Development of Pulmonary Aneurysm in Primary Pulmonary Hypertension: A Case Report

Christoph A. Nienaber, M.D.*
Rolf P. Spielmann, M.D.†
Ricardo Montz, M.D.†
Walter Bleifeld, M.D.*
and
Detlef G. Mathey, M.D.*

HAMBURG, WEST GERMANY

Abstract

Selected cases of severe primary pulmonary arterial hypertension and associated pulmonary vascular disease have been related to the oral ingestion of aminorex fumarate, an anorexigen obviously responsible for an epidemic of primary pulmonary hypertension in Western Europe between 1967 and 1970. This report describes a fifteen year follow-up of a female patient with aminorex fumarate related pulmonary hypertension and the uncommon finding of the formation of an excessive fusiform pulmonary trunk aneurysm in the late stage of the disease process. The progressive clinical course was followed by serial chest x-ray films and repeat right heart catheterization. The diagnosis of a main stem pulmonary artery aneurysm was noninvasively established by two-dimensional echocardiography and confirmed by contrast-enhanced computed tomography and radionuclide blood pool imaging. The patient is alive, thus no histologic correlate of this entity is available at present.

Case Report

I.H., a 48 year old housewife, was initially referred to the Department of Cardiology in 1968 because of dyspnea on exertion and an atypical chest pain syndrome. History revealed in 1967 an eight months' intake of aminorex fumarate, an anorexogenic drug suspected to induce primary pulmonary hypertension.[1,2] There was no evidence of other potentially predisposing events such as chest trauma, congenital cardiac defects or any inflammatory disease. In 1969

* From the Department of Cardiology, University Hospital Eppendorf, Hamburg, West Germany
† From the Department of Nuclear Medicine, University Hospital Eppendorf, Hamburg, West Germany

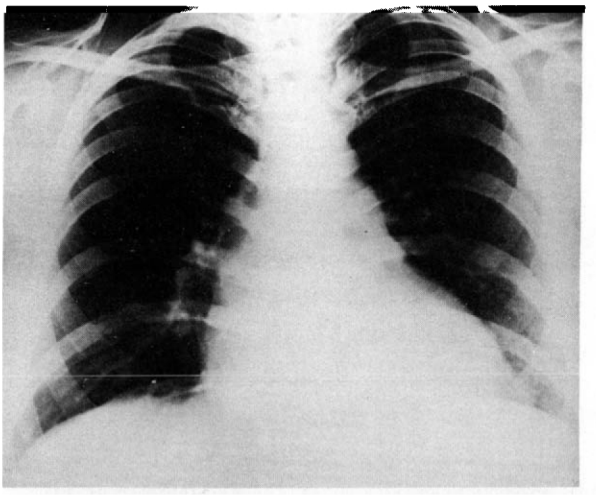

FIG. 1A. Chest roentgenograph in 1969 shows slight prominance of both main pulmonary branches and slight peripheral tapering.

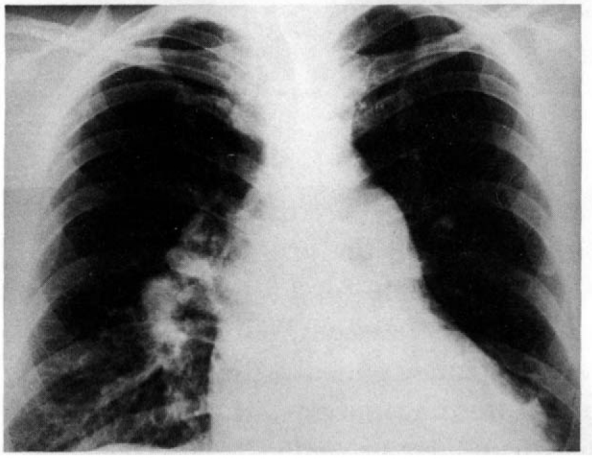

FIG. 1B. Chest X-ray in 1975 reveals a regional ectatic enlargement of the main pulmonary artery and a higher degree of peripheral tapering.

