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13th Professor A.S. Paintal Memorial Oration

Cardiac Asthma: J to RAR and Beyond

It is indeed a great honour for me to deliver the 13th Professor A.S. Paintal Memorial Oration. While standing here I look back at the luminaries who had delivered this oration previously. To be bracketed along with them, I consider myself very fortunate. For selecting me, I express my gratitude to Professor Rakesh Bhatnagar, Chairman, Governing Body, V.P. Chest Institute, Professor Arunabha Ray, Director of the Institute and my former colleagues.

Cardiac Asthma

In acute left ventricular dysfunction, there is an increase in left atrial pressure which obstructs pulmonary venous return. As a consequence, there is an increase in pulmonary venous pressure. In the airways and lung, there is an extensive communication between the pulmonary and bronchial circulations, especially in the distal bronchi and bronchioles, and in the gas-exchanging regions of the lung. Hence, the increase in pulmonary venous pressure will be transmitted to both the bronchial venules and the pulmonary venules, and the capillaries at the alveolar level. Fluid tends to leak into the extra-vascular space and there is pulmonary venous congestion. There is a natural tendency for the fluid to move away from the alveolar space to the proximal airways due to the presence of a pressure gradient between these two regions. Thus, in acute left ventricular dysfunction, fluid accumulates in the proximal airways. Distended pulmonary veins are often seen in the chest radiographs of patients with left ventricular dysfunction. When the condition is permitted to progress, it precipitates as pulmonary oedema, a clinical condition in which fluid accumulates in the alveoli.[1] The critical left atrial pressure at which pulmonary oedema occurs is usually greater than 20 mmHg.[2]

During pulmonary venous congestion, patients usually complain of "breathlessness" or "shortness of breath". There is respiratory distress resulting in "dyspnoea". "Wheeze" occurs secondary to an increase in bronchomotor tone and the term "cardiac asthma" is used to denote this condition.[3] Cough is another prominent symptom seen in these patients. As the disease state progresses to frank pulmonary oedema, the dyspnoea worsens and the patients produce considerable quantities of blood-stained sputum. Thus, the initiating factor for these respiratory symptoms appears to be the accumulation of fluid in the pulmonary extra-vascular space, especially in the proximal airways.

Experimental studies have been performed to address the mechanisms responsible for the above-mentioned symptoms. The main focus of these studies has been to investigate: (i) the changes in work of breathing due to fluid accumulation in the airways/lung and (ii) the reflexes that occur due to activation of sensory receptors in the airways/lung. The inspiratory muscles and chest wall afferents and afferents from arterial chemoreceptors do contribute to the respiratory symptoms associated with pulmonary venous congestion/oedema. However, their roles will not be presented here. Instead, I will be concentrating on the role of pulmonary vagal sensory receptors, especially the juxta-pulmonary capillary (type J) receptors and airway rapidly adapting receptors (RARs) in the reflexes, namely tachypnoea, bronchoconstriction, airway secretion and cough reported in patients with left ventricular dysfunction.

Paintal's Type J Receptors

In 1954, while working at V.P. Chest Institute, Paintal[5] identified certain vagal sensory receptors which responded specifically to suction of air from the lungs. The conduction velocity measurements demonstrated that these were connected to non-myelinated afferents. He called them as "specific pulmonary deflation receptors".[4] Continuing his studies on these receptors, Paintal observed that specific deflation of the lungs was a weak stimulus to them. He reported that these were stimulated in 0.3 sec following insufflation of halothane and within 1.5 to 2.5 sec following the injection of phenyl diguanide into the pulmonary circulation. Administration of phenyl diguanide into the systemic circulation through the left atrium failed to activate them. Based upon these findings in cats, he proposed that these receptors must be located in the interstitial tissue between the pulmonary capillary and alveolus and called them as "**juxta-pulmonary capillary or type J receptors**".[5] Electron microscopic studies revealed the existence of sensory nerve endings in this region.[6] Further, Paintal observed that the type J receptors of cats were stimulated by occlusion of left atrio-ventricular junction/aorta, inhalation of chlorine gas and injection of alloxan into the right atrium. These results made him suggest that pulmonary congestion could be the natural stimulus for these receptors.[5] It is worth mentioning here that while making these observations, Paintal did not measure the left atrial pressure during occlusion of left atrio-ventricular junction/aorta. There is the possibility that the left

