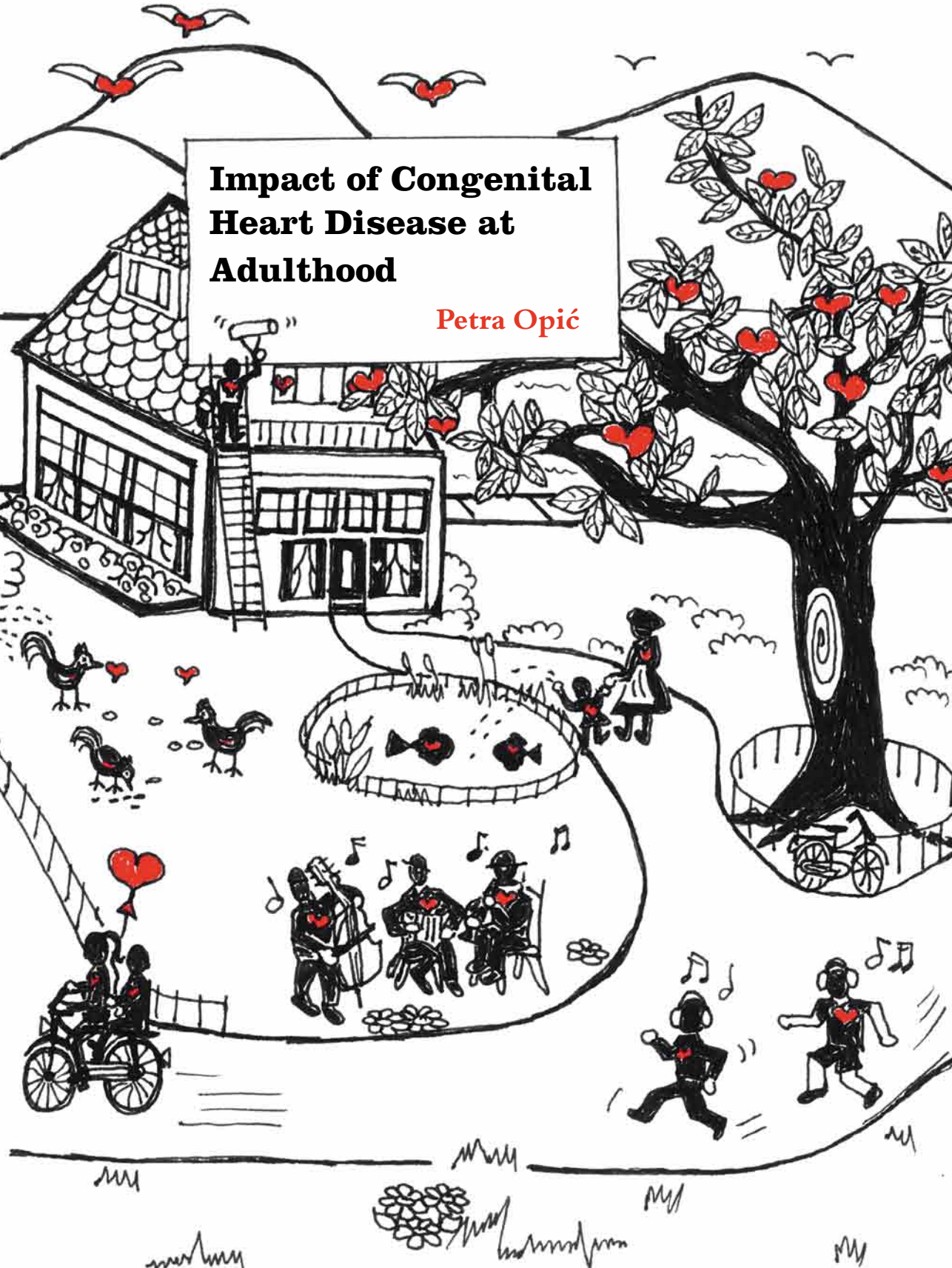
Impact of Congenital Heart Disease at Adulthood

Petra Opić



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Impact of Congenital Heart Disease at Adulthood

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Op de vensterbank in de zon zit een kat.
Hij kijkt naar de schaduwen die bewegen
op het grasveld, naar de hommels bij de
bloemen, naar de vogels onder de heg.
Zonder 'ego'.

- Bob Rigter in "*Zen tijd*"

To my family

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General introduction

GENERAL INTRODUCTION

Since the first surgical techniques for patients with congenital heart disease (ConHD) became available some 55 years ago, virtually every area of patient care has evolved substantially. These improvements lead to an increased survival for patients with ConHD, with over 90% of infants reaching adulthood.[1,2]

This increased survival lead to a shift of focus in that congenital heart disease at adult age nowadays is considered a chronic disease. Therefore, current research does not only focus on survival, but also on the quality of life of these patients. The term quality of life is broad and encompasses many dimensions of life, including – but not limited to – living conditions, wealth and employment, physical and mental health, education, leisure time, psychosocial functioning, lifestyle and social adaptation.[3,4]

In order to investigate the impact of living with a congenital heart defect at adulthood, the aims of this thesis were threefold;

1) To investigate the impact on biographical characteristics
2) To investigate the impact on psychological aspects
3) To investigate the impact on medical aspects

Three large cohort studies were designed to address the aims of this thesis, of which two were used to study biographical and psychosocial aspects, and the third was used to study medical effects of ConHD at adulthood.

The first cohort designed to study biographical and psychosocial aspects included all consecutive patients operated for congenital heart disease in the Erasmus Medical Center between 1968 and 1980, younger than 15 years at the time of surgery. The first follow-up of this unique cohort took place in 1990, where the age of the patients varied between 10 and 35 years. At the time of the second follow-up, conducted in 2001, all patients had reached adult age, ranging from 20-46 years. The present thesis focuses on the third follow-up of this worldwide unique cohort of patients, who are now between 30-55 years old. With three follow-ups completed, this cohort offered the unique possibility to study the longitudinal developments of patients with ConHD over a period of 30 years. Five diagnostic groups (Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), Pulmonary Stenosis (PS), Tetralogy of Fallot (ToF) and Transposition of the Great Arteries (TGA)) were invited to the out-patient clinic, and underwent extensive psychosocial and medical examination. During this third follow-up, new topics that are relevant to congenital heart disease in adulthood (such as sports, exercise and sexuality) were studied. Since this total cohort underwent surgery in the same institution where all three follow-ups were conducted, using the same assessment tools, longitudinal changes in psychosocial and medical variables could be used to identify problematic areas.

A second cohort, including all consecutive patients operated between 1980 and 1990 younger than 15 years at the time of surgery, was also studied. Medical, biographical and psychosocial variables were examined in a similar manner as in the first cohort. At the time of follow-up in 2010, all patients of this second cohort were between 21-34 years old.

The third cohort used to study the medical impact of ConHD at adulthood was identified from the nationwide CONgenital CORvitia (CONCOR) registry in the Netherlands and a Belgian tertiary care center adult ConHD database.[5] This cohort included all adults with ConHD and a history of pacemaker implantation. Data on medical history, pacemaker implantation, pacemaker complications, arrhythmias and major clinical complications were collected from medical records and pacemaker databases.

Included ConHD diagnoses

Normal human heart

During the fourth week of pregnancy the heart tube is formed, which undergoes a process of looping, remodeling and separation that transforms it from a tube to a heart with four chambers.[6] The heart is one of the organs that has to function almost as soon as it is formed - starting to beat shortly after its formation. By the end of the tenth week, the heart is fully functional.[6] During the fetal period, little blood flows through the lungs. Because the vascular resistance is high, blood bypasses the lungs through a connection between the left and right atrium. As soon as the infant takes its first breath after birth, major changes occur in the circulatory system, opening the pulmonary circulation (by lowering the vascular resistance in the lungs) and cutting off the blood from the placenta. This, in turn, causes changes in pressure in the heart, closing the foramen ovale.[6]

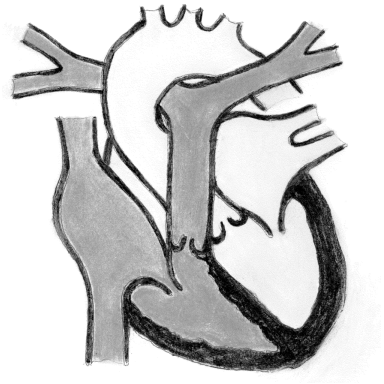


Figure 1. Normal human heart

The normal human heart consists of two separate circulatory systems, the left and right side, both divided in two chambers. Oxygen poor blood enters the heart in the right atrium, passing through the right ventricle into the lungs. From there, it enters the left atrium, and through the left ventricle into the rest of the body.[7,8]

Atrial Septal Defect (ASD)

ASD is the most common form of ConHD at adult age.[7,8] Patients who have an ASD have a connection between the left and right atrium of the heart.[7,8] Different forms of ASD are

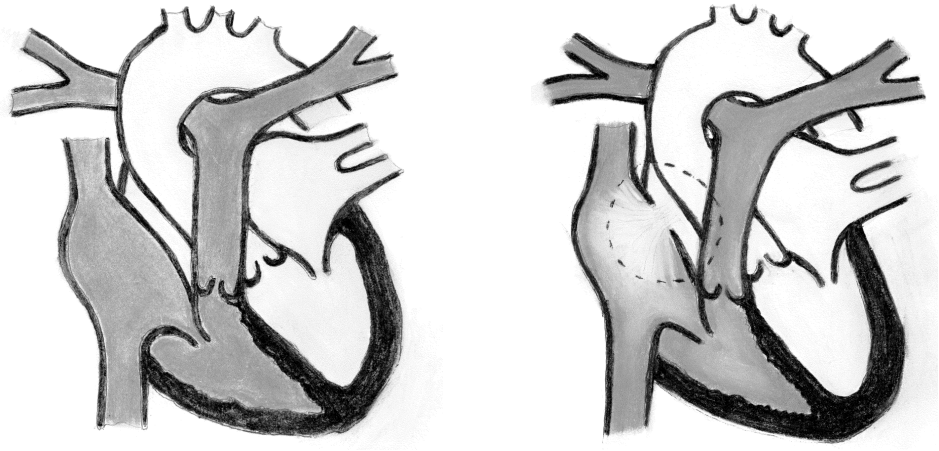


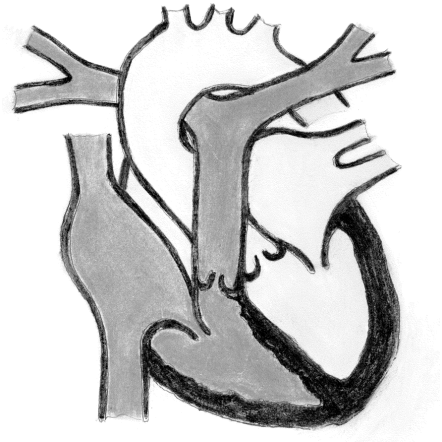
Figure 2. Normal human heart Atrial Septal Defect

known, the two most common ones being the 'ostium secundum' type defect, accounting for 70% of the cases, and the 'sinus venosus' type defect accounting for 15% of the cases.[7] Surgery has been available since roughly the 1960's.[9]

Because the left side of the heart has to supply the whole body with oxygenated blood, the pressure in the left side is higher than in the right side. This pressure difference will lead to shunting of blood from the left to the right side of the heart. This causes additional work for the right ventricle, which will have to pump more blood towards the lungs. If left untreated, this can result in enlargement (dilatation) of the right side of the heart to compensate for the additional volume.[7] This, in turn, can cause pulmonary hypertension and arrhythmias (developed due to increased stress, dilatation and additional work).[10,11] To prevent complications at adult age, patients with clinically significant ASD's are surgically corrected at young age.[7,10,11] When left untreated, most symptoms occur around the third decade of life, consisting in mostly shortness of breath and heart palpitations.[7]

Ventricular Septal Defect (VSD)

A VSD consists of a hole between the left and the right ventricle of the heart, enabling blood to flow between these two chambers.[7,8] The VSD is the most common form of ConHD at young age, but because of spontaneous closure (roughly 50%) it is less often seen in the adult population.[7] Surgical treatment has been available since roughly 1960.[12] Because the pressure in the left ventricle is higher than the pressure in the right ventricle, blood will flow from the left ventricle to the right ventricle during contraction of the heart. This will create a shunt, in which oxygenized blood will flow to the right side of the heart and re-enter the lungs. This, in turn, will lead to increased work for the left ventricle and will cause a volume overload in the lungs with the risk of pulmonary hypertension. Clinical symptoms of VSD largely depend on the size of the shunt, the localization of the shunt, the presence of pul-



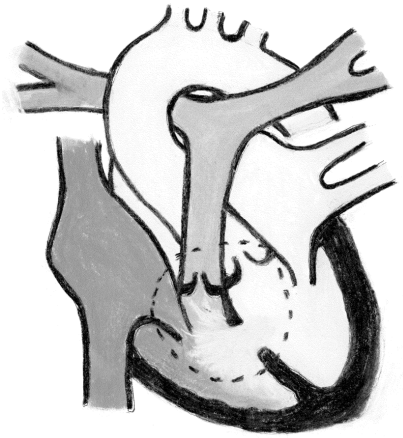


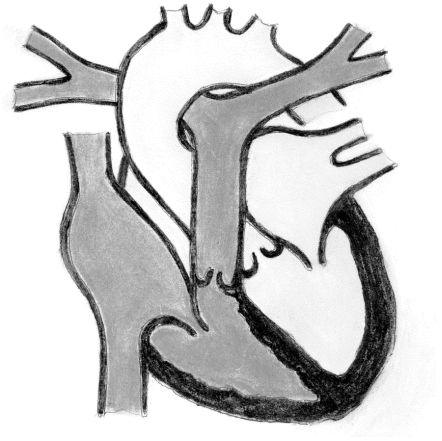
Figure 3. Normal human heart

Ventricular Septal Defect

monary hypertension and overall clinical condition of the patient. If the shunt is small and there are no additional complications, there might be an absence of symptoms.[7] On the other hand, when the shunt is large this can ultimately lead to pulmonary hypertension, increasing the pressure in the right side of the heart. If this situation continues, the pressure in the right side will become higher than in the left side, and consequently cyanosis may develop (because of right-to-left shunting of blood). Other clinical symptoms such as arrhythmias and heart failure may develop.[13,14]

Pulmonary stenosis (PS)

In pulmonary stenosis, the pulmonary valve which lies between the right ventricle and the lungs is obstructed.[7] This will lead to a higher pressure in the right ventricle enabling it to



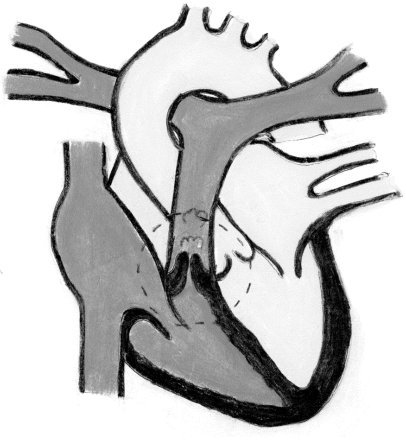


Figure 4. Normal human heart

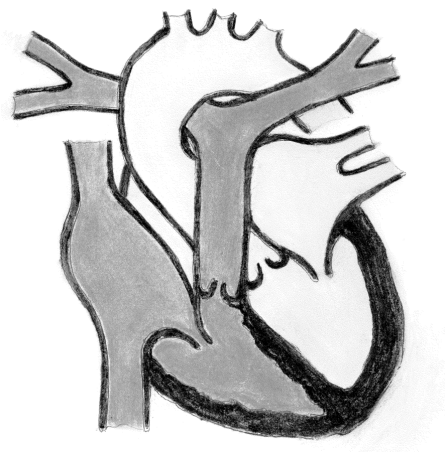
Pulmonary stenosis

pump enough blood to the lungs. Symptoms during childhood (other than a heart murmur) are rare and usually manifest themselves during adulthood.[7] In the long term, the higher pressure in the right ventricle can lead to the thickening of the walls of the right ventricle because of more muscular tissue, also known as (right ventricular) hypertrophy.[7] The hypertrophy may worsen the problem by obstructing the outflow to the lungs even more.[7] In the end, if left untreated, PS can lead to right ventricular heart failure, a condition in which the heart will not be able to pump enough blood to the lungs.[7] The prognosis of the patients largely depends on the severity of the PS.[15] Mild PS will have a good prognosis, whereas patients with severe PS may need multiple interventions, even at adult age, to ensure good survivability and quality of life.[15]

Tetralogy of Fallot (ToF)

Tetralogy of Fallot is named after the French physician Étienne-Louis Arthur Fallot, who first described this congenital heart defect in 1888.[16] Tetralogy of Fallot is the most common cyanotic ConHD amongst newborns. It is a serious congenital heart defect, which requires surgical treatment. Patients at young age can have cyanotic spells (also known as "tet spells") in which the patient becomes cyanotic and can lose consciousness. Before 1954, no surgical treatment options were available. In 1954, the first total repair of tetralogy of Fallot was done by a team led by C. Walton Lillehei at the University of Minnesota on an 11-year-old boy.[17] Surgical repair on infants has been available since 1971.[18] Nowadays, patients receive corrective surgery during the first year of life, since uncorrected Tetralogy of Fallot leads to a high mortality rate.[19,20]

In Tetralogy of Fallot, there is a problem in the embryogenesis of the ventricular septum just below the pulmonary valve. This leads to a wrong position of the aorta and pulmonary



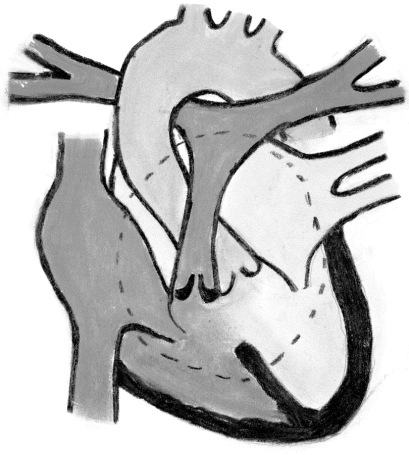


Figure 5. Normal human heart Tetralogy of Fallot

artery, which are moved towards the right side of the heart. This, in turn, leads to four different anomalies[7]:

1) Narrowing of the right ventricular outflow tract, most often by a pulmonary valve stenosis, but sometimes by the hypertrophy of the right ventricle itself (subvalvular stenosis). This will lead to a higher pressure in the right ventricle. The severity of the stenosis in the outflow tract of the right ventricle can vary greatly between patients.
2) A VSD is present. The increased pressure in the right ventricle will result in blood moving from the right side of the heart to the left side. This in turn, can lead to cyanosis.
3) The aortic root is moved towards the right of the heart, and is situated between the right and left ventricle. This will not give any clinical problems to the patient, if the VSD is closed.
4) There is right ventricular hypertrophy, caused by narrowing of the right ventricular outflow tract.

Most adult patients underwent complete surgical repair during childhood. Surgical correction consists of correction of the right ventricular outflow tract and closure of the VSD by a patch. The severity of the defect is mostly dependent on the severity of the PS.[7] During adulthood arrhythmias and a low exercise capacity may dominate the clinical picture. These symptoms may occur due to stenosis, insufficiency of the pulmonary valve or the obstructed outflow tract of the right ventricle.[7] The shunting from the VSD may also persist into adulthood.[21,22] Patients with ToF are also susceptible to the development of arrhythmias.[21,22]

Transposition of the Great Arteries (TGA)

TGA is one of the more severe forms of ConHD. It was first described at the beginning of the 19th century by Matthew Baillie.[23] In patients with TGA the pulmonary artery (which transports blood to the lungs) is connected to the left ventricle, and the aorta (which transports

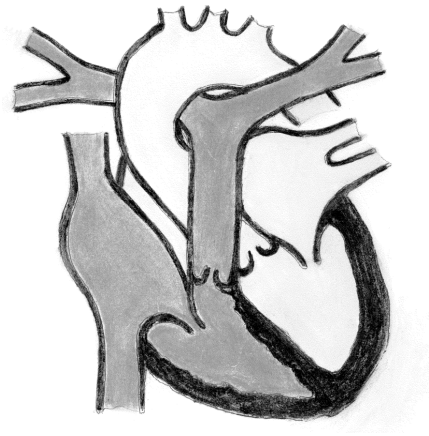
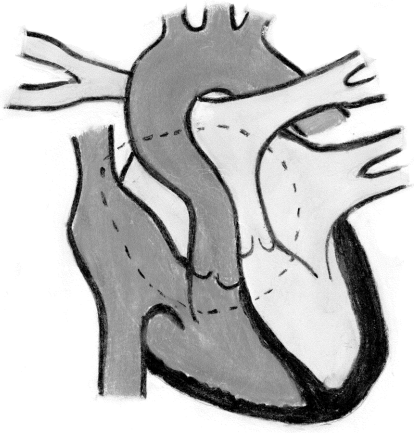


Figure 6. Normal human heart



Transposition of the Great Arteries

blood to the body) is connected to the right ventricle. This results in the left ventricle pumping blood to the lungs, and the right ventricle pumping blood to the rest of the body. The deoxygenated blood does not pass through the lungs, causing severe cyanosis in newborns. Infants can only survive in the presence of a shunt: an ASD, VSD or open duct of Botalli (which is a connection between the aorta and the pulmonary artery).[7] If no intervention has taken place by the first year, 90% of the infants will have passed away.[7]

The patients in the Erasmus Medical Center cohort from 1968 - 1980 were all operated according to the Mustard procedure (also known as the atrial switch procedure). This technique was developed by Dr. William Mustard at the Hospital for Sick Children in Toronto, Canada, in 1964.[24] This procedure connects the vena cava inferior and vena cava superior to the left ventricle by a prosthesis (baffle), and makes an ASD between the left and right atrium. This enables the blood to get oxygenated before entering the rest of the body.

Patients operated according to the Mustard procedure show many late complications.[7,25,26] The right ventricle, which lacks the morphology to act as a systemic ventricle may fail.[7,25,26] The prognosis of these patients depends strongly on the functioning of the baffle, and the functioning of the right ventricle.[7,25,26]

Impact of ConHD on biographical characteristics

Obtaining a clear picture of the biographical characteristics of patients with ConHD from literature is challenging, since many of the reported studies are conducted in different countries, where demographical factors of the normative population can vary extensively. Also the differences in age-ranges, underlying congenital diagnoses and the use of non-standardized assessment instruments in combination with small sample sizes, can hamper the interpretation of biographical data and make it hard to extrapolate the results to our own cohorts.

Living conditions

Despite difficulties comparing various study results, some features of biographical characteristics are being reported in most of the studies. Among patients with ConHD there were significantly more who had developed a dependent life style, living with their parents without a marital or quasi-marital relationship.[27-31] Literature on marital status of patients yields ambiguous results, with some studies reporting in comparison to reference groups patients with ConHD are involved either less or equally in stable relationships such as marriage.[28,30,32] Daliento et al. found that patients with ConHD have preference for an overprotective familiar setting.[28] Overprotectiveness by parents during early childhood might have played a role in the delayed process of gaining autonomy.[33] This overprotectiveness might have continued from childhood into young adulthood.[30] The way in which parents cope with the ConHD of their child has been shown to have impact on quality of life, where overprotectiveness and a psychologically controlling type of parenting is

associated with a lower quality of life at a later age and democratic parenting with a better quality of life.[34,35]

Educational attainment and occupational characteristics

Compared to normative data, lower, similar and higher levels of educational attainment have been reported.[27,30,32,36-38] Overall, patients with ConHD seem to obtain scores in the normal range of intellectual capabilities.[39] However, they may show (subtle) neuropsychological impairments, mainly involving language deficits and motor dysfunction.[39] Van Rijen et al. found a high percentage of special education (24%) in the Erasmus Medical Center cohort 10 years ago.[30] Some researchers suggested that frequent periods of cyanosis and cardiac surgery at young age can lead to neuropsychological impairments and that school absences due to hospitalizations can lead to learning problems in patients with surgically corrected ConHD.[39,40] This could explain why patients with cyanotic defects have shown a lower educational level.[27] However, at adulthood, patients might have caught up with normative samples. This can explain why literature yields conflicting results on educational level of patients with ConHD.[29,32,36,37,39,41,42] The process of catching up on educational level compared to normative data could explain why patients have jobs that are too low for their educational level.[28]

Research into the occupational status of patients with ConHD yields conflicting results, with some studies reporting lower occupational status and some reporting similar occupational status, or a higher employment rate than expected.[27-30,32,36,37,41] Especially in the academic occupational level patients seem to be underrepresented; Moons et al. reported that patients with ConHD tend to worry about employment and income. [28,43]

Impact of ConHD on psychological characteristics

Psychopathology

Patients with ConHD seem to be at an increased risk for elevated levels of psychopathology.[44-46] This was especially found in young female patients (during their early twenties), who showed higher levels of internalizing problems (such as anxiety and depression) compared to normative data.[45-47] Freitas et al. found that, compared to males, females with ConHD experience worse psychosocial adjustment, which manifests itself in more somatic complaints, anxiety/depression, aggressive behavior, attention problems, thought problems, internalizing and externalizing problems.[47] He also found that patients with poor social support showed more withdrawal and social problems.[47]

Quality of life and subjective health status

Since the term quality of life is broad and encompasses many dimensions of life, many different topics have been addressed in different studies into ConHD, using different types of questionnaires.[32,37-39,41-43,48-52]

In quality of life, distinction should be made between the subjective health status as opposed to the health-related quality of life. Subjective health status is the subjective perception by the patient of his/her state of abilities, health-related quality of life encompasses the subjective appraisal and the personal feelings of the patient about these states of abilities.[4,53] Our study has focused on the subjective health status.

In general, patients with ConHD report favorable results on overall subjective quality of life, sometimes even better compared with normative data.[49,48] Utens et al. explained this phenomenon as due to overcompensation, social desirability and "denial".[54] Despite the overall favorable quality of life, several studies have shown impairments on the physical components of subjective health status. Patients overall indicated they are satisfied with their lives.[48] The severity of the congenital heart defect often bears no relationship to reported quality of life.[30,53]

Sexual functioning

Previous studies concerning psychosocial well-being of adult patients with ConHD have largely neglected sexual functioning and only very few studies have reported on this topic.[31,55-58] Sexuality is an important part of the quality of life of patients with ConHD, and sexual problems are perceived by 10% to 20% of patients with ConHD.[31,55] Patients report more worries, distress during sexual activities and a decreased sexual self-esteem.[31,55] Females with ConHD reported sexual problems in 10%-20% of cases, 9% experienced increased or altered symptoms related to their heart during sexual activity, and nearly one-third (29%) of females with ConHD had at least once sought medical advice for menstrual discomforts.[55,56] Problems increased with worsening (cardiac) functional class, increased ConHD severity and was also increased for females with cyanotic defects.[56] Current counseling practice for sexuality, contraception and pregnancy in women with ConHD is inadequate, with females rating their level of information as unsatisfactory.[57]

Male patients with ConHD under the age of 40 engage less frequently in sexual relationships than peers from the general population.[58] Fears before or during sexual intercourse, as well as physical symptoms such as dyspnea, feelings of arrhythmia or chest pain are common.[58] A total of 10.0% of males have an erectile dysfunction according to the International Index of Erectile Function.[58]

Patients with ConHD are known to have fewer children compared with the general population, and some adult patients have renounced the idea of having children due to their cardiac malformation.[32,36,37,42]

Sports in patients with ConHD

Sport participation in adults with ConHD is a relatively new territory and many physicians are having difficulty in advising patients. Their first concern is safety and they fear that intensive or competitive sport participation will increase the risk of sudden cardiac death. Literature has reported lower physical activity for patients with ConHD and there are discrepancies and gaps in knowledge between what physicians and patients with ConHD consider safe when practising sports.[59-61,62] Patients with ConHD have reported fear of physical exercise and physicians may have been over-conservative in their advice on sports.[59,61,63] On the other hand, sport participation may also have beneficial effects. In patients with coronary artery disease sport participation was associated with increased quality of life and decreased anxiety, hostility and depression scores.[64,65]

IMPACT OF CONHD ON MEDICAL CHARACTERISTICS

In addition to impact on biographical characteristics and psychological aspects, ConHD has influence on medical characteristics. In this thesis, the focus will be on implantable pacemakers and Implantable Cardioverter Defibrillators (ICDs) in patients with ConHD.

Implantable Cardioverter Defibrillators and quality of life

The leading cause of mortality in adult patients with ConHD is sudden cardiac death (SCD).[66] In comparison with the general population, an adult patient with ConHD has a 25–100 fold increased risk to die as a result of SCD.[67] Implantable cardioverter defibrillators are used as therapy for patients that are at high risk of developing, or patients that have survived, a life- threatening cardiac arrhythmia.[68] However, the indication of ICD therapy in patients with ConHD is still a matter of debate. A recent publication by our group investigating the efficacy of ICD therapy in patients with ConHD demonstrated that 23% of all patients received an appropriate shock and 41% received at least one inappropriate shock.[69] This inappropriate shock rate is higher compared with other patient groups. Other studies reported an inappropriate shock rate of roughly 25% and an appropriate shock rate of roughly 22–30% in patients with ConHD.[68,70]

Patients with ConHD have to cope with an increased risk to die as a result of SCD.[67] In addition, inappropriate shocks delivered to patients who are fully conscious, might cause stress, anxiety for shock and anxiety for premature death, thereby worsening the psychological problems.[71,72]

Complications of pacemaker therapy

The improved survival following congenital heart surgery is hampered by both structural and electrical long-term complications, including: atrioventricular (AV) block, sinus node dysfunction and atrial arrhythmias.[73,74] Many patients with ConHD will require pacemaker therapy and are subject to lifelong need of reinterventions and follow-up.[73] Pacemaker implantation in this population can be challenging due to the complexity of the systemic venous anatomy, venous obstructions and/or residual intra-cardiac shunting.[75,76] Furthermore, pacemaker implantation at young age and the use of epicardial leads has been associated with a high incidence of lead failures during follow-up.[76-80] Due to these issues, pacemaker therapy should be considered carefully in patients with ConHD. To improve patient care, knowledge regarding the indications and impact of pacemaker therapy is essential. Unfortunately, data on complications in pacemaker implantation are scarce for the adult ConHD population and large multi-center studies are lacking.[75,76] Furthermore, most ConHD studies only focus on lead failure rate.

Arrhythmias and pacemakers in patients with ConHD

In the general population, several prospective randomized trials have demonstrated that atrial-based pacing ("physiologic pacing") reduces the incidence of atrial fibrillation compared with ventricular pacing.[81-86] This is not surprising, since loss of AV synchrony due to ventricular pacing is associated with increased natriuretic peptide levels, sympathetic nervous activation and atrial pressures; all factors associated with the development of atrial fibrillation.[87,88] Whether atrial-based pacing is beneficial in the adult ConHD population is not clear.[75]

Thesis outline

Chapter 2 addresses the biographical characteristics in two cohorts of patients with ConHD who underwent surgery at young age in the Erasmus Medical Center. The patients of the first cohort operated between 1968-1980 were studied in 2011 and the results are presented in chapter 2.1. The patients with ConHD from the Erasmus Medical Center cohort started in 2010, are investigated in chapter 2.2. Both chapters also address leisure time and social participation.

Chapter 3 addresses the psychological aspects of living with ConHD. Chapter 3.1 focuses on the development of psychopathology between three time points: namely 10, 20 and 30 years of follow-up. Subjective health is studied at 30-year follow-up only. Chapter 3.2 describes the outcome of sexuality (both for males and females with ConHD) compared to the normal population. Finally, in chapter 3.3, the participation in sports of patients with ConHD is studied and its impact on exercise capacity and quality of life is investigated.

Chapter 4 focuses on the medical aspects of living with ConHD in the pacemaker/ICD area. Chapter 4.1 describes the psychological impact of having an ICD in patients with ConHD.

Chapter 4.2 describes the incidence and type of complications induced by pacemaker therapy in patients with ConHD. Chapter 4.3 focuses on the development of arrhythmias during pacemaker therapy in patients with ConHD.

REFERENCES

1. Warnes CA. The adult with congenital heart disease: born to be bad? J Am Coll Cardiol. 2005 Jul 5; 46(1):1-8.
2. Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. N Engl J Med. 2000 Jan 27;342(4):256-63.
3. Gregory, D. Dictionary of Human Geography. Oxford: Wiley-Blackwell, 2009.
4. Moons P, Budts W, De Geest S. Critique on the conceptualisation of quality of life: a review and evaluation of different conceptual approaches. Int J Nurs Stud. 2006 Sep;43(7):891-901.
5. van der Velde ET, Vriend JW, Mannens MM, Uiterwaal CS, Brand R, Mulder BJ. CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: rationale, design, and first results. Eur J Epidemiol 2005; 20:549-57.
6. Larsen WJ. Development of the Heart & Development of the Vasculature, Chapter 7 & 8. Human Embryology. Philadelphia: Churchill Livingstone, 2001: 157-234.
7. Mulder BJM, Pieper PG, Meijboom FJ, Hamer JPM. Aangeboren hartafwijkingen bij volwassenen. Houten: Bohn Stafleu van Loghum, 2006.
8. Roelandt JRTC, Lie KI, Wellens HJJ, van de Werf F. Cardiologie. Houten: Bohn Stafleu van Loghum, 2002.
9. Mustard WT. Diversion of the venae cavae into the left atrium during closure of atrial septal defects. J Thorac Cardiovasc Surg. 1964 Mar;47:317-24.
10. Meijboom F, Hess J, Szatmari A, Utens EM, McGhie J, Deckers JW, Roelandt JR, Bos E. Long-term follow-up (9 to 20 years) after surgical closure of atrial septal defect at a young age. Am J Cardiol. 1993 Dec 15;72(18):1431-4.
11. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, van Domburg R, van Rijen EH, Utens EM, Bogers AJ, Simoons ML. Excellent survival and low incidence of arrhythmias, stroke and heart failure long-term after surgical ASD closure at young age. A prospective follow-up study of 21-33 years. Eur Heart J. 2003 Jan;24(2):190-7.
12. Mustard WT. Surgery for ventricular septal defects in infants and children. Am J Surg. 1964 Mar; 107:480-5.
13. Meijboom F, Szatmari A, Utens E, Deckers JW, Roelandt JR, Bos E, Hess J. Long-term follow-up after surgical closure of ventricular septal defect in infancy and childhood. J Am Coll Cardiol. 1994 Nov 1;24(5):1358-64.
14. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, Van Domburg R, Van Rijen EH, Utens EM, Bogers AJ, Simoons ML. Outcome of patients after surgical closure of ventricular septal defect at young age: longitudinal follow-up of 22-34 years. Eur Heart J. 2004 Jun;25(12):1057-62.
15. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, vanDomburg RT, vanRijen EH, Utens EM, Bogers AJ, Simoons ML. Long-term outcome after surgery for pulmonary stenosis (a longitudinal study of 22-33 years). Eur Heart J. 2006 Feb;27(4):482-8.
16. Fallot ELA. Contribution à l'anatomie pathologique de la maladie bleue (cyanose cardiaque). Marseille médical, 1888.
17. Lillehei CW, Cohen M, Warden HE, Read RC, Aust JB, Dewall RA, Varco RL. Direct vision intracardiac surgical correction of the tetralogy of Fallot, pentalogy of Fallot, and pulmonary atresia defects; report of first ten cases. Ann Surg. 1955 Sep;142(3):418-42.
18. Pacifico AD, Bargeron LM Jr, Kirklin JW. Primary total correction of tetralogy of Fallot in children less than four years of age. Circulation. 1973 Nov;48(5):1085-91.
19. Starr JP. Tetralogy of fallot: yesterday and today. World J Surg. 2010 Apr;34(4):658-68.

20. Bonchek LI, Starr A, Sunderland CO, Menashe VD. Natural history of tetralogy of Fallot in infancy. Clinical classification and therapeutic implications. Circulation. 1973 Aug;48(2):392-7.
21. Meijboom F, Szatmari A, Deckers JW, Utens EM, Roelandt JR, Bos E, Hess J. Cardiac status and health-related quality of life in the long term after surgical repair of tetralogy of Fallot in infancy and childhood. J Thorac Cardiovasc Surg. 1995 Oct;110(4 Pt 1):883-91.
22. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. Circulation. 1995 Apr 15;91(8):2214-9.
23. Baille M. The Morbid Anatomy of Some of the Most Important Parts of the Human Body. Walpole: Printed by G.W. Nicholas, for W. Fessenden, Bookseller, Brattleborough, 1808.
24. Mustard WT. Successful two-stage correction of transposition of the great vessels. Surgery. 1964 Mar;55:469-72.
25. Meijboom F, Szatmari A, Deckers JW, Utens EM, Roelandt JR, Bos E, Hess J. Long-term follow-up (10 to 17 years) after Mustard repair for transposition of the great arteries. J Thorac Cardiovasc Surg. 1996 Jun;111(6):1158-68.
26. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, van Domburg R, van Rijen EH, Utens EM, McGhie J, Bos E, Bogers AJ, Simoons ML. Decline in ventricular function and clinical condition after Mustard repair for transposition of the great arteries (a prospective study of 22-29 years). Eur Heart J. 2004 Jul;25(14):1264-70.
27. Kokkonen J, Paavilainen T. Social adaptation of young adults with congenital heart disease. Int J Cardiol. 1992 Jul;36(1):23-9.
28. Daliento L, Mapelli D, Russo G, Scarso P, Limongi F, Iannizzi P, Melendugno A, Mazzotti E, Volpe B. Health related quality of life in adults with repaired tetralogy of Fallot: psychosocial and cognitive outcomes. Heart. 2005 Feb;91(2):213-8.
29. Simko LC, McGinnis KA, Schembri J. Educational needs of adults with congenital heart disease. J Cardiovasc Nurs. 2006 Mar-Apr;21(2):85-94.
30. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. Eur Heart J. 2003 Apr;24(7):673-83.
31. Winter MM, Reisma C, Kedde H, Bouma BJ, Vis JC, Luijendijk P, de Witte P, Zwinderman AH, Vliegen HW, Pieper PG, van Dijk AP, Mulder BJ. Sexuality in adult patients with congenital heart disease and their partners. Am J Cardiol. 2010 Oct 15;106(8):1163-8, 1168.e1-8.
32. Sairanen HI, Nieminen HP, Jokinen EV. Late results and quality of life after pediatric cardiac surgery in Finland: a population-based study of 6,461 patients with follow-up extending up to 45 years. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2005:168-72.
33. Ong L, Nolan RP, Irvine J, Kovacs AH. Parental overprotection and heart-focused anxiety in adults with congenital heart disease. Int J Behav Med. 2011 Sep;18(3):260-7.
34. Luyckx K, Goossens E, Rassart J, Apers S, Vanhalst J, Moons P. Parental support, internalizing symptoms, perceived health status, and quality of life in adolescents with congenital heart disease: influences and reciprocal effects. J Behav Med. 2012 Nov 20. [Epub ahead of print]
35. Luyckx K, Goossens E, Missotten L, Moons P; i-DETACH investigators. Adolescents with congenital heart disease: the importance of perceived parenting for psychosocial and health outcomes. J Dev Behav Pediatr. 2011 Nov;32(9):651-9.
36. Nieminen H, Sairanen H, Tikanoja T, Leskinen M, Ekblad H, Galambosi P, Jokinen E. Long-term results of pediatric cardiac surgery in Finland: education, employment, marital status, and parenthood. Pediatrics. 2003 Dec;112(6 Pt 1):1345-50.

37. Bygstad E, Pedersen LC, Pedersen TA, Hjortdal VE. Tetralogy of Fallot in men: quality of life, family, education, and employment. Cardiol Young. 2012 Aug;22(4):417-23.
38. Ternestedt BM, Wall K, Oddsson H, Riesenfeld T, Groth I, Schollin J. Quality of life 20 and 30 years after surgery in patients operated on for tetralogy of Fallot and for atrial septal defect. Pediatr Cardiol. 2001 Mar-Apr;22(2):128-32.
39. Miatton M, De Wolf D, François K, Thiery E, Vingerhoets G. Neurocognitive consequences of surgically corrected congenital heart defects: A review. Neuropsychol Rev. 2006 Jun;16(2):65-85.
40. Wernovsky G. Current insights regarding neurological and developmental abnormalities in children and young adults with complex congenital cardiac disease. Cardiol Young. 2006 Feb;16 Suppl 1:92-104.
41. Fteropoulli T, Stygall J, Cullen S, Deanfield J, Newman SP. Quality of life of adult congenital heart disease patients: a systematic review of the literature. Cardiol Young. 2013 Feb 6:1-13. [Epub ahead of print]
42. Loup O, von Weissenfluh C, Gahl B, Schwerzmann M, Carrel T, Kadner A. Quality of life of grown-up congenital heart disease patients after congenital cardiac surgery. Eur J Cardiothorac Surg. 2009 Jul;36(1):105-11; discussion 111.
43. Moons P, De Bleser L, Budts W, Sluysmans T, De Wolf D, Massin M, Gewillig M, Pasquet A, Suys B, Vliers A. Health status, functional abilities, and quality of life after the Mustard or Senning operation. Ann Thorac Surg. 2004 Apr;77(4):1359-65; discussion 1365.
44. Utens EM, Bieman HJ, Verhulst FC, Meijboom FJ, Erdman RA, Hess J. Psychopathology in young adults with congenital heart disease. Follow-up results. Eur Heart J. 1998 Apr;19(4):647-51.
45. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Longitudinal development of psychopathology in an adult congenital heart disease cohort. Int J Cardiol. 2005 Mar 18;99(2):315-23.
46. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Medical predictors for psychopathology in adults with operated congenital heart disease. Eur Heart J. 2004 Sep;25(18):1605-13.
47. Freitas IR, Castro M, Sarmento SL, Moura C, Viana V, Areias JC, Areias ME. A cohort study on psychosocial adjustment and psychopathology in adolescents and young adults with congenital heart disease. BMJ Open. 2013 Jan 28;3(1). pii: e001138.
48. Moons P, Van Deyk K, De Bleser L, Marquet K, Raes E, De Geest S, Budts W. Quality of life and health status in adults with congenital heart disease: a direct comparison with healthy counterparts. Eur J Cardiovasc Prev Rehabil. 2006 Jun;13(3):407-13.
49. Moons P, Van Deyk K, Marquet K, De Bleser L, De Geest S, Budts W. Profile of adults with congenital heart disease having a good, moderate, or poor quality of life: a cluster analytic study. Eur J Cardiovasc Nurs. 2009 Jun;8(2):151-7.
50. Kamphuis M, Ottenkamp J, Vliegen HW, Vogels T, Zwinderman KH, Kamphuis RP, Verloove-Vanhorick SP. Health related quality of life and health status in adult survivors with previously operated complex congenital heart disease. Heart. 2002 Apr;87(4):356-62.
51. Ebenroth ES, Hurwitz RA. Long-term functional outcome of patients following the mustard procedure: the next decade of follow-up. Congenit Heart Dis. 2007 Jul-Aug;2(4):235-41.
52. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, Mussatto KA, Uzark K, Goldberg CS, Johnson WH Jr, Li J, Smith SE, Bellinger DC, Mahle WT; American Heart Association Congenital Heart Defects Committee, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council. Neurodevelopmental outcomes in children with

congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation. 2012 Aug 28;126(9):1143-72.

53. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Current subjective state of health, and longitudinal psychological well-being over a period of 10 years, in a cohort of adults with congenital cardiac disease. Cardiol Young. 2005 Apr;15(2):168-75.
54. Utens EM, Verhulst FC, Erdman RA, Meijboom FJ, Duivenvoorden HJ, Bos E, Roelandt JR, Hess J. Psychosocial functioning of young adults after surgical correction for congenital heart disease in childhood: a follow-up study. J Psychosom Res. 1994 Oct;38(7):745-58.
55. Moons P, Van Deyk K, Marquet K, De Bleser L, Budts W, De Geest S. Sexual functioning and congenital heart disease: Something to worry about? Int J Cardiol. 2007 Sep 14;121(1):30-5.
56. Vigl M, Kaemmerer M, Niggemeyer E, Nagdyman N, Seifert-Klauss V, Trigas V, Bauer U, Schneider KT, Berger F, Hess J, Kaemmerer H. Sexuality and reproductive health in women with congenital heart disease. Am J Cardiol. 2010 Feb 15;105(4):538-41.
57. Vigl M, Hager A, Bauer U, Niggemeyer E, Wittstock B, Köhn FM, Hess J, Kaemmerer H. Sexuality and subjective wellbeing in male patients with congenital heart disease. Heart. 2009 Jul;95(14): 1179-83.
58. Kaemmerer M, Vigl M, Seifert-Klauss V, Nagdyman N, Bauer U, Schneider KT, Kaemmerer H. Counseling reproductive health issues in women with congenital heart disease. Clin Res Cardiol. 2012 Nov;101(11):901-7.
59. Gierat-Haponiuk K, Haponiuk I, Chojnicki M, Jaworski R, Bakuła S. Exercise capacity and the quality of life late after surgical correction of congenital heart defects. Kardiol Pol. 2011;69(8):810-5.
60. Buys R, Van De Bruaene A, Budts W, Delecluse C, Vanhees L. In adults with atrial switch operation for transposition of the great arteries low physical activity relates to reduced exercise capacity and decreased perceived physical functioning. Acta Cardiol. 2012 Feb;67(1):49-57.
61. Swan L, Hillis WS. Exercise prescription in adults with congenital heart disease: a long way to go. Heart. 2000 Jun;83(6):685-7.
62. Moons P, De Volder E, Budts W, De Geest S, Elen J, Waeytens K, Gewillig M. What do adult patients with congenital heart disease know about their disease, treatment, and prevention of complications? A call for structured patient education. Heart. 2001 Jul;86(1):74-80.
63. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E; Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC); Association for European Paediatric Cardiology (AEPC); ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J. 2010 Dec;31(23):2915-57.
64. Lavie CJ, Milani RV. Adverse psychological and coronary risk profiles in young patients with coronary artery disease and benefits of formal cardiac rehabilitation. Arch Intern Med. 2006 Sep 25;166(17):1878-83.
65. Fredriksen PM, Kahrs N, Blaasvaer S, Sigurdsen E, Gundersen O, Roeksund O, Norgaand G, Vik JT, Soerbye O, Ingjer E, Thaulow E. Effect of physical training in children and adolescents with congenital heart disease. Cardiol Young. 2000 Mar;10(2):107-14.
66. Oechslin EN, Harrison DA, Connelly MS, Webb GD, Siu SC. Mode of death in adults with congenital heart disease. Am J Cardiol. 2000 Nov 15;86(10):1111-6.

67. Silka MJ, Hardy BG, Menashe VD, Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. J Am Coll Cardiol. 1998 Jul;32(1):245-51.
68. Khairy P, Harris L, Landzberg MJ, Viswanathan S, Barlow A, Gatzoulis MA, Fernandes SM, Beauchesne L, Therrien J, Chetaille P, Gordon E, Vonder Muhll I, Cecchin F. Implantable cardioverter-defibrillators in tetralogy of Fallot. Circulation. 2008 Jan 22;117(3):363-70.
69. Yap SC, Roos-Hesselink JW, Hoendermis ES, Budts W, Vliegen HW, Mulder BJ, van Dijk AP, Schalij MJ, Drenthen W. Outcome of implantable cardioverter defibrillators in adults with congenital heart disease: a multi-centre study. Eur Heart J. 2007 Aug;28(15):1854-61.
70. Alexander ME, Cecchin F, Walsh EP, Triedman JK, Bevilacqua LM, Berul CI. Implications of implantable cardioverter defibrillator therapy in congenital heart disease and pediatrics. J Cardiovasc Electrophysiol. 2004 Jan;15(1):72-6.
71. Sears SF Jr, Todaro JF, Lewis TS, Sotile W, Conti JB. Examining the psychosocial impact of implantable cardioverter defibrillators: a literature review. Clin Cardiol. 1999 Jul;22(7):481-9.
72. Vazquez LD, Conti JB, Sears SF. Female-specific education, management, and lifestyle enhancement for implantable cardioverter defibrillator patients: the FEMALE-ICD study. Pacing Clin Electrophysiol. 2010 Sep;33(9):1131-40.
73. Yap SC, Harris L, Chauhan VS, Oechslin EN, Silversides CK. Identifying high risk in adults with congenital heart disease and atrial arrhythmias. Am J Cardiol. 2011 Sep 1;108(5):723-8.
74. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, van Dijk AP, Vliegen HW, Grobbee DE, Mulder BJ. Mortality in adult congenital heart disease. Eur Heart J. 2010 May;31(10): 1220-9.
75. Walker F, Siu SC, Woods S, Cameron DA, Webb GD, Harris L. Long-term outcomes of cardiac pacing in adults with congenital heart disease. J Am Coll Cardiol. 2004 May 19;43(10):1894-901.
76. McLeod CJ, Attenhofer Jost CH, Warnes CA, Hodge D 2nd, Hyberger L, Connolly HM, Asirvatham SJ, Dearani JA, Hayes DL, Ammash NM. Epicardial versus endocardial permanent pacing in adults with congenital heart disease. J Interv Card Electrophysiol. 2010 Sep;28(3):235-43.
77. Sachweh JS, Vazquez-Jimenez JF, Schöndube FA, Daebritz SH, Dörge H, Mühler EG, Messmer BJ. Twenty years experience with pediatric pacing: epicardial and transvenous stimulation. Eur J Cardiothorac Surg. 2000 Apr;17(4):455-61.
78. Fortescue EB, Berul CI, Cecchin F, Walsh EP, Triedman JK, Alexander ME. Patient, procedural, and hardware factors associated with pacemaker lead failures in pediatrics and congenital heart disease. Heart Rhythm. 2004 Jul;1(2):150-9.
79. Noiseux N, Khairy P, Fournier A, Vobecky SJ. Thirty years of experience with epicardial pacing in children. Cardiol Young. 2004 Oct;14(5):512-9.
80. van der Velde ET, Vriend JW, Mannens MM, Uiterwaal CS, Brand R, Mulder BJ. CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: rationale, design, and first results. Eur J Epidemiol. 2005;20(6):549-57.
81. Healey JS, Toff WD, Lamas GA, Andersen HR, Thorpe KE, Ellenbogen KA, Lee KL, Skene AM, Schron EB, Skehan JD, Goldman L, Roberts RS, Camm AJ, Yusuf S, Connolly SJ. Cardiovascular outcomes with atrial-based pacing compared with ventricular pacing: meta-analysis of randomized trials, using individual patient data. Circulation. 2006 Jul 4;114(1):11-7.
82. Connolly SJ, Kerr CR, Gent M, Roberts RS, Yusuf S, Gillis AM, Sami MH, Talajic M, Tang AS, Klein GJ, Lau C, Newman DM. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. N Engl J Med. 2000 May 11;342(19):1385-91.

83. Andersen HR, Thuesen L, Bagger JP, Vesterlund T, Thomsen PE. Prospective randomised trial of atrial versus ventricular pacing in sick-sinus syndrome. Lancet. 1994 Dec 3;344(8936):1523-8.
84. Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T, Pedersen AK. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet. 1997 Oct 25;350(9086):1210-6.
85. Lamas GA, Lee K, Sweeney M, Leon A, Yee R, Ellenbogen K, Greer S, Wilber D, Silverman R, Marinchak R, Bernstein R, Mittleman RS, Lieberman EH, Sullivan C, Zorn L, Flaker G, Schron E, Orav EJ, Goldman L. The mode selection trial (MOST) in sinus node dysfunction: design, rationale, and baseline characteristics of the first 1000 patients. Am Heart J. 2000 Oct;140(4):541-51.
86. Toff WD, Camm AJ, Skehan JD; United Kingdom Pacing and Cardiovascular Events Trial Investigators. Single-chamber versus dual-chamber pacing for high-grade atrioventricular block. N Engl J Med. 2005 Jul 14;353(2):145-55.
87. Horie H, Tsutamoto T, Ishimoto N, Minai K, Yokohama H, Nozawa M, Izumi M, Takaoka A, Fujita T, Sakamoto T, Kito O, Okamura H, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker for atrioventricular sequence in patients with pacemakers. Pacing Clin Electrophysiol. 1999 Feb;22(2):282-90.
88. Taylor JA, Morillo CA, Eckberg DL, Ellenbogen KA. Higher sympathetic nerve activity during ventricular (VVI) than during dual-chamber (DDD) pacing. J Am Coll Cardiol. 1996 Dec;28(7):1753-8.

Part 2

Impact on Biographical Characteristics

Chapter 2.1

Psychosocial functioning of adults with congenital heart disease: outcomes of a 30-43 year longitudinal follow-up

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ABSTRACT

Objective: Investigating the long-term psychosocial and emotional outcome of cardiothoracic surgery during childhood.

Methods: Adult patients (N=251, aged 33-55 years) operated for Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), Pulmonary Stenosis (PS), Tetralogy of Fallot (ToF) or Transposition of the Great Arteries (TGA) between 1968-1980 were invited and evaluated in the Erasmus Medical Center. Psychosocial and emotional functioning was measured using standardized, validated questionnaires.

Results: Compared with normative data, our cohort of patients with ConHD showed impairments on living conditions, relationships, offspring, occupational level and income. However, patients with ConHD showed a favorable quality of life and emotional functioning compared with normative data. Patients with moderate/complex ConHD reported significantly more physical restrictions, reported more often a lack in physical strength and felt significantly more often at a disadvantage because of their ConHD compared with patients with simple ConHD. Compared to 10 years ago, outcomes on biographical characteristics such as living conditions, marital status and income improved.

