When atrial fibrillation occurs with pulmonary embolism, is it the chicken or the egg?

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Common clinical wisdom has it that the occurrence of pulmonary embolism engenders any atrial fibrillation that may accompany it. Cases are reported to remind clinicians to be alert to the possibility of pulmonary embolism in patients who present with unexplained atrial fibrillation.[1,2] To be sure, such cases are seen, and the mechanism of the atrial fibrillation is said to be acute right ventricular dilatation with "strain."

Suppose that this relation is sometimes reversed, such that atrial fibrillation causes pulmonary embolism. Any new insight into the origin of pulmonary emboli — so-called primary pulmonary emboli — would be welcome, given that a cause cannot be found in 40% of such cases.[3,4]

We know that clots form in the left atrium and that such clotting occurs at a higher rate among patients with atrial fibrillation than among those with sinus rhythm. The experience with stroke and with systemic emboli arising from the left atrium raises the possibility that emboli might also originate from the right atrium. Beyond opinion or case reports,[5,6] we have 2 threads of information suggesting that such clots could occur. First, cardiac ultrasonographers have correlated spontaneous echo contrast in the left atrium, a finding that resembles that of injected microbubbles, with the subsequent appearance of ultrasonically detectable frank clot. (Thus, this echo contrast finding is presumed to be an antecedent of clotting, perhaps rouleau or other red-cell clumping.) Spontaneous echo contrast has also been noted in the right atrium of patients with right heart abnormalities, including atrial fibrillation.[7,8] Second, the presence of atrial fibrillation is associated with changes in coagulation factors that indicate a hypercoagulable state.[9,10] This state appears to come and go with the arrhythmia.[11] It seems sensible to infer that the hypercoagulable state pertains to the right atrium as well as to the left.

We also have older information that clots do form in the right atrium, particularly in patients with atrial fibrillation. Aberg's landmark autopsy study[12] of 693 consecutive patients who had had atrial fibrillation during their last illness showed that 12.6% had clots in the left atrium and 7.5% had clots in the right, predominantly in the appendages. It is interesting that the prevalence of pulmonary embolism was similar whether thrombosis had been apparent in the deep venous system or not (8.1% and 7.7%, respectively). This suggests that the clots might have an origin other than the veins. In another autopsy study,[13] this one involving a series of patients with rheumatic mitral stenosis, almost all of those in whom intracardiac clot was found had a history of atrial fibrillation. Half of these clots were in the right atrium, again predominantly in the appendage. Moreover, among those patients in whom pulmonary embolism had occurred, half had a right atrial clot, whereas only a quarter had peripheral venous clots. Again, this suggests that some of these emboli might have originated in the right atrium.[13]

On a clinical level, the fact has been overlooked that although studies involving patients with rheumatic heart disease before the days of anticoagulant therapy showed a dramatic association between atrial fibrillation and left-sided embolism, many of these patients actually died of pulmonary embolism.[14,15] Examination of similar patients who had atrial fibrillation but not rheumatic heart disease showed that this group had an even higher proportion of pulmonary emboli compared with systemic emboli.[12] These findings point to a role for a right atrial source of pulmonary emboli.

With cohort studies we might be better able to distinguish whether the atrial fibrillation is the chicken or the egg. That there may be a detectable proportion of pulmonary embolism attributable to atrial fibrillation is suggested by the results of 3 retrospective cohort studies of patients with atrial fibrillation; among these patients, the proportion of all emboli that were pulmonary was substantial, between 8% and 31%.[16–18] Unfortunately, 2 prospective cohort studies[19,20] and the recently reported randomized trial of antithrombotic therapy in atrial fibrillation[21] provide no information on the prevalence of pulmonary embolism among patients with this condition.

