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CASE REPORT

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The role of MR imaging and cardio-pulmonary exercise test (CPET) in oncology patient – a case report

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Summary

Background: Thromboembolic complications are the second cause of mortality in patients with malignant neoplasms. Their course can be apparently asymptomatic, masked by other dominant symptoms of a malignant process. Therefore, there is a need for an unbiased diagnostic method to establish the causes of the patients' clinical condition.

Case Report: The authors present a case of a 42-year-old neoplastic male patient admitted for bone marrow transplant. Examinations performed routinely before marrow transplantation showed pulmonary embolism in CT, while Trans Thoracic Echocardiography (TTE) revealed abnormal findings in the heart. Trans Esophageal Echocardiography (TEE) was indecisive and did not discriminate between a thrombus or neoplastic character of the observed pathological structures. MR helped to identify the findings as a thrombus. For unbiased initial assessment, the patient was referred for cardio-pulmonary exercise test (CPET).

Cardiopulmonary exercise test allowed to rule out any signs of restrictive or occlusive lung disease, and along with other diagnostic tests confirmed chronic thromboembolic pulmonary hypertension (CTEPH).

Conclusions: Pulmonary embolism is found significantly more often in patients with neoplastic disease. Its course can be apparently asymptomatic, masked by other dominant symptoms of a malignant process. Magnetic resonance is a valuable tool in assessment of heart morphology, allowing proper diagnosis especially in thrombus identification, or detection of metastases. Cardiopulmonary exercise test can be useful in diagnosis and assessment of chronic thromboembolic pulmonary hypertension in apparently asymptomatic patients. CPET used in conjunction with MR seem to be a valuable combination capable of providing correct diagnosis where other methods fail.

Key words: cardiac mass • cardiopulmonary exercise test (CPET) • pulmonary embolism • chronic thromboembolic pulmonary hypertension (CTEPH) • magnetic resonance imaging

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Background

Thromboembolic complications are the second cause of mortality in patients with malignant neoplasms. Pulmonary embolism is found significantly more often in patients with neoplastic disease. Its course can be apparently asymptomatic, masked by other dominant symptoms of a malignant process. Therefore, there is a need for an unbiased diagnostic method to establish the causes of the patients' clinical condition. CPET used in conjunction with MR seem to be a valuable combination capable of providing correct diagnosis where other methods fail.

Case Report

A 42-year old patient was admitted to the Internal Disease Department of the Metropolitan Hospital in Toruń in October 2002 with complaints of abdominal pain increasing

