European Society of Cardiology
Working Group on
Myocardial & Pericardial Diseases

Newsletter

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Myocardial and Pericardial Diseases
ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®

INSIDE THIS ISSUE:

Message from the Chairman

Dear Colleagues,

Much has happened since the ESC congress in Stockholm.

In October, we attended the annual congress of our working group in A Coruna Spain. As we are a small group, we are entirely dependent on volunteers for the funding and organisation of our meeting. This year, this enormous task fell to Lorenzo Monserrat and his colleagues in A Coruna who produced a challenging and informative scientific programme. On behalf of the working group,
I thank Lorenzo for making this year's event such a success.

During the meeting, the nucleus appointed:

- Juan Gimeno as Secretary,
- Alida Caforio as Treasurer and
- Tiina Heliö as Web editor.

It is also a great pleasure to welcome the three individuals who will be joining us as study group leaders:

- Pascal McKeown (genetics);
- Sabine Pankuweit (myocarditis); and
- Massimo Imazio (pericardial disease).

We will be working with the study group leaders over the next few months to prepare our work agenda. It should be an exciting time!

Yours sincerely,

Perry Elliott, FESC

Dear Colleagues and Members of the Working Group,

It is a great responsibility and an honour for me to continue the work of our previous Web Editor, Dr. Sabine Pankuweit who has significantly developed these pages during the past few years.

Please find enclosed the 29th 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 there are some recommendations for further reading with a list of a recently published papers in the field of our Working Group.

Best wishes for all of you,

Dr. Tiina Heliö, FESC

Web-Editor

The paper of the month:

COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS): a multicentre, randomized, double-blind, placebo-controlled trial.

Imazio M, Trinchero R, Brucato A, Rovere ME, Gandino A, Cemin R, Ferrua S, Maestroni S, Zingarelli E, Barosi A, Simon C, Sansone F, Patrini D, Vitali E, Ferrazzi P, Spodick DH,

Adler Y; on behalf of the COPPS Investigators.

Eur Heart J. 2010 Aug 30; [Epub ahead of print]

Presented by Arsen D. Ristić, MD, PhD, FESC
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Introduction

The post-pericardiotomy syndrome (PPS) is a common complication of cardiac surgery, that can prolong recovery of the patient and duration of hospitalization, but also be significantly disabling and even life-threatening [1]. The size and site of pericardial effusion are related to the type of surgery, periprocedural medications, and individual response to surgical trauma. Cardiac tamponade is more common following valve surgery (73%) than coronary artery bypass grafting (CABG) alone (24%) and may be related to the preoperative use of anticoagulants [2]. Most cases of cardiac tamponade occur more than 7 days after surgery, and may develop slowly, without clear-cut clinical signs [2,3]. Independent risk factors for development of large pericardial effusion in PPS are also larger body surface area, pulmonary thromboembolism, hypertension, immunosuppression, renal failure, urgency of operation, surgical procedure other than coronary artery bypass grafting, and prolonged cardiopulmonary bypass [4]. Cardiac tamponade after cardiac surgery may also be caused by intrapericardial haematoma which most often spontaneously resolve but may also require urgent evacuation. Constrictive pericarditis may also occur after cardiac surgery. Warfarin administration in patients with early postoperative pericardial effusion imposes the greatest risk, particularly in those who did not undergo pericardiocentesis and drainage of the effusion [5].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to reduce the size of asymptomatic postoperative pericardial effusions (in 77% of the patients in one large study [3]. However, only one previous study [6] has shown the efficacy of NSAIDs for this condition and since patients who have recently had heart surgery are fragile, it is important to understand the balance of risks and benefits for this treatment. Although NSAIDs are usually given for only a short time to patients with pericardial effusions, they can cause serious adverse effects, such as upper gastrointestinal tract bleeding or perforation [7], but also myocardial infarction, acute heart failure, and acute renal failure [8]. In the February issue of this Newsletter, we have already commented the randomized study of Meurin et al. [9] performed in 5 French postoperative cardiac rehabilitation centres, including 196 patients with moderate to large persistent pericardial effusion more than 7 days after cardiac surgery. The patients were randomly assigned to diclofenac, 50 mg, or placebo twice daily for 14 days. Eleven cases of late cardiac tamponade occurred in the placebo group and 9 in the diclofenac group (P=0.64). These differences persisted after adjustment for grade of pericardial effusion at baseline, treatment site, and type of surgery. Therefore, in this trial, the use of diclofenac, 100 mg/d, did not significantly reduce the size of pericardial effusions or the risk for late cardiac tamponade. Moreover, this study confirmed that moderate to large pericardial effusion (grade 2, 3, or 4) occurring 7 to 30 days after cardiac surgery is a severe condition because 10.2% of these patients required pericardiocentesis in the 14 days after they were enrolled in the study. Obviously, an alternative option for treatment and prevention was needed.

