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Heart rate variability and pacemaker treatment in children with Fontan
circulation

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To children with Fontan circulation

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Abstract

Background

Fontan surgery is performed in children with univentricular heart defects. Arrhythmias are frequent complications, occasionally requiring pacemaker treatment. Previous data regarding indications and risk factors for pacemaker treatment in Fontan patients is limited and conflicting. Heart rate variability (HRV) reflects autonomous nervous activity controlling the sinus node and has been associated with tachyarrhythmias in both adults and children, as well as in adults with sinus node dysfunction (SND).

Aim

To study HRV, arrhythmia and pacemaker treatment in children with Fontan circulation— with the purpose of contributing to the reduction of long term complications in this patient group.

Methods

We have retrospectively reviewed pacemaker therapy in all Swedish patients who underwent Fontan surgery from 1982 to 2017 (n=599). We have also analysed HRV from 24-hour Holter ECG recordings in 112 children with Fontan circulation and in children with univentricular heart defects before bidirectional Glenn (BDG) procedure (n=47), before and on completion of Fontan surgery (n=47 and 45 respectively). Analysis was performed by power spectral analysis and Poincaré method, and results compared with healthy controls. Furthermore, HRV was analysed in Fontan patients who later required a pacemaker due to severe SND. Results were compared with Fontan patients who had SND, without indication for pacemaker treatment, with patients with Fontan circulation without SND and healthy controls. In addition we evaluated the possibility to analyse arrhythmias and HRV in 27 Fontan children using intermittent ECG recordings with a handheld devices at home during a 14-day period.

Results

After a mean follow-up of 12 years, 13% (78/599) of patients with Fontan circulation had received a pacemaker. Patients operated with the extracardiac conduit (EC) had a significantly lower prevalence of pacemaker implantation (6%) than patients with a lateral tunnel (LT) (17%). The most common pacemaker indication in patients with Fontan circulation was SND (64%). Children with Fontan circulation showed significant reductions in several HRV parameters, compared with controls. No significant differences were found between patients operated with LT versus EC (paper I). After BDG the RR interval and SD2

(representing changes in heart rate over 24-hours) significantly increased compared to pre-BDG. Compared with healthy controls, patients post-BDG, had significantly longer RR intervals and reduced overall HRV. P_{HF} (reflecting parasympathetic control of the heart) was significantly reduced after TCPC as compared to before (paper II). Fontan patients with SND showed significantly elevated SD2 (representing changes in heart rate over 24-hours), somewhat reduced in patients that later required a pacemaker (Paper V). Handheld ECG analysis revealed frequent ventricular extra systoles in one patient and episodes of supraventricular tachycardia in another. Seven Fontan patients showed reduced HRV recorded with the handheld device over a 14-day period (paper III).

Conclusions

Overall HRV was reduced in patients with univentricular heart defects during the different surgical stages of Fontan surgery, compared to healthy controls. HRV was reduced in both patients with LT and EC with no significant difference between them. After BDG heart rate was significantly reduced as compared to before. P_{HF} , reflecting the parasympathetic innervation of the heart was reduced after as compared to before TCPC. Pacemaker treatment is commonly needed in patients with Fontan circulation, and SND was the most prevalent indication for implantation. The prevalence of Fontan patients requiring pacemaker treatment was significantly lower in patients with EC. HRV analysis can contribute to management when following-up patients with Fontan circulation.

Abbreviations

AA- aortic atresia

ANOVA- analysis of variance

ANS- autonomic nervous system

AS- aortic stenosis

AV- atrioventricular

AVSD- atrioventricular septal defect

BSA- body surface area

BT- Blalock-Taussig

CI- confidence interval

DILV- double inlet left ventricle

DKS- Damus–Kaye–Stansel

DORV- double outlet right ventricle

EF- ejection fraction

EC- extracardiac conduit

ECG- electrocardiogram

HF- high frequency

HLHS- hypoplastic left heart syndrome

HRV- heart rate variability

IVC- inferior vena cava

LF – low frequency

LT- lateral tunnel

LV- left ventricle

MA- mitral atresia

NYHA - New York Heart Association

PA- pulmonary atresia

PAB- pulmonary artery banding

PDA- patent ductus arteriosus

PSD- power spectral density

RV-right ventricle

SA- sinoatrial

SD- standard deviation

SVC- superior vena cava

TA- tricuspid atresia

TCPC- total cavopulmonary connection

TGA- transposition of the great arteries

VLf- very low frequency

TP- total power

VT- ventricular tachycardia

Original papers

- I. Heart rate variability in children with Fontan circulation - lateral tunnel and extracardiac conduit
Dahlqvist JA, Karlsson M, Wiklund U, Hörnsten R, Strömvall-Larsson E, Berggren H, Hanséus K, Johansson S, Rydberg A
Pediatr Cardiol. 2012;33(2):307-15.

- II. Changes in heart rate variability during surgical stages to completed Fontan circulation
Dahlqvist JA, Wiklund U, Karlsson M, Hanséus K, Strömvall-Larsson E, Johansson Ramgren J, Berggren H, Rydberg A
In manuscript.

- III. Handheld ECG in analysis of arrhythmia and heart rate variability in children with Fontan circulation
Dahlqvist JA, Karlsson M, Wiklund U, Hörnsten R, Rydberg A
J Electrocardiol. 2014; 47 (3):374-82.

- IV. Pacemaker treatment after Fontan surgery – a Swedish national study
Dahlqvist JA, Sunnegårdh J, Hanséus K, Strömvall-Larsson E, Nygren A, Dalén M, Berggren H, Johansson Ramgren J, Wiklund U, Rydberg A
Re-submitted to Congenital Heart Disease after minor revisions.