Conclusion: Overall, patients with congenital heart disease seem to be catching up with the normal population. They are capable of leading normal lives, although occupational level and income are still lower than expected.

INTRODUCTION

Since the first surgical techniques for patients with congenital heart disease (ConHD) became available some 55 years ago, virtually every area of patient care has evolved substantially. These improvements led to an increased survival for patients with ConHD, with over 85% of infants reaching adulthood.[1,2] In order to investigate the long-term outcomes of surgery during childhood for ConHD, the Erasmus Medical Center started a longitudinal cohort study, including all consecutive patients operated between 1968 and 1980. The present study is part of this multidisciplinary cohort study and is worldwide the first study to describe the third 10-year follow-up this unique patient cohort, now 30 – 43 years after surgical correction for ConHD. The second follow-up of this same cohort took place in 2001 and the first in 1990 (the patients' age range was 10-35 at that time).

The aims of this study were three-fold;

1) To compare the biographical characteristics, emotional and social functioning (living, work, leisure time etc.) of adult patients with ConHD with normative data (corrected for age and gender where possible)
2) To investigate differences in between cardiac diagnostic groups as to biographical characteristics, emotional and social functioning
3) To investigate how the biographical characteristics, emotional and social functioning changed over a period of 10 years (from 2001 to 2011).

METHODS

Inclusion criteria and patient sample

All consecutive patients who underwent their first open heart surgery for congenital heart disease between 1968 and 1980 in the Erasmus Medical Center, and were younger than 15 years at the time of surgery were included in this study. Included diagnoses were: Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), Pulmonary Stenosis (PS), Tetralogy of Fallot (ToF) and Transposition of the Great Arteries (TGA). The first and second follow-up of this population have been described in detail before.[3-8]

The target population of this third follow-up (2011) consisted of the 412 patients who participated in the second follow-up in 2001 (all patients had reached adult age at that time). Of these patients, ten had died (causes: 6 cardiac-related, 3 unknown, 1 accident), 1 underwent heart transplantation and 28 patients were untraceable. Of the remaining 373 eligible patients, 102 refused to participate in this study due to practical reasons (work, distance to hospital). A total of 271 patients participated resulting in a response rate of 73%. Patients were classified into 2 groups of disease severity according to the classification adopted at

the American Heart Association Task Force on Adults with CHD.[9] Patients with corrected ASD, VSD and PS were classified as simple ConHD (unless they had complications such as severe ventricular dysfunction), while patients with ToF or TGA (all operated according to Mustard repair) were classified as moderate to complex ConHD.

Assessment procedure

The research protocol was approved by the institutional ethical committee and complies with the 1975 Declaration of Helsinki. All patients were approached uniformly and invited to come to the hospital for extensive cardiac and psychological examination and signed informed consent before participating. A cardiologist medically examined all patients and the semi-structured interview and psychological questionnaires were completed. Due to practical reasons (work, children), 20 patients completed the questionnaires at home. The questionnaires were administered verbally for patients who had difficulty reading or understanding the questionnaires.

Instruments and normative groups

Biographical characteristics such as living conditions, work and income, leisure time, insurances and medical consumption were assessed by a semi-structured interview.[10] Normative data were specified by sex and age wherever possible and were derived from a variety of (very large) samples of the Dutch population, so that representativeness of normative groups was warranted.[11] Sample sizes of these multiple, large normative data groups were not included in the tables to prevent confusion. Leisure time activities were assessed with standardized items derived from the Netherlands Bureau of Statistics.[11]

Emotional functioning was assessed by the psychometrically sound Dutch Personality Questionnaire (DPQ).[12] Four scales of this questionnaire were used, namely Neuroticism, Social Inadequacy, Hostility and Self-esteem. Neuroticism measures feelings of distress, depression, instability and insecurity. Social inadequacy assesses problems in social contacts. Hostility measures the extent of criticism, distrust and intolerance towards other people. Self-esteem assesses a positive attitude towards work, flexibility and being energetic and self-controlled. A high score indicates unfavorable outcomes, except on self-esteem, where a low score is unfavorable.

Quality of life was assessed by the Satisfaction with Life Scale (SWLS) which has been proven psychometrically sound for patients with ConHD.[13] Normative data was derived form a large Belgian general population sample.[13]

Social functioning. The Perceived Social Support Scale (PSSS12) was used to assess interactions and discrepancies that people experience in receiving social support from their direct environment.[14]

Statistical analyses

Categorical variables are represented by frequencies and percentages. When comparing frequencies, the chi-square test or Fisher exact test was used, where appropriate. Continuous data are presented as mean ± SD. Comparison of continuous variables between groups was made by independent sample T-tests and in case of a skewed distribution Mann-Whitney-U tests were used. Two-tailed probability values of <0.05 were considered statistically significant. Regarding income, groups were defined by the median income of the ConHD group. The statistical package IBM SPSS Statistics for Mac version 19.0 (Release 19.0.0) was used.

RESULTS

Biographical characteristics

Overall characteristics (Table 1)

At this third follow-up, compared with normative data patients were living significantly more often with their parents (p<0.0001) and less often had children (p=0.01) compared with normative data. Concerning educational level, patients with ConHD less often had a scientific educational level compared with normative data (p=0.001).

Patients with simple ConHD were significantly older (p<0.0001) and were independently more often (p=0.021) compared with patients with moderate/complex ConHD. Concerning offspring, there was no difference between simple ConHD and moderate/complex ConHD (p=0.7).

Compared to 10 years ago, patients nowadays more often were living independently (p<0.0001) and more often were married (p<0.0001). In 2001, more than half of the patients did not have any children, but nowadays the majority had children (p<0.0001). Over time the educational level has shifted, with patients now having completed a higher level of education compared to a decade ago (p<0.001).

Data on work, working conditions and income (Table 2)

Compared With normative data, patients more often had a lower occupational level (p<0.001), and less often had a higher (p=0.023) or scientific (p=0.04) occupational level. Concerning income, patients with ConHD earned less compared with normative data (p=0.03). The

Table 1. Biographical Characteristics

	2011			2001			2001 vs. 2011			Total 2011 vs. norm	
	Simple	Moderate/complex	p	Simple	Moderate/complex	p	Total 2001	Total 2011	p	Norm	p
	n=168	n=83		n=168	n=83		n=251	n=251		n=~	
Age	40.5 [37.4-45.5]	37.8 [33.6-40.9]	0.000	30.5 [27.7-35.8]	27.4 [23.6-30.6]	0.000	29.6 [26.1-34.8]	39.7 [35.9-44.9]	0.000	-	-
Male	48.8	59.0	0.127	48.8	59.0	0.127	52.2	52.2	-	-	-
Living conditions											
• With parents	3.6	9.9	0.043	10.7	25.3	0.003	15.5	5.6	0.000	2.2	0.001
• Independently	94.0	85.2	0.021	84.5	69.9	0.007	79.7	91.2	0.000	96.2	0.000
• Institution	2.4	3.7	0.685	3.6	3.6	1.000	3.6	2.8	0.625	0.8	0.004
• Other	-	1.2	0.325	1.2	1.2	1.000	1.2	0.4	1.000	0.8	1.000
Martial status											
• (No) stable relationship[a]	31.0	42.0	0.087	47.0	65.9	0.005	53.2	34.5	0.000	29.5	0.083
• Married	60.7	58.0	0.685	50.0	31.7	0.006	44.0	59.8	0.000	59.3	0.897
• Divorced	7.7	-	0.011	3.0	2.4	1.000	2.8	5.2	0.210	10.6	0.004
• Widowed[b]	0.6	-	1.000	-	-	-	-	0.4	1.000	0.6	1.000
Offspring											
• 0 children	33.7	35.8	0.748	58.4	70.7	0.060	62.5	34.4	0.000	27.0	0.010
• ≥1 children	66.3	64.2		41.6	29.3		37.5	65.6		73.0	0.010
Daily activities											
• School	0.6	-	1.000	3.0	9.8	0.026	5.3	0.4	0.002	-	-
• Job	83.2	75.6	0.152	82.4	75.6	0.206	80.2	80.7	0.665	-	-
• Combination above	3.6	4.9	0.733	-	-	-	-	4.0		-	-
• Looking for job	1.8	-	0.553	-	3.7	0.036	1.2	1.2	1.000	-	-
• Disabled	3.0	6.1	0.241	-	3.7	0.036	1.2	4.0	0.070	-	-
• Volunteer unpaid work	1.2	2.4	0.600	2.4	-	0.305	1.6	1.6	1.000	-	-

Table 1. (continued)

	2011			2001			2001 vs. 2011			Total 2011 vs. norm	
	Simple	Moderate/complex	p	Simple	Moderate/complex	p	Total 2001	Total 2011	p	Norm	p
	n=168	n=83		n=168	n=83		n=251	n=251		n=~	
• Long-term sick leave	0.6	2.4	0.253	1.2	1.2	1.000	1.2	1.2	1.000	-	-
• Work place for mentally handicapped	3.0	2.4	1.000	4.8	4.9	1.000	4.9	2.8	0.031	-	-
• Housewife/man	3.0	6.1	0.241	6.1	1.2	0.106	4.5	4.0	1.000	-	-
Educational attainment[c]											
• Lower	24.8	28.9	0.492	45.1	48.1	0.657	46.1	26.2	0.000	26.1	0.943
• Average	49.1	41.0	0.226	34.0	34.2	0.972	34.0	46.4	0.000	42.3	0.199
• Higher	22.4	22.9	0.934	16.0	16.5	0.936	16.2	22.6	0.003	20.2	0.343
• Scientific	3.6	7.2	0.213	4.9	1.3	0.278	3.7	4.8	1.000	11.4	0.001

a) All patients that do not have a (stable) relationship or are living together without marriage.
b) All patients that have been widowed, regardless of their current marital status.
c) Based on the Standaard Onderwijsindeling (Standard Educational Divisions) 2006.
Normative data were derived form the Dutch Central Bureau of statistics in 2011.[11]

Table 2. Data on work, working conditions and income

	2011			2001			2001 vs. 2011			Total 2011 vs. norm	
	Simple n=168	Moderate/complex n=83	p	Simple n=168	Moderate/complex n=83	p	Total 2001 n=251	Total 2011 n=251	p	Norm n=~	p
Occupational level[a,b]											
• Elementary	6.0	7.2	0.717	6.7	8.3	0.653	7.2	6.4	0.629	6.3	0.890
• Lower	33.8	31.9	0.782	26.0	33.3	0.257	28.4	33.2	0.155	20.6	0.000
• Average	39.1	31.9	0.305	42.7	41.7	0.888	42.3	36.8	0.222	38.6	0.628
• Higher	17.2	18.8	0.770	21.3	12.5	0.112	18.5	17.7	0.728	24.4	0.023
• Scientific	4.0	10.1	0.072	3.3	4.2	0.716	3.6	5.9	0.000	10.1	0.043
Income											
• <= 26 000	49.6	37.0	0.117	58.9	72.0	0.112	63.0	46.0	0.000	46.0	0.030
• > 26 000	50.4	63.0		41.1	28.0		37.0	54.0		54.0	
Sick-leave[c]	0.0 [0.0-1.8]	0.0 [0.0-1.4]	0.298	0.9 [0.0-4.5]	1.0 [0.0-3.2]	0.436	1.0 [0.0-3.8]	0.0 [0.0-1.6]	0.008	-	-
	5.0 ± 17.3	2.6 ± 8.0	0.272	5.8 ± 18.9	11.3 ± 52.1	0.411	4.7 ± 15.6	4.5 ± 16.1	0.899	4.2	-
Amount of hours work per week											
(Median)	36.0 [27.0-40.0]	39.0 [32.0-42.4]	0.206	38.0 [31.5-40.0]	38.0 [32.0-40.0]	0.638	38.0 [32.0-40.0]	38.0 [28.0-40.0]	0.180	-	-
Alternative: part-time/full-time[b]											
• Part-time	37.4	33.8	0.618	30.8	25.4	0.618	29.1	36.3	0.017	38.2	0.621
• Full-time	62.6	66.2		69.2	74.6		70.9	63.7		61.8	
Reason part-time											
• Heart sole reason	4.9	4.2	1.000	2.2	17.6	0.059	6.5	4.7	-	-	-
• Heart plays a role	8.2	20.8	0.104	6.7	5.9	1.000	6.5	11.8	1.000	-	-
• Heart no role	86.9	75.0	0.184	91.1	76.5	0.125	87.1	83.5	0.625	-	-

Table 2. (continued)

	2011			2001			2001 vs. 2011			Total 2011 vs. norm	
	Simple	**Moderate/complex**	**p**	**Simple**	**Moderate/complex**	**p**	Total 2001	Total 2011	**p**	**Norm**	**p**
	n=168	**n=83**		**n=168**	**n=83**		**n=251**	**n=251**		**n=~**	
Do you experience limitations in choosing a profession because of ConHD											
• A lot	3.0	12.8	0.003	-	-	-	-	6.2	-	-	-
• A little	5.5	12.8	0.046	-	-	-	-	7.8	-	-	-
• Not at all	91.5	74.4	0.000	-	-	-	-	86.0	-	-	-
Do you perform physically hard work?											
• Yes, on a regular basis	14.4	10.3	0.406	-	-	-	-	13.1	-	-	-
• Yes, sometimes	15.0	19.1	0.448	-	-	-	-	16.3	-	-	-
• No	69.9	70.6	0.922	-	-	-	-	70.1	-	-	-
• I don't know	0.7	-	0.504	-	-	-	-	0.5	-	-	-

Abbreviations: Part-time is working < 36 hours a week; Full-time is working ≥ 36 hours a week.

a) Based on the Standaard Beroepenclassificatie (Standard Occupation Classification) 2010.

b) Only patients who have a job (≥12 hours per week) are included, to make data comparable with normative data.

c) Sick-leave percentage was used instead of number of days on sick-leave, since the number of hours a person works per week may vary considerably. Persons on long-term sick-leave are included.

Normative data was derived from the Netherlands Bureau of Statistics 2010.[11] Normative data on daily activities was not available and is therefore not displayed in the table. P-values could not be calculated since data on standard deviations or ranges were missing for the normative groups.

amount of hours worked (part-time/full-time) did not differ from normative data (p=0.621). Patients reported their sick-leave to be comparable to colleagues. In line, patients indeed had the same amount of sick-leave (expressed as the percentage of days absent from work) compared with normative data (4.3% vs. 4.2%).

The majority patients with ConHD did not feel limited in choosing a profession, but patients with moderate/complex ConHD reported more frequently to feel limited compared with patients with simple ConHD (p<0.0001). Patients with simple ConHD versus moderate/complex ConHD did not differ as to the amount of hours worked per week (p=0.6) or sick-leave (p=0.4). The majority of days absent from work was unrelated to the ConHD; this was similar for patients with simple versus moderate/complex ConHD (p=0.145). Significantly more patients with moderate/complex ConHD than simple ConHD visited their doctor because of their ConHD. Patients with simple ConHD visited their doctor less often because of a cardiac related reason.

Compared to a decade ago, patients now had a higher occupational level, and nowadays significantly more patients worked in the scientific category (p<0.001). Patients also received higher income over time (p<0.001) and over time found it easier to preserve their working schedule (p<0.001). Compared to 2001, less patients reported to be treated unequally by their colleagues (p=0.043) or felt isolated form their colleagues (p=0.027).

In 2001, the majority of patients reported to be less often sick compared with colleagues. This changed significantly over time, with more patients nowadays reporting to be equally sick compared with colleagues (p=0.016).

View on ConHD (Table 3)

The majority of patients (78%) did not view their ConHD as a serious illness. Patients with moderate/complex ConHD significantly more often reported to perceive their ConHD as very serious compared with patients with simple ConHD (p=0.002). Patients perceived their life expectancy to be equal to that of the normal Dutch population (80 years). This did not differ between ConHD diagnoses (p=0.6).

Significantly more patients with moderate/complex ConHD compared with simple ConHD reported to experience physical restrictions (p<0.0001), show a lack in physical strength (p<0.0001) and sometimes felt to have less control over their body (p=0.041) Also, significantly more moderate/complex ConHD patients felt limited to go on a holiday (p=0.047), to practice sports (p=0.001), to perform a job (p=0.032) and to raise children (p=0.002) compared with patients with simple ConHD. Patients with moderate/complex ConHD felt more at a disadvantage in life because of their ConHD (p=0.002), and over time this feeling got stronger (p<0.0001).

Now significantly more (80.2%) patients do not feel restricted because of their scar (p=0.001) compared with 10 years ago (69.1%). Patients now also felt more positive about achieving their ideals in life (p=0.011).

Table 3. View on ConHD

	2011			2001			2001 vs. 2011		
	Simple n=168	**Moderate/complex n=83**	**p**	**Simple n=168**	**Moderate/complex n=83**	**p**	Total 2001 **n=251**	Total 2011 **n=251**	**p**
Contact with other ConHD patients									
• Yes	13.3	22.2	0.072	15.9	11.0	0.302	14.2	16.2	0.576
How serious is your ConHD									
• Not serious	83.7	65.8	0.002	90.1	73.2	0.001	84.4	78.0	0.026
• Moderately serious	15.1	25.3	0.053	8.6	24.4	0.001	13.9	18.4	0.126
• Very serious/bad	1.2	8.9	0.006	1.2	2.4	0.604	1.6	3.7	0.267
Life expectancy	80.0 [76.0-90.0]	80.0 [75.0-90.0]	0.641	-	-	-	-	80.0 [75.0-90.0]	-
Restriction due to scar									
• Never	80.2	80.2	0.999	73.8	59.8	0.025	69.1	80.2	0.001
• Sometimes	14.4	9.9	0.322	18.3	32.9	0.010	23.2	12.9	0.002
• Often	5.4	9.9	0.190	7.9	7.3	0.866	7.7	6.9	1.000
Self perceived physical restrictions because of heart problems									
• Never	85.5	58.8	0.000	84.8	59.8	0.000	76.4	76.8	0.897
• Sometimes	9.6	30.0	0.000	12.2	29.3	0.001	17.9	16.3	0.791
• Often	4.8	11.2	0.062	3.0	11.0	0.011	5.7	6.9	0.424
Lacks physical strength because of ConHD									
• Never	92.1	78.5	0.002	84.7	85.2	0.915	84.8	87.7	0.441
• Sometimes	4.8	15.2	0.006	14.7	12.3	0.613	13.9	8.2	0.053
• Often	3.0	6.3	0.224	0.6	2.5	0.257	1.2	4.1	0.092

Table 3. (continued)

	2011			2001			2001 vs. 2011		
	Simple	Moderate/complex	p	Simple	Moderate/complex	p	Total 2001	Total 2011	p
	n=168	n=83		n=168	n=83		n=251	n=251	
At a disadvantage because of ConHD									
• Not at all	85.5	68.4	0.002	93.9	80.2	0.001	89.3	79.9	0.000
• Moderately	10.9	27.8	0.001	4.9	17.3	0.001	9.0	16.4	0.006
• A lot	3.6	3.8	1.000	1.2	2.5	0.602	1.6	3.7	0.146
Vision on the future									
Achieving ideals									
• Positive	82.7	83.6	0.873	68.9	69.6	0.915	69.2	83.0	0.000
• Neutral	16.0	13.7	0.643	29.8	29.1	0.911	29.6	15.3	0.000
• Negative	1.2	2.7	0.590	1.2	1.3	1.000	1.2	1.7	1.000
Physical and mental wellbeing									
• Positive	70.1	64.1	0.347	75.5	70.0	0.364	73.7	68.2	0.081
• Neutral	28.7	32.1	0.590	21.5	28.7	0.211	23.9	29.8	0.072
• Negative	1.2	3.8	0.332	3.1	1.2	0.667	2.5	2.1	1.000

Table 4. Data on leisure time

	2011			2011 vs. Norm		
	Simple	Moderate/complex	p	Total 2011	Norm	p
	n=168	n=83		n=251	n = ~	
How much time per week do you spend exercising?						
• Never	35.8	56.2	0.002	42.4	42.7	0.949
• 1-5 hours	55.8	42.5	0.052	51.4	44.3	0.029
• > 5 hours	8.5	1.2	0.025	6.1	13.0	0.001
How often per month do you participate in club activities?						
• Never	64.8	76.2	0.071	68.6	62.4	0.048
• ≥ Once per month	35.2	23.8		31.4	37.6	
How much time per week do you spend drawing?						
• Never	84.2	91.2	0.132	86.5	90.0	0.087
• 1-5 hours	14.5	7.5	0.115	12.2	7.3	0.006
• > 5 hours	1.2	1.2	1.000	1.2	2.7	0.231
How much hours per week do you play an instrument?						
• Never	90.9	90.0	0.819	90.6	92.7	0.218
• 1-5 hours	7.9	5.0	0.593	6.9	5.3	0.252
• > 5 hours	1.2	5.0	0.091	2.4	2.0	0.497
How often do you visit a museum?						
• Never	68.5	57.5	0.091	64.9	86.0	0.000
• 3-11 times per year	30.3	41.2	0.090	33.9	13.0	0.000
• At least once a month	1.2	1.2	1.000	1.2	1.0	0.000
How much time per week do you spend walking?						
• Never	24.8	8.8	0.003	19.6	17.7	0.451
• 1-5 hours	52.7	62.5	0.149	55.9	63.0	0.024
• > 5 hours	22.4	28.7	0.280	24.5	19.3	0.043
How much time per week do you spend cycling?						
• Never	27.3	28.7	0.809	27.8	16.0	0.000
• 1-5 hours	60.6	57.5	0.642	59.6	66.3	0.030
• > 5 hours	12.1	13.8	0.719	12.7	17.7	0.036
How often do you go on a holiday?						
• Never	6.1	7.5	0.669	6.5	34.0	0.000
• Once a year	40.0	31.2	0.184	37.1	48.3	0.001
• More than once a year	53.9	61.3	0.279	56.3	17.7	0.000
How much hours per day do you spend watching television?						
• <1 hour	3.0	7.6	0.110	4.5	2.0	0.011
• 1-5 hours	23.2	25.3	0.713	23.9	10.0	0.000
• 5-10 hours	34.1	30.4	0.558	32.9	17.0	0.000
• 10-20 hours	29.3	25.3	0.520	28.0	38.0	0.001
• >20 hours	10.4	11.4	0.808	10.7	33.0	0.000

Table 4. (continued)

	2011			2011 vs. Norm		
	Simple	Moderate/complex	p	Total 2011	Norm	p
	n=168	n=83		n=251	n = ~	
How much time do you spend at the computer per week?						
• <30 min	17.8	19.0	0.821	18.2	-	-
• 30 - 60 min	18.4	16.5	0.710	17.8	-	-
• 1 - 2 hour	30.1	20.3	0.106	26.9	-	-
• 2 - 3 hours	9.2	15.2	0.165	11.2	-	-
• >3 hours	24.5	29.1	0.447	26.0	-	-
How often do you have contact with your family?						
• More than or once a week	82.2	88.6	0.199	84.3	-	-
• Two times per month	9.2	7.6	0.677	8.7	-	-
• Once per month	5.5	2.5	0.511	4.5	-	-
• Less than once a month	2.5	-	0.307	1.7	-	-
• Rarely/never	0.6	1.3	0.547	0.8	-	-
How often do you have contact with your friends or acquaintances?						
• More than or once a week	66.5	73.4	0.273	68.7	-	-
• Two times per month	18.3	19.0	0.896	18.5	-	-
• Once per month	7.3	3.8	0.286	6.2	-	-
• Less than once a month	3.0	1.3	0.402	2.5	-	-
• Rarely/never	4.9	2.5	0.388	4.1	-	-

Normative data were derived form the Dutch Central Bureau of statistics in 2011.[11]

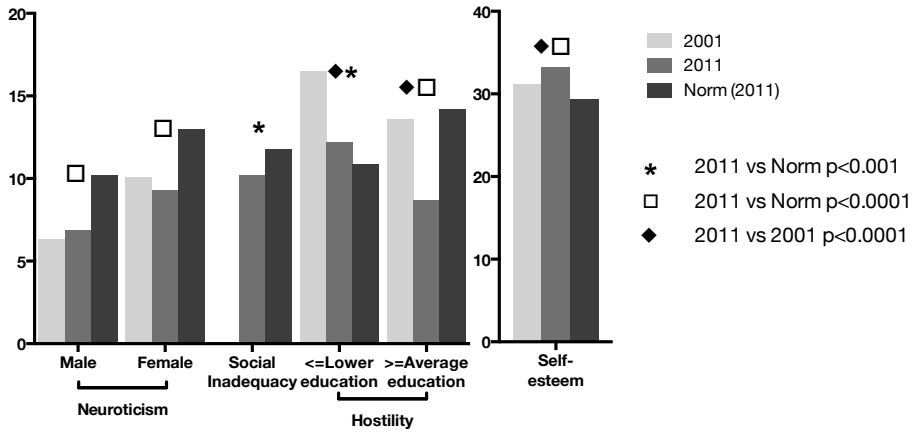
Data on leisure time (Table 4)

Compared With normative data, the entire ConHD population spent less time exercising (p=0.029) and were less engaged in clubs and social organizations. Patients with simple ConHD spent more hours exercising per week compared with patients with moderate/complex ConHD (p=0.002), however patients with moderate/complex ConHD spent more time walking compared with patients with simple ConHD (p=0.003).

EMOTIONAL AND SOCIAL FUNCTIONING

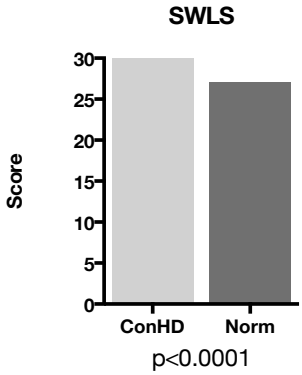
Regarding the *Dutch Personality Questionnaire* (Figure 1), compared with normative data, patients with ConHD obtained a more favorable score on all scales, including less neuroticism (for both males and females), less social inadequacy, less hostility (only for patients with an average or higher than average education) and higher self-esteem. Compared to 10 years ago, patients showed less hostility and a higher self-esteem.

Figure 1: The Dutch Personality Questionnaire of patients with ConHD in 2001 and 2011 compared with normative data



The normative data (black) was derived form the Dutch Central Bureau of Statistics (CBS), and consists data form data derived in 2011.[11] On all scores except self-esteem, a high score is less favorable. On self-esteem a high score is more favorable.

Figure 2: Satisfaction with life and overall subjective quality of life for patients with ConHD compared with normative data



Abbreviations: SWLS = Satisfaction with Life scale; ConHD = Total congenital heart disease population; Norm = Normative data.

On the *Satisfaction with Life Scale* (Figure 2) patients with ConHD obtained significantly higher score compared with normative data.

Concerning *Social support* (PSSS12), normative data were not available, rendering comparison with the average Dutch situation not possible. On social support, no significant

differences were found between patients with simple ConHD and patients with moderate/complex ConHD. Patients obtained 85.5% of the maximum score for social support from family and friends, and 100% of the maximum score for social support from a special person. These findings indicate a favorable social support.

DISCUSSION

Our cohort of patients with ConHD showed impairments on living conditions, relationships, offspring, occupational level and income. Overall, however, patients showed a favorable quality of life and emotional functioning compared with normative data.

Patients with moderate/complex ConHD reported significantly more physical restrictions, reported more often to lack physical strength and felt significantly more often at a disadvantage because of their ConHD compared with patients with simple ConHD. Compared to 10 years ago, biographical characteristics such as living conditions, marital status and income seem to have improved.

Recent follow-up (2011) versus normative data

Biographical outcome

In this study, patients less often lived independently compared with normative data, this was found especially in male patients with moderate/complex ConHD. This confirms previous findings regarding living conditions; Daliento et al. and Simko et al. described that patients with ConHD have a preference for an overprotective setting, living less independently more often compared with healthy counterparts.[15-16]

The percentage of patients married in our study (59.8%) was comparable to normative data, and in line with literature.[17-18] Patients with ConHD are known to have less offspring compared with normative data, an effect that we observed in our study as well.[17-19]

In 2001, patients in fact had more days of sick-leave from work compared with normative data ("objectively" assessed), but reported to be less often sick compared with colleagues ("subjectively" assessed). In the present follow-up, patients reported an equal amount of sick leave compared with normative data (objectively) and compare to colleagues (subjectively). These findings indicate that the gap between objective and subjective sick leave, which was found in 2001 has disappeared in the last 10 years.[5] This might indicate that when getting older, patients may acquire a more realistic perception of their actual sick leave.

Leisure time

Compared with normative data, patients with ConHD spent less time exercising and cycling, despite positive recommendations in guidelines on exercise for (young) ConHD patients.[20] Patients with moderate/complex ConHD spent less hours practicing sports and exercising, but more hours walking compared with normative data. It could be that patients with moderate/complex ConHD tried to compensate their physical limitations when practicing sports by walking more often. Although indicating they significantly more often felt limited as to going on a holiday, patients with moderate/complex ConHD did not go on holiday less often compared with patients with simple ConHD. It could have been that these patients choose a holiday that may be more suited for their physical abilities.

Quality of Life, emotional and social functioning

On both scales of (subjective) quality of life and on the personality questionnaire, patients obtained more favorable scores compared with the general Dutch population. This may indicate overcompensation, social desirability or "response shift".[3-6,21] Our results are in line with previous studies, in which a good quality of life for patients with ConHD has been reported.[13,22-24] Mostly, impairments found in quality of life studies encompass the physical issues.[19,25-28]

Changes over a period of 10 years in ConHD patients

Biographical characteristics

Compared to a decade ago, more ConHD now more often lived independently. Also, more patients were married now and had children. Our findings support the idea that ConHD patients experience a delayed process of autonomy and striving for independence.[3,16,29] Furthermore, overprotectiveness by parents at a young age might have played a role in the delayed process of gaining autonomy.[30,31] This overprotectiveness might have continued from childhood into early adolescence, and into adult age.[5]

Compared to the previous follow-up 10 years ago, patients obtained a significantly higher educational level. In this study, the cohort seems to have caught up with normative data as to education. In literature, contradictionary outcomes are found as to educational level.[16-19,23-25] This finding strengthens the idea that school absences due to hospitalizations with frequent periods of cyanosis and cardiac surgery at young age may result in learning problems and delays at school.[23,29,32] At adulthood, patients seem to have caught up with normative samples, perhaps by spending more time obtaining a higher educational level to compensate physical impairments.

During childhood and early adolescence patients had a lower educational level compared with normative data. This presumably contributed to the outcome, already a decade ago,

that the cohort was overrepresented in the lower occupational levels, and underrepresented in the higher occupational levels compared with normative data.[5] These previous findings may explain the present lower income, considering were no differences in full-time and part time work between the ConHD population and the general Dutch population. Moons et al. found more worries as to employment and income in adults with ConHD, a finding observed in our study as well; especially patients with moderate/complex ConHD more often reported a negative outlook on keeping or finding a good job.[22]

Over time, more patients appeared to work part-time, a trend not limited to ConHD patients, but visible in the Netherlands in general.[11] As with the increased educational level over time, possibly for the next generation of adults with ConHD, the occupational level may improve. Compared to 10 years ago, significantly more patients now reported to have no problems maintaining a full work schedule. It seems patients have adapted to the working hours in their field of work. Also, less patients reported to feel isolated form their colleagues. Why this is, remains unclear, it could be that patients do not speak about their ConHD, or that they found a working environment where it is accepted to talk about their ConHD.

Emotional and social functioning

When looking at quality of life, social and emotional functioning, patients with ConHD seem to perform better than their healthy counterparts. They obtained better scores on both quality of life questionnaires, and on emotional and social functioning. These findings are similar to those of van Rijen et al and Utens et al. who studied the same cohort respectively 10 and 20 years earlier, and are in line with literature.[3,5,13,22] Now, 30 years later, this seems to be an ongoing trend, with patients obtaining more favorable scores on hostility and self-esteem indicating patients are more tolerant and understanding towards others compared to 10 years ago. Possibly these findings may be explained by a high achievement motivation or overcompensation.[3,33]

Strengths and limitations

To our knowledge, this is the first published psychosocial study to compare psychosocial characteristics of ConHD patients in between two time points, patients were studied in 2001 and in 2011. To ensure that measurements at both time points were comparable, the same internationally standardized assessment instruments were used at both times. Only patients participating in both follow-ups were included. In addition, this study included the unbiased consecutive series of operated patients, so not only focusing on patients still seen regularly at the outpatient clinic.

The patients included in this study all had the diagnosis of ASD, VSD, PS, ToF or TGA. Therefore, the obtained results may not be applicable in other diagnoses, nor in all countries worldwide.

Also, normative data was not available for all biographical characteristics, which might make interpretations more difficult.

Clinical implications

Considering the present, impairments found on education and occupation we recommend timely neuropsychological screening during childhood, according to the 2008 Guidelines for the Management of Adults With Congenital Heart Disease.[24,28] Remedial teaching in case of learning problems can be offered during childhood to prevent delay in education and – by consequence – occupational status, and to optimize psychosocial outcome in these areas for our patients.

Future research

Future research should aim to investigate the quality of life and psychosocial characteristics of older patients with ConHD. This is the first generation of patients reaching middle adulthood, since each new life phase is accompanied by new and unknown challenges further longitudinal monitoring and systematic research is recommended.

CONCLUSION

Compared with normative data impairments on biographical outcomes were found, these, however, improved over time. Compared with normative data, patients obtained significantly better scores on quality of life and emotional functioning compared with normative data.

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REFERENCES

1. Warnes CA. The adult with congenital heart disease: born to be bad? J Am Coll Cardiol. 2005 Jul 5; 46(1):1-8.
2. Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. N Engl J Med. 2000 Jan 27;342(4):256-63.
3. Utens EM, Verhulst FC, Erdman RA, Meijboom FJ, Duivenvoorden HJ, Bos E, Roelandt JR, Hess J. Psychosocial functioning of young adults after surgical correction for congenital heart disease in childhood: a follow-up study. J Psychosom Res. 1994 Oct;38(7):745-58.
4. Utens EM, Verhulst FC, Meijboom FJ, Duivenvoorden HJ, Erdman RA, Bos E, Roelandt JT, Hess J. Behavioural and emotional problems in children and adolescents with congenital heart disease. Psychol Med. 1993 May;23(2):415-24.
5. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. Eur Heart J. 2003 Apr;24(7):673-83.
6. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Medical predictors for psychopathology in adults with operated congenital heart disease. Eur Heart J. 2004 Sep;25(18):1605-13.
7. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. Circulation. 1995 Apr 15;91(8):2214-9.
8. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, van Domburg R, van Rijen EH, Utens EM, McGhie J, Bos E, Bogers AJ, Simoons ML. Decline in ventricular function and clinical condition after Mustard repair for transposition of the great arteries (a prospective study of 22-29 years). Eur Heart J. 2004 Jul;25(14):1264-70.
9. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Page RL, Riegel B, Tarkington LG, Yancy CW; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease); American Society of Echocardiography; Heart Rhythm Society; International Society for Adult Congenital Heart Disease; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008 Dec 2;52(23):e143-263. doi: 10.1016/j.jacc.2008.10.001.
10. Utens EMWJ, van Rijen EH, Erdman RAM, et al. Rotterdams Kwaliteit van Leven - Interview. 2000.
11. Netherlands Central Bureau of Statistics 2011. (CBS)
12. Barelds DPH, Luteijn F, van Dijk H Starren, H. (2013). Nederlandse persoonlijkheidsvragenlijst-2 (NPV-2); Handleiding 2013. Amsterdam: Boom test uitgevers.

13. Moons P, Van Deyk K, De Bleser L, Marquet K, Raes E, De Geest S, Budts W. Quality of life and health status in adults with congenital heart disease: a direct comparison with healthy counterparts. Eur J Cardiovasc Prev Rehabil. 2006 Jun;13(3):407-13.
14. Pedersen SS, van Domburg RT, Theuns DA, Jordaens L, Erdman RA (2004) Type D personality is associated with increased anxiety and depressive symptoms in patients with an implantable cardioverter defibrillator and their partners. Psychosom Med 66(5):714–719
15. Daliento L, Mapelli D, Russo G, Scarso P, Limongi F, Iannizzi P, Melendugno A, Mazzotti E, Volpe B. Health related quality of life in adults with repaired tetralogy of Fallot: psychosocial and cognitive outcomes. Heart. 2005 Feb;91(2):213-8.
16. Simko LC, McGinnis KA, Schembri J. Educational needs of adults with congenital heart disease. J Cardiovasc Nurs. 2006 Mar-Apr;21(2):85-94.
17. Sairanen HI, Nieminen HP, Jokinen EV. Late results and quality of life after pediatric cardiac surgery in Finland: a population-based study of 6,461 patients with follow-up extending up to 45 years. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2005:168-72.
18. Nieminen H, Sairanen H, Tikanoja T, Leskinen M, Ekblad H, Galambosi P, Jokinen E. Long-term results of pediatric cardiac surgery in Finland: education, employment, marital status, and parenthood. Pediatrics. 2003 Dec;112(6 Pt 1):1345-50.
19. Bygstad E, Pedersen LC, Pedersen TA, Hjortdal VE. Tetralogy of Fallot in men: quality of life, family, education, and employment. Cardiol Young. 2012 Aug;22(4):417-23.
20. Takken T, Giardini A, Reybrouck T, Gewillig M, Hövels-Gürich HH, Longmuir PE, McCrindle BW, Paridon SM, Hager A. Recommendations for physical activity, recreation sport, and exercise training in paediatric patients with congenital heart disease: a report from the Exercise, Basic & Translational Research Section of the European Association of Cardiovascular Prevention and Rehabilitation, the European Congenital Heart and Lung Exercise Group, and the Association for European Paediatric Cardiology. Eur J Prev Cardiol. 2012 Oct;19(5):1034-65.
21. Moons P. Quality of life in adults with congenital heart disease: Beyond the quantity of life. Doctoral dissertation. Belgium: Katholieke Universiteit Leuven; 2004.
22. Moons P, De Bleser L, Budts W, Sluysmans T, De Wolf D, Massin M, Gewillig M, Pasquet A, Suys B, Vliers A. Health status, functional abilities, and quality of life after the Mustard or Senning operation. Ann Thorac Surg. 2004 Apr;77(4):1359-65; discussion 1365.
23. Miatton M, De Wolf D, François K, Thiery E, Vingerhoets G. Neurocognitive consequences of surgically corrected congenital heart defects: A review. Neuropsychol Rev. 2006 Jun;16(2):65-85.
24. Loup O, von Weissenfluh C, Gahl B, Schwerzmann M, Carrel T, Kadner A. Quality of life of grown-up congenital heart disease patients after congenital cardiac surgery. Eur J Cardiothorac Surg. 2009 Jul;36(1):105-11; discussion 111.
25. Fteropoulli T, Stygall J, Cullen S, Deanfield J, Newman SP. Quality of life of adult congenital heart disease patients: a systematic review of the literature. Cardiol Young. 2013 Feb 6:1-13.
26. Ebenroth ES, Hurwitz RA. Long-term functional outcome of patients following the mustard procedure: the next decade of follow-up. Congenit Heart Dis. 2007 Jul-Aug;2(4):235-41.
27. Kamphuis M, Ottenkamp J, Vliegen HW, Vogels T, Zwinderman KH, Kamphuis RP, Verloove-Vanhorick SP. Health related quality of life and health status in adult survivors with previously operated complex congenital heart disease. Heart. 2002 Apr;87(4):356-62.
28. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, Mussatto KA, Uzark K, Goldberg CS, Johnson WH Jr, Li J, Smith SE, Bellinger DC, Mahle WT; American Heart Association Congenital Heart Defects Committee, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council. Neurodevelopmental outcomes in children with

congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation. 2012 Aug 28;126(9):1143-72.

29. Kokkonen J, Paavilainen T. Social adaptation of young adults with congenital heart disease. Int J Cardiol. 1992 Jul;36(1):23-9.
30. Ong L, Nolan RP, Irvine J, Kovacs AH. Parental overprotection and heart-focused anxiety in adults with congenital heart disease. Int J Behav Med. 2011 Sep;18(3):260-7.
31. Claessens P, Moons P, de Casterlé BD, Cannaerts N, Budts W, Gewillig M. What does it mean to live with a congenital heart disease? A qualitative study on the lived experiences of adult patients. Eur J Cardiovasc Nurs. 2005 Mar;4(1):3-10.
32. Wernovsky G. Current insights regarding neurological and developmental abnormalities in children and young adults with complex congenital cardiac disease. Cardiol Young. 2006 Feb;16 Suppl 1:92-104.
33. Ternestedt BM, Wall K, Oddsson H, Riesenfeld T, Groth I, Schollin J. Quality of life 20 and 30 years after surgery in patients operated on for tetralogy of Fallot and for atrial septal defect. Pediatr Cardiol. 2001 Mar-Apr;22(2):128-32.

Chapter 2.2

Long-term psychosocial outcome of adults with Tetralogy of Fallot and Transposition of the Great Arteries: a historical comparison

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Keywords: Transposition of the Great Arteries, Tetralogy of Fallot, Quality of Life, Historical Comparison, Complex Congenital Heart Disease

ABSTRACT

Objective: Making a historical comparison on the long-term psychosocial outcome of cardiothoracic surgery during childhood.

Methods: Adult patients operated for Tetralogy of Fallot or Transposition of the Great Arteries between 1980-1990 (recent sample) were compared with patients who underwent surgery and were investigated ten years earlier (historical sample). Also, atrial switch and arterial switch patients within the recent sample were compared. Psychosocial functioning was measured using standardized, validated psychological questionnaires.

Results: Although the recent sample of patients overall shows a favorable quality of life, impairments were found in income, living conditions, relationships, offspring and occupational level. Compared to the historical sample, the recent sample showed no significant improvements on psychosocial functioning, except for a better educational level. The amount of educational problems (such as learning difficulties) was still high compared to normative data. Recently operated patients with Transposition of the Great Arteries (arterial switch) scored significantly better on the Short Form-36 vitality scale ($p=0.02$) compared to historical patients with Transposition of the Great Arteries (arterial switch).

Conclusions: Despite improvements in medical treatment over the past decades, hardly any change was found in psychosocial outcome of the recent patient sample compared to the historical patient sample. Especially the percentage of patients needing special education and showing learning problems remained high, while income was low compared to normative data.

INTRODUCTION

The dramatically improved long-term survival of children born with congenital heart disease has resulted in a new and growing population of adults with repaired Tetralogy of Fallot (ToF) and Transposition of the Great Arteries (TGA).[1,2] This has raised interest in the quality of life of these patients.

Adults with ToF or TGA differ from the general population by medical status and medical history, and have specific psychosocial needs and problems.[3] It has been shown that young adults with congenital heart disease obtained a lower educational and occupational level compared to normative reference groups.[4] Furthermore, as to subjective health status, patients experienced more limitations in physical functioning.[5]

Since 1980, many aspects of diagnostic, surgical and medical treatment of congenital heart disease have improved, supposedly resulting in less physiological stress on the patient. Our hypothesis is that improvements in cardiological outcome may also specifically result in more favorable long-term psychosocial outcome. To the best of our knowledge this study is the first to test this hypothesis using two cross-sectional samples of all adult patients with ToF or TGA (matched for age and cardiac diagnosis), comparing results over a 10-year period.

The objective of this study was three-fold: 1) to investigate the psychosocial outcome of adults operated recently (between 1980 – 1990) for Tetralogy of Fallot or Transposition of the Great Arteries, 2) to compare those outcomes with a matched historical cohort (operated between 1968 – 1980), and 3) to make a comparison within the recent Transposition of the Great Arteries group between patients operated with the Mustard procedure versus the arterial switch procedure.

METHODS

Study design

In this cross-sectional single center study psychosocial outcome of a recent versus a historical patient sample was compared using a comparable age-range (20-37) and comparable cardiac diagnostic groups: Transposition of the Great Arteries and Tetralogy of Fallot.

Assessment procedure

For both the recent and historical sample, the institutional ethical committee on human experimentation approved the research protocol. In both studies, patients were approached uniformly and signed informed consent before participating. All patients were medically

examined by a cardiologist in our center. The semi-structured interview and psychological questionnaires were completed in our hospital. In both samples data collection took place in the same standardized way.

Recent patient sample

Out of 164 eligible patients, 14 patients were lost to follow-up and 40 did not respond to multiple invitations. Of the remaining 110 patients, 31 refused to participate resulting into 79 participating patients.

The recent sample (n=79) consisted of all consecutive surviving patients with either Tetralogy of Fallot (ToF) (n=48) or Transposition of the Great Arteries (TGA) (n=31), who underwent their first open heart surgery in our center between 1980 - 1990, and were younger than 15 years at the time of surgery. At time of follow-up in 2010, all patients were between 20 and 35 years of age. Of the 31 patients with Transposition of the Great Arteries, 18 patients underwent arterial switch surgery (58%) and 13 patients underwent a Mustard or Senning procedure (42%). All patients with Tetralogy of Fallot had a complete correction and in 76% a right-ventricular outflow tract patch was inserted. The median follow-up time of this group was 24.2 years [22.7 – 26.5].

Excluded were patients who were not able to understand the questionnaires, or were unable to read or write Dutch.

Historical comparison

Historical patient selection

The 132 congenital heart disease patients that have been included in the historical patients sample have been described in detail previously.[4] These patients were all operated for congenital heart disease between 1968 and 1980 in our center, and were evaluated medically and psychosocially in 2000/2001. Out of this population, we excluded a total of 21 patients who did not fill in the questionnaires we needed for the historical comparison, and 3 patients were excluded because of severe mental retardation, resulting in 108 eligible patients. For both the recent and historical group, the same inclusion and exclusion criteria were maintained.

Matching procedure

Table 1 shows the characteristics of the patients that were included and excluded, for both the recent and the historical patient sample. For both samples, the same inclusion and exclusion criteria were maintained. The mean age of the 108 eligible patients in the historical sample was significantly higher than the selection of patients participating in the recent study. The mean age of the historical TGA group did not differ from the mean age in the recent group

Table 1. Overview of the included and excluded patients in the recent and historical sample

Recent group
(Total eligible N=164, Excluded N=85, Included N=79)

Amount	Reason excluded	Diagnosis	Age	Male gender (%)	NYHA (%)	LVEF	Ergometry testing (% of norm)
14	Lost to follow-up	Fallot (N=8) Switch (N=5) Mustard (N=1)	28 [24-31] (N=14)	45.2	I: 100 (N=2)	Good: 100.0 (N=2)	Missing for all patients (N=0)
31	Refused to participate	Fallot (N=27) Switch (N=4)	28 [24-31] (N=31)	35.7	I: 87.0 II: 8.7 III: 4.3 (N=23)	Good: 71.4 Mildly impaired: 23.8 Moderately impaired: 4.8 Bad: 0.0 (N=21)	84.0 [69.5-94.5] (N=13)
40	Non-responder	Fallot (N=13) Switch (N=4) Mustard (N=23)	27 [25-29] (N=40)	70.0	I: 78.8 II: 21.2 (N=33)	Good: 21.2 Mildly impaired: 42.4 Moderately impaired: 33.3 Bad: 3.0 (N=33)	74.0 [64.0-84.5] (N=17)

Historical group
(Total eligible N=169, Excluded N=61, Included N=108)

Amount	Reason excluded	Diagnosis	Age	Male gender (%)	NYHA (%)	LVEF (%)	Ergometry testing (% of norm)
37	Refused to participate	ASD (N=13) VSD (N=12) PS (N=3) Fallot (N=4) Mustard (N=5)	28 [25-34] (N=37)	42.3 (N=37)	I: 70 II: 30 (N=10)	Good: 77.8 Mildly impaired: 11.1 Moderately impaired: 11.1 (N=9)	84.0 [70.0-92.0] (N=4)

Table 1. (continued)

Amount	Reason excluded	Diagnosis	Age	Male gender (%)	NYHA (%)	LVEF	Ergometry testing (% of norm)
5	Incomplete questionnaires	Fallot	31 [24-35] (N=5)	20.0 (N=5)	I: 0 II: 0 III: 100 (N=2)	Good: 100 Mildly impaired: 0.0 Moderately impaired: 0.0 Bad: 0.0 (N=4)	Missing for all patients (N=0)
19	Age-matching	Fallot	36 [35-38] (N=19)	47.4 (N=19)	I: 43.8 II: 31.2 III: 25.0 (N=16)	Good: 84.2 Mildly impaired: 10.5 Moderately impaired: 0.0 Bad: 5.3 (N=19)	86.5 [69.0-98.3] (N=16)

Abbreviations: NYHA = New York Heart Association; LVEF = Left Ventricular Ejection Fraction; Fallot = Patients with Tetralogy of Fallot; Switch = Patients operated according to the arterial switch procedure; Mustard = Patients operated according to the Mustard procedure; ASD = Atrial Septal Defect; VSD = Ventricular Septal Defect; PS = Pulmonary Stenosis.

Overall group details of the historical sample have been described in detail previously.

Ergometry testing is presented in percentages of predicted, corrected by age, gender and body height.

(26.0 ± 3.9 vs. 26.7 ± 1.6, p=0.33), and also the amount of males and females was the same between the historical and recent group (29.1% vs. 30.8%, p=0.9). However, patients from the historical ToF group were significantly older than patients from the recent ToF group. We therefore removed 19 patients with the highest ages until age was not significantly different (27.6 ± 3.8 vs. 26.3 ± 3.4, p=0.07), also gender was the same between the historical and recent group (37.7% vs. 34.1%, p=0.71).

This resulted into 108 included patients (ToF N=53, TGA N=55).

Instruments and normative data

The psychological examination consisted of the following instruments:

Biographical characteristics, such as nationality, living conditions, marital status, offspring, educational- and occupational status were assessed by a semi-structured interview.[6] For the biographical characteristics and social functioning, recent normative data were derived from the Netherlands Central Bureau of Statistics and, wherever possible, were specified by age and sex.[7] These recent reference data were derived from a variety of normative samples. Since these concerned very large samples, the representativeness for the average Dutch situation

Table 2. Medical and biographical characteristics of the recent and historical sample compared to normative groups (in percentages)

	Recent versus normative data							Historical comparison		
	ToF	TGA			Total	Norm	Total ConHD vs. Norm p-value	Historical	Recent	Historical vs. recent p-value
		Total	Switch	Mustard						
	N=48	N=31	N=18	N=13	N=79	N~		N=108	N=61	
Age	28.5±3.5	26.1±2.7	24.0±1.2	26.7±1.6	27.5±3.4			26.8±4.0	26.4±3.1	0.5
Gender (male)	66.7	67.7	66.7	69.2	67.1			66.7	67.2	0.9
NYHA-class										
• I	95.8	92	91.7	92.3	94.5			28.9	95.7	<0.001
• II	4.2	8	8.3	7.7	5.5			53.3	4.3	<0.001
• III								17.8	-	<0.001
Mentally handicapped	8.3	3.2	5.5	0	6.3			7.4	8.2	0.9
Daily activities										0.4
• Attending education[a]	14.6	29	44.4	7.7	20.3	-	-	9.3	13.1	0.4
• Paid job[a,b]	64.6	38.7	16.7	69.2	54.4	-	-	67.3	65.6	0.8
• Combination above[b]	4.2	22.6	27.8	15.4	11.4	-	-	3.7	6.6	0.4
• Looking for work	2.1	0	0	0	1.3	-	-	4.7	1.6	0.3
• Long-term sick leave	4.2	0	0	0	2.5	-	-	3.7	3.3	0.9
• Volunteer unpaid work	2.1	0	0	0	1.3	-	-	0.9	1.6	0.7
• Protected working conditions	8.3	9.7	11.1	7.7	8.9	-	-	3.7	8.2	0.2

Table 2. (continued)

	Recent versus normative data							Historical comparison		
	ToF	TGA			Total	Norm	Total ConHD vs. Norm p-value	Historical	Recent	Historical vs. recent p-value
		Total	Switch	Mustard						
	N=48	N=31	N=18	N=13	N=79	N~		N=108	N=61	
• Housewife/man	0	0	0	0	0	-	-	1.9	0	0.3
• Other	0	0	0	0	0	-	-	4.7	0	0.09
Living conditions										
• Parents	34	54.8	66.7	38.5	42.3	23.7	<0.01	31.8	34.4	0.7
• Independently	57.4	45.2	33.3	61.5	52.6	75.6	<0.0001	65.4	59	0.4
• Institution	8.5	0	0	0	5.1	0.7	0.1	2.8	6.6	0.2
Marital status										
• No stable relationship[b,c]	59.6	80.6	88.9	69.2	67.9	51.5	<0.01	47.7	60.7	0.1
• Cohabitants	27.7	9.7	11.1	7.7	20.5	25.5	0.3	24.3	24.6	1
• Married[a]	12.8	9.7	0	23.1	11.5	23.1	<0.01	26.2	14.8	0.09
• Divorced								1.9	-	0.3
Offspring										
• No children	87.2	96.8	100	92.3	91	55.5	<0.0001	79.4	88.5	0.13
• ≥1 children	12.8	3.2	0	7.7	9	44.5		20.6	11.5	
Educational attainment[d]										
• Lower	16.7	14.3	25	10	15.9	17.9	0.7	48.1	24	0.004
• Average	53.3	57.1	75	50	54.5	43	0.1	33	52	0.02
• Higher	30	28.6	0	40	29.5	39.1	0.2	18.9	24	0.5
Educational problems										
• Special education	25	16.7	16.7	16.7	21.8	3.5		34.6	23.3	0.1
• Doubled a class	45.8	43.3	50	33.3	44.9				43.3	
• Learning difficulties	43.8	30	22.2	41.7	38.5				43.3	
Occupational level[d]										
• Elementary	3.6	0	0	0	2.5	5.6	0.2	5.4	2.3	0.4
• Lower	35.7	41.7	50	40	37.5	19.5	0.02	40.5	39.5	0.9
• Average[b]	50	16.7	50	10	40	40	1	32.4	37.2	0.6
• Higher[b]	7.1	41.7	0	50	17.5	24.1	0.3	16.2	16.3	1
• Academic	3.6	0	0	0	2.5	10.7	<0.01	5.4	4.7	0.9
Duration of employment[e]										
Part-time	16.7	18.2	50	11.1	17.1	33.8	<0.01	24	15.9	0.3
Full-time	83.3	81.8	50	88.9	82.9	66.2		76	84.1	
Male										
• Part-time[a]	9.1	11.1	50	0	9.7	12.8	0.6	10.2	6.3	0.5
• Full-time[a]	90.9	88.9	50	100	90.3	87.2		89.8	93.8	
Female										

Table 2. (continued)

	Recent versus normative data							Historical comparison		
	ToF	TGA			Total	Norm	Total ConHD vs. Norm p-value	Historical	Recent	Historical vs. recent p-value
		Total	Switch	Mustard						
	N=48	N=31	N=18	N=13	N=79	N~		N=108	N=61	
• Part-time	37.5	50	0	50	40	56.9	0.3	50	41.7	0.6
• Full-time	62.5	50	0	50	60	43.1		50	58.3	
Reason part-time work										
• Heart sole reason	12.5	0	0	0	6.7	-	-	27.8	14.3	0.5
• Heart a reason	25	0	0	0	13.3	-	-	5.6	28.6	0.1
• Heart no reason	62.5	100	100	100	80	-	-	66.7	57.1	0.7
Income										
• < €20000	63.6	66.7	80	60	64.6	41.3	<0.01	44.6	61.9	0.1
• ≥ €20000	36.4	33.3	20	40	35.4	58.7		55.4	38.6	
Sick-leave[f]	7	7.1	13.4	3.6	7	4.4		12.1	5.1	0.1
Sick-leave compared to colleagues										
• More	7.9	28.6	30	27.3	15.3	-	-	13.9	11.6	0.7
• Equal	34.2	47.6	50	45.5	39	-	-	33.3	34.9	0.9
• Less	57.9	23.8	20	27.3	45.8	-	-	52.8	53.5	0.9

Abbreviations: Fallot = Patients with Tetralogy of Fallot; TGA = Patients with transposition of the Great arteries; Switch = Patients with arterial switch (subgroup of TGA); Mustard = Patients with Mustard correction (subgroup of TGA); Part-time is working < 36 hours a week; Full-time is working ≥ 36 hours a week.
a) Significant difference Switch versus Mustard.
b) Significant difference in ToF versus TGA.
c) All patients that do not live together with a partner.
d) Persons living in institutions for mentally handicapped are excluded.
e) Only persons that have a paid job and are between 25 and 35 years of age are included.
f) Sick-leave percentage was used instead of number of days on sick-leave, since the number of hours a person works a week (full-time/part-time) might vary considerably. P-values could not be calculated since data on standard deviations or ranges were missing for the normative groups. P-values for the historical comparison were calculated using Mann-Whitney U tests because of the skewed nature of the data. Normative data was derived from the Netherlands Bureau of Statistics 2010.[7] Normative data on daily activities was not available and is therefore not displayed in the table.

was warranted. Sample sizes of these multiple and very large reference groups were not indicated in Table 2 to prevent confusion.

