European Society of Cardiology
Working Group on
Myocardial & Pericardial Diseases

Newsletter

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Editorial News

INSIDE THIS ISSUE:

Dear Members of the Working Group,

Please find enclosed the 12th 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 April case.

We would like to direct your attention to EUROPACE 2009, the congress of the European Heart Rhythm Association, taking place in Berlin on 21-24 June 2009. Don't miss the most important European congress on cardiac arrhythmias and pacing, featuring the launch of the *Beat it!* campaign, the new Einthoven Lecture, the renewal of the EHRA Board and much more...

Best wishes for all of you.

S. Pauliuvoit

The paper of the month:

A meta-analysis of randomized controlled trials in pulmonary hypertension. Galié N, Manes A, Negro L, Palazzini M, Bacchi-Reggiani ML, Branzi A. Eur Heart J 2009;30:394-403

Presented by L. Tavazzi, GVM Hospitals of Care and Research, Villa Maria Cecilia Hospital, Cotignola, Italy

Summary

Pulmonary hypertension (PH) does not belong to the conventional area of primary interest for the members of the WG on Myocardial and Pericardial diseases. However being scientifically and clinically up-dated on it may be important for at least two reasons. Firstly a major determinant of some forms of idiopathic PH (the cases of familial PH) is genetic. A variety of gene mutations and polymorphisms have been related to the pathogenesis of PH without reaching definite conclusions (1). Probably additional triggers are required for the development of the condition. However primary PH can be considered a possibly heritable cardiovascular disease, an area in which the WG is much interested. Secondly, chronic non idiopathic PH may be a component of the complex, largely ignored yet, pathophysiology of the so called heart failure with preserved left ventricular ejection fraction (HFPEF). Two recent papers deal with these two completely different forms of PH.

The idiopathic PH is a devastating disease characterized by a sustained elevation of mean pulmonary artery pressure to >25 mm Hg at rest or >30 mm Hg with exercise and with a mean wedge pressure <15 mm Hg. Although the pathogenesis of primary PH is unknown, there is consensus that after an endothelial dysfunction/injury, a strong imbalance between antithrombotic/prothrombotic, vasodilatation / vasoconstriction, and growth inhibition/promitogen forces develops. Three major pathways are recognized to play a role in this imbalance: the prostacyclin, nitric oxide, and endothelin pathways, which involve several mediators.Each of these pathways has been targeted with 3 different drug categories, namely, epoprostenol or other prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors. These agents have been tested against placebo or control, providing a consistent evidence of benefit on the clinical end points of functional capacity, albeit failing to support a survival advantage. The disease leads to progressive hypoxemia, right ventricular failure, and death, occurring from a few months to a few years after diagnosis.

A meta-analysis of all randomized controlled trials performed with such drugs published up to October 2008 have been published on the European Heart Journal (2). The main outcome measure was all-cause mortality. Twenty-one trials were included in the primary analysis (3140 patients) and two additional studies (59 patients) were included in the sensitivity analysis.
Average duration of the trials was 14.3 weeks (only!). During the short follow-up period all-cause mortality rate in the control group was 3.8%. Active treatments were associated with a reduction in mortality of 43% (RR 0.57; 95% CI 0.35–0.92; P = 0.023); the sensitivity analysis confirmed a reduction in mortality of 38% (RR 0.62; 95% CI 0.39–1.00; P = 0.048).
The cause-specific hospitalizations were reduced by 68%. Significant, although small to moderate, improvements in the hemodynamic central pattern, including pulmonary pressures and cardiac index, were also reported. The authors conclude that the results of this meta-analysis suggest, besides a clinical improvement, a benefit on survival in the patients treated with the targeted therapies approved for PH.

As acknowledged by the authors the limitations of this meta-analysis include the prolonged period of time between the publication of the first and the last RCT (about 18 years), the different duration of the trials (ranging from 8 to 36 weeks), the lack of blindness in some studies, the pooling of multiple active treatment arms (potential alteration of the trial structure), the report of secondary outcome parameters only in part of the RCTs (possible reporting bias), and potential heterogeneity in the conduct of the trials and in the definition of hospitalization for pulmonary arterial hypertension in different RCTs (no individual patients data were reviewed).

Actually, all trials reported so far in PH were short, small and (consequently) based on surrogate end-points (usually the six minutes walking distance). A longer follow-up is the prerequisite for evaluating the relationship (if any) between surrogate and hard end points. Despite PH being a rare disease, the various groups currently working in the field—as well as all other groups with the same expertise—should make an additional effort to plan and conduct large, pragmatic, and clinically-oriented clinical trials.

