

Case Reports

Chronic Thromboembolic Pulmonary Hypertension in a Patient Heterozygous for both Factor V Leiden and the G20210A Prothrombin Mutation

GEORGE K. KOURGIANNIDIS, EMMANUEL S. BRILAKIS, ATHANASIOS N. MANGINAS, DENNIS V. COKKINOS

1st Department of Cardiology, Onassis Cardiac Surgery Center, Athens, Greece

Key words:
Pulmonary hypertension, chronic pulmonary embolism, factor V Leiden, prothrombin mutation G20210A.

Coagulation abnormalities have been implicated in the pathogenesis of chronic thromboembolic pulmonary hypertension, a serious disease with poor prognosis. We describe the first case of a 32-year-old heterozygous carrier of both factor V Leiden and the G20210A prothrombin mutation who developed severe chronic thromboembolic pulmonary hypertension, and was subsequently managed successfully with pulmonary thrombarterectomy.

Manuscript received:
July 4, 2002;
Accepted:
March 31, 2003.

Address:
George
Kourgiannidis

*Onassis Cardiac
Surgery Center,
356 Syggrou Av.,
176 74, Athens,
Greece
e-mail: kgds@hol.gr*

Many mutations of coagulation factors predispose to venous thromboembolism¹. Patients with the G 1691A mutation in the factor V gene (factor V Leiden, FVL) present with a 7 times greater likelihood of deep venous thrombosis (DVT) over controls^{2,3}, particularly those with the idiopathic form⁴. Similarly the –uncombined– G 20210 mutation in the prothrombin gene increases the risk of DVT by 2.7 to 3.8 fold^{5,6}.

Heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutations are at higher risk of recurrent DVT compared to patients who are heterozygous for factor V Leiden alone⁷. It is estimated that double heterozygotes are at thromboembolic risk 20 times greater than the general population while the first episode occurs at a younger age compared with the single heterozygotes⁸. The combination of FVL and the G20210A prothrombin mutation also increases the risk of recurrent venous thrombosis^{9,10}. Recur-

rent DVT increases the risk for pulmonary embolism (PE), which may rarely result in the development of chronic thromboembolic pulmonary hypertension, especially in cases of concurrent fibrinolysis abnormalities.

We report the case of a patient heterozygous for both factor V Leiden and the G20210A prothrombin mutation who developed chronic pulmonary hypertension as a result of recurrent pulmonary embolism.

Case report

A 32-year-old man presented to our Hospital with progressive dyspnea on exertion. He had been in good state of health until 12 months prior to admission when he developed spontaneous left lower extremity DVT. A ventilation-perfusion scan demonstrated multiple bilateral unmatched perfusion defects consistent with acute multiple pulmonary emboli. He was treated with oral anticoagulation

