Pulmonary embolism and pulmonary hypertension: two issues often neglected in cardiology

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Pulmonary embolism and hypertension are important causes of disability and death in cardiovascular patients. Unfortunately, they often do not receive the attention they deserve, in part because symptoms are similar to those of other more frequent cardiovascular conditions such as acute heart failure and acute coronary syndromes. The European Society of Cardiology (ESC) published guidelines in 2008 and more recently also an updated review on the management of acute pulmonary embolism as well as guidelines on pulmonary hypertension to help clinicians manage this condition. Both manuscripts have been highly cited and downloaded, reflecting the needs of practising physicians. One has to also keep in mind that it is not only the acute management of such patients which is of importance, but also their long-term follow-up. The latter is associated with a significant disease burden. Thus, this issue comes just at the right time, reporting on novel developments in the treatment of pulmonary embolism and hypertension.

In a first truly innovative, but preliminary paper, Nils Kucher from the Inselspital in Bern, Switzerland described the use of Fixed low-dose ultrasound-assisted catheter-directed thrombolysis for intermediate and high-risk pulmonary embolism. The author’s retrospective analysis included 52 patients of whom 14 had troponin-positive high-risk and 38 intermediate-risk pulmonary embolism treated with i.v. unfractionated heparin and ultrasound-assisted catheter-directed thrombolysis with 10 mg of recombiant tissue plasminogen activator. During the 3-month follow-up, two patients died. Major non-fatal bleeding occurred in another two. Mean pulmonary artery pressure decreased significantly from 37 ± 9 mmHg at baseline to 25 ± 8 mmHg, and cardiac index increased from 2.0 ± 0.7 to 2.7 ± 0.9 L/min/m². The echocardiographic right to left ventricular dimension ratio also decreased from 1.4 ± 0.2 to 1.1 ± 0.2 at 24 h. Of note, the greatest haemodynamic benefit was found in high-risk pulmonary embolism and in those with symptoms of <14 days. The authors conclude that a standardized fixed low-dose ultrasound-assisted catheter-directed thrombolysis is associated with rapid haemodynamic improvement in intermediate-risk and high-risk pulmonary embolism with low rates of bleeding complications and mortality. This paper complements a recently published systematic review by Engelberger and Kucher, and further supports the need for a large randomized trial using this technology in intermediate- and high-risk patients in order to confirm or refute these promising early findings.

The second paper, a systematic review and meta-analysis entitled Systemic thrombolytic therapy for acute pulmonary embolism by Christophe Albéric Marti from the Geneva University Hospital in Switzerland, determined the risks and benefits of thrombolytic therapy in patients with acute pulmonary embolism. Marti et al. reviewed randomized controlled studies comparing systemic thrombolytic therapy plus anticoagulation with anticoagulation alone. Fifteen trials involving 2057 patients were included. Compared with heparin, thrombolytic therapy was associated with a significant reduction in overall mortality. This reduction, however, was not significant after exclusion of studies enrolling high-risk pulmonary embolism. Thrombolytic therapy was associated with a significant reduction in the combined endpoint of death or treatment escalation, mortality related to pulmonary embolism, and recurrence. Major haemorrhage and fatal or intracranial bleeding were significantly more frequent among patients receiving thrombolysis. The authors conclude that in patients with acute pulmonary embolism, thrombolytic therapy reduces total and embolism-related mortality and recurrence, but is associated with increased major, fatal, or intracranial haemorrhage. Interestingly, in haemodynamically stable patients, overall mortality remained unaffected, suggesting that systemic thrombolysis should be used preferentially in unstable patients.

In the third paper, Effect of nocturnal oxygen and acetazolamide on exercise performance in patients with pre-capillary pulmonary hypertension and sleep-disturbed breathing: randomized, double-blind, cross-over trial, Silvia Ulrich from the University Hospital Zurich, Switzerland reports their three-period trial. Sleep-disturbed breathing is common in pre-capillary pulmonary hypertension and impairs daytime vigilance. The effects of nocturnal oxygen therapy or acetazolamide on exercise performance and quality of life, on the other hand, remain unknown. Participants received nocturnal oxygen at a dose of 3 L/min, acetazolamide at a dose of 2 x 250 mg daily or sham nocturnal oxygen and placebo tablets, respectively. During 1 week with 1 week washout between the treatments periods. Twenty-three patients with pulmonary hypertension and sleep-disturbed breathing participated. Nocturnal oxygen saturation
significantly improved with both oxygen and acetazolamide. The 6 min walk distance improved after nocturnal oxygen. The quality of life determined by the Short Form 36 (SF-36) was, however, similar with all treatments, but right ventricular fractional area change was greater on oxygen compared with placebo and acetazolamide. The authors conclude that in patients with pre-capillary pulmonary hypertension and sleep-disturbed breathing, on optimized pharmacological therapy, nocturnal oxygen may be useful to improve walking distance, sleep-disturbed breathing, and haemodynamics.

