THROMBOSIS OF THE MAJOR PULMONARY ARTERIES

BY

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The clinical syndromes of pulmonary artery thrombosis are less well known than those of acute pulmonary embolism. Thrombosis may involve the secondary and tertiary branches, or the main right or left arteries and pulmonary trunk. Thrombosis of these larger vessels is uncommon. It is, nevertheless, being increasingly reported as a cause of striking clinical deterioration in a wide variety of predisposing illness (Ring and Bakke, 1955).

Pathogenesis

There are two main ways in which such thrombi can arise: (a) primary thrombi, and (b) secondary to pulmonary emboli. Carroll (1950), Hanelin and Eyler (1951), and Magidson and Jacobson (1955) have reported groups of cases, many showing a history of embolism or leg-vein thrombosis. The frequent finding of thrombi in the right heart or systemic veins led Brenner (1935) and Belt (1939) to conclude that most pulmonary artery thrombi are embolic in origin. Belt demonstrated by necropsy studies the sequence of changes which may follow embolism. He cites the elongated shape and characteristic mode of attachment of the thrombus, the lack of local vascular lesions, and the finding of thrombi of similar age in the peripheral veins as evidence for an embolic origin of many of these thrombi.

In six of seven cases described by Keating *et al.* (1953) there was evidence that the thrombi had arisen *in situ*, either from the direct involvement of the vessels by primary lung disease, or as a result of disease of the vessels themselves. All their patients died in acute cor pulmonale. Advanced tuberculosis and anthracosis were predisposing illnesses in the patients reported by Savocool and Charr (1941), who were able to trace the thrombosed vessels into the affected areas. The condition may develop in congenital and acquired heart disease, pulmonary hypertension and the altered dynamics of vascular shunts being predisposing factors. Thus, Kampmeier (1934) describes the condition with mitral stenosis, while interventricular septal defect (Bryson, 1949), cor triloculare (Cunningham, 1948), Fallot's tetralogy (Rich, 1948; Ring and Bakke, 1955), persistent ductus arteriosus (Whitaker, Heath, and Brown, 1955), and in particular atrial septal defect (Bedford *et al.*, 1941; Trounce, 1953; Campbell, Neill, and Suzman, 1957) may be associated with widespread pulmonary artery thrombosis. When heart disease is present a vicious circle may develop in which thrombosis further increases the strain on the heart and predisposes to further extension of thrombosis.

Other factors can play a part in pathogenesis. Malignant disease may directly involve the pulmonary arteries, or cause widespread obstruction by multiple tumour emboli (Brill and Robertson, 1937). Multiple venous thromboses in association with malignant disease may involve the pulmonary vessels and progress despite adequate anticoagulant therapy.

Abnormal blood conditions such as primary or secondary polycythaemia (Hodes and Griffith, 1941; Carroll, 1950), sickle-cell disease (Yater and Hansmann, 1936), and cryoglobulinaemia (Cugudda, 1952) will at times predispose to pulmonary artery thromboses.

Although the pathogenesis of thrombosis is usually established by consideration of the post-mortem appearances together with the clinical findings, the distinction between post-embolic and autochthonous thrombosis may not be possible even at necropsy.

Present Investigation

Now that prolonged anticoagulant therapy is possible, it is important to recognize the syndromes of chronic thrombotic obstruction of the pulmonary vessels during life. The purpose of this paper is to present the findings in 19 cases in which thrombosis of the major pulmonary arteries was confirmed at necropsy. They illustrate the wide variety of predisposing illness, the varying factors in pathogenesis, and the types of clinical illness which result.

Sixteen of the cases were chosen from 1,673 consecutive post-mortem examinations carried out at St. George's Hospital, London, during the period January, 1952, to July, 1956. Three were observed subsequently. In all cases thrombosis affected the pulmonary trunk or the main left or right branches proximal to the hilum. Patients in whom major clinical embolism was the immediate cause of death were excluded. In the patients reported here, at least three weeks had elapsed since any major embolic episode; at necropsy the thrombi were organized and adherent in all but three of the cases.