Subjective health status was assessed by the Short Form-36.[8] Good reliability and validity for the Dutch Short Form-36 has been reported.[9] Normative data were derived from a nation wide, population based Dutch health status survey.[9]

The Satisfaction with Life Scale was has been proven psychometrically sound to be used in patients with congenital heart disease.[10] Normative data was derived from a large general population sample.[10]

The Linear Analogue Scale was used to assess self-perceived quality of life. This instrument has been proven valid, reliable and responsive for the congenital heart disease population.[10] Normative data was derived from a large general population sample.[10]

Statistical analyses

In order to make the comparison between the historical and the recent sample, both datasets of the recent and historical patient samples were categorized according to the age and gender categories of normative groups. For categorical characteristics, proportions of patients are presented in percentages.

P-values were calculated on the basis of 95% confidence intervals. Because of the skewed nature of the data, Mann-Whitney-U tests were used to assess difference in outcome (Short Form-36, Satisfaction With Life Scale and Linear Analogue Scale) between diagnostic groups within the recent patient sample. Pearson Chi-square tests were used to test for differences in distributions of gender and cardiac diagnoses between both patient samples. If cell values were less than 5, the Fisher exact test was used. In order to correct for multiple comparisons, only the differences in biographical characteristics with a level of significance of lower than 0.02 were considered significant. The statistical package IBM SPSS Statistics for Mac version 19.0 (Release 19.0.0) was used. Figures were made using GraphPad Prism version 6.0a for Mac, GraphPad Software (Released July 18, 2012), La Jolla California USA.

RESULTS

Recent sample versus normative data

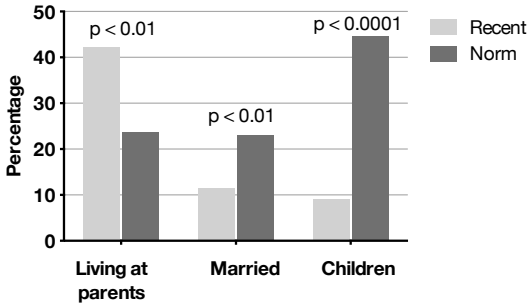
Biographical characteristics (Table 2, Figure 1 and 2)

Patients with ToF or TGA were living less often independently ($p<0.0001$), and were less often married or had a stable relationship compared to normative data ($p<0.01$). Patients with ToF or TGA were less likely to have children compared to normative data, stratified by age and gender categories ($p<0.0001$) (Figure 1).

Patients with ToF or TGA obtained a similar educational level compared to normative data, except for females aged 25 to 35 years, who less often had higher education ($p<0.05$, not listed in the Table). As to occupation, recent patients less often had an academic occupational level ($p<0.01$), and more often had a lower occupational level ($p=0.02$) compared to normative data.

Considering employment, remarkably, patients with ToF or TGA who had a paid job were less frequently working part-time ($p<0.01$) and more often working full-time compared to

Figure 1: Biographical data



Abbreviations: Living at parents = Proportion of people still living at their parents; mother/father or both; Married = The proportion of people that are married; Children = The proportion of people that have one or more children; Recent = The recent study population operated between 1980-1990; Norm = The Normative group.
p-values were calculated by chi-square tests.
Figure 1 shows the comparison on three different biographical variables between the recently operated patients with congenital heart disease (shown in light red) and a normative group (shown in dark grey).

Figure 2: Comparison on income between the recently operated congenital heart disease group and the normative group

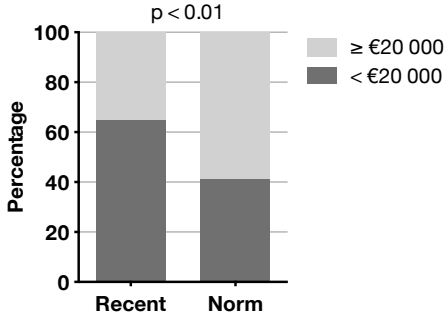
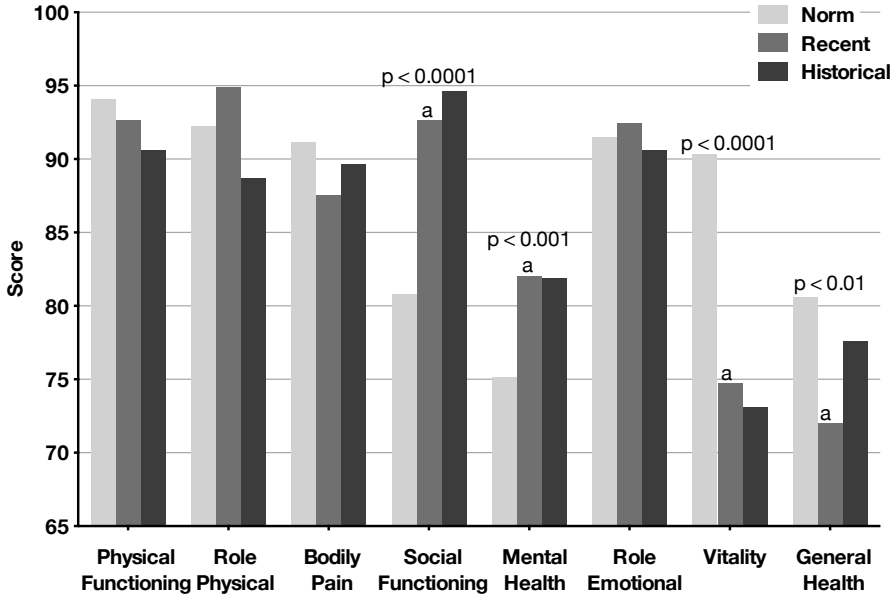


Figure 2 shows the comparison on income between the recently operated congenital heart disease group and a normative group (matched on age and gender). Shown in light grey is the proportion of the group that earns < €20 000, shown in dark grey is the proportion of the group that earns ≥ €20 000.

normative data. There was no effect of gender as to working part-time versus full-time. The ToF or TGA diagnosis did not appear to be the reason for working part-time in the majority of patients (80%). Regarding income, patients with ToF or TGA earned significantly less compared to the general Dutch population (p<0.01) (Figure 2). Finally, patients with ToF or TGA showed a significant higher percentage of sick leave compared to the general Dutch population (7% vs. 4.4%). This effect was mainly found in arterial switch patients.

Figure 3: Comparison between normative data, recently operated Tetralogy of Fallot patients and historically operated Tetralogy of Fallot patients



Abbreviations: Norm = Normative data; Recent = The recent study group operated between 1980-1990; Historical = The historical group operated between 1968-1980.

a) Significant difference between the normative group and the recently operated congenital heart disease group.

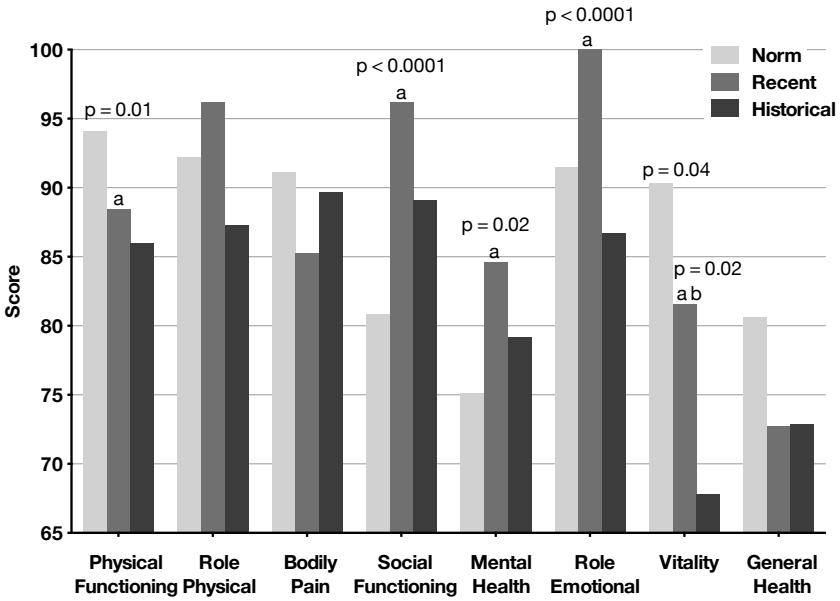
Figure 3 shows the comparison on the Short Form-36 scale for the recent patients with Tetralogy of Fallot (shown in dark grey) versus the historical patients with Tetralogy of Fallot (shown in black) and a normative group (shown in light grey). The Short Form-36 scales range from 0 to 100. Lower scores indicate poorer subjective health status, higher scores indicate a more favorable subjective health status.

Quality of Life (Table 3)

Subjective health status: Compared to normative data, the recent patient sample obtained less favorable results on bodily pain, vitality and general health scales. Patients with ToF or TGA more often experienced bodily pain ($p=0.05$) and as to vitality, reported to feel more worn out and tired ($p<0.0001$). Patients scored their general health as significantly lower and believed it was likely to get worse over time ($p<0.01$). Also, the recent sample obtained more favorable scores ($p<0.0001$) on social functioning, indicating less interference from physical or emotional problems in attending social activities. Recent patients reported a better general mental health compared to normative data ($p<0.0001$).

Compared to normative data (Figure 3) the recent Tetralogy of Fallot group obtained more favorable scores on social functioning ($p<0.0001$) and mental health ($p<0.001$). Less favorable scores for the recent Tetralogy of Fallot group were obtained on the vitality scale ($p<0.0001$) and general health scale ($p<0.01$).

Figure 4: Comparison between normative data, recently operated patients operated with the Mustard procedure and patients historically operated with the Mustard procedure



Abbreviations: Norm = Normative data; Recent = The recent study group operated between 1980-1990; Historical = The historical group operated between 1968-1980.

a) Significant difference between the normative group and the recently operated congenital heart disease group.

b) Significant difference between the recently operated congenital heart disease group and the historically operated congenital heart disease group.

Figure 4 shows the comparison on the Short Form-36 scale for the recent patients operated with the Mustard procedure (shown in dark grey) versus the historical patients operated with the Mustard procedure (shown in black) and a normative group (shown in light grey). The Short Form-36 scales range from 0 to 100. Lower scores indicate poorer subjective health status, higher scores indicate a more favorable subjective health status.

The recent Mustard group obtained more favorable scores compared to normative data, on social functioning ($p<0.0001$), mental health ($p=0.02$), role emotional ($p<0.0001$), and less favorable on physical functioning ($p=0.01$) and vitality ($p=0.04$) (Figure 4)

Within the recent sample, no differences were found between patients with Tetralogy of Fallot and patients with Transposition of the Great Arteries. When comparing Mustard and arterial switch procedures within the recent sample, two differences were found: patients operated with the arterial switch procedure reported better physical functioning compared to patients operated with the Mustard procedure ($p<0.01$). This indicates that patients with an arterial switch feel less limited in performing physical activities compared to patients operated with the Mustard procedure. Patients operated with the arterial switch procedure reported better general health compared to patients operated with the Mustard procedure ($p=0.05$).

Table 3. Mean scale scores of the recent sample and normative data on instruments

	Norm vs. ConHD					ToF vs. TGA					TGA				
	ConHD		Norm			ToF		TGA			Switch		Mustard		
	n=74		n=1742			n=44		n=30			n=17		n=13		
	x	sd	x	sd	p	x	sd	x	sd	p	x	sd	x	sd	p
SF-36															
• Physical functioning	92.8	11.3	94.1	13.2	0.3	92.6	13.5	93.0	7.1	0.3	96.5	5.2	88.5	6.9	<0.01
• Role function physical	93.2	16.2	92.2	22.3	0.6	94.9	12.7	90.8	20.2	0.6	86.8	23.6	96.2	13.9	0.2
• Bodily pain	86.7	18.7	91.1	15.1	0.05	87.5	17.2	85.5	20.9	0.8	85.8	21.0	85.2	21.5	1.0
• Social functioning	92.7	12.2	80.8	14.5	0.000	92.6	11.8	92.9	13.0	0.8	90.4	15.6	96.2	7.9	0.4
• Mental health	82.6	13.5	75.1	15.6	0.000	82.0	12.6	83.5	14.8	0.5	82.6	16.4	84.6	13.0	0.8
• Role function emotion	95.0	17.2	91.5	15	0.08	92.4	21.4	98.9	6.1	0.1	98.0	8.1	100.0	0.0	0.4
• Vitality	76.9	16.2	90.3	24.6	0.000	74.7	18.2	80.2	12.3	0.4	79.1	11.2	81.5	13.9	0.4
• General health	74.9	17.5	80.6	14.7	<0.01	72.0	17.0	79.1	17.7	0.1	84.1	15.9	72.7	18.5	0.05
SWLS	27.6	4.8	25.8	4.6	<0.01	27.5	5.1	28.3	3.7	0.7	29.1	3.1	27.4	4.2	0.5
LAS	80.2	9.0	77.1	8.9	0.02	80.1	9.7	80.3	8.0	0.9	82.2	6.5	77.9	9.3	0.1

Abbreviations: ConHD = all ConHD patients (ToF & TGA combined); Norm = Normative data for the general Dutch population corrected for age and sex where possible; ToF = Patients with Tetralogy of Fallot; TGA = Patients with Transposition of the Great Arteries, including patients operated with the arterial switch procedure and patients operated with the Mustard procedure; Switch = Patients with arterial switch operation; Mustard = Patients operated with the Mustard procedure; SWLS = Satisfaction with Life scale; LAS = Linear Analogue Scale.
The SF-36 scales range from 0 to 100. Lower scores indicate poorer subjective health status, higher scores indicate a more favorable subjective health status.

On the Satisfaction with Life Scale, the recent patients showed more favorable scores compared to normative data (p<0.01). No difference was found for patients with ToF versus patients with TGA, nor for the patients operated with the arterial switch versus the Mustard procedure (in-between TGA).

On the Linear Analogue Scale, the recent sample rated their quality of life significantly higher compared to normative data (p=0.02). No difference was found for patients with Tetralogy of Fallot versus patients with Transposition of the Great Arteries or patients with arterial switch versus patients operated with the Mustard procedure.

Recent sample versus historical sample

Medical background

A trend was visible for the age at first treatment between the recent and historical sample (Recent: median = 0.8[0.5–1.9] years. Historical: median = 1.4[0.6–4.1] years, p=0.07). The

difference in age at treatment was also observed in recent patients with Tetralogy of Fallot versus historical patients with Tetralogy of Fallot (median = 1.3[0.6–3.1], respectively 2.8[1.2-4.7] p=0.008), and a trend for recent patients operated with the Mustard procedure versus historical patients operated with the Mustard procedure (median = 0.5[0.2-0.7] respectively 0.7[0.4-2.3] p=0.08). No significant difference was found on the number of surgeries using a right-ventricular outflow tract patch between the recent sample (76%) versus the historical sample (77%) (p=0.9).

Biographical characteristics (Table 2). A trend was observed showing that the recent patients less often had a relationship (p=0.1), and were married less often (p=0.09) compared to the historical sample. Recent patients obtained a significantly higher educational level compared to the historical sample. Both recent and historical sample showed a comparable high amount of special education, 35% for the historical group and 23% for the recent group (p=0.1).

Quality of life (Figure 3 and 4)

Diagnostic groups. Figure 3 shows no differences between recent versus historical patients with Tetralogy of Fallot on any of the Short Form-36 scales. Figure 4 shows that recent patients operated with the Mustard procedure obtained more favorable scores on the vitality scale of the Short Form-36 compared to historical patients operated with the Mustard procedure (p=0.02). The other non-significant differences, except for general health, all pointed in the same direction of a better outcome for recently operated patients with Transposition of the Great Arteries.

DISCUSSION

Although the recent sample of patients with ToF or TGA overall shows a favorable quality of life, impairments were found on living conditions, relationships, offspring, occupational level, and also the income of patients with ToF or TGA is still lower than expected. Compared to the historical sample, the recent sample showed no significant improvements on psychosocial outcome, except for a better educational level.

To our knowledge, this is the first published psychosocial study making a historical comparison on long-term psychosocial outcome between a recent and historical sample of adult patients with ToF or TGA. To ensure that both samples were comparable, patients with the same diagnoses and same age-range were selected. Clinically relevant areas of psychosocial functioning were investigated, using internationally standardized assessment instruments.

Recent sample versus normative data

Biographical outcome

Although a few older studies showed similar patterns on living less independently and lower offspring rates, our recent findings still show an impressive impact on living conditions in our complex ConHD population.[11-16] The relatively young age of this patient sample cannot be the sole reason for these findings, since the same categories for age and sex were used in comparing our patient data with normative data. The low amount of offspring might be explained by the high amount of patients working full-time, but it can also be the other way around, that patients less often have children and thus keep on working full-time. The recent sample obtained a lower occupational level and was earning a significantly lower income compared to the general Dutch population. Our present findings on living conditions, marital status and occupational level all point in the same direction of being less independent and having a lower socio-economic status for patients with ToF or TGA. A delayed process of gaining autonomy and striving for independence might explain the differences in biographical outcome and occupational level.[3,11,17,18] Furthermore, overprotectiveness from parents may play a role in the delayed process of gaining autonomy.[19] This research supports previous research from Kovacs et al., Kokkonen and Pavliaanen et al., van Rijen et al. and Zomer et al.[3,11,4,20] The way in which the physician informs the parents may play a role in overprotectiveness as well.

The recent patients reported a higher amount of sick leave compared to the general Dutch population. Surprisingly, when asked about sick leave, the majority of patients with ToF or TGA reported to be less often sick compared to their colleagues. These findings point towards a gap between objective and subjective sick leave. Van Rijen explained a similar phenomenon by "denial", social desirability or overcompensation by the patients with congenital heart disease.[4]

Recent patients still experience more educational related problems compared to normative groups. The percentage of patients requiring special education in the recent sample was 24%, which is almost seven times as high as compared to normative data (3.5%). Also, 45% of our patients reported having repeated a class and 39% experienced learning difficulties. Although normative data on these two categories was not available, we assume that this is higher than in the general population.[21,22] Possible explanations for these findings are the underlying cardiac diagnoses with frequent periods of cyanosis, cardiac surgery and school absences due to hospitalizations. These unfavorable findings may be explained neuropsychological impairments in patients with surgical corrected congenital heart disease, which have been reported in reviews.[21,22] Besides pre-operative factors (genetics, structured brain injury, severity of disease), preoperative- (e.g. deep hypothermic circulatory arrest, pH-management during cooling, hemodulation) and postoperative factors (e.g. number of operations, clinical and EEG seizures), also school absenteeism may contribute to learning problems. Genetic

patterns (such as the 22q11 deletion) can play a role in impaired neuropsychological findings, however the amount of mental retardation between the recent and historical group did not differ so we do not think this has played a major role.[21,22]

Quality of life

Our recent sample reported a quality of life which was comparable or even better than that of normative groups on three different instruments (Short Form-36, Satisfaction With Life Scale, Linear Analogue Scale). Our results are in line with previous studies, in which a good quality of life for patients with Tetralogy of Fallot and patients operated with the Mustard procedure has been reported.[10,14,23-25]

On the Short Form-36 social functioning scale, recent patients obtained a more favorable outcome compared to normative data. Previous studies have shown that a favorable social functioning has a protective role against a low quality of life.[26,27] The favorable self-reported social functioning on the Short Form-36 scale could therefore be protecting our patients from a low quality of life.

Recent sample versus historical sample

Biographical outcome

The educational level of the recent sample was significantly better than that of the historical sample. This might be explained by improved social acceptance of ToF and TGA over time, stimulating patients to get the same educational levels compared to normative data. Despite this improvement, the need for special education was comparable in both samples and high compared to the general population.

The historical sample showed a higher amount of sick leave compared to normative data. This finding was also seen in the recent sample.

Quality of life

Recent patients with Tetralogy of Fallot obtained comparable scores on all Short Form-36 scales compared to historical patients with Tetralogy of Fallot.

The only significant difference found between the recent and historical patients operated with the Mustard procedure was the improved Short Form-36 vitality score for current patients. Although not significant, improvements were found on role limitations due to physical and emotional health, bodily pain, social functioning and mental health. These findings all pointed towards a better psychological functioning for patients operated with the Mustard procedure over time.

Role of Mustard versus arterial switch surgical procedures

Our data showed comparable psychosocial functioning for patients operated with the Mustard procedure versus the arterial switch patients. Within the present sample, arterial switch patients scored more favorable results on two Short Form-36 scales, namely physical functioning and general health. These findings are in line with Görler et al., who found no significant difference between Mustard and switch patients, but did describe a tendency towards a better result of the arterial repair group in general health perceptions and role limitations due to emotional problems.[28] Loup et al. found that patients operated with the Mustard/Senning procedure patients showed significantly lower scores on vitality and the psychological functioning Short Form-36 scales.[29] These findings indicate that arterial switch patients feel less limited in performing physical activities and evaluate their personal health as being better compared to patients operated with the Mustard procedure. Despite these improvements, the overall quality of life was not affected as reported on the Satisfaction With Life Scale and the Linear Analogue Scale.

Clinical implications

The more dependent life-style and high amount of special education are prominent in patients with ToF or TGA. Patients still score less favorable on vitality and general health compared to normative data. Considering the problems in the domain of education and occupation of the recent complex ConHD group, we recommend, in line with the 2008 Guidelines for the

Management of Adults With Congenital Heart Disease, timely neuropsychological screening during childhood.[29-31] Remedial teaching in case of learning problems can be offered to prevent delay in education and – by consequence – occupational status, and to optimize psychosocial outcome in these areas for our patients. In case of emotional or behavioral problems we recommend psychological counseling, preferably by a psychologist with expertise in this specific field.

When looking at the historical picture, some improvements over time can be seen, especially for patients operated with the Mustard procedure on the quality of life instruments.

Limitations

The patients included in this study either had Tetralogy of Fallot or Transposition of the Great Arteries and all these patients were followed in a tertiary academic medical center. The obtained results therefore, may not be representative for all patients with congenital heart disease.

Future research

Future research should aim to investigate the relationship between a lower occupational level and a lower income in patients with ToF or TGA, and what interventions can be implemented to decrease these impairments in socio-economic status. Also the low offspring rate and low independence should be studied further. In addition, the relation between psychological characteristics and quality of life should be investigated in more depth. A large cohort is advisable to avoid underpowered conclusions.

CONCLUSION

This article presents a comparison between psychosocial problems encountered in patients with ToF or TGA, operated between 1980 and 1990, to those of patients with ToF or TGA operated between 1968 and 1980.

Despite evident improvements in treatment, hardly any changes were found in psychosocial outcome. The recent patients showed a favorable quality of life, despite several psychosocial impairments as to relationships, offspring, lower occupational level and lower income.

REFERENCES

1. Warnes CA. The adult with congenital heart disease: born to be bad? J Am Coll Cardiol 2005; 46: 1-8.
2. Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. N Engl J Med 2000; 342:256-63.
3. Kovacs AH, Sears SF, Saidi AS. Biopsychosocial experiences of adults with congenital heart disease: review of the literature. Am Heart J 2005; 150: 193-201.
4. van Rijen EH, Utens EM, Roos-Hesselink JW, et al. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. Eur Heart J 2003; 24: 673-83.
5. van Rijen EH, Utens EM, Roos-Hesselink JW, et al. Current subjective state of health, and longitudinal psychological well-being over a period of 10 years, in a cohort of adults with congenital cardiac disease. Cardiol Young 2005; 15: 168-75.
6. Utens EMWJ, van Rijen EH, Erdman RAM, et al. Rotterdams Kwaliteit van Leven - Interview. 2000.
7. Netherlands Central Bureau of Statistics 2010.
8. Ware JE Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30: 473-83.
9. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998; 51: 1055-68.
10. Moons P, Van Deyk K, De Bleser L, et al. Quality of life and health status in adults with congenital heart disease: a direct comparison with healthy counterparts. Eur J Cardiovasc Prev Rehabil 2006; 13: 407-13.
11. Kokkonen J, Paavilainen T. Social adaptation of young adults with congenital heart disease. Int J Cardiol 1992; 36: 23-9.
12. Sairanen HI, Nieminen HP, Jokinen EV. Late results and quality of life after pediatric cardiac surgery in Finland: a population-based study of 6,461 patients with follow-up extending up to 45 years. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2005:168-72.
13. Nieminen H, Sairanen H, Tikanoja T, et al. Long-term results of pediatric cardiac surgery in Finland: education, employment, marital status, and parenthood. Pediatrics 2003; 112: 1345-50.
14. Moons P, De Bleser L, Budts W, et al. Health status, functional abilities, and quality of life after the Mustard or Senning operation. Ann Thorac Surg 2004; 77: 1359-65; discussion 65.
15. Kamphuis M, Ottenkamp J, Vliegen HW, et al. Health related quality of life and health status in adult survivors with previously operated complex congenital heart disease. Heart 2002; 87: 356-62.
16. Moons P, Van Deyk K, Marquet K, De Bleser L, De Geest S, Budts W. Profile of adults with congenital heart disease having a good, moderate, or poor quality of life: a cluster analytic study. Eur J Cardiovasc Nurs 2009; 8: 151-7.
17. Utens EM, Verhulst FC, Erdman RA, et al. Psychosocial functioning of young adults after surgical correction for congenital heart disease in childhood: a follow-up study. J Psychosom Res 1994; 38: 745-58.
18. Simko LC, McGinnis KA, Schembri J. Educational needs of adults with congenital heart disease. J Cardiovasc Nurs 2006; 21: 85-94.
19. Ong L, Nolan RP, Irvine J, Kovacs AH. Parental overprotection and heart-focused anxiety in adults with congenital heart disease. Int J Behav Med 2011; 18: 260-7.

20. Zomer AC, Vaartjes I, Uiterwaal CS, et al. Social burden and lifestyle in adults with congenital heart disease. Am J Cardiol. 2012; 109(11): 1657-63
21. Wernovsky G. Current insights regarding neurological and developmental abnormalities in children and young adults with complex congenital cardiac disease. Cardiol Young 2006; 16 Suppl 1: 92-104.
22. Miatton M, De Wolf D, François K, Thiery E, Vingerhoets G. Neuroco gnitive consequences of surgically corrected congenital heart defects: A review. Neuropsychol Rev 2006; 16: 65-85.
23. Daliento L, Mapelli D, Russo G, et al. Health related quality of life in adults with repaired tetralogy of Fallot: psychosocial and cognitive outcomes. Heart 2005; 91: 213-8.
24. Ebenroth ES, Hurwitz RA. Long-term functional outcome of patients following the mustard procedure: the next decade of follow-up. Congenit Heart Dis 2007; 2: 235-41.
25. Bygstad E, Pedersen LC, Pedersen TA, Hjortdal VE. Tetralogy of Fallot in men: quality of life, family, education, and employment. Cardiol Young. 2012 Aug; 22(4): 417-23.
26. Moons P, Gewillig M, Sluysmans T, et al. Long term outcome up to 30 years after the Mustard or Senning operation: a nationwide multicentre study in Belgium. Heart 2004; 90: 307-13.
27. Kovacs AH, Saidi AS, Kuhl EA, et al. Depression and anxiety in adult congenital heart disease: predictors and prevalence. Int J Cardiol 2009; 137: 158-64.
28. Görler H, Ono M, Thies A, et al. Long-term morbidity and quality of life after surgical repair of transposition of the great arteries: atrial versus arterial switch operation. Interact Cardiovasc Thorac Surg 2011; 12: 569-74.
29. Loup O, von Weissenfluh C, Gahl B, Schwerzmann M, Carrel T, Kadner A. Quality of life of grown-up congenital heart disease patients after congenital cardiac surgery. Eur J Cardiothorac Surg 2009; 36: 105-11; discussion 11.
30. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008; 52(23): e143-263
31. Marino BS, Lipkin PH, Newburger JW, et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation. 2012 Aug 28;126(9):1143-72.

Part 3
Impact on Psychosocial Characteristics

Chapter 3.1

Longitudinal development of psychopathology and subjective health status in congenital heart disease adults: a 30-43 year follow-up in a unique cohort

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Submitted manuscript
Keywords: Psychopathology, Subjective Health Status, Medical Predictors, Historical Comparison, Congenital Heart Disease

ABSTRACT

Objective: To determine longitudinal changes in psychopathology in a cohort of patients 30-43 years after their first cardiac surgery for congenital heart disease (ConHD) in childhood, compare outcomes at the 30-year follow-up with normative data, and identify medical predictors for psychopathology.

Design: This is the third follow-up (N=266) of a cohort operated for congenital heart disease. The first and second follow-ups of this same cohort were conducted in 1990 respectively 2001. At all three follow-ups, psychopathology was assessed with standardized, parallel questionnaires. In 2011 subjective health status was assessed by the Short-Form 36. Medical predictor variables were derived form medical examination and medical records.

Results: Over a 30-year period, proportions of patients showing psychopathology decreased significantly (N=152 complete cases).

At the 30-year follow-up, overall outcomes on psychopathology for the ConHD sample were the same or even better than for normative groups. In addition, subjective health status was better compared with normative data.

No differences were found between cardiac diagnostic groups. Medical variables that predicted the course of psychopathology over time are: the scar (as judged by the patient), results of the first cardiac surgery, and the number of hospitalizations.

Conclusions: Over a 30-year period, psychopathology decreased in patients with ConHD. Levels of psychopathology in these patients, who are now aged between 30 and 54 years were comparable or even better than normative data.

INTRODUCTION

Over the past few decades, improvements in medical treatments have led to an increased survival in patients with congenital heart disease (ConHD), with nowadays over 90% of patients reaching adulthood.[1,2] The Erasmus Medical Center started a cohort study in order to investigate the long-term outcome after surgery for ConHD during childhood (<15 years), including all consecutive patients operated between 1968 and 1980. The present study is the first study worldwide to examine the third (30-43 year) follow-up of the same unique cohort of patients, now aged between 30 and 56 years.

The first (1990) and second follow-up (2001) of this cohort showed elevated levels of psychopathology and psychosocial problems in childhood, adolescence and young adulthood.[3,4] Other researchers also reported psychopathological problems and problems regarding subjective (physical) health status in (young) adult patients with ConHD, underlining the necessity for continuing surveillance.[5-7]

Based on these previous outcomes, problems in psychosocial functioning remain expected or may have even worsened since patients now have to face the challenges of a new life phase: middle adulthood, which can be accompanied by physical and cardiac deterioration.

Unfortunately, most other studies in this field were cross-sectional or hampered by shorter follow-up periods. Limited knowledge is available concerning psychopathology and subjective health status of this first generation of patients. Also, little is known about longitudinal pathways of psychopathology from childhood through young and later adulthood.

The present study offers the unique possibility to assess the developmental pathways of psychopathology in a cohort of patients with ConHD over a period of 30 years, since assessments were done using parallel instruments. Moreover, risk factors for long-term psychopathology can be identified. The aims of this study are:

1) To determine the longitudinal development of psychopathology over a 30 year period (at 10, 20 and 30 years of follow-up) in patients who underwent surgery for ConHD at young age.
2) To compare psychopathological problems and subjective health status of adults with ConHD at the 30 year follow-up with normative groups and also in between different cardiac diagnostic groups.
3) To identify medical variables that predict the longitudinal changes in psychopathology over time.

METHODS

Inclusion criteria

Included were all consecutive patients who underwent their first open heart surgery for Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), Pulmonary Stenosis (PS), Tetralogy of Fallot (ToF), or Transposition of the Great Arteries (TGA) between 1968 and 1980 in the Erasmus Medical Center, and who were younger than 15 years at the time of surgery. The first and second follow-ups of this cohort took place in 1990 and 2001 (details were described previously.[3,8-12]).

The target population of this third follow-up, in 2011, consisted of the 412 patients who participated in both of the previous two follow-ups. Of these patients, ten were deceased (causes: 6 cardiac-related, 3 unknown, 1 shooting accident), one underwent heart transplantation, and 28 patients were untraceable. Four patients were excluded because of severe mental retardation. Of the remaining 369 eligible patients, 103 refused to participate, mostly due to practical reasons (work, distance to hospital), resulting in 266 participating patients (response rate of 71%).

Patient sample

Patients were classified into two groups of disease severity according to the classification adopted at the American Heart Association Task Force on Adults with CHD.[13] Patients with corrected ASD, VSD and PS were classified as simple ConHD, patients with ToF or TGA (Mustard) were classified as moderate/complex ConHD.

Assessment procedure

The institutional ethical committee in the Erasmus Medical Center approved the research protocol. All patients signed informed consent before participating. During their visit to the outpatient clinic, a cardiologist performed the cardiac and medical examination and patients completed psychosocial questionnaires. Questionnaires were administered verbally to patients who had difficulty reading or understanding the questionnaires. Due to practical reasons (work, children), 18 patients completed the psychosocial questionnaires at home.

Instruments and normative groups

In 1990, psychopathological problems were assessed by the Youth Self Report (YSR) and the Child Behavioral Checklist (CBCL).[14,15] In 2001, the parallel, extended versions (i.e. The Young Adult Self Report (YASR) and Young Adult Behavioral Checklist (YABCL)) were used.[16] In 2011,

the Adult Self Report (ASR) and the Adult Behavior Checklist (ABCL) were used.[17] The ABCL is a parallel version of the ASR and is to be completed by an informant who is familiar with the adult (a proxy, partner, parent or close relative). On all questionnaires, a Total Problem score, Internalizing score (anxiety/depression, somatic complaints) and Externalizing score (reflecting conflict with others) can be calculated. Normative data for 2011 was derived from the official manual since Dutch normative data was not available for same aged categories.[17]

Subjective quality of life was assessed by the Short Form-36 (SF-36).[18] Physical functioning was excluded to avoid republishing of data. Good reliability and validity for the Dutch version of the SF-36 has been reported.[19] Normative data was derived from the study of Aaronson et al.[19]

Statistical analyses

Continuous data is represented by mean ± SD, categorical variables by percentages. In case of a skewed distribution (significant Kolmgorov-Smirnov test) medians and interquantile ranges [IQR] (Q1-Q3) are displayed. Comparison between questionnaires (ASR, ABCL and SF36) and normative data was analyzed using means ± SD according to manuals. Effect sizes were calculated.[20] Percentages of patients scoring in the psychopathological range compared with normative data were compared using Binomial testing. To test the difference between ConHD diagnostic groups, t-tests or Mann-Whitney-U tests were utilized. Longitudinal comparison was tested by paired sample t-tests or Wilcoxon signed-rank tests.

When comparing categorical variables between ConHD diagnostic groups, the Chi-square or the Fisher exact test was used. Longitudinal comparison of categorical variables was computed by the McNemar test for 2x2-paired tables and the Stuart-Maxwell test for 3x3 paired tables.[21]

Prediction

Since all patients were adults in 2001, the course of psychopathology at adult age could be determined by comparing the outcomes on questionnaires between 2001 and 2011 using 88 comparable (the same) items. To identify the predictive value of medical variables on the course of psychopathology, the changes in outcomes between 2001-2011 on these 88 items were used. Some of the patients with ConHD were children in 1990. This follow-up was therefore excluded since the items were not completely comparable.

The same medical variables as in the previous two follow-ups were used. A three-phase strategy was followed for each of the seven variable 'clusters' (combination of variables, see Table 1. In phase 1, each of the separate prediction variables (univariate) was entered in a linear regression model, corrected for age and gender. This was done to explore the predictive quality of each predictor separately. In phase 2, each 'cluster' of predictors (combination of variables) was related to the ASR and ABCL outcomes (multivariate analysis) corrected for age

Table 1. Patient characteristics in 1990, 2001 and 2011

Variable	Total	ConHD classification		p
		Simple	Moderate/complex	
	n=266	n=179	n=87	
Biographical status (2011)				
Gender				
• Male	53.4	49.7	60.9	0.086
• Female	46.6	50.3	39.1	
Age[a]	39.7 [36.2-44.9]	40.4 [37.5-45.3]	38.0 [33.8-41.3]	<0.0001
Medical history				
Duration of pregnancy (weeks)	40.0 [39.0-40.0]	40.0 [39.0-40.0]	40.0 [40.0-40.0]	0.130
Weight at birth (kg)[a]	3.3 [2.8-3.6]	3.3 [2.7-3.7]	3.2 [3.0-3.6]	0.498
Palliative surgery prior to surgical repair	19.5	2.8	54.0	<0.0001
First open heart surgery and direct post-operative course				
Date first open heart surgery (days/100)[b]	28.5 [21.4-36.6]	28.1 [20.3-36.1]	31.4 [24.4-37.6]	0.046
Age first open heart surgery (years)[a]	4.8 [1.1-7.2]	5.5 [2.0-8.6]	2.3 [0.6-5.2]	<0.0001
Postoperative course (complications)	22.5	18.8	30.5	0.035
Results surgery (moderate&poor)	6.2	2.3	14.3	<0.0001
Medical course before 1990				
Percentage of hospitalizations as a result of heart problems	16.9	7.9	36.4	<0.0001
Cardiological check-ups				
• Less than once per year	45.7	69.2	34.5	0.003
• Once per year or more	54.3	30.8	65.5	
Restrictions imposed by physician	3.7	1.8	7.8	0.023
Medical course after between 1990-2001				
Percentage of hospitalizations as a result of heart problems	14.3	7.4	28.0	<0.0001
Cardiological check-ups				
• Less than once per year	46.2	67.5	33.3	0.001
• Once per year or more	53.8	32.5	66.7	
Restrictions imposed by physician	6.2	6.8	4.9	0.549
Medical course between 2001-2011				
Percentage of hospitalizations as a result of heart problems	24.0	11.4	49.4	<0.0001
Cardiological check-ups				
• Less than once per year	29.0	44.2	19.0	0.002
• Once per year or more	71.0	55.8	81.0	
Restrictions imposed by physician	6.9	4.8	11.1	0.067
Present medical status				
Medications for the heart	21.8	15.1	35.6	<0.0001
Scar judged by physician				
• Well healed	29.4	27.2	34.2	0.370
• Moderately healed	57.4	60.5	50.7	
• Poorly healed	13.2	12.3	15.1	

Table 1. (continued)

Variable	Total	ConHD classification		p
		Simple	Moderate/complex	
	n=266	n=179	n=87	
Restrictions from scar (patient)				
• Never	78.4	78.8	77.6	
• Sometimes	14.0	15.6	10.6	0.138
• Often	7.6	5.6	11.8	
Maximum exercise capacity in % of norm	89.3 ± 19.9	92.5 ± 19.2	82.7 ± 19.8	<0.0001
ECG sinus rhythm	81.1	91.1	61.2	<0.0001

a) Data are presented as Medians [Q1-Q3].
b) "Date first open heart surgery" shows the number of days/100 that elapsed since the first patient of this cohort received open-heart surgery. Data are presented as Medians [Q1-Q3].

and gender. The following clusters of medical variables were used as in the previous follow-up in 2001: medical background, first open heart surgery and post-operative course, medical course between 2001 and 2011 and medical status between 2001 and 2011. Since these phase 2 analyses were perceived as a first broad selection of predictors, a backward elimination procedure was used (p-values set to 0.20). The final model in phase 3 contained all of the significant variables from phase 2 analyses (p-values ≤ 0.05, backward elimination). Variables that showed significant results in this final phase 3 model were regarded as final predictors of ASR and ABCL outcomes. In the tables, the betas presented are the standardized coefficients betas.

For the two outcomes (ASR Total and ABCL externalizing), phase 3 analyses could not be performed because there was only 1 significant variable in the final model.

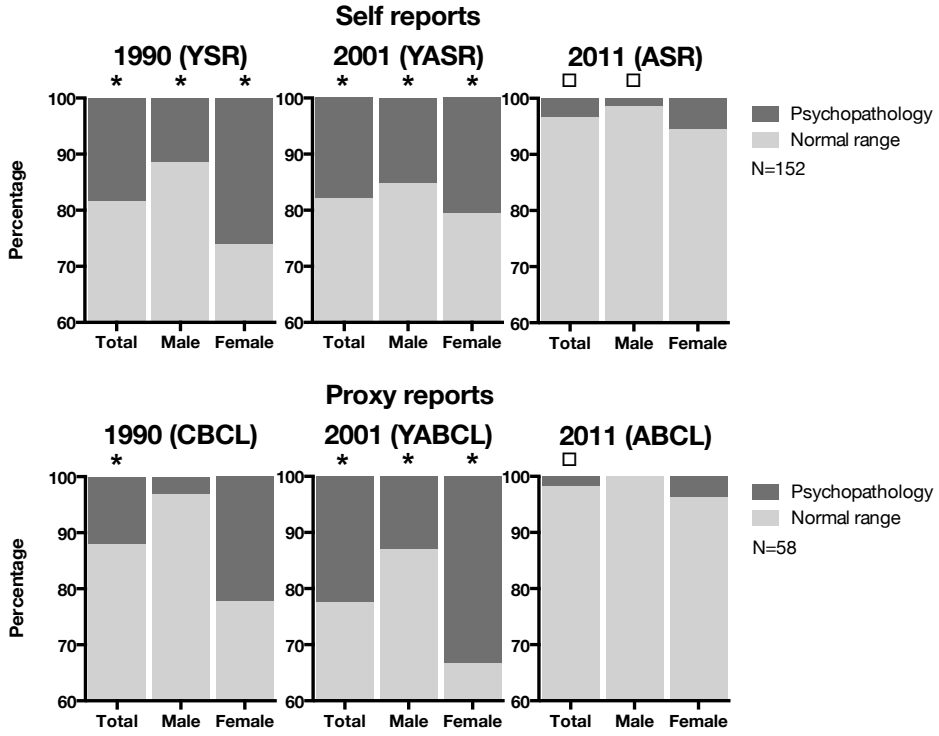
Unless otherwise specified (phase 2 regression model), two-tailed probability values of <0.05 were considered statistically significant. The statistical and graphical packages IBM SPSS Statistics for Mac, Version 20.0 (2011), R for Mac (64 bit, version 2.14.2), and GraphPad Prism version 6.0a for Mac (2012) were used.

RESULTS

Patient characteristics (assessed in 1990, 2001 and 2011, Table 1)

Patients with simple ConHD were significantly older at the 30-year follow-up (p<0.0001), underwent fewer palliative surgeries prior to surgical repair (p<0.0001), received surgery earlier (p=0.046), received corrective surgery at a later age (p<0.0001), had fewer complications (p=0.035), and better overall surgical results (p=0.004) compared with patients who had moderate/complex ConHD.

Figure 1: Percentages of the ConHD sample and normative group scoring in the ASR and ABCL psychopathological range over time



Abbreviations: 1990 = First follow-up in 1990; 2001 = Second follow-up in 2001; 2011 = Third follow-up in 2011; YSR = Youth Self Report; YASR = Young Adult Self Report; ASR = Adult Self Report; CBCL = Child Behavioral Check List; YABCL = Young Adult Behavior Check List; ABCL = Adult Behavioral Checklist.
* Indicate that the proportions of patients scoring in the psychopathological range of the corresponding ConHD total or subsample (male/female) were significantly lower in 2011.
□ indicate that in 2011 results of the corresponding ConHD total or subsample were significantly better than normative data
Same sample sizes across all three time points: Self reported (N=152) consisted of male (N=79, 52%) and female (N=73, 48%) patients, same sample sizes across all three time points. Proxy reported (N=58) consisted of male (N=31, 53%) and female (N=27, 47%) patients, same sample sizes across all three time points.
The cut-offs that indicate psychopathology are based on the 90th percentiles of the total problems presented for the normative group and were derived from the manual.[17]
Percentages of patients showing psychopathology decreased significantly over time both on the ASR (1990-2011 $p<0.0001$; 2001-2011 $p<0.0001$) and ABCL instrument (1990-2011 $p=0.031$; 2001-2011 $p<0.0001$).
Figure 1 shows that the percentage of patients showing psychopathology decreased significantly over time both on the ASR (1990-2011 $p<0.0001$; 2001-2011 $p<0.0001$) and ABCL instrument (1990-2011 $p = 0.031$; 2001-2011 $p<0.0001$).

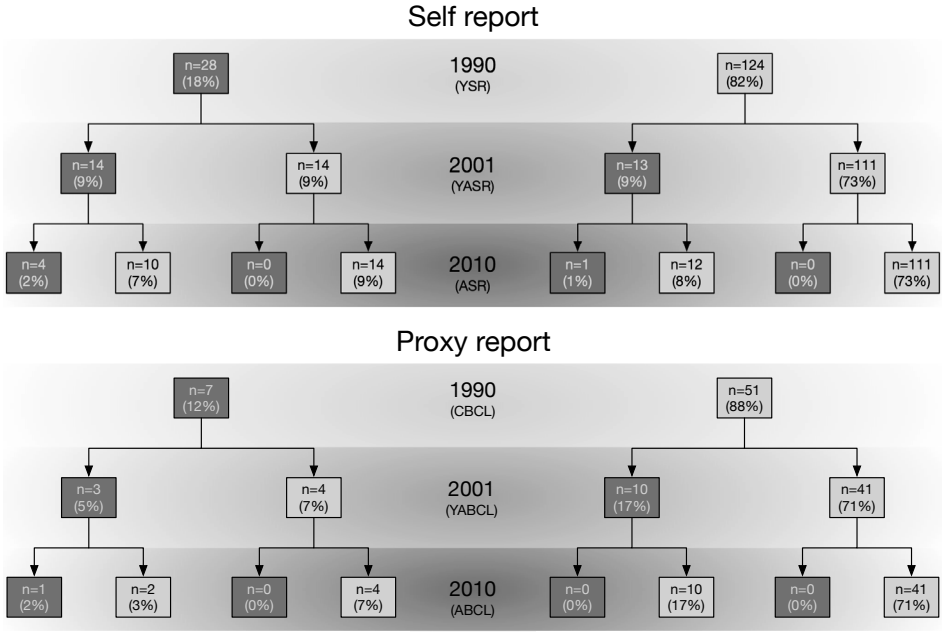
Levels of psychopathology over time

In total, 152 patients completed measurements at all three follow-ups (1990, 2001 and 2011). Figure 1 shows that the percentage of patients with psychopathology decreased significantly over time both on the self-report (1990-2011 $p<0.0001$; 2001-2011 $p<0.0001$) and proxy report instrument (1990-2011 $p = 0.031$; 2001-2011 $p<0.0001$).

Figure 2 shows the longitudinal pathways of psychopathology.

Within the ConHD sample, scores from 2001 to 2011 were compared on the 88 overlapping items of the adult questionnaires. Results showed a significant decline in the mean level of

Figure 2: Self reported and proxy reported psychopathology



Abbreviations: 1990 = First follow-up in 1990; 2001 = Second follow-up in 2001; 2011 = Third follow-up in 2011; YSR = Youth Self Report; YASR = Young Adult Self Report; ASR = Adult Self Report; CBCL = Child Behavioral Check List; YABCL = Young Adult Behavior Check List; ABCL = Adult Behavioral Checklist; Red = Score in the psychopathological range; Green = Score in the normal range.

Data are presented as N (percentage of row total). The cut-offs indicating psychopathology are based on the 90th percentiles of the total problems presented for the normative group and were derived from the manual.[17]

Self-report: half of the 28 patients (18%) who scored in the psychopathological range in 1990, obtained normal scores in 2001, and by 2011 only 2% (N=4) scored in the psychopathological range. Proxy-report: 12% (N=7) scored in the psychopathological range in 1990, and in 2011 only 2% (N=1) scored in the psychopathological range.

Figure 2 shows the longitudinal pathways of psychopathology. Half of the 28 patients (18%) who scored in the self reported psychopathological range in 1990 obtained normal scores in 2001, and by 2011 only 2% (N=4) scored in the psychopathological range again. On the proxy report 12% (N=7) scored in the psychopathological range in 1990, and in 2011 only 2% (N=1) scored in the psychopathological range again.

Total Problems, Internalizing and Externalizing items, both on the self- and proxy reports (Total Problems: YASR-ASR: p<0.0001, YABCL-ABCL: p<0.0001, Internalizing: YASR-ASR: p=0.005, YABCL-ABCL: p=0.036, Externalizing: YASR-ASR: p<0.0001, YABCL-ABCL: p<0.0001)

Mean problem scores on the ASR and ABCL in 2011 (Table 2)

Comparison between ConHD and normative data

On the ASR self-report males (aged 30-35 and 36-39) obtained significantly lower total problem scores compared with normative data. Females (aged 36-40) showed less psychopathological problems on the ASR total problem score and externalizing scale.

