Published in final edited form as:

Int J Cardiol. 2019 January 01; 274: 59–60. doi:10.1016/j.ijcard.2018.09.053.

High altitude exposure during pregnancy enhances the vulnerability of fetal heart dysfunction to ischemic stress: Epigenetic mechanisms

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There are approximately 140 million people living at high altitude areas (2,500 meters above sea level). In addition, large number of people visit high altitude areas and are exposed to high altitude environment. High altitude environment imposes a substantial challenge to human life characterized by lower partial pressure of oxygen in the atmosphere. Adults have both short-term and long-term adaptations to altitude that allow partial compensation for the lowered oxygen. However, pregnant women and their unborn babies respond to high altitude hypoxia differently as fetal arterial oxygen tensions in utero are low by adult standards even under normal conditions. Despite compensative adaptation, epidemiological studies have shown that pregnancy at high altitude is a huge burden for both mothers and fetuses. High altitude exposure increases the incidence of pregnancy complications and neonatal morbidity, such as intrauterine growth restriction (IUGR), aberrant organ development and neurobehavioral disorders in neonates [1].

Fetal hypoxia exposure is a common fetal stress that impairs fetal cardiovascular system. In the past decades, extensive studies have focused on the fetal cardiovascular responses to acute and short-term high altitude hypoxia exposure. Fetal cardiovascular responses are characterized by an increased systemic vascular resistance as well as elevated blood pressure, heart rate and cardiac output, which are mainly mediated by higher sympathetic activity [2]. However, the consequences and the underlying mechanisms of long-term high altitude hypoxia exposure on embryonic cardiovascular development are poorly understood. During the past two decades, a series of elegant studies have highlighted the fetal cardiovascular patho-physiologic adaptation to long-term high altitude hypoxia [3–6]. Longo and colleagues developed a model using pregnant sheep that are transported to high altitude (elevation 3820 m) at ~30-day gestation, where they are kept until study at ~140-day gestation. At this altitude, maternal arterial oxygen pressure is reduced to about 60 mmHg, and the fetal arterial oxygen pressure is about 19 mmHg compared with its sea-level value of ~25 mmHg [3]. Long-term high altitude hypoxia exposure in this animal model results in ~24 percent reduction of fetal cardiac output associated with an increase in fetal arterial

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Disclosure

The author declares no conflict of interest.

blood pressure. The reduction in cardiac output leads to redistribution of the blood flow and oxygen. This redistribution favors the brain and heart at the expense of the kidneys, gastrointestinal tract, and carcass in fetuses [4]. Interestingly, even though the redistribution can maintain blood flow and oxygen delivery to the heart, long-term hypoxic fetal hearts display elevated levels of cardiac ischemic biomarkers lactate dehydrogenase and citrate synthase activities [7], which lead to a hypothesis that long-term high altitude hypoxia has the potential to develop a heart ischemia-sensitive phenotype.

In this issue, the study by Zhang et al. provide a strong evidence for an increased heart susceptibility to ischemic injury and cardiac dysfunction in the hypoxic fetus with the above long-term high altitude exposure animal model [8]. Long-term high altitude hypoxia exposure had no effect on pre-ischemic baseline values of heart function but increased the left ventricle (LV) myocardial infarct size and decreased the post-ischemic recovery of LV function after ischemia/reperfusion in a Langendorff heart perfusion system. These findings indicate that long-term high altitude hypoxia plays little role in baseline fetal cardiac function but impairs the heart function when it encounters an ischemic stress challenge leading to the heart being more vulnerable to challenges by adverse stimuli. The authors further demonstrated that the mechanisms potentially responsible for the development of ischemia-sensitive phenotype of the heart involved intrinsic changes in the fetal cardiomyocytes. Remarkably, exposure to long-term high altitude hypoxia enhanced expressions of hypoxia-inducible factor-1 α (HIF-1 α). Consistent with the finding of increased HIF-1 α , there was an intrinsic increase in hypoxic biomarker miR-210 expression in the developing hearts. MicroRNAs play an important role in the epigenetic regulation of gene expression patterns by targeting the mRNA 3'UTR, resulting in the degradation of mRNAs of translational inhibition of the target transcripts. PKC ϵ gene is one of the major intrinsic cardio-protective proteins. In the high altitude hypoxic fetuses, the cardiac PKC ϵ protein expression was much lower than in normoxic fetuses. These results suggest that PKC ϵ may be one of the potential targeting genes of miR-210 in the fetal heart and the down-regulation of PKC ϵ by miR-210 could be a major molecular mechanism underlying the development of hypoxia/ischemia-sensitive phenotype. In addition to regulated by miR-210, PKC ϵ repression is likely also regulated by the DNA methylation mechanism. This study found that the cardiac DNA-methyltransferase 3 beta (DNMT3b) was over expressed in the high altitude hypoxia exposed fetuses as compared to the normoxic fetuses. Indeed, previous studies in their laboratory have demonstrated that cardiac PKC ϵ expression patterns are regulated through the DNA methylation mechanism in response to fetal stresses [9]. Autophagy may be another important mechanism potentially responsible for the development of ischemia-sensitive phenotype of the heart in the long-term hypoxic fetus. There are two important signaling pathways in the regulation of autophagy. One is the hypoxia inducible HIF-1 α /BNIP3/Beclin1/LC3II pathway and the other is the PI3K/AKT/mTOR/LC3II signaling pathway. The study showed that high altitude hypoxia increased HIF-1 α and LC3II expressions but had no effect on mTOR in the fetal hearts, suggesting that the HIF-1 α /BNIP3/Beclin1/LC3II pathway is likely a major signaling pathway underlying the high altitude hypoxia-induced over-autophagy in this animal model.

