

## ***EDITORIAL***

# **Vascular remodelling in the lung**

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In the 1960s, studies on lungs of normal, high altitude dwelling natives demonstrated distinct structural differences in the pulmonary vasculature, compared to native sea level dwellers, accompanied by mild pulmonary hypertension [1]. ARIAS-STELLA and SALDANA [2] reported an increase in medial muscle mass in the distal segments of the pulmonary arterial tree. This was considered not to be due to medial hypertrophy of muscular arteries but to the development of a muscular media in pulmonary arterioles. Similar changes have been observed in native high altitude animals, animals exposed to experimental high altitude and in man suffering from a variety of chronic lung diseases [1]. The type and extent of the structural changes, termed "vascular remodelling" ("remodeling" in the USA), are dependent on the aetiology of the pulmonary hypertension (PH) which includes hypoxia, lung injury, high blood flow, chronic embolisation and venous obstruction. PH of unknown cause is referred to as primary pulmonary hypertension. Hypoxia is the major stimulus for PH at high altitude and in chronic lung disease. Although the structural changes are generally considered secondary to hypoxic vasoconstriction, other factors may play a role. The changes include extension of longitudinal muscle into the intima as well as medial hypertrophy, in both arterioles and, to a lesser extent venules.

The consequences of remodelling, namely restriction of the vascular bed, will exacerbate pulmonary hypertension. Thus, therapeutic relief of PH depends on the reversibility of both the vasoconstriction and the remodelling. The muscular changes are essentially reversible but other irreversible changes such as intimal fibrosis and vascular ablation may occur [3]; the successful reversibility of PH in the high altitude native brought down to sea level being consistent with the lack of irreversible intimal fibrosis [1].

The study of pulmonary vascular disease has become an area of intense research over the last decade. Although it is argued that mild PH may not be relevant clinically, severe PH is indicative of poor prognosis in disease. A recent conference held in London in September 1992 entitled "The Pulmonary Vasculature in Health and Disease" brought together clinicians, pathologists, physiologists, molecular biologists, biophysicists and others, to pool the current knowledge on the pathophysiology of pulmonary vascular remodelling associated with pulmonary hypertension. "State of the art" lectures covered

vascular physiology and pathology, relevance of animal models and clinical aspects of pulmonary hypertension. The concepts of cellular and inflammatory regulation of pulmonary vascular remodelling were discussed, along with the influence of mechanical force on vessel structure and function. Major papers from this conference have recently been published in the European Respiratory Review [4] which is reviewed in this article.

In the foetus, pulmonary vascular resistance is high and blood flow is minimal; the vascular lumen being obstructed both by vasoconstriction and wall architecture. After birth, expansion of the lung (with accompanying oxygenation) is rapidly followed by a dramatic fall in pulmonary artery pressure (Ppa) occurring within 2–3 min, and a marked increase in pulmonary blood flow. Pressure continues to fall gradually, stabilising within 2–3 days at the low level which, in the normal lung, will persist throughout life. Remodelling of the pulmonary vasculature begins immediately. HAWORTH [5] reported that within 30 mins after birth the endothelial cells, which in the foetal state are cuboidal and bulge into the lumen, flatten and brick-like immature smooth muscle cells (SMC) spread out, thus increasing lumen diameter and reducing vascular resistance. The size of the vascular bed increases as new blood vessels develop with an increase in vascular innervation. There is no loss of vascular smooth muscle, as was originally thought [5]. Cellular phenotypic changes occur, with SMC synthesising the matrix proteins, elastin and collagen.

A combination of mechanical, neural and chemical influences such as prostacyclin and nitric oxide (NO), identified as an endothelial derived relaxant factor, may well be involved in both the vasodilatation and stimulation of the cellular changes. Occasionally the neonatal pulmonary circulation fails to adapt to extra-uterine conditions and pulmonary vascular resistance and pressure remain high, termed "persistent pulmonary hypertension of the newborn". STENMARK *et al.* [6] considered that there may be a failure of the transition from foetal to adult vascular cell phenotype. Further muscularisation of this "immature" pulmonary vasculature occurs, which includes migration of adventitial fibroblasts into the media and SMC into the intima. An increase in matrix proteins may fix the vessel wall in an incomplete dilated state.

Pathophysiological changes associated with development of PH in the adult lung are complex [7]. In the adult, development of PH is accompanied by vascular remodelling to what may be considered a foetal-like structure (but probably not reversion to a foetal pattern);

increased vascular muscularisation with vasoconstriction and luminal obstruction. There is cellular hypertrophy and hyperplasia with thickening of all three structural layers, namely adventitial, medial and intimal. Medial SMC migrate into the intima and secrete elastin which forms distinct internal and external elastic laminae around the new muscle. In the adventitia, fibroblasts proliferate and collagen is deposited. New blood vessels develop, originating from the endothelium. This angiogenesis may be controlled by the matrix proteins secreted by these endothelial cells [8]. Cellular phenotypic changes include precursor muscle cells and fibroblasts developing contractile features and SMC becoming secretory. STENMARK *et al.* [6] considered that some cells become "signallers" and some become "responders" to chemical messengers, possibly cytokines, stimulating vascular remodelling; cell to cell interaction playing a crucial role.

