improved survival for patients with many other types of pulmonary hypertension.

Thorax 2005;**60**:981–983.
doi: 10.1136/thx.2005.045674

Authors' affiliations
S Mehta, G J Shoemaker, Southwest Ontario Pulmonary Hypertension Clinic, Divisions of Respirology and Cardiology, Departments of Medicine, London Health Sciences Center, and The Centre for Critical Illness Research, Lawson Health Research Institute, University of Western Ontario, London, Ontario Canada

Correspondence to: Dr S Mehta, Division of Respirology, London Health Sciences Center - South Street Hospital, London, Ontario, Canada N6A 4G5; sanjay.mehta@lhsc.on.ca

SM has received consulting and speaking fees (Actelion, Encysive, Glaxo-Burroughs-Wellcome, Pfizer) and clinical investigator fees (Actelion, Encysive, Pfizer). GJS has received consulting and speaking fees (Actelion).

REFERENCES

1 **Mendeloff EN**, Meyers BF, Sundt TM, *et al.* Lung transplantation for pulmonary vascular disease. *Ann Thorac Surg* 2002;**73**:209–17.
2 **Klepetko W**, Mayer E, Sandoval J, *et al.* Interventional and surgical modalities of treatment for pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;**43**:73–80S.
3 **Doyle RL**, McCrory D, Channick RN, *et al.* Surgical treatments/interventions for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;**126**:63–71S.
4 **Pietra GG**, Edwards WD, Kay JM, *et al.* Histopathology of primary pulmonary hypertension. A qualitative and quantitative study of pulmonary blood vessels from 58 patients in the National Heart, Lung, and Blood Institute, Primary Pulmonary Hypertension Registry. *Circulation* 1989;**80**:1198–206.
5 **Geggel RL**, Carvalho AC, Hoyer LW, *et al.* von Willebrand factor abnormalities in primary pulmonary hypertension. *Am Rev Respir Dis* 1987;**135**:294–9.
6 **Fuster V**, Steele PM, Edwards WD, *et al.* Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation* 1984;**70**:580–7.
7 **Rich S**, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992;**327**:76–81.
8 **Badesch DB**, Abman SH, Ahearn GS, *et al.* Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;**126**:35–62S.
9 **Barst RJ**, Rubin LJ, Long WA, *et al.* A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996;**334**:296–302.
10 **Channick RN**, Simonneau G, Sitbon O, *et al.* Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001;**358**:1119–23.
11 **Rubin LJ**, Badesch DB, Barst RJ, *et al.* Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;**346**:896–903.
12 **Olschewski H**, Simonneau G, Galie N, *et al.* Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2003;**347**:322–9.
13 **Simonneau G**, Barst RJ, Galie N, *et al.* Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002;**165**:800–4.
14 **Robin ED**. The kingdom of the near-dead. The shortened unnatural life history of primary pulmonary hypertension. *Chest* 1987;**92**:330–4.
15 **Sitbon O**, Humbert M, Jais X, *et al.* Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005;**111**:3105–11.
16 **McLaughlin VV**, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2003;**106**:1477–82.
17 **Sitbon O**, Humbert M, Nunes H, *et al.* Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2003;**40**:780–8.
18 **Kuhn KP**, Byrne DW, Arbogast PG, *et al.* Outcome in 91 consecutive patients with pulmonary arterial hypertension receiving epoprostenol. *Am J Respir Crit Care Med* 2003;**167**:580–6.
19 **Nagaya N**, Uematsu M, Okano Y, *et al.* Effect of orally active prostacyclin analogue on survival of outpatients with primary pulmonary hypertension. *J Am Coll Cardiol* 1999;**34**:1188–92.
20 **Sitbon O**, McLaughlin VV, Badesch DB, *et al.* Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol. *Thorax* 2005;**60**:1025–30.
21 **McLaughlin VV**, Sitbon O, Badesch DB, *et al.* Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur Respir J* 2005;**25**:244–9.
22 **D'Alonzo GE**, Barst RJ, Ayres SM, *et al.* Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991;**115**:343–9.
23 **Sandoval J**, Bauerle O, Palomar A, *et al.* Survival in primary pulmonary hypertension. Validation of a prognostic equation. *Circulation* 1994;**89**:1733–44.
24 **Mehta S**. Drug therapy for pulmonary arterial hypertension: what's on the menu today? *Chest* 2003;**124**:2045–9.

Pulmonary hypertension after splenectomy

Pulmonary hypertension after splenectomy: a consequence of loss of the splenic filter or is there something more?

A J Peacock

The exact mechanism by which pulmonary hypertension develops after splenectomy remains unclear

Pulmonary arterial hypertension is a syndrome—not a disease—and has a number of causes.[1] Included in these causes are a wide range of pathoaetiologies such as HIV infection, portopulmonary hypertension, intracardiac shunt, chronic thromboembolic disease, hypoxic lung disease, connective tissue disease, idiopathic pulmonary hypertension, and familial pulmonary hypertension associated with mutation of the BMPR2 gene.

