e-mail submissions to
correspondence@lancet.com

## Pulmonary embolism

Samuel Goldhaber's Seminar on pulmonary embolism (Apr 17, p 1295)[1] made interesting reading, and raises a few issues worth discussing. The first involves the imaging techniques used to study pulmonary embolism.

Although chest CT has been used increasingly to diagnose pulmonary embolism, one of the problems with it is that it is technology-dependent and operator-dependent, especially with respect to imaging of the subsegmental pulmonary vessels. Ruiz and colleagues[2] found that, after exclusion of unreadable scans caused by motion artifacts, assessment of half the subsegmental vessels were thought to be difficult by one of two readers. Chest CT might be the preferred method of assessing patients in large centres with experience in reading CT pulmonary angiography, but ventilation-perfusion scanning probably provides better interoperator consistency in the interpretation. Chest CT is therefore a very good test to diagnose pulmonary embolism, but its safety as a test to rule out the disorder is debatable, especially in smaller centres.

Goldhaber states that high-probability or low-probability ventilation-perfusion scans can diagnose or exclude pulmonary embolism. The PIOPED study[3] he quotes, however, found that in the presence of high clinical pretest probability, the post-test probability of a low probability ventilation-perfusion scan is 56%. This is hardly sufficient to exclude pulmonary embolism purely on the basis of a low-probability ventilation-perfusion scan if the clinical pretest probability is high.

I therefore believe that the key factor in the diagnosis of pulmonary embolism is clinical assessment with clinical pretest probability. In patients with high clinical pretest probability and signs and symptoms consistent with a large pulmonary embolus, a chest CT should be the diagnostic imaging technique of choice, with a view to doing venous ultrasonography if the chest CT is non-diagnostic. On the other hand, in patients with clinical signs and symptoms consistent with a possible peripheral embolus, then a ventilation-perfusion scan should probably be the technique of choice.

The second issue worth commenting on is our failure to provide adequate prophylaxis, especially in the medical wards. Although a large randomised controlled trial has shown the benefits of 40 mg enoxaparin in reducing venous thrombosis in inpatients,[4] a brief wander through our medical wards proves that we as physicians are far behind our surgical colleagues in providing routine prophylaxis for pulmonary embolism. Furthermore, despite the convincing evidence for out-of-hospital 3–4 week prophylaxis after high-risk orthopaedic surgery,[5] it has not been widely adopted in our hospital, since the conventional view that prophylaxis should be stopped once a patient can mobilise prevails.

Goldhaber's Seminar serves as a timely reminder to reassess our practice against best evidence. Perhaps it is also time for a widespread education campaign to inform practitioners about the use and adequacy of prophylaxis for pulmonary embolism among hospital inpatients.

*K C Yee*
**kcyee@utas.edu.au**

Royal Hobart Hospital, GPO Box 1061L, Hobart, Tasmania 7001, Australia

1 Goldhaber SZ. Pulmonary embolism. *Lancet* 2004; **363:** 1295–305.
2 Ruiz Y, Caballero P, Caniego JL, et al. Prospective comparison of helical CT with angiography in pulmonary embolism: global and selective vascular territory analysis: interobserver agreement. *Eur Radiol* 2003; **13:** 823–29.
3 PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). *JAMA* 1990; **263:** 2753–59.
4 Samama MM, Cohen AT, Darmon J, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med* 1999; **341:** 793–800.
5 Eikelboom JW, Quilan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet* 2001; **358:** 9–15.

In his Seminar on pulmonary embolism,[1] Samuel Goldhaber covers nearly all aspects of treatment for this often life-threatening disease. However, he does not mention a controversial aspect of treatment. Volume loading is used to treat haemodynamically compromised patients with acute pulmonary embolism despite experimental data which suggest that volume loading after embolism might cause a leftward shift of the ventricular septum with subsequent decrease in left-ventricular end-diastolic volume and stroke work.[2] Could Goldhaber give a statement on the correct amount of fluid challenge?

*Sandra Fortunat, *Georg Röggla*
**roeggla.interne@khneunkirchen.at**

Department of Internal Medicine, General Hospital of Neunkirchen, Peischingerstrasse 19, A-2620 Neunkirchen, Austria

1 Goldhaber SZ. Pulmonary embolism. *Lancet* 2004; **363:** 1295–305.
2 Belenkie I, Dani R, Smith ER, Tyberg JV. Effects of volume loading during experimental acute pulmonary embolism. *Circulation* 1989; **80:** 178–88.

Congratulations to Samuel Goldhaber[1] on his excellent Seminar on pulmonary embolism. There is one important omission. Goldhaber makes no mention of the value of continuing heparin for at least 48 h after the achievement of therapeutic international normalised ratio (INR).

During the first 36 h of warfarin treatment, precipitous decreases in concentrations of protein C result in a transient hypercoagulable state. In-vivo prothrombin activation is a function of the balance between factor II and protein C concentrations and is not prevented until nadir concentrations of factor II are obtained, which can take 40–192 h.[2] During this time, patients are paradoxically at increased risk of thromboembolic disease and it is therefore important to overlap heparin and warfarin treatment for at least 48 h after therapeutic INR values have been achieved.

*Habib-ur-Rehman*
**habib.rehman@meht.nhs.uk**

Broomfield Hospital, Court Road, Chelmsford CM1 7ET, UK

1 Goldhaber SZ. Pulmonary embolism. *Lancet* 2004; **363:** 1295–305.
2 D'Angelo A, Della Valle P, Crippa L, Fattorini A, Pattarini E, Vigano D'Angelo S. Relationship between international normalized ratio values, vitamin K-dependent clotting factor levels and

in vivo prothrombin activation during the early and steady phases of oral anticoagulant treatment. *Haematologica* 2002; **87:** 1074–80.