Clinical Features

The ages in the present series range from 22 months to 78 years, 14 patients being over 50 years of age at the time of death. The clinical and pathological findings are summarized in the Table. Cases are divided into two main groups, Figs. 1, 2, and 3 illustrating the appearances and extent of the thrombotic obstruction of post-embolic and autochthonous thrombosis.

Group 1.—In six patients there was a history of frank pulmonary embolism during the preceding three months. In two further cases pulmonary embolism produced only minimal clinical changes, their possible significance in the resulting illness being recognized only in retrospect.

Group 2.—Of the nine examples of presumed *in situ* thrombosis, six had chronic heart disease and three emphysema. There was no definite history of thrombosis of the leg-veins, nor did necropsy reveal thrombi in the peripheral veins of similar age to the pulmonary artery thrombi. In the remaining two patients there were no progressive cardio-respiratory symptoms; at necropsy the pulmonary thrombi were pale, friable, and only lightly adherent. Their appearances suggested that they had formed terminally.

FIG. 1.—Case 1. Post-embolic thrombosis of the pulmonary arteries. A major embolic episode occurred three weeks before death. Smooth adherent thromboembolus occludes much of the lumen of both the right and left pulmonary arteries. Many of the secondary branches are affected.

The most frequently observed clinical features were increasing dyspnoea, cyanosis, and right heart failure. Dyspnoea was severe in 14 of the 19 cases, being often progressive and intractable, and at times proportionately more severe than the clinical and radiological findings suggested. Nevertheless, both dyspnoea and cyanosis were on occasion absent or minimal.

The cardio-respiratory symptoms of many of the underlying conditions make it difficult to appreciate any additional changes due to pulmonary artery thrombosis. A review of the clinical findings in this series did, however, reveal a number of features thought to be associated with the increasing thrombotic obstruction. These were the sudden onset of acute cor pulmonale with striking coldness of the extremities (Cases 9, 10, 11, and 14), paroxysmal epigastric

pains (Case 11), the development of a prolonged generalized systolic murmur (Case 5), the onset of visible pulsations in the pulmonary area with greater accentuation of the second sound (Case 15), and possibly the development of paroxysmal cardiac arrhythmias (Case 12).

Electrocardiograms were taken in 11 patients and serial records were available in nine of these. There were no constant changes, the findings in general remaining those of the underlying conditions.

In 15 of the cases radiographic examination was made during the last three weeks of life, serial records being made in nine. In one of the two cases in which screening was carried out there was expansile pulsation of the proximal portions of the dilated right pulmonary vessels which diminished abruptly distally (Case 14). The most frequent finding (11 patients) was conspicuous enlargement of the pulmonary vessel shadows. In only three of the cases could progressive ischaemic changes of the peripheral lung fields characteristic of pulmonary artery obstruction

be recognized. In some cases this was because the lung fields were obscured by the changes of effusion or infarction; in several, however, no changes of pulmonary artery obstruction were detected even though serial radiographs were compared. A further change noted (Case 13) was that of increasing accentuation of the pulmonary vessel outline due to diminished pulsation of the affected area.

The patients showed three types of clinical course. Cases 1, 2, 3, 4, 5, and 8 showed episodes of clinical pulmonary embolism, often repeated, with subacute cor pulmonale. In Cases 9, 10, 11, and 14 the post-mortem appearances suggested that the pulmonary artery thrombi had been present for some weeks, since they were well organized and firmly adherent. Nevertheless, few symptoms had resulted until the patients suddenly developed acute cor pulmonale. A gradually worsening chronic cor pulmonale was observed in one patient only (Case 6). Death occurred from other causes before cardio-respiratory symptoms were at all severe.

Discussion

The patients in the present study illustrate both post-embolic and autochthonous thrombosis. This is in accord with the case reports of Ring and Bakke (1955) and Ball, Goodwin, and Harrison (1956), and suggests that both types may occur with comparable frequency. The distinction is of practical importance in drawing attention to the group of *in situ* thrombosis of the larger pulmonary vessels as a complicating event in chronic heart or lung disease. The present cases of group 2 include emphysema, mitral stenosis, and congenital heart disease. These patients showed a history of increasing cor pulmonale, often acute, rather than of recurring clinical pulmonary embolism.

