Dear Members of the Working Group,

please find enclosed the 18th 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 October 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. Paulsen
Summary

One of the major challenges in the clinical management of patients with hypertrophic cardiomyopathy (HCM) is the identification and treatment of the small number of individuals prone to serious events and sudden cardiac death (SCD) in particular. Gimeno et al. report on the potential of exercise-induced ventricular arrhythmia as a novel additional marker of SCD risk.

In a prospective cohort study 1380 HCM patients [mean age 42 years (SD 15); 62% male; mean follow-up 54 (SD 49) month] underwent symptom limited cardiopulmonary exercise testing (CPET), echocardiography and ambulatory Holter monitoring. Main purpose was the determination of the frequency of exercise-induced ventricular arrhythmia and its relation to SCD. Clinical characteristics of patients with and without exercise-induced ventricular arrhythmia were compared, the relation of exercise-induced ventricular arrhythmia and conventional SCD risk factors and the association between exercise-induced ventricular arrhythmia and all-cause mortality were determined. Exercise-induced ventricular arrhythmia was defined as the presence of three or more consecutive ventricular beats at a rate ≥120/min. Primary endpoints in survival analysis consisted of sudden cardiac death and aborted sudden cardiac death. All cause mortality or orthotopic heart transplantation were coded as secondary end points.

27 of 1380 patients (2.0%) showed ventricular arrhythmia during CPET [mean age 40 (SD 14) years (18-64); 22 (81.5%) male], 24 had asymptomatic non-sustained ventricular tachycardia (NSVT), ventricular fibrillation (VF) occurred in three patients. During follow-up eight (29.6%) patients with exercise-induced NSVT/VF reached primary or secondary end points. Three patients with exercise-induced NSVT and two of the three exercise VF patients died suddenly. The latter died 11 and 150 month after CPET, the third exercise VF patient received an implantable cardioverter-defibrillator (ICD) and had no appropriate shocks after 66 month of follow-up. In the exercise NSVT group one patient developed syncope due to sustained ventricular tachycardia requiring resuscitation, one had an appropriate ICD discharge and one received a cardiac transplant. In comparison to patients without exercise-induced ventricular arrhythmias, patients with exercise-induced NSVT and VF showed significantly higher maximal left ventricular wall diameters, larger left atria and a higher proportion of individuals with NSVTs during Holter monitoring. Male gender was significantly dominant in the exercise NSVT/VF group (81.5% vs. 61.5%). Combined in one group exercise NSVT/VF patients had a 3.73-fold increased risk of SCD or aborted SCD while exercise-induced NSVT alone was associated with a 2.82-fold increased risk compared to patients without exercise-induced ventricular arrhythmia (p=0.002 and p=0.049, respectively). Five years survival from SCD or aborted SCD in the exercise NSVT/VF and also in the group with exercise NSVT alone was significantly lower than in patients without exercise-induced ventricular arrhythmia (81.6% and 83.3%, respectively, vs. 94.4%; p=0.002 and p=0.049, respectively).
The association of exercise-induced ventricular arrhythmia and the secondary endpoint was weaker with a significant 2.18-fold increase in risk for the combined exercise NSVT/VF group (p=0.03), showing no difference when exercise NSVT was considered alone. Eleven patients with exercise-induced NSVT/VF had 2 or more conventional risk factors for SCD. After adjustment for the number of conventional SCD risk factors exercise-induced NSVT/VF was associated with a 3.03-fold increase in risk of SCD or aborted SCD. In multivariable analysis including conventional SCD risk factors exercise-induced NSVT/VF was an independent predictor of SCD or aborted SCD (p=0.001). Study limitations are loss of follow-up in 110 patients (8.0%), defined as no clinical review ≥ 1.5 years, a selection bias towards less symptomatic patients or subjects at lower risk since 362 patients who did not successfully complete symptom limited CPET or did not fit into the age span of 15-75 years, and lack of information on medication on the date of CPET.

