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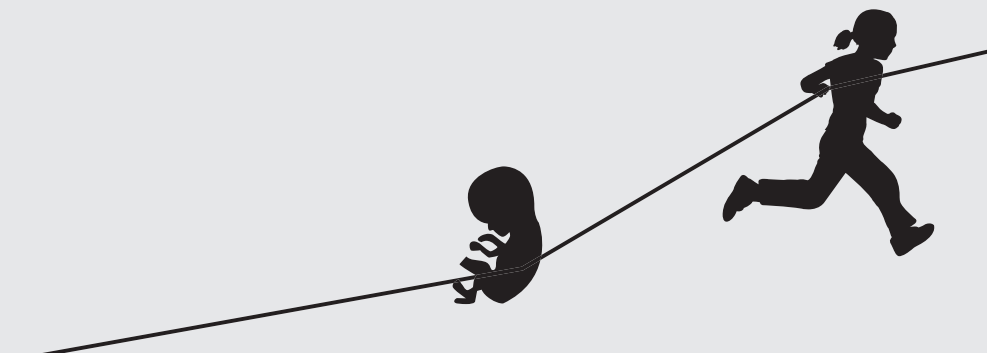
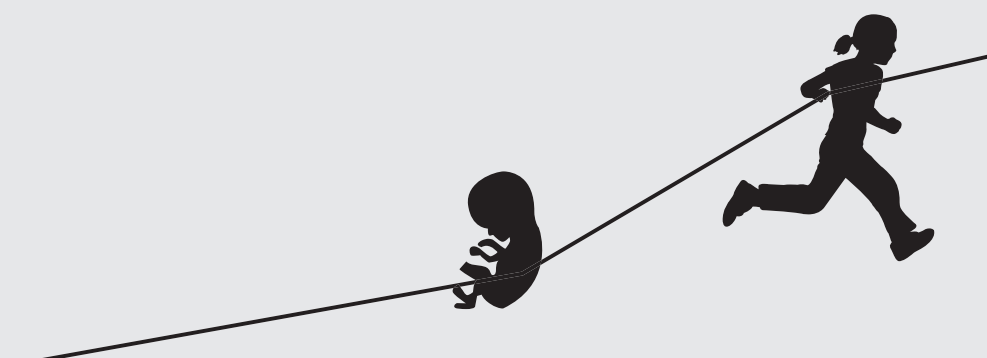
Part 1

Introduction



Chapter 1.1

General introduction and outline of the thesis



1.1 BACKGROUND

Atrioventricular septal defect (AVSD) covers a spectrum of heart anomalies with a common atrioventricular junction. AVSD comprises 7% of all congenital heart diseases (CHD) and is often associated with Down syndrome [1;2]. The nomenclature used to subdivide AVSD based on the variability in the defect in the septal tissue around the atrioventricular valves is not consistently used in literature, potentially hampering comparison of results reported between different centers. Currently, the diagnosis of AVSD is usually made prenatelly and can in specialized centers be made during early pregnancy [3]. Surgical correction of an AVSD is usually performed in early life to prevent longstanding pulmonary overflow [4]. Survival after correction is excellent in the current era. However re-operation frequency is relatively high due to regurgitation of the left atrioventricular valve (LAVV) [5]. The optimal timing for reoperation is still unclear [6].

Knowledge regarding development of CHD has markedly increased in the last decades [7]. Multiple genetic [8;9] and epigenetic [10] factors have been associated with AVSD development, but the exact pathogenesis is not completely unraveled. Evaluation of the cardiac morphology in the developing human fetus is restricted due to the limited availability of human embryonic and fetal material. Literature describes differences in morphology of AVSD between patients with Down syndrome and non-syndromic patients [11;12] and cardiac anomalies have been suggested in patients with Down syndrome without overt septal defects [13]. Blood flow through the heart has been marked as an essential factor for proper cardiogenesis [14]. Recently, high frequency ultrasound became available to analyze blood flow during the early stages of heart development in mouse embryos [15]. This allows the evaluation of the influence of blood flow during heart development.

