Netherlands
The Journal of Medicine

REVIEW

Epidemiology and management of chronic thromboembolic pulmonary hypertension

F.A. Klok[1,2*], M.V. Huisman[1]

Department of General Internal Medicine-Endocrinology, [1]Section of Vascular Medicine, Leiden University Medical Center, Leiden, the Netherlands, [2]Department of General Internal Medicine, Bronovo Hospital, The Hague, the Netherlands, *corresponding author: e-mail: F.A.Klok@LUMC.nl

ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication of acute pulmonary embolism (PE) with an estimated incidence of 0.5 to 1.5% in the Netherlands, depending on the aetiology of the PE. The underlying pathophysiological mechanism is largely unknown and may be caused by (recurrent) emboli or primarily by a characteristic arteriopathy of the pulmonary arteries. Patients with CTEPH present with nonspecific symptoms predominantly caused by right heart failure and up to 40% have no prior history of venous thromboembolism (VTE). The diagnostic approach of CTEPH aims at assessing the location and extent of the embolic obstruction to establish the operability and prognosis of the patients. A heart catheterisation for invasive pressure measurements is obligatory for the final diagnosis. CTEPH is associated with a poor prognosis if left untreated. The preferred treatment is pulmonary endarterectomy. In certain patients with inoperable disease or with persistent or recurrent pulmonary hypertension after surgery, pharmacotherapy might be beneficial.

KEYWORDS

Pulmonary embolism, chronic thromboembolic pulmonary hypertension, epidemiology, diagnosis, therapy, prognosis

INTRODUCTION

Pulmonary embolism (PE) is a common disorder with an estimated yearly incidence of 0.7 to 1 per 1000 inhabitants in the Western world. In addition to short-term adverse clinical outcomes, such as death, bleeding or recurrent emboli, the long-term prognosis of patients with acute PE is complicated by high rates of other PE-related serious clinical events including increased mortality risk, arterial cardiovascular disease, i.e. previous studies have demonstrated an increased risk for myocardial infarction and cerebral vascular accidents after PE compared with control patients, and pulmonary hypertension caused by incompletely resolved pulmonary emboli.[1,2] This last-mentioned condition, known as chronic thromboembolic pulmonary hypertension (CTEPH), is a very serious disease associated with progressive physical disability and a high mortality risk.[3-6] Pulmonary hypertension is defined by an invasively measured mean pulmonary artery pressure exceeding 25 mmHg at rest and a normal pulmonary capillary wedge or left ventricular end-diastolic pressure of less than 15 mmHg.[3-5] In addition to intraluminal thrombus organisation resulting in fibrous stenosis or complete obliteration of the pulmonary arteries, CTEPH is characterised by intense remodelling of the small pulmonary arteries in those areas that are affected but also that are spared from thromboembolic occlusion, both processes leading to a chronic increase in pulmonary vascular resistance and progressive right heart failure.[3-5] Epidemiological and clinical aspects of this disease as well as the latest evidence on the management of patients with CTEPH will be the main focus of this summary.

PATHOPHYSIOLOGY

In recent years, several plausible pathophysiological mechanisms for CTEPH have been postulated: 1) asymptomatic recurrent emboli after an initially effectively treated PE, 2) failure of resolving an acute embolus despite effective treatment or because of ineffective treatment and

3) in situ thrombus formation as a reaction to vascular remodelling from a nonthromboembolic origin, e.g. in pulmonary arterial hypertension (PAH).[6] However, numerous valid pro and contra arguments for these three mechanisms prevent the proposal of a straightforward pathophysiological concept.

The first important evidence against the first two proposed 'embolic' mechanisms is the lack of a prior history of symptomatic VTE in up to 40% of the patients with established CTEPH.[7,8] Second, a recent meta-analysis of imaging studies evaluating the thromboembolic resolution rate after acute PE found that possibly over 50% of the patients have evidence of residual emboli six months after the acute event. Only a very small proportion of these patients is at risk for developing CTEPH.[9] Third, there is a lack of correlation between elevated pulmonary artery pressure and the degree of angiographic vascular bed obstruction.[10] Furthermore, the pulmonary artery pressure can progress in the absence of recurrent PE or increased vascular obstruction rate.[10] Fourth, decreased fibrinolytic potential has not been identified in patients with CTEPH.[3,11] Finally, the remarkable resemblance between the histopathology of patients with CTEPH and those with PAH has been used as evidence against the existence of two distinct pathogenetic mechanisms.[3,11] On the other hand, there is clear evidence for a causal relation between VTE and CTEPH.[8] Further, CTEPH can be cured after a successful pulmonary endarterectomy, which opposes an underlying pulmonary artery endothelial condition.[7,12] Lastly, basic research has revealed a possible link between pulmonary emboli and the development of endothelial damage: thrombi cause a local increase in pulmonary artery endothelial permeability, resulting in an access of growth factors, cytokines and vasoreactive factors to both endothelial and pulmonary artery smooth muscle cells. These processes cause a local procoagulant and proinflammatory state and consequently initiate the remodelling process characteristic for CTEPH.[7,13]