Comment

The paper of Gimeno and co-authors stresses 2 major issues of treatment stratification of patients with HCM: risk stratification of sudden cardiac death and the risk of CPET itself. Contemporary risk stratification strategy in patients with HCM is based on 5 major risk factors - prior cardiac arrest, unexplained syncope, family history of premature sudden cardiac death, maximal left ventricular wall thickness ≥30 mm, abnormal blood pressure response to exercise, non-sustained ventricular tachycardia during 48 hours ambulatory Holter-ECG). Furthermore, other parameters are discussed to be of clinical importance like for example left ventricular outflow tract obstruction, extensive late gadolinium enhancement on MRI, intense physical exertion, exercise induced ischemia, and atrial fibrillation. While presence of two or more major risk factors is unquestionably followed by prevention of SCD by an implantable cardioverter-defibrillator, difficulties emerge in patients with only one conventional major risk factor that make up approximately 25% of HCM patients and who may still be at high risk for SCD 2. Due to the fact that ICD implantation has a major impact on lifelong morbidity and quality of life especially in young patients improvement in risk stratification is necessary. Gimeno et al. describe a significantly increased SCD risk in patients with exercise-induced ventricular arrhythmia. Furthermore exercise-induced ventricular arrhythmia predicts SCD or aborted SCD risk independently from conventional major risk factors in a multivariable analysis. Thus, exercise-induced ventricular arrhythmia appears to be a promising novel indicator of SCD risk, which especially could be taken into account in patients with only one conventional major risk factor. In several studies left ventricular outflow tract obstruction (LVOTO) was shown to be associated with increased SCD risk with varying relation of severity of LVOTO and risk. The actual study also confirms the association for resting LVOTO > 90 mmHg as a strong independent predictor of SCD. Beyond the utility as a clinical parameter in addition to the nowadays used 5 clinical risk factors appearance of exercise-induced ventricular arrhythmia could also serve as part of a future risk stratification model, which combines structural and functional parameters emphasizing on the interaction of the parameters. The fact that severe left ventricular hypertrophy in this study was not associated with SCD, in contrast to previous reports, underlines the need for a more elaborated approach functionally describing the pathophysiological substrate of HCM and thereby hopefully better predicting SCD risk. In this context further functional parameters easily assessed by CPET could be parameters of ventilatory efficiency or the ST segment hump sign (STHS). Ventilatory efficiency in HCM determined by peak VE/VCO₂ has been shown to reflect elevated intracardiac pressures at rest 3. Elevated intracardiac pressures might increase arrhythmic potential by promoting myocardial ischemia.
The prognostic value VE/VCO₂ relationship - preferably expressed as a slope - in HCM is promising and has to be elucidated in future studies. In a small study including 81 HCM patients undergoing exhaustive CPET STHS was a strong independent predictor of SCD or aborted SCD ⁴.

Besides the impact on risk stratification the study implies the issue of safety of CPET in patients with HCM. According to international guidelines exercise testing in patients with HCM is still relatively contraindicated. Thus, many physicians are reluctant to perform CPET accepting loss of information concerning risk stratification, degree of exercise limitation, evaluation of therapeutic efficiency or differential diagnosis. Few studies on the issue of CPET safety in HCM with small patient numbers each have been reported to date. Drinko et al. analyzed 263 HCM patients who underwent symptom-limited treadmill CPET with ongoing medication. They found no death, no syncope, one patient requiring cardioversion due to sustained ventricular tachycardia and 23% minor events, consisting of angina pectoris (11.7%), NSVT (4.2%), new non-sustained supraventricular tachycardia (3.0%) and pre-syncope (12.9%) ⁵. In our population of 396 HCM patients who underwent exhaustive incremental bicycle CPET under continued medication we reported no death, no syncope or sustained hemodynamically relevant tachycardias ⁶. Gimeno reports on the biggest HCM population so far that underwent CPET. No death and no sustained ventricular tachycardia occurred during the test procedure. Three patients with VF during CPET survived at least 11 month after the procedure.

Summarizing, CPET in patients with HCM may improve management of the disease with respect to risk as well as treatment stratification and appears to be safe. But, considering the low risk of VF calculated with 0.2% in the present study it is prudent to be prepared – as in every exercise testing situation.

References


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. Sabine Pankuweit, University Hospital Marburg, Department of Cardiology, Marburg, Germany

Onset of congestive heart failure and subsequent life-threatening ventricular tachyarrhythmias

Case Presentation:
A 33-year-old woman was referred to our hospital with a history of exertional dyspnea and palpitations. Congestive heart failure had been diagnosed and treated pharmacologically for 1 year. A complete atrioventricular block developed 3 months before admission and a DDD pacemaker was implanted in another hospital. A chest radiograph was normal without signs of lymphadenopathy or reticulonodularity in either lung field. Transthoracic echocardiography revealed a dilated left ventricle with a reduced ejection fraction of 30%. The patient underwent coronary angiography, which showed normal epicardial coronary arteries. Despite medical treatment for heart failure, the clinical status did not improve, and she was referred to our department for further investigation of the underlying heart disease.

