

## PULMONARY VASCULAR REACTIVITY

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Bu makalemizde, homoral ve hücrel (otokoidal) uyarıların pulmoner vasküler tonus üzerine etkisi; erişkin pulmoner dolaşımında, normalde olan düşük vasküler tonusun nasıl düzenlendiği tartışılmakta ve artmış pulmoner vasküler direncin hipoksi, akciğer hasarı ve pulmoner mikrovasküler embolizm ile ilişkisi kısaca belirtilmektedir.

Pulmoner vaskülarite çok fazla konstrüktör ve dilatatör uyarılara yanıt vermektedir, fakat çeşitli fizyolojik ve patolojik önemli duyarsızlaştırıcılar bilinmemektedir. Diğer çalışmalarda, spesifik reseptör ve sentez blokerlerinin, normal pulmoner dolaşımında ve düşük vasküler tonusun sağlanmasında, dilatasyonda oynadığı rolün tanımlanması; ve kronik havayolu hipoksisi, akciğer hasarı

ve pulmoner mikroembolizm ile ilişkili pulmoner hipertansiyon gelişmesine, konstrüktör katkısının belirlenmesi gerekmektedir.

Kronik pulmoner hipertansiyon gelişiminde hipoksik pulmoner vazokontrüksiyon mekanizması bilinmemektedir, fakat damar hücrelerinde yapılan ve salgılanan bu mediyatörlerin vasküler tonus ve artmış vasküler direncin oluşumunda önemliliğinin belirlenmesi de açıkça zordur.

**Anahtar kelimeler:** Hipoksik pulmoner vazokontrüksiyon, Pulmoner arter basıncı, Pulmoner dolaşım

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### INTRODUCTION

The aim of the present paper is to provide a review of the pathophysiology of pulmonary vascular reactivity. This was our first scientific approach to this field, and to write up the present paper, we studied and largely used concepts reported by experts of the field<sup>1-4</sup>.

### Hypoxic Pulmonary Vasoconstriction

It is well known that the long-term living at mountains especially at high-altitude change the function of those system which are responsible for oxygenation of organisms. It is especially important for pulmonary circulation, ventilation and blood system<sup>5,6</sup>.

Hypoxia is probably the most potent vasoconstrictor stimulus in the pulmonary and bronchovascular circulation, causing an increase up to 50% of pulmonary vascular resistance for a decrease of alveolar oxygen tension below 50 mmHg. Hypoxic pulmonary vasoconstriction is considered a significant defence mecha-

nism for maintaining arterial PaO<sub>2</sub>, by limiting perfusion of areas of the lung that are poorly ventilated. The vasoconstrictor effect of hypoxia makes it possible to study pulmonary vascular reactivity and provides an interesting model for studying the mechanisms of responses of the pulmonary vessels to different stimuli<sup>7</sup>.

The increase in the pulmonary vascular resistance induced by hypoxia is associated with a decrease in pulmonary blood volume, with the opening of capillaries usually not perfused, and with flow diversion or pulmonary microembolism. Interestingly, pulmonary vasoconstriction may be induced both by decrease of oxygen concentration in the alveolar air, and by decrease in the concentration of oxygen in the perfusing blood, even if the effect of the later stimulus is much less compared to the former.

There is a negative correlation between the size of the hypoxic lung segment and size of flow diversion. The smaller is area of hypoxia the larger is the degree of diversion, and smaller is the increase in pulmonary vascular resistance.

The pulmonary vascular response to hypoxia may be pharmacologically manipulated. It is enhanced by almitrin, dopamine and propanalol, whereas it is

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reduced by calcium antagonists, teophylline, beta-stimulants, vasodilators and anaesthetic gases.

Cyclooxygenase inhibitors such as aspirin, indomethacin and non-steroid anti-inflammatory agents enhance the response to hypoxia suggesting that vasodilator prostaglandins may be involved in modulating pulmonary vascular tone.

Niarchos AP et al. have shown the significant decrease in both pulmonary and systemic vascular resistance after capoten treatment in the patients with pulmonary hypertension (PHT) secondary to collagen vascular disease<sup>8</sup>. The results of Batyraliev T et al. show benefits of capoten in patients with high-altitude PHT and concurrent systemic hypertension<sup>9</sup>. The possible explanation of salutary vasodilator action of capoten in high-altitude PHT is that increased plasma rennin activity as a result of hypoxia to some extent is inhibited by capoten treatment<sup>10</sup>.