Table 2. Mean problem scores on the ASR, ABCL and SF36 in 2011

Variable	ConHD classification			ConHD compared with normative data		
	Simple n=179	Moderate/complex n=87	p	Total ConHD n=266	Norm	p
ASR Total problem scores						
Males 30-35	35.7 ± 18.4	33.9 ± 15.4	1.000	34.6 ± 16.3	43.0 ± 27.7	0.017
Males 36-39	27.0 ± 19.0	32.4 ± 27.2	0.519	28.5 ± 21.6	35.0 ± 21.9	0.007
Females 31-35	41.5 ± 26.8	44.3 ± 31.7	0.967	42.5 ± 27.8	43.4 ± 25.7	0.891
Females 36-40	29.0 ± 18.3	23.8 ± 20.3	0.079	27.7 ± 18.9	36.2 ± 22.7	0.000
ABCL Total problem scores						
Males 30-35	29.5 ± 17.3	25.7 ± 16.6	0.621	27.0 ± 16.6	34.9 ± 29.3	0.036
Males 36-39	24.8 ± 21.1	22.9 ± 16.9	0.975	24.3 ± 20.0	28.2 ± 25.2	0.120
Females 31-35	35.4 ± 21.5	24.1 ± 20.3	0.179	31.0 ± 21.2	36.3 ± 29.3	0.324
Females 36-40	22.4 ± 17.1	18.6 ± 16.7	0.184	21.5 ± 17.0	27.9 ± 23.1	0.004
	SF36					
Total ConHD sample	Simple n=179	Moderate/complex n=85	p	Total ConHD n=264	Norm	p
Role Physical	89.7 ± 26.3	89.1 ± 25.4	0.873	89.5 ± 26.0	76.4 ± 36.3	<0.0001
Bodily Pain	83.6 ± 21.8	87.3 ± 18.1	0.179	84.8 ± 20.7	74.9 ± 23.4	<0.0001
Social Functioning	91.3 ± 17.3	93.8 ± 13.5	0.209	92.1 ± 16.2	84.0 ± 22.4	<0.0001
Mental Health	83.5 ± 13.2	81.3 ± 16.4	0.232	82.8 ± 14.4	76.8 ± 17.4	<0.0001
Role Emotional	90.9 ± 24.7	92.9 ± 23.2	0.537	91.5 ± 24.2	82.3 ± 32.9	<0.0001
Vitality	72.5 ± 19.8	72.0 ± 19.7	0.868	72.3 ± 19.8	68.6 ± 19.3	0.005
General Health	75.2 ± 22.2	67.7 ± 18.7	0.005	72.7 ± 21.3	70.7 ± 20.7	0.150

Abbreviations: ASR = Adult Self-Report; ABCL = Adult Behavior Check-List.
SF36 expressed in means ± SD according to manual and published normative data. Significant differences between the total ConHD group and published normative data, using one-sample t-tests. Differences between diagnostic groups on the ASR, ABCL and SF36 were analyzed by Mann-Whitney-U tests. Cohen's D indicated a small effect size for both the ASR and the ABCL, for all male and female subgroups.[20]

According to proxy reports (ABCL), males (aged 30-35) and females (aged 36-40) showed less psychopathology on the total problem and externalizing score compared with normative data.

On all scales of the SF36 instrument, patients reported fewer problems compared with normative data, except on general health (which was comparable to normative data).

Comparison between ConHD diagnostic groups

Regarding psychopathology (ASR/ABCL) only one difference was found: on the ASR self-report, females aged between 36-40 years with simple ConHD remarkably reported more internalizing problems (anxiety and depression) compared with older females with moderate/complex ConHD (data not shown in table).

On the SF36, patients with moderate/complex ConHD reported a worse general health compared with patients who had simple ConHD (p=0.005).

Discrepancy between informants in 2011 (Table 3)

Table 3 shows the discrepancy between the level of psychopathology as reported by patients versus proxy reports.

No significant differences were found on total problem scores (p=1.000), internalizing (p=0.607) or externalizing (p=0.557) scores between patient reports and proxy reports (Total score p=1.000, internalizing score p=0.607, externalizing score p=0.557).

Table 3. Discrepancies between patients' (ASR) and their proxy's (ABCL) ratings in 2011

		ABCL	
		Normal range	Psychopathological range
ASR	Normal range	93.4%	2.4%
		91.1%	2.8%
		83.6%	7.0%
	Psychopathological range	2.8%	1.4%
		4.2%	1.9%
		5.2%	4.2%

Abbreviations: ASR = Adult Self-Report; ABCL = Adult Behavioral Checklist.
Light grey = Total score (p=1.000); Dark gray = Internalizing problems (p=0.607); Black = Externalizing problems (p=0.557).

Prediction of changes in psychopathology over time (ASR and ABCL, 2001-2011)

Due to lack of space, only the results of the final model (phase 3) are presented in Table 4.

Phase 3: the final model (Table 4)

A well-healed scar as judged by the patient was associated with a decrease in psychopathology (2011-2011) on the ASR total problem and internalizing scores (phase 2 analysis). Patients who underwent palliative surgery prior to their first cardiac surgery showed a decrease in internalizing problems (ASR 2001-2011). Patients who had poor to moderate surgical results showed an increase over the last decade in total problem and internalizing scores, as reported by others (ABCL). Fewer hospitalizations were associated with a decrease over time in problems on the ABCL total and internalizing scales.

Table 4. Final model; results of the prediction of changes in the ASR and ABCL outcomes (from 2001-2011).

			Phase3	
Outcome	Predictors	SE B	p	R^2
ASR total[a]	**Well-healed scar as judged by patient**	-0.202	0.004	0.053
ASR internalizing	Palliative surgery prior to surgical repair	-0.121	0.064	0.054
	Well-healed scar as judged by patient	-0.195	0.003	
ASR externalizing[a]	Age at follow-up in 2011	0.111	0.092	0.027
	Gender	-0.124	0.058	
ABCL total	Gender	-0.14	0.052	
	Results surgery (moderate or poor)	0.179	0.014	0.073
	Less hospitalizations because of heart problems over time	-0.144	0.046	
ABCL internalizing	Gender	-0.137	0.057	
	Results surgery (moderate or poor)	0.161	0.026	0.081
	Less hospitalizations because of heart problems over time	-0.187	0.009	
ABCL externalizing[a]	Gender	0.051	0.744	0.038

Abbreviations: ASR = Adult Self-Report; ABCL = Adult Behavioral Checklist.
a) For these outcomes results from phase 2 analysis are presented (see description in statistics section).
All separate predictor variables are listed in Table 1.

DISCUSSION

Although patients operated for ConHD overall scored significantly more often in the psychopathological range, this tendency decreased significantly over time. At the 30-year follow-up, the mean overall problem scores were comparable or even better than those of normative data. No differences were found on the self and proxy report of psychopathology between

the cardiac diagnostic groups. Medical variables that predicted changes in psychopathology from the 20 to 30 year follow-ups were: the scar (as judged by the patient), the results of the initial cardiac surgery, and the number of hospitalizations over time.

Longitudinal changes in psychopathology over 10, 20 and 30 years

This study showed that the percentages of patients scoring in the psychopathological range decreased over time, being most prominent during childhood/adolescence, then normalizing during adulthood and even reaching significantly lower levels of psychopathology during later adulthood. This decrease has been hypothesized before.[4] A possible explanation might be the normalizing of biographical characteristics. Having reached middle adulthood, our patients appear to have caught up from a prior delay in gaining autonomy. Most patients were now living independently, had formed families and had stable careers (Opić et al., submitted manuscript).[9,22] This normalization may have contributed to decreased levels of psychopathology.

Response shift is another possible explanation; patients may have different values and internal standards after a life-threatening experience (e.g. cardiac surgery) when compared with healthy peers.[23]

A third explanation could be an increase in psychopathology in the normative groups. Older age might lead to physical complaints and normative data from the manual were used. However, analyses within the ConHD sample (overlapping items) also demonstrated a significant decrease in psychopathology. Moreover, previous analyses showed that emotional functioning (Dutch Personality Questionnaire) of this sample was significantly better compared to normative data (Opić et al., submitted manuscript). We think these findings clearly demonstrate that decrease of psychopathology is not just an artifact of change in normative groups, but a significant pattern, indicated by different informants (patients/proxy's) and different instruments. ConHD patients are accustomed to coping with physical limitations, which appears to be protective for their mental health in this life phase.

Psychopathology and subjective health status compared with normative data

The adult ConHD sample showed similar/lower levels of psychopathology and overall, subjective quality of life was more favorable compared with normative data.

A decade ago, especially young females (age range ≤27 years) showed elevated rates of psychopathology which seemed related to disease-specific uncertainties associated with that specific life phase (e.g. sexual relationships, contraception, pregnancy, having children).[4,8,24] During the 20-year follow-up, it was already shown that patients who were in their late twenties had more favorable outcomes on psychopathology than younger patients. The present findings confirm this trend, which now appears to continue into middle adulthood.

Medical variables that predict psychopathology in 2011

Scar

According to self-reports (ASR), a well-healed scar, as judged by the patient was the only predictor for a decrease in psychopathology from the 20 to 30 year follow-up period. In the previous follow-up, the cardiac scar was already a significant predictor, thus can be considered a stable risk factor for psychopathology throughout adult life.[25] Negative feelings regarding the surgical scar have a negative impact on feelings of self-esteem and self-confidence.[26]

Ten years ago, the cardiac scar predicted both internalizing and externalizing problems. Patients who now reported fewer restrictions from their scar showed a significant decrease on internalizing problems only (e.g. anxiety/depression) over the last decade. Literature has shown that with older age, patients seem to have accepted the scar and find it less important.[5,26]

Although the scar now does not have a significant influence on externalizing problems anymore, it can be concluded that the scar remains a significant factor for the mental health of patients with ConHD, even in middle adulthood.

Gender

A decade ago, female patients (20-27 years) were especially at risk for significantly elevated levels of psychopathology. This was attributed to disease specific concerns and worries during that period in their lives.[4,10] Now, non-significant decreases in psychopathology for females in later adulthood were found both on the self-report and proxy outcomes. This can be explained by the end of a stressful period in their lives.[27] Nowadays, these females have "settled down" and have found their way in society (job, relationship, family life).[27] The present results underline the importance of assessing psychosocial outcomes for both genders separately.

Medical history

Proxy reports (ABCL) showed that significant predictors for changes in psychopathology over the last decade were: less hospitalizations over time and better results at initial surgery. These variables reflected the medical history of the patient. Van Rijen et al previously found that the number of hospitalizations was associated with an elevated risk for long-term psychopathology.[10] These findings reflect that hospitalizations have an ongoing, long-lasting influence on psychopathology of patients, even into middle adulthood, from the perspective of people close to the patient (proxy reports). This has not been reported in previous literature.

Moderate or poor results from the first cardiac surgery in childhood was also a significant predictor for psychopathology in our cohort, as seen in proxy reports. A possible explanation is that moderate/poor results led to more concerns and anxiety in parents considering the long-term development of the cardiac status over time. This might have continued into

adulthood and might possibly have influenced this picture.[10,28] Overprotectiveness has been associated with a lower quality of life at a later age and may have consequences for long-term mental health.[5,29]

Strengths and limitations

This study is the first to report on levels of psychopathology in a cohort of ConHD adults between three time points: namely 10, 20 and 30 years of follow-up. Internationally-validated, questionnaires and a multi-informant approach were used to measure psychopathology and subjective health status for five diagnostic groups and both genders.

Since this is a one-center study and all patients underwent surgery before 1980, obtained results may not be generalizable to patients with ConHD who underwent surgery after 1980, when medical treatment of patients with ConHD was much improved; nor to patients with more complex or inoperable diagnosis (e.g. univentricular heart).

Future recommendations

In the next decade, deterioration in cardiological function and also acquired heart disease may occur in patients with ConHD of middle age. This may have a negative impact on their mental health and subjective health status. Therefore, further systematic longitudinal follow-up of these patients is recommended.

CONCLUSIONS

Over a 30 year period, psychopathology clearly decreased in patients operated for congenital heart disease, now aged between 30 and 54 years.

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REFERENCES

1. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol. 2011 Nov 15;58(21):2241-7.
2. Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. N Engl J Med. 2000 Jan 27;342(4):256-63.
3. Utens EM, Verhulst FC, Erdman RA, Meijboom FJ, Duivenvoorden HJ, Bos E, Roelandt JR, Hess J. Psychosocial functioning of young adults after surgical correction for congenital heart disease in childhood: a follow-up study. J Psychosom Res. 1994 Oct;38(7):745-58.
4. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Longitudinal development of psychopathology in an adult congenital heart disease cohort. Int J Cardiol. 2005 Mar 18;99(2):315-23.
5. Kovacs AH, Sears SF, Saidi AS. Biopsychosocial experiences of adults with congenital heart disease: review of the literature. Am Heart J. 2005 Aug;150(2):193-201.
6. Moons P, Van Deyk K, De Bleser L, Marquet K, Raes E, De Geest S, Budts W. Quality of life and health status in adults with congenital heart disease: a direct comparison with healthy counterparts. Eur J Cardiovasc Prev Rehabil. 2006 Jun;13(3):407-13.
7. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, Mussatto KA, Uzark K, Goldberg CS, Johnson WH Jr, Li J, Smith SE, Bellinger DC, Mahle WT; American Heart Association Congenital Heart Defects Committee, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation. 2012 Aug 28;126(9):1143-72.
8. Utens EM, Verhulst FC, Meijboom FJ, Duivenvoorden HJ, Erdman RA, Bos E, Roelandt JT, Hess J. Behavioural and emotional problems in children and adolescents with congenital heart disease. Psychol Med. 1993 May;23(2):415-24.
9. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. Eur Heart J. 2003 Apr;24(7):673-83.
10. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Medical predictors for psychopathology in adults with operated congenital heart disease. Eur Heart J. 2004 Sep;25(18):1605-13.
11. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. Circulation. 1995 Apr 15;91(8):2214-9.
12. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, van Domburg R, van Rijen EH, Utens EM, McGhie J, Bos E, Bogers AJ, Simoons ML. Decline in ventricular function and clinical condition after Mustard repair for transposition of the great arteries (a prospective study of 22-29 years). Eur Heart J. 2004 Jul;25(14):1264-70.
13. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Page RL, Riegel B, Tarkington LG, Yancy CW; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults

With Congenital Heart Disease); American Society of Echocardiography; Heart Rhythm Society; International Society for Adult Congenital Heart Disease; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008 Dec 2;52(23):e143-263.

14. Achenbach TM. Manual for the Youth Self-Report and 1991 Profile. Burlington: University of Vermont, Department of Psychiatry. (1991b)
15. Achenbach TM. Manual for the Child Behavior Checklist/4-18 and 1991 Profile. Burlington: University of Vermont, Department of Psychiatry. (1991a)
16. Achenbach TM. Manual for the Young Adult Self-Report and Young Adult Behavior Checklist. Burlington: University of Vermont, Department of Psychiatry. (1997)
17. Achenbach TM. Manual for the ASEBA Adult Forms & Profiles. Burlington: University of Vermont, Department of Psychiatry, 2003. (2003)
18. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun;30(6):473-83.
19. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol. 1998 Nov;51(11): 1055-68.
20. Cohen J. Statistical Power Analysis for the Behavioral Sciences (second ed.), 1988. Lawrence Erlbaum Associates.
21. Maxwell AE. Comparing the classification of subjects by two independent judges. Br J Psychiatry. 1970 Jun;116(535):651-5.
22. Zomer AC, Vaartjes I, Uiterwaal CS, van der Velde ET, Sieswerda GJ, Wajon EM, Plomp K, van Bergen PF, Verheugt CL, Krivka E, de Vries CJ, Lok DJ, Grobbee DE, Mulder BJ. Social burden and lifestyle in adults with congenital heart disease. Am J Cardiol. 2012 Jun 1;109(11):1657-63.
23. Moons P. Quality of life in adults with congenital heart disease: Beyond the quantity of life. Doctoral dissertation. Belgium: Katholieke Universiteit Leuven; 2004.
24. Utens EM, Bieman HJ, Verhulst FC, Meijboom FJ, Erdman RA, Hess J. Psychopathology in young adults with congenital heart disease. Follow-up results. Eur Heart J. 1998 Apr;19(4):647-51.
25. Kańtoch MJ, Eustace J, Collins-Nakai RL, Taylor DA, Bolsvert JA, Lysak PS. The significance of cardiac surgery scars in adult patients with congenital heart disease. Kardiol Pol. 2006 Jan;64(1): 51-6; discussion 57-8.
26. Horner T, Liberthson R, Jellinek MS. Psychosocial profile of adults with complex congenital heart disease. Mayo Clin Proc. 2000 Jan;75(1):31-6.
27. Cyranowski JM, Frank E, Young E, Shear MK. Adolescent onset of the gender difference in lifetime rates of major depression: a theoretical model. Arch Gen Psychiatry. 2000 Jan;57(1):21-7.
28. DeMaso DR, Campis LK, Wypij D, Bertram S, Lipshitz M, Freed M. The impact of maternal perceptions and medical severity on the adjustment of children with congenital heart disease. J Pediatr Psychol. 1991 Apr;16(2):137-49.
29. Ong L, Nolan RP, Irvine J, Kovacs AH. Parental overprotection and heart-focused anxiety in adults with congenital heart disease. Int J Behav Med. 2011 Sep;18(3):260-7.

Chapter 3.2

Sexual functioning is impaired in adults with congenital heart disease

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ABSTRACT

Background: To investigate the overall sexual functioning and disease specific sexual problems in congenital heart disease (ConHD) patients, for both genders and different cardiac diagnostic groups, and compare these with Dutch normative data. Also disease specific sexual problems were investigated.

Methods: From a longitudinal cohort of patients, operated for ConHD between 1968-1980, 254 patients (median age: 40, 53.4% male) were included in this study: atrial septal defect (n=72), ventricular septal defect (n=71), pulmonary stenosis (n=30), tetralogy of Fallot (n=53) and transposition of the great arteries (n=28). Patients completed internationally validated, generic questionnaires and also disease specific instruments on sexual functioning.

Results: Patients showed a delay in starting sexual activities compared to peers. Females with ConHD scored significantly worse compared to normative data on all scales of sexual functioning, indicating a broad range of sexual problems and 15% showed clinical levels of sexual dysfunction. Of the males, 14% suffered from erectile dysfunction. Males with ConHD scored worse on erectile function, orgasmic function and satisfaction regarding their sexual life compared with normative data. No differences were found between the different cardiac diagnoses

The majority of patients reported disease specific worries and fears about the use of contraceptives, heredity, pregnancy and delivery. Patients indicated to have been suboptimally informed about sexuality in early adolescence.

Conclusions: This study shows that sexual functioning is impaired in ConHD adults. Providing information to patients about sexuality, pregnancy, delivery and heredity should be improved, and given at young age.

INTRODUCTION

The number of adults with congenital heart disease (ConHD) is steadily increasing due to the successes of pediatric cardiology and open-heart surgery. This nascent demographic phenomenon is creating major issues concerning the optimal medical and psychological management of these patients.[1-3] Adults with ConHD have very specific needs, both on medical and psychosocial topics. Previous studies concerning psychosocial well-being and quality of life in adult ConHD patients have largely neglected sexual functioning and only very few studies have reported on this topic.[4]

As part of a longitudinal study following a large cohort of consecutive patients operated for ConHD at young age, we investigated sexual functioning 30-43 years after cardiac surgery. Sexual functioning was assessed with both internationally validated instruments and disease-specific questionnaires, for males and females separately.

The aims of this study are:

1) To investigate the overall sexual functioning, for both sexes and different cardiac diagnostic groups, and compare this with the general population.
2) To investigate disease specific problems in sexual functioning.

METHODS

Inclusion criteria

The original cohort exists of all consecutive patients who underwent their first open heart surgery for Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), Pulmonary Stenosis (PS), Tetralogy of Fallot (ToF) or Transposition of the Great Arteries (TGA) between 1968 and 1980 in the Erasmus Medical Center, and were younger than 15 years at the time of surgery. This cohort has already been investigated in 1990/1991 and in 2000/2001. The baseline characteristics, medical and psychosocial results of these investigations have been reported in detail previously.[5-10]

The target population of this third follow-up (2010-2011) consisted of the 412 patients who participated in the previous 2 follow-ups. Of these patients, ten had died (causes: 6 cardiac-related, 3 unknown, 1 accident), 1 underwent heart transplantation and 28 patients were untraceable. Of the remaining 373 eligible patients, 102 refused to participate in this study due to practical reasons (work, distance to hospital), leading to a response rate of 73%.

Patient sample

Of the 271 patients who participated and completed psychological instruments, 17 patients refused to complete the questionnaires on sexual functioning. Patients were classified into

2 groups of disease severity according to the classification adopted at the American Heart Association Task Force on Adults with CHD.[11] Patients with corrected ASD, VSD and PS were classified as simple ConHD (unless they had complications such as severe ventricular dysfunction), while patients with ToF or TGA (all operated with a Mustard repair) were classified as moderate to complex ConHD.

Assessment procedure

The research protocol was approved by the institutional ethical committee and complies with the 1975 Declaration of Helsinki. All patients were approached uniformly and invited to visit the hospital for extensive cardiac and psychological examination. All participating patients signed informed consent before participating. During their visit, a cardiologist performed the cardiac and medical examination. The semi-structured interview and psychological questionnaires were completed during the hospital visit. Due to practical reasons (work, children), 20 patients completed the questionnaires at home. The questionnaires were administered verbally for patients who had difficulty reading or understanding the questionnaires.

Instruments and normative groups

The Female Sexual Function Index (FSFI) is a multidimensional and standardized self-report questionnaire used to assess 6 domains of sexual functioning in females.[12] The FSFI has shown good discriminative validity between females with and without sexual problems.[12-14]

The Female Sexual Distress Scale-Revised (FSDS-R) is a 12 item self-report questionnaire used to assess sexual related personal distress indicating sexual dysfunction. The FSDSR measures the psychological distress encountered during sexual intercourse.[12,15]

If a patient scores within the clinical range on both the FSFI and the FSDSR, this is classified as a DSM-IV sexual disorder. Normative data for both the FSFI and FSDSR were derived from Kuile et al.[12] Normative data on sexual dysfunctions in the general Dutch population were derived from the Rutgers Foundation.[16]

The International Index of Erectile Function (IIEF) is a multidimensional self-report questionnaire that measures erectile function and sexual functioning in males.[17] Normative data for the IIEF questionnaire was derived from Rosen et al.[17] Normative data on erectile dysfunction in the general Dutch population was derived from the Rutgers Foundation.[17]

The ConHD Specific Problems related to Sexual Functioning (CSSP) is a structured self-report specifically designed for this study by 2 congenital cardiologists and a psychologist specialized in ConHD to assess the impact of ConHD on sexual functioning (unpublished questionnaire Utens et al. 2010). Normative data on general sexual functioning of the Dutch population was derived from the Rutgers Foundation.[16,18]

Statistical analyses

Categorical variables are represented by frequencies and percentages. Where appropriate, a chi-square test or Fisher's exact test was used when comparing frequencies. Data on generic questionnaires (FSFI, FSDSR, IIEF) were analyzed conform to international manuals using means and standard deviations.[12,17] Data on disease-specific questionnaires are represented with medians and interquantile ranges because of the skewed nature of the data. Comparison of continuous variables between groups was made by one-way ANOVA tests. In case of a skewed distribution Wilcoxon signed rank tests were used. Univariate binary logistic regression (forced entry model) was used to test for effects of medication on erectile function and for the effects of educational level, occupational level and income on sexual dysfunctions in both men en women. Two-tailed probability values of <0.05 were considered statistically significant. The statistical packages IBM SPSS Statistics for Mac version 19.0 (Release 19.0.0) and R (64 bit) for Mac, version 2.14.2 were used to preform the calculations.

RESULTS

Baseline characteristics (Table 1)

The baseline characteristics of the 254 included patients (53.5% male, median age 40 years) are summarized in Table 1. A total of 97% was heterosexual, 2% was homosexual and 1% was bisexual. The majority of patients were married (59.3%), and 84.5% reported to be sexually active. Patients with moderate/complex ConHD used cardiac medication significantly more often than the patients with simple ConHD (p=0.004) and on average, had a worse systemic ventricular function (p<0.001).

Table 1. Baseline characteristics

Variable	Total	ConHD classification			ConHD diagnosis					
		Simple	Moderate/ complex	p	ASD	VSD	PS	ToF	TGA	p
	n=254	n=173	n=81		n=72	n=71	n=30	n=53	n=28	
Age	40 [36-45]	40 [37-45]	38 [34-41]	0.000	43 [39-47]	39 [35-43]	39 [37-45]	40 [35-45]	36 [33-38]	0.000
Gender										
• Male	53.5	50.3	60.5	0.129	37.5	60.6	56.7	56.6	67.9	0.022
• Female	46.5	49.7	39.5		62.5	39.4	43.3	43.4	32.1	
Marital status										
• Unmarried	16.7	15.6	19.0	0.504	19.4	14.1	10.0	15.7	25.0	0.535
• Cohabitants	21.0	20.2	22.8	0.644	19.4	16.9	30.0	25.5	17.9	0.546
• Married	62.3	64.2	58.2	0.367	61.1	69.0	60.0	58.8	57.1	0.726

Table 1. (continued)

Variable	Total	ConHD classification		p	ConHD diagnosis					p
		Simple	Moderate/ complex		ASD	VSD	PS	ToF	TGA	
	n=254	n=173	n=81		n=72	n=71	n=30	n=53	n=28	
Medication										
• No medication	76.5	82.1	64.3	0.004	76.6	84.8	88.5	72.7	50.0	0.004
• Aspirin	4.9	3.8	7.1	0.287	4.7	1.5	7.7	9.1	3.8	0.327
• Calcium antagonist	0.9	0.6	1.4	0.524	-	1.5	-	-	3.8	0.447
• Beta-blocker	7.5	5.8	11.4	0.136	7.8	6.1	-	6.8	19.2	0.150
• Nitrate	-	-	-	-	-	-	-	-	-	-
• Anti-arrhythmics	2.2	1.9	2.9	0.646	3.1	-	3.8	2.3	3.8	0.426
• Digitalis	0.9	-	2.9	0.095	-	-	-	-	7.7	0.026
• Duretics	3.1	2.6	4.3	0.680	1.6	4.5	-	-	11.5	0.080
• ACE inhibitor	8.0	3.8	17.1	0.001	1.6	7.6	-	9.1	30.8	0.000
• Cholesterol lowering	3.1	2.6	4.3	0.680	4.7	-	3.8	6.8	-	0.160
• Oral anticoagulation	4.9	3.2	8.6	0.083	4.7	3.0	-	2.3	19.2	0.028
Systemic ventricular function										
• Good	62.9	86.4	29.8	0.000	92.4	80.0	75.0	46.3	-	0.000
• Mildly impaired	24.8	11.9	42.9	0.000	7.6	15.0	25.0	48.1	33.3	0.000
• Moderately impaired	7.9	-	19.0	0.000	-	-	-	-	53.3	0.000
• Severely impaired	4.5	1.7	8.3	0.035	-	5.0	-	5.6	13.3	0.052

Abbreviations: ASD = Atrial Septal Defect; PS = Pulmonary Stenosis; TGA = Transposition of the Great Arteries; ToF = Tetralogy of Fallot; VSD = Ventricular Septal Defect.
Data are presented as n %, unless indicated otherwise. Continuous data are presented as median [interquartile range (IQR)].

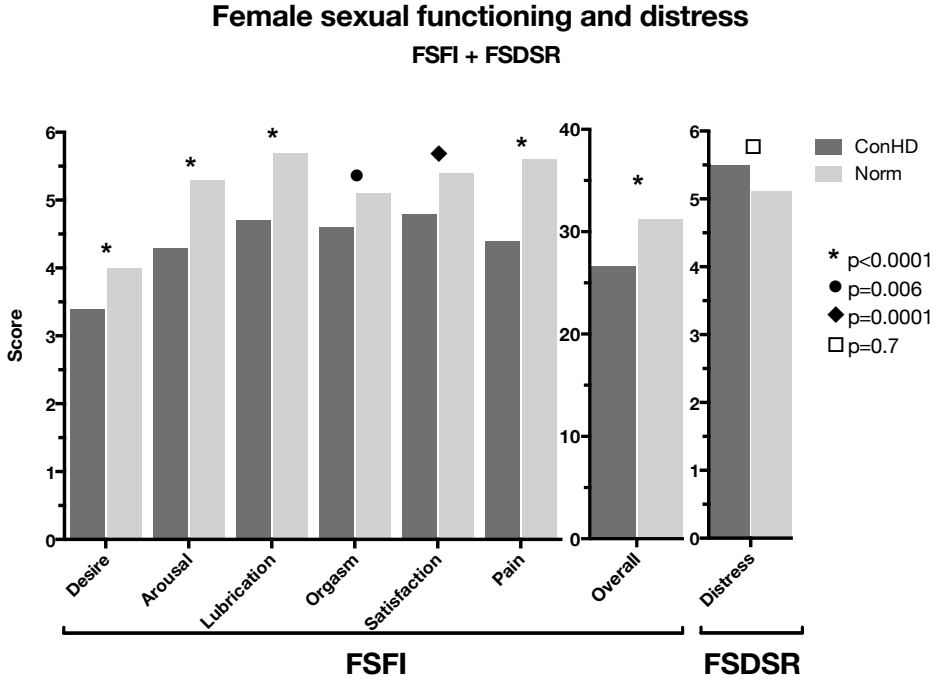
Gender specific sexual functioning compared to normative data

Females (FSFI and FSDSR) (Figure 1)

On all sexual functioning scales (FSFI questionnaire), females with ConHD scored significantly worse compared to normative data, indicating a broad range of sexual problems; with younger females showing worse outcome compared to older females (groups based on median age of 39 years) ($p<0.0001$). However, on the FSDS-R scale assessing sexual distress indicating pathological sexual dysfunction, females obtained similar results compared to normative data. A pathological sexual disorder was present in 14.6% of our female patients compared to 17.7% in the reference group ($p=0.5$).[18]

In-between ConHD diagnostic groups: No difference was found on either of the questionnaires between diagnostic groups.

Figure 1



Abbreviations: ConHD = All congenital heart diseases together; Norm = Normative data.
A high score indicates favorable sexual functioning. On the distress scale, a high score indicates high distress. Data are presented using means.

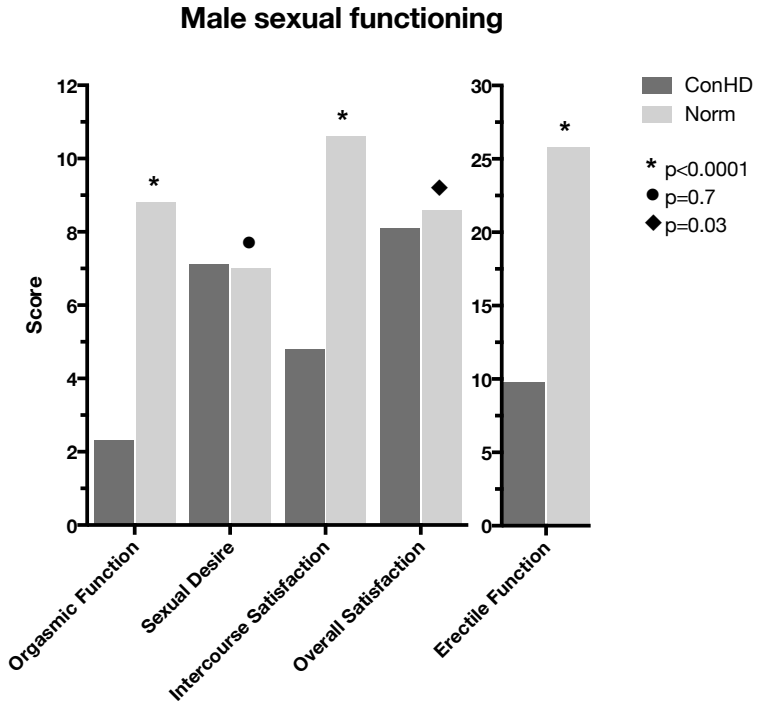
Effect of systemic ventricular function: Univariate logistic regression showed no significant effects of systemic ventricular function on the prevalence of sexual disorders in females (FSDSR, FSFI and clinical score).

Effects of socio-economic status: Univariate logistic regression showed no significant effects of occupational level, educational level and income on the prevalence of sexual disorders in females (FSDSR, FSFI and clinical score).

Males (IIEF) (Figure 2)

Males with ConHD scored worse on erectile function, orgasmic function, intercourse satisfaction and overall satisfaction compared to normative data. This result indicates a broad range of sexual problems. A total of 13.7% of males scored within the clinical range of having erectile dysfunction. This is more than twice as high as in normative data stratified by age (5.9%, p=0.002). Patients with erectile dysfunction were not significantly older than patients without (p=0.8). The use of beta-blockers did not have an effect on erectile function in this population (p=0.9).

Figure 2



Abbreviations: ConHD = All congenital heart diseases together; Norm = Normative data.
A high score indicates favorable sexual functioning. Data are presented using means.

Diagnostic groups: No difference was found between the different ConHD diagnoses.

Effect of systemic ventricular function: Univariate logistic regression showed no significant effects of systemic ventricular function on the prevalence of sexual disorders in males (IIEF and clinical score).

Effects of socio-economic status: Univariate logistic regression showed no significant effects of occupational level, educational level and income on the prevalence of sexual disorders in males (erectile disorders on the IIEF).

Disease specific problems related to sexual functioning (Table 2 – Table 4)

Gender specific sexual aspects are shown in Table 2. Females had their first menstrual period at a median age of 13 years, which is comparable to the general Dutch population. Cardiac complaints worsened in 11% of females during menses. Menstrual complaints mainly consisted of pain (41.7%) and excessive blood loss (35.1%). A total of 19.8% required medical treatment for menstrual related problems.

Table 2. Female disease specific sexually related aspects, fears & worries

	Total N=118		ConHD classification: Simple N=86		ConHD classification: Moderate/complex N=32		p
	N	%	N	%	N	%	
At what age did you get your first menstrual period?							
• Age (median [IQR])	13 [12-14]		13 [12-14]		13 [12-14]		0.5
Do you get more complaints from your ConHD or do the complaints change before or after your menstrual period?							
• Yes	13	11.0	9	10.5	4	12.5	0.7
Have you ever experienced one of the following complaints?							
• >5 weeks between menses	11	9.5	10	11.8	1	3.2	0.3
• <5 weeks between menses	7	6.1	7	8.4	-	-	0.2
• Excessive blood loss	40	35.1	27	32.5	13	41.9	0.3
• Painful menses	48	41.7	36	42.9	12	38.7	0.7
• 6 months no menses	14	12.4	12	14.5	2	6.7	0.3
• Spotting	5	11.6	10	12.2	4	12.9	1.0
Did you ever need medical attention for menstrual complaints?							
• Yes	23	19.8	17	20.0	6	19.4	0.9
Are you (pre)menopausal?							
• Yes	19	16.5	17	20.5	2	6.3	0.1
• Age (median [IQR])	45 [42-47]		45 [42-47]		44 [42-44]		0.5
Are you receiving medical treatment for your (pre)menopause?							
• Yes	3	2.6	2	2.4	1	3.1	1.0

Abbreviation: IQR = Interquantile Range.
Data are displayed as n %, unless indicated otherwise.

Problems before, during and after sexual activity (Online supplemental Table 3)

Patients in our study were on average 18 years old when they first had sexual intercourse. On average, they had 1 sexual partner during the past 3 months. Roughly a quarter of patients (24.7%) had sexual intercourse between zero and one times per month, 23.3% had sexual intercourse between 2 to 3 times per month, almost a third (28.4%) had sexual intercourse four to nine times per month and the rest (11.4%) had sexual intercourse more than nine times per month.

The majority (76.5%) of patients felt satisfied with their overall physical appearance. Obesity was the main reason why some of the patients felt dissatisfied. When rating the appearance of their scar, patients scored a 5.8 on a scale from 1 to 10 (1 = ugly, 10 = beautiful). The surgical scar made 11.4% of patients feel ashamed and less attractive during sexual activity. This was reported significantly more often by females (17.5% versus 6.2% in males, p=0.004).

Of all patients, 11.7% reported having problems with sexual activities because of their ConHD. This was observed more frequently in females compared to males (16.2% versus

Online supplemental Table 3. Male and female disease specific fears and worries

	Total N=254		ConHD classification				p	Gender				p
			Simple N=173		Moderate/ complex N=81			Male N=136		Female N=118		
	N	%	N	%	N	%		N	%	N	%	
How old were you when you first had sexual intercourse?												
• (median [IQR])	18 [16-20]		18 [16-20]		18 [16-20]		0.8	18 [16-20]		18 [16-20]		0.8
In the past three months, how many sexual partners have you had?												
• Sexual partners (median [IQR])	1 [1-1]		1 [1-1]		1 [1-1]		0.5	1 [1-1]		1 [1-1]		0.2
In the past month, how often did you have sexual intercourse?												
• None - One	67	24.7	51	28.0	16	18.0	0.1	40	27.6	27	24.1	0.2
• Two to three	63	23.2	44	24.2	19	21.3	0.6	29	20.0	34	27.0	0.2
• Four to nine	77	28.4	44	24.2	33	37.1	0.027	41	28.3	36	28.6	1.0
• Above nine	31	11.4	25	13.7	6	6.7	0.1	16	11.0	15	11.9	0.8
Are you satisfied with your overall appearance?												
• Satisfied	202	76.5	134	74.9	68	80.0	0.4	114	80.9	88	71.5	0.075
• Neutral	41	15.5	31	17.3	10	11.8	0.2	19	13.5	22	17.9	0.3
• Dissatisfied	21	8.0	14	7.8	7	8.2	0.9	8	5.7	13	10.6	0.1
Please rate on a scale from 1 to 10 how you feel about the appearance of your scar												
• (median [IQR])	6 [4-8]		6 [4-8]		6 [5-8]		0.1	6 [5-8]		6 [4-8]		0.2
During sexual activity, do you experience any of the following complaints because of your heart disease?												
• Fear of rejection	10	3.7	5	2.7	5	5.6	0.3	5	3.4	5	4	1.0
• Fear of excessive tiredness	12	4.4	7	3.8	5	5.6	0.5	6	4.1	6	4.8	1.0
• Fear of infarction	9	3.3	6	3.3	3	3.4	1.0	4	2.8	5	4.0	0.7
• Fear of sudden death	6	2.2	3	1.6	3	3.4	0.4	2	1.4	4	3.2	0.4
• Ashamed/less attractive because of scars	31	11.4	21	11.5	10	11.2	0.9	9	6.2	22	17.5	0.004
Do you have problems before, during or after sexual intercourse because of your heart disease?												
• Yes	29	11.7	12	7.1	17	21.8	0.001	10	7.7	19	16.2	0.037
My heart disease plays a major influence on the starting and maintaining of a relationship												
• (Entirely) true	29	11.6	15	8.9	14	17.5	0.048	15	11.4	14	12.0	0.9
• (Entirely) false	220	88.3	154	91.1	66	82.5		117	88.6	103	88.1	
My heart disease has a big influence on my sexual life												
• (Entirely) true	24	9.6	13	7.6	11	13.8	0.1	11	8.3	13	11.1	0.4
• (Entirely) false	226	90.4	157	92.4	69	86.3		122	91.7	104	88.9	
I cannot fully enjoy my sexual life because of my heart disease												
• (Entirely) true	14	5.6	8	4.7	6	7.5	0.4	6	4.5	8	6.8	0.4
• (Entirely) false	236	94.4	162	95.3	74	92.5		127	95.5	109	93.2	
Do you have to stop prematurely with sexual activities because of heart complaints?												
• No	231	93.9	159	94.6	72	92.3	0.5	122	93.8	109	94.0	1.0
• Rarely	13	5.3	7	4.2	6	7.7	0.3	7	5.4	6	5.2	0.9

Online supplemental Table 3. (continued)

	Total N=254		ConHD classification: Simple N=173		ConHD classification: Moderate/complex N=81		p	Gender: Male N=136		Gender: Female N=118		p
	N	%	N	%	N	%		N	%	N	%	
• Often	1	0.4	1	0.6	-	-	1.0	1	0.8	-	-	1.0
• Almost always	1	0.4	1	0.6	-	-	1.0	-	-	1	0.9	0.5
In the past month, how often did you not enjoy sexual activity?												
• Occasionally/Often	44	18.6	33	20.5	11	14.7	0.3	17	13.1	27	25.5	0.015
In the past month, how often did you feel insecure about sexual intercourse?												
• Occasionally/Often	37	15.7	28	17.5	9	12.0	0.3	17	13.2	20	18.9	0.2
In the past month, how often did you not get aroused during sexual activity?												
• Occasionally/Often	45	19.5	33	20.6	12	16.9	0.5	11	8.7	34	32.4	0.000
In the past month, how often were you afraid to have sexual intercourse?												
• Occasionally/Often	7	3.0	5	3.1	2	2.8	1.0	2	1.6	5	4.7	0.3
In the past month, how often were you worried about your sex life?												
• Occasionally/Often	56	23.8	38	23.5	18	24.7	0.8	23	18.0	33	30.8	0.021
Were you ever forced to sexual activities against your will?												
• Yes	19	7.8	11	6.6	8	10.3	0.3	6	4.6	13	11.3	0.051
Are you using any sleep medication, or medication to calm you down?												
• Yes	15	6	8	4.7	7	8.9	0.2	8	6	7	6	
How well are you informed about the influence of sexual activities on your heart disease?												
• (median [IQR])	2 [1-6]		2 [1-6]		2 [1-6]		0.8	2 [1-5]		2 [1-7]		0.064
Would you like to receive more information about the possible influence of sexual activities on your heart disease?												
• Yes	42	17.2	27	16.4	15	19.0	0.6	24	18.5	18	15.8	0.6
• No	95	38.9	64	38.8	31	39.2	0.9	54	41.5	41	36.0	0.4
• Not interested	107	43.9	74	44.8	33	41.8	0.7	52	40.0	55	48.2	0.2

Abbreviations: IQR = Interquantile Range.
Data are displayed as n %, unless indicated otherwise.

7.7%, p=0.037), and more frequently in moderate/complex ConHD patients compared to simple ConHD patients (21.8% versus 7.1%, p=0.001). In addition, 11.6% of all patients reported that their ConHD had a great influence on starting and maintaining a relationship. Remarkably this was reported significantly more often in the simple ConHD group compared to the moderate/complex ConHD group (17.5% versus 8.9%, p=0.048). Overall, patients did not have to prematurely cease with sexual activity due to heart complaints.

About 1 in every 5 patients reported not having enjoyed sexual activity (18.6%), having feelings of insecurity (15.7%) or felt unable to achieve sexual arousal during sexual activity (19.5%) within the last month. Not enjoying sexual activity was reported more often by females compared to males (25.5% versus 13.1%, p=0.015).

About 1 in 4 patients worry about their sex life (23.8%). This was reported more frequently by females (30.8% versus 18.0%, p=0.021).

A total of 7.8% of patients reported having been forced to perform sexual activity against their will. This finding was higher in females compared to males (11.3% versus 4.6%, p=0.05).

When asked to rate the information provided by physicians about sexuality and ConHD, patients scored a 2.0 on average on a 1-10 Likert scale (1 = not being informed about the influence of sexuality on ConHD, 10 being optimally informed). Almost half of the patients (45%) rated the provided information on the possible side effects of sex on their heart condition as 1, and 68% of patients scored ≤5 (unsatisfactory).

Contraceptives, pregnancy and heredity (Online supplemental Table 4)

Patients began using contraceptives at a median age of 18 years. The most used contraceptive was the condom, followed by oral contraceptives and sterilization. 10.9% of males were sterilized, versus 5.9% of females (p=0.166). A minority of patients (4.7%) became pregnant while using contraception.

The vast majority of patients (86.2%) never discussed the possible side effects of different methods of contraceptives with their physicians. There was a strong gender difference in information received from the physician; with females asking and receiving more information. Despite this, only 20% of women reported to have received information from their physicians regarding the use of contraceptives. Of this group, 56% had to actively ask for this information. Females reported having a greater fear of being infertile compared to males (26.2%

Online supplemental Table 4. Facts and concerns regarding contraceptives, pregnancy and heredity

	Total N=254		ConHD classification				p	Gender				p
			Simple N=173		Moderate/complex N=81			Male N=136		Female N=118		
	N	%	N	%	N	%		N	%	N	%	
How old were you when you started to use contraceptives?												
• Age in years (median [IQR])	18 [16-19]		18 [16-19]		18 [16-20]		0.5	18 [17-20]		17 [16-19]		0.036
Have you ever had an unplanned pregnancy despite the use of contraceptives?												
• Yes	11	4.7	9	5.6	2	2.7	0.5	4	3.3	7	6.2	0.4
Have you ever had an unplanned pregnancy without the use of contraceptives?												
• Yes	7	3.0	6	3.7	1	1.4	0.4	6	4.9	1	0.9	0.1
Did your physician give you information about the possible side effects that different contraceptives may have?												
• Physician started conversation	14	6.3	11	7.1	3	4.3	0.6	3	2.7	11	9.6	0.050
• I asked it myself	17	7.6	7	4.5	10	14.5	0.009	3	2.7	14	12.3	0.010
• Never spoke about it	193	86.2	137	88.4	56	81.2	0.1	104	94.5	89	78.1	0.000

Online supplemental Table 4. (continued)

	Total N=254		ConHD classification					Gender				
			Simple N=173		Moderate/complex N=81		p	Male N=136		Female N=118		p
	N	%	N	%	N	%		N	%	N	%	
Would you like to receive more information about the possible side effects of different contraceptives?												
• I would like more information	28	12.7	13	8.4	15	22.4	0.004	7	6.4	21	18.9	0.005
• I have enough information	66	29.9	45	29.2	21	31.3	0.8	29	26.4	37	33.3	0.3
• No interest	127	57.5	96	62.3	31	46.3	0.026	74	67.3	53	47.7	0.003
If you have sexual intercourse, how often do you use a condom?												
• Never	156	70.6	115	74.2	41	62.1	0.071	77	64.2	79	78.2	0.022
• Rarely	10	4.5	4	2.6	6	9.1	0.069	5	4.2	5	5.0	1.0
• Sometimes	13	5.9	12	7.7	1	1.5	0.1	10	8.3	3	3.0	0.1
• Often	11	5.0	7	4.5	4	6.1	0.7	5	4.2	6	5.9	0.5
• Always	31	14.0	17	11.0	14	21.2	0.045	23	19.2	8	7.9	0.016
In the past month, how often did you worry about the ability to have children?												
• Never	210	90.1	144	90.0	66	90.4	1.0	115	91.3	95	88.8	0.5
• Occasionally	13	5.6	9	5.6	4	5.5	1.0	7	5.6	6	5.6	1.0
• Often	10	4.3	7	4.4	3	4.1	1.0	4	3.2	6	5.6	0.5
Have you ever been afraid of infertility?												
• Yes	42	18.8	33	21.4	9	12.9	0.1	14	12.0	28	26.2	0.007
Have you ever been afraid about the heredity of your heart disease?												
• Yes	117	52.2	74	48.4	43	60.6	0.089	48	41.0	69	64.5	0.000
Have you ever been afraid of any harmful effects of your heart disease on your child?												
• Yes	77	34.5	46	30.3	31	43.7	0.050	37	32.2	40	37.0	0.4
Have you ever been afraid of not having enough energy to raise a child?												
• Yes	19	8.6	7	4.6	12	16.9	0.002	7	6.1	12	11.2	0.2
Have you ever been afraid of a possible lower life expectancy while raising children?												
• Yes	23	10.3	9	5.9	14	19.7	0.002	13	11.1	10	9.3	0.7
Do you feel your heart disease is a limiting factor in having children?												
• Yes	33	14.6	17	11.0	16	22.2	0.027	9	7.6	24	22.2	0.002
Are you afraid that pregnancy can have a negative influence on your heart?												
• Yes	23	21.3	9	11.5	14	46.7	0.000	-	-	23	21.3	
Are you afraid that pregnancy can have a negative effect on your overall health?												
• Yes	23	21.3	8	10.3	15	50.0	0.000	-	-	23	21.3	
Are you afraid that the delivery of your child will have a negative influence on your heart?												
• Yes	30	28.0	12	15.6	18	60.0	0.000	-	-	30	28.0	
Are you afraid that the delivery of your child will have a negative influence on your overall health?												
• Yes	23	21.5	8	10.4	15	50.0	0.000	-	-	23	21.5	

Abbreviations: IQR = Interquantile Range.
Data are displayed as n %, unless indicated otherwise.

versus 12.0%, p = 0.007). In addition, females reported experiencing more feelings of fear concerning the heredity of their ConHD (64.5% versus 41.0%, p<0.0001). The fear of harmful effects of their heart disease on the outcome of their child was reported by 34.5% of patients. This was reported significantly more often in patients with moderate/complex ConHD (43.7% versus 30.3%, p=0.05). Patients with moderate/complex ConHD also had significantly more fears of not having enough energy to raise children (16.9% versus 4.6%, p=0.002) and fears of a lower life expectancy as a disability to fully raise children (19.7% versus 5.9%, p=0.002). ConHD was a limiting factor in the decision of having children in 14.6% of patients, mostly in females compared to males (22.2% versus 7.6% p=0.002) and in patients with moderate/complex ConHD compared to simple ConHD patients (22.2% versus 11.0%, p=0.027).

A total of 21.3% of females feared that pregnancy would have a negative influence on their heart or on their overall clinical condition. This was found more often in females with moderate/complex ConHD (p<0.0001). In addition, some of the females feared that delivery would have a negative effect on their heart (28.0%) and overall health (21.5%). Both of these findings were higher in females with moderate/complex ConHD group compared to females with simple ConHD (p<0.0001).

DISCUSSION

The present study shows a broad range of sexual problems in both men and women with ConHD. Concern over sexual health appeared to be stronger in women. Sexual functioning was significantly impaired compared to normative data. Concern over sexual health appeared to be stronger in women. Our female patients reported a wide range of problems, including a lower sexual desire, less arousal, and more pain during sexual intercourse. The proportion of male patients with erectile dysfunction was more than twice as high as in the general population. Male sexual functioning was clearly impaired as to satisfaction regarding intercourse and orgasmic function. Our female patients reported a wide range of problems, including a lower sexual desire, less arousal, and more pain during sexual intercourse.

No differences were found between cardiac diagnostic groups on generic questionnaires into sexual functioning. However, disease-specific instruments showed that patients with moderate/complex ConHD viewed their ConHD as a limiting factor in having children. Concerns included not having enough energy in raising children, having a lower lower life expectancy, potentially harmful effects of the pregnancy on their child, their heart and overall health.

Disease specific problems related to sexual functioning

An important issue is whether the surgical scar influences personal feelings and hereby indirectly the sexual functioning of patients. Some patients indicated that the scar was part of their body and a symbol that their life had been saved. Earlier in life about half of patients from this same cohort reported to have been troubled by their scar.[8] Now, 10 years later, during the third follow-up of this cohort, a minor proportion of patients still felt ashamed because of their scar and felt less attractive. This was especially seen in females. However, compared to the 2 previous follow-ups, these numbers seem to have declined. A possible explanation is that with older age, patients seem to have accepted the scar and find it less important. This hypothesis is supported by Horner et al. who described that patients reported to conceal or hide their scars mostly during adolescence.[19] Most problems were observed around 20 years of age, the age that many people start a relationship. This may imply that the desire of young females to correct their scar by plastic surgery should be taken seriously, but does seem age-related and is often not a problem after 10 years.

Patients from our study lost their virginity at a significantly older age compared to the general Dutch population.[18] It has been reported that a lower educational level is associated with an early age of losing virginity.[18] Taking into account the lower educational level of the present cohort the significantly older age when losing virginity is even more noticeable.[7] In our opinion this finding can be explained by possible overprotection from parents.[20] In addition, the later age at which patients become independent and gain autonomy could play a role.[21-23] Finally, feelings of uncertainty or feelings about being less attractive might play a role here. Previously, during the second follow-up of this study at a younger age, our patients reported feeling limited due to their surgical scars. This could also have contributed to fear of rejection, which may cause patients to become sexually active at a later age.

Gender-specific sexual functioning

In our study we found that female patients had their first menstrual period at a median age of 13 years, which is in line with literature and normative data.[18,24] There was no difference between simple and moderate/complex ConHD patients.

Although females obtained significantly worse outcomes on the FSFI compared to normative data, the prevalence of sexual disorders in females (14.6% had clinical range on both the FSFI and FSDSR) did not differ from the general Dutch population. A possible explanation for this is that the FSDSR instrument is not sensitive enough to measure distress in females with ConHD. In contrast to the study of Reid et al. we did not find that females with a moderate/complex ConHD had significantly more sexual partners indicating promiscuity.[25] This could however be explained by the age difference: the patients in our study are older.

Of the male patients, 13.7% experienced a clinical level of erectile dysfunction, which is higher than reported previously using the same instruments in ConHD patients, and over twice as high as in the general Dutch population.[18,26]

Contraceptives, pregnancy and heredity

This study also shows areas in outpatient care to which more attention should be paid. Only a minority of patients (13.8%) reported to have been fully informed about how sexuality, pregnancy, and contraceptives can influence their heart and overall general health.[27-30] 20% of females reported to have been informed regarding contraceptives by their physician. Studies have shown poor knowledge about contraceptives with many misconcepts.[31-32] Of course at the age of 40 this probably is not a big issue anymore, but there seems to be a clear need for counseling provided at a younger age, preferably before puberty. Information could be provided by pediatric cardiologists, but also by nurse practitioners or patient organizations.

Clinical implications

Since this cohort has reached the age of 30-56 years, and most patients have children, the need for sexually oriented information may have disappeared, and may be higher in younger patients. Patients reported to have had worries and fears in the past about the heredity of ConHD, harmful effects on the unborn child and infertility. Patients were also worried about the harmful effects of pregnancy and delivery on their own heart and overall health.[19,25,28] Caregivers should bear in mind that patients wish to receive information about contraceptives and sexual activities.[32] Therefore, we would recommend that patients receive disease specific information regarding sexual activities at young age, before planning to have children. Considering that most hospitals have combined transfer of patients from pediatric to adult clinics, this would provide a perfect opportunity to counsel patients about this problem, for instance by a nurse practitioner. Highlighted topics should at least include the safe use of contraceptives, sexual activities, pregnancy and delivery.