Summary of the paper

At the hotline session of the this year European Society of Cardiology (ESC) Congress in Stockholm, Massimo Imazio presented the results of the COPPS trial (COlchicine for the Prevention of the Post-pericardiotomy Syndrome) which was published on the very same day as the fast-track ESC clinical trial update in the European Heart Journal [10]. The aim of the COPPS trial was to test the efficacy and safety of colchicine for the primary prevention of the post-pericardiotomy syndrome. The COPPS study was performed in 6 Italian centres, as a double-blind, randomized, non-commercial trial. On the third post-operative day, 360 patients (mean age 65.7+12.3 years, 66% males), 180 in each treatment arm, were randomized to receive placebo or colchicine (1.0 mg twice daily for the first day followed by a maintenance dose of 0.5 mg twice daily for 1 month in patients ≥70 kg, and half of the doses for patients weighting less than 70 kg or intolerant to the highest dose). The primary efficacy endpoint was the incidence of post-pericardiotomy syndrome at 12 months. Secondary endpoint was the combined rate of disease-related hospitalization, cardiac tamponade, constrictive pericarditis, and relapses. Colchicine significantly reduced the incidence of the post-pericardiotomy syndrome at 12 months compared with placebo (respectively, 8.9 vs. 21.1%; P=0.002; number needed to treat - 8). Colchicine also reduced the secondary endpoint (respectively, 0.6 vs. 5.0%; P=0.024). The rate of side effects (mainly related to gastrointestinal intolerance) was similar in the colchicine and placebo groups (respectively, 8.9 vs. 5.0%; P=0.212).

Discussion

The COPPS trial was designed to assess the efficacy and safety of colchicine for the primary prevention of the PPS. This study is an important step ahead in the series of randomized trials addressing important issues in the management of pericardial diseases, designed and conducted by Massimo Imazio. Colchicine is efficacious, inexpensive, and safe medication proven for the treatment and prevention of pericarditis. The exact mechanism of colchicine action is not fully understood. Most of the pharmacological effects of colchicine on cells involved in inflammation appear to be related to its capacity to disrupt microtubules.[10] Colchicine inhibits the process of microtubule self-assembly by binding b-tubulin with the formation of tubulin–colchicine complexes. This action takes place either in the mitotic spindle or in the interphase stage, thus colchicine inhibits the movement of intercellular granules and the secretion of various substances. By this mechanism, colchicine is able to inhibit various leucocytes functions, and this effect should be the most significant for the anti-inflammatory action. Moreover, colchicine shows a preferential concentration in leucocytes and its peak concentration may be more than 16 times the peak concentration in plasma. This seems to be related to its therapeutic effect.