Perhaps the question of cause and effect could be addressed by studying patients with pulmonary embolism. Some studies involving consecutive patients with pulmonary embolism have included electrocardiography results. Atrial fibrillation has been found in 0% to 4% of cases.[22–24] When this finding was pursued in patients with suspected pulmonary emboli by evaluating factors that might be used to predict a positive lung scan or pulmonary angiogram result, the atrial fibrillation was not found to be a positive predictor.[25,26] A case–control approach has been tried in 2 studies directed at atrial arrhythmia generally. All patients in whom pulmonary embolism was suspected were evaluated. Cases in which pulmonary embolism was con-

firmed were compared with those in which it proved to be absent. The overall rate of atrial arrhythmia was similar between the 2 groups.[27,28] However, the proportion of all patients in these studies with atrial fibrillation was 13%, which suggests that patients in whom a diagnosis of pulmonary embolism is suspected and then dismissed are a poor group for purposes of this comparison because they have other risk factors for atrial fibrillation, such as hypertension or coronary artery disease.[25]

The hypothesis that atrial fibrillation leads to pulmonary embolism could be tested more directly. Prospective cohort studies involving atrial fibrillation patients and controls would be ideal because they would establish unequivocally whether the atrial fibrillation antedates the pulmonary embolus. This approach would also provide a reliable estimate of any etiologic fraction attributable to the atrial fibrillation. The fact that this relation has not been evident in those studies already reported suggests that the incidence of pulmonary embolism is lower than the 5% annual incidence of systemic embolism found in these studies. Another explanation for the absence of data on this possible connection is the underdetection of pulmonary embolism. For this reason, prospective studies would have to include some sort of regular surveillance, probably lung scans. A case–control approach might prove more practical because cases would accumulate more quickly. Another advantage of this approach is that it would enable an examination for absence of other causative factors for pulmonary embolism, notably venous thrombosis, other states involving hypercoagulation and cancer. What is needed is a comparison of patients with pulmonary embolism with control patients in terms of history of atrial fibrillation. The controls would need to be selected with care to exclude those with confounding factors that could cause either pulmonary embolism or atrial fibrillation or both. The case–control approach is limited, however, by the fact that atrial fibrillation can be intermittent, potentially causing patients to present with the embolism but without the fibrillation.

The need to establish whether this causal relation exists seems academic, considering that the risk of systemic embolism in atrial fibrillation is, in itself, sufficient reason to recommend anticoagulant therapy. There are, however, pragmatic reasons to find out if the relation is real. If it were known for certain that atrial fibrillation caused a particular pulmonary embolus, intervention might be aimed at the fibrillation directly, in addition to that directed at the clotting. A patient with atrial fibrillation who, for whatever reason, is not receiving anticoagulants might be advised differently once the risk of a pulmonary embolus was added to the particular risk and benefit considerations. Finally, a causal connection, once we know about it, opens the way to new types of interventions, the nature of which we are not able to predict at present.

