Hemodynamic Studies in a Case of Carcinoid Cardiovascular Syndrome

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Numerous reports of cases of malignant carcinoid associated with acquired cardiovascular abnormalities have appeared in the medical literature since this syndrome was first recognized as a clinical entity. Despite the fact that the intracardiac abnormalities characteristic of this interesting disease are almost exclusively confined to the right side of the heart, catheterization studies have only infrequently been mentioned and no truly complete hemodynamic data have been included in the case reports published to date.

Of the valvular lesions encountered in the carcinoid cardiovascular syndrome, tricuspid insufficiency is the most frequently seen; right atrial tracings exemplifying this condition appear in the communications of Björck, Axen, and Thorson and Sjoerdsma, Weissbach, and Udenfriend. However, cardiac catheterization data supporting the diagnoses of tricuspid stenosis, pulmonary stenosis, and pulmonary insufficiency, which may also occur in association with functioning carcinoid, have not come to our attention.

Serotonin or 5 hydroxytryptamine (5-HT), the elaboration of which by the argentaffine cells has been generally accepted as the pathogenic agent responsible for the cardiovascular manifestations of malignant carcinoid, has been shown to produce pulmonary hypertension in animals. The occurrence of pulmonary hypertension in the reported cases of carcinoid cardiovascular disease, however, has not been frequent. Sparks and Towbridge reported that cardiac catheterization established the diagnosis of pulmonary hypertension in their case but the actual pressures were not stated. In McKusick’s excellent review mention was made of a patient with the carcinoid syndrome who was catheterized by Dr. Richard J. Bing in 1949, and who showed elevation of the pulmonary artery pressure. Unfortunately, neither clinical nor hemodynamic data relating to this patient were published.

Mattingly and Sjoerdsma specifically stated that the 4 cases studied by them did not have pulmonary hypertension, although in one of the cases, cardiac catheterization was not done, and in another the catheter could not be passed from the right atrium into the right ventricle. In the remaining 2 cases, actual intracardiac pressures were not listed.

Because of the relative paucity of reports dealing with detailed hemodynamic studies in the carcinoid cardiovascular syndrome, the following case is presented. It is also believed that this case is of general interest in that it so well typifies the extracardiac characteristics of this comparatively recently described disease.

Case Report

A 72-year-old Negro was first admitted to Mount Sinai Hospital of Cleveland on February 22, 1955, complaining of “liver trouble.” Six months prior to hospitalization, he had first become aware of upper abdominal pain and it had become increasingly severe, particularly during the previous 3 or 4 weeks. This pain usually began following meals, but otherwise showed no particularly characteristic features. He had been a “moderate” drinker all his adult life. The outstanding finding on physical examination consisted of a markedly enlarged liver whose edge extended down to the umbilicus and was described as smooth and firm. The patient also had a marked purple-red discoloration of the face and, as a result, the diagnosis of polycythemia vera was actually con-
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sidered. Hematologic study, however, quickly ruled out this impression as it disclosed a moderate anemia. The red cell count was 3.60 million per mm.\(^3\), hemoglobin was 10.4 Gm. per cent, and the hematocrit level was 37 per cent. Other blood chemical studies were normal.

The electrocardiogram showed frequent atrial and ventricular premature beats, left axis deviation, flat T in lead I, prominent P wave in leads II and aVF, inverted T wave in aVL and inverted T in V\(_{1-6}\). The chest roentgenogram showed slight cardiac enlargement, the aorta was elongated and tortuous, and no pulmonary infiltration was present. An intravenous pyelogram showed a linear calcification in the midline and in the right lower quadrant, which was interpreted as a markedly redundant aorta with aneurysmal dilatation in the region of the aortic bifurcation and involving the right common iliac artery. There was minimal hydrophrosis of the right kidney, and hydro-ureter was present to the level of the aneurysm, beyond which the ureter was not seen. The barium enema was negative except for a diverticulum of the hepatic flexure. A gastrointestinal series was essentially negative.