The present findings also support the observations that the right artery is more often affected than the left (Savacool and Charr, 1941). Even when thrombosis is bilateral, they point out that older lesions may often be identified in the right branches with recent extension to the left. They suggest that this may be related to the differing anatomy of the blood vessels at the lung roots.

Diagnosis has seldom been established during life. The condition may, however, be strongly suspected when there is a history of venous thrombosis of the legs followed by cardio-respiratory symptoms. That the time interval before cardio-respiratory symptoms may be measured in years is illustrated by a number of striking case reports (Means and Mallory, 1931; Covey, 1943; Madigson and Jacobson, 1955). In none of the present cases did the time between leg-vein thrombosis and embolic symptoms exceed three months. We have under treatment a further case in which subacute cor pulmonale has developed three and a half years after deep femoral vein thrombosis and in which radiological changes suggest pulmonary artery obstruction. It is well recognized that the clinical features of pulmonary embolism may be minimal; their significance was overlooked in Case 6 of the present series.

The condition may also be suspected when there is unexplained deterioration in any of the known predisposing cardiac or respiratory illnesses. The present findings support the view that *in situ* pulmonary artery thrombosis is particularly liable to occur when local vascular disease is severe, advanced vascular pathological changes being present in seven of the nine examples.

There may be changes in the physical signs. Changing heart signs were noted in three patients and epigastric pains in one patient. Severe attacks of epigastric pain were a striking feature in the patients studied by Middleton (1943) and in two reported by Magidson and Jacobson (1955). Syncopal attacks related to acute embolic episodes may be observed (Ball *et al.*, 1956).

The condition may first be suspected radiologically. The characteristic changes have been described by Westermarck (1948). These include right-sided heart enlargement, dilatation of the pulmonary artery proximal to the obstruction, with alteration of the vessel contour, and increased trans-

FIG. 2.—Case 13 *In situ* thrombosis of the pulmonary arteries. The arteries contain grey adherent laminated thrombus. Many of the peripheral vessels are occluded.

FIG. 3.—Case 11. Bilateral thrombosis of the pulmonary arteries. The relationship of the thrombus to atheroma of the vessels is seen in the right branch (below).

lucency of the lung fields distal to the obstruction. Keating *et al.* (1953) draw attention to the accentuation of the vessel outline due to diminished pulsations of the affected area. Three of the fifteen patients in the present series who had radiographs showed such changes, and screening was of assistance in a further case. Frequent and comparable radiographs in cases of cor pulmonale are of obvious value in the detection of the changes.

Electrocardiography did not suggest the diagnosis in the present cases, although the change to right-axis deviation from pre-existing left-axis deviation may be striking (Keating *et al.*, 1953).

The increasing use of angiography may confirm the diagnosis more often in the future. Obstruction to the major arteries has been demonstrated by this means (Carroll, 1950), and to the segmental vessels (Aitchison and McKay, 1956).

The present cases illustrate the variability of clinical effects attributable to massive pulmonary artery thrombosis. That these may be minimal is shown in Cases 6, 7, 8, and 18. This is in accord with evidence that in the experimental animal much of the pulmonary circulation may be obstructed without the development of progressive symptoms (Gibbon, Hopkinson, and Churchill, 1932), and with the necropsy findings in Cases 9, 10, 11, and 14, when virtually no progressive symptoms occurred until the patient suddenly developed acute cor pulmonale.

The most frequent clinical course was that of repeated embolic episodes or of an overwhelming acute cor pulmonale. Only one patient in the present series showed a slowly progressive chronic cor pulmonale. This type of illness may be the least frequent of the clinical syndromes of pulmonary artery thrombosis.

