Suppression of myocardial HIF-1 by pubertal insulin resistance compromises metabolic adaptation and impairs cardiac function in patients with cyanotic congenital heart disease

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Topic(s):
Congenital Heart Disease – Pathophysiology and Mechanisms

Background:
Cyanotic congenital heart disease (CCHD) is a complex pathophysiological condition involving systemic chronic hypoxia (CH). A proportion of CCHD patients are unoperated due to various reasons. These patients remain CH all their lives and are at increased risk of heart failure as they age. Hypoxia activates cellular metabolic adaptation to balance energy demands by accumulation of hypoxia-inducible factor 1-α (HIF-1α).

Purpose:
The aim of this study was to determine the effect of CH on cardiac metabolism and function in CCHD patients and how it relates with age. The mechanistic role of HIF-1α in this process was investigated and potential therapeutic targets were explored.

Methods:
CCHD patients (n = 20) were evaluated for cardiac metabolism and function by positron-emission tomography/computed tomography and magnetic resonance imaging. Heart tissues collected during surgical intervention were subjected to metabolomic and protein analyses. CH rodent models were generated to enable continuous observation of changes in cardiac metabolism and function. The role of HIF-1α in cardiac metabolic adaptation to CH was investigated using genetically modified animals and isotope-labeled metabolomic-pathway tracing studies.

Results:
Prepubertal CCHD patients had glucose-dominant cardiac metabolism and normal cardiac function. By comparison, among patients who had entered puberty, the level of myocardial glucose uptake and glycolytic intermediates were significantly lower, but fatty acids were significantly higher, along with decreased left ventricular ejection fraction. These clinical phenotypes were replicated in CH rodent models. In patients and animals with CH, myocardial HIF-1α was upregulated prior to puberty, but was significantly downregulated during puberty. In cardiomyocyte-specific Hif-1α-knockout mice, CH failed to initiate the switch of myocardial substrates from fatty acids to glucose, leading to inhibition of ATP production and impairment of cardiac function. Increased insulin resistance (IR) suppressed myocardial HIF-1α and was responsible for cardiac metabolic maladaptation under CH during puberty. Pioglitazone significantly reduced myocardial IR, restored glucose metabolism, and improved cardiac function in pubertal animals.

Conclusions:
In CCHD patients, maladaptation of cardiac metabolism occurred during puberty, impairing cardiac function. HIF-1α was identified as the key regulator of cardiac metabolic adaptation under CH but its expression was suppressed by pubertal IR. The use of pioglitazone during puberty might help improve cardiac function in these patients.
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The CCHD patient suffers from cardiac metabolic maladaptation and impairment of cardiac function during puberty. (A) Correlation between patient age and left-ventricular ejection fraction, evaluated by cardiac MRI (n = 20). (B) Correlation between patient age and left-ventricular glucose uptake, evaluated by cardiac 18F-FDG PET/CT (n = 10). (C) Representative images of cardiac MRI and 18F-FDG PET/CT from CCHD patients at different ages. (D) Nontargeted metabolomics was performed in cardiac tissues from prepubertal and pubertal patients. The PCA model shows the separation of clusters between the two groups. (E) The heatmap includes 24 metabolites with significant differences between the two groups. Glycolytic intermediates are shown in red text. (F) Targeted lipidomics was performed in cardiac tissues from prepubertal and pubertal patients. The PCA model shows the separation of clusters between the two groups. (G) The heatmap shows relative levels of detected fatty acids in the two groups. Fatty acids with significant differences are named in red text.