In a fourth article, on the ‘Effect of imatinib as add-on therapy on echocardiographic measures of right ventricular function in patients with significant pulmonary arterial hypertension’,10 Amil M. Shah from the Brigham and Women’s Hospital in Boston evaluated whether 24 weeks of add-on therapy with imatinib compared with placebo improves right ventricular function assessed by echocardiography at baseline, 12 weeks, and 24 weeks in 74 patients randomized to imatinib or placebo in the IMatinib in Pulmonary arterial hypertension, a Randomized Efficacy Study (IMPRES) trial. Imatinib is a specific inhibitor of the Bcr-Abl protein tyrosine kinase that has activity against platelet-derived growth factor (PDGF)-driven pathways, an effect that appears to be crucial for its potential use in pulmonary hypertension. In this study, right ventricular function was assessed by tissue Doppler tri-cuspid annular peak systolic velocity, tricuspid annular plane systolic excursion, right ventricular Tei index, and fractional area change. At week 24, patients randomized to imatinib demonstrated greater improvements in these right ventricular performance indexes compared with placebo, except tricuspid annular plane systolic excursion. Imatinib therapy was also associated with a reduction in peak tricuspid regurgitation velocity, as well as an increase in left ventricular size and early diastolic relaxation velocity. Thus, the authors conclude that in patients with advanced pulmonary arterial hypertension who remain symptomatic on at least two drugs, treatment with imatinib is associated with improvements in echocardiographic measures of right ventricular function as well as left ventricular size and early diastolic relaxation.

The last contribution is a Current Opinion article entitled ‘The year in cardiology 2014: peripheral circulation’17 that complements the topics of this issue, Victor Aboyans from the Dupuytren University Hospital in Limoges, France reviews the most recent progress in vascular medicine and discusses the recently published guidelines of the ESC on this subject.15 They note that in 2014 the debate on the indication of revascularization in asymptomatic carotid disease continued, while another debate regarding the use of surgery vs. stenting addressed some new issues regarding the long-term cardiac risk of these patients. Renal artery intervention trials were disappointing. Neither renal denervation (at least in the Symplicity HTN-3 trial13,14) nor renal artery stenting led to better blood pressure control or outcome. In contrast, in lower extremity artery disease, endovascular techniques became major alternatives to surgery, even in distal arteries, with the use of drug-eluting balloons. In 2014, the ESC published its first guidelines on aortic diseases,15 emphasizing the role of cardiologists in the screening of abdominal aorta aneurysm during echocardiography exams for cardiac indications. Among surrogate endpoints, aortic stiffness—as also reported in this journal16,17—is of increasing interest, with new data and a meta-analysis confirming its ability to stratify risk, whereas carotid intim-media thickness showed a less favourable performance in terms of reclassifying patients into risk categories beyond risk scores. As regards venous disease, new data suggest that d-dimers and residual venous thrombosis may help in the decision to continue or stop anticoagulation after a deep vein thrombosis.

We hope that this issue of the European Heart Journal is of interest to our readers.

References
A 47-year-old man without medical history presented with new onset angina and progressive exertional dyspnoea, New York Heart Association class III. A crescendo murmur corresponded to systolic turbulent flow in the left ventricular outflow tract (LVOT), coinciding with a thickened sharp-edged basal septum of 14 mm with ring-like structure on transthoracic (Panel A and B) and transoesophageal echocardiography (Panel C). Pseudonormal diastolic LV function and normal aortic valve morphology and function were noted. The ascending aorta measured 46 mm. Moderate subvalvular LVOT obstruction at rest with a peak gradient of 36 mmHg was found. Computed cardiac tomography (Panel D) and LV angiography (Panel E) both demonstrated a large LVOT subvalvular membrane with supra membraneous cage-like cavity and excluded coronary artery stenosis. Severe dyspnoea and immediate tachycardia (144 b.p.m.) limited bicycle exercise test at only 100 W. A metoprolol 100 mg trial reduced resting gradient to 21 mmHg, however, without providing symptomatic relief as severe dyspnoea and tachycardia re-occurred after 20 squads with a peak gradient increase to 28 mmHg.

Subaortic valvular membrane is a rare entity requiring surgery if symptomatic and/or peak gradient ≥ 50 mmHg. We speculate unfavourable diastology caused excessive steep LV end-diastolic pressure increase transmitted to the pulmonary vasculature, leading to symptoms disproportional to LVOT gradient. The patient underwent uneventful resection of the funnel-shaped complete subvalvular membrane (Panel F, arrows) with limited Morrow procedure and supracoronary aorta ascendens replacement by a 24 mm woven, collagen-coated graft, leading to complete resolution of complains, LVOT gradient and exercise capacity restoration 2 months later.

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