Future studies should further investigate the pathogenesis behind the above-described observed associations. It is generally appreciated that CTEPH may not be explained simply by either unresolved or recurrent emboli, or by in-situ thrombosis only, and that all three processes are likely to contribute to the disease mechanism of CTEPH.

EPIDEMIOLOGY

Incidence of CTEPH

The true incidence and prevalence of CTEPH in the general population are unknown.[3] The incidence of CTEPH after acute PE, however, has been reported to vary between 0.1 and 8.8%.[3,14-17] This wide range can be explained by important differences in the inclusion and diagnostic criteria between relevant studies: selection of patients was often based on the aetiology of the acute PE excluding patients with permanent or temporary risk factors for VTE, patients with further comorbid conditions associated with pulmonary hypertension were frequently excluded and the diagnosis of CTEPH was not always confirmed by right heart catheterisation.[3,14-17]

In the widely quoted study by Pengo *et al.,* 223 patients diagnosed with acute PE were followed for a mean period of 94.3 months.[14] Patients who had otherwise unexplained dyspnoea on exertion or at rest were considered to have CTEPH and underwent echocardiography. In the presence of supportive findings on echocardiography, further diagnostic tests including right heart catheterisation were performed. The cumulative incidence of CTEPH was 1.0% after six months, 3.1% after 12 months and 3.8% after 24 months.[14] Notably, because of strict exclusion criteria including the presence of pre-existing exertional dyspnoea or diseases that could have caused nonthromboembolic pulmonary hypertension, an unknown but relevant proportion of the patients were not included in the final analysis.

The incidence of CTEPH after acute PE was evaluated in a recent study by our department.[18] In order to construct a representative study population, all consecutive patients diagnosed with an episode of acute PE in the period between 1 January 2001 and 1 July 2007 in the Leiden University Medical Center (Leiden, the Netherlands) and affiliated teaching hospital Medical Center Haaglanden (The Hague, the Netherlands) were eligible for study inclusion, irrespective of age, medical history or comorbid conditions. The clinical and outpatient charts of these patients were searched for an established diagnosis of pulmonary hypertension. When present, all relevant data regarding the diagnosis, treatment and follow-up of these patients were collected. Further, the cause of death from all patients who had died before the start of the study (1 July 2007) was verified with the treating physician or general practitioner. Finally, all surviving patients who were not yet diagnosed with pulmonary hypertension were contacted and interviewed regarding their medical history and current clinical condition. All these patients were invited for a transthoracic echocardiography that was followed by right heart catheterisation and conventional pulmonary angiography when one of the predefined echocardiographic criteria for suspected pulmonary hypertension was met.[18] CTEPH was diagnosed according to the most recent international guidelines.[5] Of the 877 identified patients with acute PE, 11 (1.3%) were excluded due to geographical reasons, 259 (30%) had died and four (cumulative incidence 0.57%, 95% confidence interval (CI) 0.02 to 1.2%) were diagnosed with CTEPH.[18] The risk for CTEPH after unprovoked PE, i.e. PE according in the absence of thrombotic risk factors, was three times higher (cumulative incidence 1.5%, 95% CI 0.08 to 3.1%).[18] The

main limitation of this study was the lack of objective tests to rule out CTEPH in the patients who had died and those who refused or were not able to participate. In those patients, CTEPH was considered not present if an alternative cause of death was reported or in the absence of unexplained exertional dyspnoea. Of note, these diagnostic criteria were also applied by Pengo *et al*.[14]