Summary: Left-sided heart failure (HF) is known to cause PH, but the development and severity of PH in HF is highly variable, and contributing factors are not fully understood. There is now growing appreciation that PH is common and may be severe in elderly patients with HF with preserved left ventricular ejection fraction (HFpEF). However, the true prevalence and severity of PH in HFpEF from the general community remain unknown. Common to left ventricular failure regardless of EF, increased left-sided filling pressure leads to pulmonary venous hypertension (HTN). Beyond this post-capillary contribution to PH, a reactive increase in pulmonary arterial tone or intrinsic arterial remodelling can result in a superimposed pre-capillary component of pulmonary arterial hypertension.
This was confirmed in a community-based study of 244 HFpEF patients (age 76 ± 13 years; 45% male) followed up using Doppler echocardiography over 3 years (3). Control subjects were 719 adults with HTN without HF (age 66 ± 10 years; 44% male).In HFpEF, PH was present in 83% vs 8% in controls and the median (25th, 75th percentile) pulmonary arterial systolic pressure (PASP) was 48 (37, 56) mm Hg. PASP increased with pulmonary wedge pressure (PCWP) ($r = 0.21$; $p < 0.007$). Adjusting for PCWP, PASP was higher in HFpEF than in hypertensive patients without clinically incident HF ($p < 0.001$). The PASP distinguished HFpEF from hypertension without HF with an area under the receiver-operating characteristic curve of 0.91 ($p < 0.001$) and strongly predicted mortality in HFpEF (hazard ratio: 1.3 per 10 mm Hg; $p < 0.001$).
In fact, the greater severity of PH in HFpEF may be caused by an additional pre-capillary component of pulmonary arterial hypertension, which might be related to a progressive desensitization or loss of production of regulatory endothelial agents (NO, prostaglandins) and mediated by reactive increases in pulmonary arterial tone or development of a congestive arteriopathy characterized by pulmonary arteriolar remodelling, medial hyperplasia, and intimal fibrosis, as shown to occur in patients with mitral stenosis or systolic HF. The individual propensity to develop such responses may lead hypertensive patients to develop HFpEF. The presence of a pre-capillary component in addition to post-capillary PH in HFpEF raises the potential that aside from therapies aimed at reducing pulmonary venous congestion, those aimed at pulmonary arterial hypertension may also have a role in the treatment of HFpEF. To date, there are no proven therapies in HfpEF.
Finally, a short up-date. The last "paper of the month" that I posted on the web a few months ago dealt with the Tako-tsubo syndrome. I reported and discussed a few findings supporting the hypothesis that the transient and regional myocardial dysfunction that characterizes the syndrome would be sympathetically mediated.

Recently a paper from J. Abraham et al, published in the JACC (4) reports 9 cases of "stress cardiomyopathy", precipitated immediately by the intravenous administration of epinephrine (6 cases) or dobutamine (3 cases), evaluated by coronary angiography, and with serial echocardiography and cardiac enzymes. Interestingly these cases reproduced the classical features of the left ventricular ballooning syndrome (including normal coronary angiography and mild enzyme elevation) showing all 3 previously described variants: with apical (3 cases), midventricular (2 cases) and basal (4 cases) asynergy. The left ventricular ejection fraction, initially dropped to 35% in average (IQR:35%-40%), recovered in one week (median 7 days, IQR 4 to 13 days). These findings further strongly support an excessive symptomatic stimulation or individual hypersensitivity to cathecholamines as central to pathogenesis of this unique syndrome.

References

1. Galié N, Torbicki A, Barst R, et al. Guidelines of diagnosis and treatment of pulmonary arterial hypertension. Eur Heart J 2004;25;2243-2278.
2. Galié N, Manes A, Negro L, et al. A meta-analysis of radnomized controlled trials in pulmonary hypertension. Eur Heart J 2009;30:394-403
3. Lam CSP, Roger VL, Rodeheffer RJ, et al. Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction. A Community-Based Study. J Am Coll Cardiol, 2009; 53:1119-1126.
4. Abraham J, Mudd JO, Kapur N, et al. Stress cardiomyopathy after intravenous administration of cathecolamines and Beta-receptor antagonists. J Am Coll Cardiol 2009;53:1320-5.