In this issue of *Thorax* Jaïs *et al*[2] have examined the clinical background of 257 patients referred to their centre for treatment of chronic thromboembolic pulmonary hypertension (CTEPH). They found that 8.6% of the patients had a history of splenectomy compared with 2.5% of patients with idiopathic pulmonary hypertension (IPH) and 0.4% in the general population. They concluded that splenectomy alone had caused thromboembolism and hence the pulmonary hypertension in these patients. But is this true?

Chronic thromboembolic disease has been defined as "pulmonary hypertension caused by the absence of thrombus resolution after acute pulmonary embolism which has resulted in sustained obstruction of the pulmonary circulation". This view is probably outdated because in 50% of cases there is no definite history of venous thrombosis and it is likely that many cases are a consequence of in situ thrombosis.[3] Bonderman *et al*[4] have recently looked at the medical conditions that increased the risk of CTEPH in 109 consecutive patients and found that splenectomy increased the relative risk of this condition by a factor of 13.

The findings of Jaïs *et al*[2] and Bonderman *et al*[4] are not new—for example, Hoeper *et al*[5] found an 11.5% incidence of splenectomy in 61 patients with pulmonary hypertension. In the papers by Jaïs *et al*[2] and Hoeper *et al*[5] it appears that splenectomy increases the risk of both IPH *and* CTEPH. For example, Jaïs *et al* found an incidence of splenectomy of 2.5% even in the patients with IPH. Interestingly, of the 22/257 with CTEPH who had had splenectomy, only eight were suitable for treatment by the standard operation of thromboendarterectomy, which suggests that they had distal disease. This raises the issue of the continuity between CTEPH, the thrombotic variant of IPH, and small vessel IPH

without thrombosis. It may well be that the primary problem is not simply one of increased coagulability due to loss of the splenic filter but one of abnormal endothelial surface resulting in in situ thrombosis or another factor. Certainly, in IPH the survival can be doubled simply by the use of warfarin and, in these cases, there is no history of venous thromboembolism.[6]

The simplest explanation for the finding of Jaïs *et al*[2] and of the other authors who have studied this problem is that, following splenectomy, there is both thrombocytosis and also increased numbers of damaged circulating red cells which will activate these platelets leading to in situ thrombosis. There is some evidence for this view. For example, we know that in the haemolytic disorders where there is an excess of haemolysed red cells there is also excess coagulability as shown by the increased capacity of the red cells to generate thrombin.[7] This phenomenon was discovered in patients with thalassaemia intermedia, but there are a number of reports of CTEPH in patients with other haemolytic disorders—for example, pyruvate kinase deficiency,[8] congenital spherocytosis,[9] and stomatocytosis.[10] The complicating factor is that, for many of these conditions, splenectomy is a treatment and therefore it is difficult to differentiate between hypercoagulability caused by the splenectomy per se and hypercoagulability caused by the underlying haemolytic disease. Furthermore, we do not know whether it is simply the prothrombotic component of the disease that is important or whether there is some other factor which could lead to pulmonary hypertension separately from pulmonary vascular thrombosis. For example, haemoglobin released from haemolysed red cells present in the plasma would scavenge nitric oxide which is an important pulmonary vasodilator.

Certainly, when splenectomy is performed to treat a haemolytic disorder, the combination of the haemolytic disorder and the splenectomy seem to increase the likelihood of pulmonary thromboembolism further, due in part to the excess thrombin generated by the abnormal red cells. Cappellini *et al*[7] studied a large group of adults with both thalassaemia intermedia and thalassaemia major for up to 10 years and found a high prevalence of thromboembolic events, particularly in the splenectomised patients, which was associated with an enhanced capacity to generate thrombin by the thalassaemic red cells. This enhanced capacity was not seen in patients who had a splenectomy for other reasons—that is, it was not a function of the splenectomy per se. It is likely, however, that the splenectomy exacerbated the situation by the reduced clearance of abnormal red cells. This would suggest that, in many cases, it is not splenectomy alone which causes the problem but splenectomy in the face of an underlying haemolytic disorder. There is some evidence for this view. Boxer *et al*[11] studied 318 otherwise fit patients who had been treated by splenectomy and found that 75% had increased platelet levels immediately following the operation but there were no increased incidence of venous thromboembolism. This may be because the thrombocytosis normally diminishes following splenectomy and it is only if it persists that the pulmonary hypertension develops. For example, Rostagno *et al*[12] described a patient who suffered CTEPH associated with long standing thrombocytosis but, when the thrombocytosis was treated, there was improvement in both the clinical state and in the pulmonary haemodynamics. Marvin and Spellberg[13] described another patient who had thrombocytosis and developed pulmonary hypertension and right heart failure following splenectomy, but treatment of the thrombocytosis with hydroxyurea improved both vascular and cardiac function.

