Ultrasound assessment of genetic mutated mouse models, Vegf+/120 a model for Tetralogy of Fallot

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Background – Although hemodynamics play an important role in cardiogenesis and abnormal blood flow through the developing heart might result in congenital heart disease, up till now studies in embryos/fetuses of genetic mutated mouse models mainly focused on the cardiac morphology and the availability of hemodynamic data is limited. High-frequency ultrasound is a promising technique for assessment of morphology as well as hemodynamics along mouse heart development. Here we performed ultrasound experiments in fetuses of the Vegf+/120 mouse model, that has a cardiac phenotype resembling Tetralogy of Fallot.

Methods – A timed breeding program was initiated with Vegf+/120 mice, resulting in fetuses of following genotypes: Vegf+/+ (wildtype), Vegf+/120 (heterozygous) both showing normal heart development and Vegf 120/120 (mutant, Tetralogy of Fallot like phenotype). Trans-abdominal high-frequency ultrasound assessments were performed in fetuses of sedated (Isoflurane 1.5%) pregnant Vegf+/120 mice under stable vital parameters (heart and respiratory rate and body temperature). Hemodynamic and morphological assessments were performed in fetuses at 14.5 and 17.5 days post conception (dpc). Following the ultrasound experiments of 17.5 dpc the fetal hearts were harvested for genotyping and ex-vivo immunohistochemical studies, including 3-dimensional reconstructions.

Results – Whereas the heart rate in wildtype and Vegf+/120 increases along fetal development that of Vegf120/120 fetuses decreased significantly. Morphological assessment could be performed of the different cardiac segments. The presence of structural heart malformations like ventricular septal defects during the ultrasound experiments in Vegf120/120 were confirmed by ex-vivo morphological studies at 17.5dpc. Furthermore, reliable pulsed-wave Doppler flow recordings could be performed across the developing mitral, tricuspid, aortic and pulmonary valves. An abnormal course of Doppler flow patterns were observed in Vegf120/120, for example a decreasing trend of the E/A-ratio across the developing tricuspid valve.

Conclusion - High-frequency ultrasound is a useful method for longitudinal assessment of (ab-)normal heart development in fetuses of a genetic mutated mouse models. In the future, this technique will help to further unravel the role of hemodynamics in the development of congenital heart disease.

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