### **Mechanisms of Hypoxic Pulmonary Vasoconstriction**

The mechanism of hypoxic pulmonary vasoconstriction is unknown. Interestingly, the stimulus (by hypoxia) applies at the alveolar-capillary structure and response (vasoconstriction) develops at the pre-capillary arteries, meaning that a transduction of the stimulus must be operating. Definitely the transduction of the signal is calcium dependent, because calcium antagonist inhibit hypoxic vasoconstriction, whereas agents that enhance calcium influx into lung cells increase hypoxic vasoconstriction<sup>11,12</sup>. Whether hypoxia acts directly on calcium translocation or a calcium dependent mediator is involved remains to be established. Several manipulations may modify the pulmonary vascular response to hypoxia: acidosis and inhibitors of oxidative phosphorylation enhance pulmonary vascular reactivity, whereas prostacyclin decreases pulmonary reactivity<sup>13,14,15</sup>.

A lot of discussion is still present about the mediators involved in constriction of the vascular smooth muscle. Catecholamines, histamine, serotonin, prostaglandin and thromboxane have been investigated, none of which seems to be essential. Leukotrienes C4 and D4 have a potent pulmonary vasoconstrictor effect, and have recently been proposed as the mediators mainly involved in PHT<sup>16</sup>.

Most investigators have reported a depressing effect of hypoxia on the rennin-angiotensin-aldosterone system (RAAS), particularly on angiotensin-converting-enzyme<sup>17,18,19</sup>. In contrast, there are reports

of increase in angiotensin-converting-enzyme after exposure to hypoxia<sup>20,21,22</sup>. Exogenous hypoxia can be said, to depress adrenal aldosterone synthesis, and this may occur despite the rise in plasma renin activity (PRA) observed in several studies<sup>20,21,22</sup>. The dissociation between PRA and aldosterone synthesis can be to a certain extent attributed to the effect of ANF, which shows increases during hypoxia<sup>10,23</sup>.

According to the data, obtained by Sordanbekova JK, et al among permanent high-altitude residents there are individuals with normal and elevated pulmonary arterial pressure<sup>23,24</sup>. These two group of patients have different sensitivity to hypoxia. These differences are obvious despite the practically identical level of hypoxic mixtures. Individuals with high sensitivity to hypoxia have elevated PPA and pulmonary vascular resistance even at rest, leading to the forming of stable form of high-altitude PHT. Highlanders with normal sensitivity and pulmonary arterial pressure have a hidden increase of pulmonary vascular resistance during hypoxia and have a conversational character and reflect the changes of neurohumoral regulation of pulmonary circulation.

Human studies indicate that subjects with high sensitivity to hypoxia respond not only by greater increase in P<sub>PA</sub> and ANF but also by lesser decreases in aldosterone and PRA levels, which may be related to high-altitude PHT<sup>21,22,23</sup>. Normo-responders respond to hypoxia by more pronounced decrease in PRA and aldosterone, and the rises in ANF levels play a certain role in the observed dissociation in RAAS.

### **The Pathophysiology of Pulmonary Hypertension**

An important characteristic of the pulmonary arterial bed is the heterogeneity of its vasoconstrictor response to a variety of stimuli. One example is high-altitude pulmonary edema, which results from acute PHT due to hypoxia, that occurs only in a small portion of the normal population<sup>25,26</sup>.

Although some patients with congenital heart disease and intracardiac shunts develop severe PHT, other with similar sized shunts do not<sup>27,28</sup>. Some patients with mitral stenosis develop extreme PHT, whereas, others with identical valve areas do not<sup>29</sup>. Understanding the heterogeneity of pulmonary vascular responses to this stimuli, than, explains why some patients with secondary PHT appear to have a level of PPA that is out of proportion to their underlying disease<sup>30</sup>. It also explains why only some

patients exposed aminorex ingestion developed PHT<sup>31</sup>. These patients have been referred to as "hyperreactors" with respect to pulmonary vasomotor responses. It is possible that many (if not all) of the people developing PHT are hyperreactors.

### Clinical Presentation

Pulmonary hypertension often presents with non-specific symptoms. The most common symptom of PHT is dyspnea. Although lung function is intrinsically normal, hyperventilation to compensate arterial hypoxemia is developed and the sensation of hyperventilation is interpreted as dyspnea by the patient. Initially, dyspnea is most notable during exercise, but as the disease progresses it occurs at rest.

Syncope may also be an early symptom of PHT. In most case it is effort related, believed due to a limited ability to increase cardiac output with activity. Some patients may present with syncope at rest. In these cases an arrhythmic cause for the syncope should be considered. A benign tachyarrhythmia could produce marked systemic hypotension due to reduced cardiac output.