atrial pressure could have gone beyond 20 mmHg and caused pulmonary oedema. Inhalation of chlorine gas and injection of alloxan would have disrupted the anatomical integrity of the pulmonary vasculature – again resulting in pulmonary oedema. Nevertheless, the results lent strong evidence for the involvement of type J receptors in causing reflexes associated with pulmonary oedema.

While the type J receptors were stimulated by the right atrial injection of phenyl diguanide in cats, in the dog, and the monkey, these were activated by capsaicin.[7,8] In man, it was lobeline which stimulated them.[9] In all the species, type J receptor activation resulted in either tachypnoea or apnoea. Besides the respiratory responses, type J receptor stimulation in man caused certain sensations notably choking and pressure in the throat and upper chest.[10] Dry cough occurred following intensification of the sensations.[11] Majority of subjects who suffered from high altitude pulmonary oedema and in whom breathlessness was a major symptom, also reported to have similar sensations as observed with lobeline.[10] These reports reiterate the significance of type J receptors in generating reflex responses associated with pulmonary oedema. In the literature, the type J receptors are often termed as 'pulmonary C-fiber receptors'.

Experimental Method for Producing Pulmonary Venous Congestion/Oedema

In order to elucidate the reflex mechanisms that get activated during left ventricular dysfunction, it is essential to devise a technique that raises the pressure in the pulmonary veins, causes accumulation of fluid in the proximal airways initially, and later on, in the alveoli. Partial obstruction of the mitral valve is one condition that serves this purpose. In experimental animals, after anesthesia and thoracotomy, it can be produced by positioning a balloon in the left atrium through the left auricular appendage. Inflation of the balloon with small, fixed volumes of normal saline will cause partial obstruction of the mitral valve and raise the left atrial pressure in a controlled manner. A catheter can be inserted through the same opening for measurement of left atrial pressure.[12] The advantage of this technique are that left atrial pressure can be held constant at a desired level. It can be graded, maintained for a long duration and used for causing pulmonary venous congestion (mean left atrial pressure < 20 mmHg) or pulmonary oedema (mean left atrial pressure > 20 mmHg). Finally, it is reversible, i.e., on deflating the balloon, the left atrial pressure falls back to the basal value.

Airway Rapidly Adapting Receptors

The RARs are connected to myelinated vagal afferents and are generally believed to be located in the proximal airways. These are known as RARs as these give a high frequency response and adapt rapidly to a maintained hyperinflation of the lungs. These are stimulated by inhalation of irritant gases, such as ammonia and tussigenic agents, such as cigarette smoke. Their activation results in coughing. Hence, these are often referred to as "irritant" or "cough" receptors.

Even though the existence of these receptors was reported as early as 1946 by Knowlton and Larrabee[13], other than their significance in the cough response to airway irritants, not much attention was paid to their physiological significance. Since the natural stimulus for their activation was not known and since these responded to special situations, in one of his reviews Paintal dismissed them as a separate group of receptors and called them as a 'variant' of pulmonary stretch receptors. This conclusion was based upon the reasoning that there was considerable overlap of their properties with the pulmonary stretch receptors.

However, the experiments performed by me in collaboration with late Professor C.T. Kappagoda at the University of Alberta, Edmonton, Canada and University of California, Davis, USA and at V.P. Chest Institute, University of Delhi using the technique described above demonstrated that the RARs not only responded to fluid fluxes caused by left ventricular dysfunction, but also produced the associated respiratory reflexes.[14] These studies established firmly the pathophysiological significance of the RARs.