The patient was discharged on March 5, 1955, with the diagnoses of Laennee's cirrhosis, aortic aneurysm, and arteriosclerotic cardiovascular disease.

The patient discontinued his use of alcoholic beverages and subsequently felt quite well until approximately July 1958, when he was again seen because of development of edema of the lower half of the body. He was treated with chlorothiazide and meralluride, to which he responded well. He developed mild intermittent diarrhea, which gradually increased in severity and occasionally contained blood. His appetite was not impaired, however, and there was no nausea or vomiting. Occasional upper abdominal distention was relieved by belching. In July 1958, his feet began to swell again and diuretics were started with some relief. The patient at no time complained of chest pain, exertional dyspnea, or paroxysmal nocturnal dyspnea. Periodic or paroxysmal flushing of the face had never occurred. Because of increasing diarrhea and a palpable hard abdominal mass in the right lower quadrant, the patient was readmitted.

Physical examination at this time disclosed telangiectases with purple-red discoloration on the face and forehead. Areas of stasis dermatitis were present over both lower legs. The heart was slightly enlarged to the left. A grade-II systolic murmur was heard best at the fourth and fifth intercostal spaces, just to the left of sternum. The rhythm was regular. Examination of the abdomen disclosed the liver edge to be palpable 2 fingerbreadths below the costal margin. A mass of indefinite size and contour was present in the right lower quadrant. A large right inguinal hernia was noted. On rectal examination the prostate was fleshy to be enlarged, but smooth and with no masses. There was marked edema of the lower extremities extending up to the thighs.

Laboratory studies disclosed a hemoglobin of 9.8 Gm. per cent, hematocrit 29 per cent, white blood count 5,500 per mm.\(^3\), differential normal, sedimentation rate 19 mm. per hour, prothrombin time 16.9 seconds, with control of 14.3 seconds, 3+ cephalin flocculation test, albuminuria, and 30 to 40 white blood cells per high-power field in the urine.

On the posteroanterior chest roentgenogram the heart appeared to be enlarged in the region of the left ventricle, but the high diaphragm seemed to contribute to this appearance. In the lateral view the left ventricle was definitely rounded posteriorly. There was no pulmonary infiltration.

The barium enema showed several scattered diverticula. A well-defined filling defect seen along the medial margin of the cecum was constantly visualized throughout the original filling with barium and on the subsequent air study. This filling defect was evidently produced by an amorphously calcified mass adjacent to the cecum and apparently continuous with the calcified aorta, which was previously demonstrated and described as a sacular aneurysm of either abdominal aorta or upper portion of the right iliac artery. A gastrointestinal series also showed a mass in the right lower quadrant separating some of the small bowel loops in this area but apparently not involving the small bowel intrinsically. Electrocardiogram showed only minor changes from the tracing of 1955, with lower amplitude of QRS and widened splintered S in leads II, III, aVF, and V\(_{6}\).

At laparotomy a large retroperitoneal tumor was found in the right lower quadrant behind the cecum and terminal ileum. Metastatic tumor was also noted in the liver and in the cul-de-sac. A biopsy of the liver and a peritoneal lymph node were taken, and an ileotransverse colostomy was done. During the operative procedure the anesthesiologist noted progressive increase in expiration time and resistance.

Histologie sections revealed the liver and lymph node to be partially replaced by a tumor composed of distinct nests of moderately sized cells. Their nuclear appearance was uniformly benign. The cytoplasm was relatively slight in amount and poorly defined. The cells tended to have an alveolated appearance and frequently exhibited central areas of cavitation and even adenoid for-
The patient was discharged from the hospital to be followed by his private physician.

**DISCUSSION**

Consideration of all the data in this case indicates that all the cardinal features of the carcinoid cardiovascular syndrome were present, including telangiectases with "cynotic" flush, diarrhea, bronchospasm, and a right-sided valvular heart lesion. Carcinoid tissue metastatic to the liver actively secreting 5 hydroxytryptamine was proved pathologically and by urinary excretion of 5 hydroxy indoleacetic acid.