On admission, the patient complained of dyspnea on exertion, and heart failure was categorized as NYHA class III. Clinical examination revealed an irregular pulse at 110 beats per min and a blood pressure of 110/70 mm Hg. Chest auscultation was normal. There was a mild pansystolic murmur consistent with mitral regurgitation. No other signs of congestive heart failure were evident. A treadmill test had to be terminated at 75 W due to dyspnea.

Echocardiography showed a markedly dilated left ventricle with an end-diastolic diameter of 76 mm. The interventricular septal thickness was 7 mm, and the left ventricular posterior wall was 9 mm. The left ventricular ejection fraction was estimated as 25%, and a moderate mitral regurgitation was observed. Transesophageal echocardiography was undertaken to further assess the severity of mitral regurgitation and to exclude a source of thromboembolism. The mitral leaflets were structurally unaltered, and the mechanism of mitral regurgitation was attributed to annular dilatation. The echogenicity of the myocardium appeared normal.

A 12-lead electrocardiogram showed atrial fibrillation and a left bundle branch block. A Holter electrocardiogram recording performed showed several self-limiting episodes of torsade de pointe ventricular tachycardia (fig. 1). On the following day, the patient was resuscitated due to ventricular fibrillation. Within the next 12 h, several episodes of ventricular tachycardia were observed and successfully terminated by electrical cardioversion.

What do you think is the diagnosis in this patient, which further investigations should be performed?
Answer for the previous “Clinical case of the month” presented in October

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

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

What happened to the patient?

A large cardiac silhouette on thorax X-ray and ST-elevations in the ECG were suggestive of pericardial affision. Bed-side echocardiography demonstrated a remarkable pericardial effusion, 20-27mm in diastole (Fig. 3). Right atrium collapsed during inspirium. The left ventricular global systolic function was normal, LVEDD was 45mm and left ventricular wall thicknesses 10-11mm. Doppler echocardiography showed marked respiratory variation of the mitral inflow. The clinical findings were compatible with cardiac tamponade. Pericardiocentesis was done and 350ml of purulent secretion was obtained. After that a drain was inserted. Bacterial staining of the pericardial fluid showed Gram positive cocci and later bacterial culture confirmed that they were pneumococci. The diagnosis was pneumococcal sepsis, pneumonia and purulent pericarditis. The recovery was slow but uneventful. Pericardial drain could not be removed until three weeks later.

Since the patient had been previously healthy, factors predisposing to a fulminant infection were sought. No solid tumors or signs of other malignancies were observed. HIV serology was negative. The main laboratory finding was persistent hypogammaglobulinemia. The serum concentration of IgM was 0,18 g/l (normal range 0,36-2,59g/l), that of IgG was 3,6g/l (normal range 6,8-15g/l) and IgA was 0,17g/l (normal range 0,88-4,84 g/l). The levels of all IgG subclasses were low. The proportion of CD19 B-cells was low and the proportion of CD4/8 T-lymphocytes was 0,4, decreased. After the pneumonic infiltrates had resolved, HRCT (high resolution computed tomography) of the lungs showed still diffuse centrilobular nodularity and mediastinal lymphadenopathy compatible with GLILD, granulomatous lymphocytic interstitial lung disease. Splenomegaly was observed. After further immunological analyzes and missing responses to vaccination, the findings were compatible with a common variable immunodeficiency (CVID). The patient needs lifelong immunoglobulin substitution. Two years and five months after the near fatal infection, the patient is well. The regular medication comprises subcutaneous immunoglobulin substitution and prednisone.
Pericarditis and tamponade

Pericardial tamponade is a medical emergency in which pericardial effusion increases the intrapericardial pressure and leads to hemodynamic collapse. The clinical diagnosis is based on typical presentation (tachycardia, hypotension, marked decrease of systolic pressure during inspirium while diastolic blood pressure remains unchanged) and demonstration of pericardial effusion usually by echocardiography. Immediate pericardial drainage is absolutely indicated. Various infectious or non-infectious agents may cause pericardial effusion. Bacterial pericarditis is a rare and fulminant disease and fatal, if untreated. This condition may be overlooked in a septic patient.

Common variable immunodeficiency (CVID)

CVID is a primary immunodeficiency affecting B-cells. Typically, the serum concentrations of IgG are low and there is a failure to produce antibodies in response to immunization or infection. Also T-cell abnormalities occur. CVID is often complicated by a multisystemic granulomatous disease, usually in the lungs. Splenomegaly and hilar and mediastinal lymphadenopathy are common findings in CVID patients.

References

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


