The Distribution of Extremity Blood Flow before and after Vagectomy in a Patient with Hypertrophic Pulmonary Osteoarthropathy*

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A patient with hypertrophic pulmonary osteoarthropathy associated with adenocarcinoma of the left upper lobe was studied before and after suprahilar vagectomy by arm and lung scans following left brachial artery injection of labelled albumin microspheres, digital plethysmography and forearm arterial oxygen differences. Preoperatively, the distribution of microspheres to the extremity beyond the level of the skeletal proliferative changes was decreased and a large portion of the microspheres bypassed the microcirculation of the extremity and appeared on the lung scan. After vagectomy, the distribution of microspheres to the hand was improved and few microspheres reached the lungs. In addition, the forearm arteriovenous oxygen difference increased following vagectomy without significant changes in digital flow. These studies suggest that the increased blood flow in extremities with hypertrophic pulmonary osteoarthropathy results from the development of arteriovenous shunts and that these shunts close following vagectomy.

Around 1890, the independent observations of Marie1 and Bamberger2 provided the basis for the recognition of hypertrophic pulmonary osteoarthropathy as a distinct clinical entity. These authors identified subperiosteal new bone formation in the long bones of involved extremities to be the pathologic lesion underlying the clinical manifestations of swelling, pain and tenderness. In 1915, Locke3 linked clubbing of the fingers to the arthralgic symptoms and skeletal proliferative changes as a triad. Unfortunately, the subsequent medical literature has frequently failed to make the distinction between simple clubbing of the fingers and hypertrophic pulmonary osteoarthropathy so that these two conditions have become inseparable in the minds of many if not most physicians. While hypertrophic pulmonary osteoarthropathy is nearly always associated with clubbing of the fingers, the latter usually occurs separately. Although the distinction between the two conditions may eventually be shown to represent only a difference in the degree of expression of a common etiologic factor, it is none the less important clinically. Unlike clubbing, which in itself is innocuous, hypertrophic pulmonary osteoarthropathy causes disabling pain and is nearly always associated with an intrathoracic malignancy, whose detection the skeletal symptoms may proceed by years.4

The nature and cause of the increased extremity blood flow which seems to be an important part of hypertrophic pulmonary osteoarthropathy remains uncertain. However suprahilar vagectomy has been shown to result in a prompt reduction in both extremity pain and blood flow.5

In a patient with hypertrophic pulmonary osteoarthropathy presented in this report, differences were demonstrated in both the distribution of regional blood flow and the degree of arteriovenous shunting in an involved extremity before and after vagectomy.

Case Report

A 50-year-old Negro man was admitted to the medical service of The Johns Hopkins Hospital with the chief complaint of "arthritis" of 17 months' duration. At that time, the patient discovered that his legs were swollen "to twice their normal size." Several weeks later he began to experience progressive discomfort and stiffness in the joints of

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This study was supported in part by United States Public Health grant GM10548.

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both arms and legs. He consulted several physicians and was treated for "heart trouble," a "kidney disorder," and "rheumatoid arthritis" without significant relief. Six months prior to admission, he began to lose weight and develop tender swelling of both breasts. His condition deteriorated to the point where he became totally bedridden and developed three sacral decubiti which precipitated his admission to The Johns Hopkins Hospital. He had no respiratory symptoms until two weeks before his admission when he developed left-upper chest and shoulder pain which was aggravated by deep breathing and movement.

On physical examination, his temperature was 100°F, and he appeared both acutely and chronically ill with marked wasting of the muscles and subcutaneous tissues. There was tender, bilateral gynecomastia measuring 5 cm in diameter. Over the left upper lung field, there was dullness to percussion, poorly transmitted breath sounds and pectoriloquy. The lower border of the liver was palpated four fingerbreadths below the right costal margin in the midclavicular line. Over the sacrum, there were three decubitus ulcers. The range of motion of all joints of both upper and lower extremities was limited by pain. The skin was finely textured and warm and there was moderate nonpitting edema over the lower third of the arms and legs. The bones in these areas felt thickened and were tender to palpation. Signs of moderate effusion were present in both knee joints. The fingers and toes showed marked clubbing.