In the COPPS study, colchicine significantly reduced the incidence of the PPS and its related complications providing evidence for the first time that pharmacological prevention of the PSS is possible and safe. Most of the PPS events (85% of all PPS) occurred in the first month, and thus a preventive treatment with colchicine for the first 4 weeks following surgery seems appropriate. No severe side effects were documented, and gastrointestinal side effects were equally distributed between the colchicine and placebo groups. Diarrhoea is relatively common, affecting up to 10% of patients on colchicine treatment for pericarditis. The use of weight-adjusted doses without a loading dose and especially lower doses (i.e. 0.5 mg/day to 0.5 mg bid.) may be a way to reduce this side effect, improving drug compliance. The major study limitation is related to the definition of the PPS since there is no general agreement on this issue. The definition used in the study was taken from the preliminary study from Israel [11] assuming

that the diagnosis can be established If at least 2 out of the following 5 diagnostic criteria are present:

1. Fever lasting beyond the first post-operative week without evidence of systemic or focal infection
2. Pleuritic chest pain
3. Friction rub
4. Evidence of pleural effusion
5. Evidence of new or worsening pericardial effusion

Nevertheless, in the COPPS study, colchicine showed to reduce all 5 above listed major components of the PPS showing a true preventive effect even on several components of the pleuro-pericardial involvement after cardiac surgery.

Although postoperative pericardial effusion is frequent and potentially severe, few randomized, controlled trials have examined treatment for this condition. Recommendation given in the ESC Guidelines [12] to treat postoperative pericardial effusion with NSAIDs was based on the results of the double-blind, placebo-controlled, randomized study by Horneffer et al. [13] applying a 10-day course of ibuprofen or indomethacin. Of 1019 adult patients undergoing cardiac operations during a 14-month period, a diagnosis of postpericardiotomy syndrome was made in 187, and 149 were enrolled in the study. Diagnosis was based on the presence of at least two of the following: fever, anterior chest pain, and friction rub. Drug efficacy was defined as the resolution of at least two of these criteria within 48 hours of drug initiation. Ibuprofen and indomethacin were 90.2% and 88.7% effective, respectively, and both were significantly more effective than placebo (62.5%, p = 0.003). The occurrence of side effects, including nausea, vomiting, renal failure, and fluid retention, was low in all groups (13.1% for ibuprofen, 16.1% for indomethacin, and 16.7% for placebo [p = not significant). Length of hospital stay, incidence of ischemic events, and accumulation of significant pericardial effusions were similar in all groups. The results of this study suggested that both ibuprofen and indomethacin provide safe and effective symptomatic treatment for postpericardiotomy syndrome.

The COPPS trial was designed according to the results of the preliminary prospective, randomized, double-blind study on primary prevention of postpericardiotomy syndrome performed by Finkelstein et al [11] in 163 patients who underwent cardiac surgery in two centres in Israel. On the 3rd postoperative day, the patients were randomly assigned to receive colchicine (1.5 mg/day) or placebo for 1 month. All were evaluated monthly for the first 3 postoperative months for development of postpericardiotomy syndrome. Of the 111 patients who completed the study, 47 (42.3%) received colchicine and 64 (57.7%) placebo. There was no statistically significant difference between the groups in clinical or surgical characteristics. The postpericardiotomy syndrome was diagnosed in 19 patients (17.1%), 5/47 cases (10.6%) in the colchicine group and 14/64 (21.9%) in the placebo group. However the study was underpowered and the difference showed only a trend toward statistical significance (p < 0.135). This dilemma was resolved by the COPPS trial that was sufficiently powered to address this important question.

In conclusion, colchicine is safe and efficacious in the primary prevention of the PPS and its related complications and may halve the risk of developing the syndrome following cardiac surgery. Such a finding is particularly important for clinical practice because the post-operative management may be complex, troublesome and empirical anti-inflammatory therapy may not be efficacious. Primary prevention of postperiocardiotomy syndrome using short-term perioperative steroid treatment or intrapericardial steroid treatment or its combination with colchicine should be still further evaluated.