Samuel Goldhaber's otherwise excellent Seminar on pulmonary embolism[1] includes in the risk factors a discussion of hormonal factors that must be challenged.

Pregnancy, hormone replacement therapy (HRT), and oestrogen-containing oral contraceptives are known to increase the incidence of venous thromboembolism (VTE).[2,3] However there is no evidence that progestogen-only methods of contraception, which include pills, implants, injectables, and intrauterine devices, significantly alter haemostatic variables or increase the risk of VTE.[4] Indeed, these preparations are often recommended to women with a past history of VTE or with an inherited or acquired prothrombotic state.

I would agree that a past history of VTE is an absolute contraindication to the oestrogen-containing contraceptive and would also suggest that a strong family history of VTE and an inherited prothrombotic state constitute absolute contraindications rather than the relative described in the article. Other oestrogen-containing contraceptives such as the vaginal ring or patch are also likely to increase the incidence of VTE; however, whether this increase will be lower than that seen with comparable oral preparations, as it is with HRT,[5] remains to be established.

The use of the term "generations" in the description of oestrogen-containing oral contraceptives relates solely to the progestogen content of the preparation and has nothing to do with the dose of oestrogen. It has recently been suggested that the term be abandoned owing to the introduction of newer progestogens and to avoid the confusion the term caused. There is evidence that reducing the dose of ethinyl oestradiol in the oestrogen-containing oral contraceptives to 50 μg resulted in a lowering in the incidence of VTE; however, in users of oestrogen-containing oral contraceptives containing less than 50 μg of ethinyl oestradiol, the risk of VTE is unrelated to the dose.

*Gillian Robinson*
**gillian.robinson@southwarkpct.nhs.uk**

Southwark Primary Care Trust, St Giles Hospital, St Giles Road, London SE5 7RN, UK

1 Goldhaber S. Pulmonary embolism. *Lancet* 2004; **363:** 1295–305.
2 Beral V, Banks E, Reeves G. Evidence from randomised controlled trials on the long term effects of hormone replacement therapy. *Lancet* 2002; **360:** 942–44.
3 Meade TW, Greenberg G, Thompson SG. Progestogens and cardiovascular reaction associated with oral contraceptives and a comparison of the safety of the 50μg and 30μg preparations. *BMJ* 1980; **280:** 1157–61.
4 Guillebaud J. Contraception: your questions answered, 4th edn. London: Churchill Livingstone, 2004.
5 Scarabin P-Y, Oger E, Plu-Bureau G, on behalf of the ESTHER Study Group. Differential association of oral and transdermal oestrogen–replacement therapy with venous thromboembolism risk. *Lancet* 2003; **362:** 428–32.

## Author's reply

Multidetector-row spiral CT technology has overcome the past limitations of CT and has emerged as the preferred imaging technique for patients suspected of having acute pulmonary embolism. Tiny, peripheral subsegmental emboli are well visualised. New-generation scanners seem to be virtually as accurate as catheter pulmonary angiography for detection of pulmonary embolism.[1]

The problem with clinical assessment and scoring of "clinical pretest probability" is that the scoring system is heavily weighted towards one subjective question: "Is an alternative diagnosis more likely than pulmonary embolism?" Despite valiant efforts to create a reliable formula and scorecard, the assessment of clinical pretest probability remains best achieved through gestalt, intuition, and experience.

As Sandra Fortunat and Georg Röggla state, volume loading is controversial and potentially dangerous in haemodynamically compromised patients with acute pulmonary embolism. When right heart pressures are elevated on physical examination or doppler echocardiography, fluid administration can precipitate further deterioration of cardiac function. These patients will benefit from the early use of vasopressors.[2] The optimum vasopressor is uncertain, but my three favourites are dopamine, phenylephrine, and vasopressin. They are selected and administered empirically.

Kwang Yee reminds us to be vigilant and insist on venous thromboembolism prophylaxis in our hospital inpatients. In a prospective registry of 5451 patients with ultrasound-confirmed deep-vein thrombosis, only 1147 (42%) of the 2726 who had deep-vein thrombosis diagnosed while in hospital had received prophylaxis within the previous 30 days.[3]

Habib-ur-Rehman makes the excellent point that heparin should be administered for at least 5 days after starting warfarin to prevent paradoxical hypercoagulability due to depletion of protein C.

The risk of fatal pulmonary embolism from oral contraceptives is small, perhaps as low as 1 per 10 million woman-years.[4] However, this risk does seem to be higher for women taking birth control pills that contain the third-generation progestogens desogestrel or gestodene. A meta-analysis indicates that third-generation oral contraceptives could triple the risk of venous thromboembolism compared with second-generation oral contraceptives.[5]

*Samuel Z Goldhaber*
**sgoldhaber@partners.org**

Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA

1 Schoepf UJ, Goldhaber SZ, Costello P. Spiral computed tomography for acute pulmonary embolism. *Circulation* 2004; **109:** 2160–67.
2 Wood K. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. *Chest* 2002; **121:** 877–905.
3 Goldhaber SZ, Tapson VF. A prospective registry of 5,451 patients with ultrasound-confirmed deep vein thrombosis. *Am J Cardiol* 2004; **93:** 259–62.
4 Parkin L, Skegg DCG, Wilson M, Herbison GP, Paul C. Oral contraceptives and fatal pulmonary embolism. *Lancet* 2000; **355:** 2133–34.
5 Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. *BMJ* 2001; **323:** 1–9.

Samuel Goldhaber's impressive Seminar[1] omits sickle-cell haemoglobin C disease from the list of risk factors.

The strong reaction between haemoglobins S and C explains why several patients with the disease have more thromboinfarctive events than patients