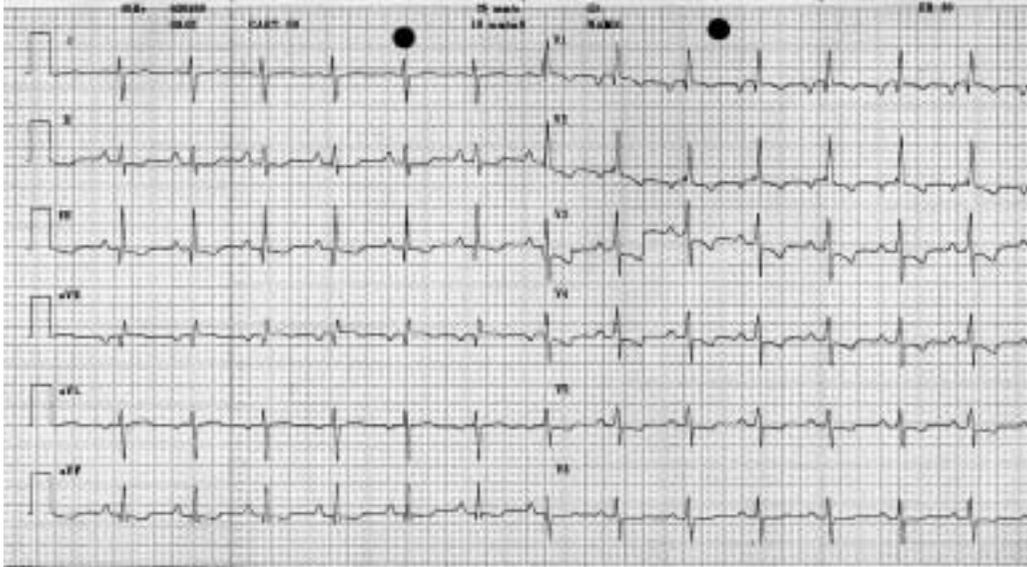


Figure 1. Patient electrocardiogram.

with acenocoumarol. His INR remained therapeutic (2.0-3.0) at routine monthly measurements.

Six months prior to admission the patient developed progressive dyspnea on exertion and mild symmetric lower extremity pitting edema. Echocardiography revealed severe pulmonary hypertension with an estimated pulmonary artery systolic pressure of 80 mmHg. A repeat ventilation-perfusion scan demonstrated extension of the perfusion defects, consistent with new pulmonary emboli.

A spiral computed tomogram of the chest and the abdomen with intravenous contrast demonstrated mild chronic ground glass changes in the apices of both lungs and multiple filling defects and narrowing of both pulmonary arteries.

An attempt to lyse the pulmonary artery thrombi with intravenous streptokinase did not improve the pulmonary artery pressures. Because of the pulmonary emboli recurrence in spite of adequate oral anticoagulation therapy a filter was placed in the inferior vena cava. During an investigation for hypercoagulable state the patient was found to be heterozygous for both factor V Leiden and the G20210A prothrombin mutation. Examination for antiphospholipid antibodies was negative. Factors C and S could not be evaluated because the patient was already on oral anticoagulation therapy; homocysteine was within normal limits.

His past medical history was unremarkable except for the deep venous thrombosis and the pulmonary hypertension. Acenocoumarol was his only

medication. There was no family history of deep venous thrombosis or pulmonary embolism, however the patient was an active smoker (one pack per day).

Physical examination was significant for a left parasternal lift, a loud S_2 and a third heart sound. There was 2+ bilateral lower extremity pitting edema. Complete Blood Count and biochemistry were normal. The INR was 3.1. Electrocardiography demonstrated normal sinus rhythm with a heart rate of 83, right ventricular hypertrophy, qR in V_1 with secondary ST - T wave changes, as well as biatrial hypertrophy (Figure 1). Chest radiography showed cardiomegaly and an increase in the size of the hila; the peripheral pulmonary vasculature appeared normal. On transthoracic echocardiography the right ventricle was dilated and hypertrophic with an ejection fraction of 30%. Systolic pulmonary artery pressure was estimated at 80 mmHg. Paradoxical motion of the interventricular septum and mild tricuspid regurgitation were also present, whereas the left ventricle had normal size and function. No intracardiac shunt was present. A pulmonary angiogram was performed. Pulmonary artery pressure was 81/19 mmHg, mean pulmonary artery pressure was 50 mmHg, the cardiac index was 1.9 liters/min/m² and the pulmonary vascular resistance was 11.8 Woods Units. Multiple filling defects were seen in the branches of both pulmonary arteries (Figure 2a, 2b), confirming the diagnosis of chronic thromboembolic pulmonary hypertension. Seven months after the hospital admission the patient underwent successful pulmonary throm-

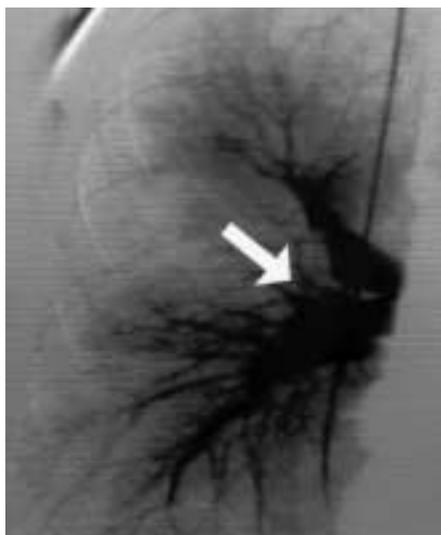


Figure 2a. Selective right pulmonary artery angiography. Filling defect at the origin of the right middle lobar branch (arrow).

