Nuclear Medicine in Respiratory Disease

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In this presentation I would like to make two points clear that are essential to the understanding of nuclear medicine in respiratory disease. One is about interrelationship between regional perfusion and ventilation in the lungs which is the basis of gas-exchange or respiration, and the other is regarding evaluation of non-respiratory lung function, especially of mucociliary clearance mechanism by using nuclear medicine as a tool.

I. Interrelationship between regional ventilation and regional perfurion

1) Ventilation subordinates perfusion

Perfusion changes in the lungs are seen not only in patients with pulmonary vascular diseases and parenchymal diseases in general, but also in patients with airway diseases. Pulmonary parenchymal diseases are usually diagnosed with the help of conventional chest x-rays but diagnoses of both pulmonary vascular and airways disease are often elusive radiologically.

If pulmonary vascular lumen is occluded or made narrower, perfusion distal to the vascular lesion is naturally absent or diminished. Pulmonary embolism and stenosis are the cases. Perfusion abnormalities in the absence of vascular disorders are also well know; bronchostenosis, bronchiectasis, obstructive airway, diseases, etc. Unless there are distinct abnormalities on chest x-rays, differentiation between pulmonary vascular diseases and airways disease is greatly facilitated by nuclear medicine techniques.

The principle here is that perfusion is always subordinate to ventilatory changes except in the early phase of perfusion changes when perfusion dominates ventilation only transiently as will be described later.

Since von Euler and Liljestrand's experiment, hypoxia has been known to cause pulmonary hypertension due to hypoxic vasoconstriction[1]. This phenomenon is nowadays studied by using perfusion lung imaging techniques.

When the right and left lungs are given different gases for inhalation through a Carlens tube, the lung which inhales a gas of lower oxygen concentration shows a diminished perfusion[2]. When ventilation of one whole lung is suspended instead, perfusion also decreases rapidly as soon as ventilation is interrupted and it reaches a plateau level in 3-5

minutes. This phenomenon is observed not only in the neurologically intact lung but also in the denervated reimplanted lung[3]. Thus it seems certain that either hypoxic gas itself or secondarily induced alveolar hypoxia (or possibly hypercapnia) might be a factor in controlling regional perfusion.

To further this point, the right upper lobe of either the normal dog or the dog with reimplanted right lung was artificially ventilated through a balloon catheter with gas mixtures of various oxygen and carbon dioxide concentrations to induce different alveolar oxygen and carbon dioxide tension, while the rest of the lungs maintained ambient air breathing[4,5]. Regional perfusion was diminished when the lobe was artificially ventilated with hypoxic gases, indicating the presence of regional hypoxic vasoconstiction but regional perfusion increased with hyperoxic gases, indicating hyperoxic recruitment of the pulmonary vascular beds and/or hyperoxic vasodilation. Regional perfusion responses to various alveolar oxygen tensions were similar in the normal and the denervated right upper lobes. Integrity of the nervous system doesn't seem to be required so long as the pulmonary vascular responses to alveolar oxygen tensions are concerned[5]. Pulmonary vascular beds seem to sense the regional alveolar oxygen tensions via some apparatus to adjust regional perfusion. In this sense, an "oxygen sensing device" could be present in the interstitial space in the vicinity of the pulmonary vascular beds. Alveolar hypercapnia, on the other hand, has little effect on regional perfusion except under concurrent alveolar hyperoxia where perfusion increment is somewhat curtailed by alveolar hypercapnia[6]. Hypoxic vasoconstriction is abolished by isoproternol but propranolol can antagonize the action of isoproterenol in the hypoxic region of the lung[7].

Therefore it has become certain that alvelar hypoxia plays an important role to regulate regional perfusion distribution. Clinically regional hypoventilation from any cause can induce corresponding perfusion changes, but not vice versa.

2) Perfusion's transient dominance over regional ventilation

By examining patients with suspected pulmonary embolism we found that ventilation could be intact in non-perfused or embolic lung regions[8]. In other words, if we find normal or near-normal ventilation in the region of absent perfusion, we can tell that the underlying pathology migh tbe pulmonary vascular in origin. One might ask why, because hypoventilation associated with vascular occlusion is well known as was shown by Severinghaus and others[9].

