Pulmonary Vasculature in Congenital Diaphragmatic Hernia

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Persistent pulmonary hypertension (PPH) together with pulmonary hypoplasia accounts for the high mortality among patients with congenital diaphragmatic hernia (CDH). It has been demonstrated that there is an increase in muscular mass in the pulmonary arteries and within the peripheral arteries of lungs of infants who have CDH complicated by PPH. The most striking change in the pulmonary arterial wall in patients who have PPH is reported to be increased medial thickness, especially muscularization of intraacinar arteries. We have recently reported that in addition to changes in arterial media, increased adventitial thickness is a consistent feature of PPH in CDH patients, and these adventitial changes occur in large as well as in small pulmonary arteries, and are as great as those observed in the media. Comparison of the pulmonary vasculature in newborns and stillborns with congenital diaphragmatic hernia has shown that the degree of adventitial and medial thickness and area is significantly increased for arteries of all sizes in newborns with CDH complicated by PPH and stillborns with CDH compared to controls.

The exact mechanism of arterial adventitial and medial changes in CDH patients complicated by PPH is unknown. Evidence in animal models of pulmonary hypertension suggest that the smooth muscle cells play a critical role in the pathogenesis of the vascular changes of pulmonary hypertension by modifying the connective tissue phenotype of surrounding cells in the vessel wall. Recent studies suggest that the phenotypes if various matrix-producing cells can be modulated by several growth factors. Transforming growth factor- (TGF-), a potent pulmonary vascular remodelling in patients with primary pulmonary hypertension as well as in CDH patients complicated by PPH. More recently, work from our laboratory reported increased insulin-like growth factor (IGF-1) expression in hypoplastic CDH. IGF-1 is an important paracrine 'autocrine foetal growth factor known to stimulate smooth muscle cell proliferation. It has been linked to pulmonary vascular smooth muscle hyperplasia in experimental pulmonary hypertension. We have also shown markedly increased TNF-mRNA expression in human newborn and stillborn CDH hypoplastic lungs. TNF- has been proposed to play a central role in the development of pulmonary vasoconstriction. There is increasing evidence to suggest that TNF- is an important proximal mediator in the sequence of events leading to the
development of pulmonary hypertension with a dramatic increase in pulmonary vascular distance. Our data on pulmonary structural abnormalities in stillborns with CDH lead us to speculate that a prenatal imbalance may exist between synthesis or activity of various growth factors and peptides, resulting in excessive muscularization of the pulmonary arteries during foetal life.