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Fetoplacental vascular reactivity is altered in fetuses with congenital diaphragmatic hernia

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Objective

Infants with congenital diaphragmatic hernia (CDH) often develop severe pulmonary hypertension and frequently fail to respond to vasodilator therapies. The fetal pulmonary and placental vasculatures are exposed to the same circulating factors and respond similarly to certain stimuli (e. g. hypoxia). We hypothesised that changes in the fetal pulmonary vessels are also present in the fetoplacental vessels, providing opportunities to predict individual treatment responses.

Methods

The vascular reactivity of fetoplacental arteries from healthy and CDH fetuses was studied using wire myography. Vasoconstriction was evaluated using the thromboxane A2 agonist U46619, angiotensin II, and endothelin-1. Vasodilation was assessed using bradykinin, the nitric oxide (NO)-donor sodium nitroprusside (SNP), the adenylate cyclase activator forskolin, and the prostacyclin analogue iloprost. The effects of phosphodiesterase inhibitors sildenafil and milrinone on responses to SNP, forskolin, and U46619 were additionally evaluated. Placental gene expressions of receptors and enzymes involved in the altered pathways were measured using quantitative polymerase chain reaction.

Results

CDH fetoplacental arteries (n=6) constricted more strongly to U46619 and dilated less to bradykinin and SNP than healthy arteries (n=8). Vasodilation to iloprost and forskolin, and vasoconstriction to endothelin-1 were not different between both groups. Angiotensin II did not induce vasoconstriction. Preincubation with the phosphodiesterase inhibitors sildenafil and milrinone did not affect responses to SNP, forskolin, or U46619. The expression of guanylate cyclase 1 soluble subunit alpha 1 and protein kinase cyclic guanine monophosphate (cGMP)-dependent 1 was significantly lower in CDH compared with healthy placentas.

Conclusion

CDH fetoplacental arteries exhibit enhanced vasoconstriction through the thromboxane A2 receptor, and attenuated vasodilation through the NO-cGMP pathway. These alterations correspond with currently described pulmonary vascular alterations in CDH. Thus, fetoplacental vessels may provide a unique opportunity to study and predict pulmonary vascular responses in infants who are at risk to develop pulmonary vascular diseases.