Primary Pulmonary Aspergillosis with High Fibrinolytic Activity in the Aortic Intima*

M. E. Pelczar, M.D., Pia Glas-Greenwalt, M.D., and T. Astrup, Ph.D.

Frozen sections of the aorta of a patient with pulmonary aspergillosis were studied for fibrinolytic activity by the histochemical fibrin slide technique. High fibrinolytic activity, caused by a plasminogen activator, was observed along the aortic intima. This unusual observation suggests the existence of a potential for development of fibrinolytic activity in the normal, inactive aortic endothelium of man.

This case report suggests a possible association between pulmonary aspergillosis and an enhanced fibrinolytic activity of the aortic endothelium.

The fibrinolytic activity of tissues is caused by a cellular agent capable of activating a humoral zymogen, plasminogen, to the blood proteinase, plasmin.1 Assays of this plasminogen activator in extracts of the intima of the human aorta, normal or arteriosclerotic, showed a nearly complete lack of activator,2,3,4 while the intima of the inferior vena cava was found highly active.4 Through the use of a histochemical fibrin slide technique, Todd5 could localize the plasminogen activator to the venous endothelium with little or no activity in the endothelium of systemic arteries, an observation subsequently confirmed by several authors, including ourselves. Noticing unusual fibrinolytic activity in detached endothelium of the arteries of a limb amputated for sarcoma under "bloodless" conditions, Todd6 suggested that vascular endothelium may have a great fibrinolytic potential, though some stimulus, such as damage, might be required for its release. We report the unexpected finding of a high fibrinolytic activity related to the aortic endothelium of a patient with primary pulmonary aspergillosis.

CASE REPORT

Pertinent clinical data were as follows: A 69-year-old woman was seen at the emergency room because of shortness of breath. Hoarseness had developed three years prior to admission and had gradually become severe. For several months difficulty in swallowing and loss of appetite were noticed, and considerable loss of weight developed. For one month she had complained of shortness of breath and coughing and was treated for congestive heart failure only to have her symptoms worsen. At admission the patient was confused and markedly emaciated. The pulse rate was 90 and irregular. Temperature was 98.9°F (orally) and blood pressure 110/90. Respirations were short and labored. Cyanosis was absent. There were frequentextrasystoles and gallop rhythm. ECG depicted a wandering atrial pacemaker with premature ventricular contractions, left ventricular hypertrophy, and anterior myocardial ischemia. Chest x-ray film showed collapse of the left upper lung with mediastinal shift to the left and infiltrate in the right upper lobe. Hematocrit was 32 percent; hemoglobin, 10.0 gm per 100 ml. White blood count was 7,700/mm3 with normal differential count. Results of urine analysis were normal. The patient died on the second hospital day.

Pulmonary aspergillosis was diagnosed post mortem with Aspergillus fumigatus cultured from abscesses in both lungs. The fungus had invaded the pulmonary parenchyma radically. Dense pleural adhesion and fibrous thickening were found along the posterior aspect of the left lung. A clear, yellow-brown effusion (180 ml) was present in the right pleural cavity. There was moderate atherosclerosis of the coronary arteries and aorta. The weight of the heart was 250 gm. There was mild hypertrophy of the right and left ventricles but no significant dilatation. The myocardium was light brown with cells filled with lipofuscin pigment. The liver showed portal fibrosis and striking deposits of lipochrome pigment in the hepatic cells. Additional autopsy findings were unremarkable.

From a segment of the descending thoracic aorta, refrigerated overnight in saline, samples with grossly normal intima and with moderate atherosclerosis were dissected and frozen in small aluminum containers placed in acetone-dry ice. Sections were cut at 8 µ to 10 µ on a cryostat microtome and collected on precooled microscope slides. After brief drying in the air, the sections were covered with a mixture of bovine plasminogen-rich fibrinogen and bovine thrombin. The slides were left for 20 minutes in a moist chamber at 10 to 15°C for clot stabilization and then incubated at 37°C for periods ranging from 30 to 90 minutes. Following fixation in formaldehyde, the sections were stained with Harris' alum hematoxylin and mounted with glycerin jelly. Other details were as described before.7

Intensive lysis appeared as a clear, ribbon-shaped zone along an apparently intact intimal surface after 30 minutes of incubation, and increased in size with prolonged incubation, and the usual, well-demarcated focal zones of lysis in the adventitia were seen related to intact or torn vascular structures (Fig 1). Sagittal sections or imprints obtained on frozen slides from the fresh luminal surface showed intensive lysis related to endothelial cells. Lysis was absent along intimal surfaces of atheromatous areas, where close examination showed that most of the endothelium had been lost, possibly

*From St. Agnes Hospital, Baltimore, and The James F. Mitchell Foundation, Institute for Medical Research, Washington, DC.
Supported by Grant HE-05020 from US Public Health Service, National Institutes of Health, National Heart and Lung Institute.
Reprint requests: Dr. Astrup, Institute for Medical Research, The James F. Mitchell Foundation, 5401 Western Avenue, NW, Washington, D.C. 20015

CHEST, VOL. 61, NO. 4, APRIL, 1972
Using human fibrinogen in the fibrin slide technique, we have been unable to verify their observations on the material available to us.

