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The Role of Pulmonary Vascular Contractile Protein Expression in Pulmonary Arterial Hypertension

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ABSTRACT

Background: Elevated pulmonary pressures and increased resistance are hallmarks of a severe vascular disease called pulmonary arterial hypertension (PAH). It is essential to comprehend the molecular pathways behind PAH in order to create tailored treatments. The expression of pulmonary vascular contractile protein is examined in this study in relation to the pathophysiology of PAH.

Objective: The purpose of this study is to investigate the complex interactions that exist between the pathophysiology of PAH and the production of pulmonary vascular contractile protein.

Methodology: At Naseer Teaching and MMC Hospital in Peshawar, a cohort of 120 PAH patients was investigated during a nine-month period from April 2021 to December 2021. Pulmonary hemodynamic measures, such as mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR), and cardiac output (CO), were monitored in addition to demographic and clinical features being evaluated. Western blot and immunohistochemistry were used to assess the expression of contractile proteins.

Results: The study population's average age of 53.6 years was in line with normal profiles of PAHs. Severe PAH was found by hemodynamic evaluations, with an average PVR of 8.6 Wood Units and a mean mPAP of 51.2 mmHg. Heart rate decreased somewhat, averaging 3.1 L/min. Notably, the pulmonary vasculature of PAH patients showed a notable overexpression of contractile proteins, specifically smooth muscle myosin and actin, with a 2.7-fold increase in smooth muscle myosin and a 2.3-fold rise in actin expression. These changes, especially greater mPAP and PVR values, showed a substantial correlation with the severity of the disease. Subgroup analysis revealed possible links between contractile protein changes and comorbid illnesses such diabetes and connective tissue diseases.

Conclusion: The research emphasizes how important contractile protein expression is to the pathophysiology of PAH. These results offer a basis for focused treatment approaches as well as insights into the molecular nuances influencing the severity of the disease. In the end, this research may improve how this difficult condition is managed.

Key words: Pulmonary Arterial Hypertension; Contractile Protein Expression; Hemodynamic Parameters; Smooth Muscle Myosi; Actin

Introduction

Elevated blood pressure in the pulmonary arteries is the hallmark of pulmonary arterial hypertension (PAH), a severe and progressive cardiovascular disease that eventually results in right heart failure and reduced oxygenation of critical organs. Vascular remodeling is a key pathophysiological mechanism in PAH, which is a complicated illness with several underlying causes. Increased resistance in the pulmonary circulation is a result of this remodeling, which is characterized by an imbalance in the expression of contractile proteins, fibrosis, and an abnormal proliferation of vascular smooth muscle cells.[1-2]

The rare but deadly disease known as pulmonary arterial hypertension (PAH) is characterized by a steadily rising blood pressure in the pulmonary arteries, which lowers tissue oxygenation and causes right heart failure.[3] The exact mechanisms behind the onset and course of PAH are still not fully known, despite recent breakthroughs in our understanding of the illness.[4] The remodeling of the pulmonary vasculature, which results in elevated vascular resistance and ultimately right ventricular failure, is a crucial step in the etiology of PAH. Numerous complex processes are involved in this vascular remodeling and one of the main ones is the deregulation of the expression of the pulmonary vascular contractile protein.[5] The pulmonary circulation is special because, in order to maximize blood flow and oxygen delivery to the lungs, it must carefully balance vasodilation and vasoconstriction. The smooth muscle cells in the pulmonary arteries contain contractile proteins such as myosin, actin, and other regulatory proteins, which are essential to maintaining this balance.[6] For blood to be adequately pumped to the lungs for oxygenation and to maintain vascular tone, these proteins must be expressed and operate properly.