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 Ewa Podolecka, MD, Zofia T. Bilinska, MD, PhD
Institute of Cardiology, Warsaw, Poland

Title: " Recurrent NSTE-ACS in a Female Patient with Progressive Myocardial Dysfunction"

Case Presentation:

We present the case of a 44-year-old woman with diabetes mellitus, which has been treated with insulin for 10 years. The patient is after strumectomy due to nodular goiter treated substitutionally with 1-thyroxin, reports dyspnea for the last 6 months, limited effort tolerance and chest discomfort. On admission ECG revealed sinus rhythm (65') and left bundle branch block (QRS=140 ms). Echocardiography revealed the size of the heart cavities within the normal range, though at the upper limit, generalized hypokinesis and left ventricle ejection fraction at 51%. Coronary arteries assessed in coronarography were found normal with a slower flow. The patient had an elevated level of Troponin I to 0.69 ng/ml (N: 0,00 – 0,10 ng/ml) and CK-MB activity to 30.7 U/L (N: 0 – 6 U/L). Thyroid stimulating hormone (TSH) was normal 2.3 uIU/mL (N: 0.4 – 4.0 uIU/mL), and hemoglobin A1C was significantly elevated -7.8%. Aspirin at a dose of 75 mg, angiotensin-converting enzyme inhibitor (ACE-I) and simvastatin were introduced. The dose of insulin was modified. Despite systematic and better-controlled pharmacotherapy, dyspnea and chest discomfort recurred. Within the next two years the patient was hospitalized several times due to the exacerbation of the above-mentioned complaint and recurrent pulmonary edema. Lab tests revealed repeatedly increased Troponin I levels (0.12 – 0.69 ng/ml) and increased CK-MB activity (23.4 – 72.1 U/L). Because of the symptoms and increased Troponin I levels a check-up coronarography was performed after one year. Coronary arteries were found normal. Echocardiography revealed left ventricle slightly bigger, decreasing left ventricle ejection fraction – 45% and mitral incompetence (++). The patient was discharged with recommended standard treatment with aspirin, ACE-I and statin (simvastatin at 20 mg/d), along with insulin and l-thyroxin. Despite systematic treatment complaints recurred.

Question1: Do you think the patient should undergo endomyocardial biopsy? If she were your patient, would you do it?

Soon the patient was again hospitalized in the Institute of Cardiology due to exacerbated complaints accompanied by an increase Troponin I level (0.18 ng/ml). Left bundle branch block in ECG. Echocardiography was similar as examination a year before. Tests for autoimmune diseases were performed. IgA class anti-endomysial antibodies were identified; positive test, very high titer (1:5120). Gastroduodenoscopy with the small intestine biopsy was done. The examination revealed grade IV villous atrophy as well as the small intestine lamina propria and endothelium lymphocytosis. The diagnosis of celiac disease was based on the laboratory and biopsy findings. Gluten-free diet was introduced.

Question 2: Would you treat the patient with steroids ?

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

"Pear-like tumour of the pericardium disappearing after pericardioscopy and biopsy – cholesterol pericarditis and lipoma of the pericardium and pleura"

by **Arsen Ristić,** Petar Đukić, Vesna Božić, Bosiljka Vujisić-Tešić, Siniša Stojković, Petar M. Seferović. Department of Cardiology, Department of Cardiac Surgery and Department of Pathology, Institute of Cardiovascular Diseases, Clinical Centre of Serbia and Belgrade University School of Medicine, Belgrade, Serbia

Answers:

Due to the continuous production of large amounts of sero-haemorrhagic fluid the patient was referred to pericardiectomy. Subtotal pericardiectomy was performed, but surprisingly 5x3 cm large tumour, previously confirmed by echocardiography, computed tomography, intracardiac echocardiography, and pericardioscopy was not present at the time of surgery any longer. Perhaps, a lipomatous content of the tumour was drained after the biopsy. However, several similar tumours (Figure 2) were detected in the left pleura and removed during the same surgical procedure. In addition, 300 ml of thick chylous effusion was evacuated from the left pleura. The final diagnosis established from the biopsy samples taken by pericardioscopy and the samples taken during the surgery was cholesterol pericarditis with the chronic inflammation (foreign body granulomatous inflammation around the cholesterol crystals) as well as the benign pleural lipoma. Pear-like infiltration of the visceral pericardium in front of the right ventricle was most probably also a lipoma which collapsed after taking several biopsy samples. After the surgery, there was no relapse of either pericardial or pleural effusion and the patient was discharged from the hospital on antihypertensive medication and statins. During the 24 months follow-up the patients was stable, with no symptoms, no pericardial or pleural effusion and no recurrences of lipomatous tumours. He was even able to return to his previous profession – acting in the classical theatre.