Strengths and study limitations

This study is the first to report on gender-specific sexual functioning in a systematically followed consecutive series of 30-56 year old patients. Both internationally validated generic questionnaires and disease specific instruments were used to measure sexual functioning for both genders. Where possible, outcomes were compared to normative data. Unfortunately, data on sexual functioning in males is scarce. There was no Dutch IIEF data of male reference groups for the Netherlands. Therefore, IIEF normative data from the USA was used. The patients included in this study all had the diagnosis of ASD, VSD, PS, ToF or TGA, and all were

followed in an adult tertiary care center in the Netherlands. Therefore, the obtained results may not be applicable for all ConHD patients, nor in all countries worldwide. The FSDSR instrument may not have been specific enough to detect clinical levels of problems with sexuality in females.

Future recommendations

With increasing age, it can be expected that erectile disorders and menopausal complaints in ConHD patients may worsen. Systematic follow-up of sexual function is therefore recommended in this population since the present patients with ConHD already show high levels of sexual dysfunction. Attention for and information on sexual functioning should be organized for adolescents with ConHD. The extent in which these findings can be extrapolated to other heart conditions is unknown and should be investigated.

CONCLUSIONS

Sexual functioning in ConHD adults has largely been neglected in psychosocial research. Our study shows that sexual functioning is hampered substantially in adults with ConHD. Importantly, providing information to patients about sexuality, pregnancy, delivery and heredity should be improved and given at a younger age to assure the best holistic care.

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REFERENCES

1. van der Linde D, Konings EE, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol 2011; 58:2241-7.
2. Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. N Engl J Med 2000; 342:256-63.
3. Warnes CA. The adult with congenital heart disease: born to be bad? J Am Coll Cardiol 2005; 46: 1-8.
4. Moons P, Van Deyk K, Marquet K, De Bleser L, Budts W, De Geest S. Sexual functioning and congenital heart disease: Something to worry about? Int J Cardiol 2007; 121:30-5.
5. Utens EM, Verhulst FC, Erdman RA, et al. Psychosocial functioning of young adults after surgical correction for congenital heart disease in childhood: a follow-up study. J Psychosom Res 1994; 38: 745-58.
6. Utens EM, Verhulst FC, Meijboom FJ, et al. Behavioural and emotional problems in children and adolescents with congenital heart disease. Psychol Med 1993; 23:415-24.
7. van Rijen EH, Utens EM, Roos-Hesselink JW, et al. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. Eur Heart J 2003; 24:673-83.
8. van Rijen EH, Utens EM, Roos-Hesselink JW, et al. Medical predictors for psychopathology in adults with operated congenital heart disease. Eur Heart J 2004; 25:1605-13.
9. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. Circulation 1995; 91:2214-9.
10. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, et al. Decline in ventricular function and clinical condition after Mustard repair for transposition of the great arteries (a prospective study of 22-29 years). Eur Heart J 2004; 25:1264-70.
11. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008; 52:e143-263.
12. ter Kuile M, Brauer M, Laan E. De Female Sexual Function Index (FSFI) en de Female Sexual Distress Scale (FSDS): Psychometrische eigenschappen in een Nederlandse populatie. Tijdschrift voor Seksuologie 2009; 33-3:207-222
13. Meston CM. Validation of the Female Sexual Function Index (FSFI) in women with female orgasmic disorder and in women with hypoactive sexual desire disorder. J Sex Marital Ther 2003; 29: 39-46.
14. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. J Sex Marital Ther 2005; 31:1-20.
15. Derogatis L, Clayton A, Lewis-D'Agostino D, Wunderlich G, Fu Y. Validation of the female sexual distress scale-revised for assessing distress in women with hypoactive sexual desire disorder. J Sex Med 2008; 5:357-64.
16. de Graaf H, Kruijer H, van Acker J, Meijer S. Seks onder je 25ste (2012). 1st ed. Rutgers WPF/Soa aids Nederland. Eburon, Delft.

17. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997; 49:822-30.
18. Bakker F, Vanwesenbeeck I. Sexuele gezondheid in Nederland 2006. 1st ed. Rutgers Nisso Groep 2006. Eburon, Delft.
19. Horner T, Liberthson R, Jellinek MS. Psychosocial profile of adults with complex congenital heart disease. Mayo Clin Proc 2000; 75:31-6.
20. Ong L, Nolan RP, Irvine J, Kovacs AH. Parental overprotection and heart-focused anxiety in adults with congenital heart disease. Int J Behav Med 2011; 18:260-7.
21. Kovacs AH, Sears SF, Saidi AS. Biopsychosocial experiences of adults with congenital heart disease: review of the literature. Am Heart J 2005; 150:193-201.
22. Simko LC, McGinnis KA, Schembri J. Educational needs of adults with congenital heart disease. J Cardiovasc Nurs 2006; 21:85-94.
23. Kokkonen J, Paavilainen T. Social adaptation of young adults with congenital heart disease. Int J Cardiol 1992; 36:23-9.
24. Vigl M, Kaemmerer M, Niggemeyer E, et al. Sexuality and reproductive health in women with congenital heart disease. Am J Cardiol 2010; 105:538-41.
25. Reid GJ, Siu SC, McCrindle BW, Irvine MJ, Webb GD. Sexual behavior and reproductive concerns among adolescents and young adults with congenital heart disease. Int J Cardiol 2008; 125:332-8.
26. Vigl M, Hager A, Bauer U, et al. Sexuality and subjective wellbeing in male patients with congenital heart disease. Heart 2009; 95:1179-83.
27. Hargrove A, Penny DJ, Sawyer SM. Sexual and reproductive health in young people with congenital heart disease: a systematic review of the literature. Pediatr Cardiol 2005; 26:805-11.
28. Uzark K, VonBargen-Mazza P, Messiter E. Health education needs of adolescents with congenital heart disease. J Pediatr Health Care 1989; 3:137-43.
29. Kamphuis M, Verloove-Vanhorick SP, Vogels T, Ottenkamp J, Vliegen HW. Disease-related difficulties and satisfaction with level of knowledge in adults with mild or complex congenital heart disease. Cardiol Young 2002; 12:266-71.
30. Verstappen A, Pearson D, Kovacs AH. Adult congenital heart disease: the patient's perspective. Cardiol Clin 2006; 24:515-29, v.
31. Rogers P, Mansour D, Mattinson A, O'Sullivan JJ. A collaborative clinic between contraception and sexual health services and an adult congenital heart disease clinic. J Fam Plann Reprod Health Care 2007; 33:17-21.
32. Kaemmerer M, Vigl M, Seifert-Klauss V, et al. Counseling reproductive health issues in women with congenital heart disease. Clin Res Cardiol 2012; 101:901-7.

Chapter 3.3

Sports participation and physical fitness in adults with congenital heart disease

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ABSTRACT

Objective: To investigate the effect of sports participation in adults with corrected congenital heart disease (ConHD) on objective and subjective physical functioning, and to investigate the safety of sports participation in adults with ConHD.

Methods: Included were all patients who underwent corrective surgery for Atrial Septal Defect, Ventricular Septal Defect, Pulmonary Stenosis, Tetralogy of Fallot or TGA (Mustard repair) in our center between 1968 and 1980 and who had a follow-up both in 2001 and 2011. In both 2001 and 2011 patients filled in questionnaires on sports participation, subjective physical functioning and quality of life. Subjective physical functioning and quality of life were measured using standardized, validated psychological questionnaires. Objective exercise capacity was measured by means of ergometric (bicycle) testing.

Results: Patients with moderate/complex ConHD showed worse exercise capacity ($p=0.001$) and oxygen uptake ($p<0.0001$) compared to patients with simple ConHD. Patients with simple ConHD showed a normal exercise capacity (92.4% of norm), whereas patients with moderate/complex ConHD showed a decreased exercise capacity (82.8% of norm).

We found no association between practising sports and death.

Half of ConHD patients were practising sports in 2001 and 2011, more than half of these involved high-dynamic types of sports. Multivariate analysis showed that practising sports was correlated with an increase in exercise capacity, this effect being larger for patients who practiced more hours of sports per week.

Conclusion: Engaging in sports can increase the exercise capacity of adults with ConHD and appears to be relatively safe.

INTRODUCTION

Since the first surgical techniques for patients with congenital heart disease (ConHD) became available some 55 years ago, virtually every area of patient care has evolved substantially. These improvements have led to an increased survival for patients with ConHD, with over 90% of infants reaching adulthood.[1] In order to investigate the long-term outcomes after surgery for ConHD, the Erasmus Medical Center started a longitudinal cohort study, which included all consecutive patients with ConHD who were operated between 1968 – 1980 and investigated every 10 years.

Sports participation in adults with ConHD is a relatively new territory and many physicians are having difficulty in advising patients. Their first concern is safety, and, especially in the past, the fear that intensive or competitive sports participation will increase the risk of sudden death has had its impact. In addition, advising and prescribing the right sports activity is challenging.[2] There are discrepancies and gaps in knowledge concerning the appreciation of the safety of practising sports between physicians and patients with ConHD.[2,3]

Yet, participation in sports may also have beneficial effects. In patients with coronary artery disease sports participation is associated with an increased quality of life and decreased scores of anxiety, hostility and depression.[4,5] In the current study we examined the effect of sports participation in adults with corrected ConHD on objective and subjective physical functioning.

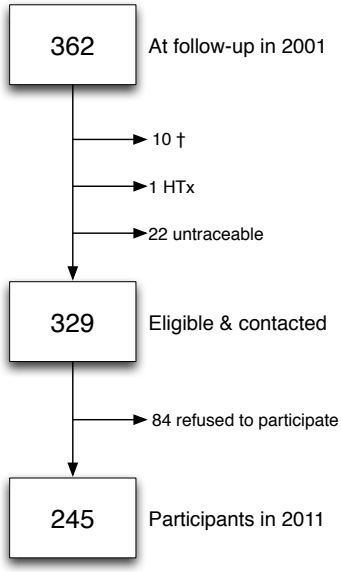
METHODS

Inclusion criteria

The original cohort consists of all consecutive patients who underwent their first open heart surgery for Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), Pulmonary Stenosis (PS), Tetralogy of Fallot (ToF) or Transposition of the Great Arteries (TGA) between 1968 and 1980 in the Erasmus Medical Center, and were younger than 15 years at the time of surgery. This cohort has been investigated in 1991 and in 2001, and the baseline characteristics, medical and psychosocial results of these investigations have been reported in detail previously.[6-11]

The target population of this third follow-up (2011) consisted of the 362 patients who participated in the previous follow-up in 2001. Of these patients, 10 died (causes: 6 cardiac-related, 3 unknown, 1 accident), 1 underwent heart transplantation and 22 patients were untraceable. Of the remaining 329 eligible patients, 245 patients participated again, leading to a response rate of 74%. The 245 patients previously examined both in 2001 and 2011 form the final sample of this study (Figure 1).

Figure 1: Flow-chart of patient inclusion



Assessment procedure

The research protocol was approved by the institutional ethical committee of the Erasmus Medical Center. This study complies with the 1975 Declaration of Helsinki. All patients were approached uniformly and were invited to visit the outpatient clinic for cardiac and psychological examination. All participating patients provided written informed consent before participating. During the outpatient visit, a cardiologist performed cardiac and medical examination and an exercise test was performed. The sports and psychosocial questionnaires, which are described in detail below, were completed during the hospital visit. Due to practical reasons (work, children), 17 patients completed the questionnaires at home. The questionnaires were administered verbally for patients who had difficulty reading or understanding the questionnaires.

Instruments and normative groups

Sports participation was measured using four items of the internationally well-known Baecke questionnaire for assessing habitual physical activity in epidemiological studies.[12] Because the hours of sports participation are categorical by nature, data were categorized using the classification of the Dutch Central Bureau of Statistics (CBS), which was also used to obtain normative data representative for the average Dutch population.[13] The categories "A lot of sports" (more than 5 hours of sports per week), "Little/Moderate" (in between 1 and 5 hours of

sports per week) and "None" (no exercise or sports) were used. The types of sports are based on the study of Mitchell et al.[14]

Maximal *exercise capacity* was assessed by bicycle ergometry with gradual increments of workload of 20 Watts per minute. Exercise capacity was compared to that of normal individuals corrected for age, gender, body height and weight. Exercise capacity <85% of the predicted value was considered to be decreased. VO2 max was measured only in 2011 and not in 2001.

In 227 patients arrhythmias and average heart frequency were assessed by 24-hour continuous ambulatory ECG (Holter) monitoring with 3 tracings per patient.

Subjective physical functioning was assessed by the physical functioning scale of the SF-36.[15] This scale measures the amount of limitation in physical activities due to health problems. Good reliability and validity for the Dutch version of the SF-36 has been reported.[16]

Self-perceived quality of life was assessed by the Linear Analogue Scale Quality of Life (LAS). The LAS has been proven valid, reliable, and sensitive for the ConHD population.[17]

Statistical analyses

Patients were classified into two groups of disease severity according to the classification adopted at the American Heart Association Task Force on Adults with CHD.[18] Patients with corrected ASD, VSD and PS were classified as simple ConHD (unless they had complications such as severe ventricular dysfunction), while patients with ToF or TGA (all operated with a Mustard repair) were classified as moderate to complex ConHD.

Continuous data are presented by means ± SD. In case of a skewed distribution (significant Kolmgorov-Smirnov test or highly skewed histogram by visual inspection) medians and interquantile ranges [IQR] (Q1-Q3) are displayed. The SF36 PF scale is analyzed with means ± SD according to the manual. To assess the difference between ConHD diagnostic groups (simple versus moderate/complex), t-tests or Mann-Whitney-U tests were utilized. Longitudinal comparison was assessed by paired sample t-tests or Wilcoxon signed-rank tests.

Categorical variables are represented by percentages. When comparing categorical variables between ConHD diagnostic groups (simple versus moderate/complex) the Chi-square test or the Fisher exact test were used. Longitudinal (repeated measures) comparison of categorical variables was analyzed by the McNemar test for 2x2 paired tables.

Linear regression with a forced entry model was used to assess the association between the exercise capacity (ergometric bicycle testing) (dependent) versus sports (independent), the SF36 PF scale (dependent) versus sports (independent) and the LAS scale (dependent) versus sports (independent). Sports are expressed here as "Little/moderate exercise", which is between 1-5 hours of sports per week and "A lot of exercise", which is 5+ hours of sports per week (categories according to the Dutch Central Bureau of Statistics[13]). Logistical re-

gression using a backward LR model was used to assess the association between mortality and practising sports, odds ratios (OR) and 95% confidence intervals (95%CI) are reported. Included variables were complexity of ConHD (simple versus moderate/complex), age, systemic ventricular function, age and sports (yes/no). Variables were chosen by an experienced cardiologist (JR).

Two-tailed probability values of <0.05 were considered statistically significant. The statistical program IBM SPSS Statistics for Mac, Version 20.0 (Released 2011) was used for all statistics. Figures were made using GraphPad Prism version 6.0a for Mac, GraphPad Software (Released July 18, 2012), La Jolla California USA.

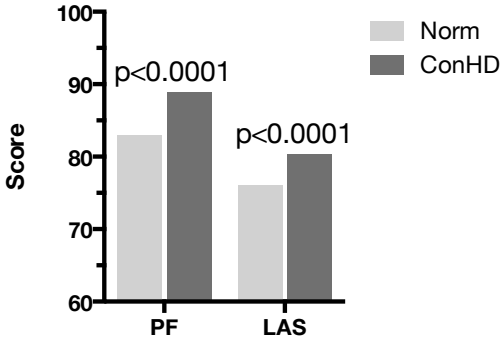
RESULTS

Patient characteristics (Table 1)

No significant and relevant differences were found in the patients who did and did not participate in 2011 as regards age, gender, ConHD, exercise capacity or amount of exercise per week.

Patients with simple ConHD were significantly older compared to the moderate/complex group (median 41 versus 38 years, p<0.0001). The simple ConHD group used less medication, p=0.002. Patients with moderate/complex ConHD showed worse exercise capacity (p=0.001) and oxygen uptake (p<0.0001) compared to patients with simple ConHD. Patients with simple ConHD showed a normal exercise capacity (92.4% of normal), whereas patients with moderate/complex ConHD showed a decreased exercise capacity (82.8% of normal). In 2011, patients were using medication more frequently compared with 2001 (p<0.0001), especially beta-blockers (p<0.0001), ACE inhibitors (p=0.003) and oral anticoagulation (p=0.008).

Figure 2: Quality of life in 2011 compared to normative data



Abbreviations: PF = Subjective Physical Functioning (SF36 scale); LAS = Linear Analogue Scale.

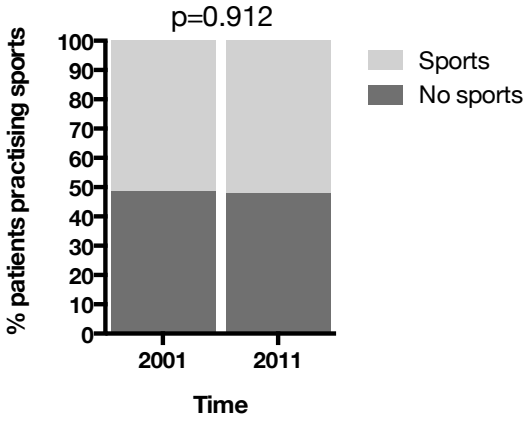
Table 1. Patient characteristics in 2001 and 2011

Variable	2001	2011	2001 vs. 2011	2011		p
			p	Simple	Moderate/complex	
	n=245	n=245		n=165	n=80	
Age	29.7 [26.5-34.8]	39.7 [36.2-44.9]	0.000	40.8 [37.5-45.5]	37.9 [33.7-41.3]	0.000
Gender						
• Male	52.2	52.2	-	49.1	58.8	0.156
Smoking						
• Yes	21.6	18.1	0.185	20.1	13.7	0.239
• Amount/day	10 [5-20]	10 [5-20]	0.218	15 [5-22]	7 [2-10]	0.036
Systemic Ventricular Function						
• Good	77.2	66.1	0.000	84.7	29.1	0.000
• Mild dysfunction	10.6	22.9	0.000	14.0	40.5	0.000
• Moderate dysfunction	7.8	7.6	0.481	0.6	21.5	0.000
• Bad	4.4	3.4	1.000	0.6	8.9	0.002
Medication use[a]						
• Any medication	4.9	23.8	0.000	17.7	36.4	0.002
• Aspirin	0.5	5.0	0.002	4.3	6.5	0.459
• Calcium antagonist	-	0.8	-	0.6	1.3	0.538
• Betablocker	1.0	8.3	0.000	5.5	14.3	0.021
• Nitrate	-	-	-	-	-	-
• Anti-arrhythmics	0.5	2.5	0.125	1.8	3.9	0.387
• Digitalis	2.0	0.8	0.500	-	2.6	0.038
• Diuretics	-	2.9	-	1.8	5.2	0.147
• ACE inhibitor	2.5	7.9	0.003	3.0	18.2	0.000
• Cholesterol lowering	-	-	-	-	-	-
• Oral anticoagulation	0.5	5.4	0.008	3.0	10.4	0.019
Exercise capacity						
• % of norm	89.1 ± 20.7	89.3 ± 20.2	0.674	92.4 ± 19.5	82.8 ± 20.2	0.001
• VO2	-	85.6 ± 22.5	-	90.2 ± 22.9	75.9 ± 18.2	0.000
Problems in sports participation	-	16.0	-	10.4	28.4	0.000

a) The sum of medication use is > 100% because some patients use multiple medications.

Patients with ConHD reported a better subjective physical functioning compared to normative data (88.9 ± 16.9 versus 83.0 ± 22.8, p<0.0001) and subjective quality of life (80.4 ± 10.8 versus 76.1 ± 9.4, p<0.0001) compared to normative data (Figure 2). Despite the fact that the LVEF has decreased over time, and the use of medication has increased over time, no significant difference was found between the number of ConHD patients practising sports in 2001 and 2011 (Figure 3).

Figure 3: Sports participation in ConHD patients over time (2001 compared to 2011)



Abbreviations: 2001 = Follow-up in 2001; 2011 = Follow-up in 2011.
Reported p-values are values compared to normative data.

Mortality, heart frequency and arrhythmias and sports participation (Table 2)

Of the 362 participating patients in 2001, 10 patients died in the course of 10 years. Details of all deaths can be found in Table 2. Logistical regression showed an association between death and moderate/complex ConHD (OR[95%CI]: 6.4[1.5-26.9]), but no association between practising sports and death was found.

In the 245 patients with two follow-up times, 24-hour ECG monitoring was available for 227 patients. Univariate analysis did not show an association between practising sports and PVC's, SVT's or average heart frequency. There was an association between practising sports and VT's (OR[95%CI]: 0.3[0.1-0.7]), this association disappeared in multivariate testing (OR[95%CI]: 0.9[0.5-1.5]).

Details on sports in patients with ConHD (Figure 4 & Table 3)

There was no difference in percentage of patients who were practising sports between 2001 and 2011. Patients with complex ConHD practised fewer hours of sports in 2011 compared to normative data (Figure 4).

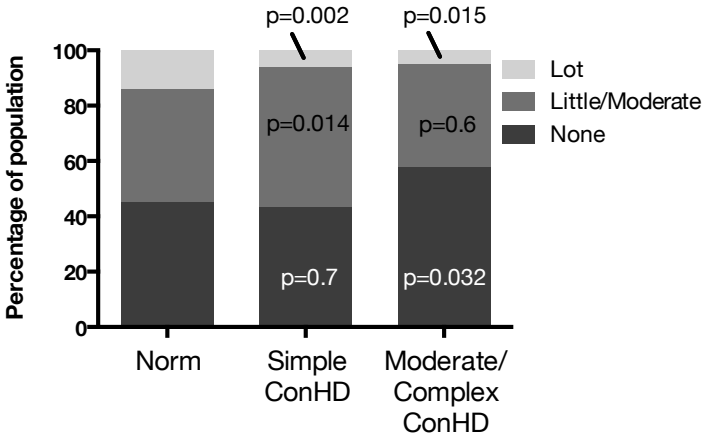
The type of sports are listed in Table 3. In order to make the type of sports comparable with literature, all sports were classified by the recommendations for physical activity in ConHD patients.[19] More than half of the patients were involved in high-dynamic types of sports.

Table 2. Data on patients that died between 2001 and 2011

Age	Gender	ConHD	Date of Surgery	BMI	Hyper-tension	Hours of sports[b]	Type of sport	Died how	ECG + Pacemaker	Systemic ventricular function	Systemic AV-valve	Pulmonary valve	Arrhyth-mias
33	male	TGA[a]	1974	28	No	0-1	Tennis match	During tennis	No pacemaker	Mildly reduced	N/A	Moderate regurgitation	No
41	male	Fallot	1988	32	No	1-5	Jogging	Shortly after jogging	Endocardial DDD since 1981 (no ICD)	Mildly reduced	N/A	Severe regurgitation	Sick-Sinus Syndrome
52	male	VSD	1968	27	No	5+	Fitness, rowing, running	Unknown	RBTB	Good	Light regurgitation	Light regurgitation	No
45	female	ASD	1972	25	Yes	1-5	Unknown	Unknown	No pacemaker	Good	Light regurgitation	No regurgitation	No
51	female	Fallot	1968	18	No	0	-	Heart failure	Endocardial VVI since 1990 (no ICD)	Bad	No regurgitation	No regurgitation	Sick-Sinus Syndrome
28	male	VSD	1980	18	No	0	-	Fluid in longs, cardiac arrest	No pacemaker	Moderately reduced	No regurgitation	No regurgitation	No
41	male	TGA[a]	1973	21	No	0	-	Unrecognized VF by ICD	Epicardial VVI since 1996 (ICD)	Bad	Severe regurgitation	Moderate regurgitation	Sick-Sinus Syndrome
32	male	Fallot	1980	32	No	5+	Fitness, soccer	Shot to death	RBTB	Mildly reduced	Light regurgitation	N/A	No
32	female	Fallot	1974	19	No	0-1	Hiking, walking	Heart failure	RBTB	Good	No regurgitation	No regurgitation	No
28	male	Fallot	1978	27	No	0-1	Surfing	VF	RBTB	Good	No regurgitation	N/A	No

a) All operated according to the Mustard procedure.
b) Per week.

Figure 4: Sports participation in 2011 versus normative data



Abbreviations: Lot = More than 5 hours of sports per week; Little/Moderate = In between 1 and 5 hours of sports per week; None = Patient does not exercise or practice sports.
Categories are based on normative data derived from the Dutch Central Bureau of statistics.[13]

Table 3. Type of sports participation of ConHD patients in 2011

Increasing static component	High 30.9%	23.0%	1.3%	6.6%
	Moderate 43.4%	4.6%	3.3%	35.5%
	Low 25.7%	9.2%	0.7%	15.8%
		Low 36.8%	Moderate 5.3%	High 57.9%
		Increasing dynamic component		

Data is for total ConHD group.
Table based on the study of Mitchell et al.[14]

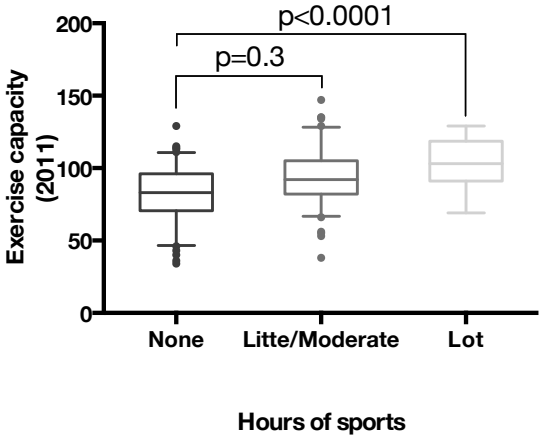
Results from regression analysis in 2011 (Figure 5 & Table 4)

Figure 5 shows the relationship between exercise capacity and number of hours sports practice per week. A regression analysis was performed to investigate the effect of sports participation on exercise capacity, physical functioning and quality of life on the study population in 2011 (Table 4).

Effect of sports on exercise capacity

Multivariate analysis showed that practising sports was correlated with an increase in exercise capacity, this effect being larger for patients who practised more hours of sports per week. A good exercise capacity in 2001 predicts a good exercise capacity in 2011. Adjusted

Figure 5: Relationship between exercise capacity and hours of sports practiced



Abbreviations: None = Patient does not exercise or practice sports; Little/Moderate = 1 to 5 hours of sports per week; Lot = 5+ hours of sports per week.
The X-axis represents the hours of sports practiced in 2011. On the Y-axis the exercise capacity is shown. Practising > 5 hours/week sports per week or more results in a better exercise capacity.

R square = 0.519; F8,212 = 30.62, p<0.0001 (using the forced entry method), variables are shown in Table 4.

Effect of sports on subjective physical functioning (SF36)

Multivariate analysis showed that a good exercise capacity in 2001 predicted a better subjective physical functioning in 2011. Female gender is associated with a lower subjective physical functioning. Adjusted R square = 0.187; F6,229 = 9.98, p<0.0001 (using the forced entry method), variables are shown in Table 4.

Effect of sports on subjective quality of life (LAS)

On subjective quality of life, multivariate analysis showed that only exercise capacity in 2001 predicted a good quality of life in 2011. No effect of practising sports on subjective quality of life was found. Adjusted R square = 0.060; F2,226 = 8.27, p<0.0001 (using the forced entry method), variables are shown in Table 4.

DISCUSSION

Our study showed that patients with moderate/complex ConHD less often engage in sports compared to the general Dutch population, and that sports participation in adults with

Table 4. Linear regression analysis on data collected in 2011

Variable	2011						
	B	SE B	Beta	t	p-value	95%CI	
						Lower	Upper
Bicycle testing							
Univariate							
• **Stopped exercising**	-8.18	3.64	-0.15	-2.25	0.026	-15.34	-1.01
• **Little/Moderate exercise**	8.58	2.64	0.21	3.25	0.001	3.37	13.78
• **A lot of exercise**	15.10	5.49	0.18	2.75	0.006	4.29	25.91
• **Bicycle testing in 2001**	0.71	0.05	0.71	14.70	0.000	0.62	0.81
• **Age**	0.84	0.25	0.22	3.41	0.001	0.36	1.33
• Female gender	1.50	2.70	0.04	0.56	0.580	-3.83	6.83
• **Complex ConHD**	-9.83	2.82	-0.23	-3.49	0.001	-15.38	-4.28
• **Mild impaired SYSVF**	-7.12	3.20	-0.15	-2.23	0.027	-13.43	-0.82
• **Moderately impaired SYSVF/Bad SYSVF**	-17.03	4.32	-0.26	-3.94	0.000	-25.55	-8.51
Multivariate (Adj. R^2=0.519)							
• Constant	10.06	10.09		1.00	0.320	-9.82	29.94
• Stopped exercising	1.55	3.02	0.03	0.52	0.607	-4.40	7.51
• **Little/Moderate exercise**	7.06	2.31	0.17	3.06	0.002	2.52	11.60
• **A lot of exercise**	11.43	4.48	0.13	2.55	0.011	2.60	20.27
• **Bicycle testing in 2001**	0.64	0.05	0.63	11.88	0.000	0.54	0.75
• Age	0.33	0.19	0.09	1.70	0.090	-0.05	0.71
• Complex ConHD	3.74	2.60	0.09	1.44	0.153	-1.39	8.86
• Mild impaired SYSVF	-1.48	2.62	-0.03	-0.57	0.572	-6.64	3.68
• Moderately impaired SYSVF/Bad SYSVF	-7.53	3.90	-0.11	-1.93	0.055	-15.23	0.16
Subjective Physical Functioning (SF-36)							
Univariate							
• **Stopped exercising**	-6.51	2.90	-0.14	-2.25	0.026	-12.21	-0.80
• **Little/Moderate exercise**	5.60	2.15	0.17	2.60	0.010	1.36	9.83
• **A lot of exercise**	9.50	4.62	0.13	2.06	0.041	0.41	18.60
• **Bicycle testing in 2001**	0.31	0.05	0.37	6.09	0.000	0.21	0.41
• Age	-0.16	0.20	-0.05	-0.81	0.418	-0.56	0.23
• **Female gender**	-7.35	2.13	-0.22	-3.46	0.001	-11.53	-3.16
• Complex ConHD	-4.49	2.30	-0.13	-1.95	0.052	-9.03	0.04
• Mild impaired SYSVF	-3.48	2.59	-0.09	-1.34	0.181	-8.59	1.63
• Moderately impaired SYSVF/Bad SYSVF	-2.78	3.48	-0.05	-0.80	0.427	-9.64	4.09
Multivariate (Adj. R^2=0.187)							
• **Constant**	72.15	7.31		9.87	0.000	57.74	86.55
• Stopped exercising	-1.01	3.08	-0.02	-0.33	0.742	-7.07	5.05
• Little/Moderate exercise	3.71	2.36	0.11	1.57	0.117	-0.94	8.36

Table 4. Linear regression analysis on data collected in 2011 (continued)

	2011						
Variable	B	SE B	Beta	t	p-value	95%CI	
						Lower	Upper
• A lot of exercise	5.24	4.75	0.07	1.10	0.271	-4.11	14.59
• **Bicycle testing in 2001**	0.29	0.05	0.34	5.32	0.000	0.18	0.40
• **Female gender**	-7.37	2.06	-0.22	-3.58	0.000	-11.43	-3.31
• Complex ConHD	-0.23	2.29	-0.01	-0.10	0.919	-4.74	4.27
	Quality of Life (LAS)						
Univariate							
• Stopped exercising	-1.12	1.90	-0.04	-0.59	0.555	-4.86	2.62
• **Little/Moderate exercise**	3.48	1.40	0.16	2.49	0.014	0.73	6.24
• A lot of exercise	2.44	2.98	0.05	0.82	0.414	-3.43	8.31
• Age	-0.01	0.13	-0.01	-0.08	0.933	-0.27	0.25
• **Bicycle testing in 2001**	0.13	0.04	0.23	3.57	0.000	0.06	0.19
• Female gender	-0.54	1.42	-0.03	-0.38	0.703	-3.33	2.25
• Complex ConHD	-0.53	1.51	-0.02	-0.35	0.723	-3.50	2.43
• Mild impaired SYSVF	0.60	1.72	0.02	0.35	0.726	-2.79	4.00
• Moderately impaired SYSVF/Bad SYSVF	-0.40	2.32	-0.01	-0.17	0.863	-4.97	4.17
Multivariate (Adj. R^2=0.060)							
• **Constant**	68.87	3.19		21.60	0.000	62.59	75.15
• Little/moderate exercise	2.68	1.40	0.13	1.91	0.057	-0.08	5.44
• **Bicycle testing in 2001**	0.11	0.04	0.21	3.16	0.002	0.04	0.18

Abbreviations: B = Unstandardized coefficient Beta; SE B = Standard error of the unstandardized coefficient Beta; Beta = Standardized coefficient Beta; 95%CI = 95% Confidence Interval; ConHD = Congenital Heart Disease; SYSVF = Systemic Ventricular Function; SF36 = Short-Form 36; LAS = Linear Analogue Scale.
Linear regression model was made using the forced entry method.

ConHD increases exercise capacity, but not the subjective perceived physical functioning, nor the subjectively perceived quality of life.

Sports participation in patients with ConHD

Compared to the general Dutch population, the patients with ConHD that do practise sports did so for fewer hours per week. The study of Immer et al. reported a higher rate of practising sports compared to the general population, this was both in patients with simple and complex forms of ConHD.[20] Other studies were more in line with our findings, also reporting lower physical activity for ConHD patients.[21,22] Patients with more complex forms of ConHD have been shown to have a reduced exercise capacity, as is also found in our study (average 82.3%

of norm).[23] This finding could provide an explanation that almost one third of the complex patients in our study experience difficulties during sports participation. Patients with simple ConHD lesions obtained scores on exercise testing which were 7% lower compared to the general Dutch population, corrected by size, gender and age, this is not significantly different. Our patients with simple ConHD practised fewer hours of sports per week compared to the general population.

Safety of sports

A difficult topic is the safety of sports participation. The rare example of a young man with an operated congenital condition suffering sudden death on the soccer field is dramatic and immediately strict regulations are proposed. On the other hand many patients with moderate-complex ConHD do participate in sports without problems and can even reach the absolute top, like Shaun White who won Olympic gold twice. Proper studies on this topic are lacking and the current guidelines on sports participation are based solely on expert opinion. In our cohort we found no relation between sports participation and (cardiac) mortality, heart frequency or arrhythmias. Although this is the first report based on longitudinal data, no firm conclusions can be drawn due to the relatively small numbers. Larger series are clearly required. Takken et al. have published guidelines for children with ConHD concerning physical activity, recreational sports and exercise training.[19] Recommendations regarding sports activities for adults need to be based on the patients' abilities, the impact on the underlying haemodynamics and the risk of acute decompensation and arrhythmias.[24] Advice on the type of sports activity should be based on the type of sport and anticipated effort levels, and if needed can be supervised by a physician first.[5,24] Exercise testing can provide insight into the current status of the patient and can help the physician advising the patient in choosing a sports activity.[25] ConHD patients have been known to report fear of undertaking physical exercise and also physicians may have been over-conservative in their advice on participating in sports activities.[2,21,24]

Effects of sports on exercise capacity, physical functioning and quality of life

Since ConHD patients had their ConHD from birth, they might consider their current condition as normal. This could result in overestimation of physical abilities, and a favorable subjective physical functioning score, although sports participation is hampered, an effect which is seen in our study.[26,27] Self-reported physical functioning does not seem to correlate with objective exercise capacity.[26] The high scores on the subjective physical functioning scales found in our study seem to be in contrast with studies published before, where lower levels of physical functioning have been reported for ToF males.[28] Low levels of physical functioning in patients with ConHD reflect the limitations patients encounter in daily life.[29] Overestimation

of physical capabilities might result in patients choosing a sport that might potentially harm their health. In our study we found that a total of 6.1% of patients practise sports in the highest static and haemodynamic component. Patients from our study frequently practise sports with a high haemodynamic component or middle-high static component. Patients with ConHD are known to have a reduced exercise capacity and peak oxygen uptake compared to normative data.[21,23,26,30,31] This depressed exercise capacity might be partially explained by low physical activity.[22] Literature on the relationship between exercise capacity and subjective physical functioning or quality of life yields ambiguous results, with some studies reporting that an active lifestyle in ConHD patients has shown positive correlations between exercise capacity or peak oxygen uptake and perceived physical functioning and some studies finding moderate to no relationships at all.[5,22,26,27,32,33] Our study showed that patients who actively practise sports show an increased exercise capacity compared to patients who stopped practising sports or never practised any sports at all. Fredriksen et al. already showed that children and adolescents can improve their peak oxygen uptake after an intervention.[5] Our findings show that adult patients with ConHD can improve their exercise capacity by practising sports and increasing hours of practising sports is associated with an increase in exercise capacity. Both the subjective physical functioning and the subjective quality of life do not appear to be correlated with the amount of sports practise. The prevalence of depressive symptoms appears to have a larger impact on quality of life than exercise capacity.[33]

Strengths and study limitations

This is the first study to report on the effect of sports on mortality, exercise capacity and psychological well-being in ConHD patients over a course of 10 years. To measure subjective physical functioning and subjective quality of life, internationally validated generic questionnaires were used.

The patients included in this study had one of the following diagnoses: ASD, VSD, PS, ToF or TGA, and all were followed in an adult tertiary care center in the Netherlands. Not all invited patients participated. Therefore, the obtained results may not be applicable to all ConHD patients, nor in all countries worldwide. The results of the safety of sports from the logistic regression (mortality, heart frequency and arrhythmias) should be drawn with caution since our data is not powered for such a conclusion. Despite this lack in power we decided to report our data, as no other data is available in literature yet.

Future research

The gap of knowledge on the safety and effectiveness of physical activity and intervention programs in patients with ConHD warrant further research in order to be able to accurately and safely guide ConHD patients to a more active lifestyle. In our study, the physical function-

ing scale of the SF36 was used. It would also be interesting to study the effect of exercise on anxiety or depression scales.

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Conflict of interests

None declared.

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REFERENCES

1. Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. N Engl J Med. 2000 Jan 27;342(4):256-63.
2. Swan L, Hillis WS. Exercise prescription in adults with congenital heart disease: a long way to go. Heart. 2000 Jun;83(6):685-7.
3. Moons P, De Volder E, Budts W, De Geest S, Elen J, Waeytens K, Gewillig M. What do adult patients with congenital heart disease know about their disease, treatment, and prevention of complications? A call for structured patient education. Heart. 2001 Jul;86(1):74-80.
4. Lavie CJ, Milani RV. Adverse psychological and coronary risk profiles in young patients with coronary artery disease and benefits of formal cardiac rehabilitation. Arch Intern Med. 2006 Sep 25;166(17):1878-83.
5. Fredriksen PM, Kahrs N, Blaasvaer S, Sigurdsen E, Gundersen O, Roeksund O, Norgaand G, Vik JT, Soerbye O, Ingjer E, Thaulow E. Effect of physical training in children and adolescents with congenital heart disease. Cardiol Young. 2000 Mar;10(2):107-14.
6. Utens EM, Verhulst FC, Erdman RA, Meijboom FJ, Duivenvoorden HJ, Bos E, Roelandt JR, Hess J. Psychosocial functioning of young adults after surgical correction for congenital heart disease in childhood: a follow-up study. J Psychosom Res. 1994 Oct;38(7):745-58.
7. Utens EM, Verhulst FC, Meijboom FJ, Duivenvoorden HJ, Erdman RA, Bos E, Roelandt JT, Hess J. Behavioural and emotional problems in children and adolescents with congenital heart disease. Psychol Med. 1993 May;23(2):415-24.
8. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. Eur Heart J. 2003 Apr;24(7):673-83.
9. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Medical predictors for psychopathology in adults with operated congenital heart disease. Eur Heart J. 2004 Sep;25(18):1605-13.
10. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. Circulation. 1995 Apr 15;91(8):2214-9.
11. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, van Domburg R, van Rijen EH, Utens EM, McGhie J, Bos E, Bogers AJ, Simoons ML. Decline in ventricular function and clinical condition after Mustard repair for transposition of the great arteries (a prospective study of 22-29 years). Eur Heart J. 2004 Jul;25(14):1264-70.
12. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr. 1982 Nov;36(5):936-42.
13. Netherlands Central Bureau of Statistics 2011. (CBS)
14. Mitchell JH, Haskell W, Snell P, Van Camp SP. Task Force 8: classification of sports. J Am Coll Cardiol. 2005 Apr 19;45(8):1364-7.
15. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun;30(6):473-83.
16. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol. 1998 Nov;51(11): 1055-68.

17. Moons P, Van Deyk K, De Bleser L, Marquet K, Raes E, De Geest S, Budts W. Quality of life and health status in adults with congenital heart disease: a direct comparison with healthy counterparts. Eur J Cardiovasc Prev Rehabil. 2006 Jun;13(3):407-13.
18. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Page RL, Riegel B, Tarkington LG, Yancy CW; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease); American Society of Echocardiography; Heart Rhythm Society; International Society for Adult Congenital Heart Disease; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008 Dec 2;52(23):e143-263. doi: 10.1016/j.jacc.2008.10.001.
19. Takken T, Giardini A, Reybrouck T, Gewillig M, Hövels-Gürich HH, Longmuir PE, McCrindle BW, Paridon SM, Hager A. Recommendations for physical activity, recreation sport, and exercise training in paediatric patients with congenital heart disease: a report from the Exercise, Basic & Translational Research Section of the European Association of Cardiovascular Prevention and Rehabilitation, the European Congenital Heart and Lung Exercise Group, and the Association for European Paediatric Cardiology. Eur J Prev Cardiol. 2012 Oct;19(5):1034-65.
20. Immer FF, Althaus SM, Berdat PA, Saner H, Carrel TP. Quality of life and specific problems after cardiac surgery in adolescents and adults with congenital heart diseases. Eur J Cardiovasc Prev Rehabil. 2005 Apr;12(2):138-43.
21. Gierat-Haponiuk K, Haponiuk I, Chojnicki M, Jaworski R, Bakuła S. Exercise capacity and the quality of life late after surgical correction of congenital heart defects. Kardiol Pol. 2011;69(8):810-5.
22. Buys R, Van De Bruaene A, Budts W, Delecluse C, Vanhees L. In adults with atrial switch operation for transposition of the great arteries low physical activity relates to reduced exercise capacity and decreased perceived physical functioning. Acta Cardiol. 2012 Feb;67(1):49-57.
23. Fredriksen PM, Veldtman G, Hechter S, Therrien J, Chen A, Warsi MA, Freeman M, Liu P, Siu S, Thaulow E, Webb G. Aerobic capacity in adults with various congenital heart diseases. Am J Cardiol. 2001 Feb 1;87(3):310-4.
24. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E; Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC); Association for European Paediatric Cardiology (AEPC); ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J. 2010 Dec;31(23):2915-57.
25. Diller GP, Dimopoulos K, Okonko D, Uebing A, Broberg CS, Babu-Narayan S, Bayne S, Poole-Wilson PA, Sutton R, Francis DP, Gatzoulis MA. Heart rate response during exercise predicts survival in adults with congenital heart disease. J Am Coll Cardiol. 2006 Sep 19;48(6):1250-6.

26. Gratz A, Hess J, Hager A. Self-estimated physical functioning poorly predicts actual exercise capacity in adolescents and adults with congenital heart disease. Eur Heart J. 2009 Feb;30(4): 497-504.
27. Hager A, Hess J. Comparison of health related quality of life with cardiopulmonary exercise testing in adolescents and adults with congenital heart disease. Heart. 2005 Apr;91(4):517-20.
28. Bygstad E, Pedersen LC, Pedersen TA, Hjortdal VE. Tetralogy of Fallot in men: quality of life, family, education, and employment. Cardiol Young. 2012 Aug;22(4):417-23.
29. Vigl M, Niggemeyer E, Hager A, Schwedler G, Kropf S, Bauer U. The importance of socio-demographic factors for the quality of life of adults with congenital heart disease. Qual Life Res. 2011 Mar;20(2):169-77.
30. Fredriksen PM, Pettersen E, Thaulow E. Declining aerobic capacity of patients with arterial and atrial switch procedures. Pediatr Cardiol. 2009 Feb;30(2):166-71
31. Kempny A, Dimopoulos K, Uebing A, Moceri P, Swan L, Gatzoulis MA, Diller GP. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life--single centre experience and review of published data. Eur Heart J. 2012 Jun;33(11):1386-96.
32. Lemmer J, Heise G, Rentzsch A, Boettler P, Kuehne T, Dubowy KO, Peters B, Lemmer B, Hager A, Stiller B; German Competence Network for Congenital Heart Defects. Right ventricular function in grown-up patients after correction of congenital right heart disease. Clin Res Cardiol. 2011 Apr; 100(4):289-96.
33. Müller J, Hess J, Hager A. Minor symptoms of depression in patients with congenital heart disease have a larger impact on quality of life than limited exercise capacity. Int J Cardiol. 2012 Feb 9; 154(3):265-9.

Part 4
Impact on Medical Characteristics

Chapter 4.1

Psychosocial impact of implantable cardioverter defibrillators (ICD) in young adults with Tetralogy of Fallot.

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ABSTRACT

Objective: To investigate the psychosocial impact of having an implantable cardioverter defibrillator (ICD) in adults with Tetralogy of Fallot (ToF).

Methods: Included were 26 ToF-patients with an ICD (age 44 ± 12 years), and two control groups consisting of 28 ToF-patients without an ICD (age 40 ± 10 years) and a group of 35 ICD-patients of older age without ToF (age 72.0 ± 8 years). This last control group was chosen to represent the "older general ICD population" with acquired heart disease seen at the outpatient clinic. Psychosocial functioning encompassed daily functioning, subjective health status, quality of life, anxiety, depression, coping and social support.

Results: ToF-patients with ICD showed diminished psychosocial functioning in comparison to ToF-patients without ICD. This was reflected by diminished subjectively perceived physical functioning ($p=0.01$), general health perception ($p<0.01$) and a lower satisfaction with life ($p=0.02$). In comparison to older ICD-patients, ToF- patients with ICD showed less satisfaction with life ($p=0.03$), experienced more anxiety ($p=0.01$) and showed less favorable coping styles, although physical functioning was better for ToF-patients with ICD than for older ICD-patients ($p=0.01$). More inappropriate shocks were found in ToF-patients with ICD compared to the older ICD-patients.

Conclusion: In patients with ToF, ICD implantation had a major impact on psychosocial functioning which should be taken into account when considering ICD implantation in these young patients. To help improve psychosocial functioning, psychological counseling attuned to the specific needs of these patients may be useful.

INTRODUCTION

The leading cause of mortality in adult patients with congenital heart disease (ConHD) is sudden cardiac death (SCD).[1] In comparison with the general population, an adult patient with ConHD has a 25–100 fold increased risk to die as a result of SCD.[2] Implantable cardioverter defibrillators (ICDs) are being used as therapy for patients that are at high risk for developing, or have survived a life- threatening cardiac arrhythmia.[3] However, the indication of ICD therapy in patients with ConHD is still a matter of debate. A recent publication from our group investigating the efficacy of ICD therapy in ConHD patients demonstrated that 23% of all patients received an appropriate shock, and 41% of the investigated patients received at least one inappropriate shock.[4] This inappropriate shock rate is higher than in other patient groups. Other studies reported an inappropriate shock rate of around 25%, and an appropriate shock rate of around 22–30% in ConHD patients.[3,5]

Congenital heart disease patients not only have to cope with an increased risk to die as a result of SCD.[2] In addition, the implantation of an ICD with associated inappropriate shocks, which occur when the patient is fully conscious, may cause anxiety for shock, anxiety for premature death and stress, hereby worsening the psychological problems.[6,7] Patients receiving ICD therapy may show reduced quality of life, subjective health status and diminished social functioning. Anxiety and fear for ICD discharge does not only affect the patient, it can also influence the behavior of relatives and friends surrounding the patient. Sometimes these "significant others" experience fear and anxiety, which may have a cumulative anxiety arousing effect on the patient.[8] The aim of this study was to investigate the psychosocial impact that ICD therapy has in (young) adults with Tetralogy of Fallot (ToF). We chose patients with ToF because most of the ICD implantations in the ConHD population occur in these patients.[3]

Two control groups were selected; the first control group consisted of ToF-patients without an ICD. We selected these patients to investigate the impact of the ICD while holding the groups comparable on cardiac diagnosis and hemodynamic burden. The second control group consisted of older acquired heart disease ICD patients. This group represents the "general" ICD population as seen in an outpatient clinic. By choosing this group, we could make a comparison with a "general" average ICD patient. Age may be a factor in acceptance of an ICD. Also, knowledge about the psychosocial functioning of patients with an ICD comes from studies focusing on these "regular ICD-patients". These patients are older and have acquired heart disease. The psychosocial problems seen in these older patients may be quite different than those seen in younger ConHD patients receiving ICD therapy. Young patients do not only experience the problems associated with the ICD but also carry the burden of having grown-up with a congenital heart defect. They also experience more inappropriate shocks than non-ConHD patients.[4] These shocks may lead to anxiety, psychosocial problems and avoidance behavior, limiting patients in social contacts, and leisure time activities. In addition, overprotective parents of ConHD patients may be a limiting factor as well. Therefore,

we hypothesized that the psychosocial impact of receiving ICD therapy in young ConHD patients may be more substantial.

Finally, we wanted to compare whether styles of coping and adjustment to ICD therapy differed between younger ConHD patients with an ICD (ToF+ICD) and older patients with acquired heart disease receiving ICD therapy (ICD), when adjusted for the time-period of receiving ICD therapy.

METHODS

Study design and population

This is a cross-sectional, multicenter study.

Inclusion criteria

Our database consisted of three groups. The first group consisted of Fallot-patients with ICD (ToF+ICD). This population was selected using the CONCOR registry in The Netherlands and a Belgian tertiary care center adult ConHD database.[9] The CONCOR registry is a nationwide database consisting of adult patients with ConHD, including medical history. The selection of this patient sample is described in detail in the paper of Yap et al.[4] This group was used as the study population. The second group consisted of Fallot-patients without ICD (ToF) and was also identified using the CONCOR registry. This ToF group consisted of 28 patients without significant differences in age, sex and NYHA class compared to the study group ToF+ICD. We used this group as our first control group. The third group (ICD) consisted of 35 older ICD-patients with another form of heart disease, mainly ischaemic heart disease. These patients did not have ConHD. This group was identified using the Erasmus MC ICD registry, and did not show significant differences regarding gender com- pared to the ToF+ICD group. We used this last group as our second control group. For all selected patients, data were collected form medical records, with permission of the patients and physicians.

This study was approved by the institutional ethical committees. All patients provided informed consent before participating in this study.

Patient sample

Of the 44 eligible patients from the ToF+ICD group, 13 were lost to follow-up and 3 patients died before inclusion in this study. The present patient sample consisted of the remaining 28 adults of whom two refused to participate, resulting in a response rate of 93% for the ToF+ICD group. The mean age of this group was 44 years (±12 years).

There were no differences between participants and non- participants on age, age at Fallot correction, shunt before correction, reoperations, age at ICD implantation, follow- up time, indication for ICD implantation, NYHA class or the amount of shocks.

In order to ensure that ICDs of patients are programed optimally, patients visited the outpatient clinic every 6 months, or sooner if they had complaints. The functionality of the ICD device was assessed by skilled technicians and adapted if necessary. All appropriate and inappropriate shocks were recorded.

Indications for ICD implantation in ToF-patients

The index event before ICD implantation was spontaneous sustained ventricular tachycardia (VT) in 14 patients (54%), cardiac arrest in 5 patients (19%), (pre) syncope in 5 patients (19%) and other in 2 patients (8%).

Assessment procedure

All patients were approached uniformly and signed an informed consent before participating. All patients completed the questionnaires at home and returned them by mail. Missing items were retrieved by means of a telephone call.

Instruments

The psychological examination consisted of the following questionnaires.

Biographical characteristics

A semi-structured questionnaire was designed to assess biographical variables such as nationality, living conditions, marital-, educational- and occupational status.[10] The educational attainments were evaluated excluding two patients living in institutions because of psychosocial problems.

Subjective health status

The subjective health status was assessed by the SF-36 Health Survey.[11] Good reliability and validity for the Dutch version of the SF-36 has been reported.[12]

Satisfaction with Life Scale

The Satisfaction with Life Scale (SWLS) was used as an indicator of the satisfaction with life. This scale has been proven psychometrically sound to be used in ConHD patients.[13]

Linear Analogue Scale Quality of Life

The Linear Analogue Scale (LAS) was used to measure self- perceived quality of life. The LAS has been proven valid, reliable and responsive for the ConHD population.[13]

Hospital Anxiety and Depression Scale (HADS)

This scale measures the presence and severity of anxiety and depression in patients. The HADS has been validated for the general Dutch population and is stable across medical settings and age groups.[14,15]

Utrecht Coping List

The Utrecht Coping List (UCL) is a reliable and standardized self-report questionnaire of coping styles. The satisfactory validity of the UCL has been described else- where.[16] Construct validity and predictive validity has been examined for the UCL.