To fill the gap, experiments have been programmend to study ventilation changes from immediately after pulmonary arterial occlusion for many hours and days. We have found that regional ventilation is indeed diminished immediately after vascular occlusion, but that diminution lasts for less than 6 hours at the longest in the dog with a return of normal regional ventilation thereafter. Hyoventilation was concluded to be due to a transient bronchoconstriction induced by a sudden loss of pulmonary arterial perfusion. Unless complications such as pulmonary edema or pneumonia developed, normal ventilation returned regionally in less than 6 hours following perfusion was stopped. The reason why there was a gap between our clinical finding and laboratory data was attributed to the difference

in the phase of the same process of vascular occlusion when studies were made. We studied patients at least several hours after pulmonary embolism developed, whereas laboratory data was most likery obtained almost immediately after vascular occlusion was made.

Anyway this is one of the basic rationalizations of the present day "ventilation and perfusion lung imagings" in respiratory nuclear medicine.

II. Non-respiratory lung function

The lung's primary role as an exchanger of oxygen and carbon dioxide has overshadowed the other aspect of lung function which has little direct relation to respiration but is important to maintain respiration as smooth as possible.

We call this aspect of lung function non-respiratory lung function. Mucociliary clearance meahanism is one example of this non-respiratory lung function. Little attention has been paid to its clinical evaluation so far. We have used sequential imaging technique following radioaerosol inhalation to assess mucociliary clearance mechanism[11] but it was nothing but a qualitative estimation of the clearance. Instead of aerosol inhalation, we placed a radioactive droplet at the carina of the dog, and made a frequent imaging of the tracer and found that a tracer was transported over the normal tracheal mucosa at the average velocity of 12 mm/min. When the dogs wers exposed to cigarette smoke, the tracheal transport velocity was slowed down as the number of cigarettes smoked. increased. This study prompted us to make a more frequent measurement of radioactivity following aerosol inhalation so that we could see movement of inhaled aerosol in the lungs and we finally arrived at the idea of "radioaerosol inhalation lung cine-scintigraphy" or "aerosol cine-scintigraphy" in short[13][14]. This method consists of inhalation of ultrasonically generated ^{99m}Tc-albumin aerosol (mean diameter 3.73 μ geometric standard deviation 1.73[15] and a continuous measurement of radioactivity over the thorax for 30 to 120 min with a gamma camera connected to a computer to generate serial 10 sec images and these images were displayed at 18 images per second. Thus the actual motion of deposited aerosol in the lungs by inhalation could be visualized as it was transported or cleared from the lungs by mucociliary clearance mechanism or simply by coughing or hawking. Two kinds of time activity curves were also retrieved from the computer after selecting appropriate regions of interest by a light pen. One was a regional clearance curve indicative of actual clearance from the lung region selected and the other a transit curve to evaluate transport velocity between the two spots indicated by the light pen. In normals clearance was always cephalad in direction and continuous and steady in time sequence. Its velocity over the trachea was 8-12 mm/min. The cephalad steady transport was disturbed in pathological conditions. In bronchogenic carcinoma transport was stopped or slowed at the site of cancer infiltration. In obstructive airways disease not only slowing but also stasis, retrograde migration or even going astray int the opposite bronchus was observed. In bronchiectasis slow clearance was seen in the ipsilateral lung. In immotile-cilia syndrome spontaneous clearance didn't occur. Coughing and hawking played an important role in clearance in disease status. They were often only propellant factors for clearance.

Aerosol cine-scintigraphy appears to offer an extremely useful methodology to the study of mucociliary clearance mechanism in health and disease in man.

Nuclear medicine has offered valuable and indispensable methodology to medical science in general and the welfare of mankind and respiratory medicine is .no exception in benefitting from it. The basic concepts of interrelationship between regional ventilation and regional perfusion have evolved from the application of this methodology since nuclear medicine was applied to clinical and laboratory studies in the field of respiratory medicine.

There has been no clinically available method to study non-respiratory lung function so far, but this very nuclear medicine has enabled us to have an insight into mucociliary clearance mechanism of the lungs by revealing what is actually taking place in the lungs.

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