

# Can Aerobic Training Restore the Vascular Dysfunction Induced by Intrauterine Growth Restriction? Evidences from Experimental Studies

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## ABSTRACT

Aerobic training is used as a non-pharmacological treatment to improve vascular function in cardiometabolic conditions, but its potential effects in minimize the deleterious adaptations induced by IUGR in long-term are poorly investigated. In this mini review we sought to briefly highlight how aerobic training seems to counteract the effects of IUGR in the vascular function.

**Keywords:** Aerobic Training; Exercise; Intrauterine Growth Restriction; Fetal Programming; Vascular Function

## Introduction

### Fetal Programming – Brief Concepts

The casual association between abnormalities in the fetal development (eg., intrauterine growth restriction (IUGR) or prematurity) and the incidence of chronic conditions (eg., hypertension, coronary artery disease and stroke) in long-term was first proposed by Professor Barker [1,2]. These observations led to postulate the Fetal Programming Hypothesis or Barker's Hypothesis. Fetal programming takes place during critical windows of intrauterine development inducing permanent adaptations in target organs [3,4]. Its etiology is multifactorial and complex. Stressor agents including, poor maternal nutrition during pregnancy, glucocorticoid exposure, preeclampsia, hypoxia, and advanced maternal age have been described as potential drivers to programming the cardiovascular function in the offspring [5-9].

### How does Fetal Programming Modulate the Endothelial Function?

IUGR can compromise the full development of target organs (eg., brain, kidney, heart, and blood vessels) directly involved in

the cardiovascular control [5,8,10-12]. Humans and animals submitted to IUGR show deleterious changes in vascular function, as increased vasoconstrictor response and impairment in modulatory function of endothelium, resulting in reduced vasodilatation endothelium-dependent [13-17]. The mechanisms already described showed increase vasoconstriction to endothelin-1 in mesenteric arteries as well as hyperreactivity to Angiotensin II (Ang II) in both in the microvasculature in vivo in situ and in isolated aortic rings [16,18,19]. The increase in the Ang II response is at least in part due to reduction in the expression of AT2 receptors of Ang II [18]. Furthermore, reduction in nitric oxide enzyme activity (NOS), and increased in eNOSThr495 phosphorylation were also reported, resulting in lower nitric oxide production [17,20]. Higher reactive oxygen species (ROS) concentration due to reduction in antioxidant enzymes and higher activity of pro oxidative enzymes also collaborate to decrease the NO bioavailability [18].

Factors involved in the endothelium repair, as the endothelial progenitor cells (EPCs) are also compromised under IUGR conditions in both humans and animals. Ligi et al reported lower func-

tional capacity of EPCs extracted from umbilical cord in premature neonates [21]. Consistently, we found in adult IUGR rats reduction in the number of EPCs-forming colonies and increased number of senescent cells not only in the peripheral blood but also in the bone marrow compartment [20]. These findings evidence that IUGR can program EPCs properties early in life and its effect persist into adulthood.

### Is the Aerobic Training an Effective Tool to Abolish the Effects of IUGR in the Vasculature?

Despite aerobic training has been used as a safety and powerful non-pharmacological treatment in chronic conditions, including hypertension, diabetes and obesity [22,23], its potential effects on the outcomes induced by IUGR are not widely investigated. Given that IUGR might be an additional risk factor for developing cardiometabolic conditions in long-term and that aerobic training drives positive effects in those conditions, it is plausible hypothesize that aerobic training could counteract the deleterious effects induced by IUGR in the vasculature. In fact, we observed that male adult IUGR rats submitted to aerobic training protocol (5 days per week, 60 minutes per day, 10 weeks of low-moderate aerobic training between 50-60% of their maximal capacity) reduced the high vasoconstrictor response to Ang II in aortic rings. This effect was mediated in part due to increase in the AT2 receptors expression [18]. Additionally, aerobic training normalized the expression of p47phox subunit of NADPH oxidase and upregulated the manganese isoform of superoxide dismutase enzyme contributing to lower the ROS concentration in this vascular bed [18]. Later, Reyes et al also reported that in males aerobic training improved the vasodilatation mediated by the endothelium-derived hyperpolarization factor in gastrocnemius arteries. However, no effects on the vasculature were observed in female IUGR submitted to the same aerobic training protocol [8] This interesting observation in females led us to hypothesize that the effects of aerobic training seem to be sex-specific in rats submitted to IUGR.

### Conclusion

Fetal programming has a high potential to promote deleterious cardiovascular effects in long-term. However, the life style, a modifiable factor, can prevent or reduce those negative outcomes. Low-moderate aerobic training seems to be an effective tool to restore vascular alterations induced by IUGR at least in male offspring, reducing the risk to develop cardiovascular events in long-term.

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