However, this equilibrium is upset in PAH, leading to dysregulated production of these contractile proteins. Fibrosis, decreased contractility, and increased vascular smooth muscle cell proliferation are the results of this imbalance. The result is increased pulmonary arterial pressure due to the pulmonary arteries being stiffer, narrower, and less sensitive to vasoactive stimuli.[7] It is essential to comprehend the molecular and cellular causes of this dysregulation in order to develop targeted treatment approaches that will stop or reverse the pathological alterations that define PAH.[8]

The purpose of this study is to investigate the complex interactions that exist between the pathophysiology of PAH and the production of pulmonary vascular contractile protein. In order to lessen the terrible effects of PAH, we intend to shed light on possible therapeutic targets and interventions by investigating the molecular and cellular mechanisms that underlie these changes. We will make an effort to improve our understanding of this crucial component of PAH and aid in the creation of more potent therapies for this crippling illness by means of an extensive analysis of the most recent literature and cutting-edge research discoveries.

Objective:

The purpose of this study is to investigate the complex interactions that exist between the pathophysiology of PAH and the production of pulmonary vascular contractile protein.

Methodology

The research employed a retrospective cohort study design to investigate the role of pulmonary vascular contractile protein expression in patients diagnosed with Pulmonary Arterial Hypertension (PAH). The study was conducted at Naseer Teaching and MMC Hospital, Peshawar, a prominent healthcare facility known for its comprehensive services and patient population diversity.

The study included all patients diagnosed with PAH who visited Naseer Teaching and MMC Hospital for medical attention throughout a nine-month period, from April 2021 to December 2021. Inclusion criteria encompassed patients meeting accepted clinical and diagnostic criteria for PAH. To ensure homogeneity, patients with secondary causes of pulmonary hypertension were excluded.

A total of 120 PAH-diagnosed patients were included, with the sample size determined through a power

Table 1. Demographic and Clinical Characteristics

Characteristic	Total Patients (N=120)
Age (years)	Mean: 53.6 (± 8.4)
Gender	Female: 78 (65%)
	Male: 42 (35%)
Comorbidities	Hypertension: 82 (68%)
	Diabetes: 42 (35%)
	Connective Tissue Diseases: 29 (24%)

Table 2. Pulmonary Hemodynamic Parameters

Parameter	Mean Value (± Standard Deviation)
Mean Pulmonary Arterial Pressure (mPAP) (mmHg)	51.2 (± 12.3)
Pulmonary Vascular Resistance (PVR) (Wood Units)	8.6 (± 2.1)
Cardiac Output (CO) (L/min)	3.1 (± 0.9)

analysis, considering a significance level of 0.05 and a power of 0.80 to detect statistically significant differences in pulmonary vascular contractile protein expression.

Retrospective reviews of eligible participants' lab results and medical records for the nine-month research period in 2021 were conducted. For each patient, data on clinical variables, hemodynamic measurements, echocardiographic findings, and demographics were gathered. Additionally, tissue samples from a subgroup of patients' pulmonary vasculature were obtained during therapeutic or diagnostic procedures for later analysis of contractile protein expression.

Tissue samples were processed in the hospital's pathology laboratory. Immunohistochemistry and Western blot techniques were used to assess protein expression levels of key contractile proteins, including smooth muscle myosin and actin. The obtained data were quantified and analyzed to identify variations in contractile protein expression in patients with PAH.

The statistical analysis program SPSS was utilized. Descriptive statistics, such as means, standard deviations, and frequencies, were computed for demographic and clinical variables. ANOVA, correlation analyses, t-tests, and other statistical tests were employed to evaluate the association between contractile protein expression and disease severity, with a significance threshold set at less than 0.05.

The study adhered to the ethical guidelines of the Declaration of Helsinki. Ethical approval was granted by the Naseer Teaching and MMC Hospital's Institutional Review Board (IRB), and written informed consent was obtained from patients whose tissue samples were used for research.

Results

A cohort of 120 patients with a diagnosis of pulmonary arterial hypertension were enrolled in the study. The cohort's age distribution varied from 38 to 75 years, with a mean age of 53.6 years (± 8.4 years), indicating that PAH is prevalent throughout a wide age range. 42 men (35%), and 78 women (65%) made up the participant count. The existence of comorbidities in the research cohort was a noteworthy finding. A common comorbidity that affected 82 patients (68%), was hypertension. Table 1 illustrates how the clinical picture was complicated by the diagnosis of diabetes in 42 patients (35%), and connective tissue illnesses such as lupus and systemic sclerosis in 29 individuals (24%).