- V. Sinus node dysfunction in patients with Fontan circulation; could heart rate variability be a predictor for pacemaker implantation?
Dahlqvist JA, Wiklund U, Karlsson M, Hanséus K, Strömvall-Larsson E, Nygren A, Eliasson H, Rydberg A
Re-submitted to Pediatric Cardiology after minor revisions.

Sammanfattning på svenska

Bakgrund

Barn som föds med enkammarhjärta genomgår hjärtoperationer i flera steg, operationsmetoden kallas Fontankirurgi. Det är vanligt att dessa patienter drabbas av hjärtrytmrubbningar och ibland behövs pacemakerbehandling. Tidigare forskning på denna patientgrupp kring riskfaktorer för hjärtrymrubbningar och pacemakerbehandling är få och delvis motstridiga. Hjärtfrekvensvariabilitet (HRV) används för att studera det autonoma (icke-viljestyrda) nervsystemets kontroll på sinusknutan. Förändrad HRV har tidigare associerats till olika typer av rytmrubbning.

Syfte

Att studera HRV, hjärtrytmrubbning och pacemakerbehandling hos barn och ungdomar med enkammarhjärta för att i förlängningen kunna bidra till förbättrad uppföljning avseende sena komplikationer i denna patientgrupp.

Metoder

Vi har studerat alla patienter som genomgått Fontan kirurgi i Sverige från 1982 till 2017 (n=599), avseende pacemakerbehandling. Vi har också analyserat HRV från 24-timmars-EKG-registreringar hos 112 barn och ungdomar med enkammarhjärta och jämfört med 66 friska jämnåriga. HRV analyserades före och efter de olika operationsstegen i Fontankirurgin. Dessutom analyserades HRV från 24-timmars EKG före pacemakerimplantation hos patienter som senare behövde pacemakerbehandling p.g.a. uttalad sinusknutedysfunktion (SND) och jämfördes med patienter med enkammarhjärta och SND men utan pacemakerbehandling, patienter med enkammarhjärta utan SND och med friska jämnåriga. Vi undersökte också möjligheten att använda korta (30 sekunder) registreringar s.k. ”tum-EKG” för analys av hjärtrytmrubbning och HRV.

Resultat

Under 12 års uppföljning efter Fontankirurgi fick 13% (78/599) av patienterna pacemakerbehandling. Bland patienter som opererats med operationsmetoden extrakardiell tunnel (EC) hade en signifikant lägre andel behov av pacemaker (6%) jämfört med dem som opererats enligt metoden lateral tunnel (LT) i förmaket (17%). Den vanligaste indikationen för pacemakerimplantation var SND (64%). Pacemakerbehandling var vanligare vid vissa typer av underliggande hjärtfel; mitralis atresi (MA; 44%), dubbelt utflöde från höger kammare (DORV; 24%) och dubbelt inflöde till vänster kammare (DILV; 20%). Barn med enkammarhjärta hade nedsatt HRV, jämfört med friska jämnåriga. Vi fann ingen skillnad avseende HRV när det gäller EC och LT. Efter operationssteget

bidirektionell Glenn kirurgi (BDG) fann vi signifikant längre RR-intervall (=lägre puls) jämfört med före. Patienter med SND hade signifikant förhöjning av HRV parameter SD2 (som speglar dygnsförändringar i HRV) jämfört med friska kontroller och SD2 var något lägre hos dem som behövde pacemaker p.g.a. SND. Tum-EKG undersökningen visade hjärtrymrubbning hos två och låg HRV hos sju patienter.

Slutsats

Barn, ungdomar och vuxna med enkammarhjärta är en växande patientgrupp med successivt förbättrad överlevnad. Det är viktigt att uppmärksamma sena komplikationer såsom hjärtrymrubbning. Analys av hjärtfrekvensvariabilitet skulle i förlängningen kunna bidra till förbättrad uppföljning för att tidigt identifiera hjärtrymrubbningar.

Introduction/ Background

Univentricular heart malformations

Univentricular heart defects are considered one of the most complex diagnoses in congenital heart disease. This group consists of different malformations of the heart, which all have in common, that the heart cannot be repaired to a normal two ventricle circulation. The underlying cardiac malformations resulting in univentricular circulation can be due to; atresia of one of the atrioventricular (AV) valves (tricuspid or mitral atresia (MA)); because the AV valves both empty into the same ventricle (double inlet left or right ventricle) or common AV valve and only one well-developed ventricle (unbalanced atrioventricular defect). Another common type of univentricular malformation is the hypoplastic left heart syndrome. Additional rare types of cardiac malformations include pulmonary atresia with intact ventricular septum (PA/IVS), double outlet right ventricle (DORV) with remote ventricular septum defect (VSD), extreme Ebstein's anomaly of the tricuspid valve or cases where lesions such as significant straddling of the AV valves, multiple large ventricular septal multilevel outflow obstructions, or a combination of these may make the univentricular pathway a less risky and more predictable choice of treatment(1).

