Fetal cardiovascular characterization in a rabbit model of intrauterine growth restriction

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Objective
Intrauterine growth restriction (IUGR) affects up to 10% of all pregnancies, but no therapeutic strategies so far have been demonstrated to be effective to diminish IUGR. If we could determine how the specific features due to fetal programming are reproduced in an animal model of IUGR, such a model would open doors to further interventional studies. In this study, we aim to characterize the pattern of cardiovascular remodeling in an established IUGR rabbit model at structural and functional levels.

Methods
IUGR was induced in pregnant New Zealand White rabbits on day 25 of gestation by selective surgical ligation of the uteroplacental vessels, and fetuses were delivered five days later by cesarean section. Fetal echocardiography was performed in uterus before fetal extraction, using Vevo 3100 ultrasound system. Then, frozen micro-sections of the heart were histologically characterized by the analysis of organ biometry, fibrosis, lipids and glycogen depositions and angiogenesis. Two experimental groups, control (N=30) and IUGR (N=36), were compared using the unpaired t-test or the Wilcoxon rank-sum test, depending on the normality of the variables.

Results
A significant reduction of birthweight (IUGR mean 34 g (SD 6) vs control 45 g (7), p<0. 001) and heart weight (IUGR 0. 21 g (0. 04) vs control 0. 25 g (0. 05), p<0. 001) could be demonstrated in IUGR fetuses with a relative increase of heart weight in relation to body weight (IUGR 0. 61% (0. 07) vs control 0. 57% (0. 08), p=0. 047), suggesting myocardial hypertrophy. Fetal echocardiography also revealed hypertrophic hearts in IUGR fetuses after adjusting by fetal body weight, as indicated by left ventricular (LV) myocardial wall thickness (IUGR 3. 105 mm/g (0. 786) vs control 2. 149 mm/g (0. 383), p<0. 001). Measurements relating to cardiac function showed decreased longitudinal motility (tricuspid annular plane systolic excursion: IUGR 1. 039 mm (0. 421) vs control 1. 449 mm (0. 407), p=0. 019) in IUGR. Accordingly, histological measurements adjusted by body weight also indicated hypertrophy of IUGR hearts (LV wall: IUGR 4. 253 mm/g (0. 836) vs control 3. 379 mm/g (0. 541), p<0. 001, IVS: IUGR 4. 656 mm/g (1. 175) vs control 3. 855 mm/g (0. 741), p=0. 001, RV wall: IUGR 3. 667 mm/g (0. 748) vs control 3. 078 mm/g (0. 560), p<0. 001). In addition, IUGR hearts presented significantly larger whole area (IUGR 70. 066 mm2/g (11. 270) vs control 57. 714 mm2/g (9. 390), p<0. 001) and larger RV cavity (IUGR 3. 883 mm2/g (2. 766) vs control 2. 336 mm2/g (1. 663), p=0. 007), with a trend for larger LV cavity (IUGR 3. 941 mm2/g (2. 528) vs control 3. 080 mm2/g (1. 624), p=0. 10). Further histological analysis by Sirius Red, Periodic Acid-Schiff, and Oil Red attested that neither fibrosis nor deposits of glycogen or lipids, respectively, were detected to the level for causing cardiac structural changes in IUGR fetuses compared to their control.

Conclusion
Our data suggests cardiomegaly and eccentric cardiac hypertrophy with decreased longitudinal motion in IUGR rabbit fetuses. Confirming the cardiovascular phenotype of an IUGR rabbit model would allow us to broaden its application, including the use of the model to examine therapeutic effects in the hypertrophic heart.