As noted above, the most common valvular lesion found in association with malignant carcinoid is tricuspid insufficiency and this disorder was most prominent in the present case. The explanation for the almost constant finding of tricuspid insufficiency is thought to be the endocardial fibrosis involving the right atrium and ventricle. This causes shortening and thickening of the chordae tendineae and prevents complete closure of the tricuspid valve. The exact mechanism by which the endocardium undergoes this fibroplastic change is poorly understood but is thought to result from the high concentrations of serotonin to which the right side of the heart is subjected. This occurs by virtue of its receiving almost directly the output of the argentaffine cells in the metastatic carcinoid tissue of the liver via the hepatic vein and inferior vena cava. That these lesions practically never occur on the left side of the heart is considered to be due to removal of the serotonin in the lungs by means of the enzyme mono-amine oxidase, which is found in the pulmonary vascular bed and which has been shown to inactivate the 5-OH tryptamine. 7

In the case under consideration, the tricuspid insufficiency was thought to be responsible in great measure for the anasarca
and for the considerable reduction in cardiac output. The diastolic gradient existing between the right atrium and right ventricle was not considered to be great enough to justify the additional diagnosis of tricuspid stenosis. The cardiac catheterization data likewise failed to establish the presence of any lesion affecting the pulmonary valves.

As mentioned earlier, pulmonary hypertension has only rarely been found in the comparatively few cases in the literature in which cardiac catheterization has been performed. Unfortunately, in the 2 cases in which pulmonary hypertension was found, the actual level of the pulmonary artery pressure was not given. It is somewhat surprising that pulmonary hypertension has not been a prominent finding, in view of the very striking effect of infused serotonin on the pulmonary artery pressure of experimental animals. In our case, a minimal, although definite, elevation of the pulmonary artery pressure was found. Many explanations are actually available for the apparent paradox of a normal, or only minimally elevated, pulmonary artery pressure in the presence of a substance, 5-hydroxytryptamine, which has been shown to have such propensities for elevating the pulmonary artery pressure under experimental conditions. The most obvious explanation would be the circumstance that the cardiac catheterization was not performed during a "paroxysm" comparable to the periodic flush these patients often have during which presumably a large amount of 5-OH tryptamine is liberated into the circulation. Assuming, however, that this is not the factor, other theoretical considerations can be entertained. The nature of the right-sided cardiac lesions in the carcinoid syndrome, i.e., tricuspid insufficiency as in our case, or tricuspid stenosis and pulmonary stenosis, would of themselves tend to lower pulmonary artery pressure. The reduced cardiac output, whether primary or secondary to the anatomic lesion, would likewise operate in the same direction with respect to the pulmonary artery pressure. In contrast to acute experiments with serotonin, the patient with long-standing increase in circulating serotonin might be expected to have developed adaptive mechanisms, either reflex or enzymatic in nature, for more effective neutralization of the pulmonary hypertensive effect of the serotonin.

The esophageal pressure, as noted in table 1, was slightly elevated in our case, thus indicating a corresponding increase in the intrathoracic or intrapleural pressure. This was considered to reflect an element of bronchospasm with consequent elevation of the intra-alveolar pressure. That bronchospasm proved to be of clinical significance in
Fig. 2. Slow paper speed showing, from above down, pulmonary artery, brachial artery, and esophageal pressures. Control values are shown followed by those obtained after occlusion of the right main pulmonary artery. Reserpine was infused with the cuff still inflated so that these values must be compared with those immediately preceding.

This case was illustrated by the difficulty experienced by the patient during surgery when expiratory obstruction and air trapping developed. As is well recognized, increased bronchomotor tone is an important and frequent manifestation of the carcinoid syndrome and is likewise considered to result from the smooth muscle stimulating properties of serotonin. It is suggested that the slight elevation in pulmonary artery pressure in our patient was secondary to bronchospasm, either from circulating serotonin or mild emphysema.