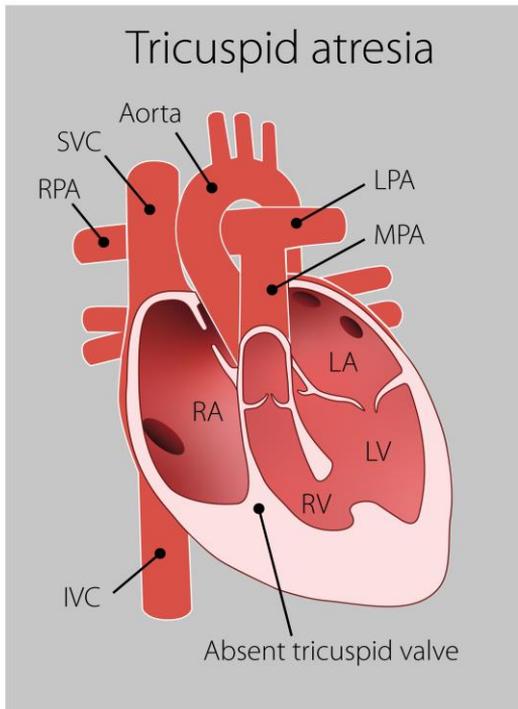
Hypoplastic left heart syndrome (HLHS): is the most common form of univentricular heart defects and occurs in 2.3-2.6 per 10 000 live births (2-4). The classic variant of HLHS is characterised by a diminutive left ventricle (LV) with small left-sided structures and endocardial fibroelastosis. There is a variability of both obstructions (aortic atresia (AA)/MA), (AA/mitral stenosis (MS)), (aortic stenosis (AS)/MS) and size of the LV, ascending aorta and aortic arch. The malformation is ductal-dependent, and without treatment the patient dies in the neonatal period (5). The babies are also dependent on an un-restricted atrial septal defect (ASD) which allows oxygenated and deoxygenated blood to mix. With modern medical and surgical management there has been a large improvement in survival, however, HLHS is still one of the most challenging univentricular malformations to treat and in a recent study the 6-year transplant-free survival rate was 64%(6).

Double inlet left ventricle (DILV): In DILV both atria empty into the left ventricle through two separate AV valves. The dominant left ventricle connects to the rudimentary right ventricle through a VSD. DILV is a heterogeneous anomaly based on presence of ventriculo-arterial discordance, size of VSD, and semilunar valve hypoplasia or stenosis (1). Consequently, a new-born with DILV might have restrictive pulmonary blood flow, unrestrictive pulmonary blood flow with or

without systemic outflow tract obstruction, or a balanced circulation. In a recent follow-up study 10-year freedom from death or transplantation was 87% (7).

Tricuspid atresia (TA): In TA there is an absence of the tricuspid valve, and a hypoplasia of the right ventricle. In most of the cases there is a VSD. In approximately 75% the relationship between the aorta and pulmonary artery is normal, and in 25 % there is a ventriculo-arterial discordance, the pulmonary valve can be atretic, stenotic or normal (8). TA occurs in 0.5-0.8 per 10 000 live births (3, 9). The Fontan operation was first described for TA (10).

Figure 1. Tricuspid atresia with VSD.



SVC= superior vena cava, IVC= inferior vena cava, RA= right atrium, RV= right ventricle, MPA=mean pulmonary artery, RPA= right pulmonary artery, LPA= left pulmonary artery, LA=left atrium and LV= left ventricle.

Atrioventricular defect (AVSD): Fontan surgery is required in unbalanced AVSD and could also be the best alternative if there is straddling of the AV valve with two well-developed ventricles (11). In the unbalanced AVSD, there is hypoplasia of either the right or left ventricle. In most cases, the right ventricle is the dominant ventricle, since generally right ventricular hypoplasia is better tolerated than left ventricular hypoplasia (12). When the AV valve sits more over one ventricle than the other, the contralateral ventricle is typically hypoplastic. Unbalanced atrioventricular AVSD occurs in approximately 10% of patients with AVSD (12).

Pulmonary atresia with intact ventricular septum (PA/IVS): is characterized by complete obstruction to right ventricular outflow with varying degrees of right ventricular and tricuspid valve hypoplasia and of anomalies of the coronary circulation. Patients with a more severe hypoplasia of the tricuspid valve and the right ventricle are more likely to have fistulae between the right ventricle and the coronary arteries (13). PA/IVS is a ductal dependent lesion since there is no blood-flow from the right ventricle to the pulmonary arteries. Babies present as cyanotic due to an atrial level right to left shunt. The pulmonary arteries are small, but their architecture and branching are otherwise normal. PA/IVS is reported to occur in approximately 4 out of 100 000 live births, among them about 20% need a Fontan palliation (14, 15).

Mitral atresia (MA): In MA, the mitral valve is either imperforate or absent and there is a postero-inferior incomplete left ventricle. There is considerable morphologic heterogeneity, which influences the hemodynamic picture. When an even tiny ventricular septum is recognizable, a hypoplastic ventricular chamber almost always exists anteriorly (16).

Heterotaxia syndrome: Heterotaxia, or isomerism occurs in approximately 1 out of 10 000 live births and is characterized by isomeric findings in the thoracic organs and random arrangement of the abdominal organs (17, 18). Patients with heterotaxia syndrome constitute a subgroup of patients with Fontan circulation, and experience high rates of late morbidity and mortality (19). Right atrial isomerism has been shown to be associated with asplenia, morphologic right ventricle, a common atrioventricular valve, pulmonary atresia or pulmonary stenosis, anomalous pulmonary venous drainage (partial or total and with obstruction) and interrupted inferior vena cava (IVC) (20). Children with left atrial isomerism have an absence or hypoplasia of the sinoatrial node and are more likely to have congenital atrioventricular block or a junctional rhythm (18, 20).

Fontan circulation

The Fontan procedure was first described as a palliative operation for tricuspid atresia in 1971(10). Nowadays the Fontan procedure has been modified, and is used in a wide spectrum of univentricular heart defects unsuitable for a biventricular repair. Fontan surgery re-routes the venous return from the superior vena cava (SVC) and IVC to the pulmonary arteries without a pumping ventricle. Pulmonary blood flow is driven by central venous pressure and is augmented mainly by the peripheral skeletal muscle pump (21). For this circulation to be effective, the patient must have a low pulmonary vascular resistance, relatively normal systolic and diastolic function of the single ventricle, and sufficiently large pulmonary arteries to avoid any mechanical resistance.