Clinical and Pathological Features of 19 Cases of Pulmonary Artery Thrombosis

Case No.	Age	Sex	History	Duration of Recent Symptoms	Predisposing Conditions	Thrombosis Site	Heart Weight	Lung Vessels		Lung Infarction	
								Major Artery Atheroma	Arterioles		
Group 1. Following Pulmonary Embolism											
1	48	M	Post-operative embolism. Femoral-vein ligation. Increasing dyspnoea and haemoptyses	3 weeks	Embolism	Bilateral	—	—	—	++	
2	56	M	Cardiac infarction — progressive dyspnoea and haemoptyses. Death in congestive failure	9	„	Antero-septal infarction — mural thrombi	Left branch	720 g.	—	++	
3	66	M	Venous thrombosis right leg. Pulmonary embolism. Spastic weakness right arm. Thrombosis left leg	5	„	Unsuspected hypernephroma. Multiple venous thromboses	Right „	540 g.	—	Intimal thickening	++
4	66	M	Venous thrombosis left leg. Pulmonary embolism. Left cephalic vein thrombosis. Recurring pleural effusion	3 months		Carcinoma left bronchus. Multiple venous thromboses	„ „	370 g.	—	—	—
5	45	M	Emphysema and cor pulmonale 3 years. Leg-vein thrombosis and embolism	3 weeks		Recent embolism left branch—old thrombosis of right branch	Bilateral	450 g.	++	Severe arteriosclerosis	+
6	69	F	“Feverish chill” followed by dyspnoea on exertion and persistent tachycardia	3 months		Embolism. Death from peritonitis due to perforation	„	360 g.	—	—	—
7	73	F	Hypertensive heart failure. Transient left apical chest pain. Re-admitted after insulin overdosage	3	„	Hypertensive heart disease. Diabetes. Prolonged coma	Left branch	420 g.	—	Intimal thickening	+
8	70	M	Fractured neck of femur—pinned. Increasing right hemiplegia post-operatively	3 weeks		Polycythaemia rubra vera. Hypertension	Bilateral	480 g.	—	„	+
Group 2. In Situ Thrombosis											
9	64	M	Chronic bronchitis and emphysema. Sudden acute cor pulmonale	24 hours		Emphysema	Right branch	330 g.	++	—	+
10	62	F	Parkinsonism 3 years. Kyphoscoliosis. Slight dyspnoea on exertion. Sudden acute cor pulmonale	8 weeks		„	Bilateral	380 g.	++	Severe arteriosclerosis	+
11	62	M	Chronic bronchitis, worse 1 year. Recent epigastric pains. Acute cor pulmonale	48 hours		„	„	—	+	„	?
12	26	M	6 years' increasing dyspnoea. Recent right lower lobe “pneumonia.” Congestive failure with fibrillation	3 months		Persistent ductus. Aortic coarctation	Right branch	650 g.	++	Moderate arteriosclerosis	+
13	62	M	6 years' auricular flutter. Well controlled until 3 months before death	3	„	Atrial septal defect. Mural cardiac thrombi	Bilateral	750 g.	++	Severe arteriosclerosis	++
14	52	M	Increasing dyspnoea with paroxysmal fibrillation. Sudden acute cor pulmonale	7	„	Lutembacher's syndrome	Right	630 g.	++	„	++
15	39	F	16 years' mitral stenosis. Episodes of congestive failure	2 weeks		Mitral stenosis	Bilateral and pulmonary conus	555 g.	+	Arteriosclerosis. Fibrinoid necrosis. Elastic fragmentation	++
16	68	F	6 months' increasing dyspnoea. Acute cor pulmonale	6 months		„ „	Bilateral hilar. Thrombi red and not organized	600 g.	+	Severe arteriosclerosis	+
17	68	F	2 years' congestive failure and fibrillation. Sudden acute cor pulmonale	3 days		„ „	Left	600 g.	+	Moderate arteriosclerosis	+
Group 3. Other Cases											
18	22 mths	M	3 days' fever and petechial rash	3 days		Pneumococcal septicaemia. Mastoiditis. Thrombus pale and not organized	Left branch	—	—	—	+
19	78	M	Cerebral vascular accident 3 weeks before death	3 weeks		Cerebral infarction. Prolonged coma	Bilateral	300 g.	—	—	+

Summary and Conclusions

Thrombosis of the major pulmonary arteries is being increasingly recognized as a complicating event in a variety of illnesses.