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References

1. Brown AK, Newton P, Hamilton EAG, Anderson V. Recurrent pulmonary thromboembolism presenting with cardiac arrhythmias. *Thorax* 1979;34:380-3.
2. Black J. Deep-vein thrombosis and pulmonary embolism. *Lancet* 1993; 342:352-3.
3. Guintini C, Di Ricco G, Marini C, Melillo E, Palla A. Pulmonary embolism: epidemiology. *Chest* 1995;105(1 Suppl):3S-9S.
4. Goldhaber SA, Grodstein F, Stampfer MJ, Manson JE, Codditz GA, Speizer FE, et al. A prospective study of risk factors for pulmonary embolism in women. *JAMA* 1997;277:642-5.
5. Klein HO, Bakst A, Kaplinsky E. Pulmonary embolism and atrial fibrillation [letter]. *Am J Cardiol* 1988;61:498.
6. O'Toole L, McLean KA, Channer KS. Pulmonary embolism presenting with atrial fibrillation. *Lancet* 1993;342:1050.
7. Black IW, Hopkins AP, Lee LCL, Walsh WF. Left atrial spontaneous contrast echo: a clinical and echocardiographic analysis. *J Am Coll Cardiol* 1991;18:398-404.
8. DeGeorgia MA, Chimowitz MI, Hepner A, Armstrong WF. Right atrial spontaneous contrast: echocardiographic and clinical features. *Int J Card Imaging* 1994;10:227-32.
9. Lip GYH. Does atrial fibrillation confer a hypercoagulable state? *Lancet* 1995;346:1313-4.
10. Kahn SR, Solymoss S, Flegel KM. Nonvalvular atrial fibrillation: evidence for a prothrombotic state. *CMAJ* 1997;157:673-81.
11. Sohara H, Amitani S, Kurose M, Miyahara K. Atrial fibrillation activates platelets and coagulation in a time-dependent manner: a study in patients with paroxysmal atrial fibrillation. *J Am Coll Cardiol* 1997;29:106-12.
12. Aberg H. Atrial fibrillation. I: A study of atrial thrombosis and systemic embolism in a necropsy material. *Acta Med Scand* 1969;185:373-9.
13. Jordan RA, Scheifley CH, Edwards JE. Mural thrombosis and arterial embolism in mitral stenosis. *Circulation* 1951;3:363-7.
14. Sawyer CG, Bolin LB, Stevens EL, Daniel LB, O'Neil NC, Hayes DM. Atrial fibrillation: its etiology, treatment and association with embolization. *South Med J* 1958;51:84-93.
15. Rowe JC, Bland EF, Sprague HB, White PD. The course of mitral stenosis without surgery: ten- and twenty-year perspectives. *Ann Intern Med* 1960;52:741-9.
16. Nakagawa K, Itatsu H. Statistical observations of atrial fibrillation and flutter. *Iryo* 1968;22:990-6.
17. Godtfredsen J. Atrial fibrillation: etiology, course and prognosis. A follow-up study of 1212 cases [thesis]. Copenhagen: University of Copenhagen, Faculty of Medicine; 1975. p. 144.
18. Kopecky SL, Gersh BJ, McGoon MD, Whisnant JP, Holmes DR, Ilstrup DM, et al. The natural history of lone atrial fibrillation: a population-based study over three decades. *N Engl J Med* 1987;317:669-74.
19. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham Study. *N Engl J Med* 1982;306:1018-22.
20. Flegel KM, Shipley MJ, Rose G. Risk of stroke in non-rheumatic atrial fibrillation. *Lancet* 1987;1:526-9.
21. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. *Arch Intern Med* 1994;154:1449-57.
22. Sasahara AA, Hyers TM, Cole C, Ederer F, Murray JA, Wenger NK, et al. The urokinase pulmonary embolism trial. Chapter X: Clinical and electrocardiographic observations. *Circulation* 1973;157(II Suppl):60-5.
23. Stein PD, Dalen JE, McIntyre KM, Sasahara AA, Wenger NK, Willis PW. The electrocardiogram in acute pulmonary embolism. *Prog Cardiovasc Dis* 1975;17:247-57.
24. Stein PD, Terrin ML, Hales CA, Palevsky HI, Saltzman HA, Thompson BT, et al. Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. *Chest* 1991;100:598-603.
25. Hoellerich VL, Wigton RS. Diagnosing pulmonary embolism using clinical findings. *Arch Intern Med* 1986;146:1699-704.
26. Celi A, Palla A, Petruzelli S, Carrozzi L, Jacobson A, Cella G, et al. Prospective study of a standardized questionnaire to improve clinical estimate of pulmonary embolism. *Chest* 1989;95:332-7.
27. Petruzzelli S, Palla A, Pieraccini F, Donnamaria V, Giuntini C. Routine electrocardiography in screening for pulmonary embolism. *Respiration* 1986;50:233-43.
28. Donnamaria V, Palla A, Petruzzelli S, Manganelli P, Baldi S, Giuntini C. A way to select on clinical grounds patients with high risk for pulmonary embolism: a retrospective analysis in a nested case–control study. *Respiration* 1995;62:201-4.

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