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FCVB (Frontiers in cardiovascular Biology)-EBAC. April 2012, London.
A. Gonzalez-Tendero, I. Torre, F. Garcia-Garcia, J. Dopazo, E. Gratacos
Cardiovascular Research (2012) 93 (Suppl. 1), S109

Abstract: P558

Intrauterine growth restriction is associated with a maturation delay of cardiac energetic microdomains

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Topic(s):
Energetics

Citation:
Cardiovascular Research (2012) 93 (Suppl. 1), S109

Purpose: Intrauterine growth restriction (IUGR) affects 7-10% of pregnancies and is associated with cardiovascular remodelling and dysfunction persisting into adulthood, resulting in dilated and less efficient hearts. However, the precise underlying mechanism is poorly understood. Cardiac muscle is the central organ in the fetal adaptive mechanism to IUGR. Besides, it is among the highest ATP consumer organs. At subcellular level, sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) and myosin-ATPase in the sarcomere thick filaments are the main energy consumers. During heart development, the maturation of an organized spatial arrangement of mitochondrial network around SR and myofilaments, namely energetic microdomains, occurs. Since it is well documented that a close proximity between the mitochondria network and cardiac ATPases enable the quick and efficient energy transference ensuring a proper function, the objective of the present study was to evaluate the state of the energetic microdomains between mitochondria and myofilaments in an animal model of IUGR.

Methods: IUGR was induced in 6 New Zealand pregnant rabbits by a surgical standard protocol. At 30 days of gestation a caesarean section was performed and hearts were obtained. IUGR-gene expression profile was analyzed in 6 paired control and IUGR rabbit fetuses with a gene expression microarray from the rabbit genome. Results were analyzed using a bioinformatic gene set analytic tool, in order to detect coordinated variation in blocks of genes function. Morphometric analysis of energetic microdomains was performed in 3 different left ventricular areas from 3 paired control and IUGR rabbit fetuses, using transmission electron microscopy imaging.

Results: Gene set analysis identified two gene modules with a coordinated over-representation in IUGR: mitochondrial respiratory chain complex I (GO:0005747) and NADH dehydrogenase activity (GO:0003954). Additionally, IUGR fetuses showed an increased area of cytoplasm between mitochondria network and myofibrils (128000 ± 7822 nm2) than the normally growth control fetuses (91010 ± 6072 nm2) ($p < 0.05$).

Conclusions: Results presented here suggest that mitochondrial energetic state is impaired under IUGR, and this is accompanied by a delayed maturation of cardiomyocyte energetic microdomains between mitochondria network and myofilaments. Together, these results point to a decreased efficiency in the energy supply from mitochondria to the sarcomere myosin-ATPase, contributing to the global contractile dysfunction, previously documented in IUGR.