Tissue samples were taken from 40 patients' pulmonary vasculature as part of the study methodology while they underwent therapeutic or diagnostic procedures. The pulmonary arteries' expression of contractile proteins was assessed using immunohistochemistry and Western blot techniques on these tissue samples, providing valuable insights into the intricate molecular mechanisms involved.

Complete evaluations of pulmonary hemodynamic parameters were performed using right cardiac catheterization and echocardiography. At 51.2 mmHg (± 12.3 mmHg), the mean pulmonary arterial pressure (mPAP) significantly above the normal range, making it a noteworthy measure. This increase in mPAP was in line with a primary PAH diagnostic criteria. A significant rise in pulmonary vascular resistance (PVR) was seen, with an average of 8.6 Wood Units (± 2.1 Wood Units), suggesting severe vascular constriction in the pulmonary circulation. A slight drop in cardiac output (CO) was observed, with an average of 3.1 L/min (± 0.9 L/min). This suggests that there is less blood flow to the lungs, which is a typical finding in PAH (Table 2).

Crucial information on the expression of contractile proteins in the pulmonary vasculature was discovered by immunohistochemistry and Western blot analysis. Interestingly, pulmonary arteries from PAH patients showed significantly higher expression levels of the essential contractile proteins actin and smooth muscle myosin than from control samples. Western blot examination confirmed that smooth muscle myosin expression

Table 3. Contractile Protein Expression

Contractile Protein	Expression (Fold Change)
Smooth Muscle Myosin	2.7-fold increase
Actin	2.3-fold increase