Thus, the criteria for the procedure includes: normal ventricular function, adequate pulmonary artery size, no distortion of pulmonary arteries from prior shunt surgery, low pulmonary artery pressure (below 15 mmHg), low pulmonary vascular resistance (<4 Woods units/m²), no AV valve leakage, normal heart rhythm and no right atrial enlargement (10). Normal systemic venous drainage was previously a criteria, however a modification of the Fontan procedure, the Kawashima procedure, is used for patients with abnormal systemic venous drainage due to an interrupted IVC nowadays (22).

Since 1971, the surgical technique has developed from the atrio-pulmonary to the total cavopulmonary connection (TCPC). TCPC involves a connection to re-route the venous return from the SVC and IVC to the pulmonary arteries. The surgery is usually staged to give the body time to adjust to the large hemodynamic changes.

Management

In all ductal-dependant congenital heart defects intravenous prostaglandin E1 are administrated to maintain a patent ductus arteriosus (PDA) as soon as the diagnosis is suspected.

Stage I procedures

The majority of neonates with univentricular heart defects need to undergo neonatal cardiac surgery. Depending on the underlying malformation, different procedures are required to provide for sufficient blood flow to both the pulmonary and the systemic circulations. This Stage I procedure is performed during the first weeks of life.

Systemic-pulmonary shunts (modified Blaulock-Taussig (BT)-shunt) or central shunts: In order to secure blood-flow to the pulmonary arteries a baby with TA

and pulmonary atresia or severe pulmonary stenosis will need a systemic-pulmonary shunt. The shunt is typically small (3.5 mm) and designed to last only a few months.

Atrial septectomy or septostomy: is performed in heart defects dependent on a non-restrictive shunt at the atrial level, for example in a baby with HLHS and a restrictive ASD may require a balloon atrial septostomy (23).

Pulmonary arterial banding (PAB): is performed when there is over-circulation to the pulmonary arteries, for example in a baby with DILV.

Norwood operation: with a modified BT-shunt or RV (right ventricle)-PA (pulmonary artery)-(Sano)-shunt is performed in HLHS. During the Norwood procedure a neo-aorta is created by dividing the pulmonary artery and using the transected pulmonary artery as well as homograft material, to construct a new ascending aorta and aortic arch. The small native aorta is incorporated into the graft.

Damus-Kaye-Stansel procedure: is performed in patients with a univentricular heart defect with systemic outflow obstruction, for example in HLHS.

A minority of patients with univentricular defects have balanced systemic and pulmonary circulations, and thus may not need to go through a stage I surgery. For example is a baby with TA and PS where the restriction of pulmonary blood-flow is enough to ensure adequate oxygenation of the blood, but without pulmonary over-circulation.

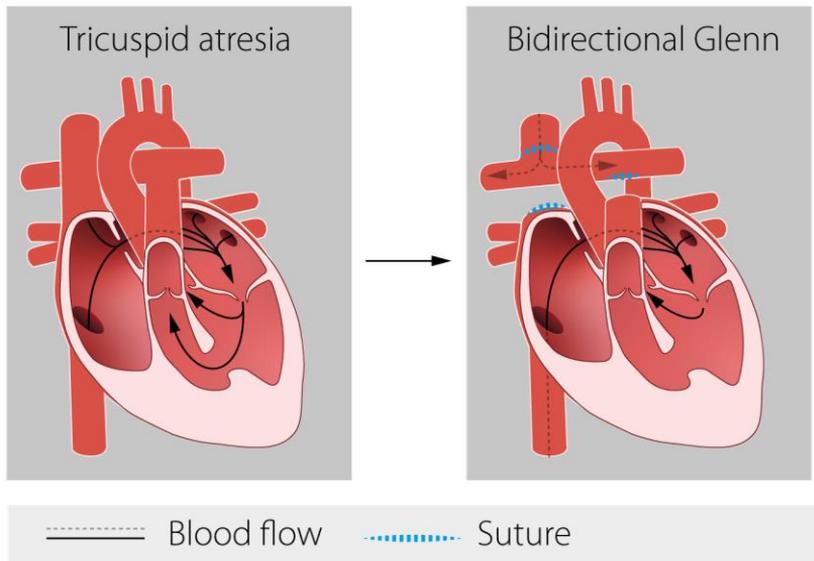
Bidirectional Glenn procedure (BDG)

Stage II of the Fontan procedure is the BDG or bidirectional cavopulmonary connection (BCPC), which involves transection of the SVC and, oversewing of the proximal end. The distal end is anastomosed end-to-side with the pulmonary arteries. This is typically performed between three to six months of age. At this point the pulmonary vascular resistance has declined and the pulmonary arteries have grown to an adequate size. During BDG procedure shunts or PA-bands are removed.

The Glenn shunt circulation is characterised by passive flow. Venous return passively drains from the SVC into the pulmonary arteries. Advantages of the Glenn circulation are that the pulmonary blood flow now is effective and adequate, and the single ventricle now has a reduced pressure and volume load.

However, since the IVC empties to the single ventricle that pumps the blood to the systemic circulation the child will still be cyanotic (Figure 2).

Figure 2. Bidirectional Glenn (BDG).



To the left: An example of univentricular heart (Tricuspid atresia and ventricular septum defect) before BDG. To the right: In the BDG procedure the superior vena cava (SVC) is connected to the pulmonary arteries.

Completion of Fontan circulation

In earlier days the atrio-pulmonary Fontan, was used. In this operation the right atrial appendage was directly anastomosed to the pulmonary artery, providing a pathway for blood from the IVC and SVC to the pulmonary circulation. The atrial septum was left intact, and there should be no residual shunting between the atria. This form of Fontan is associated with more late complications and may need conversion to cavopulmonary connection at a later date (24).

