The heart in Down syndrome
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Each year approximately 1400 children are born in the Netherlands with a heart defect. Life expectancy of these patients has greatly improved over the past decades, especially as a result of the development of new corrective operative techniques. As a consequence of the successes of cardiac surgery, the majority of these children now reach adulthood. For persons with Down syndrome, life expectancy has increased likewise, as cardiac surgery is no longer rejected in newborns with Down syndrome. Nowadays a cardiac screening is advised within 3 months after birth as almost 50 percent of the neonates with Down syndrome have a congenital heart defect. However cardiac screening and cardiac surgery was not standard therapy in patients who were born before 1980s. Probably, a group of ‘older’ Down patients has never had cardiac evaluation or treatment and now live with the consequences of an uncorrected congenital heart defect. One major complication is pulmonary arterial hypertension and Eisenmenger syndrome, in which irreversibly increased pulmonary vascular resistance may ultimately lead to a reversal of the systemic-to-pulmonary shunt leading to cyanosis, diminished exercise capacity and heart failure. In this thesis the treatment and clinical condition of patients with pulmonary arterial hypertension, with focus on Down syndrome has been explored. Secondly, the heart of persons with Down syndrome without structural congenital heart defects has been studied.

Part 1: Down syndrome

Chapter 1 (general introduction) describes an extensive overview of cardiovascular disorders in patients with Down syndrome. Also the latest genetic insights are discussed in this chapter. Chapter 2 shows an epidemiological model on the prevalence and survival of adults with Down syndrome in the Netherlands by combining empirical data, including data of birth registries and international data. This model provides useful data on changes of birth incidence, population prevalence and age profile of the Dutch adult population and can be used to estimate future developments. We undertook a study (Chapter 3) to investigate the use of the six minute walk test in patients with Down syndrome, a test that is used frequently in research trials to investigate exercise capacity in patients with pulmonary hypertension. We conclude that this test in not feasible in patients with Down syndrome because it is inversely related to the level of intellectual disability and not
to the existence of pulmonary hypertension. Chapter 4 describes the outcome of a national echocardiography screening in patients with Down syndrome living in residential centres. We find a prevalence of known congenital heart disease of 16% in more than 1100 participants. However, the cardiac status is unknown in many subjects. Echocardiography screening reveals an underdiagnosis of congenital heart disease in 17% of the screened subjects. In chapter 5 we investigate left ventricular mass and volume in adults with Down syndrome with structural normal hearts. Surprisingly, both left ventricular mass and volume are significantly smaller in these adult subjects compared to healthy controls. These differences seem not to exist in childhood. Possibly, these differences are lifestyle-related, because adults in residential centres are in general physically more inactive. We conclude that physical inactivity may lead to cardiac atrophy. We further examine the cardiac function of adults with Down syndrome with structural normal hearts in chapter 6 by measuring the cardiac output after light exercise testing and conclude that adults with Down syndrome are less able to raise their cardiac output compared to controls. The smaller cardiac volumes may cause the lower cardiac output. Chapter 7 shows an interesting case of a female with Down syndrome and a fibrillin-1 mutation. The specific features of Down syndrome may cover the diagnosis of Marfan syndrome.

Part 2: Eisenmenger syndrome in patients with Down syndrome

Chapter 8 gives an overview of the literature on the treatment effect of bosentan in patients with pulmonary arterial hypertension due to systemic to pulmonary shunting in presence of a congenital heart defect. Bosentan treatment improves exercise capacity, however larger randomized studies are needed to conclude a survival benefit. Chapter 9 and 10 describe the treatment effect of bosentan on exercise capacity and quality of life in patients with Eisenmenger syndrome (with and without Down syndrome). Initially in chapter 9, a positive effect can only be found in the first 3 months of treatment in patients with Down syndrome. However in chapter 10, the extended follow-up study fails to demonstrate a sustained effect in patients with Down syndrome. The use of the six-minute walk test in patients with Down syndrome may cause this negative result. (see chapter 3). In chapter 11 we conclude that bosentan treatment cause a sustained improvement of exercise capacity after 4 years of follow-up. Chapter 12 is focused on the complete group of patients with
congenital heart disease. Patients with congenital heart disease are frequently treated during childhood by surgical correction. However in most cases complete recovery is not possible. Late complications like arrhythmias and heart failure may develop in adulthood. We show the results of a national campaign to identify patients who are lost to cardiac follow up. A large amount of ‘lost’ patients are registered in CONCOR, the national database of congenital heart disease, and new defects are found.