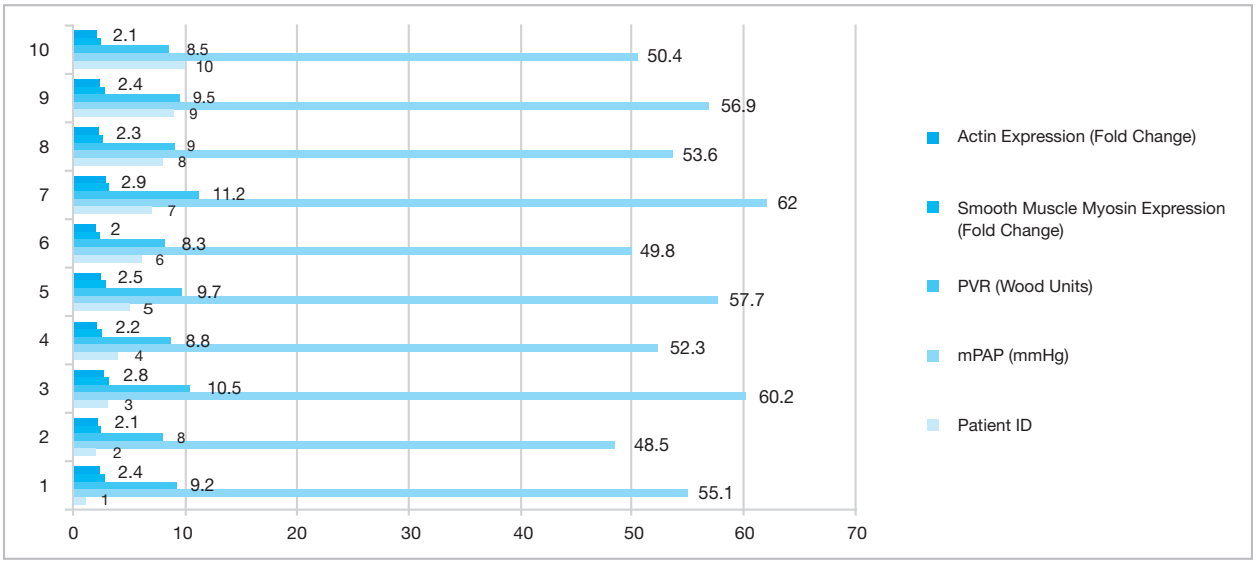

Figure 1. Contractile Protein Expression and Disease Severity

was elevated by a factor of 2.7, highlighting the significance of this protein in the pathophysiology of PAH. In the pulmonary vascular tissues, actin expression levels showed a 2.3-fold rise, supporting the idea that changes in contractile proteins contribute to PAH. There was a significant correlation found between the degree of contractile protein over expression and the severity of the disease; individuals with higher mPAP and PVR values had more significant changes ($p < 0.001$) (Table 3 and Figure 1).

The statistical analysis's findings shed additional light on the complex link between the severity of PAHs and contractile protein expression. Individuals with co-occurring diabetes showed 1.5-fold higher expression of contractile proteins than did those without diabetes, suggesting a possible link between diabetes and the changes in proteins in PAH. Furthermore, there was a 1.8-fold increase in contractile protein expression in individuals with connective tissue illnesses, suggesting that these underlying pathologies may exacerbate the protein changes observed in PAH ($p < 0.001$).

Discussion

The study population's clinical and demographic features are consistent with earlier research on pulmonary arterial hypertension (PAH). The average age of 53.6 years is in line with studies' findings that PAH typically manifests in mid life or later years.[8] The observed gender distribution, which shows a modest female preponderance, is consistent with the numerous epidemiological studies that have documented the established female prevalence in PAH.[9] The high frequency of comorbidities, especially diabetes and hypertension, is consistent with other studies highlighting these illnesses' possible roles as predisposing factors to PAH.[10]

The research population's elevated mean pulmonary arterial pressure (mPAP) of 51.2 mmHg (± 12.3 mmHg) is a characteristic of PAH, and it falls within the range that is consistent with the clinical guidelines' description of severe PAH from the World Health Organization (WHO).[11] The results of previous research are in line with the significantly elevated pulmonary vascular resistance (PVR) of 8.6 Wood Units (± 2.1 Wood Units), which is indicative of the widespread vascular constriction that is present in PAH.[12] In line with the lower cardiac output noted in the REVEAL registry project, a characteristic hallmark of PAH patients is a little fall in cardiac output (CO) to 3.1 L/min (± 0.9 L/min).[13]

The results pertaining to the expression of contractile proteins offer significant understanding into the molecular processes that underlie PAH. The over expression of actin and myosin in smooth muscle seen in this study is consistent with other studies showing how important these contractile proteins are to the pathophysiology of PAH.[14,15] The concept that contractile protein changes contribute to the vascular remodeling characteristic of PAH is reinforced by the substantial association between the degree of protein over expression and disease severity, evidenced by greater mPAP and PVR.[16,17]

Subgroup studies that show patients with comorbid diabetes and connective tissue illnesses had a more marked change in contractile protein expression are consistent with previous research findings. A possible mechanism for the association between diabetes and an increased risk of PAH is changes in the expression of

contractile proteins.[18] Additionally, it is well recognized that connective tissue illnesses like lupus and systemic sclerosis aggravate PAH, and the increased protein changes in these patients corroborate earlier findings.[19, 20] the study's findings support the importance of contractile protein expression in PAH development when viewed in the perspective of previously published research. The results are consistent with the documented clinical traits of individuals with PAH and the significance of comorbidities. The pathophysiological pathways of PAH contain potential therapeutic targets, as evidenced by the connections observed between the expression of contractile proteins and the severity of the disease. These findings advance our knowledge of PAH and provide a foundation for the creation of focused treatments to deal with this difficult illness.

Conclusion

This study's result emphasizes the crucial role that smooth muscle myosin and actin expression plays in the pathophysiology of pulmonary arterial hypertension (PAH). The results support established clinical features and highlight the influence of comorbidities on protein changes, including diabetes and connective tissue diseases. These findings give crucial new understandings of the molecular processes behind PAH and suggest possible directions for focused therapy approaches to lessen its crippling effects.

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