Total Cavopulmonary connection (TCPC)

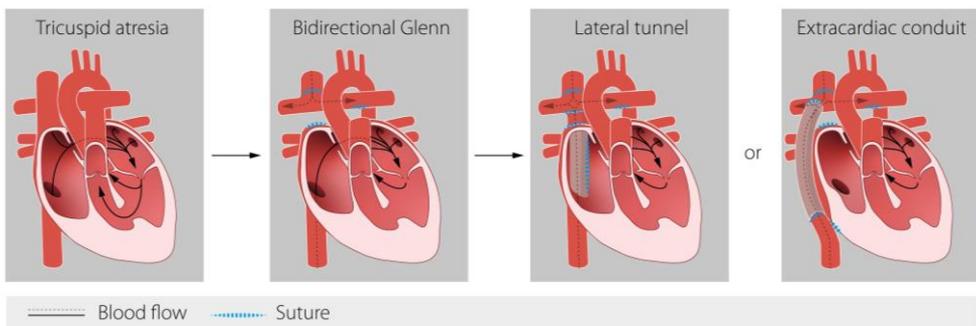
The stage III procedure, TCPC, involves connection of the IVC to the pulmonary arteries and is performed at 2-4 years of age. By this time blood oxygen saturation

will have decreased. After the TCPC the venous return flows passively into the pulmonary arteries, then the oxygenated blood returns to the single ventricle which pumps to the systemic circulation. This procedure results in the child being relieved of cyanosis. The deoxygenated coronary sinus is typically left to drain into the systemic circulation, consequently the patient does usually not have a 100 % blood oxygen saturation.

Lateral tunnel (LT) and extracardiac conduit (EC)

The surgical technique used for IVC connection in TCPC surgery, described in 1988 (25) has evolved from an intra-atrial lateral tunnel (LT) to the extracardiac conduit (EC) (Figure 3). The intra-atrial LT surgery is performed via cardiopulmonary bypass and cardioplegic arrest (or induced ventricular fibrillation). A GORE-TEX® baffle is constructed in order to direct the blood flow from the IVC to the superior end of an atriopulmonary anastomosis. A small portion of atrium remains in the circuit to provide growth potential, and acts to minimise the risk of dilatation and arrhythmias compared to the older atrio-pulmonary Fontan method. Thus, there is still scarring in the right atrium after the LT operation. The EC was described in 1990 (26). The IVC is transected and the cardiac end is over sewn. A GORE-TEX® tube graft is sutured to the IVC and the other end of the tube is connected end to side to the right PA.

Figure 3. Surgical stages of Fontan circulation.



To the left: example of univentricular heart (TA and VSD) before BDG. In the middle to the left: In the BDG procedure the superior vena cava (SVC) is connected to the pulmonary arteries. To the right: The two variants of the total cavopulmonary connection (TCPC); lateral tunnel (LT) or extracardiac conduit (EC).

The EC has several theoretical advantages, including flexibility in anatomically difficult situations (heterotaxy), the avoidance of sinus node manipulation, decreased suture lines and pressure in the right atrium (decreasing arrhythmogenic potential), and avoidance of cardioplegic arrest since no access to the right atrium is needed (27, 28). Potential drawbacks of the EC Fontan include the lack of growth potential and the risk of thrombosis in the prosthetic conduit. These theoretical advantages of EC versus LT have not been fully investigated, and controversy remains in this field (27, 29, 30).

In Sweden the Fontan type of surgery was sporadically used until the beginning of the 1990s before developing into routine management in patients with univentricular heart defects. A centralisation process was performed in 1992 and the pediatric hospitals in Gothenburg and Lund were assigned to perform all pediatric cardiac surgery. Beginning in 1998, the preferred surgical method in Sweden has switched from LT to EC.

Fenestration

A fenestration can be created during TCPC surgery. A fenestration is a small defect that allows shunting between the venous and systemic circulations. After Fontan surgery a fenestration offers a bypass, which reduces venous congestion, and increasing ventricular pre-load ultimately leading to increased cardiac output. With the increase in cardiac output comes a decrease in arterial saturation. Fenestration has been proven to minimise post-operative low cardiac output, pleural and pericardial effusions and ascites, as well as long-term complications such as diminished exercise performance, and protein-losing enteropathy (PLE) (31-33). The mechanism for this is that flow through the fenestration increases systemic ventricular preload, which in turn improves cardiac output. In addition, in LT TCPC, the fenestration limits the increase in systemic venous pressure and thereby might inhibit development of postoperative pleural effusion and ascites. Despite the potential benefits of fenestration, there are drawbacks including the risks of systemic embolization and systemic desaturation (34). In approximately 30-40% of the patients fenestrations close spontaneously; it can also be closed by a catheter intervention (34, 35). In Sweden fenestration is not routinely used.

Physiology of the Fontan circulation

Optimal cardiac output in the Fontan circulation requires attention to volume status (preload), vascular resistance (afterload), heart rate, rhythm, and myocardial contractility.

The normal heart has two ventricles that pump blood in synchrony to the pulmonary and systemic circulations. In the Fontan circulation, the blood-flow to, and through, the pulmonary circulation is driven passively by the remaining post capillary energy. Since there is no ventricle pumping to the pulmonary circulation, systemic venous pressure remain elevated compared to a normal biventricular circulation (36). Many of the common problems seen post-Fontan surgery are related to resistance in the pulmonary vascular bed. High resistance in the pulmonary vasculature creates a bottleneck, with congestion upstream and restricted flow downstream (36). In a Fontan circulation it is necessary that the systemic venous pressure, the resistance in the pulmonary vasculature and the ventricular filling pressures remains low. The contractility of the ventricle can increase the cardiac output to a certain degree, but the pulmonary vascular resistance has a much larger influence on cardiac output. The limit of the cardiac output is the preload, and well developed pulmonary arteries is extremely important (36). Thus, the Fontan patient do not tolerate hypovolemia or arrhythmias well (37).