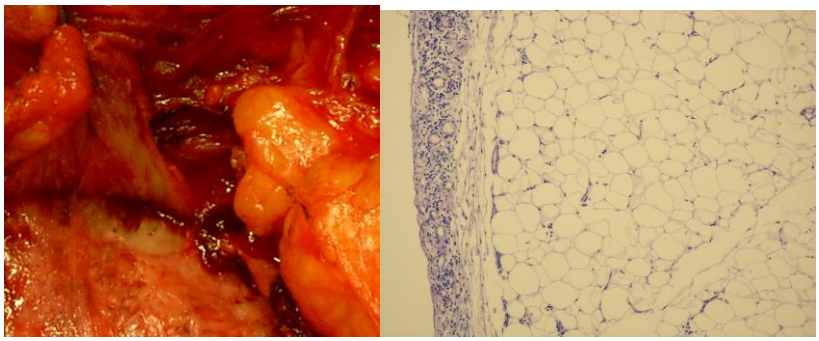

Figure 2. Intraoperative findings demonstrating extensive inflammatory changes on the visceral and parietal pericardium, thickened parietal pericardium and infiltration in the left pleural space (white arrow). Surprisingly, no tumorous infiltration of the visceral pericardium could be visualized in front of the right ventricle any more. Right-sided image reveals histological examination from the pleural tumour – pleural lipoma.

Cholesterol pericarditis

Cholesterol pericarditis is a rare complication of chronic pericardial effusion or chronic scarring of the pericardium [1, 2] and is exacerbated by cholesterol crystals. Common underlying causes include tuberculous pericarditis, autoimmune rheumatic diseases, and pericardial trauma [2, 3]. When a pericardial effusion is relatively acute, its cholesterol content remains in solution. However, when the pericardial effusion is chronic, the normal ability to dissolve cholesterol is impaired and cholesterol crystals are deposited in the pericardium and effusion [4-6]. The fluid is clear, in contrast to chylopericardium, and classically is said to have a glittering "gold paint" appearance, as it was the case with our patient at the first pericardiocentesis [7, 8]. However, any other macroscopic appearance of pericardial effusion apart from the "gold paint" is not excluding the diagnosis.

The effusions tend to be large. The concentration of cholesterol equals or exceeds that of the blood, often attaining values above 500 mg/dL (13 mmol/L) [8]. Unfortunately, estimation of cholesterol level was not a part of our routine evaluation of the pericardial effusion, which turned out to be wrong in this specific case. The pericardial effusion associated with myxedema also has a high cholesterol concentration, but crystals are usually absent.
Blood associated with inflammation is thought to be the source of cholesterol in the pericardial fluid, and evidence of current or previous haemorrhage is usually evident. The pericardium is thicker than normal (Figure 2 left) and its inner surface is lined with plaques and cholesterol deposits. The histological findings include fibrosis, inflammatory cells, cholesterol clefts and crystals of variable geometry, and giant cell granulomata.
Treatment includes pericardiocentesis, which is seldom effective over the long-term because the effusions tend to recur and can cause tamponade at any time. This procedure also fails to address the thick, scarred pericardium and does not prevent the late development of constrictive pericarditis. Thus, optimal therapy is radical pericardiectomy with additional treatment of the underlying cause of chronic pericarditis [9].

References

1. Maisch B, Ristić AD. The classification of pericardial disease in the age of modern medicine. Curr Cardiol Rep 2002; 4(1): 13-21.
2. Maisch B, Soler-Soler J, Hatle L, Ristić AD. Pericardial diseases. In: Serruys PW, Camm AJ, Lüscher TF, eds. The ESC Textbook of Cardiovascular Medicine. Blackwell Publishing Ltd., London 2006, 517-34.
3. Pankuweit S, Ristić AD, Seferović PM, Maisch B. Bacterial pericarditis: diagnosis and management. Am J Cardiovasc Drugs 2005:5(2):103-12.
4. Raposo L, Andrade MJ, Ferreira J, Aguiar C, Abecasis M, Ramos S, Reis AB, Martins AP, Pais MJ, Gomes RS. Cholesterol pericarditis--relapsing pericardial effusion in a patient with rheumatoid arthritis. Rev Port Cardiol. 2005 May;24(5):737-45.
5. Ford EJ, Bear PA, Adams RW. Cholesterol pericarditis causing cardiac tamponade. Am Heart J. 1991 Sep;122(3 Pt 1):877-9.
6. Noiri E, Itoh T. Disorder of pericardial fluid cholesterol metabolism in cholesterol pericarditis. Jpn J Med. 1991 Jul-Aug;30(4):393.
7. Spodick, DH. The Pericardium. A comprehensive textbook, Marcel Dekker, New York 1997. p.84.
8. Brawley, RK, Vasko, JS, Morrow, AG. Cholesterol pericarditis. Considerations of its pathogenesis and treatment. Am J Med 1966; 41:235.
9. Maisch B, Seferović PM, Ristić AD, Erbel R, Rienmüller R, Adler Y, Tomkowski W, Thiene G, Yacoub MH. European Society of Cardiology Guidelines: Diagnosis and management of the pericardial diseases. Executive summary. Eur Heart J 2004; 25(7):587-610.