In summary, adaptive capability and vulnerability of organs to stressors could be a common mechanism for developmental programming of health and disease. Long-term high altitude

exposure adversely affects fetal cardiac programming leading to a high vulnerability to ischemic challenges. An increase in hypoxic biomarkers induces an excess autophagy and results in an epigenetic down-regulation of the cardio protective gene (PKC ϵ) expression via the DNA methylation or the miR-201 signaling pathway in the developing hearts. Whether this aberrant fetal heart development persists into postnatal life and increases the risk of cardiovascular diseases remain to be determined. Fetal cardiovascular system produces a compensatory and pathologic adaptation to high altitude challenges. Understanding the molecular mechanisms of the adaptation will help us decreasing the development of adverse changes in the fetal heart and simultaneously preserving the beneficial effects of the adaptation process.

References

- [1]. Moore LG, Charles SM, Julian CG. Humans at high altitude: hypoxia and fetal growth. *Respir. Physiol. Neurobiol* 178 (2011) 181–90. doi: 10.1016/j.resp.2011.04.017. [PubMed: 21536153]
- [2]. Giussani DA, Spencer JA, Moore PJ, Bennet L, Hanson MA. Afferent and efferent components of the cardiovascular reflex responses to acute hypoxia in term fetal sheep. *J. Physiol* 461 (1993) 431–49. [PubMed: 8350271]
- [3]. Gilbert RD, Pearce WJ, Longo LD. Fetal cardiac and cerebrovascular acclimatization responses to high altitude, long-term hypoxia. *High. Alt. Med. Biol* 4 (2003) 203–213. [PubMed: 12855052]
- [4]. Kamitomo M, Alonso JG, Okai T, Longo LD, Gilbert RD. Effects of long-term, high-altitude hypoxemia on ovine fetal cardiac output and blood distribution. *Am. J. Obstet. Gynecol* 169 (1993) 701–707. [PubMed: 8372883]
- [5]. Kamitomo M, Longo LD, Gilbert RD. Right and left ventricular function in fetal sheep exposed to long-term high-altitude hypoxemia. *Am. J. Physiol* 262 (1992) H399–405. [PubMed: 1539699]
- [6]. Longo LD, Hull AD, Long D, Percy WJ. Cerebrovascular adaptation to high altitude hypoxemia in fetal and adult sheep. *Am. J. Physiol. Regul. Integr. Comp. Physiol* 264 (1993) R65–R72.
- [7]. Ohtsuka T, Gilbert RD. Cardiac enzyme activities in fetal and adult pregnant and nonpregnant sheep exposed to high-altitude hypoxemia. *J. Appl. Physiol* 79 (1995) 1286–1289. [PubMed: 8567574]
- [8]. Zhang P, Ke J, Li Y, Huang L, Chen Z, Huang X, Zhang L, Xiao D. Long-term exposure to high altitude hypoxia during pregnancy increases fetal heart susceptibility to ischemia/reperfusion injury and cardiac dysfunction. *Int. J. Cardiol* 2018 7 9 pii: S0167–5273(18)31904–1. doi: 10.1016/j.ijcard.2018.07.046. [Epub ahead of print].
- [9]. Patterson AJ, Chen M, Xue Q, Xiao D, Zhang L. Chronic prenatal hypoxia induces epigenetic programming of PKC ϵ gene repression in rat hearts. *Circ. Res* 107 (2010) 365–73. [PubMed: 20538683]