Responses of Rapidly Adapting Receptors to Acute Elevation of Left Atrial Pressure

In the anesthetised artificially ventilated and thoracotomised dog, the left atrial pressure was elevated by 10 mmHg by partial obstruction of the mitral valve using the method detailed above and it was held constant for 15 minutes. The responses of RARs were examined. It was observed that there was a significant stimulation of the RARs which started in the first minute of elevation of left atrial pressure and persisted for the entire 15 minutes suggesting that unlike their response (of rapid adaptation) to hyperinflation, these exhibited no evidence of adaptation. When the study was extended to pulmonary C-fiber (type J) receptors, no significant stimulation was observed.[15] Subsequent experiments in the dog[12], rabbit[16] and the monkey[17] revealed that the RARs could be stimulated even by mild increments in left atrial pressure of about 5 mmHg. Later on, it was observed that other manipulations which were aimed to increase the pulmonary extra-vascular fluid volume, such as plasmapheresis[18] and pulmonary lymphatic obstruction[12] also stimulated

the RARs significantly. As observed with left atrial pressure elevation, the stimulation of RARs was sustained. All these findings suggested that the natural stimulus for the RARs could be a fluid flux in the proximal airways.[1] They also revealed that the RARs should be strategically located to detect such fluid fluxes. The conventional view at that time was that the RARs were located in the epithelial and sub-epithelial layers of the mucosa of the proximal airways as these responded to inhalation of irritant chemicals. Based upon our findings, we proposed that that the RARs might also be located in close apposition to bronchial venules from where these could be stimulated by fluid fluxes.[1] Indeed, histological studies using electron microscope demonstrated the presence of presumptive RARs in the vicinity of bronchial venules.[19]

As mentioned earlier, in patients with pulmonary venous congestion, there is tachypnoea, wheeze, increased airway secretion, cough and dyspnoea. The immediate question that comes to our mind is whether RAR stimulation in this situation can give rise to these responses reflexly.

Reflexes Produced During Pulmonary Venous Congestion

Changes in bronchomotor tone and involvement of rapidly adapting receptors

In addition to pulmonary venous congestion, several pharmacological agents, such as histamine and prostaglandin derivatives activated the RARs. Along with RAR stimulation, these increased the bronchomotor tone also. It was proposed that a part of the increase in the bronchomotor tone was due to a reflex caused by the activation of RARs.[20]

In order to delineate the role of RARs in the "wheezing" reported in patients with left ventricular dysfunction, we carried out an investigation in the anesthetised, artificially ventilated and thoracotomised dog.[21] The change in the tone of a segment of posterior trachealis muscle (recorded by a tension transducer) to pulmonary venous congestion (mean left atrial pressure increased by 10 mmHg and kept constant for 5 minutes) was examined. Raising the left atrial pressure increased the trachealis muscle tension which was maintained for the whole 5 min. On relieving the left atrial pressure, the muscle tension returned to the basal level. Bilateral cooling of the cervical vagi to 8 °C abolished the response suggesting that the increase in tracheal tone was due to a reflex mediated by stimulation of receptors connected to myelinated vagal afferents. Cooling of the nerves to 6-8 °C is used as a technique to differentiate the responses mediated by the myelinated and non-myelinated afferents. If the response to a stimulus is abolished on cooling the nerve to 6-8 °C, it will establish that receptors connected to myelinated afferents are involved; if it is still present, it will prove that it is due to the activation of receptors connected to non-myelinated afferents.[22] Both RARs and pulmonary stretch receptors are connected to myelinated vagal fibers. Since the pulmonary stretch receptors cause bronchodilation, the study provided direct evidence that the RARs were involved in the respiratory wheeze associated with cardiac asthma.