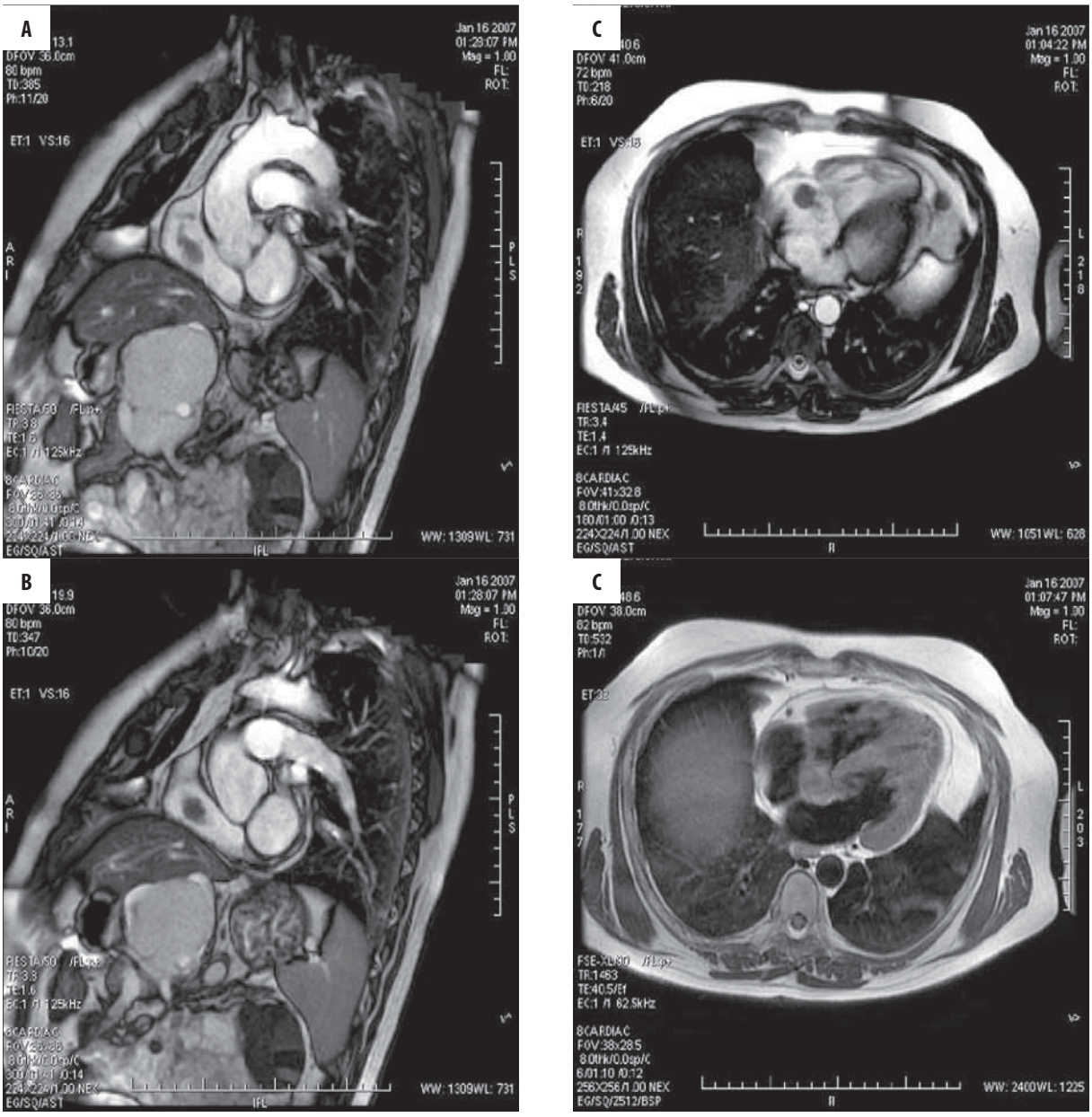


Figure 1. FIESTA images in parasagittal (**A,B**) and transverse (**C,D**) planes. Pathological hypointensive masses are visible in right ventricle (a – arrow) and right atrium (b – arrow). Mass in the right atrium moves with heart movement. In diastole, it is present in the plane of the valve (c –arrow) and in systole moves into the right atrium (d – arrow).

for a few months. After physical examination, laboratory studies and additional diagnostic procedures like US and CT, the patient was diagnosed with testicular carcinoma with metastases to the right lung, abdominal and supraclavicular lymph nodes. Right unilateral orchidectomy was performed with pathology result – teratoma immnaturu, yolk sacktumor et chorioncarcinoma testis **T1N3M1aS2**. In November 2002, BEP chemotherapy scheme (bleomycin + etoposide + cisplatin) was applied. After four courses, due to lack of full remission (as manifested by increased level of AFP and visible pathology in the abdomen), additional two courses of EP (etoposide + cisplatin) were applied. Chemotherapy was finished in March 2003 after 6 courses (4 BEP + 2 EP).