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10. Imazio M, Trinchero R, Brucato A, Rovere ME, Gandino A, Cemin R, Ferrua S, Maestroni S, Zingarelli E, Barosi A, Simon C, Sansone F, Patrini D, Vitali E, Ferrazzi P, Spodick DH, Adler Y; on behalf of the COPPS Investigators. COlchicine for the Prevention of the Post-pericardiotomy Syndrome (COPPS): a multicentre, randomized, double-blind, placebo-controlled trial. Eur Heart J. 2010 Aug 30; [Epub ahead of print]

11. Finkelstein Y, Shemesh J, Mahlab K et al. Colchicine for the prevention of postpericardiotomy syndrome. *Herz* 2002;**27**:791-4.

12. Maisch B, Seferovic PM, Ristic AD, et al. Task Force on the Diagnosis and Manage-ment of Pericardial Diseases of the European Society of Cardiology. Guidelines on the diagnosis and management of pericardial diseases. Executive summary. Eur Heart J 2004;25(7):587-610.

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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

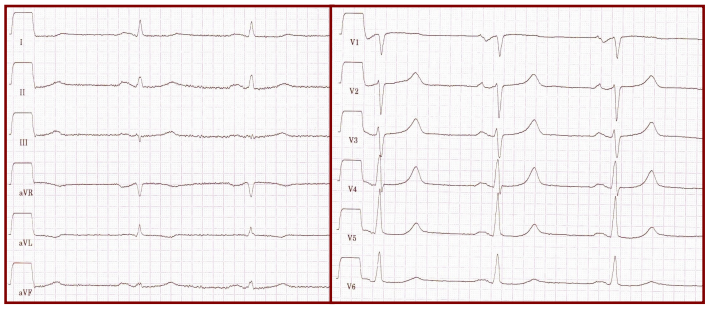
Presented by Dr. Barbara Pfeiffer and Prof. Hubert Seggewiss,
Medizinische Klinik 1, Leopoldina Krankenhaus Schweinfurt, Germany.

A 39-year old male with complicated hypertrophic obstructive cardiomyopathy

Case Presentation

A 39 year-old male patient was admitted to our hospital to evaluate and plan the therapeutic strategy of hypertrophic obstructive cardiomyopathy that was diagnosed only a few months before. He suffered from dyspnea class III, palpitations and presyncope after a syncope in 2001. Medical treatment with verapamil led to a deterioration of his symptoms. After change to ß-blocker symptoms improved but still persisted.
The patient's father suffered from CAD. The brother had no signs of cardiac disease at non-invasive testings. His paternal grandfather died possibly of sudden cardiac death. Genetic testing showed a mutation in MYBPC3.

At physical examination the patient had a typical 4/6 systolic murmur on 5L2 with increase at Valsalva manoeuvre.



The ECG illustrated sinus rhythm, but no severe left ventricular hypertrophy (fig. 1).

Fig. 1:

ECG

Echocardiography showed asymmetric hypertrophy with septal thickness of 27 mm and posterior wall of 17 mm (fig. 2).