The intimal activity in the aortic specimen of our patient is related to the endothelial lining. The aortic adventitia showed the usual pattern of focally distributed areas of lysis related to the vasa vasorum. In all sections the fibrinolytic activity was caused by a plasminogen activator, and there was no unspecific proteinase activity. A direct correlation between the marked fibrinolysis in the aortic endothelium and our patient's disease cannot be established. Although several strains of Aspergillus are known to produce proteolytic enzymes, A fumigatus is not reported among them. In contrast, aspergillosis caused by this organism is associated with fibrinous exudation and a fibrin-containing expectoration. Fibroin exudation had apparently occurred in the pleura of our patient, and arterial changes with moderate atherosclerosis were also present. There were no major preexisting illnesses which could account for the high fibrinolytic activity or be made responsible for an increased susceptibility to the fungus infection. For this reason we have retained the term "primary pulmonary aspergillosis," although the adequacy of this terminology is debated. The patient's history, as well as the existence of arteriosclerotic changes which probably would not have occurred in the presence of a fibrinolytic endothelium, suggest that the fibrinolytic activity of the aortic intima is a recent phenomenon, possibly related to the pulmonary aspergillosis. Our observations are limited because additional material was unobtainable when the unsuspected finding was made. However, the potential of the normally inactive human aortic endothelium to become highly fibrinolytic seems established by our finding. It remains to be determined how the realization of this potential is brought about.

ACKNOWLEDGMENT: Thanks are due to Emile R. Mohler, M.D., Chairman, Department of Medicine, St. Agnes Hospital, for initiating the joint study.

REFERENCES

6 Todd AS: The tissue activator of plasminogen and thrombosis. in Thrombosis and Anticoagulant Therapy (W. Walker, Editor), London: E and S Livingstone Ltd, 1960, p 25
7 Kwaan HC, Astrup T: Demonstration of cellular fibrinolytic activity by the histochemical fibrin slide technique. Lab Invest 17:140, 1967


During handling of the specimen. Tested for unspecific proteinase activity on slides prepared with plasminogen-free fibrinogen, none of the samples showed lytic activity.

DISCUSSION

The marked fibrinolysis related to the normal, intact intima of the patient's aorta is impressive. Never before have we seen a similar degree of lysis related to a human aortic intima, assayed either by the extraction method or studied by the histochemical technique. Regularly we found extracts of the aortic intima to be inactive, with only an occasional trace of fibrinolytic activity, except for two instances of CO-poisoning in young men in whom low concentrations of plasminogen activator were observed. The absence of fibrinolytic activity in the intima of the normal human aorta has been confirmed by several investigators, though Onoyama and Tanaka have reported a high fibrinolytic activity of the human aortic intima, through use of an extraction method as well as the histochemical fibrin slide technique, and replacing the bovine fibrinogen with human fibrinogen.

CHEST, VOL. 61, NO. 4, APRIL, 1972
Persistent Left Superior Vena Cava Complicating Pacemaker Catheter Insertion

Leonda Garcia, M.D.;** Richard S. Levine, M.D., F.C.C.P.;* Warren Kossowsky, M.D.;† and Alan F. Lyon, M.D.†

Transvenous pacemaker therapy was complicated by the presence of a persistent left superior vena cava and absence of the right superior vena cava. The correct diagnosis was made during life by venous angiography and enabled successful therapy to be instituted utilizing the transthoracic placement of pacemaker electrodes.

The transvenous catheter technique for pacemaker therapy of complete heart block has met with widespread acceptance, since its clinical introduction in 1958.† Complications associated with its use have included infection, cardiac perforation, venous fibrillation, pulmonary emboli, and failure to pace due to catheter tip displacement.‡ Recently, a case was reported in which pacemaker failure and death was believed to occur secondary to catheter tip displacement due to anomalous venous return to the heart.§

This report describes a patient, requiring a pacemaker, in whom a similar venous anomaly was recognized during life. The transthoracic approach to pacemaker implantation was utilized successfully.

CASE REPORT

The patient, a 79-year-old white woman, was first seen at The Brookdale Hospital Center in 1968. She had had a slow heart rate for many years. Three years prior to admission, she had collapsed and pacemaker therapy was advised. The patient refused and was placed on isoproterenol tablets three times per day. Since then, the pulse rate had generally remained slow, but she also experienced episodes of paroxysmal rapid heart beating. These latter episodes were associated with dyspnea and angina pectoris. Just prior to admission she had an attack of syncope and fell down a flight of stairs.

Physical Examination: The blood pressure was 140/90. The pulse rate was slow, varying between 35 and 40, and was occasionally irregular. The neck veins were distended and hepatojugular reflux was present. The lungs were clear to auscultation. The heart was not enlarged and no gallop or murmur was detected. There was moderate prebital edema.

The electrocardiogram showed sinus bradycardia with a rate varying between 30 and 40. There were occasional premature nodal ventricular contractions. Atrial activity was occasionally absent and there was A-V nodal escape rhythm. The initial chest x-ray film showed no abnormalities of the heart or lungs. The aorta was widened and calcified on chest roentgenogram.

A demand type transvenous catheter pacemaker was inserted through the left cephalic vein. The catheter course was noted by the surgeon to be atypical and persistent left superior vena cava was suspected at that time. Although some difficulty in manipulation was noted, the catheter was passed down the left cava, through the coronary sinus and into the right atrium. From there is was deflected off the lateral wall of the atrium and into the right ventricle where effective pacing was obtained (Fig 1). The QRS complex on the electrocardiogram demonstrated the expected left bundle branch block pattern.

The patient was discharged from the hospital and apparently did well for 23 months when she again noted slow pulse rate and experienced marked dizziness. She was readmitted and the electrocardiogram showed ineffective pacemaker activity at a slow rate with an underlying sinus bradycardia varying with atrial standstill and a nodal escape rhythm. The pacemaker battery pack was replaced by the surgeon, but under fluoroscopy, it was noted that the catheter tip was no longer located within the right ventricle. Attempts at manipulating the permanent catheter were repeatedly unsuccessful but a more rigid, No. 7, temporary pacemaker catheter was introduced through the previously described route followed by effective pacing. An angiogram was performed.

Figure 1. Pacemaker catheter entering heart through persistent left superior vena cava.