Implanted Devices Adjustment Scale

The Implanted Device Adjustment Scale (IDAS) measures the psychological adjustment of a patient to an implanted (ICD) pacemaker. The IDAS has been described valid, reliable and responsive.[17]

Perceived Social Support Scale

The Perceived Social Support Scale 12 item version (PSSS12) measures the interactions and discrepancies that people experience in receiving social support from their direct environment.[18]

Statistical methods

Biographical characteristics were analyzed using Chi- Square tests. Because of the skewed nature of the data, Mann–Whitney U tests were used to test for differences between the ToF+ICD group versus both control groups on all questionnaires. Comparison with normative data was made using Students' t tests, since raw data for the norm groups were not available, and only mean and standard deviations were available. Descriptive statistics of continuous variables are expressed as medians with quartiles. Stepwise multiple regression was used to correct for age at implantation, and the higher age in the ICD group. The data were analyzed using the statistical package SPSS PSAW 17.0.2 ENG for Windows, Release 17.0.2 (Mar 11, 2009).

RESULTS

Population characteristics

Biographical characteristics

The main biographical and medical characteristics for the three groups are outlined in Table 1. No differences in gender were found between the three groups. Patients from the ToF+ICD

Table 1. Biographical & medical characteristics

	ToF+ICD (N=26)		ToF (N=28)		ICD (N=35)		Group effect	
	N	%	N	%	N	%	ToF+ICD vs. ToF (p-value)	ToF+ICD vs. ICD (p-value)
Response rate		93%				88%		
Gender								
Male	15	(57.7%)	19	(67.9%)	28	(80.0%)	0.4	0.06
Age[a]	44	(±11.58)	40	(±10.26)	72	(±8.28)	0.1	<0.0001
Nationality								
• Dutch	18	(69.2%)	28	(100.0%)	35	(100.0%)	<0.01	<0.0001
• Belgian	8	(30.8%)	0	(0.0%)	0	(0.0%)	<0.01	0.001
Living conditions								
• With parents	2	(7.7%)	3	(10.7%)	0	(0.0%)	1.0	0.1
• Living alone	21	(80.8%)	22	(78.6%)	34	(97.1%)	0.1	0.02
• Institution/home replacement	3	(11.5%)	3	(10.7%)	1	(2.9%)	1.0	0.1
Marital status								
• No relationship	8	(30.8%)	8	(28.6%)	2	(5.7%)	0.9	0.02
• Stable relationship	0	(0.0%)	2	(7.1%)	0	(0.0%)	0.5	-
• Cohabitant	1	(3.8%)	6	(21.4%)	0	(0.0%)	0.1	0.2
• Married	15	(57.7%)	9	(32.1%)	21	(60.0%)	0.06	0.9
• Divorced	1	(3.8%)	0	(0.0%)	1	(2.9%)	0.5	0.8
• Cohabitant or married after divorce	1	(3.8%)	1	(3.6%)	1	(2.9%)	1.0	0.8
• Widowed	0	(0.0%)	2	(7.1%)	8	(22.9%)	0.5	0.02
• Stable relationship or married after being widowed	0	(0.0%)	0	(0.0%)	2	(5.7%)	-	0.2
Occupational level								
• Elementary	0	(0.0%)	1	(3.6%)	0	(0.0%)	1.0	-
• Lower	3	(11.5%)	6	(21.4%)	0	(0.0%)	1.0	0.5
• Average	7	(26.9%)	8	(28.6%)	6	(17.1%)	0.3	0.3
• Higher	3	(11.5%)	8	(28.6%)	1	(2.9%)	0.5	1.0
• No job/missing data	13	(50.0%)	5	(17.9%)	28	(80.0%)	-	-
Educational attainment[b]								
• Lower	2	(7.7%)	2	(7.1%)	8	(22.9%)	1.0	0.1
• Average	17	(65.4%)	21	(75.0%)	20	(57.1%)	0.7	0.3
• Higher	5	(19.2%)	5	(17.9%)	5	(14.3%)	1.0	0.5
• Other	0	(0.0%)	0	(0.0%)	1	(2.9%)	-	-
• Missing	1	(3.8%)	0	(0.0%)	0	(0.0%)	-	-
Medical data								
Age Fallot correction (yrs.)[a]	9.9	(±10.80)	5.9	(±3.91)	-	-	0.1	-
Shunt before correction	8	(30,8%)	13	(48.1%)	-	-	0.2	-

Table 1. (continued)

	ToF+ICD (N=26)		ToF (N=28)		ICD (N=35)		Group effect	
	N	%	N	%	N	%	ToF+ICD vs. ToF (p-value)	ToF+ICD vs. ICD (p-value)
Reoperations	15	(57.7%)	12	(44.4%)	-	-	0.3	-
Age at implantation (yrs.)[a]	36.5	(±11.25)	-	-	64.7	(±8.19)	-	<0.0001
Follow-up (yrs.)[a]	7.9	(±3.73)	-	-	7.4	(±2.08)	-	0.5
Indication for ICD								
• Primary prevention	6	(23.1%)	-	-	13	(37.1%)	-	0.2
• Secondary prevention	20	(76.9%)	-	-	22	(62.9%)	-	0.2
NYHA-Class								
• I	19	(73.1%)	24	(85.7%)	9	(25.7%)	0.2	<0.0001
• II	5	(19.2%)	3	(10.7%)	24	(68.6%)	0.5	<0.0001
• III	2	(7.7%)	1	(3.6%)	2	(5.7%)	0.6	1.0
Brady pacing[c]	7	(33.3%)	0	(0.0%)	15	(42.9%)	-	0.5
QRS duration[a]	176	(±27.2)	150	(±25.2)	138	(±39.3)	<0.01	<0.0001
RV dilatation								
• None	2	(10.0%)	6	(21.4%)	-	-		-
• Moderate	11	(55.0%)	18	(64.3%)	-	-	0.195	-
• Severe	7	(35.0%)	4	(14.3%)	-	-		-
RV function								
• Good	10	(50.0%)	26	(92.9%)	-	-	<0.01	-
• Reduced	10	(50.0%)	2	(7.1%)	-	-		-
Pulmonary regurgitation								
• None / Mild	12	(63.2%)	13	(46.4%)	-	-		-
• Moderate	6	(31.6%)	5	(17.9%)	-	-	0.05	-
• Severe	1	(5.3%)	10	(35.7%)	-	-		-
Inappropriate ICD shocks	10	(38.5%)	-	-	5	(14.3%)	-	0.03
Appropriate ICD shocks	2	(7.7%)	-	-	11	(31.4%)	-	0.03

Abbreviations: ToF+ICD = Patients with Tetralogy of Fallot with an ICD; ToF = Patients with Tetralogy of Fallot (without an ICD); ICD = Patients with ICD (without congenital heart disease); NYHA = New York Heart Association class.

a) Data are presented as mean (±SD).

b) Excluding two patients living in institutions because of psychosocial problems.

c) There were 5 patients in the ToF+ICD group of which the ECG could not be examined.

The bold numbers in the text indicate significant results.

group were living significantly less often on their own compared to patients from the ICD group. Patients in the ToF+ICD group more often had no relationship and were less often widowed than the older ICD patients. After adjusting for higher age at implantation in the ICD group, it appeared that this variable did not have an effect on the SF-36 results.

No significant differences were found between the three groups with respect to occupational level or educational attainment. In all three groups, the majority had an average educational attainment.

Medical characteristics

No significant difference was found regarding age, the amount of surgical procedures or re-operations between the ToF+ICD and the ToF group. As we selected older ICD patients to represent the "normal" ICD population as our second control group, the patients in the ToF+ICD group were younger than those in the ICD group. Also, patients in the ToF+ICD group were (as planned) significantly older at the time of surgical Fallot correction than patients from the ToF group. Both indication for ICD implantation (primary and secondary) and follow-up time after ICD did not differ between the two groups. The majority of patients in the ICD group were NYHA class II resulting in a significant difference with regard to the ToF+ICD group and the ToF group (majority NYHA class I). When com- paring QRS duration, a significant difference was found between all three groups. Group ToF+ICD had the highest QRS duration (176 ms.) followed by the ToF group (150 ms.) and the ICD group (138 ms.). No difference was found between the ToF+ICD and ToF groups when comparing right ventricular dilatation. Right ventricular function was significantly worse in the ToF+ICD group compared to the ToF group ($p<0.01$). Remarkably, patients from the ToF+ICD group less often had severe pulmonary regurgitation compared to patients form the ToF group. When analyzing the occurrence of appropriate and inappropriate shocks, a significantly higher incidence of inappropriate shocks was observed in the ToF+ICD group versus the ICD group ($p=0.03$). Also, the absolute number of inappropriate shocks was higher in the ToF+ICD group ($p=0.03$) and also the amount of appropriate shocks was higher in the ToF+ICD group ($p=0.03$).

Scores on instruments (see Table 2)

Subjective health status (SF36)

On all SF-36 scales except for one, the median for the ToF+ICD group was lower, indicating more unfavorable outcomes, than for the ToF group. Two significant group effects between the ToF+ICD group versus the ToF group were found: patients from the ToF+ICD group scored significantly lower on physical functioning compared to the ToF group ($p=0.01$) and also on general health perceptions patients from the ToF+ICD group scored significantly lower than the ToF group ($p<0.01$). When comparing the ToF+ICD versus the ICD group, one significant group effect was found. On physical functioning the ToF+ICD group obtained a higher, more favorable mean score than the ICD group ($p=0.01$). No other significant differences were found between the three groups.

Table 2. Mean scores for the different instruments

	ToF+ICD (N=26)		ToF (N=28)		ICD (N=35)		Normdata			Group effect		
	Median	IQR	Median	IQR	Median	IQR	Mean	sd	N	ToF+ICD vs. ToF (p-value)	ToF+ICD vs. ICD (p-value)	ToF+ICD vs. Norm (p-value)
SF-36												
• Physical functioning	82.5	[58.8 - 91.3]	95.0	[76.3 - 100]	60.0	[40.0 - 75.0]	93.1	11.7	1742	0.01	0.01	<0.01
• Social functioning	87.5	[62.5 - 100]	100.0	[75.0 - 100]	87.5	[62.5 - 100]	91.2	15.9	1742	0.1	0.7	<0.001
• Role limitations due to physical functioning	75.0	[25.0 - 100]	100.0	[50.0 - 100]	50.0	[0.0 - 100]	89.5	24.1	1742	0.1	0.2	<0.01
• Role limitations due to emotional functioning	100.0	[66.7 - 100]	100.0	[75.0 - 100]	100.0	[66.7 - 100]	88.9	26.1	1742	0.5	0.7	0.2
• General mental health	72.0	[55.0 - 85.0]	80.0	[68.0 - 91.0]	84.0	[72.0 - 92.0]	81.5	14.1	1742	0.2	0.1	<0.01
• Vitality	60.0	[45.0 - 75.0]	75.0	[50.0 - 83.8]	65.0	[50.0 - 75.0]	75.1	15.4	1742	0.1	0.8	<0.001
• Bodily pain	82.0	[61.5 - 100]	100.0	[74.0 - 100]	84.0	[72.0 - 100]	84.3	17.3	1742	0.3	0.8	0.2
• General health perceptions	52.0	[38.8 - 62.0]	69.5	[52.0 - 82.0]	55.0	[42.0 - 67.0]	80	14.5	1742	<0.01	0.5	<0.001
SWLS	24.0	[13.5 - 29.0]	28.0	[21.3 - 31.0]	28.0	[22.0 - 30.0]	25.5	5	109	0.02	0.03	0.03
LAS	70.0	[68.0 - 77.8]	80.0	[70.0 - 86.5]	70.0	[60.0 - 75.0]	75.4	9	110	0.1	0.4	0.1
HADS												
• Anxiety	6.0	[2.0 - 9.0]	4.0	[3.0 - 6.0]	2.0	[1.0 - 5.0]	5.1	3.6	199	0.2	0.01	0.4
• Depression	2.0	[1.0 - 3.0]	1.5	[0.0 - 4.0]	3.0	[2.0 - 6.0]	3.4	3.3	199	0.8	0.1	0.4
UCL												
• Active problem solving	18.0	[14.8 - 21.0]	19.0	[17.0 - 21.8]	17.0	[15.0 - 20.0]	18.6	4	2205	0.2	0.9	0.2
• Palliative reactions	17.5	[15.0 - 20.0]	16.5	[14.0 - 20.0]	15.0	[12.0 - 18.0]	16.1	4.4	2205	0.3	<0.01	0.03
• Avoiding/waiting	15.5	[13.0 - 17.0]	16.5	[14.3 - 18.0]	16.0	[13.0 - 19.0]	14.9	4.2	2205	0.2	0.7	0.4
• Seeking social support	14.5	[11.8 - 17.0]	14.5	[13.0 - 17.0]	11.0	[8.0 - 13.0]	12.3	3.6	2205	0.8	<0.0001	<0.01

Table 2. (continued)

	ToF+ICD (N=26)		ToF (N=28)		ICD (N=35)		Normdata			Group effect		
	Median	IQR	Median	IQR	Median	IQR	Mean	sd	N	ToF+ICD vs. ToF (p-value)	ToF+ICD vs. ICD (p-value)	ToF+ICD vs. Norm (p-value)
• Passive reaction pattern	10.0	[9.0 - 15.3]	10.5	[8.3 - 12.8]	9.0	[9.0 - 11.0]	10.8	3.7	2205	0.4	0.2	0.2
• Expression of emotions	6.5	[5.0 - 8.0]	6.0	[6.0 - 8.0]	5.0	[4.0 - 6.0]	6.3	1.9	2205	0.8	0.01	0.3
• Reassuring thoughts	12.0	[10.0 - 14.0]	11.5	[10.0 - 13.0]	11.0	[9.0 - 13.0]	11.8	2.9	2205	0.7	0.2	0.7
IDAS												
• Anxiety/Fear	21.0	[18.0 - 29.5]	-	-	19.0	[14.0 - 24.0]	-	-	-	-	0.1	-
• Attitude	9.0	[7.0 - 12.5]	-	-	9.0	[6.0 - 10.0]	-	-	-	-	0.2	-
• Preparation	8.0	[6.8 - 10.3]	-	-	7.0	[6.0 - 11.0]	-	-	-	-	0.5	-
• Bodily awareness	6.0	[4.0 - 8.0]	-	-	5.0	[4.0 - 7.0]	-	-	-	-	0.2	-
PSSS12												
• Significant others	28.0	[23.8 - 28.0]	28.0	[22.0 - 28.0]	26.0	[19.0 - 28.0]	-	-	-	0.6	0.1	-
• Family support	24.5	[18.8 - 27.3]	23.5	[17.3 - 25.0]	22.0	[16.0 - 27.0]	-	-	-	0.4	0.2	-
• Friends support	21.5	[17.8 - 25.3]	24.0	[20.0 - 25.8]	19.0	[16.0 - 24.0]	-	-	-	0.3	0.4	-
• Total score	73.5	[62.5 - 79.0]	69.5	[65.3 - 76.0]	65.0	[50.0 - 78.0]	-	-	-	0.7	0.2	-

Abbreviations: ToF+ICD = Patients with Tetralogy of Fallot with an ICD; ToF = Patients with Tetralogy of Fallot (without an ICD); ICD = Patients with ICD (without congenital heart disease); IQR = Interquantile range; SF-36 = Short-form 36; SWLS = Satisfaction with Life Scale; LAS = Linear Analogue Scale; HADS = Hospital Anxiety and Depression Scale; UCL = Utrecht Coping List; IDAS = Implanted Devices Adjustment Scale.

a) Group effect: indicates difference between mean ranks between groups, as calculated by a Mann–Whitney U test.

The bold numbers in the text indicate significant results.

Satisfaction with Life Scale

Patients of the ToF+ICD group scored significantly lower compared to patients from the ToF group (p=0.02). Also, a significantly lower score was found in the ToF+ICD group compared to the ICD group (p=0.03).

Linear Analogue Scale Quality of Life

The ToF+ICD group showed a trend towards a less favorable result than the ToF group (p=0.06).≤

Hospital Anxiety and Depression Scale

Patients from the ToF+ICD group reported significantly more anxiety than patients from the ICD group (p=0.01). No other significant differences were found on the anxiety and depression scale between the three groups.

Utrecht Coping List

Patients from the ToF+ICD group scored significantly higher on Palliative reactions (i.e. seeking diversion in unhealthy manners) compared to patients from the ICD group (p<0.01). Also significantly higher scores were found on seeking social support in the ToF+ICD group compared to the ICD group (p<0.0001). Patients from the ToF+ICD group also scored higher on expressions of (negative) emotions compared to the ICD-patients group (p=0.01). No differences in scores were found between the ToF+ICD and the ToF group. No other significant differences were found on the other scales of the UCL.

Implanted Devices Adjustment Scale

No significant differences were found between the two ICD groups on any of the IDAS domains.

Perceived Social Support Scale

No significant differences were found between the three groups on any of the PSSS12 domains.

Primary versus secondary indication for ICD implantation

In order to assess whether the indication for ICD implantation had effect on the outcomes, we compared the scores on different scales of patients with a primary indication versus a secondary indication for ICD implantation.

In the ToF+ICD group, no significant differences were found between the two indication groups. In the ICD group, no significant differences were found between the two indication

groups, except for the body awareness scale of the IDAS. Here, patients with a secondary indication showed less favorable outcome.

When combining the ToF+ICD group with the ICD group, a less favorable outcome on the UCL scale in palliative reactions was observed for patients with secondary indication for ICD.

Normative data

When comparing the ToF+ICD group with normative data, the following results were obtained.

Subjective health status (SF36)

Normative data for the Dutch population were obtained from Aaronson et al.[12] Patients from the ToF+ICD group obtained significantly lower results on physical functioning, social functioning, role limitations due to physical functioning, general mental health, vitality and general health perceptions. No significant difference on the SF-36 scales bodily pain and role limitations due to emotional functioning were found.

Satisfaction with Life Scale

Normative data were obtained from Moons et al.[13] Patients from the ToF+ICD group obtained significantly less favorable outcomes compared to the general Belgium population.

Linear Analogue Scale Quality of Life

Normative data were obtained from Moons et al.[13] No significant differences were found between the ToF+ICD group compared to the normative data.

Hospital Anxiety and Depression Scale

Normative data for the HADS have been obtained from Spinhoven et al.[14] When comparing the ToF+ICD group with normative data, no significant differences were found.

Utrecht Coping List

Normative data for the Dutch population were obtained from Schreurs et al.[16] Patients from the ToF+ICD group obtained significantly less favorable outcomes on palliative reactions and seeking social support.

DISCUSSION

The main finding of this study is that ToF-patients with an ICD show less favorable psychosocial functioning com- pared to ToF-patients without ICD and to the older acquired heart disease ICD-patients.

To our knowledge, this is the first psychosocial study carried out in this specific group, Fallot-patients with ICD. Data were compared with two control groups: Fallot- patients without ICD and older "regular" ICD-patients without ConHD. Clinically relevant areas of psychosocial functioning together with medical correlates for psycho- social outcomes were investigated, using standardized and validated questionnaires.

Psychosocial functioning and ICD therapy

Despite a younger age (40 vs. 72 years) and lower NYHA class (I vs. II), Fallot-patients with ICD scored less favorable on instruments assessing subjective health status, anxiety, satisfaction with life and coping (more negative emotions, more palliative reactions such as smoking and drinking and less seeking of social support) compared to older ICD-patients. After correction for the higher age in the ICD group using stepwise multiple regression, all conclusions drawn remained the same.

In contrast to the overall good quality of life reported before, in our study we found that Fallot-patients with ICD showed a less favorable quality of life outcome than Fallot-patients without ICD.[13] Our findings, together with the findings from literature indicate that the ConHD back- ground of these ICD-patients cannot be the sole reason for the lower quality of life observed in this study. In fact, they confirm our hypothesis that ICD therapy in young ConHD patients is associated with worse psychosocial functioning. Between the study of Yap et al. and the start of our own study, patients with less favorable medical outcome have died in the ToF+ICD group.[4] This means that it might even be possible that our present outcomes could have been worse as we face a positive selection of patients.

Anxiety in Fallot-patients receiving ICD therapy

We found anxiety to be a problematic psychosocial reaction for young Fallot-patients receiving ICD therapy. This is in line with the review of Sears et al.[19] Our results on anxiety were statistically significant and in addition clear trends were observed in the other data, also pointing towards the same direction of a less favorable psychological outcome for Fallot-patients with ICD compared to both control groups. In addition, patients reported a lower satisfaction with life.

In literature, a clinical cut-off value of 8 is considered clinically significant on the anxiety scale of the HADS.[20] Our ToF+ICD group obtained a median score of 6 and did not show a significant difference on anxiety level compared to normative data. This finding might be

explained by assuming that the HADS instrument may not be sensitive enough to screen for disease-specific anxiety in this unique ConHD population. We assume that using a clinical interview, high levels of anxiety might have been found, as in the article of Bromberg et al.[21]

Role of appropriate and inappropriate ICD shocks

The present data show that Fallot-patients receiving ICD therapy have a higher rate of inappropriate ICD discharges compared to "regular" ICD-patients. Despite optimal programing, 39% of the Fallot-patients with ICD suffered from one or more inappropriate ICD shocks. The inappropriate shock rate was higher than reported in previous studies in non-ConHD patients.[3,5] Since Fallot-patients are known to have a high arrhythmia burden, the inappropriate shocks we found may be due to atrial arrhythmias.[4,22–24]

Furthermore, ToF ICD-patients are in general younger than the traditional ICD-patient group and tend to lead more active lives, practising sports and other leisure activities. These activities inducing sinus tachycardia may result in inappropriate ICD therapy. Not only the inappropriate shock rate in ToF+ICD patients was higher than that in the older ICD group but also the number of inappropriate shocks per patient was significantly higher. As most inappropriate shocks occur when the patient is fully conscious, this may have serious psychosocial con- sequences and it may lead to serious anxiety and stress, possibly resulting in avoidance behavior. Our findings are in line with Vasquez et al., who showed that ICD patients who had a history of more inappropriate shocks with age below 50 and female gender were at higher risk for developing psychosocial problems.[7] Moreover, avoidance behavior has been reported for ICD patients, which may be a limiting factor in social and sexual activities, but also in practising sports. Out of fear for an ICD discharge, 39% of the ICD-patients avoid physical exertion, even though physical exercise is well known to have a beneficial effect on health and can be effective in preventing depression.[25]

Although there is lack of evidence in mortality benefit, the threshold for using ICD therapy in ConHD patients seems to have lowered over time. The guidelines for ICD implantation in this patient population are based on limited data. With the high rate of inappropriate shocks, balancing the benefit-risk ratio for ICD implantation remains difficult, especially taking psychosocial problems into account.

Medical background

The differences in QRS duration as seen in Table 1 could be explained by the ConHD background in combination with pacemaker therapy differences between groups. ToF- patients have a higher QRS duration as a result of right ventricular dilatation, diminished function, or post-surgery for their ConHD background. Some of the patients in the ToF+ICD group also received constant pacing therapy next to the ICD therapy which may also have resulted into a

longer QRS duration. The long QRS duration seen in the ToF+ICD group can also be the result of selection, as a QRS duration >180 ms. is a predictor for SCD and may have been used as a criterium for ICD implantation.[26] Despite the diminished RV function, patients in the ToF+ICD group were in good clinical condition with the majority being in NYHA class I.

Clinical implications

When considering ICD therapy in young patients, the psychosocial impact should be taken into account. The findings in this study provide a solid argument for careful assessment and counseling in patients with Tetralogy of Fallot. The threshold for ICD implantation should be high, especially in case of primary prevention. In patients needing an ICD, routinely applied comprehensive and multidisciplinary psychosocial aftercare is advised. We see an opportunity for a shared decision-making model in this situation. In this way, patients can become well informed about all possible consequences of ICD therapy, and can decide the best treatment option together with the clinician.

In order to facilitate acceptance of ICD therapy, we recommend cognitive behavioral techniques such as psycho-education, cognitive re-appraisal and relaxation techniques to improve quality of life of these patients. These techniques have been found to improve the quality of life in the "general" older ICD population.[7,27,28]

Limitations

The patients included in this study were all followed in a tertiary (academic) medical center. Therefore, this study may not be representative for all Fallot-patients. In addition, although we tried to create comparable groups, some differences were present. Furthermore, because of the small sample size, often encountered in these patient groups, several nearly significant trends were observed. With a larger sample size these trends might have become significant.

Although no significant differences were found between the three groups, a trend was visible in which the older ICD patients more often had male gender.

Unfortunately, data regarding psychosocial interventions (so called "medical consumption" or "psychotherapeutic counseling") are not systematically available.

Furthermore, as could be expected, a significant age difference was found between the ToF+ICD and the - by definition - older ICD group, which resulted in a later age at implantation in the ICD group. In addition, patients with the Belgian nationality (N = 8) were only found in the ToF+ICD group. To which extent these inter-group differences have influenced our results is unknown.

Despite the fact that patients in the ICD group were more often in NYHA class II compared to the ToF and the ToF+ICD group, we remarkably found that our younger NYHA class I ToF+ICD

patients obtained less favorable results than the other ICD group with worse NYHA class. This noteworthy finding reflects the psychosocial importance of our results in the ToF+ICD group.

Future research

Future research should investigate the role of inappropriate shocks on psychosocial outcome in a larger cohort, as the current cohort was not large enough to perform further subanalyses. In addition, the impact of ICD therapy in young adults with ConHD on activities such as practising sports, sexuality and driving a car should be studied.[29] We recommend using a semi-structured clinical interview to assess these points, as questionnaires may not be specific enough.

Different programing strategies, such as the application of antitachycardia pacing therapy and higher rate cut-offs for arrhythmia detection, may prevent inappropriate ICD therapy and may have a beneficial effect on psychosocial functioning.

Recently, the subcutane ICD (sICD) has been introduced for patients requiring ICD therapy.[30,31] In this study, sICD therapy appeared to have a very low rate of inappropriate shocks. This therefore may be a good alternative for ConHD patients who require ICD therapy and suffer from a lot of inappropriate shocks. The sICD is relatively easy to implant, and because the leads are subcutaneous, replacement and complication rates appear to be lower as well. Future research could concentrate on the application and psychosocial impact of having an sICD in ConHD patients.

CONCLUSION

Implantable cardioverter defibrillators implantation has a major psychosocial impact in young adults with ToF. This group shows clinically significant psychosocial problems that have to be recognized and treated appropriately. The information obtained from this study can be used to guide adequate counseling and development of interventions aimed at enhancing psychosocial functioning and improving quality of life. Our results provided information that is not readily apparent from routine clinical investigations.

REFERENCES

1. Oechslin EN, Harrison DA, Connelly MS, Webb GD, Siu SC (2000) Mode of death in adults with congenital heart disease. Am J Cardiol 86(10):1111–1116
2. Silka MJ, Hardy BG, Menashe VD, Morris CD (1998) A popu- lation-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. J Am Coll Cardiol 32(1):245–251
3. Khairy P, Harris L, Landzberg MJ, Viswanathan S, Barlow A, Gatzoulis MA, Fernandes SM, Beauchesne L, Therrien J, Chetaille P, Gordon E, Vonder Muhll I, Cecchin F (2008) Implantable cardioverter-defibrillators in tetralogy of Fallot. Circulation 117(3):363–370
4. Yap SC, Roos-Hesselink JW, Hoendermis ES, Budts W, Vliegen HW, Mulder BJ, van Dijk AP, Schalij MJ, Drenthen W (2007) Outcome of implantable cardioverter defibrillators in adults with congenital heart disease: a multi-centre study. Eur Heart J 28(15):1854–1861
5. Alexander ME, Cecchin F, Walsh EP, Triedman JK, Bevilacqua LM, Berul CI (2004) Implications of implantable cardioverter defibrillator therapy in congenital heart disease and pediatrics. J Cardiovasc Electrophysiol 15(1):72–76
6. Sears SF Jr, Todaro JF, Lewis TS, Sotile W, Conti JB (1999) Examining the psychosocial impact of implantable cardioverter defibrillators: a literature review. Clin Cardiol 22(7):481–489
7. Vazquez LD, Conti JB, Sears SF (2010) Female-specific educa- tion, management, and lifestyle enhancement for implantable cardioverter defibrillator patients: the FEMALE-ICD study. Pacing Clin Electrophysiol 33(9):1131–1140
8. Sowell LV, Sears SF Jr, Walker RL, Kuhl EA, Conti JB (2007) Anxiety and marital adjustment in patients with implantable cardioverter defibrillator and their spouses. J Cardiopulm Rehabil Prev 27(1):46–49
9. van der Velde ET, Vriend JW, Mannens MM, Uiterwaal CS, Brand R, Mulder BJ (2005) CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: rationale, design, and first results. Eur J Epidemiol 20(6):549–557
10. Utens EMWJ, van Rijen EHM, Erdman RAM, Verhulst FC 2000. Rotterdams Kwaliteit van Leven—Interview
11. Ware JE Jr (1992) Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30(6):473–483
12. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E (1998) Translation, validation, and norming of the Dutch language ver- sion of the SF-36 Health Survey in community and chronic dis- ease populations. J Clin Epidemiol 51(11): 1055–1068
13. Moons P, Van Deyk K, De Bleser L, Marquet K, Raes E, De Geest S, Budts W (2006) Quality of life and health status in adults with congenital heart disease: a direct comparison with healthy counterparts. Eur J Cardiovasc Prev Rehabil 13(3):407–413
14. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM (1997) A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 27(2):363–370
15. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67(6):361–370
16. Schreurs PJG, van de Willige G, Brosschot JF, Tellegen B, Graus GMH (1993) De Utrechtse Coping Lijst: UCL, omgaan met problemen en gebeurtenissen, herziene handleiding 1993

17. Beery TA, Baas LS, Matthews H, Burroughs J, Henthorn R (2005) Development of the implanted devices adjustment scale. Dimens Crit Care Nurs 24(5):242–248
18. Pedersen SS, van Domburg RT, Theuns DA, Jordaens L, Erdman RA (2004) Type D personality is associated with increased anxiety and depressive symptoms in patients with an implantable cardioverter defibrillator and their partners. Psychosom Med 66(5):714–719
19. Sears SF, Matchett M, Conti JB (2009) Effective management of ICD patient psychosocial issues and patient critical events. J Cardiovasc Electrophysiol 20(11):1297–1304
20. 20. Bjelland I, Dahl AA, Haug TT, Neckelmann D (2002) The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 52(2):69–77
21. Bromberg JI, Beasley PJ, D'Angelo EJ, Landzberg M, DeMaso DR (2003) Depression and anxiety in adults with congenital heart disease: a pilot study. Heart Lung 32(2):105–110
22. Khairy P, Aboulhosn J, Gurvitz MZ, Opotowsky AR, Mongeon FP, Kay J, Valente AM, Earing MG, Lui G, Gersony DR, Cook S, Ting JG, Nickolaus MJ, Webb G, Landzberg MJ, Broberg CS (2010) Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. Circulation 122(9): 868–875
23. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S (1995) Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic find- ings. Circulation 91(8):2214–2219
24. Magnin-Poull I, De Chillou C, Miljoen H, Andronache M, Aliot E (2005) Mechanisms of right atrial tachycardia occurring late after surgical closure of atrial septal defects. J Cardiovasc Elec- trophysiol 16(7):681–687
25. Lemon J, Edelman S, Kirkness A (2004) Avoidance behaviors in patients with implantable cardioverter defibrillators. Heart Lung 33(3):176–182
26. Gatzoulis MA, Till JA, Somerville J, Redington AN (1995) Mechanoelectrical interaction in tetralogy of Fallot. QRS pro- longation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. Circulation 92(2):231–237
27. Pedersen SS, van den Broek KC, Sears SF Jr (2007) Psycho- logical intervention following implantation of an implantable defibrillator: a review and future recommendations. Pacing Clin Electrophysiol 30(12):1546–1554
28. Irvine J, Firestone J, Ong L, Cribbie R, Dorian P, Harris L, Ritvo P, Katz J, Newman D, Cameron D, Johnson S, Bilanovic A, Hill A, O'Donnell S, Sears S Jr (2011) A randomized controlled trial of cognitive behavior therapy tailored to psychological adaptation to an implantable cardioverter defibrillator. Psychosom Med 73(3):226–233
29. Groeneveld PW, Matta MA, Suh JJ, Yang F, Shea JA (2007) Quality of life among implantable cardioverter-defibrillator recipients in the primary prevention therapeutic era. Pacing Clin Electrophysiol 30(4):463–471
30. Bardy GH, Smith WM, Hood MA, Crozier IG, Melton IC, Jor- daens L, Theuns D, Park RE, Wright DJ, Connelly DT, Fynn SP, Murgatroyd FD, Sperzel J, Neuzner J, Spitzer SG, Ardashev AV, Oduro A, Boersma L, Maass AH, Van Gelder IC, Wilde AA, van Dessel PF, Knops RE, Barr CS, Lupo P, Cappato R, Grace AA (2010) An entirely subcutaneous implantable cardioverter-defi- brillator. N Engl J Med 363(1):36–44
31. Dabiri Abkenari L, Theuns DA, Valk SD, Van Belle Y, de Groot NM, Haitsma D, Muskens-Heemskerk A, Szili-Torok T, Jordaens L (2011) Clinical experience with a novel subcutaneous implantable defibrillator system in a single center. Clin Res Cardiol 100(9):737–744

Chapter 4.2

Complications of pacemaker therapy in adults with congenital heart disease: a multicenter study.

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ABSTRACT

Background: To investigate indications and complications of permanent cardiac pacing in adults with congenital heart disease (CHD).

Methods and Results: Two-hundred and seventy-four CHD patients were identified who underwent permanent pacemaker implantation between 1972 and 2009. The indication for pacing was acquired sinus node or AV node conduction disease (63%), sinus node or AV node conduction disease after cardiac surgery (28%), and drug/arrhythmia-related indications (9%). Patients with complex CHD received a pacemaker at younger age (23 versus 31 years, $p<0.0001$) and more often received an epicardial pacing system (51% versus 23%, $p<0.0001$) compared to those with simple or moderate CHD. Twenty-nine patients (10.6%) had a peri-procedural complication during the primary pacemaker implantation (general population: 5.2%). The most common acute complications were lead dysfunction (4.0%), bleeding (2.6%), pocket infection (1.5%) and pneumothorax (1.5%). During a median follow-up of 12 years, pacemaker-related complications requiring intervention occurred in 95 patients (34.6%). The most common late pacemaker-related complications included lead failure (24.8%), pacemaker dysfunction/early battery depletion (5.1%), pacemaker migration (4.7%) and erosion (4.7%). Pacemaker implantation at younger age (<18 years) was an independent predictor of late pacemaker-related complication (adjusted hazard ratio 1.68, 95% confidence interval 1.07 to 2.63, $p=0.023$).

Conclusions: The risk of peri-procedural complications seems higher in the CHD population compared to the general population and more than one-third of CHD patients encountered a pacemaker-related complication during long-term follow-up. This risk increases for those who receive a pacemaker at younger age.

INTRODUCTION

The population of adult patients with congenital heart disease (CHD) is rapidly expanding due to advances in pediatric cardiology and cardiothoracic surgery over the past several decades.[1,2] However, this improved survival following congenital heart surgery is hampered by both structural and electrical late sequelae including atrioventricular (AV) block, sinus node dysfunction and atrial arrhythmias.[3,4] Many will require pacemaker therapy and are subject to lifelong need for reinterventions and follow-up.[3] Pacemaker implantation in this population may be a challenge due to the complexity of the systemic venous anatomy, venous obstructions and/or residual intra-cardiac shunting.[5,6] Furthermore, pacemaker implantation at young age and the use of epicardial leads has been associated with a high incidence of lead failures during follow-up.[6-10] Because of these issues, pacemaker therapy should be considered carefully in the patient with CHD. To improve patient management, knowledge regarding the indications and impact of pacemaker therapy is essential. Unfortunately, these data are scarce for the adult CHD population and large multi-center studies are lacking.[5,6] Furthermore, most CHD studies only focus on lead failure rate. The objective of the present multi-center study is to investigate the indications, peri-procedural and late complications of permanent pacemaker therapy in adults with CHD.

METHODS

For the present retrospective study, all adults with CHD and a history of pacemaker implantation were identified from the participating centers using the nationwide CONgenital CORvitia (CONCOR) registry in the Netherlands and a Belgian tertiary care center adult CHD database.[11] Excluded from analysis were patients with a primary electrical disease or cardiomyopathy. We also excluded patients with an implantable cardioverter defibrillator as we previously published our experience with this specific patient group.[12] Crosscheck with the local pacemaker registries of the four participating tertiary centers revealed a total of 274 patients. The central medical Ethics Committee in the Netherlands and the local Belgian Ethics Board approved the protocol. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.[13]

Data were collected from medical records and pacemaker databases. Baseline data prior to pacemaker implantation were registered from the patient records including, gender, congenital anatomic diagnosis, surgical procedures, and history of atrial arrhythmias. The complexity of the CHD diagnosis was defined as simple, moderate or complex according to the classification adopted at the American Heart Association Task Force on Adults with CHD.[14] Detailed information concerning the pacemaker implantation was recorded, including age at implan-

tation, indication for pacemaker implantation, method of implant (endocardial/epicardial), pacing mode (AAI, VVI, DDD, or VDD), and peri-procedural complications. Peri-procedural pacemaker complications were defined as complications occurring in the first 30 days after initial pacemaker implantation. Follow-up data included late pacemaker complications (>30 days of implantation), major clinical complications and pacemaker reinterventions. Major clinical complications included endocarditis (not pacing system-related), hospitalization for heart failure, stroke, heart transplantation, aborted sudden cardiac death, and death.

Documented pacemaker complications were: bleeding (any swelling of the pocket with clinical suspicion of hematoma requiring intervention), pacing system-related endocarditis, erosion (skin penetration of the pacemaker requiring intervention), lead failure (leads repaired, repositioned, replaced, or abandoned due to fracture, insulation break, dislodgment, or abnormalities in pacing or sensing), pacemaker dysfunction/early battery depletion (pacemaker malfunction requiring pacemaker replacement or early battery depletion necessitating replacement <3 years post implant), pacemaker migration (requiring pacemaker repositioning), pneumothorax (absence of lung markings over the lung ipsilateral to the pacemaker pocket assessed from x-ray), pocket infection (superficial wound infection), and ventricular arrhythmias (related to lead manipulation). Normal elective replacement of a pacemaker (>3 years post-implant) or pacemaker upgrade was not considered a pacemaker complication.

Statistical methods

Continuous data are presented as mean ± SD. In the case of skewed data, medians and interquartile ranges (IQR) were used. Categorical variables are represented by frequencies and percentages. Comparison of continuous variables between groups was made by unpaired Student's t-tests. In the case of a skewed distribution, the Mann–Whitney U test was used. When comparing frequencies, the chi-square test or Fisher's exact test was used, where applicable.

Potential predictors of late pacemaker-related complications were identified by means of Cox regression models, and hazard ratios (HR) and 95% confidence intervals (95%CI) are reported. Variables with a $p<0.10$ on univariable analysis were included in a multivariable model. Two-tailed probability values <0.05 were considered statistically significant. Statistical analysis was performed using the statistical package R (64 bit) for Mac, version 2.14.2.

RESULTS

Patient characteristics, pacemaker indications, procedural details

The baseline characteristics of the 274 included patients with CHD are summarized in Table 1. Patients with complex CHD comprised 36% of the population, and were mainly patients with transposition of the great arteries (after atrial correction or congenitally corrected transposition) or single ventricle physiology (Figure 1). The first implant for most patients occurred in adulthood (70%). Patients with complex CHD underwent primary pacemaker implantation at younger age compared to those with simple/moderate CHD (median age 23 versus 31 years, p<0.0001). Furthermore, patients who received an epicardial pacing system were younger at implantation compared to those with an endocardial pacing system (median age 14 versus 31 years, p<0.0001). The primary pacemaker devices were implanted between March 1972 and Jan 2009.

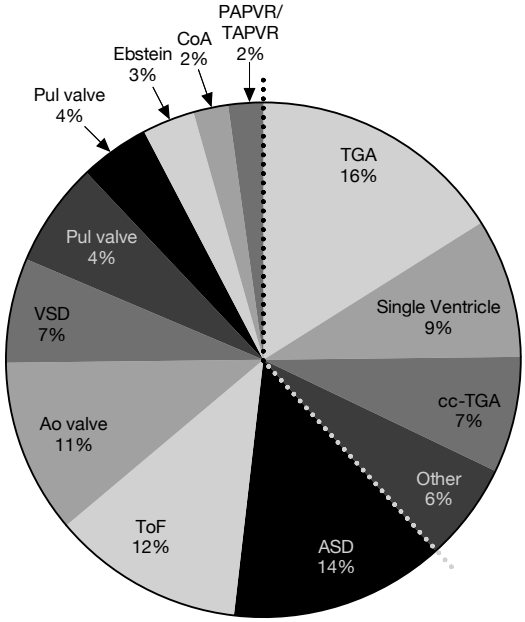
The major indication for pacemaker therapy was acquired sinus node or AV node conduction disease (63%), the majority of patients had undergone surgery years previously. Seventy-seven patients (28%) required pacing within 30 days after cardiac surgical repair or palliation. The remainder (9%) required pacing for drug-refractory atrial arrhythmias or drug-induced bradycardia.

Table 1. Baseline characteristics at first pacemaker implantation

Variable	Total (n=274)	Simple/moderate CHD (n=175)	Complex CHD (n=99)	p-value
Age at first implantation (years), median [IQR]	26 [15-39]	31 [18-44]	23 [12-28]	<0.0001
First implant <18 years	83 (30)	46 (26)	37 (37)	0.06
Male gender	152 (55)	92 (53)	60 (61)	0.20
History of atrial arrhythmias	103 (38)	63 (36)	40 (40)	0.52
Indication for pacemaker				
• Acquired SSS	91 (33)	56 (32)	35 (35)	0.001
• Acquired AV block	81 (30)	47 (27)	34 (34)	
• Surgical AV block	70 (26)	57 (33)	13 (13)	
• Drug-refractory atrial arrhythmias or drug-related bradycardia	25 (9)	14 (8)	11 (11)	
• Surgical SSS	7 (3)	1 (1)	6 (6)	
Initial pacing mode				
• Physiologic pacing (DDD, AAI, VDD)	239 (65)	113 (65)	66 (67)	0.86
Implantation technique:				
• Endocardial leads	184 (67)	135 (77)	49 (49)	<0.0001
• Epicardial leads	90 (33)	40 (23)	50 (51)	

Abbreviations: AV = Atrioventricular; SSS = Sick Sinus Syndrome.
Data are presented as n (%), unless stated otherwise.

Figure 1. Distribution of congenital anatomic diagnosis



Abbreviations: Ao valve = Aortic valve; ASD = Atrial Septal Defect; AVSD = Atrioventricular Septal Defect; cc-TGA = Congenitally corrected Transposition of the Great Arteries; CoA = Coarctation of the Aorta; Ebstein = Ebstein's anomaly; PAPVR/TAPVR = Partial Anomalous Pulmonary Venous Return / Total Anomalous Pulmonary Venous Return; Pul valve = Pulmonary valve; Single Ventricle = Single Ventricle physiology (e.g. Fontan); TGA = Transposition of the Great Arteries; ToF = Tetralogy of Fallot; VSD = Ventricular Septal Defect.

Patients with complex CHD more often received an epicardial pacing system compared to those with simple/moderate CHD (51% versus 23%, p<0.0001). Reasons for implanting an epicardial system were small body size or young age (n=22, 24%), complex systemic venous anatomy or venous access problems (n=20, 22%), concomitant cardiac surgery (n=17, 19%), right-sided mechanical AV valve (n=10, 11%), intra-cardiac shunt (n=5, 6%), endocarditis (n=2, 2%), and unknown reason (n=14, 16%). There were no differences in pacing mode between patients with complex and simple/moderate CHD.

Table 2 provides an overview of pacemaker details in the five most common CHD groups. Patients with complete transposition of the great arteries usually required a pacemaker for acquired sick sinus dysfunction. In contrast, patients with aortic valve disease are more prone to surgical AV block. In addition, patients with single ventricle physiology are at high risk of atrial arrhythmias and a significant proportion requires a pacemaker related to treatment of atrial arrhythmias.

Table 3 summarizes the initial mode of pacing and change in mode over time. The majority of patients (59%) received atrial-based/physiologic pacing (i.e., AAI, DDD, VDD) at baseline

Table 2. Overview of pacemaker details in the five most common CHD groups

Variable	Complete TGA (n=45)	Single Ventricle physiology (n=25)	Tetralogy of Fallot (n=33)	Aortic valve disease (n=30)	ASD secundum (n=37)
Clinical					
• Age at first implantation (years), median [IQR]	23 [10-27]	24 [15-30]	33 [17-41]	34 [22-50]	35 [18-52]
• Follow-up duration (years), median [IQR]	15 [9-20]	8 [2-15]	13 [6-26]	10 [6-16]	12 [8-26]
• Male gender	69%	52%	61%	73%	41%
• History of atrial arrhythmias	44%	64%	39%	13%	51%
Indication for pacemaker					
• Acquired SSS	60%	28%	48%	7%	43%
• Acquired AV block	13%	36%	27%	30%	27%
• Surgical AV block	7%	12%	18%	60%	16%
• Drug-refractory atrial arrhythmias or drug-induced bradycardia	11%	20%	6%	3%	14%
• Surgical SSS	9%	-	-	-	-
Pacemaker details					
• Physiologic pacing	53%	88%	58%	77%	62%
• Epicardial leads	42%	76%	12%	17%	22%
Pacemaker complications					
• Peri-procedural complications	13%	12%	15%	-	8%
• Late pacemaker-related complications	38%	20%	24%	23%	32%

Abbreviations: ASD = Atrial Septal Defect; AV = Atrioventricular; SSS = Sick Sinus Syndrome; TGA = Transposition of the Great Arteries, ASD = Atrial Septal Defect.
Data are presented as percentages, unless stated otherwise.

Table 3. Mode of Pacing at Baseline and at Most Recent Follow-Up

Baseline	Follow-up	Number of patients (%)
AAI	AAI	16 (6%)
AAI	DDD	5 (2%)
VVI	VVI	55 (20%)
VVI	DDD	36 (13%)
VVI	AAI	4 (2%)
DDD	DDD	136 (50%)
DDD	VVI	15 (6%)
DDD	AAI	1 (0.4%)
VDD	VDD	3 (1%)
VDD	DDD	2 (0.7%)
VDD	VVI	1 (0.4%)

and during follow-up, while 40 patients (15%) were upgraded from ventricular to atrial-based/physiologic pacing (i.e. VVI to DDD or VVI to AAI). The pacemaker was upgraded to an implantable cardioverter defibrillator in 20 patients (7%) during follow-up.

Peri-procedural complications

Twenty-nine patients (10.6%) experienced one or more peri-procedural complications (<30 days after implantation) during their first pacemaker implantation (Table 4). The most common complication was lead failure requiring intervention (4.0%). Patients with complex CHD showed a trend towards more peri-procedural complications compared to those with simple/moderate CHD (15% versus 8%, p=0.07). There was a numerical decrease in the incidence of peri-procedural complications when primary pacemaker implantations in a more contemporary cohort (1997-2009) were compared to an earlier cohort (1972-1996), however, this was not statistical significant (7.6% versus 13.4%, p=0.12). Younger age (<18 years) at implantation was not associated with a higher peri-procedural complication rate (7.4% versus 11.9%, p=0.27).

Table 4. Peri-procedural complications during first pacemaker implantation

Complication	Total (n=274)	Simple/ moderate CHD (n=175)	Complex CHD (n=99)	p-value	General population[a]
Total number of patients	29 (10.6)	14 (8.0)	15 (15.2)	0.07	5.2%
• Early lead failure	11 (4.0)	5 (2.9)	6 (6.1)	0.21	2.3%
• Bleeding	7 (2.6)	3 (1.7)	4 (4.0)	0.26	0.8%
• Pneumothorax	4 (1.5)	2 (1.1)	2 (2.0)	0.62	0.5%
• Pocket infection	4 (1.5)	2 (1.1)	2 (2.0)	0.62	0.1%
• Ventricular arrhythmias	2 (0.7)	-	2 (2.0)	0.13	0.1%
• Other	2 (0.7)	2 (1.1)	-	0.54	0.8%

Abbreviation: CHD = Congenital Heart Disease.
a) Modified from Nowak et al.[14]
Data are presented as n (%).

Late pacemaker-related complications

During a median follow-up period of 12 years (IQR 6-19 years) 95 patients (35%) experienced a late pacemaker-related complication (Table 5). The most common observed complication was lead failure in 68 patients (25%). A large proportion of patients experienced an infection-related complication (pocket infection 4.4%, pacing system-related endocarditis 2.5%). The cumulative rate of late pacemaker-related complication was 8, 19, 28 and 41% at 1, 5, 10 and 15 years, respectively.

Table 5. Late pacemaker-related complications

Variable	Total population (n=274)
Duration of follow-up (years), median [IQR]	12 [6-19]
Total number of patients	95 (34.6)
• Late lead failure	68 (24.8)
• Pacemaker dysfunction/ early battery depletion	14 (5.1)
• Pacemaker migration	13 (4.7)
• Erosion	13 (4.7)
• Pocket infection	12 (4.4)
• Pacing system-related endocarditis	7 (2.5)
• Other	9 (3.3)

Data are presented as n (%), unless stated otherwise.

Predictors of late pacemaker-related complications

Five variables were evaluated as possible predictors for late pacemaker-related complications: young age at implantation (<18 years), complex CHD, epicardial leads, pacemaker implantation before 1997 and female gender. Only young age at implantation (<18 years) was an independent predictor of late pacemaker-related complications (adjusted hazard ratio 1.68, 95% confidence interval 1.07 to 2.63, p=0.023) (Table 6, Figure 2).

Long-term outcome

During follow-up, a large proportion of patients was hospitalized for heart failure (n=41, 15%) and ultimately four patients underwent heart transplantation (1.5%). Other clinical events were stroke (n=13, 4.7%), aborted sudden cardiac death (n=13, 4.7%) and endocarditis not related to the pacing system (n=8, 2.9%). Twenty-three patients (8.4%) died during follow-up at a mean age of 46 ± 17 years. The cumulative rate of survival was 99, 96 and 92% at 5, 10 and 15 years, respectively.

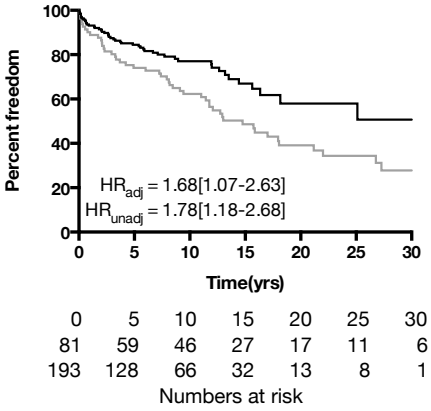
Table 6. Predictors of late pacemaker-related complications in CHD patients receiving pacemaker therapy

	Univariate analysis		Multivariate analysis	
Variable	Hazard ratio [95% CI]	p-value	Hazard ratio [95% CI]	p-value
Young age (<18 years) at implantation	1.78 [1.18-2.68]	0.006	1.68 [1.07-2.63]	0.023
Complex CHD	0.94 [0.62-1.43]	0.78	-	
Epicardial leads	1.43 [0.95-2.14]	0.09	0.84 [0.53-1.34]	0.52
Pacemaker implantation before 1997[a]	1.30 [0.80-2.12]	0.29	-	
Female gender	1.25 [0.83-1.86]	0.29	-	

Abbreviation: CHD = Congenital Heart Disease.

a) Compared to the period 1997-2009.

Figure 2. Pacemaker-related complication event-free survival in two age cohorts



Abbreviations: HRadj = Adjusted Hazard Ratio; HRunadj = Unadjusted Hazard Ratio; <18 years = <18 years of age at first pacemaker implantation; ≥18 years = ≥18 years of age at first pacemaker implantation.

DISCUSSION

Several anatomical and pathological issues render pacemaker implantation in patients with CHD more difficult compared to the general population.[5,6] Our study shows that the incidence of peri-procedural complications in patients with CHD seems higher than in the general population (10.6% versus 5.2%).[15] Furthermore, more than one-third of our cohort (34.6%) experienced a late pacemaker-related complication during a median follow-up of 12 years. The most common late complication was lead failure necessitating intervention.

CHD patients are prone to rhythm and conduction disease, which is not surprising considering the underlying congenital cardiac defect, longstanding hemodynamic alterations, and the consequences of surgical interventions. Our study demonstrates that the indication for pacemaker therapy is associated with the underlying congenital anatomical diagnosis and the associated cardiac surgical procedures (Table 2). Sinus node dysfunction is a common late sequela in patients who underwent atrial surgery, while acquired AV conduction disorders are more common in those with displacement of the AV node outside the triangle of Koch. Furthermore, certain operations are associated with a high risk of AV block due to proximity of the AV conduction tissue. Besides conduction disorders, drug-refractory atrial arrhythmias are important late complications especially in Fontan patients palliated with an atriopulmonary connection.[16]

Implantation of a pacemaker in a patient with CHD can be challenging. Our study population experienced more peri-procedural complications (10.6%) compared to the general population. Using data from a large-scale German prospective pacemaker registry (n=17.826, mean age 75 ± 10 years), the incidence of peri-procedural complications after first pacemaker implantation was 5.2% in a non-CHD population.[15] It is possible that the observed higher

peri-procedural complication rate in our cohort is related to the younger age of the study population and not to presence of congenital heart disease in itself. However, in our study population age was not associated with peri-procedural complication rates.