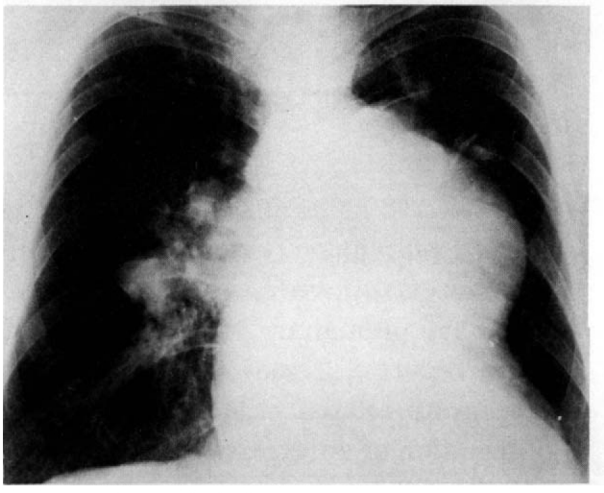

FIG. 1C. In 1984 chest X-ray demonstrated massive pulmonary trunk enlargement and peripheral oligemia.

slight peripheral acrocyanosis and a soft systolic murmur over the tricuspid valve area was noted. Routine laboratory tests including VDRL were all normal. A twelve-lead electrocardiogram showed an incomplete right bundle branch block, a PQ-interval of 180 ms and right axis deviation. Resting heart rate was 99 beats/minute. Chest X-ray demonstrated slight prominence of both main pulmonary arteries and tapering of peripheral vessels (Figure 1a). Fluoroscopic examination disclosed mildly exaggerated pulsations of secondary pulmonary arterial branches suggestive of elevated pulmonary pulse pressure. Right heart catheterization confirmed severely elevated pulmonary pressure of 130/65, mean 80 mmHg. Mean right atrial pressure was 23 mmHg. In 1975, regional ectatic enlargement of the main pulmonary artery was found combined with a higher degree of peripheral tapering (Figure 1b). The PQ-interval was increased to 210 ms. In 1984 she presented with marked cyanosis due to arterial hypoxemia and dyspnea at rest. The PQ-interval was prolonged to 230 ms, right bundle branch block and further right axis deviation was documented. On a chest X-ray film massive enlargement