The admission hematocrit was 32 percent. Total bilirubin was 0.3 mg percent, alkaline phosphatase 11.1 King-Armstrong units, sulfobromophthalein (BSP) retention less than 3 percent, and serum glutamic oxaloacetic transamine (SGOT), 25 units. Liver scan revealed enlargement but no focal defects. Total serum protein was 5.9 gm percent; albumin, 2.3 gm percent; and globulin, 3.6 gm percent with an increased alpha fraction. The chest x-ray film (Fig 1) showed a large left upper lobe infiltrate suggestive of neoplasm. No bony metastases were seen, but skeletal films of the arms and legs revealed extensive subperiosteal new bone formation characteristic of hypertrophic pulmonary osteoarthropathy (Fig 2). Bronchoscopy revealed a polypoid lesion partly occluding the left upper lobe orifice, biopsy of which was interpreted as a moderately well-differentiated adenocarcinoma. Sputum cytology revealed anaplastic cells. Result of scalene node biopsy was negative.

Five hundred microcuries \textsuperscript{113}I indium labelled albumin microspheres of $50 \pm 10$ micron diameter were injected into the left brachial artery 15 cm above the elbow. Subsequent scans of both left arm and lungs are shown in Figure 3A. These indicated that relatively few microspheres were trapped in the capillaries of the hand and fingers and that a significantly large portion of the microspheres had passed through the microcirculation of the extremity to become lodged in the lungs. The oxygen difference between blood samples withdrawn from the brachial artery and the antecubital vein at the time of this study was 2.8 volumes percent.

On completion of these studies, the patient was operated upon. After preliminary abdominal exploration failed to reveal liver metastases, a left lateral thoracotomy was carried out through the bed of the excised fifth rib. Exploratory dissection revealed extensive mediastinal node involvement which precluded a curative resection. Because of anticipated technical difficulties, palliative resection was declined in favor of vagectomy. Strain gauge plethysmography of the left middle finger was performed intraoperatively. This suggested that section of the vago nerve above the pulmonary hilus resulted in little immediate change in digital blood flow (Fig 4).

The patient had a difficult postoperative course initially, marked by atelectasis and recurrent pleural effusions. In the second postoperative week, scans of the left arm and lungs were repeated after injection of another 500 \textmu c of labelled microspheres into the left brachial artery. These showed

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{image1.png}
\caption{Chest x-ray film showing large left upper lobe infiltrate.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{image2.png}
\caption{X-ray film of left arm and hand revealing extensive hypertrophic pulmonary osteoarthropathy. The subperiosteal new bone formation is most marked in the distal ulna and radius.}
\end{figure}

\textbf{DIS. CHEST, VOL. 56, NO. 1, JULY 1969}

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improved distribution of radioactivity to the hands and fingers, but minimal activity over the lungs (Fig 3 B). The arteriovenous oxygen difference at this time was 3.8 volumes percent.

During the initial postoperative period, the patient was almost completely relieved of his extremity pain. However, by the third week, there was a return of mild skeletal discomfort which was readily controlled by the administration of propoxyphene hydrochloride (Darvon). At the end of the third postoperative week, the patient developed increasing respiratory distress and died.

FIGURE 3. Scans of the left arm and lungs following injection of 500 µc. of 113m-indium labelled albumin microspheres of 50 ± 10 micron diameter are compared (A) before and (B) after vagectomy. Note the relatively sparse activity in the hand and fingers and high activity in the lungs before vagectomy and the reversal of these features following vagectomy.

DISCUSSION

The major pathologic feature of hypertrophic pulmonary osteoarthropathy is subperiosteal new bone formation which takes place cylindrically around the distal ends of the long bones of the extremities and is characterized by a vascular, edematous osteoid matrix. The areas of skeletal involvement are tender and usually associated with a deep-seated, aching or burning pain which is aggravated by dependency. The connective tissue overlying the periosteum in these areas is also marked by proliferative changes and contains numerous large, thick-walled vascular channels which histologically and radiographically appear to be arteriovenous anastomoses. The overlying skin is usually finely textured and warm and proliferative changes in the subcutaneous tissues result in a diffuse, firm nonpitting edema, which adds to the cylindrical enlargement of the distal arms and legs. Another feature is chronic synovitis, most frequently involving the knees, which is characterized by thickening of the extra-articular connective tissue, joint effusions and even degenerative changes of the articular cartilages. Arthralgia, stiffness and limitation of the motion of the involved joints may so dominate the clinical picture that the patient may be treated for “arthritis” for months before the true nature of the underlying condition becomes evident.