After completion of treatment, there was partial remission of neoplastic changes in the abdomen, almost total remission of changes in the lungs, decrease in size of supraclavicular lymph nodes and normalization of AFP level. In June 2004, however, in follow-up abdominal CT, there was an increase in size of neoplastic changes, without significant increase in levels of other markers. Since June 2005, the patient's overall condition deteriorated: symptoms like abdominal pain increased, there was marked growth of the tumors, this time with significant increase of AFP level. In August 2005, the patient underwent retroperitoneal lymph node dissection (RPLND). In December 2005, the patient started VeIP scheme chemotherapy (vinblastine + ifosfamide + cisplatin). There were planned 4–6 courses of chemotherapy, two extractions of bone

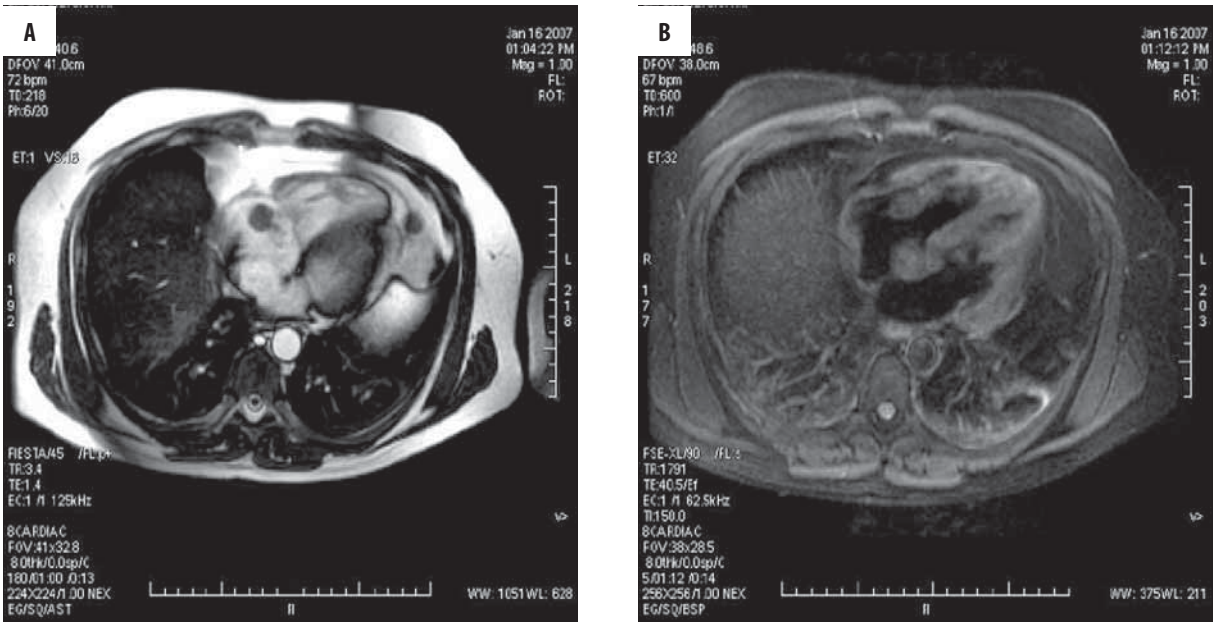


Figure 2. Double IR (**A**) and triple IR with fat saturation (**B**) images. Hypointense, compared to myocardium, pathological structures in right atrium and right ventricle (a and b – arrows).

marrow and two courses of high dose chemotherapy with autologous bone marrow transplantation. Progression was observed, however, after two courses of chemotherapy and the scheme was changed to TIP (paclitaxel + ifosfamide + cisplatin).

The first bone marrow extraction was performed on February 12, 2006, the second on April 20, 2006. Before the second extraction on April 18, 2006 the patient had ECHO of the heart where chambers of the heart were within limits of size, with appropriate LV wall thickness and thickening, without valvular defects, or pericardial fluid.

Two months later, in June 2006, the patient was admitted to Oncology Clinic of the Military Institute of Medicine for continuation of TIP chemotherapy and preparation for bone marrow transplantation. Upon admission, the patient's overall status was satisfactory, without complaints. Physical examination was insignificant, without dyspnea or edema. Laboratory tests were within normal limits. ECG showed moderate tachycardia, 100 BPM, without changes in the ECG tracings.