Risk factors for CTEPH

In a recently published controlled retrospective cohort study, prevalent CTEPH cases were collected in three European CTEPH referral centres and compared with nonthromboembolic precapillary PAH cohorts at the same institutions. The study population consisted of 687 patients diagnosed between 1996 and 2007. Blood groups other than 0 (odds ratio (OR) 2.1, 95% CI 1.1 to 3.9), a history of malignancy (OR 3.8, 95% CI 1.5 to 10), lupus anticoagulant/antiphospholipid antibodies (OR 4.2, 95% CI 1.6 to 12), previous VTE (OR 4.5, 95% CI 2.4 to 9.1), recurrent VTE (OR 15, 95% CI 5.4 to 43), thyroid replacement therapy (OR 6.1, 95% CI 2.7 to 15), splenectomy (OR 18, 95% CI 1.6 to 2.4), ventriculo-atrial shunts and infected pacemakers (OR 76, 95% CI 7.7 to 10) were more often associated with CTEPH.[8] Importantly, these odds ratios can not be applied to daily clinical presence in patients with acute PE since a history of venous thromboembolic disease was lacking in 40% of the CTEPH patients. Pengo, who used acute PE as the main inclusion criteria of his study, found younger age (OR 1.8 per 10 years age difference, 95% CI 1.2 to 1.9), larger perfusion defects at diagnosis (OR 2.2 per decile decrement in perfusion, 95% CI 1.5 to 3.3), unprovoked PE (OR 5.7, 95% CI 1.4 to 23) and recurrent PE (OR 19, 95% CI 4.5 to 80) to be independent predictors of CTEPH after acute PE.[14]

DIAGNOSTIC MANAGEMENT

Clinical signs and symptoms

Patients with CTEPH typically present with nonspecific symptoms of right heart failure: progressive dyspnoea on exertion, fatigue, palpitations, syncope, haemoptysis or chest pain.[3,4] Physical examination may reveal findings consistent with pulmonary hypertension and/or right-sided heart failure: a prominent component of S2, a systolic murmur of tricuspid regurgitation or a diastolic murmur of pulmonary valve regurgitation, jugular venous distension, lower-extremity oedema, hepatomegaly, ascites and cyanosis. The nonspecific symptoms and the often unremarkable physical examination in the early course of the disease contribute to diagnostic delay. However, exertional dyspnoea or a progressive decline in exercise capacity out of proportion to that expected, considering coexisting medical conditions, should raise the suspicion of CTEPH. A possible diagnostic algorithm in the above-mentioned cases is demonstrated in *figure 1*.

Diagnostic tests

Studies defining the optimal diagnostic management in case of suspected CTEPH are lacking. Nonetheless, experts agree that the primary evaluation of these patients should be focused on determining the degree of pulmonary hypertension and cardiac compromise present, to confirm the diagnosis CTEPH by ruling out alternative conditions and to establish surgical accessibility and the potential operability of the patient. This diagnostic algorithm should at least consist of transthoracic echocardiography, pulmonary function tests, high resolution computed tomography (CT) of the chest, VQ lung scan and right heart catheterisation for invasive pressure measurements and conventional pulmonary artery angiography.[3,5,19,20] The use of CT or MRI for pulmonary angiography or cardiac functional measurements in the diagnostic management of patients with suspected CTEPH is yet to be determined. However at present, these imaging modalities cannot replace right heart catheterisation.[5,19]

In the presence of a completely normal echocardiography or ventilation perfusion scintigraphy, the diagnosis of CTEPH is highly unlikely.[5] In addition, recent yet unpublished data from our department suggest that a combination of an ECG without signs of right ventricular overload in combination with a normal NT-pro-BNP level also virtually excludes CTEPH (*figure 1*): even with high assumed disease prevalences of up to 10%, the negative predictive value of this model proved to be over 99%.