Although the transvenous approach is the first choice, this approach may not be suitable for those with small body size, an intra-cardiac shunt, anatomic constraints (i.e. Fontan), a right-sided mechanical valve or absence of venous access. One-third of our study population received epicardial leads. This is in agreement with other large single-center studies in adults with CHD (Table 7).[5,6] Interestingly, in our study the use of epicardial leads was not associated with a higher incidence of late pacemaker-related complications. This is in contrast to

Table 7. Comparison of studies of pacemaker therapy in adults with CHD

Variable	Walker 2004 (5)	McLeod 2010 (6)	Opić 2012
Study design	Single-center, retrospective	Single-center, retrospective	Multi-center, retrospective
Time period	NA	1967-2005 (38 y)	1972-2009 (37 y)
Number of patients	168	106	274
Male	47%	50%	55%
Complex CHD	40%	50%	36%
Indication for pacemaker			
• Acquired SSS	19%	40%	33%
• Acquired AV block	27%	33%	30%
• Surgical AV block	37%	15%	26%
• Drug-refractory atrial arrhythmias or drug-induced bradycardia	9%	12%	9%
• Surgical SSS	8%	0%	3%
Age at first implantation (years)[b]	28	37 ± 19	26 [15-39]
First implant <18 years	33%	16%	30%
Epicardial leads	37%	33%	33%
Peri-procedural complications during first implantation	NA	12%[a]	11%
Duration of follow-up (years)[b]	11 ± 9	12 ± 14	26 [15-39]
Late pacemaker-related complications	NA	NA	35%
Lead failure during follow-up	27%	24%[c]	25%
Pocket infection	3.6%	4%	4.4%
Erosion	1.1%	NA	4.7%
Pacing system-related endocarditis	0.6%	NA	2.5%
Mortality	2.4%	20%	8.4%

Abbreviation: NA = Not Available.

a) Excluding failed or difficult placement.

b) Data are presented as mean ± SD or median [IQR].

c) Unit of analysis: number of leads.

previous studies demonstrating a higher lead-failure rate in those with epicardial pacing systems.[6-10] Previous studies have shown that the use of steroid-eluting epicardial leads render the lead failure rate comparable to endocardial leads.[10,17]

Data with regard to late pacemaker-related complications in adults with CHD is scarce; most studies only report lead failures.[5,6] Our study demonstrates a high incidence of late pacemaker-related complications after primary device implantation. The overall cumulative 10-year rate of late pacemaker-related complications requiring intervention is 24%. Younger age at implantation (<18 years) was independently associated with a higher risk of late pacemaker-related complications. This might be explained by the rapid body growth, more active lifestyle and more frequent traumatic events rendering these patients more prone to lead failure, pacemaker migration and erosion. Finally, protracted pacemaker procedures in patients with complex anatomy may render these patients more prone to both acute and late pacing-system-related infections. Our data shows that patients with complex CHD are younger when receiving their first pacemaker compared to those with simple/moderate CHD. The combination of above mentioned factors may explain why younger patients experience more late pacemaker-related complications.

Study limitations

This study has limitations inherent to any retrospective study. The most important limitation is the potential for missing complications, which were not described in medical records. However, if we have underestimated the complication rate, this only strengthens our conclusion that the CHD population is at higher risk of peri-procedural pacemaker complications compared to the general population. Furthermore, the comparison to other CHD studies may be hampered by differences in definitions of pacemaker-related complications (Table 7).

The multi-center design limited our ability to collect information on certain risk factors, including pacing and sensing thresholds and lead impedances, the precise method of transvenous vascular access, or the precise types of fixation methods and materials used. The patient sample is drawn from an adult-based practice and hence skewed towards this age group. Therefore, the patients who died or were lost to follow-up before reaching adulthood are not addressed in this study and this could introduce bias. Finally, although our study is the largest multicenter study in adults with CHD, some of our analyses may be underpowered. Therefore, the conclusions of the present study must be drawn with caution.

CONCLUSION

In this large multi-center study of adult patients with CHD receiving pacemaker therapy, we found a high incidence of peri-procedural and late pacemaker-related complications. More than one third of patients will experience a late pacemaker-related complication during long-term follow-up. The most common late complication was lead failure. Age proved to be an independent predictor of late pacemaker-related complications, with a 68% increased relative risk in CHD patients younger than 18 year. Our data stress that meticulous follow-up is mandatory in this population to identify potential pacemaker complications, especially in the younger and active CHD population.

REFERENCES

1. Warnes CA. The adult with congenital heart disease: born to be bad? J Am Coll Cardiol 2005; 46: 1-8.
2. Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. N Engl J Med 2000; 342:256-63.
3. Yap SC, Harris L, Chauhan VS, Oechslin EN, Silversides CK. Identifying high risk in adults with congenital heart disease and atrial arrhythmias. Am J Cardiol 2011; 108:723-8.
4. Verheugt CL, Uiterwaal CS, van der Velde ET, et al. Mortality in adult congenital heart disease. Eur Heart J 2010; 31:1220-9.
5. Walker F, Siu SC, Woods S, Cameron DA, Webb GD, Harris L. Long-term outcomes of cardiac pacing in adults with congenital heart disease. J Am Coll Cardiol 2004; 43:1894-901.
6. McLeod CJ, Attenhofer Jost CH, Warnes CA, et al. Epicardial versus endocardial permanent pacing in adults with congenital heart disease. J Interv Card Electrophysiol 2010; 28:235-43.
7. Sachweh JS, Vazquez-Jimenez JF, Schondube FA, et al. Twenty years experience with pediatric pacing: epicardial and transvenous stimulation. Eur J Cardiothorac Surg 2000; 17:455-61.
8. Fortescue EB, Berul CI, Cecchin F, Walsh EP, Triedman JK, Alexander ME. Patient, procedural, and hardware factors associated with pacemaker lead failures in pediatrics and congenital heart disease. Heart Rhythm 2004; 1:150-9.
9. Noiseux N, Khairy P, Fournier A, Vobecky SJ. Thirty years of experience with epicardial pacing in children. Cardiol Young 2004; 14:512-9.
10. Silvetti MS, Drago F, Grutter G, De Santis A, Di Ciommo V, Rava L. Twenty years of paediatric cardiac pacing: 515 pacemakers and 480 leads implanted in 292 patients. Europace 2006; 8: 530-6.
11. van der Velde ET, Vriend JW, Mannens MM, Uiterwaal CS, Brand R, Mulder BJ. CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: rationale, design, and first results. Eur J Epidemiol 2005; 20:549-57.
12. Yap SC, Roos-Hesselink JW, Hoendermis ES, et al. Outcome of implantable cardioverter defibrillators in adults with congenital heart disease: a multi-centre study. Eur Heart J 2007; 15: 1854-61.
13. Coats AJS and Shewan LG. Statement on Authorship and Publishing Ethics in the International Journal of Cardiology. Int J Cardiol 2011; 153: 239-40.
14. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008; 52:e143-263.
15. Nowak B, Misselwitz B, Erdogan A, et al. Do gender differences exist in pacemaker implantation?--results of an obligatory external quality control program. Europace 2010; 12:210-5.
16. Stephenson EA, Lu M, Berul CI, et al. Arrhythmias in a contemporary fontan cohort: prevalence and clinical associations in a multicenter cross-sectional study. J Am Coll Cardiol 2010; 56:890-6.
17. Fortescue EB, Berul CI, Cecchin F, Walsh EP, Triedman JK, Alexander ME. Comparison of modern steroid-eluting epicardial and thin transvenous pacemaker leads in pediatric and congenital heart disease patients. J Interv Card Electrophysiol 2005; 14:27-36.

Chapter 4.3

Atrial-based pacing has no benefit over ventricular pacing in preventing atrial arrhythmias in adults with congenital heart disease.

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ABSTRACT

Aims: To determine whether atrial-based pacing prevents atrial arrhythmias in adults with congenital heart disease (CHD) compared with ventricular pacing.

Methods and Results: All adult CHD patients from 4 participating centers with a permanent pacemaker were identified. Patients with permanent atrial arrhythmias at pacemaker implantation and patients who received a pacemaker for treatment of drug-refractory atrial arrhythmias were excluded. The final study population consisted of 211 patients (52% male, 36% complex CHD) who received a first pacemaker for sick sinus dysfunction (n=82) or atrioventricular block (n=129) at a median age of 24 years (interquartile range [IQR], 12 to 34). A history of atrial arrhythmias at implantation was present in 49 patients (23%). Atrial-based pacing was the initial pacing mode in 139 patients (66%) while the others (34%) received ventricular pacing. During a median follow-up of 13 years (IQR, 7 to 21), 90 patients (43%) developed an atrial arrhythmia. Multivariate analysis demonstrated no significant effect of atrial-based pacing on subsequent atrial arrhythmias (hazard ratio [HR], 1.53; 95% confidence interval [CI], 0.91 to 2.56; P=0.1). Independent predictors of atrial arrhythmia were history of atrial arrhythmias (HR, 5.55; 95% CI, 3.47 to 8.89; P<0.0001), older age (≥18 years) at pacemaker implantation (HR, 2.29; 95% CI, 1.29 to 4.04; P=0.005) and complex CHD (HR, 1.57; 95% CI, 1.01 to 2.45; P=0.04).

Conclusion: In contrast to the general population, atrial-based pacing was not associated with a lower incidence of atrial arrhythmia in adults with CHD.

INTRODUCTION

Atrial arrhythmias play an important role in the management of adults with congenital heart disease (CHD).[1] The prevalence of atrial arrhythmias is approximately 15% in the adult CHD population, and the risk of developing atrial arrhythmias increases steadily with age.[2] Atrial arrhythmias contribute significantly to morbidity and mortality in this population.[2-4] Therefore, strategies to reduce the burden of atrial arrhythmias in this population are highly welcome.

An interesting subgroup is the adult CHD population with bradycardia indications for permanent pacemaker implantation. In the general population, several prospective randomized trials have clearly demonstrated that atrial-based pacing ("physiologic pacing") reduces the incidence of atrial fibrillation compared with ventricular pacing.[5-10] This is not surprising, as loss of AV synchrony due to ventricular pacing is associated with increased natriuretic peptide levels, sympathetic nervous activation and atrial pressures; all factors associated with the development of atrial fibrillation.[11,12] Whether atrial-based pacing is also beneficial in the adult CHD population is not clear.[13] The aim of the present multi-center study is to investigate whether atrial-based pacing prevents atrial arrhythmias in adults with CHD.

METHODS

For the present retrospective observational study, all adults with CHD and pacemaker implantation were identified using the nationwide CONgenital CORvita (CONCOR) registry in the Netherlands, and a Belgian tertiary care adult CHD database.[14] The central medical ethic committee in the Netherlands and the local Belgian Ethics Board approved the protocol. This study complies with the declaration of Helsinki.

Data were collected from medical records and pacemaker databases. Baseline data prior to pacemaker implantation were registered from the patient records including gender, congenital anatomic diagnosis, surgical procedures and history of atrial arrhythmias. The complexity of the CHD diagnosis was defined as simple, moderate or complex according to the classification adopted at the American Heart Association Task Force on Adults with CHD.[15] Detailed information concerning pacemaker implantation was recorded and included age at implantation, indication for pacemaker implantation, method of implant (endocardial/epicardial), pacing mode (AAI/VVI/DDD/VDD) and the occurrence of sustained atrial arrhythmias during follow-up. Atrial-based pacing, which includes AAI, DDD and VDD, was compared to ventricular pacing (VVI). The end-point was the occurrence of sustained atrial arrhythmias (i.e., intra-atrial reentrant tachycardia, atrial tachycardia, atrial fibrillation) documented by ECG, Holter or stored logs.

Statistical analysis

Continuous data are presented as mean ± SD or median with interquartile ranges (IQR) as appropriate. Categorical variables are represented by frequencies and percentages. Comparison of continuous variables between groups was made by unpaired Student's t-tests. In the case of a skewed distribution, the Mann-Whitney U test was used. When comparing frequencies, the chi-square test or Fisher exact test was used, where appropriate.

Cumulative freedom from atrial arrhythmias was constructed with the use of the Kaplan-Meier method and groups were compared by log-rank statistics. To determine predictors of sustained atrial arrhythmias during follow-up, univariate and multivariate Cox proportional hazard models were constructed after proportional hazard assumptions were verified. The patient was set as unit of analysis and time to first atrial arrhythmia was determined. Candidate variables included: atrial-based pacing, older age (≥ 18 years) at pacemaker implantation, complex CHD, female gender, history of atrial arrhythmia, endocardial pacing system, and sick sinus syndrome. Two-tailed probability values of <0.05 were considered statistically significant. Statistical analysis was performed using the statistical package R (64 bit) for Mac, version 2.14.2.

RESULTS

Patient characteristics

Crosscheck with local pacemaker registries of the four participating tertiary centers revealed a total of 274 patients. After exclusion of 63 patients with permanent or drug-refractory atrial arrhythmias at implantation, 211 patients comprised the final study population. The baseline characteristics of the included patients are summarized in Table 1. Patients with complex CHD comprised 37% of the population, and were mainly patients with transposition of the great arteries and single ventricle physiology. The majority of patients (66%) received atrial-based pacing at initial implantation. There were important baseline differences between patients with atrial-based pacing and those with ventricular pacing. Patients with ventricular pacing more often had the first pacemaker implantation at pediatric/adolescent age (64% versus 22%, $p<0.001$) and in an older era (before 1994) (75% versus 21%, $p<0.001$). Furthermore, an epicardial pacing system was more often used in patients with ventricular pacing (49% versus 25%, $p<0.001$). There was no difference in the complexity of the underlying CHD or the prevalence of a history of atrial arrhythmias between the two groups.

Table 1. Baseline characteristics at first pacemaker implantation

Variable	Total (n=211)	Atrial-based pacing (n=139)	Ventricular pacing (n=72)	p-value
Age at first implantation (years)[a]	24 [12-34]	26 [19-39]	12 [7-26]	<0.001
First implant <18 years	77 (36%)	31 (22%)	46 (64%)	<0.001
Male gender	110 (52%)	72 (52%)	38 (53%)	0.9
Complex CHD	79 (37%)	52 (37%)	27 (38%)	1.0
History of atrial arrhythmia	49 (23%)	36 (26%)	13 (18%)	0.2
Pacemaker implantation before 1994	83 (39%)	29 (21%)	54 (75%)	<0.001
Indication for pacemaker				
• Acquired sick sinus syndrome	78 (37%)	45 (32%)	33 (46%)	0.05
• Acquired atrioventricular block	69 (33%)	51 (37%)	18 (25%)	0.09
• Surgical atrioventricular block	60 (28%)	41 (29%)	19 (26%)	0.6
• Surgical sick sinus syndrome	4 (2%)	2 (1%)	2 (3%)	0.6
Pacing mode				
• AAI(R)	14 (7%)	14 (10%)	-	<0.001
• DDD(R)	120 (57%)	120 (86%)	-	
• VDD(R)	5 (2%)	5 (4%)	-	
• VVI(R)	72 (34%)	-	72 (100%)	
Implantation technique				
• Endocardial leads	141 (67%)	104 (75%)	37 (51%)	<0.001
• Epicardial leads	70 (33%)	35 (25%)	35 (49%)	

Abbreviation: CHD = Congenital Heart Disease.
a) Expressed as median with interquartile ranges.

Atrial arrhythmias during follow-up

During a median follow-up of 13 years, 90 patients (43%) developed atrial arrhythmias. Of these 90 patients, 58 patients (64%) had intra-atrial reentrant tachycardia/atrial tachycardia and 32 patients (36%) had atrial fibrillation as the first presenting atrial arrhythmia. The cumulative rate of atrial arrhythmias was 21%, 29%, and 39% at 5, 10 and 15 years, respectively. Univariate predictors of atrial arrhythmias are depicted in Table 2. Atrial-based pacing, history of atrial arrhythmias, older age (≥18 years) at pacemaker implantation, sick sinus syndrome, complex CHD and endocardial pacing system were identified as significant univariate predictors of atrial arrhythmias. Multivariate analysis, including all significant univariate predictors, demonstrated that only a history of atrial arrhythmias, older age (≥18 years) at pacemaker implantation, and complex CHD were independent predictors of atrial arrhythmias. Atrial-based pacing was not an independent predictor of sustained atrial arrhythmias during follow-up (HR, 1.53; 95% CI, 0.91 to 2.56; P=0.1).

Table 2. Predictors of atrial arrhythmia in CHD patients receiving pacemaker therapy

	Univariate analysis		Multivariate analysis	
Variable	**Hazard ratio [95% CI]**	**p-value**	**Hazard ratio [95% CI]**	**p-value**
History of atrial arrhythmia	6.90 [4.40-10.8]	<0.0001	5.55 [3.47-8.89]	<0.0001
Older age (≥18 years) at implant	2.74 [1.71-4.40]	<0.0001	2.29 [1.29-4.04]	0.005
Sick sinus syndrome	1.99 [1.32-3.01]	0.001	1.50 [0.96-2.36]	0.08
Atrial-based pacing	1.89 [1.19-3.01]	0.007	1.53 [0.91-2.56]	0.1
Complex CHD	1.67 [1.10-2.54]	0.02	1.57 [1.01-2.45]	0.04
Endocardial pacemaker	1.66 [1.06-2.62]	0.02	1.10 [0.65-1.86]	0.7
Female gender	0.71 [0.47-1.08]	0.1		

Abbreviation: CHD = Congenital Heart Disease.

Subgroup analysis

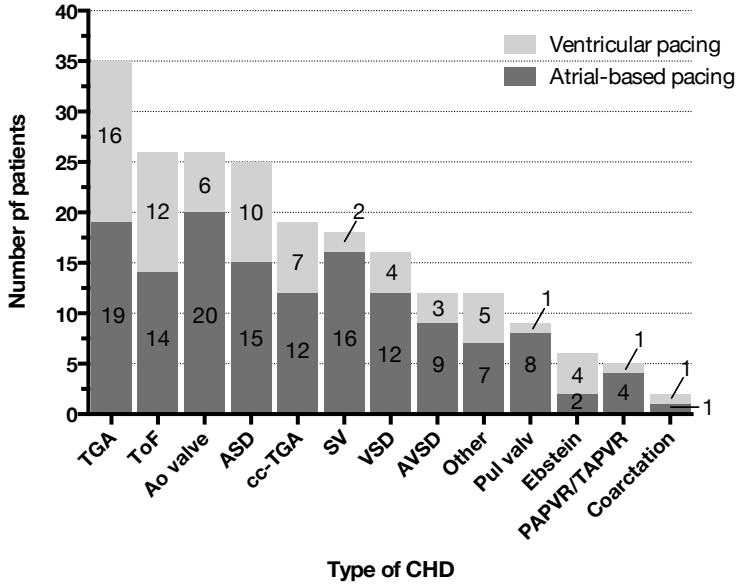
Subgroup analysis demonstrates that patients with single ventricle physiology had a high prevalence of previous atrial arrhythmias (50%) at pacemaker implantation (Table 3). Interestingly, no patient with aortic valve disease was known with a history of atrial arrhythmia prior to implantation. During follow-up, patients with a single ventricle physiology were more prone to develop atrial arrhythmias compared to the other groups (Figure 3, Table 3).

Table 3. Overview of pacemaker details and atrial arrhythmias in selected CHD groups

Variable	**Complete TGA[a] (n=35)**	**Tetralogy of Fallot (n=26)**	**Aortic valve disease (n=26)**	**ASD secundum (n=25)**	**Single Ventricle physiology (n=18)**	**p-value**
Clinical and pacemaker data:						
• Age at first implantation (years)[b]	18 [8-25]	28 [15-40]	34 [18-51]	27 [15-45]	24 [13-29]	
• Male gender	69%	62%	73%	36%	44%	0.03
• First implant <18 years	49%	39%	23%	32%	33%	0.33
• History of atrial arrhythmias	29%	23%	0%	28%	50%	0.004
• Atrial-based pacing	54%	54%	77%	60%	88%	0.05
• Epicardial leads	46%	12%	15%	28%	72%	0.07
Follow-up data:						
• 5-year rate of atrial arrhythmias	20%	25%	0%	21%	51%	
• 10-year rate of atrial arrhythmias	32%	30%	11%	27%	60%	

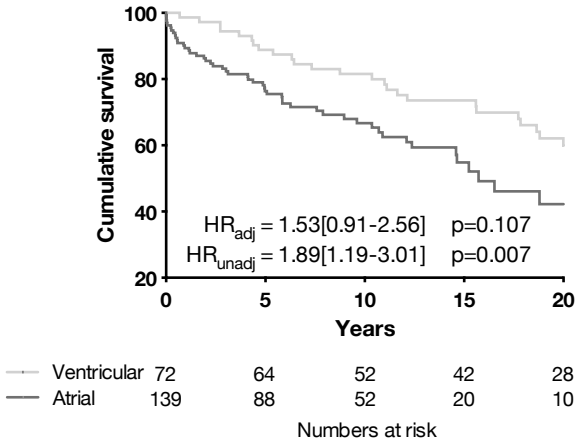
Abbreviations: TGA = Transposition of the Great Arteries; ASD = Atrial Septal Defect.
a) Atrial repair.
b) Expressed as median with interquartile range.

Figure 1: CHD diagnosis stratified by pacing mode at initial implantation



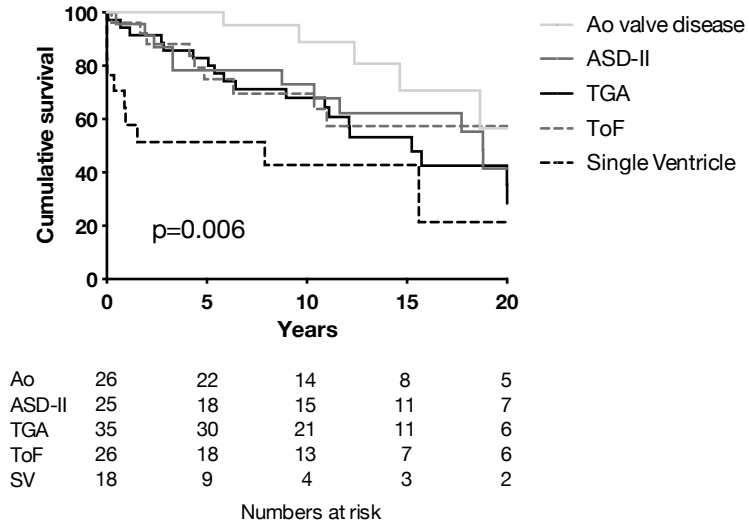
Abbreviations: Ao valv = Aortic valve disease; ASD = Atrial Septal Defect; AVSD = Atrioventricular Septal Defect; cc-TGA = Congenital Corrected Transposition of the Great Arteries; PAPVR/TAPVR = Partial Anomalous Pulmonary Venous Return / Total Anomalous Pulmonary Venous Return; Pul valv = Pulmonary valve disease; SV = Single Ventricle physiology; TGA = Transposition of the Great Arteries; TOF = Tetralogy of Fallot; VSD = Ventricular Septal Defect.

Figure 2. Freedom from atrial arrhythmias for ventricular pacing and atrial-based pacing in patients with CHD



Abbreviations: HRadj = Adjusted Hazard Ratio; HRunadj = Unadjusted Hazard Ratio; Ventricular = Ventricular pacing; Atrial = Atrial-based pacing.

Figure 3. Freedom from atrial arrhythmias in selected CHD groups after pacemaker implantation



Abbreviations: Ao valve disease = Aortic valve disease, ASD-II = Secundum Atrial Septal Defect, ToF = Tetralogy of Fallot, TGA = Transposition of the Great Arteries; SV = Single Ventricle physiology.

Table 4. Peri-procedural complication rates for atrial-based and ventricular pacing

Complication	Total (n=211)	Atrial-based (n=139)	Ventricular (n=72)	p-value
Total number of patients	22 (10.4%)	11 (7.9%)	11 (15.3%)	0.1
• Lead failure	9 (4.3%)	5 (3.6%)	4 (5.6%)	0.5
• Bleeding	3 (1.4%)	3 (2.2%)	-	0.5
• Pneumothorax	2 (0.9%)	2 (1.4%)	-	0.5
• Pocket infection	4 (1.9%)	-	4 (5.6%)	0.01
• Ventricular arrhythmias	2 (0.9%)	-	2 (2.8%)	0.1
• Other	2 (0.9%)	1 (0.7%)	1 (1.4%)	1.0

Peri-procedural complications

Overall, the peri-procedural complication rate is comparable between patients with atrial-based pacing and those with ventricular pacing (Table 4). When looking at the different complications, there was a higher incidence of pocket infection in those with ventricular pacing when compared to those with atrial-based pacing (5.6% versus 0%, P=0.01).

DISCUSSION

In the general population without CHD, atrial-based pacing is beneficial in reducing the incidence of atrial fibrillation compared with ventricular pacing.[5-10] The present multi-center study, however, demonstrates that the beneficial effects of atrial-based pacing cannot be extrapolated to the adult CHD population. After correction for important confounders, the incidence of atrial arrhythmias was not different between atrial-based pacing and ventricular pacing. These findings suggest that the mode of pacing does not play an important role in adults with CHD for the reduction of atrial arrhythmias.

Patients with CHD are prone to rhythm and conduction disease, which is not surprising considering the underlying congenital cardiac defect, abnormal anatomy, longstanding hemodynamic alterations, and the consequences of surgical interventions. Atrial arrhythmias are a burden to the adult CHD population and are associated with increased morbidity and mortality.[2-4] These arrhythmias may be difficult to treat pharmacologically and may require (a combination of) catheter ablation or atrial antitachycardia pacing.[16,17] The purpose of the present study was to explore whether the pacing mode may play a role in the prevention of atrial arrhythmias in CHD patients who had a bradycardia indication for permanent pacing.

Loss of AV synchrony due to ventricular pacing may contribute to increased atrial arrhythmogenesis. A meta-analysis by Healey et al., summarizing the data of 5 randomized trials in patients without CHD, demonstrated that atrial-based pacing reduced the incidence of atrial fibrillation (HR, 0.80; 95% CI, 0.72 to 0.89; P<0.001) and stroke (HR, 0.81; 95% CI, 0.67 to 0.99, P=0.035) compared with ventricular pacing.5

Interestingly, our study cohort showed no beneficial effect of atrial-based pacing in preventing atrial arrhythmias. Unexpectedly, we found that atrial-based pacing was associated with an increased risk of atrial arrhythmias in the univariate analysis (HR, 1.89; 95% CI, 1.19 to 3.00, P=0.006). This can be explained by the older age at pacemaker implantation of the cohort who received atrial-based pacing. In the multivariate analysis, the pacing mode was not a predictor of atrial arrhythmias. One previous single-center study demonstrated that atrial-based pacing did not appear to be protective against subsequent atrial arrhythmias.[13] The reason for this lack of beneficial effect of atrial-based pacing may be inherent to the increased vulnerability of the adult CHD population for atrial arrhythmias due to increased natriuretic peptides, altered loading conditions and presence of surgical atrial scar.[18,19] The loss of AV synchrony induced by ventricular pacing may add little incremental arrhythmogenic risk in such patients, and therefore atrial-based pacing may not be as beneficial as in the general population. This is in agreement with results from the Mode Selecton Trial (MOST) in Sinus-Node Dysfunction, where a significant reduction in atrial fibrillation with DDDR pacing when compared with ventricular pacing was observed solely in the subgroup of patients without a history of atrial fibrillation.[9] These results support that pacing mode

selection is less important with respect to later development of atrial fibrillation in patients who already are at high risk of developing atrial fibrillation.

Another explanation for the lack of beneficial effect of atrial-based pacing may be related to the type of atrial arrhythmias in the CHD population. In the present study, the majority of patients with atrial arrhythmias during follow-up experienced intra-atrial reentry tachycardia. Approximately one-third of patients had atrial fibrillation. This ratio is in accordance with a previous study in adult CHD patients who underwent electrical cardioversion.[20] Atrial-based pacing may be less beneficial for the prevention of intra-atrial reentrant tachycardia than atrial fibrillation.

With regard to predictors for future arrhythmias after pacemaker implantation, the group of Harris identified a history of atrial arrhythmias as an independent predictor.[13] In addition, we identified older age (≥18 years) at pacemaker implantation and complex CHD as independent predictors of atrial arrhythmias. In particular, patients with single ventricle physiology, mostly Fontan patients with an atriopulmonary connection, are at increased risk of developing atrial arrhythmias later in life (Figure 3). Previous electrophysiological mapping studies have shown that Fontan patients undergo progressive adverse atrial mechano-electrical remodeling with increasing age, rendering them more prone to atrial arrhythmias.[19]

It is important to stress that the primary aim of the current study was to investigate the role of pacing mode on the incidence of atrial arrhythmias. This study does not evaluate the potential beneficial effects of atrial-based pacing, by maintaining AV synchrony, on hemodynamic parameters, risk of heart failure and avoidance of symptoms related to pacemaker syndrome.

The current study demonstrated a relative high proportion of patients who received ventricular pacing as the initial pacing mode (34%). Implantation of the pacemaker in an older era (before 1994) or at pediatric/adolescent age may explain this phenomenon. The beneficial effects of dual-chamber pacing became more appreciated from the early 1990's,7,8 However, in the pediatric population there is still some debate whether dual-chamber pacing is superior to ventricular pacing.[21]

Finally, the rate of peri-procedural complications in the general population without CHD is nearly twice as high with atrial-based pacing compared with ventricular pacing (6.2% versus 3.2%), primarily due to a significant increase in the rate of lead failure and infection.5 Our study cohort did not confirm this difference in overall peri-procedural complication rate between patients with atrial-based pacing or ventricular pacing. However, CHD patients with ventricular pacing did demonstrate more pocket infections (5.6% versus 0%, P=0.01).

Study Limitations

This study has limitations inherent to any retrospective study. The major limitation of the present study is the observational study design, which renders the data subject to selec-

tion bias. We tried to overcome this limitation by using a multivariate analysis including all potential confounders. Clearly, this approach cannot replace a randomized controlled trial design. Furthermore, despite its relative large size due to its multicenter nature, this study may be underpowered to demonstrate a potential benefit of atrial-based pacing. In addition, the heterogeneity of pacemaker settings limited our ability to draw conclusions with regard to desired pacemaker settings. Due to the retrospective study design, we had incomplete echocardiographic data limiting our ability to correct for potential confounders such as atrial dilatation or significant atrioventricular regurgitation. Finally, the patient sample is drawn from an adult-based practice and hence skewed towards this age group. Therefore, the patients who died or were lost to follow-up before reaching adulthood are not addressed in this study. Considering above mentioned limitations, the conclusions of the present study must be drawn with caution.

CONCLUSION

Compared with ventricular pacing, the use of atrial-based pacing was not associated with a lower incidence of atrial arrhythmias in adults with CHD. There is a high vulnerability for developing atrial arrhythmias, especially intra-atrial reentrant tachycardia, which is largely determined by older age, underlying atrial substrate, and prior atrial arrhythmias. Atrial-based pacing may be less beneficial for the prevention of intra-atrial reentrant tachycardia than atrial fibrillation. In order to develop effective therapies for preventing atrial arrhythmias, future research should focus on understanding the pathophysiology of atrial arrhythmias in adults with CHD.

REFERENCES

1. Walsh EP, Cecchin F. Arrhythmias in adult patients with congenital heart disease. Circulation 2007; 115:534-45.
2. Bouchardy J, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Bottega N et al. Atrial arrhythmias in adults with congenital heart disease. Circulation 2009; 120:1679-86.
3. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, van Dijk AP et al. Mortality in adult congenital heart disease. Eur Heart J 2010; 31:1220-9.
4. Yap SC, Harris L, Chauhan VS, Oechslin EN, Silversides CK. Identifying high risk in adults with congenital heart disease and atrial arrhythmias. Am J Cardiol 2011; 108:723-8.
5. Healey JS, Toff WD, Lamas GA, Andersen HR, Thorpe KE, Ellenbogen KA et al. Cardiovascular outcomes with atrial-based pacing compared with ventricular pacing: meta-analysis of randomized trials, using individual patient data. Circulation 2006; 114:11-7.
6. Connolly SJ, Kerr CR, Gent M, Roberts RS, Yusuf S, Gillis AM et al. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. N Engl J Med 2000; 342:1385-91.
7. Andersen HR, Thuesen L, Bagger JP, Vesterlund T, Thomsen PE. Prospective randomised trial of atrial versus ventricular pacing in sick-sinus syndrome. Lancet 1994; 344:1523-8.
8. Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T et al. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet 1997; 350:1210-6.
9. Lamas GA, Lee KL, Sweeney MO, Silverman R, Leon A, Yee R et al. Mode Selection Trial in Sinus-Node Dysfunction. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. N Engl J Med 2002; 346:1854-62.
10. Toff WD, Camm AJ, Skehan JD. Single-chamber versus dual-chamber pacing for high-grade atrioventricular block. N Engl J Med 2005; 353:145-55.
11. Horie H, Tsutamoto T, Ishimoto N, Minai K, Yokohama H, Nozawa M et al. Plasma brain natriuretic peptide as a biochemical marker for atrioventricular sequence in patients with pacemakers. Pacing Clin Electrophysiol 1999; 22:282-90.
12. Taylor JA, Morillo CA, Eckberg DL, Ellenbogen KA. Higher sympathetic nerve activity during ventricular (VVI) than during dual-chamber (DDD) pacing. J Am Coll Cardiol 1996; 28:1753-8.
13. Walker F, Siu SC, Woods S, Cameron DA, Webb GD, Harris L. Long-term outcomes of cardiac pacing in adults with congenital heart disease. J Am Coll Cardiol 2004; 43:1894-901.
14. van der Velde ET, Vriend JW, Mannens MM, Uiterwaal CS, Brand R, Mulder BJ. CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: rationale, design, and first results. Eur J Epidemiol 2005; 20:549-57.
15. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008; 52: e143-263.

16. Stephenson EA, Casavant D, Tuzi J, Alexander ME, Law I, Serwer G et al. Efficacy of atrial antitachycardia pacing using the Medtronic AT500 pacemaker in patients with congenital heart disease. Am J Cardiol 2003; 92:871-6.
17. Yap SC, Harris L, Silversides CK, Downar E, Chauhan VS. Outcome of intra-atrial re-entrant tachycardia catheter ablation in adults with congenital heart disease: negative impact of age and complex atrial surgery. J Am Coll Cardiol 2010; 56:1589-96.
18. Bolger AP, Sharma R, Li W, Leenarts M, Kalra PR, Kemp M et al. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. Circulation 2002; 106: 92-9.
19. Yap SC, Harris L, Downar E, Nanthakumar K, Silversides CK, Chauhan VS. Evolving electroanatomic substrate and intra-atrial reentrant tachycardia late after fontan surgery. J Cardiovasc Electrophysiol 2011; 23:339-45.
20. Kirsh JA, Walsh EP, Triedman JK. Prevalence of and risk factors for atrial fibrillation and intra-atrial reentrant tachycardia among patients with congenital heart disease. Am J Cardiol 2002;90: 338-40.
21. Horenstein MS, Karpawich PP. Pacemaker syndrome in the young: do children need dual chamber as the initial pacing mode? Pacing Clin Electrophysiol 2004;27:600-5.

Part 5
Summary & Discussion

Chapter 5.1

Summary

SUMMARY

In this thesis the impact of living with congenital heart disease (ConHD) at adulthood is described. Three different aspects of living with a ConHD were studied: impact on biographical characteristics, on psychological characteristics and on medical characteristics. **Chapter 1.1** provided a small general introduction, and described the five most common forms of ConHD namely: the Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), Pulmonary Stenosis (PS), Tetralogy of Fallot (ToF) and Transposition of the Great Arteries (TGA). Since ConHD is viewed as a chronic disease nowadays, the focus of many studies has shifted from survival to quality of life.

Impact on biographical characteristics

Biographical characteristics encompass different properties of every day life of the patient. In this thesis biographical characteristics were assessed by a semi-structured interview, including - but not limited to - living conditions, marital status, offspring, employment, income and leisure time activities. In addition, questionnaires were administered to assess quality of life, emotional functioning and social functioning.

Chapter 2.1 described the biographical characteristics of the cohort that was operated at the Erasmus Medical Center between 1968 (the start of the open heart surgery in Rotterdam) and 1980. During the third follow-up of this cohort in 2011, participants were between the age of 30 and 55 years. This cohort has already been examined in 1990 (first follow-up) and 2001 (second follow-up) at the Erasmus Medical Center. A comparison over time could be made since this was the third follow-up of the same patients. Where possible, biographical characteristics were compared with normative data from the Dutch general population.

The main findings in this chapter showed that patients with ConHD less often lived independently, were married less often, had fewer children, had a lower occupational level and had a lower income in comparison with the general Dutch population. Positive findings were that patients with a congenital heart defect showed a better quality of life and emotional functioning in comparison with the general population. Patients with a complex heart defect (ToF and TGA) reported a lack of strength more frequently, and indicated that they felt at a disadvantage with respect to patients with a milder heart defect.

Compared with 10 years ago, there was an improvement in biographical aspects in this cohort. Nowadays, patients lived more independently and were married more often compared to a decade ago. Despite an overall lower income compared with Dutch normative data, patients with ConHD obtained a higher income over time. The educational level of the cohort also improved over the last ten years. These results show that the biographical aspects improved over time, but they are still less favorable compared with the general Dutch population.

Chapter 2.2 compared the biographical aspects of two different cohorts, which were operated in different time areas, 10 years apart. This study focused on patients with a complex congenital heart defect, namely ToF and TGA. The most recent cohort was operated between 1980 and 1990 and was now between 20 and 37 years old. The historical cohort was operated between 1968 and 1980 (for this cohort the data from 2001 was used). To ensure that both populations were comparable only the patients with ToF and TGA from the historical cohort, who were operated with the same surgical techniques and had a comparable age-range, were included. In both cohorts the same questionnaires were used. Where possible, results were compared with the general Dutch population.

Despite a favorable quality of life in the most recent cohort, differences were found between the recent study population and the general Dutch population. Biographical outcomes such as relationships, children, occupational level and income were less favorable compared with the general Dutch population and did not improve over time. Compared with the historical cohort, the recent cohort showed a better educational level. However, the number of patients with learning problems in the recent cohort was still high.

In conclusion we did not find clear improvements on biographical and psychosocial aspects over time, despite improvements in medical and surgical techniques over time. Particularly the percentage of patients in the recent cohort that had followed special education was still high and the income level was lower compared with normative data.

Impact of psychological aspects

Three chapters are dedicated to investigate the impact on psychological aspects. The cohort, which was used for these three studies, was operated between 1968 and 1980. During the third follow-up in 2011, all patients were between 30 and 55 years old (first follow-up in 1990, second follow-up in 2001).

In **chapter 3.1** we examined the longitudinal development of psychopathology and subjective health status in patients with ConHD. Psychopathological problems were measured with the Adult Self Report (ASR), which was filled in by the patient, and with the Adult Behavioral Checklist (ABCL), which was filled in by a family member, partner or close friend (proxy). The following domains were investigated: anxiety/depression, withdrawn behavior, somatic complaints, thought problems, attention problems, rule breaking behavior, aggressive behavior and intrusive behavior. A score was considered psychopathological when the total score (sum of all answers on each problem item) was above the cutoff point for psychopathology; in other words if the score fell in the deviant psychopathological range. Since comparable instruments were used for assessment of the cohort during the first and second follow-up, it was possible to investigate longitudinal pathways of psychopathology over a timespan of 30 years.

We found that the percentage of patients that scored within the psychopathological range decreased over time. At the third follow-up, overall mean levels of psychopathology (mean average problem scores on the different sub-domains), were comparable with, or even better compared with normative data. Subjective health status was also more favorable in comparison with normative data. No different results were found between different congenital heart defects.

Predictors for the changes in psychopathology were:

1) The patients' perception of their scar. A positive subjective evaluation of the surgical scar was the only predictor for a decrease in self-reported psychopathology over time.
2) Patients who had poor to moderate surgical results (as judged by the physician) showed an increase over the last decade in total problem and internalizing scores. This was, however, reported by proxy's (family, partner or friends of the patient) only.
3) Fewer hospitalizations over time was a predictor for less psychopathology according to the reports of proxy's regarding the patients.

Chapter 3.2 focused on sexuality, a neglected area of research in patients with ConHD. Both males and females completed a generic questionnaire on sexual functioning. Where possible, results were compared with normative data. In addition, a disease specific questionnaire was developed for this study to investigate sexual problems, which were possibly related to having a ConHD. This questionnaire was filled in by both males and females.

This study shows that patients with ConHD report a broad range of sexual problems and have a higher level of sexual dysfunction compared with normative data. Patients with ConHD start sexual activities at a later age compared to the general population. Especially females report many problems, including less sexual desire, less arousal and more pain during intercourse compared to the general population. They also reported concerns about a possible negative influence of pregnancy on their own heart condition and physical health. Male patients with ConHD showed levels of erectile dysfunction which were twice as high compared with the general population, also orgasmic function was impaired. They were less often satisfied with intercourse compared to the general population. Overall, we did not observe any differences in sexual problems between different cardiac diagnostic groups. However, patients with moderate/complex forms of ConHD reported to feel more limited in starting a family because of low energy levels or a lower life expectancy. Many patients indicated they were not properly informed about sexuality during their adolescence.

This study shows that counseling on sexual functioning in patients with ConHD deserves more attention.

Chapter 3.3 focused on the impact of ConHD on practising sports. Patients filled in questionnaires on what type of sports they were engaged in, and how many hours a week they spent on sports. Also a questionnaire on subjective physical functioning and self-perceived quality of life were administered. In addition, data from exercise tests were used. Results were

compared with Dutch normative data where possible. Measurements were performed both in 2001 and 2011.

Patients with moderate/complex ConHD were less often engaged in sports compared with the general Dutch population, and the patients that were engaged in sports practised fewer hours of sports per week. Many patients that were engaged in sports practised sports with a high dynamic component like cycling or rowing. Practising sports led to an increased exercise capacity, but did not influence subjective physical functioning nor subjectively perceived quality of life.

Impact on medical characteristics

To investigate the impact of medical characteristics in patients with ConHD, this part of the thesis focused on implantable cardioverter defibrillators and pacemakers. Many patients with ConHD are eventually dependent on pacemaker therapy.

The leading cause of mortality in adult patients with ConHD is sudden cardiac death. An adult patient with ConHD has a 25-100 fold increased risk to die as a result of sudden cardiac death. Implantable cardioverter defibrillators (ICDs) are being used as therapy for patients that are at high risk for developing, or have survived a life- threatening cardiac arrhythmia. However, the indication for primary ICD therapy in patients with ConHD is still a matter of debate because of the high incidence of inappropriate shocks. In **chapter 4.1** we investigated the impact of inappropriate ICD shocks in patients with ConHD. Patients with ConHD are typically younger than the general ICD population and have a more active lifestyle. Because of these characteristics they have an increased risk of inappropriate ICD shocks. In this study we focused on patients with ToF, since these patients most often need ICD therapy.

We found more inappropriate shocks in patients with ToF compared to patients without ICD. Our study showed that ICD therapy in these young adult patients had a clear negative impact on psychosocial functioning. We observed worse outcomes on subjective physical functioning, general health perceptions and satisfaction with life. We also investigated the difference between patients with both ToF and an ICD, and with patients who have an ICD for other types of heart disease (mainly ischemic heart disease). Patients with an ICD but without ConHD were significantly older (average 72 years) compared with patients who had ToF and an ICD (average 44 years). Despite the fact that patients with ToF and an ICD were younger and reported a better physical functioning, they had more anxiety, were less satisfied with their lives and showed less favorable coping styles. The higher amount of inappropriate shocks in patients with ConHD offers a good explanation for the negative impact on psychosocial functioning.

Pacemaker implantation in a patient with ConHD can be challenging. **Chapter 4.2** focuses on the occurrence of complications in pacemaker therapy in patients with ConHD. To investigate this, we selected patients with ConHD and a pacemaker from a large national database, and combined these data with local databases in the participating hospitals (Erasmus MC (Rotterdam, the Netherlands), UMC st. Radboud (Nijmegen, the Netherlands), Leids Universitair Medisch Centrum (Leiden, the Netherlands) en het UZ Leuven (Leuven, Belgium)). Most patients with ConHD received their pacemaker at childhood, and patients with complex ConHD were younger at the time of implantation compared with patients who had simple forms of ConHD. They also received epicardial leads more often. The most common indications for pacemaker implantation in patients with ConHD were acquired sinus node disease or surgical AV node conduction disease.

We found that 11% of the patients had one or more complications shortly (within 30 days) after pacemaker implantation, which is twice as high compared with the general population. The most frequent complications were: lead problems, bleeding, pocket infections and pneumothorax. During 12 years of follow-up, 35% of patients developed late complications (30 days or more after pacemaker implantation). The most common complications were: lead fracture, pacemaker dysfunction (including early battery depletion) and migration or erosion of the pacemaker. Pacemaker implantation at an early age (<18 years) was associated with more complications during follow-up.

This study showed that pacemaker implantation in patients with ConHD is associated with higher risks for complications during follow-up, especially in patients who needed a pacemaker at early age.

Patients with ConHD are prone to rhythm and conduction diseases such as atrial fibrillation. In **chapter 4.3** we investigated whether atrial pacing in patients with ConHD has a protective effect on the occurrence of atrial fibrillation, as is the case in the general population. The same study population as in chapter 4.2 was used. We excluded patients who received pacemaker therapy and had chronic atrial fibrillation, which did not respond to medication. We found one or more episodes of atrial fibrillation in 23% of patients with ConHD. Two thirds of this population received atrial pacing, the rest had a form of ventricular pacing. During the 13 years of follow-up, 43% of patients developed an atrial arrhythmia. We did not find an association between atrial pacing and a reduced chance of atrial fibrillation. Former episodes of atrial fibrillation, together with implantation of the pacemaker at adult age (>18 year) were predictive for the reoccurrence of atrial fibrillation. In conclusion, atrial pacing does not seem to have a beneficial effect on the prevention of atrial arrhythmias in patients with ConHD.

Chapter 5.2

General Discussion

GENERAL DISCUSSION

To investigate the impact of living with a congenital heart defect at adulthood (ConHD), this thesis focused on three domains: the impact on biographical characteristics, on psychological characteristics and on medical aspects. This chapter provides a brief summary of the main findings, which are presented in the previous chapters, and presents an interpretation of these findings by relating them to published literature.

Impact on biographical characteristics

Our studies have shown that crucial biographical characteristics (such as living conditions, relationships and income) of patients with ConHD are impaired compared with normative data, although clear improvements over time were found.

A more independent lifestyle has been described in literature before.[1-10] Considering our results, we can conclude that impaired living conditions are mostly present during young adulthood, and normalize later in life.

Our study showed an improvement over time concerning long-term stable relationships. Differences in age-ranges could explain why literature on marital status yields ambiguous results, with some studies reporting patients with ConHD are either less or equally involved in a stable relationship such as marriage compared with normative data.[1,4,5,9]

It has been described in literature that patients with ConHD seem to live less independently, more often in an overprotective setting, and experience a delayed process of gaining autonomy and striving for independence.[1,11,12,13] Overprotectiveness by parents during early childhood might have played a role in the delayed process of gaining autonomy, continuing from childhood into young adulthood.[2,3,9,11,12,13]

We found lower educational levels in patients compared with normative data. Preoperative factors (such as genetics, structured brain injury, severity of disease, extended period of hypoxaemia during infancy, deep hypothermic circulatory arrest, pH-management during cooling, hemodulation) and postoperative factors (e.g. number of operations, clinical and EEG seizures), and school absenteeism may contribute to learning problems, lowering educational level at younger age.[3,14-16] Although patients still showed an impaired educational level compared with normative data in our present follow-up (patients now being between 33 and 55 years of age), we saw that educational level improved over time. A possible explanation for this improvement could be that patients with ConHD have spent more time and efforts during a longer period (e.g., during late adolescence and thereafter) to obtain a higher educational level to compensate for physical impairments. This could also be an explanation why previous studies, using different and mostly younger samples, yielded contra-dictionary outcomes.[2,4,5,15,17-19]

The lower educational level, with improvement over time, explains the observed lower occupational level. This could explain why literature yields conflicting results on occupational status and employment rate as well.[1-5,9,17,19] The lower occupational level explains why patients show impairments in income.

Considering our findings that educational level can improve over time, the occupational level might improve over time as well, possibly for a next generation of adults with ConHD. Nowadays significantly more patients reported to have no problems maintaining a full work schedule compared with 10 years ago. It seems patients have adapted to the working hours in their field of work. Also, fewer patients reported to be treated unequally by, or to feel isolated form their colleagues. The reason for this improvement is not completely clear. It could be that over time it has become more accepted to have a heart defect in the working field. Another explanation could be that when reaching middle adulthood, more persons with an acquired heart disease or other somatic conditions are present in the working field, which may have a normalizing influence on ConHD patients.

Especially patients with moderate/complex ConHD reported a negative outlook on keeping or finding a good job, a result that has been described before.[6]

An interesting development has been observed concerning sick-leave. A decade ago, in the previous follow-up of our cohort, a gap was observed between objective and subjective sick-leave (compared with normative data, patients had a higher sick leave, but reported to be sick less often). This was explained by denial, social desirability, response shift or overcompensation.[9,20,21] Interestingly, we did not observe this effect anymore, suggesting that patients may acquire a more realistic perception of their actual sick leave when getting older, reaching middle adulthood.

Considering the impairments in the domain of education and occupation, we recommend timely neuropsychological screening during childhood.[18,22,23] Remedial teaching in case of learning problems can be offered to prevent delay in education and – by consequence – occupational status and concomitant income level, and to optimize psychosocial outcome in these areas for our patients.

Although the above findings provide an overview in problems in biographical characteristics, it is important to stress that continued research is mandatory to see how the trends that we observed will progress over time. With this information we can inform patients and parents even better at young age about their expectations in life. This information will also provide doctors and psychologists a good basis to better guide their patients and anticipate on problems such as the delayed process of autonomy.

Impact on psychological characteristics

We found that quality of life, subjective health status, social and emotional functioning (social inadequacy, neuroticism, hostility and self-esteem) were favorable, in fact even better when

compared with normative data. These findings are similar to those found 10 and 20 years earlier, and are in line with literature.[6,9,19,20,24] The good outcomes on quality of life, subjective health status, social and emotional functioning seem to be an ongoing trend with increasing age. Possibly these findings may be explained by a high achievement motivation, denial or overcompensation.[9,20,25]

Concerning psychopathology, literature reports that patients with ConHD are at an increased risk for psychopathological problems.[11,12,26-30] However, at our 30-year follow-up we found that outcomes on psychopathology were the same or even better compared with normative groups. Moreover, percentages of patients scoring in the deviant range of psychopathology decreased significantly over time. A decade ago, at the 20-year follow-up, this decrease of psychopathology from young into middle adulthood was already hypothesized.[29] One explanation for this decrease in psychopathology may be normalization of biographical outcomes. Having reached middle adulthood, our patients appear to have caught up a delay in gaining autonomy. The majority of our cohort had now formed families and had jobs.[9,31] Another explanation may be a response shift: this phenomenon reflects that patients may have different values and internal standards than healthy peers after having survived a life-threatening experience (such as cardiac surgery).[21] Finally also increased psychopathology in normative groups may play a role. Since the normative groups now also fell into the middle-aged category, they might suffer from somatic conditions as well, possibly resulting in increase of mental health problems. However, we think the decrease in psychopathology found is not just an artifact of change in normative groups, since longitudinal analyses within the ConHD clearly confirmed the decrease in psychopathology.

A broad scale of medical predictors was used to predict changes in psychopathology over time. A positive subjective evaluation of the cardiac scar was the only predictor for a decrease in self-reported psychopathology, from 20 to 30 year follow-up. Negative feelings regarding the surgical scar have a negative impact on feelings of self-esteem and self-confidence. Since the scar was already a significant predictor for long-term psychopathology a decade ago, we conclude that the cardiac scar remains a significant factor for the mental health of patients with ConHD, even in middle adulthood.

With improved surgical techniques over time, it would be interesting to see if there are differences in psychopathology between our study population and patients operated in later decades. In addition, over time, the cardiac function in our study population may deteriorate, causing symptoms and disabilities. This underlines the need for psychopathological evaluation in the future, to be able to determine the relationship between psychopathology and decreasing cardiac function.

Concerning sexual functioning, females with ConHD reported more problems on all scales of sexual functioning and 15% fell in the range of clinical sexual disorders. Male sexual function-

ing was also clearly impaired, especially regarding orgasmic function and satisfaction with intercourse.

As already hypothesized in literature, the view on the surgical scar could have contributed to fear of rejection and a negative body image, which in turn may have caused patients to become sexually active at a later age.[1,11,27,32] This might imply that the desire of young patients to correct their scar by plastic surgery should be taken seriously. However, as described above, a positive subjective evaluation of the scar at an older age is associated with a decrease in psychopathology over time.[30] This indicates that patients seem to accept their scar and find it less important with older age.[1,11,27,32] It would be interesting for future research to see if psychological counseling on the surgical scar in younger patients with ConHD decreases the desire to perform plastic surgery on the scar and possibly the levels of psychopathological complaints.

In literature it has been observed that lower educational level is associated with losing virginity at an earlier age.[33] Taking into account the lower educational level observed in our study, the significantly older age of losing virginity is even more noticeable.[9] In addition, the later age at which patients become independent and gain autonomy could play a role in delayed sexuality.[2,3,9,11,12,13] In contrast to literature we did not find that problems with sexuality increased with worse cardiac functional class, nor that females with a moderate/complex ConHD had significantly more sexual partners indicating promiscuity.[34,35] This could be explained by the older age of the patients in our cohort.