Results

Examinations performed routinely before marrow transplantation on June 20, 2006, showed pulmonary embolism in CT, while Trans Thoracic Echocardiography (TTE) revealed elongated hypoechogenic flaccid structure (40×6 mm) in the right outflow tract, most likely connecting to subvalvular structures, and another hypoechogenic moving structure (35×15 mm) probably connecting to one of the cusps – thrombus? myxoma? Tip of the port most likely in the right atrial ostium of VCS, ejection fraction 65%. Immediately performed Trans Esophageal Echocardiography (TEE) was indecisive and did not discriminate between thrombus or neoplastic character of the observed pathological structures.

The patient was referred for MR of the heart. The examination was performed on GE Signa Excite 1.5T HD, with dedicated 8-channel cardiac coil and ECG gating. This allowed to improve the signal to noise ratio and reduce the time of controlled breath holds.

Examination protocol included assessment of heart morphology and function, rest perfusion and imaging of the delayed enhancement. It consisted of the following sequences:

1. FIESTA in short and long axis as well as in four-chamber view;
2. T_1 double and triple IR with fat saturation;
3. FGRE for rest perfusion assessment;
4. FGRE for delayed enhancement assessment.

Slice thickness was 8 mm for FIESTA and IR sequences and 6 mm for perfusion and delayed enhancement sequences.

Deleyed enhancement was assessed after 15 minutes from i.v. administration of paramagnetic contrast media in dose 0.2 mmol/kg.

No changes in myocardial contractility, LV wall thickness and thickening, or wall movement were observed. No areas of pathological enhancement were detected within the myocardium.

FIESTA images showed a pathological mass 18 mm in diameter moving back and forth with blood flow at the level of tricuspid valve (Figure 1A–D). It was impossible to detect connection point of its stalk (valve cusp? wall of right atrium?). Signal characteristics were not typical of tissue – neoplastic composition; the structure did not enhance neither in the perfusion nor delayed enhancement phase. Another similar, however smaller and thinner in cross section, juxtraseptal structure was visible in the lumen of the right ventricle. The observed pathological structures were most likely thrombi (low signal intensity in GE cine, stronger in