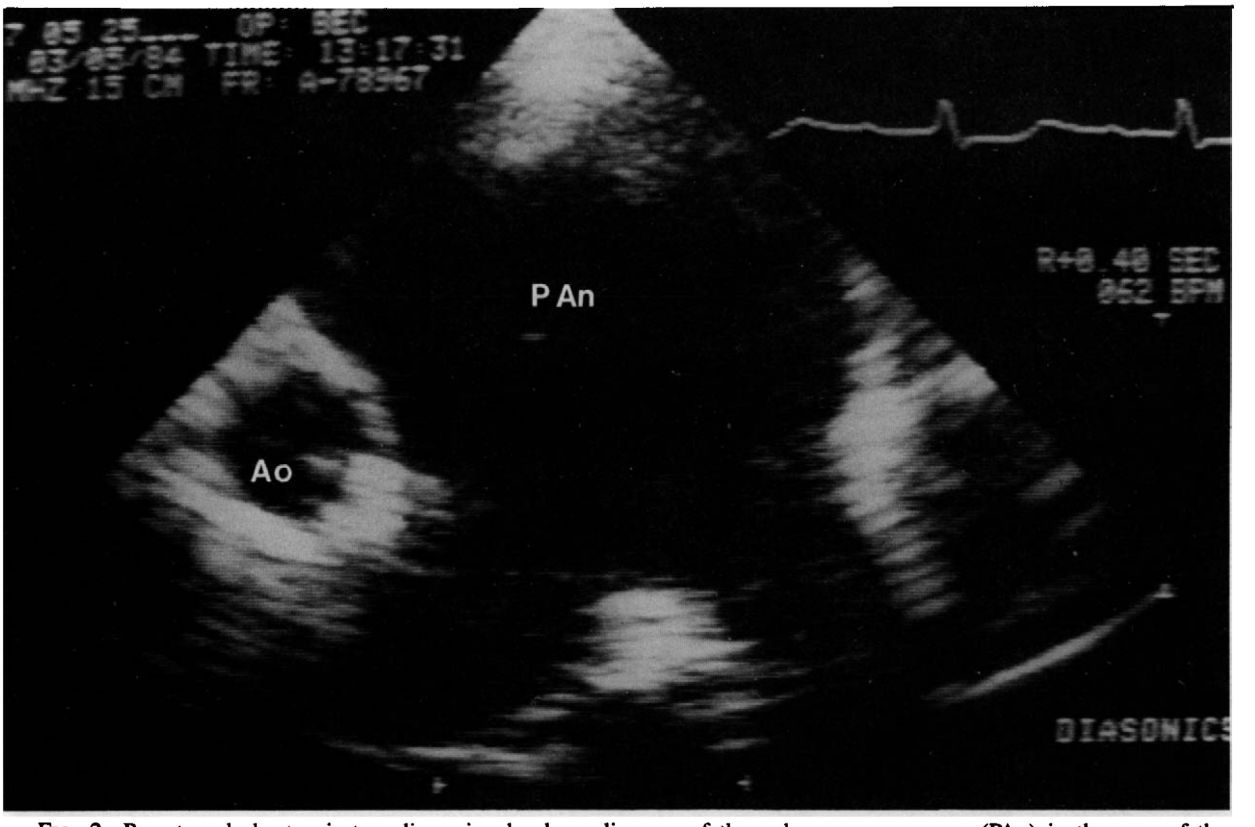

FIG. 2. Parasternal short axis two-dimensional echocardiogram of the pulmonary aneurysm (PAn) in the area of the pulmonary artery bifurcation. Ao=aorta.

of the pulmonary trunk and peripheral oligemia was seen (Figure 1c). Echocardiography showed a pulmonary artery diameter of 70 mm in contrast to a 30 mm aortic diameter, resulting in an aortic/pulmonary diameter ratio of 0.43 (Figure 2). Spontaneous echo-reflections in the pulmonary trunk suggested low local flow. The right ventricle was enlarged and hypertrophied with a wall thickness of 15 mm. There was paradoxial septal movement toward a small left ventricle. Contrast-enhanced computerized tomography confirmed the excessive pulmonary aneurysm with dimensions similar to the echocardiographic dimensions. A ventilation-perfusion lung scan demonstrated no evidence of past pulmonary embolism or veno-occlusive disease. Gated equilibrium radionuclide angiography using ultrashort-lived krypton-81m revealed dilated right-sided chambers and a massive concentric fusiform enlargement of the pulmonary main stem extending to the right pulmonary artery. The outward pulsation of the aneurysmatic structure was in synchrony with right ventricular systole (Figure 3). Pulmonary artery pressures were systemic (108/45, mean 72 mmHg), whereas the mean right atrial pressure was 9 mmHg. Diagnostic breathing of 100 percent oxygen and prostacyclin infusion into the pulmonary artery[3] did not significantly affect the pulmonary vascular resistance of 1777 dynes $\times$ sec $\times$ cm^{-5} or the systemic arterial resistance of 2100 dynes $\times$ sec $\times$ cm^{-5}. The patient is in New York Heart Association functional class IV and currently on oral digoxine and diuretic medication combined with overnight and frequent daily oxygen insufflation.