The role of matrix protein synthesis/degradation appears to be important. An increase in an elastolytic enzyme, as yet unidentified, appears to accompany the development and progression of PH [9]. Elastin and collagen metabolism is markedly increased [9–11]. An increase in matrix protein turnover will be accompanied by an increase in potentially cytotoxic by-products which may contribute to vascular cell damage. Inflammatory processes may be involved in remodelling [12] and there is evidence of mitogen production at the end of a coagulation cascade [13].

The initial cause of the remodelling determines the nature and extent of the structural changes. JONES [14] described different cellular pathways for vascular remodelling; the pathway being determined by the cause of the PH, although the end-result of vascular muscularisation may be similar. The reactivity of the altered vessels is also dependent on the structural changes and thus dependent on the cause of the PH [7]. The consequences of pulmonary vessels that show "an increase in wall mass producing a diffusely narrowed lumen and vessel with altered mechanical and functional properties" [6] was discussed by a number of speakers. They considered that these remodelled vessels demonstrate abnormal responses to mechanical and chemical stimuli, including the shear stress accompanying raised blood flow through the narrowed vessels. This may involve the release of cytokines such as platelet derived growth factor, transforming growth factor and insulin-like growth factor (PDGF, TGF, IGF), and endothelin, a potent pulmonary vasoconstrictor, which stimulate cellular growth and produce further remodelling [15]. Thus, a cycle of remodelling causing an increase in pulmonary artery pressure (Ppa) stimulating further remodelling, may be initiated. Cells such as fibroblasts respond to mechanical stress by replicating and releasing growth factors [16]. SMC and endothelial cells, which normally have a low replication rate, show increased DNA synthesis if exposed to increased mechanical load and growth factors [17], conditions found in PH. CAROSI and McINTIRE [18] described how changes in mechanical stress could alter cellular production of vasoactive materials; this allied to an abnormal vascular reactivity may influence both vasoconstriction and vascular remodelling. The transmission and transduction of

mechanical forces and chemical stimuli within the vascular structure was discussed by WINLOVE and PARKER [19].

For the clinician, the question of treatment is unresolved, and this Review does not include a paper on the subject. The initial treatment is to remove the cause, if possible. The longer the duration of the PH, the more irreversible the remodelling may become. If the PH is due to cardiac defects, it can be alleviated by corrective surgery. For other forms of PH, vasodilators may reduce pulmonary artery pressure by relieving the vasoconstriction. Ideally, they need to be specific for the pulmonary vasculature or administered directly to the lung. Present candidates include oxygen (for PH of chronic hypoxia), nitric oxide, prostacyclin and natriuretic peptides. Reversal of the structural changes is more complex. Vasodilators may reduce mechanical stress, by increasing luminal diameter and decreasing flow rates. This could initiate some regression of remodelling; although these agents may also have direct anti-proliferative properties. Such regression has been seen in animal models of chronic hypoxia on return to normoxia [20, 21], after treatment with ligustrazine (the active principle of a Chinese herbal remedy) [22] and also after treatment with atrial natriuretic peptide (ANP) or inhibitors of neutral endopeptidase, an enzyme responsible for ANP breakdown, [23]. Agents which reduce matrix proteins, such as anti-proteases, may have a part to play. Although the structural changes may contribute to the persistence and even progression of pulmonary hypertension, we should take care to consider KEELEY's comment [24] that vascular remodelling may initially be a protective adaptation to increased physical forces exerted when Ppa is raised.

Much of the experimental evidence reported is from studies using animal models of pulmonary hypertension. However, animal models may not reproduce the exact changes seen in man. HERGET [25] considered that animal models may only have a limited usefulness in testing new therapeutic agents although an analysis of species differences helps us to understand the pathophysiological mechanisms. Some evidence of genetic control of pulmonary vascular resistance has been provided by comparison of different animal strains and transgenic work [11]. Cross-breeding studies between the spontaneously pulmonary hypertensive rat, the Fawn Hooded, and a normotensive strain found transmission of PH to back-cross and second filial generation offspring, showing its heritable basis [26].

Identification and suppression or modification of genes controlling growth promoting factors, cell-cell regulation and other signallers for remodelling, may provide novel treatments in the future. Some preliminary animal studies of such genetic manipulation in the systemic vasculature have already been made [27]. Transgenic studies involving the increase in genetic expression of intrinsic vasodilators, such as ANP, may also prove useful. KLINGER *et al* [28] found attenuation of hypoxic right ventricular hypertrophy and pulmonary vascular remodelling, in transgenic mice which overexpress ANP; plasma ANP levels being raised tenfold.

In summary, the Review [4] reflects the diversity of

the pulmonary circulation in health and disease. REEVES [29], in his summing up of the conference, referred to the arterial wall as a "virtual cauldron of vasomotor, chemotactic and growth promoting factors, of inflammatory and coagulation regulated mediators, the effect of which are modulated by cell to cell signalling". Thus, as suggested in a recent review of the current research into systemic vascular biology [27], a major task for the future is an integration of the multiple disciplines to help gain further knowledge of diverse mechanisms for regulation of vascular tone, metabolic activity and structure, in order to assist in treatment and diagnosis of vascular disease.

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