The single ventricle, during the stages to complete Fontan circulation, is exposed to different volume loading conditions. During fetal life and after the initial palliation there is a large volume overload, approximately 250-350% of normal/body surface area (BSA) (38). After BDG, the volume load is reduced to about 90% of normal /BSA (38). The Fontan operation will result in further reduction of volume loading to 50-80 % of load of the normal ventricular load (38). During exercise a person with Fontan circulation will experience limitations compared to persons with normal biventricular hearts. During exercise, in a normal circulation, pulmonary blood flow is increased though reduction of pulmonary vascular resistance due to vasodilatation and increased work of the right ventricle. A person with Fontan circulation has two major disadvantages during exercise; firstly, the reactivity of the pulmonary vasculature is limited and a right ventricle is absent (36). Regular exercise may have positive effects on the pulmonary vascular resistance by vessel recruitment and vasodilatation (39). Secondly, a regular atrial rhythm with AV synchrony is one of the most important prerequisites for the long-term effective functioning of this preload dependent circulation, especially during exercise.

In this abnormal type of circulation, even mild forms of arrhythmia may therefore be deleterious for the patient with Fontan circulation by hampering cardiac output.

Prognosis

Due to advances in surgical methods and pre-, peri- and post-operative medical care for these patients, life expectancy is steadily improving. Post-operative survival 20 years after Fontan procedure is approximately 85% (32, 40). In patients over 16 years, the incidence of sudden death is moderately elevated; 2.1/1000 patient years, compared with all patients with congenital heart disease with an event rate of 0.4 deaths/1000 patient years (41). Co-morbidities or complications are becoming more and more important. Early detection of Fontan associated disease is the key to reduce mortality.

Complications

Improvements of the diagnostics, cardiac surgery, and intensive care procedures have made it possible for children with different complex univentricular heart malformations to be palliated with excellent survival (28, 32, 40). Patients with Fontan circulation enjoy a nearly normal life, including mild-to-moderate physical activities (42). In a large study of Fontan survivors more than 90% were in New York Heart Association (NYHA) class I or II (43). As patients live longer, long term outcomes and late complications are now becoming more apparent.

Follow-up of patients with Fontan circulation is challenging since there is a high risk for morbidity and mortality and also a large variability between patients with very good and very poor outcome (40). Many factors such as underlying anatomical diagnosis, elevated right atrial or central venous pressure, history of PLE contribute to mortality or heart transplantation (40).

PLE: is a rare and troublesome complication of the patients (44). The pathophysiology is not fully understood. A multifactorial proposed mechanism include; a response to the altered hemodynamics, especially low cardiac output with increased mesenteric vascular resistance, an inflammatory process and an altered function of the enterocytes (45). During follow-up symptoms of diarrhoea, abdominal pain, peripheral oedema, pleural and pericardial effusions, ascites and failure to thrive indicate PLE. Laboratory results show low serum albumin and increased alpha-1-antitrypsin in faeces (46). Treatment of PLE is individualised, with the aim of improving cardiac output. Underlying arrhythmia causing decrease in cardiac output should be ruled out. Pacemaker treatment may be indicated. PLE is considered an indication for heart transplantation.

Plastic bronchitis: Is a very serious rare complication. In plastic bronchitis bronchial casts obstruct the airways (47). Plastic bronchitis may require takedown of the Fontan circuit or cardiac transplantation (48).

Liver disease: Liver disease is an increasingly recognised complication post Fontan palliation. Hepatic fibrosis progressing to high grade cirrhosis, and even hepatocellular carcinoma, is a serious complication in adults with Fontan circulation (49).

Kidney disease: Patients with Fontan circulation are often at risk of developing reduced kidney function. The pathophysiological mechanisms proposed are end-organ dysfunction due to low cardiac output and venous congestion (50).

Thrombosis: Patients with univentricular heart defects are at increased risk of thromboembolic events though out life. In the neonatal period, occlusion of the systemic-pulmonary shunt is a significant risk with devastating consequences (51). As patients get older thromboembolic events continues to be a common complication (52). Patients with atrial arrhythmia are at increased risk of thromboembolism (52).

Fontan failure

The Fontan circulation is initially well-tolerated by most patients. Early Fontan circuit failure is most commonly the result of underappreciated preoperative risk factors or intraoperative myocardial injury (53).

Several factors contribute to the ventricular dysfunction seen in patients with Fontan circulation. The heart defect can in some cases involve some grade of cardiomyopathy. A morphological right ventricle can adapt to the hemodynamic demands of a Fontan circulation, but over time, it is more likely that a morphological right ventricle than a morphological left ventricle fails (54). The accumulated effect of multiple surgeries, as well as periods of with a volume-overloading of the ventricle during neonatal and childhood palliation may negatively impact long-term ventricular function (53). Furthermore, in the Fontan circulation, the ventricle must drive cardiac output through two resistance beds, resulting in a chronic increase in pressure work (55).

Arrhythmia

Atrial arrhythmias and sinus node dysfunction are the most frequent complications in patients with Fontan circulation (42, 56-62). The development of any arrhythmia, including both tachyarrhythmias and bradyarrhythmias, has been shown to be independent predictors of late Fontan failure and of sudden death (60).