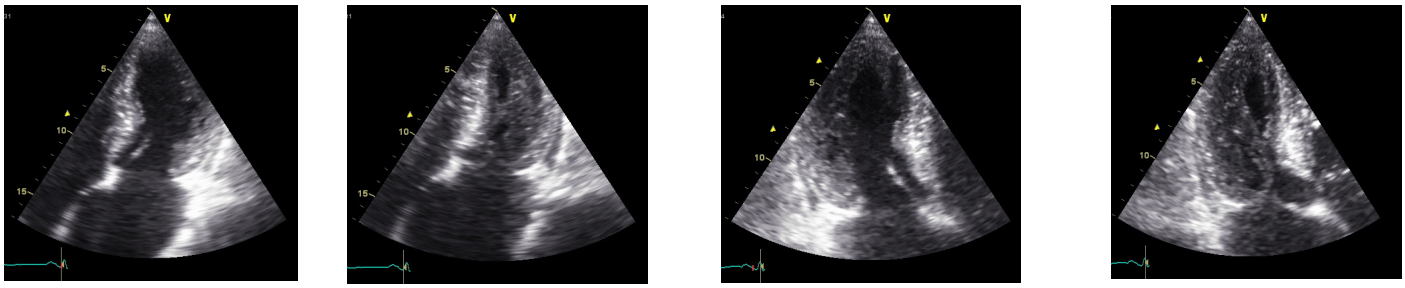


Fig. 2*: Diastolic and systolic 4- and 3-chamber-view*

The systolic function was normal whereas his diastolic function was abnormal. He had a SAM (II°-III°)-related mild to severe mitral regurgitation (fig. 3). There was not only a subaortic LVOT-obstruction but also a mid-ventricular with an intracavitary gradient of 120 mmHg at rest (fig. 3 and 4) with increase at Valsalva manoeuvre. The left atrium was already dilated with 56 mm.

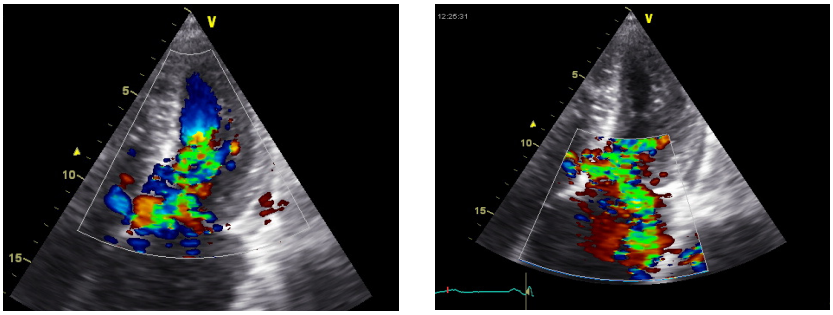


***Fig. 3**: Midventricular and LVOT-obstruction in color Doppler and mitral regurgitation*

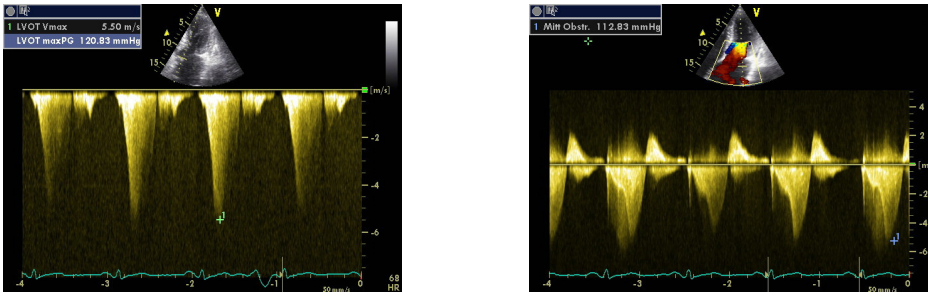
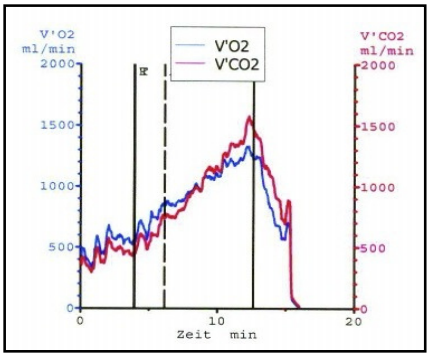


***Fig. 4**: CW-Doppler showing midventricular and LVOT obstruction*



Cardiopulmonary exercise testing (bicycle test) was performed up to 106 Watts after 8 minutes. Maximal oxygen uptake (peak VO2) was reduced to 16.1 ml/kg/min (46% predicted peak VO2) (fig. 5).

***Fig. 5**: Cardiopulmonary exercise test VO2*

Blood pressure response was normal from 120/90 mmHg to 160/80 mmHg. Holter-ECG showed sinus rhythm, parasystole, short runs of supraventricular tachycardia and non-sustained VT. The cardiac MRI showed diffuse myocardial fibrosis.