The finding that splenectomy alone seems to be benign, but that splenectomy in the face of an underlying haemolytic disorder results in a high incidence of pulmonary hypertension (for example, Aessopos *et al*[14] found that 59% of patients with thalassaemia intermedia who had had splenectomy developed thromboembolic pulmonary hypertension) suggests that it is a combination of the two factors—namely, an abnormality of red cells (and possibly platelets) and splenectomy—that leads to pulmonary hypertension and in situ thrombosis. However, there is other evidence that splenectomy can cause pulmonary hypertension in patients who do not have haemolytic disorders. For example, Elstein *et al*[15] showed that, in 134 patients with Gaucher's disease, 7% had pulmonary hypertension detected by echocardiography. It is interesting that most of these had been treated by splenectomy. In the paper by Jaïs *et al*[2] in this issue of *Thorax* only four of the 22 patients who developed CTEPH after splenectomy had a haemolytic disorder, and in most of the others the spleen had been removed for trauma.

What is of great interest is the long time interval (range 2–35 years) between the splenectomy in the patients studied by Jaïs *et al*[2] and the development of thromboembolic pulmonary hypertension. This suggests either that the development of pulmonary hypertension is a very slow process or that some additional factor developed which resulted in a prothrombotic state, perhaps a change in endothelial function or a change in red cell characteristics.

From the above it is clear that splenectomy is a risk for thromboembolic hypertension, particularly in patients who have had splenectomy for a haemolytic disorder. It is also clear that clinicians should watch these patients carefully and consider whether long term anticoagulation would be appropriate. We should also keep an eye on patients who have had splenectomy for other reasons because they do not appear to be immune from the development of pulmonary hypertension. The exact mechanism by which pulmonary hypertension develops after splenectomy, even in patients with underlying haemolytic disorders, remains unclear but provides a fascinating model for future research.

Thorax 2005;**60**:983–984.
doi: 10.1136/thx.200X.043216

Correspondence to: Professor A J Peacock, Scottish Pulmonary Vascular Unit, Western Infirmary, Glasgow G11 6NT, UK; apeacock@udcf.gla.ac.uk

REFERENCES

1 **Simonneau G**, Galie N, Rubin LJ, *et al*. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004;**43**:5–12S.
2 **Jaïs X**, Ioos V, Jardim C, *et al*. Splenectomy and chronic thromboembolic pulmonary hypertension. *Thorax* 2005;**60**:1031–34.
3 **Egermayer P**, Peacock AJ. Is pulmonary embolism a common cause of pulmonary hypertension? Limitations of the embolic hypothesis. *Eur Respir J* 2000;**15**:440–8.
4 **Bonderman D**, Jakowitsch J, Aldbrecht C, *et al*. Medical conditions increasing the risk of chronic thromboembolic pulmonary hypertension. *Thromb Haemost* 2005;**93**:512–6.
5 **Hoeper MM**, Neidermeyer J, Hoffmeyer F, *et al*. Pulmonary hypertension after splenectomy? *Ann Intern Med* 1999;**130**:506–9.
6 **Rich S**, Kauffmann E, Levy PS. The effect of high dose calcium channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992;**327**:76–81.
7 **Cappellini MD**, Robbiolo L, Bottasso BM, *et al*. Venous thromboembolism and hypercoaguability in splenectomised patients with thalassaemia intermedia. *Br J Haematol* 2000;**111**:467–73.
8 **Chou R**, DeLoughery TG. Recurrent thromboembolic disease following splenectomy for pyruvate kinase deficiency. *Am J Haematol* 2001;**67**:197–9.
9 **Jardine DL**, Laing AD. Delayed pulmonary hypertension following splenectomy for congenital spherocytosis. *Int Med J* 2004;**34**:214–6.
10 **Murali B**, Drain A, Seller D, *et al*. Pulmonary thromboendarterectomy in a case of hereditary stomatocytosis. *Br J Anaesth* 2003;**91**:739–41.
11 **Boxer MA**, Braun J, Ellman L. Thromboembolic risk of postsplenectomy thrombocytosis. *Arch Surg* 1978;**113**:808–9.
12 **Rostagno C**, Prisco D, Abbate R, *et al*. Pulmonary hypertension associated with long standing thrombocytosis. *Chest* 1991;**99**:1303–5.
13 **Marvin KS**, Spellberg RD. Pulmonary hypertension secondary to thrombocytosis in a patient with myeloid metaplasia. *Chest* 1993;**103**:642–4.
14 **Aessopos A**, Farmakis D, Karagiorga M, *et al*. Cardiac involvement in thalassemia intermedia: a multicenter study. *Blood* 2001;**97**:3411–6.
15 **Elstein D**, Klutstein MW, Lahad A, *et al*. Echocardiographic assessment of pulmonary hypertension in Gaucher's disease. *Lancet* 1998;**351**:1544–6.