Tachyarrhythmia

Supraventricular tachycardia (SVT)

The most common type of supraventricular tachycardia in Fontan patients is intra-atrial reentrant tachycardia (63). Risk factors for development of atrial tachycardia include heterotaxia syndrome, SND, older age at Fontan procedure, early postoperative tachycardia, atrio-pulmonary type of Fontan, and duration of follow-up since Fontan procedure (64-67). In the atrio-pulmonary Fontan there is a “stretch” in the right atrium, this contributes to the high incidence of arrhythmia (60, 67). Other pathophysiological mechanisms are fibrosis, scarring and suture lines within the atrial tissue that act as a substrate for atrial reentrant circuits to develop (68, 69). With the development of the EC Fontan surgical technique there was a hope of reduction in the incidence of arrhythmia. Since the EC conduit minimises atrial incisions, late complications like SND and atrial tachycardia were expected to decline (60, 70). Concerning late tachyarrhythmia after TCPC surgery studies comparing LT and EC have shown mixed and conflicting results. Lower incidence of atrial tachycardia in the EC group compared to the LT group has been shown in some studies (27, 71, 72), but other studies have shown no difference in the incidence of late atrial tachycardia between LT and EC Fontans (73, 74).

In the patient with Fontan circulation, persistent atrial tachycardia is a serious condition, associated with morbidity and mortality (37, 75). When arrhythmia presents careful investigation concerning electrolyte and thyroid function but also ventricular function, AV-regurgitation, outflow obstruction, obstruction in the Fontan circuit is mandated. Immediate treatment options include electrical cardioversion, overdrive pacing manoeuvres or anti arrhythmic drugs. Long-term therapies include anti-arrhythmic drugs, intermittent cardioversions, catheter ablation or Fontan revision surgery combined with Maze procedure (63, 76, 77).

Ventricular tachycardia (VT)

Ventricular arrhythmia is not as common as atrial tachycardia, however VT and complex ventricular extra systoles occur among children and adolescents with Fontan circulation (62, 71). VT is assumed to be an important cause of sudden death in patients with Fontan circulation (40). However, the clinical relevance of asymptomatic ventricular arrhythmia is, found on Holter recordings in children with Fontan circulation, is uncertain; non-sustained VT was not associated with sudden cardiac events in patients with Fontan palliation in one study (78).

Bradycardia

Sinus node dysfunction (SND)

SND is found in 11-45% of patients with Fontan circulation (29, 58, 59, 71, 79-82). SND is broad array of abnormalities in sinus node and atrial impulse formation and propagation (83). A definition often used in pediatric cardiology research studies is one or more of the following: 1) minimal or mean heart rate 2 standard deviations (SD) below the mean value for age and gender (84), 2) a dominant junctional rhythm, 3) sinus pauses of three or more seconds on Holter recording and/or 4) peak heart rate during exercise lower than 80% of the predicted value for age and gender (56, 71).

SND in patients with Fontan circulation is likely to occur as a result of either damage to the sinus node during surgery or reduced blood supply to the sinus node that may result in fibrosis (58, 81, 85). In some cases the underlying anatomy, such as left atrial isomerism, may contribute to development of SND (18, 86). Late SND is more likely to occur in patients with SND in the early postoperative period (56). A lower incidence of SND in patients with EC when compared with LT has been shown in some studies (79, 81, 87). In contrast, others have found a higher incidence of SND among patients with EC when compared with patients with LT (29, 58).

Sinus node dysfunction is often associated with limited exercise capacity. With loss of AV-synchrony, there is a risk of aggravation of AV valve regurgitation, which in turn may contribute to development of atrial tachycardia through atrial remodeling (88, 89). Pacemaker treatment is indicated when the SND is associated with documented symptoms (83, 90). Symptoms compatible with cerebral hypoperfusion include syncope, pre-syncope dizziness and fatigue associated to bradycardia. Furthermore, an inadequate heart rate response to physical activity “chronotropic incompetence” is a symptom of SND (83, 90).

Atrio-ventricular (AV) block

AV block may occur spontaneously, more commonly in certain univentricular heart defects (heterotaxy syndrome, AVSD, AV/VA discordance) or following surgical procedures or catheter interventions (90). Surgical AV block was significantly more common in patients with univentricular heart defects (3.29%) compared to patients after cardiac surgery for bi-ventricular repair (0.87%) {Marshall, 2016 #428}. The aetiology to surgical AV block is described as multifactorial; transection of the conduction system, as well as ischemia, oedema, and blunt trauma as isolated features or in combination, are all described as probable causes of AV block (91).

Pacemaker implantation

Previous studies have reported a 7-25% incidence of permanent pacemaker implantation in patients with Fontan circulation (59, 61, 92, 93). Two studies have shown left morphology of the single ventricle to be a risk factor for pacemaker implantation (92, 93), however, other studies could not find this correlation (28, 62). Stephenson et al. reported that Fontan survivors with L-looping registered in the North American Pediatric Heart Network Fontan Cross-sectional cohort had an increased need for pacemaker treatment (62). Another study on the same cohort showed that patients with pacemakers were taking a greater number of medications, and had undergone more cardiac procedures (92). Additionally, one study has found that the risk for permanent pacemaker implantation was higher after LT than after EC Fontan surgery (93). However, other studies did not find LT to be associated with a higher risk of pacemaker implantation than EC, after adjusting for time after Fontan surgery (59, 71, 74).

Criteria for pacemaker implantation in Fontan patients include; SND with documented symptomatic bradycardia, chronotropic incompetence, tachy-brady syndrome, high degree of AV-block or any degree of AV-block associated with symptoms, ventricular dysfunction or ventricular arrhythmias presumed to be due to AV-block (83, 90).