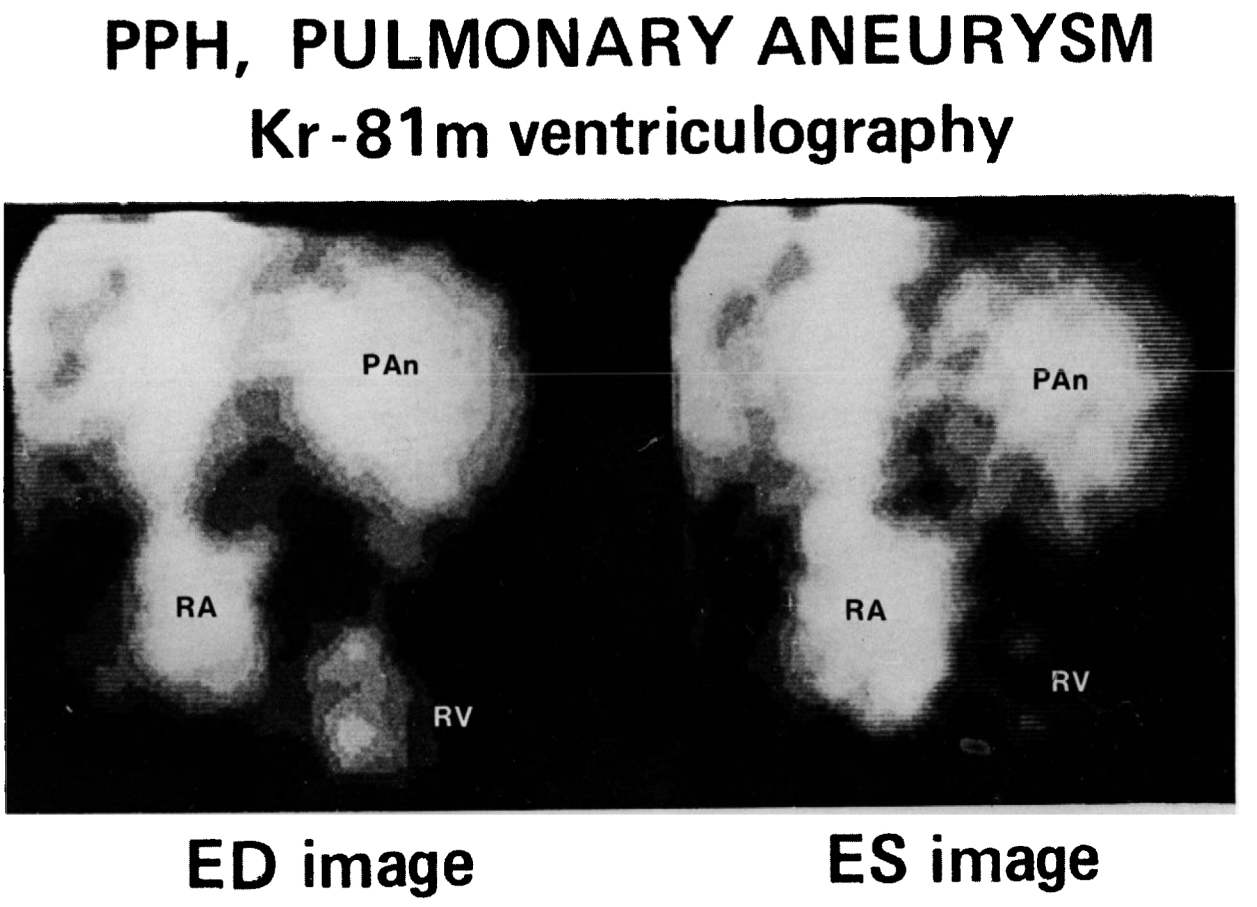

FIG. 3. Gated equilibrium krypton-81m scintigram in right anterior oblique view showing the right atrium (RA), the right ventricle (RV) and a massive pulmonary aneurysm (PAn). ED=end diastole, ES=end systole.

Discussion

The syndrome of "primary" pulmonary vascular hypertension has been described since 1891 when Romberg[4] reported a case with right ventricular hypertrophy and "pulmonary arterial sclerosis" without obvious causal disease. An interesting recent advance in human pathology of the pulmonary vasculature has been the demonstration that pulmonary hypertension and hypertensive pulmonary vascular disease can be induced by diet.[5] This observation has stimulated great interest since a recent epidemic of primary pulmonary hypertension from 1968 to 1972 in Switzerland, West Germany and Austria coincided impressively with the availability and oral ingestion of the anorexigen aminorex fumarate (2-amino-5-phenyl-2-oxazoline);[6] its chemical structure resembles adrenaline and amphetamine and exerts its anorexogenic action directly onto the central nervous system.[7] This drug was exclusively marketed in those three countries from 1967 to October, 1968 followed by an increased incidence of primary pulmonary hypertension from 0.87 percent of adult patients studied by cardiac catheterization during a 12-year period from 1955 to 1966 to 15.4 percent during the years 1967 and 1968.[6]

After withdrawal from the market in October, 1968 a markedly declining incidence of

primary pulmonary hypertension was observed;[6,8] no significant change in the incidence of the disease was found in countries of the world where the drug has not been marketed. In addition to this geographical and temporal evidence for a causal relation between aminorex fumarate intake and the development of primary pulmonary hypertension some histological and necropsy studies provide insight into pathological features of this disease process.[9,10] The elastic pulmonary arteries including the pulmonary arterial trunk often reveal patchy artheromatosis[9-11,19,18] due to long-term pressure overload resulting in subintimal thickening, intima and/or media rupture[12] with potential aneurysma formation.[13] Necrotizing arteriitis is also not uncommon in primary pulmonary hypertension[14,15] since the elevation of the pulmonary artery pressure is usually rapid and severe.

In this specific case the onset of systemic arterial pressure in the pulmonary vascular bed occurred indeed rapidly and could have led to regional necrotizing arteritis with subsequent aneurysm formation in the late stage of the disease process especially considering the long-term exposure to systemic arterial pressure and the ineffectiveness of vasodilating interventions. Since other potential predisposing events such as trauma, syphilis or congenital defects were securely excluded we conclude that aneurysma formation may be a late complication in the setting of aminorex fumarate related long-standing primary pulmonary hypertension.[1,2,16]

Conclusion

New diagnostic non-invasive imaging techniques such as two-dimenional echocardiography and radionuclide blood pool imaging[17] have great potential and are safe alternatives to pulmonary contrast cineangiography[18] for the evaluation of patients with primary pulmonary hypertension. Particular attention should be paid to potential aneurysma formation.

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Christoph A. Nienaber, M.D.
Department of Cardiology
University Hospital Eppendorf
Martinistr. 52
2000 Hamburg 20
West Germany

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