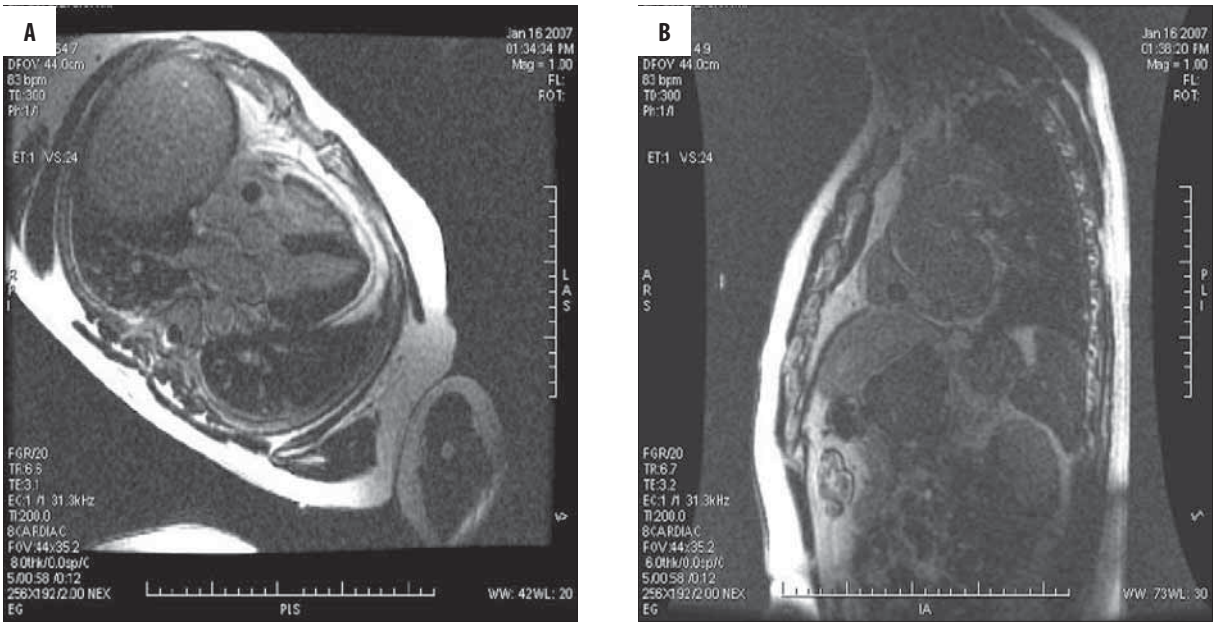


Figure 3. Delayed enhancement FRGE sequence images in four-chamber view (**A**) and parasagittal plane (**B**). Non-enhancing mass in right atrium (a and b – arrows).

double and triple IR with fat saturation, lack of contrast enhancement) (Figure 2A,B, Figure 3A,B).

Consulting team of cardiologists and cardiosurgeons recommended conservative treatment with therapeutic doses of anticoagulants. Having in mind that the patient was asymptomatic, however suspected of chronic thromboembolic pulmonary hypertension, for obtaining unbiased initial assessment patient was referred for cardiopulmonary exercise test (CPET). The results allowed for marrow transplantation qualification and future assessment of efficacy of the treatment.

The CPET examination was conducted on ZAN 680 cyckloergometer with Oxilink pulseoxymeter according to Rampe 10W/min protocol. Examination was finished due to patient fatigue. Peak oxygen consumption was VO_{2peak}=15,89 ml/kg/min, which is 45% of normal value for age and sex. Oxygen consumption at anaerobic threshold was VO_{2AT}=10, 9 ml/kg/min. Due to compensating tachycardia there was a marked decrease of O_2 pulse (VO_2/HR) (Figure 4A). After reaching the anaerobic threshold, steady increase of ventilation equivalents for O_2 and CO_2 were observed (VE/VO_{2max}=50,7 and VE/VCO_{2max}=42,8) (Figure 4B), typical of pulmonary perfusion defect and developing pulmonary hypertension. Bad prognosis was confirmed by the value of $VE\text{-}VCO_{2slope}$>35. The ratio of dead space and tidal volume was elevated during exercise without physiological decrease, typical of abnormal pulmonary circulation (Figure 4C). Cardiopulmonary exercise test allowed to rule out any signs of restrictive or occlusive lung disease. Diagnostic examinations confirmed chronic thromboembolic pulmonary hypertension (CTEPH).