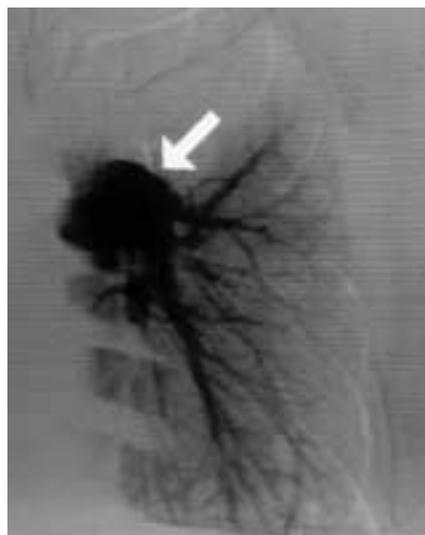


Figure 2b. Selective left pulmonary artery angiography. Upper lobar (arrow) and peripheral lower lobar branches occlusion.

boendarterectomy (Figure 3), with subsequent symptomatic improvement on postoperative and 6 month examination.

Discussion

After initial acute PE it is probable that in over 99% of patients lysis occurs, so that there is no significant pulmonary vascular obstruction¹¹. However if the acute emboli are not lysed within 1 to 2 weeks, the embolic material may become attached to the pulmonary arterial wall leading to obstruction and chronic pulmonary hypertension. The pathogenesis of this unfavorable reaction has not been completely explained. Recurrent embolic events, in situ thrombosis around areas of previous emboli, remodeling of clot in large and medium-size vessels, or progressive changes in the pulmonary microvasculature, have been proposed as responsible mechanisms¹². Many patients with persistent pulmonary hypertension after the initial episode, do not show signs of recurrent thromboembolism. A hypercoagulable state –as in our case– has been proposed as a risk factor. Indeed, an increased prevalence of lupus anticoagulant and deficiencies of protein C, S and antithrombin III have been found in this patient population¹³. The prevalence of at least one thrombophilic factor has been reported up to 75%¹⁴. The pathogenetic role of “newer” hypercoagulable factors such as factor V Leiden and the G20210A prothrombin muta-

tion has not been thoroughly elucidated. It seems that FVL is not a strong predisposing factor for the complication of pulmonary hypertension. Indeed, FVL is found to be less frequent in patients with pulmonary embolism than in patients with DVT only⁸. Whether this event is a consequence of thrombus characteristics or the low prevalence of proximal DVT, which predisposes to PE remains unclear^{10,17-19}. The coexistence of G20210A prothrombin mutation augments the hypercoagulable status in FVL patients resulting in thromboembolic complications, as

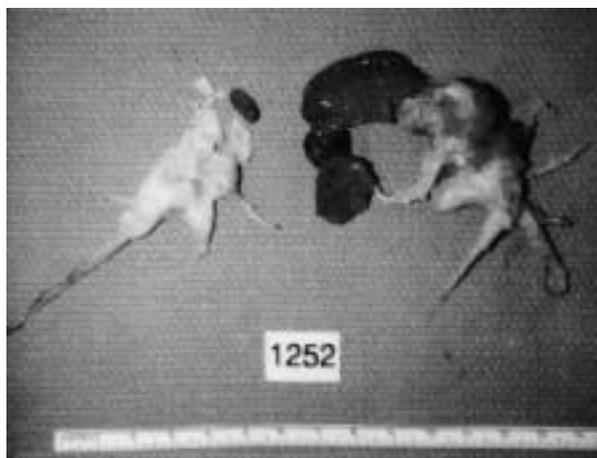


Figure 3. Surgical preparation. Segments of bilateral thrombarterectomy and significant amount of intraluminal thrombus are shown.

already mentioned. It is of interest that chronic thromboembolic pulmonary hypertension with this gene combination has not previously reported.