Also after birth, in children and adults with (congenital and acquired) heart disease, intra-cardiac blood flow plays an important role in cardiac remodeling [16] and can be evaluated with echocardiography and MRI. Data on cardiac function long-term after AVSD correction is scarce. As the LAVV after AVSD correction has an aberrant morphology, intra-cardiac blood flow might be affected in these patients, possibly resulting in less efficient flow. Furthermore, quantification of LAVV regurgitation showed to be challenging with echocardiography in patients after AVSD correction [17]. 4-dimensional velocity-encoded cardiac magnetic resonance imaging (4DFlow MRI) allows direct quantification of intra-cardiac blood flow [18]. Moreover, newly available applications to visualize blood flow, such as streamlines [19] and particle tracing [20] and analysis of vortex formation [21;22] potentially provide further insight into intra-cardiac blood flow pathways in healthy hearts and those with CHD.

AIM

The first aim of this thesis was to review current knowledge, as well as current unclarities regarding the development, morphology, diagnosis and treatment of AVSD (**Part 1**). The second aim was to study the pathology of AVSD in human and rodents, using microscopic analysis, gene expression patterns, electrophysiological studies including optical mapping as well as high frequency ultrasound measurements in developing hearts (**Part 2**). Finally, cardiac function long-term after AVSD correction was analysed with special emphasis on intra-cardiac flow patterns with the use of 4DFlow MRI in corrected AVSD patients and healthy controls. (**Part 3**).

OUTLINE OF THE THESIS

In **Part 1, Chapter 1.2** the available literature regarding developmental aspects, involved genetic and epigenetic factors, nomenclature, anatomy, diagnosis, surgical techniques and outcome of AVSD is summarized. In this bench to bedside review special consideration is given to differences between non-syndromic AVSD and AVSD in patients with Down syndrome.

Subsequently, in **Part 2** of this thesis the developmental aspects of AVSD are further investigated. In **Chapter 2.1** the membranous septum and atrioventricular valves, that are aberrantly evolved in AVSD hearts, are studied in depth in patients with Down syndrome without an AVSD, as literature suggests that abnormalities are also present in this patient group. In **Chapter 2.2** the possibilities and limitations of fetal echocardiography to detect CHD in the first trimester in human are examined and correlated with morphology in fetal human specimens. Fetal echocardiography in mice allows analyses of intra-cardiac flow during heart development. In **Chapter 2.3** reference values of high frequency fetal echocardiography in subsequent developmental stages of wild type mouse embryos are provided and discussed. This technique is combined with optical mapping, immunohistochemical analysis and qPCR in **Chapter 2.4**, to analyze heart development in a mouse model with a mutation in the Vascular Endothelial Growth Factor gene, which in human is associated with AVSD and Tetralogy of Fallot. In this chapter special attention is given to the inflow tract of the heart, including the sinoatrial node.

In **Part 3** of this thesis, long-term follow-up data of corrected AVSD patients is provided. In **Chapter 3.1** an overview of the clinical use of 4DFlow MRI is given and novel blood flow visualization applications are discussed. In **Chapter 3.2** streamline visualization is used to optimize left ventricular inflow quantification and differences in inflow direction between healthy controls and corrected AVSD patients are analysed. The difference in intra-ventricular blood flow between patients and controls is further investigated with the use of particle tracing in **Chapter 3.3**. In **Chapter 3.4** a novel MRI method to assess velocity propagation, a parameter used to analyze diastolic function, is described. In **Chapter 3.5**, a previously published method to analyse three-dimensional quantitative vortex core formation in the left ventricle [22] is ap-

plied in corrected AVSD patients to study the impact of the abnormal LAVV and the lateral inflow direction on vortex formation. In **Chapter 3.6** 4DFlow MRI with retrospective valve tracking and streamline evaluation is used to characterize and directly quantify regurgitation of the LAVV in corrected AVSD patients. In **Chapter 3.7** the blood flow in the left atrium in patients with LAVV regurgitation after AVSD correction is described with the use of streamlines, vortex extraction, particle tracing and quantification of pulmonary vein flow.

Part 4 summarizes the key findings of this thesis and discusses future perspectives.

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ABBREVIATIONS

2D	Two dimensional
3D	Three dimensional
4D	Four dimensional
A-peak	Late diastolic filling peak
AVSD	Atrioventricular septal defect
CHD	Congenital heart disease
CMR	Cardiovascular magnetic resonance
CX	Connexin
DS	Down syndrome
EF%	Ejection fraction
E-peak	Early diastolic filling peak
LA	Left atrium
LAVV	Left atrioventricular valve
LV	Left ventricle
MRI	Magnetic resonance imaging
SAN	Sinoatrial node
VEGF	Vascular endothelial growth factor