Angina, which can be very typical in character, is also a common symptom in patients with PHT. It is most often precipitated by stress, suggesting that it may present right ventricular ischemia. Indeed, in animal studies, biochemical evidence of right ventricular ischemia was demonstrated in the presence of increased right ventricular afterload.

Most of the other symptoms noted in PHT relate to right ventricular dysfunction, most notably fatigue, edema and peripheral cyanosis. Recurrent laryngeal nerve compression from an enlarged pulmonary artery producing hoarseness (Other's syndrome) is also described, but this is uncommon.

The physical examination of a patient with PHT is revealed right-sided third and fourth heart sound. Tricuspid regurgitation is extremely common and often is the most notable auscultatory finding. Pulmonary ejection and regurgitant murmurs may also be heard. Associations have been made between the severity of the physical findings and the hemodynamics, including the presence of a third heart sound and tricuspid regurgitation associated with increased right atrial pressure and reduced cardiac output.

### Diagnostic Evaluation

In PHT, the electrocardiogram (ECG) may demonstrate signs of right ventricular hypertrophy, such as tall right precordial R waves, right axis deviation and right ventricular strain<sup>32</sup>. Sinus rhythm

seems to be rule, since no patient with chronic atrial fibrillation and primary PHT has yet been reported. In fact, there is notable disparity regarding the absence of atrial arrhythmias in patients with PHT when compared with patients with cor pulmonale, in whom atrial arrhythmias are very common<sup>33</sup>. The latter group, however, usually does not have as severe PHT and restricted cardiac output as seen in the patients with PHT. This suggests possibility of extreme dependency upon atrial systole in patients with PHT, and perhaps that atrial fibrillation is incompatible with survival.

The chest radiograph is inferior to the ECG in detecting PHT, but it may show evidence of underlying lung disease<sup>34</sup>. The chest radiographic findings of patients with PHT include enlargement of the main and hilar pulmonary arteries with pruning of the peripheral vasculature often noted. As a rule the lung fields are clear, although increased bronchovascular marking at the bases have been described in pulmonary veno-occlusive disease<sup>35</sup>. A good quality upright posterior-anterior and lateral chest radiography is an important initial screening test in PHT to help exclude lung disease as the underlying cause. It should be kept in mind, though, that clear lung field on a chest radiography do not exclude interstitial lung disease as a possible etiology<sup>36</sup>.

Pulmonary function tests are necessary in the work-up a patient with PHT to rule out underlying obstructive airways disease.

All patients present with unexplained PHT should undergo two-dimensional echocardiography with Doppler flow studies. Echocardiography is the most useful imaging modality for detecting PHT and excluding underlying cardiac disease<sup>37</sup>. Confirmation of PHT is based on identification of tricuspid regurgitation. The addition of mean right atrial pressure to the peak tricuspid jet velocity gives an accurate non-invasive estimate of peak pulmonary pressure. The typical appearance of an echocardiogram in patient with severe PHT shows right ventricular dilatation and hypertrophy. Midsystolic closure of the pulmonic valve is commonly seen and is demonstrated by Doppler studies to be caused by a reflected pressure wave that is produced by the high pulmonary vascular resistance which results in transient retrograde blood flow.

Cardiac catheterization should be performed in patients with unexplained PHT<sup>38</sup>. Besides allowing the exclusion of other cardiac causes, it also establishes the severity of the disease and allows assessment of prognosis. Because congenital heart disease can

often be missed (particularly in patients with ostium secundum atrial septal defects) as an underlying cause of PHT, it is our preference to exclude the presence of intracardiac shunt by performing hydrogen survey at the time of catheterization, even if our index of suspicion is low. Pulmonary angiogram is essential for patients in whom pulmonary thromboembolism is suspected to confirm the diagnosis.

Other diagnostic modalities have been used in the diagnosis of PHT. Because right ventricular ejection fraction is inversely proportional to the pulmonary artery pressure, the determination of PHT from radionuclide ventriculography is a popular technique at some centres<sup>39</sup>. This technique also allows the determination of hemodynamics during exercise and the effects of drugs on exercise performance<sup>40</sup>.

Computed tomography (CT) has also been used as an aid in the diagnosis of PHT. CT allows a precise, noninvasive measurement of the diameter of the pulmonary arteries, from which estimation of the mean pulmonary artery pressure can be made<sup>41</sup>. CT has also been reported to be useful in distinguishing pulmonary veno-occlusive disease in patients with PHT.

Pulmonary artery diameter can be precisely measured from magnetic resonance imaging (MRI). In addition, MRI can evaluate the severity of PHT by providing direct measurements of right ventricular wall thickness, which also correlates with mean pulmonary artery pressure<sup>42, 43,44</sup>.

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