Tachypnoea and involvement of rapidly adapting receptors

Until we started reporting our observations, the general belief had been that RAR stimulation resulted in augmented breaths. This response was considered as a protective reflex since collapse of the lungs stimulated the RARs[17] which in turn produced deep breaths to open up the closed alveoli. However, there had been some studies[20,23] which suggested that RAR stimulation could result in tachypnoea, especially during administration of chemicals, such as histamine and bradykinin. A preliminary report in cats suggested that tachypnoea resulted during pulmonary venous congestion also.[24]

In a detailed investigation in the dog, we provided convincing evidence that during pulmonary venous congestion produced by partial obstruction of the mitral valve (elevation of left atrial pressure by 5 mmHg), there was clearly tachypnoea.[25] This response was demonstrated in the spontaneously breathing as well as the artificially ventilated dogs. In the former, the intrapleural pressure was used as an index of respiration and in the latter, the activity from single phrenic units was recorded. In the spontaneously breathing dog, an increase in left atrial pressure by 5 mmHg increased the breathing rate with shortening of inspiratory and expiratory durations. In the artificially ventilated dog, this stimulus caused an increase in the number of phrenic bursts with an increase in total number of impulses/min. The responses in both the groups of dogs were abolished by cooling of the vagi to 8 °C suggesting that these were mediated by receptors connected to myelinated vagal afferents. Since pulmonary stretch receptor activation caused slowing of respiration, it was proposed that the reflex tachypnoea observed during pulmonary venous congestion was due to stimulation of the RARs.

Airway secretion and involvement of rapidly adapting receptors

To my knowledge, there has been no study which has examined the effect of pulmonary venous congestion on mucus secretion from the airways. However, there is enough evidence suggesting that RAR activation results in an increase in airway secretion. This

phenomenon was demonstrated in the dog after specific activation of the RARs by decreasing the pulmonary compliance. The secretion of mucus was estimated using the "tantalum hillock" method. There was an increase in the number of hillocks per unit time following activation of RAR by reducing the compliance. The response was blocked by cooling the vagi to 6 °C suggesting that the response was mediated by myelinated fibers presumably from RARs.[26] Another study demonstrated that the reflex increase in mucus secretion with cigarette smoke inhalation was attenuated after cooling the vagi to 7 °C. Since cigarette smoke inhalation stimulated the RARs,[17,27] it may be concluded that these are involved in this reflex. From these findings, it is extrapolated that the RARs contribute to increased mucus secretion during pulmonary venous congestion.

Cough and involvement of rapidly adapting receptors

In a systematic study on the location of RARs, it was demonstrated that there was a greater concentration of RARs at the carinal region and at the points of bronchial branchings.[28] These are the areas from where cough can be elicited easily by mechanical probing. Additionally, the nerve endings in the epithelial and sub-epithelial regions were shown to be connected to myelinated vagal afferents.[29,30] Further, the RARs could be stimulated by many tussigenic agents. For instance in a study performed in the monkey, we demonstrated that the RARs were stimulated by ammonia, cigarette smoke, alcohol, acetone and ether.[17] Vagal cooling studies demonstrated that cough produced by tussigenic stimuli could be abolished at a temperature which blocked the conduction in RAR afferents.[31] All these observations suggest that the cough reported in cardiac asthma could be due to RAR stimulation.

Conclusions

The nature of the responses of RARs and type J receptors to fluid fluxes in the lung caused by acute elevation of left atrial pressure is of interest. With mild increments in left atrial pressure (3-5 mmHg), there is a significant sustained activation of the RARs. There is a progressive increase in their activity as the left atrial pressure is increased to 10 mmHg and further to 25 mmHg. In contrast, the type J receptors are not activated significantly by the small elevations in left atrial pressure. However, these are clearly activated when the left atrial pressure exceeds 20 mmHg. These results indicate that the RARs are the first group of receptors that get activated during acute left ventricular dysfunction when the left atrial pressure is rising gradually. Hence, these are responsible for initiating the associated reflexes. Thereafter, at a stage when pulmonary oedema occurs, there is the recruitment of the type J receptors. Along with RARs, these would also contribute to the symptoms of left ventricular dysfunction.

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