Fig. 1).

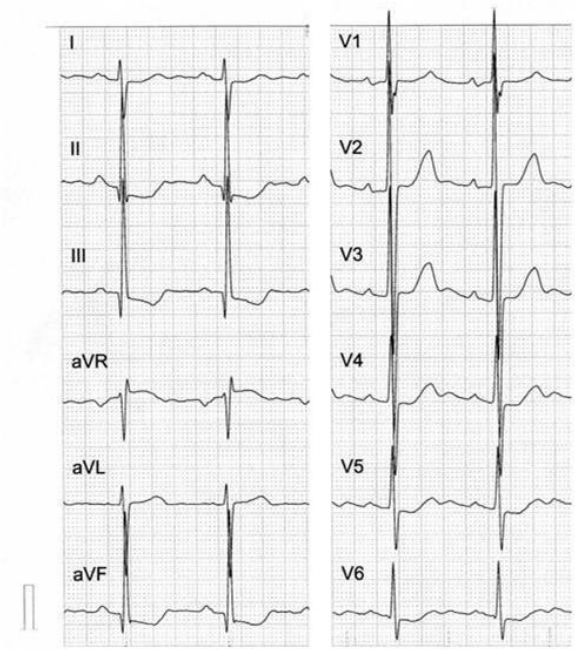

Fig. 1
12-lead standard ECG: sinus rhythm 62 bpm, right axis deviation, biatrial enlargement, RV hypertrophy, RSR' V1, Q waves in leads II,III, aVF QRS=120ms, QT 490ms, ST-T changes in infero-lateral leads.

In 2009, there was a significant deterioration in exercise capacity, the patient was unwilling to leave his place. CMR was performed (Fig. 2) showing biatrial enlargement (LA>>RA), both ventricles of normal size and contracting well LVEF 69%, RVEF 56%; corrected LV mass was 71 g/m^2, N:59-93; corrected RV mass was at the upper limit of normal: 28g/m^2, N:14-30, myocardial thickness: IVSD 12, PW-9mm, of interest no late enhancement after gadolinium injection was found.

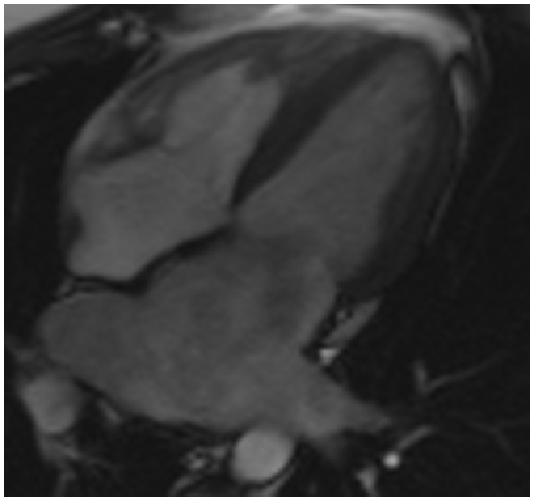

Fig. 2
MRI four-chamber CINE SSFP view - large dilatation of both atria (LA>>RA) with nondilated ventricles.

His Nt-proBNP level was not high (388 ng/ml), and the patient had detectable troponin I of 0.04 ng/ml. By the end of 2009, MVO_2 was 14 ml/kg/min, and together with the patient, we decided once more to approach the issue of HTX, this time with the assessment of pulmonary vascular reactivity. During sinus rhythm of 70 bpm, right heart catheterization demonstrated again increased pulmonary artery pressures (PAP 71/29/47 mmHg), pulmonary capillary wedge pressures (PCWP 31/39/28 mmHg), thus TG was 19 mmHg. Cardiac output was normal (CO – 6.2 l/min), and pulmonary vascular resistance was increased (PVR – 2.8 Wood units), however SVR was normal: 12.4 Wood units. After aerolised iloprost inhalation TG dropped from 19 to 14 mmHg, but pulmonary artery systolic pressure was 64 mmHg. Due to the presence of pulmonary hypertension, we introduced sildenafil at 12.5 mg po, but after the second dose the patient developed atrial fibrillation and needed a cardioversion to return to sinus rhythm. No further attempts were made.

Question 3: Would you have referred the patient for heart transplantation at this time point?

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

"ACUTE PERICARDITIS WITH CARDIAC TAMPONADE IN A YOUNG PATIENT: RARE ETIOLOGICAL BACKGROUNG WITH A PROLONGED, LIFE TREATENING COURSE"

by Arsen D. RISTIĆ, Ivan MILINKOVIĆ, Petar M. SEFEROVIĆ. Department of Cardiology, Clinical Centre of Serbia and Belgrade University School of Medicine, Belgrade, Serbia

Diagnosis, case resolution and treatment

According to the recommendations of the American rheumatology association (1), our patient fulfilled 4 of 11 criteria for diagnosis of systemic lupus erythematosus:

1. Polyserositis, 2. Haematological manifestations-relative lymphopenia, 3. Immunology manifestations with positive anti-dsDNK antibodies and 4. Positive antinuclear antibodies. However, initial clinical presentation was obscured, most probably with a viral infection accompanied (high CRP, cardiac tamponade), initially negative anti-nuclear antibodies, and gastrointestinal side-effects of applied antibiotic and tuberculostatic medications. In addition, signs of organisation of the chronic pericardial effusion with an unexplained, prolonged low-grade fever also suggested a possibility for tuberculous pericarditis (2-4)(excluded only by a favourable 2-year clinical course after a rapid discontinuation of tuberculostatic medications due to the subacute pancreatitis). After the proper management of acute cardiac tamponade (2, 5) our patient was haemodynamicaly stable, but only after initiation of low-dose steroid treatment our she became afebrile (very quickly) and all signs of poliserositis disappeared (pericardial and both pleural effusions and ascites). With adequate physical therapy, the signs of subatelectasis in portions of previous encapsulated pleural effusion also disappeared. Patient was discharged three months after the admission, in stabile condition, afebrile two weeks prior discharge, with no symptoms what so ever, and normal laboratory parameters, on low fat and protein diet and suggestion for regular controls of gastroenterologist and rheumatologist and on low doses of corticosteroids (Methylprednisolone 16 mg once daily with Chloroquine). Signs of pancreatitis resolved during the further 3 months. During the subsequent 2-year follow-up no recurrences of pericardial effusion and no progression of the systemic autoimmune diseases was noted despite the steroid treatment was subsequently reduced to 4 mg of methylprednisolone once daily) with no signs of constriction or any other complication.

Systemic lupus erythematosus (SLE) is chronic inflammatory disease of unknown aetiology that targets joints, kidneys, lungs, nervous system, seroses, and other organs. The prevalence among other systemic diseases is 20-80 on 100.000 cases (1,6). SLE may cause a pericardial effusion in about 30% of cases [1,2]. Although it may be recurrent, pericardial effusion is most often small (6). Cardiac tamponade occurs as initial manifestation of the disease occurs in less than 1% of cases (6-9). In our registry of 1200 patients with pericardial effusion this was the first cardiac tamponade in a patient with SLE. As in our case, when SLE is properly diagnosed and treated, involvement of the pericardium has a good prognosis (2,3). For recurrent forms an alternative treatment option would be intrapericardial instillation of triamcinolone (10).

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