The clinical and pathological findings are summarized in 19 further examples. In eight cases thrombosis was consequent on previous pulmonary embolism, in nine the findings suggested that autochthonous thrombosis had occurred. In two cases the pathogenesis was not established with certainty.

The pathogenesis and clinical effects are briefly discussed. Many of the patients have severe disease of the heart or lungs. The variability of the clinical effects attributable to pulmonary artery thrombosis is stressed. In this series they ranged from minimal changes to sudden intractable right heart failure.

Although the clinical changes are often masked by the underlying illness, the diagnosis may be suggested by a history of thrombophlebitis or embolism, by the occurrence of new and unexpected clinical signs and symptoms in the course of one of the predisposing illnesses, and on occasion by the radiological appearances.

Some patients show an illness characterized by recurrent embolization; in others the presence of thrombotic obstruction is virtually symptomless until the onset of acute cor pulmonale. Less frequently, the thrombosis gives rise to a chronic cor pulmonale.

Thrombosis of the major pulmonary arteries may therefore have to be considered in the diagnosis of any case of acute, subacute, or chronic cor pulmonale.

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ANAEMIA OF UNCERTAIN ORIGIN IN INFANCY

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Severe anaemia in infancy and childhood is often seen at University College Hospital, Ibadan, Nigeria. In most cases anaemia occurs in association with conditions such as kwashiorkor, cancrum oris, tuberculosis, and chronic sepsis. Sick-cell anaemia is also relatively common. However, many patients present, especially during the first two years of life, with severe anaemia unassociated with other recognizable diseases and not due to the sickle-cell gene. There has been much speculation about the aetiology and pathogenesis of anaemia in this latter group, and malignant tertian malaria and dietary deficiencies (chiefly protein and iron) have long been regarded as the most likely causal factors. Little has been done, however, to verify these speculations. We report here the results of investigation and treatment of 24 of these cases selected from 85 similar cases which occurred among 1,318 admissions to the children's ward during the period October, 1955, to June 30, 1956.

Case Selection.—In a busy ward with a very rapid turnover of cases, one cot was set aside and used exclusively for the investigation of children under 2 years of age with severe anaemia (haemoglobin, 5.9 g./100 ml. or lower). Sick-cell anaemia and anaemia complicating some other illness were excluded. The 24 cases presented were those who were admitted into this cot.

Methods

Besides routine clinical examination the following were done: Tuberculin-testing by the Heaf technique was routinely performed and the majority of children had an x-ray examination of the chest and wrists. Haemoglobins were estimated, using Keeler M.R.C. grey wedge photometers (100% = 14.8 g./100 ml.). Thin blood films were stained with Leishman's and thick films with Field's stain. Supravital preparations, stained with brilliant cresyl blue (dried alcoholic solution), were made for reticulocyte determination (Whitby and Britton, 1953). Bone marrow was obtained by iliac crest puncture (Rubinstein, 1950), and smears were stained by Leishman and also by May-Grünwald-Giemsa. Differential marrow counts were made using the terminology of Dacie and White (1949) and red-cell maturation curves constructed (Pontoni, 1936). Serum protein estimation was performed by the biuret method, using a photoelectric colorimeter. Results were checked monthly against Kjeldahl. Liver-function tests consisted of thymol turbidity, zinc sulphate turbidity, alkaline phosphatase, and serum bilirubin, all performed with standard techniques. In four patients the serum cholesterol and in two the total serum lipids were estimated. Plasma volume estimation based on the single-injection technique of Chinard (1951) using Evans blue was performed on four patients before and after treatment. Sickling of the red cells was tested for by using a freshly prepared 2% solution of sodium metabisulphite. Cases showing sickling had samples of haemoglobin submitted for paper electrophoresis.

"Extra Care Stops Falls" is the slogan adopted by the Royal Society for the Prevention of Accidents for this year's National Industrial Safety Week, which is to be held from September 29 to October 4. The theme forms the basis of a nationwide campaign directed to both managements and workers with the object of reducing the toll of industrial accidents, and particularly those associated with falls of persons. In 1956, 22,548 persons were absent from work as a result of injuries following falls, equal to 14.1% of all reported industrial accidents.