There is evidence to suggest that increased blood flow through involved extremities is an invariable accompaniment of hypertrophic pulmonary osteoarthropathy and may play a role in the development of the above pathologic features. This increased blood flow has been usually demonstrated by plethysmographic techniques. The observations of Mendlowitz are particularly significant since simple clubbing was differentiated from hypertrophic pulmonary osteoarthropathy. In 25 patients with simple clubbing, he found the average digital flow to be significantly increased over that of 23 control subjects, but none of the three patients studied with hypertrophic pulmonary osteoarthropathy had digital flows greater than the mean of the controls. Holling and co-workers studied extremity blood flow in three patients with hypertrophic pulmonary

FIGURE 4. Intra-operative strain gauge plethysmographic recordings of the left middle finger before and after supraboral section of the left vagus showing little immediate change in digital flow.
ostearthropathy using mercury-in-rubber strain gauge plethysmography. At the level of the thigh, upper and mid calf and ankle, the recorded blood flow was several times greater than that in 25 control subjects. Unfortunately digital flows were not included in this comparison. Comparison between changes in flow at the knee and at the mid calf levels in response to iontophoresis with adrenalin suggested to these authors that the increased flow was distributed to skin, connective tissue or bone rather than to muscle.

Earlier attempts to study arteriovenous shunting with arterial injections of \(^{131}\)I labelled macro-aggregated albumin (MAA) have not been satisfactory because of variations in the size and shape of the particles,\(^{10}\) but no difference between the distribution of such particles in the upper extremities of normal persons and in patients with simple clubbing could be demonstrated.\(^{11}\) The particles used in this study possess several features which make them more suitable. They consist of more uniform 50 ± 10 micron microspheres of human serum albumin. They are nonallergenic, metabolizable and have no significant toxic or hemodynamic effects in the dosage used. Immediately prior to administration, the microspheres are labelled with short lived \(^{118}\)In-dium. Metabolism of the microspheres allows the radioactive label to be cleared from the circulation within several hours. The relative distribution of such microspheres is dependent upon the arterial flow to the region which the injected artery perfuses. A scan of the region reveals the distribution of injected microspheres trapped in the microcirculation. The portion of injected microspheres that bypass the capillary circulation, i.e., those passing through vascular channels larger than 40 microns, lodge in the pulmonary capillary bed. Thus lung scanning serves as an indication of arteriovenous shunting in the region of distribution of the injected artery.

In the case reported, the preoperative scan of the left arm following injection of labelled microspheres into the brachial artery demonstrated that relatively few particles reached, or were trapped in, the microcirculation of the hands. Concomitant lung scan indicated that a significant proportion of these microspheres passed through arteriovenous anastomoses in the limb to reach the lungs. There are two alternative explanations for these observations: (1) The arteriovenous shunts were mainly present in the hands and fingers and the capillary circulation was bypassed by most of the microspheres distributed to this area. (2) The arteriovenous shunts were located proximally in the area most involved with hypertrophic pulmonary osteoarthropathy, i.e., the distal radius and ulna, and that shunting at this level resulted in decreased flow to distal capillary beds. These possibilities are not mutually exclusive. However, the digital flow studies of Mendlowitz would favor the second explanation as the major contributing factor since, in contrast to simple clubbing, digital flow in hypertrophic pulmonary osteoarthropathy was found to be normal or decreased.