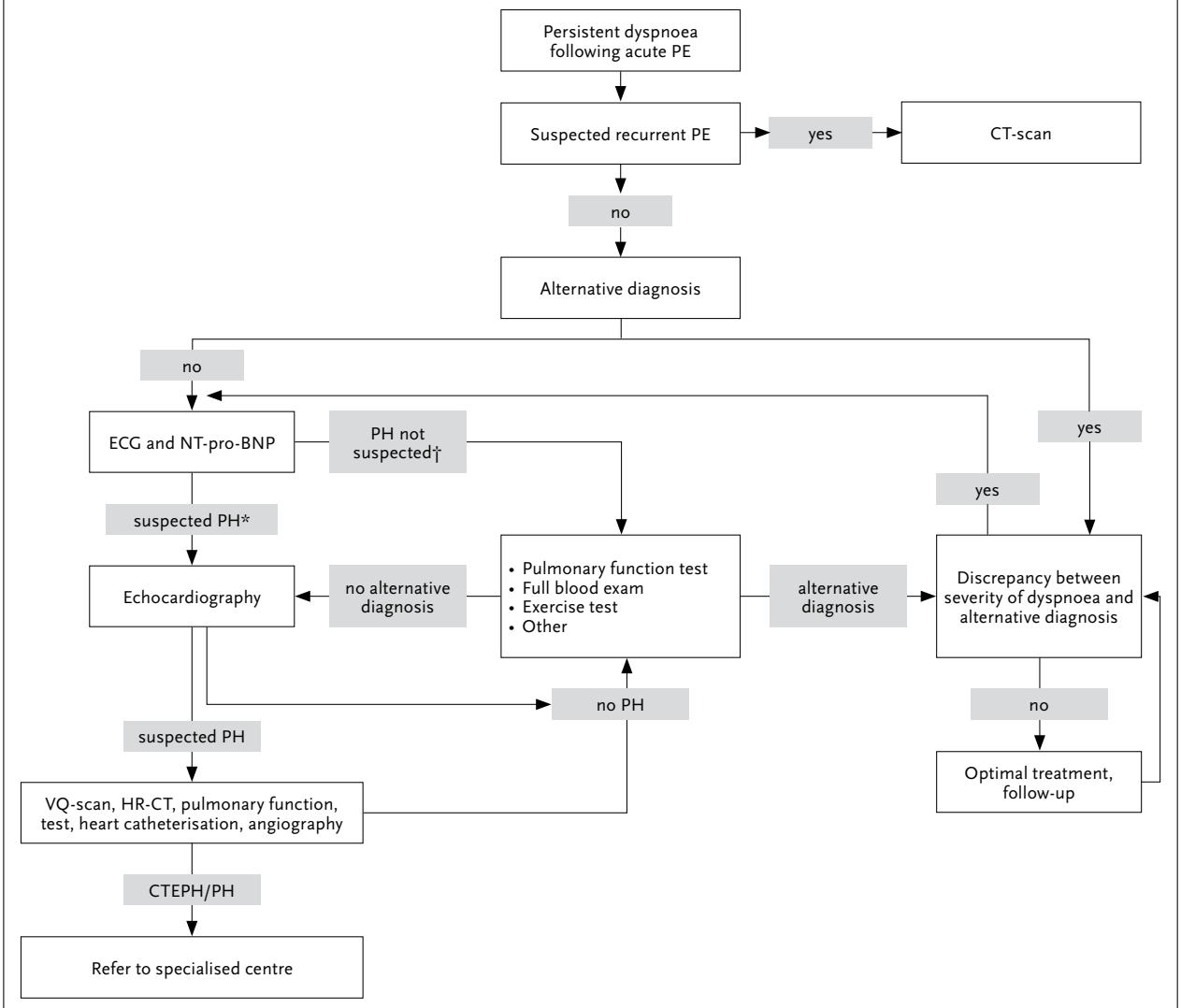
Screening for CTEPH

Potential screening programs for CTEPH after PE should employ tools that are noninvasive, widely available and applicable, and importantly, that can distinguish patients who are in early stages of CTEPH from those who are not at risk of developing this condition. Because of the lack of understanding of the natural history of CTEPH, the absence of preventive treatment measures in very early stages of the disease as well as the very low risk of developing CTEPH following acute PE, screening for CTEPH does not seem warranted. In addition, one study showed a very low yield of an echocardiography based screening program on top of routine clinical care, underlining the former recommendation.[18]

TREATMENT AND PROGNOSIS

Historical data indicate that if left untreated, CTEPH is associated with a poor five-year survival, ranging from 10 to 40% dependent on degree of elevation of the pulmonary artery pressure.[6] Although patients with CTEPH should receive lifelong anticoagulation treatment for the prevention

Figure 1. *Proposed diagnostic algorithm in patients with persistent exertional dyspnoea following acute pulmonary embolism*