QUESTION:

What is your therapeutic strategy?

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

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

by Dr. Tiina Heliö [1] and Dr. Sari Aaltonen [2],
[1] Helsinki University Central Hospital, Department of Medicine, Division of Cardiology, Helsinki, Finland
[2] Helsinki University Central Hospital, Department of Medicine, Division of Nephrology, Helsinki, Finland

Diagnosis and further management

The main initial observations were hypertensive crisis, alveolar oedema, renal failure and acute heart failure. Echocardiography showed thickened left ventricular walls, systolic and diastolic dysfunction.

The reason for extremely high blood pressure was sought. The patient did not use drugs. She used to have every now and then some salty liquorice but not every day. Contraception pills could have caused hypertension but usually it would have been milder. The possibilities of primary hyperaldosteronism, acromegaly, Liddle's syndrome, Cushing's disease, pheochromocytoma, thyroid dysfunction, primary hyperparathyreosis or undiagnosed coarctation of the aorta were excluded.

The possibility that both left ventricular hypertrophy and renal failure could have been caused by a storage disease or by amyloidosis, was discussed. In further evaluation, there was no evidence of a monoclonal gammopathy.

The ethiology of renal failure was examined further. It remained unclear, whether it was acute or chronic. The findings in the renal ultrasound were nonremarkable. Renal MRI did not show any abnormalities and angiography demonstrated normal renal arteries, no signs of fibromuscular dysplasia or atherosclerosis. Renal biopsy done in November 2009 was representative with 22 glomeruli. There were no signs of a glomerulonephritis. Immunofluorescence stainings were negative in glomeruli. There was no amyloid. The main finding was significant, concentric, onion-like obliteration of small arterioles with hyalin deposits and fibrinoid necrosis. The biopsy findings were compatible with malignant hypertension, systemic scleroderma, haemolytic uremic syndrome or thrombocytopenic thrombotic purpura (TTP). The patient did not have findings diagnostic for scleroderma. The difficulty in swallowing passed by and the results of the oesophageal manometry were normal. The possibility of TTP was excluded by repeatedly normal thrombocyte count. The patient did not have coeliac disease or SLE not to speak about epidemic nephropathy.

It was concluded that the process was probably initiated by malignant hypertension. This view was supported by the fact that the proteinuria disappeared as normotension was achieved with enalapril, bisoprolol and amlodipin. Renal failure may have possibly been worsened by the use of ASA. ECG (Fig.3) left ventricular systolic function (Fig. 4), mitral inflow pattern and Em/Am of the mitral valve lateral annulus (not shown) had normalized by February 2010. Since the cardiac abnormalities were interpreted to be secondary to renal disease,EMB was not considered.