Comparative studies before and after vagectomy support this concept. The digital strain gauge plethysmographic studies in our patient revealed little immediate change in total flow after vagectomy. It is possible that the effects of general anesthesia, thoracotomy, and prior manipulation of hilar structures may have obscured a change. However, Holling\(^{9}\) also observed that while flow at the level of the mid calf decreased markedly after vagectomy, digital flow did not change significantly. The postoperative microsphere study indicated that the relative distribution of nutrient or capillary blood flow of the hands and fingers was significantly improved following vagectomy. This combination of improved capillary flow in the hand in the absence of improved total blood flow as measured by digital plethysmography is consistent with the closing of arteriovenous shunts. Comparative lung scans after microsphere injection into the brachial artery indicated that a marked degree of arteriovenous shunting existed preoperatively and that this essentially disappeared following vagectomy. There was over 20 times as much activity reaching the lungs through shunts before vagectomy compared to that after vagectomy. This would account for the increase in the arteriovenous oxygen difference across the arm from 2.8 to 3.8 volumes percent following vagectomy, a phenomenon previously observed by Semple and McCluskie.\(^{12}\)

Our studies do not answer the question of the primary etiologic factor underlying the skeletal and vascular abnormalities which constitute hypertrophic pulmonary osteoarthropathy. The current state of knowledge on this subject has been reviewed by Holling.\(^{13}\) However the characteristic pattern of regional blood flow distribution and arteriovenous shunting which these studies have demonstrated in hypertrophic pulmonary osteoarthropathy as well as the reversal of these changes by vagectomy, may contribute to the eventual identification of the underlying mechanism.

**Conclusion**

The distribution of blood flow within the arm and hand of a patient with hypertrophic pulmonary osteoarthropathy was studied before and after suprahilar vagectomy. After the injection of \(^{118}\)Indium-

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labelled albumin microspheres of 50 ± 10 micron diameter into the left brachial artery, arm, hand and lung scans were performed together with arteriovenous oxygen differences and digital plethysmography. Together with the findings of other investigators, our studies suggest that: (1) The major portion of the increase in extremity blood flow associated with hypertrophic pulmonary osteoarthropathy passes through arteriovenous anastomoses. (2) These anastomoses are located mainly in the areas of the characteristic proliferative changes of bone and connective tissue and that they may "steal" flow from distal capillary beds. (3) Vagotomy appeared to reduce this arteriovenous shunting and improve distribution of blood flow to distal capillary beds.

References

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Predilection of the Right Hemithorax for Disease

Composite experience shows that certain pathologic conditions occur with higher frequency on the right side than on the left side of the chest. This holds true even when direct spread of the disease, such as amebiasis, hydatid disease, from the liver is discounted. The same consideration applies to the higher right lateralization of chylothorax which is attributable to the fact that the thoracic duct in the chest is to the right of the vertebral column in greater part of its course. Middle lobe syndrome is thought to be due to lack of collateral ventilation through pores of Kohn rather than to bronchial obstruction by enlarged lymph nodes. In adults as well as in children, pneumonia and lung abscess are seen more often on the right side than on the left. In sarcoïdosis of the lung which is preceded by hilar lymph node involvement, pulmonary pathology is more pronounced on the right side. The same holds true of sarcoïd enlargement of the tracheobronchial and paratracheal lymph nodes. Primary bronchogenic carcinoma develops in the right lung in 56–63 per cent of all cases. It is assumed to be the result of deposition of larger amounts of carcinogens in this location as compared to the opposite side. The incidence of pulmonary infarction is substantially higher on the right side than on the left. In congestive heart failure, unilateral pleural effusion is more likely to be found in the right pleural cavity. Almost all instances of interlobar effusion ("vanishing tumor of the lung," "phantom lung tumor") are observed on the right side. In patients with Meigs' syndrome, hydrothorax is detectable in the right hemithorax in 70 per cent of cases, in the left hemithorax in 10 per cent and bilaterally in 20 per cent. As to the reason for this predilection, the following anatomic, structural, circulatory and functional factors are to be considered. The right lung is larger than the left lung, the volume ratio being 53–56 per cent of the total lung volume for the right lung and 44–47 per cent for the left lung. The right main bronchus is more perpendicular than the left. As to pulmonary circulation, about 55 per cent of the blood volume from the right ventricle flows through the right lung. The intrapleural pressure is somewhat more negative on the right side than on the left. Concerning pulmonary function, authoritative reports show that as percentage of the total of both lungs the following data apply to the right lung: vital capacity 52–54 per cent, tidal volume 53–57 per cent, minute volume 54–55 per cent.

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