The therapy of combined FVL and G20210A prothrombin mutation patients is chronic anticoagulation¹⁸. Thromboendarterectomy is the indicated therapy when chronic thromboembolic hypertension supervenes^{19,20}. The inferior vena cava filter seems of no value, but it contributes to the prevention of further thromboembolism.

Future studies are needed to clarify the role of heterozygosity for both factor V Leiden and the G20210A prothrombin mutation in the pathogenesis of chronic thromboembolic pulmonary hypertension.

References

1. Seligsohn U, Lubetski A: Genetic susceptibility to venous thrombosis. *N Engl J Med* 2001; 344: 1222-1231.
2. Rosendaal FR, Koster T, Vanderbroucke JP, et al: High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). *Blood* 1995; 85: 1504-1508.
3. Major DA, Sane DC, Harrington DM: Cardiovascular implications of the factor V Leiden mutation *Am Heart J* 2000; 140: 189-195.
4. Ridker PM, Hennekens CMA, Lindpaintner K, et al: Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. *New Engl J Med* 1995; 332: 912-917.
5. Poort S, Rosendaal F, Reitsma P, et al: A Common Genetic Variation in the 3' Untranslated Region of the Prothrombin Gene Is Associated With Elevated Plasma Prothrombin Levels and an Increase in Venous Thrombosis. *Blood* 1996; 88: 3698-3703.
6. Margaglione M, Brancaccio V, Giuliani N, et al: Increased Risk for Venous Thrombosis in Carriers of the Prothrombin GA²⁰²¹⁰ Gene Variant *Ann Intern Med* 1998; 129: 89-93.
7. Makris M, Preston FE, Beauchamp NJ, et al: Co-inheritance of the 20210A allele of the prothrombin gene increases the risk of thrombosis in subjects with familial thrombophilia. *Thromb Haemost* 1997; 78: 1436-1439.
8. Emmerich J, Rosendaal F, Cattaneo M, et al: Combined Effect of Factor V Leiden and Prothrombin 20210A on the Risk of Venous Thromboembolism. *Thromb Haemost* 2001; 86: 809-816.
9. De Stefano V, Martinelli I, Mannucci PM, et al: The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. *N Engl J Med* 1999; 341: 801-806.
10. Miles JS, Miletich J, Goldhaber S, Hennekens C, Ridker P: G20210A Mutation in the Prothrombin Gene and the Risk of Recurrent Venous Thromboembolism. *JACC* 2001; 37: 215-218.
11. Benotti JR, Ockene JS, Alpert JS, Dalen JE: The clinical profile of unresolved pulmonary embolism. *Chest* 1983; 84: 669-678.
12. Peterson K: Acute Pulmonary Embolism. Has its evolution been redefined? (Editorial) *Circulation* 1999; 99: 1280-1283.
13. Auger WR, Channick RN, Kerr KM, et al: Evaluation of patients with suspected chronic thromboembolic pulmonary hypertension. *Semin Thorac Cardiovasc Surg* 1999; 2: 179-190.
14. Colonio C, Martinuzzo E, Forastiero R, et al: Thrombophilic factors in chronic thromboembolic pulmonary hypertension. *Blood Coagulation and Fibrinolysis*. 2001; 12: 427-432.
15. Perrier A: Deep Vein Thrombosis and Pulmonary Embolism. A single Disease Entity With Different Risk Factors? *Chest* 2000; 118: 1234-1236.
16. Bounameaux H: Factor V Leiden paradox: risk of deep-vein thrombosis but not of pulmonary embolism. *Lancet* 2000; 356: 182-183.
17. Girard P: Factor V Leiden Paradox. *Lancet* 2000; 356: 1028-1029.
18. Bauer K: The Thrombophilias: Well-Defined Risk Factors with Uncertain Therapeutic Implications. *Ann. Intern Med* 2001; 135: 367-373.
19. Daily PO, Dembitsky WP, Jamieson SW: The evolution and the current state of the art of pulmonary thromboendarterectomy. *Semin Thorac Cardiovasc Surg* 1999; 2: 152-163.
20. Madani MM, Jamieson SW: Chronic thromboembolic pulmonary hypertension. *Curr Treatment Options Cardiovasc Med* 2000; 2: 141-148.