Males in our study showed an increased amount of erectile dysfunction, which was twice as high as reported in normative data.[33] Fears before or during sexual intercourse, as well as physical symptoms such as dyspnea, feelings of arrhythmia or chest pain have been reported before and can contribute to sexual problems.[36]

Perhaps one of the most striking findings in this part of our study was the poor knowledge on sexuality and contraceptives as reported by patients. Our findings underline the need that providing timely comprehensive information and counseling on sexuality at a young age in patients with ConHD is warranted.[37-41]

The findings in our study indicate that it is important to provide information to patients with ConHD about sexuality, pregnancy, delivery and heredity. This could be organized in by individual counseling or in the form of educational programs for patients with ConHD. The most appropriate timing to offer this information is during (early) adolescence, for example when patients switch to the adult outpatient clinic. When patients reach middle adulthood, it can be expected that erectile disorders and menopausal complaints in ConHD patients may occur. Systematic follow-up of sexual function is therefore recommended in this population since the present patients with ConHD already show high levels of sexual dysfunction.

Considering the fact that sexuality is an important part of life and the observed elevated levels of sexual problems in our patients, it is striking that counseling for sexual problems is a neglected field. We recommend that in case of sexual problems, referral should take place

to a sexologist or mental health professional (psychologist or psychiatrist) with experience in this specific field.

In our study we found that practising sports was associated with an increase in exercise capacity over time. This might indeed be beneficial for patients with ConHD, who are known to have a reduced exercise capacity and peak oxygen uptake compared with normative data.[42-46] A positive attitude toward sports participation might especially be important since a lower exercise capacity might be partially explained by low physical activity.[47]

In contrast to literature, we did not find an association between sport participation and an increase in self-perceived physical functioning nor in subjective quality of life.[47-51] It has been hypothesized that the prevalence of depressive symptoms has a larger impact on quality of life than exercise capacity.[52] Patients with ConHD have reported fear of physical exercise and physicians may have been over-conservative in their advice on sports.[42,53,54] Literature has shown discrepancies and gaps in knowledge between what physicians and patients with ConHD consider safe when practising sports.[37,42,47,53] Previously, overestimation of physical abilities by patients with ConHD had been reported, which might explain favorable subjective physical functioning scores, despite hampered sports participation.[45,50] However, we did not find such a positive effect on subjective physical functioning. Overestimation of physical capabilities might result in patients choosing a sport that might potentially harm their health.

The gap of knowledge on the safety and effectiveness of physical activity and intervention programs in patients with ConHD warrants further research to be able to accurately and safely guide ConHD patients to a more active lifestyle. Systematic randomized controlled trials, conducted in sufficiently large sample sizes, should be performed to investigate the efficacy and safety of physical activity, sports, and exercise training on exercise capacity and quality of life in adult patients with ConHD. Preferably this should be done by including patients from multiple centers, if needed across different countries. Detailed and standardized information of type of sport practiced together with 24-hour continuous ECG monitoring (Holter), echocardiography and exercise testing should be gathered.

Impact on medical characteristics

Implantable Cardiac Defibrillators (ICDs) are being used in patients with ConHD that have survived, or are at high risk of developing a life-threatening cardiac arrhythmia.[55-59] The indication for primary ICD therapy in patients with ConHD is still a matter of debate because of the high incidence of inappropriate shocks.[57,60,61] Not only did we observe a higher inappropriate shock rate in patients with ConHD, we also found more shocks per patient. These inappropriate shocks could be triggered by atrial arrhythmias, or the more active lifestyle with sinus tachycardia in the often young patients with ConHD.[60,62] Inappropriate shocks delivered to patients who are fully conscious, might cause stress, anxiety for shock and anxiety for premature death, thereby causing psychological problems, a finding supported by the results of our

study.[63-65] We set up a study investigating the psychosocial impact of having a ICD in patients with ConHD and found that ICD therapy had a significant impact on quality of life. Moreover, out of fear for a ICD discharge 39% of ICD-patients try to avoid physical exertion.[66]

Future research should be conducted in a larger cohort, as the current cohort was not large enough to perform further sub-analyses. In addition, the impact of ICD therapy in young adults with ConHD on activities such as practising sports, sexuality and driving a car should be studied. Different programming strategies, such as the application of anti-tachycardia pacing therapy and higher rate cutoffs for arrhythmia detection, may prevent inappropriate ICD therapy and may have a beneficial effect on psychosocial functioning, moreover the application of subcutane ICD's could play a beneficial role.[67,68] If possible, the implantation of a ICD should be done with a shared-decision making model, in which the patient is informed of the impact of possible inappropriate shocks. This information might help patients to better cope with inappropriate shocks.

Patients with ConHD are prone to rhythm and conduction disease because of the underlying congenital cardiac defect, longstanding hemodynamic alterations and the consequences of surgical interventions.[69,70] Pacemaker implantation in this population can be challenging due to the complexity of the systemic venous anatomy, venous obstructions and/or residual intra-cardiac shunting.[71,72] Unfortunately, data on complications in pacemaker implantation are scarce for the adult ConHD population.[71,72] In our study we observed that patients with ConHD experience more than twice as much peri-procedural complications after pacemaker implantation compared with the general population, especially if the implantation occurs at young age.[73] In contrast to literature, we did not observe that the use of epicardial leads was associated with a higher lead failure.[72,74-78] Previous studies have shown that the use of steroid-eluting epicardial leads render the lead failure rate comparable to endocardial leads.[78,79]

Several prospective randomized trials in the general population have demonstrated that atrial-based pacing ("physiologic pacing") reduces the incidence of atrial fibrillation compared with ventricular pacing.[80-85] This is not surprising, since loss of AV synchrony due to ventricular pacing is associated with increased natriuretic peptide levels, sympathetic nervous activation and atrial pressures. These are all factors associated with the development of atrial fibrillation.[84,86,87] Literature has shown it is not clear whether atrial-based pacing is also beneficial in the adult with ConHD.[71] We found that physiological pacing did not prevent the development of atrial arrhythmias in patients with ConHD. Older age at implantation (≥18 years of age) and complex ConHD were associated with the development of atrial arrhythmias. A history of atrial arrhythmias has been identified as a predictor of future arrhythmias in literature before.[71] In our study mainly patients with single ventricle physiology (mostly Fontan patients with an atriopulmonary connection) were at increased risk of developing

atrial arrhythmias later in life. Previous electrophysiological mapping studies have shown that Fontan patients undergo progressive adverse atrial mechano-electrical remodeling with increasing age, rendering them more prone to atrial arrhythmias.[88] So probably in these patients with a structural abnormal heart, atrial fibrillation occurs independent of the pacing mode.

To develop effective therapies for preventing atrial arrhythmias, future research should focus on understanding the pathophysiology of atrial arrhythmias in adults with ConHD even better.

REFERENCES

1. Daliento L, Mapelli D, Russo G, Scarso P, Limongi F, Iannizzi P, Melendugno A, Mazzotti E, Volpe B. Health related quality of life in adults with repaired tetralogy of Fallot: psychosocial and cognitive outcomes. Heart. 2005 Feb;91(2):213-8.
2. Simko LC, McGinnis KA, Schembri J. Educational needs of adults with congenital heart disease. J Cardiovasc Nurs. 2006 Mar-Apr;21(2):85-94.
3. Kokkonen J, Paavilainen T. Social adaptation of young adults with congenital heart disease. Int J Cardiol. 1992 Jul;36(1):23-9.
4. Sairanen HI, Nieminen HP, Jokinen EV. Late results and quality of life after pediatric cardiac surgery in Finland: a population-based study of 6,461 patients with follow-up extending up to 45 years. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2005:168-72.
5. Nieminen H, Sairanen H, Tikanoja T, Leskinen M, Ekblad H, Galambosi P, Jokinen E. Long-term results of pediatric cardiac surgery in Finland: education, employment, marital status, and parenthood. Pediatrics. 2003 Dec;112(6 Pt 1):1345-50.
6. Moons P, De Bleser L, Budts W, Sluysmans T, De Wolf D, Massin M, Gewillig M, Pasquet A, Suys B, Vliers A. Health status, functional abilities, and quality of life after the Mustard or Senning operation. Ann Thorac Surg. 2004 Apr;77(4):1359-65; discussion 1365.
7. Kamphuis M, Ottenkamp J, Vliegen HW, Vogels T, Zwinderman KH, Kamphuis RP, Verloove-Vanhorick SP. Health related quality of life and health status in adult survivors with previously operated complex congenital heart disease. Heart. 2002 Apr;87(4):356-62.
8. Moons P, Van Deyk K, Marquet K, De Bleser L, De Geest S, Budts W. Profile of adults with congenital heart disease having a good, moderate, or poor quality of life: a cluster analytic study. Eur J Cardiovasc Nurs. 2009 Jun;8(2):151-7.
9. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. Eur Heart J. 2003 Apr;24(7):673-83.
10. Winter MM, Reisma C, Kedde H, Bouma BJ, Vis JC, Luijendijk P, de Witte P, Zwinderman AH, Vliegen HW, Pieper PG, van Dijk AP, Mulder BJ. Sexuality in adult patients with congenital heart disease and their partners. Am J Cardiol. 2010 Oct 15;106(8):1163-8, 1168.e1-8.
11. Kovacs AH, Sears SF, Saidi AS. Biopsychosocial experiences of adults with congenital heart disease: review of the literature. Am Heart J. 2005 Aug;150(2):193-201.
12. Ong L, Nolan RP, Irvine J, Kovacs AH. Parental overprotection and heart-focused anxiety in adults with congenital heart disease. Int J Behav Med. 2011 Sep;18(3):260-7.
13. Claessens P, Moons P, de Casterlé BD, Cannaerts N, Budts W, Gewillig M. What does it mean to live with a congenital heart disease? A qualitative study on the lived experiences of adult patients. Eur J Cardiovasc Nurs. 2005 Mar;4(1):3-10.
14. Wernovsky G. Current insights regarding neurological and developmental abnormalities in children and young adults with complex congenital cardiac disease. Cardiol Young. 2006 Feb;16 Suppl 1:92-104.
15. Miatton M, De Wolf D, François K, Thiery E, Vingerhoets G. Neurocognitive consequences of surgically corrected congenital heart defects: A review. Neuropsychol Rev. 2006 Jun;16(2):65-85.
16. Moons P, Gewillig M, Sluysmans T, Verhaaren H, Viart P, Massin M, Suys B, Budts W, Pasquet A, De Wolf D, Vliers A. Long term outcome up to 30 years after the Mustard or Senning operation: a nationwide multicentre study in Belgium. Heart. 2004 Mar;90(3):307-13.

17. Fteropoulli T, Stygall J, Cullen S, Deanfield J, Newman SP. Quality of life of adult congenital heart disease patients: a systematic review of the literature. Cardiol Young. 2013 Feb 6:1-13. [Epub ahead of print]
18. Loup O, von Weissenfluh C, Gahl B, Schwerzmann M, Carrel T, Kadner A. Quality of life of grown-up congenital heart disease patients after congenital cardiac surgery. Eur J Cardiothorac Surg. 2009 Jul;36(1):105-11; discussion 111.
19. Bygstad E, Pedersen LC, Pedersen TA, Hjortdal VE. Tetralogy of Fallot in men: quality of life, family, education, and employment. Cardiol Young. 2012 Aug;22(4):417-23.
20. Utens EM, Verhulst FC, Erdman RA, Meijboom FJ, Duivenvoorden HJ, Bos E, Roelandt JR, Hess J. Psychosocial functioning of young adults after surgical correction for congenital heart disease in childhood: a follow-up study. J Psychosom Res. 1994 Oct;38(7):745-58.
21. Moons P. Quality of life in adults with congenital heart disease: Beyond the quantity of life. Doctoral dissertation. Belgium: Katholieke Universiteit Leuven; 2004.
22. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, Mussatto KA, Uzark K, Goldberg CS, Johnson WH Jr, Li J, Smith SE, Bellinger DC, Mahle WT; American Heart Association Congenital Heart Defects Committee, Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Stroke Council. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation. 2012 Aug 28;126(9):1143-72.
23. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Page RL, Riegel B, Tarkington LG, Yancy CW; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease); American Society of Echocardiography; Heart Rhythm Society; International Society for Adult Congenital Heart Disease; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008 Dec 2;52(23):e143-263.
24. Moons P, Van Deyk K, De Bleser L, Marquet K, Raes E, De Geest S, Budts W. Quality of life and health status in adults with congenital heart disease: a direct comparison with healthy counterparts. Eur J Cardiovasc Prev Rehabil. 2006 Jun;13(3):407-13.
25. Ternestedt BM, Wall K, Oddsson H, Riesenfeld T, Groth I, Schollin J. Quality of life 20 and 30 years after surgery in patients operated on for tetralogy of Fallot and for atrial septal defect. Pediatr Cardiol. 2001 Mar-Apr;22(2):128-32.
26. Kovacs AH, Saidi AS, Kuhl EA, Sears SF, Silversides C, Harrison JL, Ong L, Colman J, Oechslin E, Nolan RP. Depression and anxiety in adult congenital heart disease: predictors and prevalence. Int J Cardiol. 2009 Oct 2;137(2):158-64.
27. Horner T, Liberthson R, Jellinek MS. Psychosocial profile of adults with complex congenital heart disease. Mayo Clin Proc. 2000 Jan;75(1):31-6.

28. Utens EM, Bieman HJ, Verhulst FC, Meijboom FJ, Erdman RA, Hess J. Psychopathology in young adults with congenital heart disease. Follow-up results. Eur Heart J. 1998 Apr;19(4):647-51.
29. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Longitudinal development of psychopathology in an adult congenital heart disease cohort. Int J Cardiol. 2005 Mar 18;99(2):315-23.
30. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Medical predictors for psychopathology in adults with operated congenital heart disease. Eur Heart J. 2004 Sep;25(18):1605-13.
31. Zomer AC, Vaartjes I, Uiterwaal CS, van der Velde ET, Sieswerda GJ, Wajon EM, Plomp K, van Bergen PF, Verheugt CL, Krivka E, de Vries CJ, Lok DJ, Grobbee DE, Mulder BJ. Social burden and lifestyle in adults with congenital heart disease. Am J Cardiol. 2012 Jun 1;109(11):1657-63.
32. Kańtoch MJ, Eustace J, Collins-Nakai RL, Taylor DA, Bolsvert JA, Lysak PS. The significance of cardiac surgery scars in adult patients with congenital heart disease. Kardiol Pol. 2006 Jan;64(1): 51-6; discussion 57-8.
33. Bakker F, Vanwesenbeeck I. Sexuele gezondheid in Nederland 2006. 1st ed. Rutgers Nisso Groep 2006. Eburon, Delft.
34. Vigl M, Kaemmerer M, Niggemeyer E, Nagdyman N, Seifert-Klauss V, Trigas V, Bauer U, Schneider KT, Berger F, Hess J, Kaemmerer H. Sexuality and reproductive health in women with congenital heart disease. Am J Cardiol. 2010 Feb 15;105(4):538-41.
35. Reid GJ, Siu SC, McCrindle BW, Irvine MJ, Webb GD. Sexual behavior and reproductive concerns among adolescents and young adults with congenital heart disease. Int J Cardiol. 2008 Apr 25; 125(3):332-8.
36. Vigl M, Hager A, Bauer U, Niggemeyer E, Wittstock B, Köhn FM, Hess J, Kaemmerer H. Sexuality and subjective wellbeing in male patients with congenital heart disease. Heart. 2009 Jul;95(14): 1179-83.
37. Moons P, De Volder E, Budts W, De Geest S, Elen J, Waeytens K, Gewillig M. What do adult patients with congenital heart disease know about their disease, treatment, and prevention of complications? A call for structured patient education. Heart. 2001 Jul;86(1):74-80.
38. Uzark K, VonBargen-Mazza P, Messiter E. Health education needs of adolescents with congenital heart disease. J Pediatr Health Care. 1989 May-Jun;3(3):137-43.
39. Hargrove A, Penny DJ, Sawyer SM. Sexual and reproductive health in young people with congenital heart disease: a systematic review of the literature. Pediatr Cardiol. 2005 Nov-Dec;26(6): 805-11.
40. Kaemmerer M, Vigl M, Seifert-Klauss V, Nagdyman N, Bauer U, Schneider KT, Kaemmerer H. Counseling reproductive health issues in women with congenital heart disease. Clin Res Cardiol. 2012 Nov;101(11):901-7.
41. Kamphuis M, Verloove-Vanhorick SP, Vogels T, Ottenkamp J, Vliegen HW. Disease-related difficulties and satisfaction with level of knowledge in adults with mild or complex congenital heart disease. Cardiol Young. 2002 May;12(3):266-71.
42. Gierat-Haponiuk K, Haponiuk I, Chojnicki M, Jaworski R, Bakuła S. Exercise capacity and the quality of life late after surgical correction of congenital heart defects. Kardiol Pol. 2011;69(8):810-5.
43. Fredriksen PM, Veldtman G, Hechter S, Therrien J, Chen A, Warsi MA, Freeman M, Liu P, Siu S, Thaulow E, Webb G. Aerobic capacity in adults with various congenital heart diseases. Am J Cardiol. 2001 Feb 1;87(3):310-4.
44. Fredriksen PM, Pettersen E, Thaulow E. Declining aerobic capacity of patients with arterial and atrial switch procedures. Pediatr Cardiol. 2009 Feb;30(2):166-71.

45. Gratz A, Hess J, Hager A. Self-estimated physical functioning poorly predicts actual exercise capacity in adolescents and adults with congenital heart disease. Eur Heart J. 2009 Feb;30(4): 497-504.
46. Kempny A, Dimopoulos K, Uebing A, Moceri P, Swan L, Gatzoulis MA, Diller GP. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life--single centre experience and review of published data. Eur Heart J. 2012 Jun;33(11):1386-96.
47. Buys R, Van De Bruaene A, Budts W, Delecluse C, Vanhees L. In adults with atrial switch operation for transposition of the great arteries low physical activity relates to reduced exercise capacity and decreased perceived physical functioning. Acta Cardiol. 2012 Feb;67(1):49-57.
48. Lavie CJ, Milani RV. Adverse psychological and coronary risk profiles in young patients with coronary artery disease and benefits of formal cardiac rehabilitation. Arch Intern Med. 2006 Sep 25;166(17):1878-83.
49. Fredriksen PM, Kahrs N, Blaasvaer S, Sigurdsen E, Gundersen O, Roeksund O, Norgaand G, Vik JT, Soerbye O, Ingjer E, Thaulow E. Effect of physical training in children and adolescents with congenital heart disease. Cardiol Young. 2000 Mar;10(2):107-14.
50. Hager A, Hess J. Comparison of health related quality of life with cardiopulmonary exercise testing in adolescents and adults with congenital heart disease. Heart. 2005 Apr;91(4):517-20.
51. Lemmer J, Heise G, Rentzsch A, Boettler P, Kuehne T, Dubowy KO, Peters B, Lemmer B, Hager A, Stiller B; German Competence Network for Congenital Heart Defects. Right ventricular function in grown-up patients after correction of congenital right heart disease. Clin Res Cardiol. 2011 Apr; 100(4):289-96.
52. Müller J, Hess J, Hager A. Minor symptoms of depression in patients with congenital heart disease have a larger impact on quality of life than limited exercise capacity. Int J Cardiol. 2012 Feb 9; 154(3):265-9.
53. Swan L, Hillis WS. Exercise prescription in adults with congenital heart disease: a long way to go. Heart. 2000 Jun;83(6):685-7.
54. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E; Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC); Association for European Paediatric Cardiology (AEPC); ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J. 2010 Dec;31(23):2915-57.
55. Silka MJ, Hardy BG, Menashe VD, Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. J Am Coll Cardiol. 1998 Jul;32(1):245-51.
56. Oechslin EN, Harrison DA, Connelly MS, Webb GD, Siu SC. Mode of death in adults with congenital heart disease. Am J Cardiol. 2000 Nov 15;86(10):1111-6.
57. Khairy P, Harris L, Landzberg MJ, Viswanathan S, Barlow A, Gatzoulis MA, Fernandes SM, Beauchesne L, Therrien J, Chetaille P, Gordon E, Vonder Muhll I, Cecchin F. Implantable cardioverter-defibrillators in tetralogy of Fallot. Circulation. 2008 Jan 22;117(3):363-70.
58. Khairy P, Aboulhosn J, Gurvitz MZ, Opotowsky AR, Mongeon FP, Kay J, Valente AM, Earing MG, Lui G, Gersony DR, Cook S, Ting JG, Nickolaus MJ, Webb G, Landzberg MJ, Broberg CS; Alliance for Adult Research in Congenital Cardiology (AARCC). Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. Circulation. 2010 Aug 31;122(9):868-75.

59. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. Circulation. 1995 Apr 15;91(8):2214-9.
60. Yap SC, Roos-Hesselink JW, Hoendermis ES, Budts W, Vliegen HW, Mulder BJ, van Dijk AP, Schalij MJ, Drenthen W. Outcome of implantable cardioverter defibrillators in adults with congenital heart disease: a multi-centre study. Eur Heart J. 2007 Aug;28(15):1854-61.
61. Alexander ME, Cecchin F, Walsh EP, Triedman JK, Bevilacqua LM, Berul CI. Implications of implantable cardioverter defibrillator therapy in congenital heart disease and pediatrics. J Cardiovasc Electrophysiol. 2004 Jan;15(1):72-6.
62. Magnin-Poull I, De Chillou C, Miljoen H, Andronache M, Aliot E. Mechanisms of right atrial tachycardia occurring late after surgical closure of atrial septal defects. J Cardiovasc Electrophysiol. 2005 Jul;16(7):681-7.
63. Sears SF Jr, Todaro JF, Lewis TS, Sotile W, Conti JB. Examining the psychosocial impact of implantable cardioverter defibrillators: a literature review. Clin Cardiol. 1999 Jul;22(7):481-9.
64. Vazquez LD, Conti JB, Sears SF. Female-specific education, management, and lifestyle enhancement for implantable cardioverter defibrillator patients: the FEMALE-ICD study. Pacing Clin Electrophysiol. 2010 Sep;33(9):1131-40.
65. Sears SF, Matchett M, Conti JB. Effective management of ICD patient psychosocial issues and patient critical events. J Cardiovasc Electrophysiol. 2009 Nov;20(11):1297-304.
66. Lemon J, Edelman S, Kirkness A. Avoidance behaviors in patients with implantable cardioverter defibrillators. Heart Lung. 2004 May-Jun;33(3):176-82.
67. Bardy GH, Smith WM, Hood MA, Crozier IG, Melton IC, Jordaens L, Theuns D, Park RE, Wright DJ, Connelly DT, Fynn SP, Murgatroyd FD, Sperzel J, Neuzner J, Spitzer SG, Ardashev AV, Oduro A, Boersma L, Maass AH, Van Gelder IC, Wilde AA, van Dessel PF, Knops RE, Barr CS, Lupo P, Cappato R, Grace AA. An entirely subcutaneous implantable cardioverter-defibrillator. N Engl J Med. 2010 Jul 1;363(1):36-44.
68. Dabiri Abkenari L, Theuns DA, Valk SD, Van Belle Y, de Groot NM, Haitsma D, Muskens-Heemskerk A, Szili-Torok T, Jordaens L. Clinical experience with a novel subcutaneous implantable defibrillator system in a single center. Clin Res Cardiol. 2011 Sep;100(9):737-44.
69. Yap SC, Harris L, Chauhan VS, Oechslin EN, Silversides CK. Identifying high risk in adults with congenital heart disease and atrial arrhythmias. Am J Cardiol. 2011 Sep 1;108(5):723-8.
70. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, van Dijk AP, Vliegen HW, Grobbee DE, Mulder BJ. Mortality in adult congenital heart disease. Eur Heart J. 2010 May;31(10):1220-9.
71. Walker F, Siu SC, Woods S, Cameron DA, Webb GD, Harris L. Long-term outcomes of cardiac pacing in adults with congenital heart disease. J Am Coll Cardiol. 2004 May 19;43(10):1894-901.
72. McLeod CJ, Attenhofer Jost CH, Warnes CA, Hodge D 2nd, Hyberger L, Connolly HM, Asirvatham SJ, Dearani JA, Hayes DL, Ammash NM. Epicardial versus endocardial permanent pacing in adults with congenital heart disease. J Interv Card Electrophysiol. 2010 Sep;28(3):235-43.
73. Nowak B, Misselwitz B; Expert committee 'Pacemaker', Institute of Quality Assurance Hessen, Erdogan A, Funck R, Irnich W, Israel CW, Olbrich HG, Schmidt H, Sperzel J, Zegelman M. Do gender differences exist in pacemaker implantation?--results of an obligatory external quality control program. Europace. 2010 Feb;12(2):210-5.
74. Sachweh JS, Vazquez-Jimenez JF, Schöndube FA, Daebritz SH, Dörge H, Mühler EG, Messmer BJ. Twenty years experience with pediatric pacing: epicardial and transvenous stimulation. Eur J Cardiothorac Surg. 2000 Apr;17(4):455-61.

75. Fortescue EB, Berul CI, Cecchin F, Walsh EP, Triedman JK, Alexander ME. Patient, procedural, and hardware factors associated with pacemaker lead failures in pediatrics and congenital heart disease. Heart Rhythm. 2004 Jul;1(2):150-9.
76. Noiseux N, Khairy P, Fournier A, Vobecky SJ. Thirty years of experience with epicardial pacing in children. Cardiol Young. 2004 Oct;14(5):512-9.
77. van der Velde ET, Vriend JW, Mannens MM, Uiterwaal CS, Brand R, Mulder BJ. CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: rationale, design, and first results. Eur J Epidemiol. 2005;20(6):549-57.
78. Silvetti MS, Drago F, Grutter G, De Santis A, Di Ciommo V, Ravà L. Twenty years of paediatric cardiac pacing: 515 pacemakers and 480 leads implanted in 292 patients. Europace. 2006 Jul;8(7): 530-6.
79. Fortescue EB, Berul CI, Cecchin F, Walsh EP, Triedman JK, Alexander ME. Comparison of modern steroid-eluting epicardial and thin transvenous pacemaker leads in pediatric and congenital heart disease patients. J Interv Card Electrophysiol. 2005 Oct;14(1):27-36.
80. Healey JS, Toff WD, Lamas GA, Andersen HR, Thorpe KE, Ellenbogen KA, Lee KL, Skene AM, Schron EB, Skehan JD, Goldman L, Roberts RS, Camm AJ, Yusuf S, Connolly SJ. Cardiovascular outcomes with atrial-based pacing compared with ventricular pacing: meta-analysis of randomized trials, using individual patient data. Circulation. 2006 Jul 4;114(1):11-7.
81. Connolly SJ, Kerr CR, Gent M, Roberts RS, Yusuf S, Gillis AM, Sami MH, Talajic M, Tang AS, Klein GJ, Lau C, Newman DM. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. N Engl J Med. 2000 May 11;342(19):1385-91.
82. Andersen HR, Thuesen L, Bagger JP, Vesterlund T, Thomsen PE. Prospective randomised trial of atrial versus ventricular pacing in sick-sinus syndrome. Lancet. 1994 Dec 3;344(8936):1523-8.
83. Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T, Pedersen AK. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet. 1997 Oct 25;350(9086):1210-6.
84. Lamas GA, Lee K, Sweeney M, Leon A, Yee R, Ellenbogen K, Greer S, Wilber D, Silverman R, Marinchak R, Bernstein R, Mittleman RS, Lieberman EH, Sullivan C, Zorn L, Flaker G, Schron E, Orav EJ, Goldman L. The mode selection trial (MOST) in sinus node dysfunction: design, rationale, and baseline characteristics of the first 1000 patients. Am Heart J. 2000 Oct;140(4):541-51.
85. Toff WD, Camm AJ, Skehan JD; United Kingdom Pacing and Cardiovascular Events Trial Investigators. Single-chamber versus dual-chamber pacing for high-grade atrioventricular block. N Engl J Med. 2005 Jul 14;353(2):145-55.
86. Horie H, Tsutamoto T, Ishimoto N, Minai K, Yokohama H, Nozawa M, Izumi M, Takaoka A, Fujita T, Sakamoto T, Kito O, Okamura H, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker for atrioventricular sequence in patients with pacemakers. Pacing Clin Electrophysiol. 1999 Feb;22(2):282-90.
87. Taylor JA, Morillo CA, Eckberg DL, Ellenbogen KA. Higher sympathetic nerve activity during ventricular (VVI) than during dual-chamber (DDD) pacing. J Am Coll Cardiol. 1996 Dec;28(7):1753-8.
88. Yap SC, Harris L, Downar E, Nanthakumar K, Silversides CK, Chauhan VS. Evolving electroanatomic substrate and intra-atrial reentrant tachycardia late after Fontan surgery. J Cardiovasc Electrophysiol. 2012 Apr;23(4):339-45.

Part 6
Appendix

Chapter 6.1

Dutch summary

SAMENVATTING

In dit proefschrift wordt de impact van het hebben van een aangeboren hartafwijking op volwassen leeftijd onderzocht. Hiertoe worden zowel biografische, psychologische als enkele medische aspecten bekeken. In **hoofdstuk 1.1** wordt na een korte algemene introductie een overzicht gegeven van de vijf meest voorkomende aangeboren hartafwijkingen, namelijk het Atrium Septum Defect (ASD), Ventrikel Septum Defect (VSD), Pulmonaalklep Stenose (PS), Tetralogie van Fallot (ToF) en Transpositie van de Grote Arteriën (TGA). Omdat een aangeboren hartafwijking tegenwoordig als een chronische ziekte wordt beschouwd, is de focus van veel onderzoeken verschoven van overleving naar kwaliteit van leven.

Impact op biografische kenmerken

Biografische kenmerken omvatten eigenschappen die het dagelijkse leven van de patiënt betreffen. In deze studie werden biografische karakteristieken onderzocht door het afnemen van een semi-gestructureerd interview. De kenmerken die zijn onderzocht omvatten onder andere: leef omstandigheden, burgerlijke status, kindertal, werk, inkomen en vrijetijdsbesteding. Tevens werden er vragenlijsten afgenomen om een inschatting te maken van bijvoorbeeld de kwaliteit van leven, het emotioneel functioneren en de sociale steun.

In **hoofdstuk 2.1** worden de biografische kenmerken beschreven van het cohort uit het Erasmus MC, dat geopereerd was tussen 1968 (de start van de open hart chirurgie in Rotterdam) en 1980, en op het moment van deelname (in 2011) tussen de 30 en 55 jaar oud was. Deze groep was al tweemaal eerder onderzocht in het Erasmus Medisch Centrum (eerste follow-up in 1990, tweede follow-up in 2001). Omdat dit de derde follow-up was van hetzelfde cohort mensen, kon er een vergelijking over de tijd worden gemaakt. De biografische kenmerken werden vergeleken met de algemene Nederlandse bevolking, om te kijken of patiënten met een aangeboren hartafwijking verschillen met de algemene bevolking.

De belangrijkste uitkomsten van dit hoofdstuk waren dat patiënten met een aangeboren hartafwijking minder vaak zelfstandig woonden ten opzichte van de algemene bevolking, en juist meer thuis bij hun ouders. Ook waren ze minder vaak getrouwd, hadden ze minder kinderen, hadden werk van een lager niveau en verdienden minder vergeleken met hun leeftijdsgenoten zonder aangeboren hartafwijking. Positieve uitkomsten waren dat patiënten met een aangeboren hartafwijking een betere kwaliteit van leven en emotioneel functioneren lieten zien ten opzichte van de algemene bevolking. Patiënten met complexe vormen van aangeboren hartafwijkingen (ToF en TGA) rapporteerden vaker dat ze fysieke kracht misten, en dat ze zich in het nadeel voelden ten opzichte van mensen met een mildere aangeboren hartafwijking.

Vergeleken met 10 jaar geleden was er vooruitgang in biografische kenmerken in de patiënten populatie. Patiënten lieten in vergelijking met 10 jaar geleden zien dat ze vaker

zelfstandig waren gaan wonen, vaker getrouwd waren en tegenwoordig een hoger inkomen hadden, ook al was dit inkomen nog steeds lager vergeleken met leeftijdsgenoten zonder aangeboren hartafwijking. Ook hadden de patiënten met aangeboren hartafwijkingen in loop van de tijd een beter opleidingsniveau behaald. Deze resultaten geven aan dat de biografische kenmerken voor patiënten met aangeboren hartafwijkingen over de tijd heen verbeteren, hoewel ze nog wel minder gunstig zijn ten opzichte van de algemene bevolking.

In **hoofdstuk 2.2** zijn de biografische kenmerken vergeleken tussen twee cohorten patiënten die in een verschillend tijdvak zijn geopereerd. Dit onderzoek richtte zich alleen op de mensen met de wat meer complexere aangeboren hartafwijkingen, namelijk patiënten met ToF of TGA. Het meest recente cohort was geopereerd tussen 1980 en 1990 en was nu tussen de 20 en 37 jaar oud. Het historische cohort was geopereerd tussen 1968 en 1980, van dit cohort zijn de data uit 2001 gebruikt. Om ervoor te zorgen dat de beide populaties vergelijkbaar zouden zijn, zijn uit het historische cohort alleen de ToF en TGA patiënten geselecteerd die een vergelijkbare leeftijd hadden en met vergelijkbare operatietechnieken zijn geopereerd. Ook zijn in beide populaties dezelfde vragenlijsten afgenomen.

De resultaten zijn ook vergeleken met de algemene Nederlandse bevolking. Hoewel de kwaliteit van leven gunstig was in het recente cohort, werden er wel verschillen gevonden ten opzichte van de algemene bevolking, die uitvielen in het nadeel van het cohort. De biografische uitkomsten zoals relaties, kinderen, werk en inkomen waren ook in deze studie minder gunstig ten opzichte van leeftijdsgenoten zonder aangeboren hartafwijking, en waren over de tijd heen niet verbeterd. Wel werd een beter opleidingsniveau gevonden voor het recente cohort. De hoeveelheid patiënten die leerproblemen hebben gehad was hoog.

Geconcludeerd kan worden dat er geen duidelijke vooruitgang gevonden werd in de psychosociale uitkomsten van het meest recente cohort (geopereerd tussen 1980-1990) ten opzichte van het historische cohort geopereerd voor 1980, ondanks grote vooruitgang in de medische behandeling van aangeboren hartafwijkingen over de afgelopen decennia. Vooral het percentage patiënten dat speciaal onderwijs had gevolgd en leerproblemen had gehad was hoog en het inkomen was nog steeds lager in vergelijking met normatieve data.

Impact op psychologische kenmerken

Om de impact op psychologische kenmerken te onderzoeken, hebben we dit gedeelte in drie hoofdstukken verdeeld. Al deze drie artikelen zijn geschreven op grond van het Erasmus MC cohort dat geopereerd was tussen 1968 en 1980, en tijdens de studie tussen de 30 en 55 jaar oud was. Dit betrof de derde follow-up van dit wereldwijd unieke cohort (eerste follow-up in 1990, tweede follow-up in 2001).

Hoofdstuk 3.1 behandelt de ontwikkeling van psychopathologie over de tijd in patiënten met een aangeboren hartafwijking, en kijkt ook naar de subjectieve gezondheidstoestand. Psychopathologische problemen werden gemeten met de Adult Self Report (ASR) die door de patiënt zelf in werd gevuld, en met de Adult Behavioral Checklist (ABCL) die door een familielid, partner of goede vriend/vriendin werd ingevuld. De volgende deelgebieden werden onderzocht: angst/depressie, teruggetrokken gedrag, lichamelijke problemen zonder duidelijke oorzaak, denkproblemen, aandachtsproblemen, regel-overschrijdend gedrag, agressief en intrusief gedrag. Er was sprake van psychopathologie als de totale probleem score (som van antwoorden op alle items) boven het afkap-punt voor psychopathologie lag; met andere woorden als de score in de deviante, psychopathologische range lagen. Omdat vergelijkbare instrumenten waren gebruikt in 1990 en 2001, kon een beeld worden verkregen van het verloop van de psychopathologie over een periode van 30 jaar. Deze studie laat zien dat in de loop van de tijd het aantal patiënten dat in de psychopathologische range scoort minder wordt, en uiteindelijk vergelijkbaar wordt met de algemene bevolking. Bij de 30-jaar follow-up waren over het algemeen de uitkomsten op psychopathologie (gemiddelde probleemscores op de deelgebieden) vergelijkbaar met of zelfs beter dan normatieve data. De subjectieve gezondheidstoestand was ook beter in vergelijking met normatieve data. Er zijn geen verschillen gevonden tussen diagnostische groepen.

Kenmerken die voorspellend bleken te zijn voor veranderingen in psychopathologie waren:

1) De manier waarop de patiënt tegen zijn/haar litteken aankijkt. Een positieve houding tegenover het eigen litteken was de sterkste voorspeller voor minder psychopathologie.
2) Een slecht chirurgisch resultaat, zoals bepaald door de arts, was voorspellend voor meer psychopathologie over de tijd heen. Dit werd echter alleen gerapporteerd door bekenden van de patiënt, over de patiënt.
3) Minder ziekenhuisopnamen waren voorspellend voor minder psychopathologie zoals gerapporteerd door familieleden/bekenden van de patiënt.

In **hoofdstuk 3.2** komt een onderbelicht onderwerp van onderzoek naar patiënten met een aangeboren hartafwijking aan bod, namelijk het seksueel functioneren. Om dit te onderzoeken is er gevraagd naar het seksueel functioneren, in zowel mannen als vrouwen. Daarnaast is er speciaal voor dit onderzoek een ziekte-specifieke vragenlijst ontwikkeld die in kaart brengt of er verbanden zijn tussen seksuele problemen en het hebben van een aangeboren hartafwijking. Alle resultaten zijn (waar mogelijk) vergeleken met de algemene Nederlandse bevolking. Dit hoofdstuk laat zien dat patiënten met aangeboren hartafwijkingen een breed scala aan seksuele problemen rapporteren, en een verhoogde hoeveelheid seksuele problemen hebben ten opzichte van de algemene bevolking. Patiënten met aangeboren hartafwijkingen beginnen later met seksuele activiteiten ten opzichte van de algemene bevolking. Vooral vrouwen rapporteren een breed scala aan problemen. Vrouwen met een aangeboren

hartafwijking gaven aan een verminderde seksuele behoefte is te hebben, ze worden minder opgewonden en hebben meer pijn tijdens geslachtsgemeenschap vergeleken met de algemene bevolking. Vrouwen uitten zorgen over een negatieve invloed van een mogelijke zwangerschap op hun eigen hart en hun algemene lichamelijke gezondheid. Mannen met een aangeboren hartafwijking hebben twee keer zo vaak erectiestoornissen ten opzichte van de algemene bevolking, laten ook een verminderde orgasmefunctie zien en zijn minder vaak tevreden over geslachtsgemeenschap ten opzichte van de algemene bevolking.

Er waren geen verschillen tussen de verschillende diagnosegroepen in problemen met seksualiteit. Wel was het zo dat de patiënten met een meer complexe hartafwijking vaker rapporteerden dat ze hun hartafwijking als een beperkende factor zien voor het krijgen van kinderen. Ze rapporteerden zorgen over een te laag energieniveau of lagere levensverwachting voor het opvoeden van kinderen. Tenslotte gaven veel patiënten aan dat ze onvoldoende waren geïnformeerd over seksualiteit in hun pubertijd.

Dit artikel laat zien dat het seksueel functioneren in patiënten met een aangeboren hartafwijking meer aandacht verdient en dat hier actie moet worden ondernomen.

In **hoofdstuk 3.3** wordt de impact van het hebben van een aangeboren hartafwijking op sporten onderzocht. Patiënten hebben voor dit onderzoek vragenlijsten ingevuld over hoeveel uur ze per week sportten en welk type sport ze deden. Ook werden vragenlijsten over fysiek functioneren en een vragenlijst over kwaliteit van leven ingevuld. Waar mogelijk werden de resultaten vergeleken met gegevens van de algemene Nederlandse bevolking. Patiënten met een meer complexere aangeboren hartafwijking deden minder vaak aan sport vergeleken met de algemene bevolking, en als ze wel sporten dan besteedden ze hier minder uren aan. De patiënten die wel aan sport deden beoefenden vaak sport met een hoogdynamische impact zoals wielrennen of roeien. Het doen van sport leidde tot een betere inspanningscapaciteit, maar het zelf gerapporteerde fysiek functioneren en de kwaliteit van leven werden niet beïnvloed.

Impact op medische kenmerken

Om de impact van aangeboren hartafwijkingen op medische aspecten te onderzoeken, hebben we ons vooral gericht op pacemakers en implantable cardioverter defibrillators, omdat veel patiënten met een aangeboren hartafwijking op den duur aangewezen zijn op pacemaker therapie.

Patiënten met aangeboren hartafwijking hebben een verhoogde kans om te overlijden aan een plotse hartstilstand. Om dat te voorkomen, wordt vaak Implantable Cardioverter Defibrillator (ICD) therapie aangeboden. Naast dat het levensreddend kan zijn, heeft deze therapie ook nadelen voor patiënten, ze kunnen namelijk een onterechte schok krijgen. In

hoofdstuk 4.1 hebben we de impact van de ICD therapie inclusief de onterechte schokken onderzocht in patiënten met een aangeboren hartafwijking, De mensen met een aangeboren hartafwijking zijn typisch veel jonger en hebben een veel actievere leefstijl dan de meestal oudere hartpatiënten die een ICD krijgen, door deze kenmerken hebben ze een verhoogde kans op een onterechte schok. We hebben ons hier gefocust op patiënten met ToF, omdat dit de grootste groep patiënten was met een ICD. Er werden meer onterechte schokken gevonden in ICD-patiënten met ToF in vergelijking met ICD-patiënten die geen ToF hadden. Uit ons onderzoek bleek dat het hebben van een ICD bij deze jonge hartpatiënten een duidelijk negatieve impact heeft op het psychosociaal functioneren. Zo deden de ICD-patiënten met een ToF het slechter met betrekking tot het subjectief fysiek functioneren, hun zelf gerapporteerde persoonlijke gezondheid en scoorden ze lager op tevredenheid met het eigen leven dan patiënten met een ToF zonder ICD. Ook hebben we de patiënten met ToF en een ICD vergeleken met oudere hartpatiënten die een ICD hadden, maar geen aangeboren hartafwijking. De patiënten met een ICD en geen aangeboren hartafwijking waren significant ouder (leeftijd gemiddeld 72 jaar) dan de patiënten met een aangeboren hartafwijking (leeftijd gemiddeld 44 jaar).

Ondanks het feit dat de patiënten met een aangeboren hartafwijking jonger waren en een beter fysiek functioneren rapporteerden in vergelijking met oudere ICD patiënten, waren ze angstiger, minder tevreden met hun leven, en konden ze minder goed omgaan met problemen (minder goede coping stijlen). Het verhoogde aantal onterechte schokken gevonden in patiënten met aangeboren hartafwijkingen zou een goede verklaring kunnen zijn voor de belangrijke negatieve impact op psychosociaal functioneren. Verder onderzoek is nodig om dit precies in kaart te brengen.

Implantatie van een pacemaker kan gepaard gaan met het optreden van complicaties. Patienten met een aangeboren hartafwijking hebben vaak op jonge leeftijd al een pacemaker nodig, en zullen daarom vaak langer de tijd hebben om complicaties te ontwikkelen vergeleken met "normale pacemaker patiënten", wat vaak mensen zijn die op oudere leeftijd een pacemaker krijgen. In **hoofdstuk 4.2** hebben we geprobeerd in kaart te brengen of patiënten met een aangeboren hartafwijking vaker complicaties hebben vergeleken met mensen zonder aangeboren hartafwijking, ook het type complicaties is onderzocht. We hebben hiervoor alle patiënten met een aangeboren hartafwijking en een pacemaker getraceerd uit een grote landelijke database, waar patiënten uit verschillende ziekenhuizen in Nederland zijn opgenomen. We hebben deze gegevens gecombineerd met lokale ziekenhuis databases uit het Erasmus MC (Rotterdam), UMC st. Radboud (Nijmegen), Leids Universitair Medisch Centrum (Leiden) en het UZ Leuven (Leuven, België). De meest voorkomende redenen tot pacemaker implantatie waren spontaan verworven sinusknoop- of AV knoop geleidingsstoornissen of sinusknoop- of AV knoop geleidingsstoornissen ten gevolge van cardiale chirurgie. Patiënten met een meer complexe vorm van een aangeboren hartafwijking waren jonger ten tijde van

de pacemaker implantatie en kregen vaker een epicarciaal pacemaker systeem (dit is een systeem waarbij de draden van de pacemaker aan de buitenzijde van het hart zijn bevestigd). In totaal had 11% van de patiënten een complicatie tijdens of vlak na (binnen 30 dagen) de eerste pacemaker implantatie, dit is twee keer zoveel als in de algemene bevolking. De meest voorkomende complicaties binnen 30 dagen na implantatie waren: problemen met de pacemaker draden, bloedingen, infectie van de pacemaker pocket en een klaplong (pneumothorax). Gedurende een follow-up van 12 jaar ontwikkelden 35% van de patiënten een complicatie. De meest voorkomende complicaties waren: pacemaker draad breuk, disfunctie van de pacemaker inclusief vroegtijdige batterij uitputting, verplaatsing (migratie) of erosie van de pacemaker. Pacemaker implantatie op de kinderleeftijd (<18 jaar) was geassocieerd met meer complicaties op de lange termijn. Pacemaker implantatie bij patiënten met een aangeboren hartafwijking geeft dus een verhoogd risico op complicaties vergeleken met de algemene bevolking, in het bijzonder bij patiënten die op jonge leeftijd een pacemaker nodig hebben. Extra aandacht voor deze complicaties kan mogelijk tot verbetering leiden in de toekomst.

Omdat patiënten met een aangeboren hartafwijking (mede vanwege chirurgie) een verhoogde kans hebben op ritmestoornissen zoals atrium fibrilleren (boezem fladderen), hebben wij in **hoofdstuk 4.3** onderzocht of atriaal pacen in patiënten met aangeboren hartafwijkingen beschermt tegen atrium fibrilleren, zoals het geval is in de algemene bevolking. Dezelfde populatie als in hoofdstuk 8 werd gebruikt. Patiënten die een pacemaker hadden gekregen vanwege chronisch atrium fibrilleren, welke niet reageerde op medicatie werden uitgesloten van deelname aan deze studie. In totaal had 23% van de patiënten een of meerdere episoden van atriale ritmestoornissen gehad in het verleden. Twee derde (66%) van de populatie werd atriaal gepaced, de rest van de populatie had een vorm van ventriculaire pacing. Gedurende de 13 jaar follow-up ontwikkelde 43% van de patiënten een atriale arritmie. Er werd geen verband aangetoond tussen atriaal pacen en de kans op atriale ritmestoornissen, dit in tegenstelling tot verwacht. Eerdere episoden van atriale ritmestoornissen waren voorspellend voor het opnieuw ontwikkelen van atriale ritmestoornissen, alsmede implantatie van de pacemaker op volwassen leeftijd (>18 jaar). Concluderend lijkt atriaal pacen geen evident voordeel te bieden op het voorkomen van atriale ritmestoornissen bij deze patiënten.

Chapter 6.2

Curriculum Vitae

CURRICULUM VITAE

Petra Opić was born on November 26th, 1984 in Čakovec, Croatia. In 2002 she obtained the HAVO diploma (sg. De Amersfoortse Berg, NT profile with Biology) and she completed Croatian secondary school (Antun Mihanović, Veenendaal). In 2004 she obtained the Atheneum diploma (sg. De Amersfoortse Berg, NT profile with Biology1&2). After graduating from the Atheneum, she started medical school at the Erasmus University in Rotterdam, where she was active in various committees (Student-representative 2005, 2006, 2007 and Student-member educational board 2005, 2006). During the second year in medical school, she was invited to join a Master of Science in Clinical Research curriculum for excellent students. The final year of this curriculum she joined a research program at the congenital cardiology department in the Erasmus Medical Center (supervisor: prof.dr. JW. Roos-Hesselink). In 2010 she both completed the Master of Science Clinical Research (Netherlands Institute for Health Sciences, Rotterdam, summer session Johns Hopkins, Baltimore, USA) and she also graduated from the preclinical years of medical school (doctorate diploma, Erasmus University Rotterdam).

From 2010 until 2013 she worked on her PhD thesis entitled "Impact of Congenital Heart Defects at Adulthood" at the department of Congenital Cardiology and Child- and Adolescent Psychiatry/Psychology at the Erasmus Medical Center in Rotterdam (supervision: prof.dr. JW. Roos-Hesselink and dr. EMWJ. Utens). During this research period, she was active in the PhD Day committee.

At the moment she is completing her medical internships, which she expects to finish in May 2015.

Chapter 6.3

Portfolio

Ph.D. PORTFOLIO

Personalia

Name Ph.D. Student:	Petra Opić
Erasmus MC Departments:	Congenital Cardiology Child and Adolescent Psychiatry/Psychology
Research school:	Cardiovascular Research School (COEUR), Erasmus MC, Rotterdam, the Netherlands
Promotor:	Prof.Dr. J.W. Roos-Hesselink
Copromotor:	Dr. E.M.W.J. Utens
Ph.D. period:	2010 - 2013

Education

2005 - 2010	Doctorate in medicine, Erasmus University Rotterdam, Rotterdam, the Netherlands
2007 - 2010	Master of Science in Clinical Research, Netherlands Institute of Health Sciences, Rotterdam, the Netherlands
2010 - 2013	Ph.D., Erasmus Medical Center, Rotterdam, the Netherlands

Core courses & seminars

2011	Heart Failure Research course (Cardiovascular Research School Erasmus University Rotterdam (COEUR))
2011	Basic course on 'R' (dept. Molecular medicine), Rotterdam, the Netherlands
2011	Basic Rules & Regulations for Clinical Research (BROK) course, EMWO, Amersfoort, the Netherlands
2012	Research Integrity course (dept. Medical Ethics), Rotterdam, the Netherlands
2012	Vascular Clinical Epidemiology course, COEUR, Rotterdam, the Netherlands
2012	Congenital Cardiology course, COEUR, Rotterdam, the Netherlands
2012	Capita Selecta courses, Rotterdam, the Netherlands
2010-2012	Research seminars, COEUR, Rotterdam, the Netherlands
2012	Seminars Epidemiology & Biostatistics (dept. Biostatistics), Rotterdam, the Netherlands
2012	Seminar Child and Adolescent Psychiatry/Psychology (Prof.Dr. A. Quittner), Rotterdam, the Netherlands
2012-2013	Statistical Journal club (supervisor Prof.Dr. E. Boersma), Rotterdam, the Netherlands
2010-2013	Congenital Cardiology Journal club (supervisor Prof.Dr. JW Roos-Hesselink), Rotterdam, the Netherlands
2010-2013	Monthly Quality of Life meetings for PhD students (supervisor Dr. EMWJ. Utens), Rotterdam, the Netherlands

Attended Symposia and conferences

2010	Karel V symposium, Utrecht, the Netherlands
2010	GUCH 2010, Lund, Sweden
2010	Symposium on Myocardial Infarction, Rotterdam, the Netherlands
2010	NVVC Najaarscongres, Egmond aan Zee, the Netherlands
2011	Karel V symposium, Utrecht, the Netherlands

2011	AEPC Psychosocial Symposium, Lake Balaton, Hungary
2011	NVVC Voorjaarscongres, Arnhem, the Netherlands
2011	PAOS ASR&ABCL Psychosocial Conference
2012	Karel V symposium, Utrecht, the Netherlands
2012	NVVC Voorjaarscongres, Noordwijkerhout, the Netherlands
2013	AEPC Psychosocial Symposium, Köln, Germany
2013	Bayes 2013, Rotterdam, the Netherlands

Teaching

2011	Supervising second-year medical students in writing a review
2011	Supervising fourth-year medical student in writing article
2012	Supervising second-year medical students in writing a review
2012	Supervising fourth-year medical student in writing article
2012	Lecture on the Stuart-Maxwell test in the Journal club of statistics

Committees

2011	COEUR PhD Day organization committee, function: member
2012	COEUR PhD Day organization committee, function: president
2012	Discovery Festival 2012, function: member
2013	COEUR PhD Day organization committee, function: advisor

Conference presentations & posters

2010	NVVC Najaarscongres Egmond aan Zee, the Netherlands (presentation)
2011	AEPC Psychosocial Symposium, Lake Balaton, Hungary (presentation)
2011	COEUR Research Seminar, Rotterdam, the Netherlands (presentation)
2012	NVVC Voorjaarscongres Noordwijkerhout, the Netherlands (presentation)
2012	WEON Conference, Rotterdam, the Netherlands (2 posters)
2012	ESC Conference, Munich, Germany (poster)
2013	AEPC Psychosocial Symposium, Köln, Germany (presentation)

Awards

2010	Best presentation in the session "General Cardiology", NVVC, Egmond aan Zee, the Netherlands
2013	Young Investigator Award, AEPC Psychosocial Symposium, Köln, Germany

Chapter 6.4

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Walking with you in the gentle rain
Our robes are soaked through,
But on the lotus leaves
Not a drop remains.

Modified from *"Zen mind, beginners mind"*,
by Richard Baker, poem for Shunryu Suzuki

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