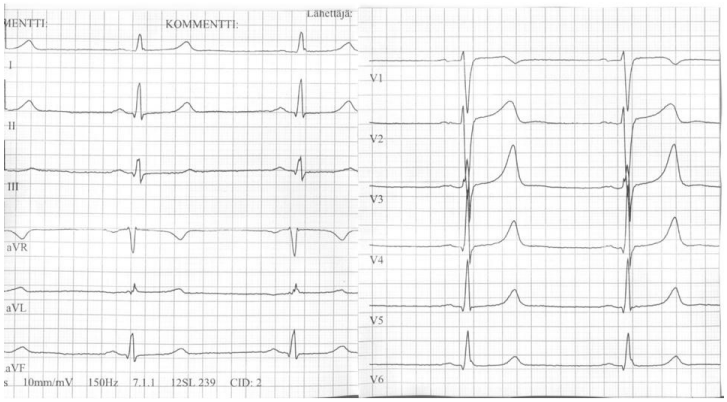
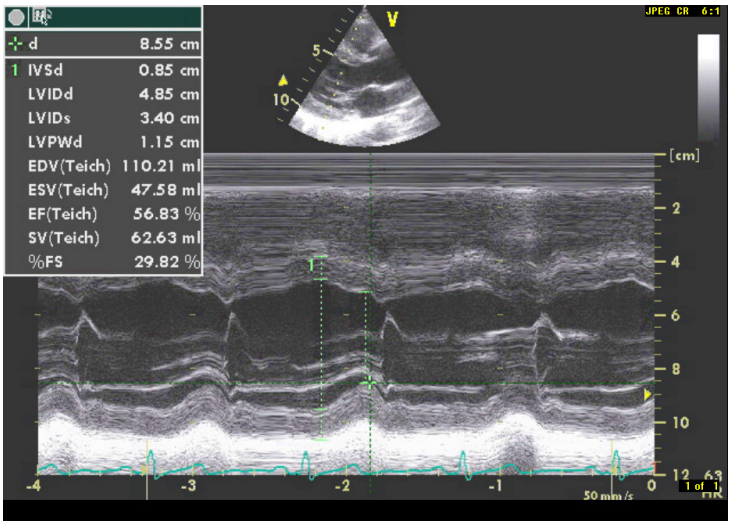


Figure 3.

As the ECG taken in August 2010 is compared to those taken in November 2009, a remarkable resolution of the LVH changes can be observed.

Figure 4.

The left ventricular wall thickness and systolic function had improved rapidly as demonstrated by the echocardiography carried out in February 2010.



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

1) **Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy.**
Sliwa K, Hilfiker-Kleiner D, Mebazaa A, Pieske B, Buchmann E, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, van Veldhuisen DJ, Watkins H, Shah AJ, Seferovic PM, Elkayam U, Pankuweit S, Mouquet F, McMurray JJ. Eur J Heart Fail. 2010; 12:767-78.

2) **Prognostic impact of familial screening in dilated cardiomyopathy.**
Moretti M, Merlo M, Barbati G, Di Lenarda A, Brun F, Pinamonti B, Gregori D, Mestroni L, and Sinagra G. Eur J Heart Fail. 2010;12:922-927.

3) **Survival After Cardiac transplantation in Patients With Hypertrophic Cardiomyopathy.**
Maron MS, Kalsmith BM, Udelson JE, Li W, and DeNofrio D. Circ Heart Fail. 2010;3:574-579.

4) **Nebulette Mutations Are Associated With Dilated Cardiomyopathy and Endocardial Fibroelastosis.**
Purevjav E, Varela J, Morgado M, Kearney DL, Taylor MD, Arimura T, Moncman CL, McKenna W, Murphy RT, Labeit S, Vatta M, Bowles NE, Kimura A, and Boriek AM. JACC. 2010;56:1493-1502.

5) **Prophylactic Implantable Defibrillator in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia and No Prior Ventricular Fibrillation or Sustained Ventricular Tachycardia.**
Corrado D, Calkins H, Link MS, Leoni L, Favale S, Bevilacqua M, Basso C, Ward D, Santini M, Buja G, Iliceto S, Estes III NAM, Wichter T, McKenna WJ and Thiene G. Circulation. 2010 Sep 21; 122(12); 1144-1152.

6) **Metabolic Modulator Perhexiline Corrects Energy Deficiency and Improves Exercise Capacity in Symptomatic Hypertrophic Cardiomyopathy.**
Abozguia K, Elliott P, McKenna W, Phan TT, Nallur-Shivu G, Ahmed I, Maher AR, KAur K, Taylor J, Henning A, Ashrafian H, Watkins H,and Frenneaux M. Circulation. 2010;122:1562-1569.

7) **Evidence for Marfan cardiomyopathy.**
Alpendurada F, Wong J, Kiotsekoglou A, Banya W, Child A, Prasad SK, Pennell DJ, and Mohiaddin RH. Eur J Heart Fail. 2010; 12:1085-1091.