†Normal age- and sex-corrected NT-pro-BNP levels and no evidence of right ventricular overload on ECG. *Elevated age- and sex-corrected NT-pro-BNP levels or evidence of right ventricular overload on ECG (right axis deviation, right bundle branch block or right ventricular hypertrophy); PE = pulmonary embolism; CTEPH = chronic thromboembolic pulmonary hypertension; PH = pulmonary hypertension; CT = computed tomography; ECG = electrocardiogram; VQ = ventilation perfusion.

of recurrent venous thromboembolism, this cannot prevent disease progression.[5] Surgical intervention with pulmonary endarterectomy (PEA) is the preferred treatment of CTEPH.[3,12] The success of PEA is based on the concept that a true endarterectomy, establishing a dissection plane to free the thrombotic residua from the native vessel wall, and not an embolectomy is necessary. The pulmonary artery is optimally exposed during periods of circulatory arrest and deep hypothermia to achieve a bloodless operative field.[12] The goal of PEA is to improve pulmonary haemodynamics, exercise capacity, symptoms and survival. The procedure may be curative in appropriately selected patients and is associated with an improved six-year survival rate of 75%.[21-23] There is general consensus that current surgical techniques allow removal of organised thrombi whose proximal extent is in the main or lobar pulmonary arteries.[12] Consequently, PEA is contraindicated in patients with predominantly distal CTEPH, with severe comorbid conditions associated with increased perioperative mortality (in particular obstructive or parenchymal lung disease) or those with a preoperative haemodynamic profile with limited anticipated postoperative improvement. These patients as well as patients with persistent or recurrent pulmonary hypertension after PEA might be appropriate candidates for pharmacotherapy. Several open-label studies with prostaglandin derivatives, endothelin receptor antagonists and phosphodiesterase type 5 inhibitors in patients with CTEPH have been reported, and most suggest haemodynamic or clinical improvement.[23-26] Up to now, only one randomised clinical trial has been performed in patients with inoperable CTEPH.[27] In this study, a 16-week

treatment with the oral dual endothelin receptor antagonist bosentan resulted in a significant reduction in pulmonary vascular resistance and NT-pro-BNP levels as compared with placebo. However, the treatment did not show any effect on the six-minute walking distance nor an improvement in the time to clinical worsening.[27] There is no evidence that pharmacotherapy in patients with CTEPH is associated with either increased survival or, when used as preoperative bridging therapy, with improved postoperative outcome. In general, patients with CTEPH should be referred to an expert centre for either PEA or inclusion in clinical trials.

CONCLUSION

CTEPH is a very serious but infrequent complication of acute PE. The underlying pathophysiological mechanism is largely unknown and may be due to (recurrent) emboli or pulmonary artery endothelial dysfunction. Patients with CTEPH present with nonspecific symptoms predominantly caused by right heart failure and up to 40% have no prior history of venous thromboembolism. The diagnostic approach of CTEPH aims at assessing the location and extent of the embolic obstruction to establish the operability and prognosis of the patients. Invasive pressure measurements should be performed in all suspected cases based on abnormal echocardiography. The preferred treatment is PEA although in certain patients with inoperable disease or with persistent or recurrent pulmonary hypertension after surgery, pharmacotherapy might be beneficial.