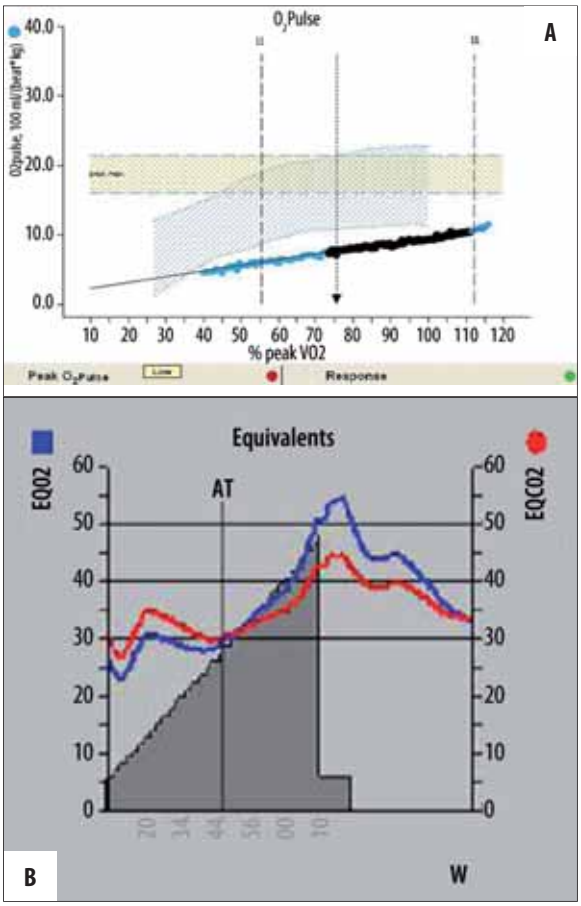
Discussion

Thromboembolic complications are the second cause of death in patients with malignant neoplasms [1]. Changes in blood predisposing for these complications can be found in 90% of patients. Thrombi are found extremely often in the tumors and surrounding tissues in post mortem examinations, which can suggest direct involvement of neoplastic cells in pathogenesis of thrombus [2]. Thrombi can complicate the course of all neoplastic malignancies. In neoplastic patients known thrombogenic risk factors – all components of Virchow's triad – are seen quite frequently. It is common for tumors to invade the adjacent blood vessels. Involvement of the inferior vena cava (as in the case of the described patient) has been reported in patients with large malignancies of kidneys (5–9%), adrenals and testes [3]. Within the tumor, neoplastic cells and invading macrophages secrete cytokines destroying antithrombogenic properties of the endothelium. Compression of the vessel by the mass of the expanding tumor can lead to its total occlusion. Over 90% of patients have changed parameters of clot formation and fibrinolysis. Increased concentration of fibrinogen, platelet count, FDA and D-dimer levels correlate with the neoplastic process and can be used as markers of progress of the disease as well as response to therapy [4–6]. Neoplastic cells often are the direct source of thrombogenic agents.

The frequency of clinically evident thromboembolic complications is estimated at 15%.

They are more frequent in post mortem examinations. This discrepancy arises from high incidence of apparently asymptomatic complications. A patient with a neoplasm has moderately elevated markers of chronic inflammatory process. Inflammatory cytokine cascade, together with possible mild cytopenia, result in some level of permanent fatigue. Any additional weakening is considered to be related with progress of the primary neoplastic process, leading to general avoidance of exertion.

The most common manifestation of thromboembolic complications is deep venous thrombosis and associated pul-



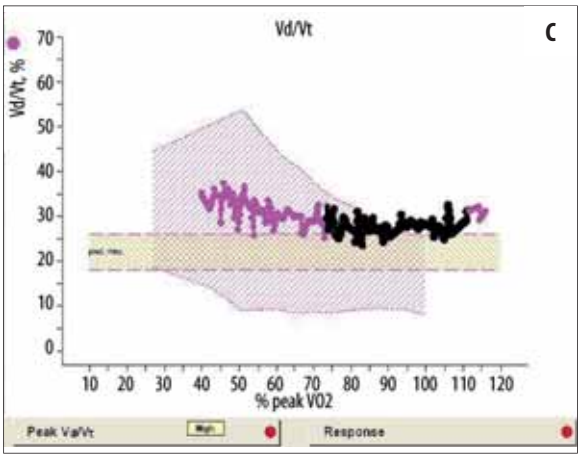


Figure 4. (**A**) Plot of O_2 pulse. Marked decrease of O_2 pulse (VO_2/HR) visible (black and blue plot out of the shaded range) – result of low oxygen consumption and high heart rate, typical of pulmonary hypertension and heart failure. (**B**) Plot of ventilation equivalents for O2 and CO_2. After reaching the anaerobic threshold, steady increase of ventilation equivalents for O_2 and CO_2 was observed (VO_{2max}=50,7 and VE/VCO_{2max}=42,8), typical of pulmonary perfusion defect and developing pulmonary hypertension. (**C**) Plot of dead space and tidal volume (VD/VT) – elevated during exercise without physiological decrease, typical of abnormal pulmonary circulation.

monary embolism. In the natural course of pulmonary embolism thrombi are either completely resolved or with minimal residue, leading to return of normal pulmonary circulation. In case of neoplastic patients, however, for reasons yet unknown, thrombi within the pulmonary vessels are not reabsorbed. On the contrary, they are epithelialized, which leads to vessel occlusion and development of chronic thromboembolic pulmonary hypertension – CTEPH. The estimated frequency of CTEPH in general population amounts to 0.1–0.5% of patients after an episode of acute pulmonary embolism [7]. This episode can be asymptomatic in the majority of patients with CTEPH. Thrombi are tightly bound to the media of the pulmonary artery, replacing healthy intima and can lead to stenosis, or even total occlusion of the vessel. Interesting is the fact that we can observe in the stenosed vessels changes typical of pulmonary arteriopathy, impossible to be differentiated from the ones found in primary pulmonary hypertension.