Temporary unilateral pulmonary artery occlusion was included in our hemodynamic studies for the purpose of assessing the possible element of intrinsic pulmonary vascular disease in the carcinoid cardiovascular syndrome. The technic utilized and the results obtained in normal individuals with this
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method have been described in detail elsewhere. As noted in table 1 and figure 2, occlusion of the right main pulmonary artery with an inflatable balloon effected a rise in the main pulmonary artery pressure which was comparatively small and fell within the standards considered to be normal. This result provides evidence for the conclusion that no significant degree of involvement of the pulmonary vasculature existed in this case. Although numerous necropsy studies have been reported in cases of carcinoid cardiovascular syndrome, no description of the pulmonary vessels in this disease has come to our attention. In view of the profound fibroplastic effect of serotonin, presumably on the endocardium of the right atrium and ventricle, and the tricuspid and pulmonary valves, it appeared reasonable to speculate as to the probability of intimal proliferative changes in the pulmonary artery and its branches. However, in view of the normal response to unilateral pulmonary artery occlusion, it would seem highly doubtful that any degree of fixed pulmonary resistance, based on sclerotic changes in the pulmonary vasculature, existed.

Numerous pharmacologic agents have been described as antagonists to serotonin such as yohimbine, ergot, chlorpromazine, reserpine, atropine, and diphenylhydramine. However, the only preparation that has ever been shown to have any clinical salutary effect on the symptoms of carcinoid is rauwolfia. With reserpine infusion, a definite lowering of the pulmonary artery pressure ensued. This we considered to be significant inasmuch as no concomitant change in the brachial artery pressure occurred during the period of observation. It should be mentioned that approximately 1 hour after the administration of reserpine, the systemic pressure fell. The temporal response to reserpine was therefore quite different in the pulmonary and systemic circuits, suggesting a different mechanism of action in these circuits and supporting the concept that serotonin is inactivated in the lung.

Summary
A case of malignant carcinoid metastatic to the liver with the typical features of the carcinoid cardiovascular syndrome has been presented. Hemodynamic data obtained at cardiac catheterization indicated the presence of tricuspid insufficiency, low cardiac output, and slight pulmonary hypertension. Unilateral pulmonary artery occlusion studies were reported that suggest the absence of intrinsic pulmonary vascular disease in this syndrome. The paradox of infrequent instances of significant pulmonary hypertension in the presence of serotonin in the reported cases of carcinoid cardiovascular syndrome was discussed. The effect of reserpine on pulmonary artery pressure was reported.

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Summario in Interlingua
Es presentate un caso de maligne metastase carcinoide al hepat, exhibente le aspectos typic de carcinoide syndrome cardiovascular. Datos hemodynamic obtenite per catheterismo cardiac indicava le presentia de insufficientia tricuspidal, basse valores del rendimento cardiae, e leve grades de hypertension pulmonar. Studios a occlusion unilateral de arteria pulmonar suggestione le abenteia de intrinsec morbo pulmono-vascular in iste syndrome. Es discutite le paradoxo del infrequentia de significative grades de hypertension pulmonar in le presentia de serotonin in le reportate casos de carcinoide syndrome cardiovascular.

References


SCIENCE AND FEELING
J. Arthur Thomson
British: professor of natural history, editor and author; 1861-1933

Truly, science as science is unemotional and impersonal, and its analytic, atomizing, or anatomizing methods are apt, in their matter-of-factness, to seem antagonistic to artistic unities and poetical interpretations. But here must be learned the lesson of patience and openmindedness, and here the limitations of science must be borne in mind. The poetry of the men of feeling must not contradict the formulations of the man of science, but they are speaking different languages, and we may know by feeling some aspect of reality which eludes us in scientific analysis. Our delight in fine scenery is not less real than our knowledge of the geology. Both are pathways to reality. When science makes minor mysteries disappear, greater mysteries stand confessed. For one object of delight whose emotional value science has inevitably lessened—as Newton damaged the rainbow for Keats—science gives back double. Science widens and clears the emotional window. There are great vistas to which science alone can lead, and they make for elevation of mind.—The Outline of Science, Vol. 4, p. 1165. From Great Companions, Readings on the Meaning and Conduct of Life from Ancient and Modern Sources. Vol. I, Boston, The Beacon Press, 1952.
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