REFERENCES

1. Klok FA, Zondag W, van Kralingen KW, van Dijk AP, Tamsma JT, Heyning FH, et al. Patient outcomes after acute pulmonary embolism. A pooled survival analysis of different adverse events. Am J Respir Crit Care Med. 2010;181:501-6.
2. Klok FA, Mos ICM, Broek L, Tamsma JT, Rosendaal FR, de Roos A, et al. Risk of arterial cardiovascular events in patients after pulmonary embolism. Blood. 2009;114:1484-8.
3. Hoeper MM, Mayer E, Simonneau G, Rubin LJ. Chronic thromboembolic pulmonary hypertension. Circulation. 2006;113:2011-20.
4. Fedullo PF, Auger WR, Kerr KM, Rubin LJ. Chronic thromboembolic pulmonary hypertension. N Engl J Med. 2001;345:1465-72.
5. Hoeper MM, Barberà JA, Channick RN, Hassoun PM, Lang IM, Manes A, et al. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol. 2009;54 (Suppl 1):S85-96.
6. Riedel M, Stanek V, Widimsky J, Prerovsky I. Long-term follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. Chest. 1982;81:151-8.
7. Tuder RM, Abman SH, Braun T, Capron F, Stevens T, Thistlethwaite PA, Haworth SG. Development and pathology of pulmonary hypertension. J Am Coll Cardiol. 2009;54(Suppl 1):S3-9.
8. Bonderman D, Wilkens H, Wakounig S, Schäfers HJ, Jansa P, Lindner J, et al. Risk factors for chronic thromboembolic pulmonary hypertension. Eur Respir J. 2009;33:325-31.
9. Nijkeuter M, Söhne M, Tick LW, Kamphuisen PW, Kramer MH, Laterveer L, et al. Christopher Study Investigator. The natural course of hemodynamically stable pulmonary embolism: Clinical outcome and risk factors in a large prospective cohort study. Chest. 2007;131:517-23.
10. Azarian R, Wartski M, Collignon MA, Parent F, Hervé P, Sors H, et al. Lung perfusion scans and hemodynamics in acute and chronic pulmonary embolism. J Nucl Med. 1997;38:980-3.
11. Egermayer P, Peacock AJ. Is pulmonary embolism a common cause of chronic pulmonary hypertension? Limitations of the embolic hypothesis. Eur Respir J. 2000;15:440-8.
12. Keogh AM, Mayer E, Benza RL, Corris P, Dartevelle PG, Frost AE, et al. Interventional and surgical modalities of treatment in pulmonary hypertension. J Am Coll Cardiol. 2009;54(Suppl 1):S67-77.
13. Bogatcheva NV, Garcia JG, Verin AD. Molecular mechanisms of thrombin-induced endothelial cell permeability. Biochemistry (Mosc). 2002;67:75-84.
14. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, et al. for the Thromboembolic Pulmonary Hypertension Study Group. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004;350:2257-64.
15. Becattini C, Agnelli G, Pesavento R, Silingardi M, Poggio R, Taliani MR, et al. Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism. Chest. 2006;130:172-5.
16. Dentali F, Donadini M, Gianni M, Bertolini A, Squizzato A, Venco A, et al. Incidence of chronic pulmonary hypertension in patients with previous pulmonary embolism. Thromb Res. 2009;124:256-8.
17. Miniati M, Monti S, Bottai M, Scoscia E, Bauleo C, Tonelli L, et al. Survival and restoration of pulmonary perfusion in a long-term follow-up of patients after acute pulmonary embolism. Medicine (Baltimore). 2006;85:253-62.
18. Klok FA, van Kralingen KW, van Dijk APJ, et al. Prospective cardiopulmonary screening program to detect chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. Haematologica 2009; doi:10.3324/haematol.2009.018960.
19. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009;53:1573-619.
20. Auger WR, Fedullo PF, Moser KM, Buchbinder M, Peterson KL. Chronic major-vessel thromboembolic pulmonary artery obstruction: appearance at angiography. Radiology. 1992;182:393-8.
21. Archibald CJ, Auger WR, Fedullo PF, Channick RN, Kerr KM, Jamieson SW, et al. Long-term outcome after pulmonary thromboendarterectomy. Am J Respir Crit Care Med. 1999;160:523-8.
22. Jamieson SW, Kapelanski DP, Sakakibara N, Manecke GR, Thistlethwaite PA, Kerr KM, et al. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. Ann Thorac Surg. 2003;76:1457-62.
23. Condliffe R, Kiely DG, Gibbs JS, Corris PA, Peacock AJ, Jenkins DP, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med. 2008;177:1122-7.
24. Ghofrani HA, Schermuly RT, Rose F, Wiedemann R, Kohstall MG, Kreckel A, et al. Sildenafil for long-term treatment of nonoperable chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med. 2003;167:1139-41.
25. Bresser P, Fedullo PF, Auger WR, Channick RN, Robbins IM, et al. Continuous intravenous epoprostenol for chronic thromboembolic pulmonary hypertension. Eur Respir J. 2004;23:595-600.
26. Hoeper MM, Kramm T, Wilkens H, Schulze C, Schäfers HJ, Welte T, et al. Bosentan therapy for inoperable chronic thromboembolic pulmonary hypertension. Chest. 2005;128:2363-7.
27. Jaïs X, D'Armini AM, Jansa P, Torbicki A, Delcroix M, Ghofrani HA, et al; Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension Study Group. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. J Am Coll Cardiol. 2008;52:2127-34.