Patients after an incident of acute pulmonary embolism enter the initial period of stability referred to clinically as the "honeymoon period". During this period, the patient's overall condition improves, with only mild reduction of physical exercise tolerance. Further clinical course depends on therapy and recurrence of thromboembolic incidents, which only rarely can lead to increase of pulmonary pressure and progress of the disease. The leading cause of deterioration of patients' status is growth of already present thrombi and progress of, initially unaffected, small pulmonary vessel destruction, due to pulmonary hypertension [8,9]. The final stages include full symptoms of uncompensated pulmonary heart, leading to death.

CTEPH diagnosis is based upon perfusion scintigraphy of the lungs, contrast-enhanced CT, pulmonary angiography. Some authors suggest exercise tests, because one of the early manifestations of CTEPH can be exertional hypoxemia and significant ventilation disturbances. These parameters can be used as noninvasive markers to quantify the progress or regression of the disease.

Pulmonary endarterectomy is the treatment of choice in patients with CTEPH. Precise preoperative diagnosis and selection, technique used, experience of the operator and appropriate postoperative care are factors having the greatest impact on the successful outcome [10]. Selection of patients for surgical procedure depends on the size and location of the thrombus with regard to the severity of pulmonary hypertension. Thrombi in the proximal parts of the vessels are the best for surgical intervention, while in distal segments suggest worse outcome.

In some severe cases, lung transplantation is considered.

In differential diagnosis the possibility of thrombi originating from the pathology in the chambers of the heart has to be taken into account. Most frequently this is the case in patients with atrial flutter. In oncology, it can be associated with either primary (most often myxoma) or metastatic (most often teratoma) neoplastic disease. Additional diagnostic imaging examinations not only can identify thrombi in chambers of the heart but also quite often visualize the cause of their formation, including neoplasms. They facilitate monitoring of the progress/response to treatment of

the disease and prompt qualification for cardiosurgical procedure [11]. Correct diagnosis can indicate the most appropriate therapy and the most probable outcome.

Magnetic resonance imaging MRI is especially useful in this field. MR examination, despite its limitations such as long examination time and susceptibility to motion artifacts has many advantages making it useful and unique among diagnostic imaging methods in noninvasive cardiac examinations:

1. Highest, among imaging methods, tissue contrast resolution – due to dependence of signal registered from imaged tissues on their histochemical composition tissue characterization is superior than in other imaging methods.

2. Ability to visualize function of organs in motion – due to application of dedicated multichannel coils and high temporal resolution of the imaged phases it is possible to perform perfusion/viability studies of the myocardium. In addition, often pathological changes (such as neoplasm or infracted tissue for example) posses unique wash-in/wash-out characteristics, allowing for better differentiation.

3. Imaging in any plane – this allows for obtaining native images in the plane most appropriate for the given pathology examined; in case of heart examinations, double-oblique images in planes corresponding to typical US examination planes.

Conclusions

Pulmonary embolism is found significantly more often in patients with neoplastic disease. Its course can be apparently asymptomatic, masked by other dominant symptoms of a malignant process.

Magnetic resonance is a valuable tool in assessment of heart morphology, allowing proper diagnosis, especially in thrombus identification, or detection of metastases.

Cardiopulmonary exercise test can be useful in diagnosis and assessment of chronic thromboembolic pulmonary hypertension in apparently asymptomatic patients. These patients, often with metastases in the lungs, frequently receive highly cardio- and pulmotoxic drugs, affecting the clinical image of the disease.

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