SND is one of the major indications for pacemaker implantation among patients with Fontan circulation (94). Pacemaker treatment for SND has a favourable effect on hemodynamics, may relieve symptoms such as fatigue and permits effective treatment with anti-arrhythmic drugs (80). Pacemaker treatment may also protect against atrial reentrant tachycardias in patients with tachy-brady syndrome (95). In patients with Fontan circulation, pacemaker implantation has been shown to predict adverse events, such as death or heart transplantation (96). In the Pediatric Heart Network Fontan Cross-Sectional Study, patients with pacemakers were shown to have poorer functional status and mildly decreased systolic ventricular function compared to patients without pacemakers (92). Cardiac resynchronization therapy (CRT) is a well-recognized treatment in systolic heart failure in patients with biventricular hearts. There is limited evidence for CRT in Fontan circulation. Recommendations for CRT say that it may be considered in single ventricle patients with an ejection fraction (EF) $\leq 35\%$, NYHA function Class II-IV, or wide QRS complex ≥ 150 milliseconds (90).

Epicardial pacing is the preferred method in patients with Fontan circulation (97). A transvenous approach can be used but it is technically challenging and there are risks of Fontan obstruction and thromboembolism (98).

ECG monitoring after Fontan surgery

Ambulatory ECG-Holter monitoring, often for 24-hours, is widely used to screen for arrhythmia (99). Periodic cardiovascular exercise testing, in order to exclude chronotropic incompetence, arrhythmia during exercise or desaturation is also recommended (100).

Intermittently occurring arrhythmia may be hard to detect on conventional Holter-recordings (101, 102). Another option for rhythm surveillance is a handheld patient activated ECG device. In paper III we used the Zenicor®-ECG (Figure 4). This hand-held ECG device allows multiple short (30 second) recordings of ECG over a longer period of time than possible with a Holter monitor. ECG trace bipolar extremity lead I is recorded when the patients press their thumbs against two sensors on the hand-held device. One of the first clinical applications for the hand-held ECG was for detection of recurrent atrial fibrillation (AF) (103). In adults, intermittent short ECG recording during a four week period proved more effective in detecting AF and paroxysmal supraventricular tachycardia in patients with ambiguous symptoms arousing suspicions of arrhythmia than 24-hour Holter ECG (104). In children hand-held ECG has been evaluated for detection of paroxysmal supraventricular tachycardia with 92% sensitivity (105). Ability to identify abnormal ECGs in the same study showed a 77% sensitivity and 92% specificity (105).

Figure 4. ECG recording with hand-held device

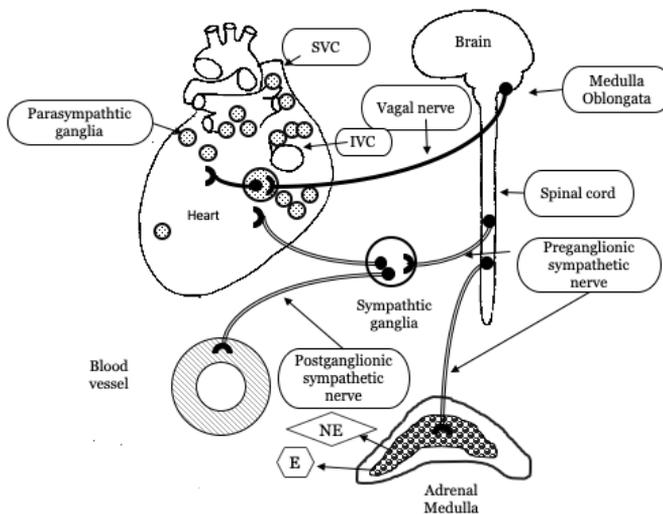


The autonomic control of the circulation

The autonomic nervous system (ANS) acts unconsciously and among other functions it regulates the circulation by the sympathetic and the parasympathetic limbs. The latter generally have opposite effects on the circulation, where one system activates a physiological response and the other one inhibits it. The sympathetic nervous system acts like a mobilizing system and the parasympathetic nervous system is a dampening system. By controlling the sinoatrial (SA) node, the sympathetic nervous system increases the heart rate and the contractility of the heart muscle, whereas the parasympathetic nervous system decreases heart rate. The parasympathetic nervous control originates in the vasomotor centre in the medulla oblongata and affects the heart via the vagal nerve (Figure 5). The pre-ganglionic neurons pass close to the aorta and superior vena cava and branch into epicardial subplexuses (106). Small nerve fibres form an extensive neural network of interconnecting nerve fibres. These nerves innervate the atria, SA and AV nodes, conducting tissue and ventricles (107). Histological studies have investigated the positioning and location of the cardiac ganglia. In the normal human heart the right atrium is innervated by two subplexuses, the left atrium by three, the right ventricle by one, and the left ventricle by three subplexuses (106). Each ganglionated plexus is composed of sympathetic, parasympathetic and mixed nerve fibres (108). In a study of the topography of the human heart 836 ± 76 ganglia were identified and by estimating the number of neurons within epicardiac ganglia, it was calculated that approximately 43000 intrinsic neurons might be present in adult hearts and 94000 neurons in young hearts (fetuses, neonates, and children) (106). The human epicardiac ganglia are formed and located in their definitive position already from 15 weeks after gestation (109). Large populations of cardiac ganglia are located adjacent to the nodal tissue of the heart. The SVC and IVC have moderate collections of cardiac ganglia on their posterior surfaces. In particular, the SVC, near the junction of the right atrium and inferior to the SA node, is moderately populated with ganglia (110).

The sympathetic nerves arise from the paravertebral ganglia, where the Stellate ganglion is particularly important (111) (Figure 5). The adrenal medulla is considered a modified sympathetic ganglion. Cells in the adrenal medulla are innervated by sympathetic preganglionic neurons and medulla release norepinephrine and epinephrine to the circulation. The sympathetic activity is mediated via norepinephrine which has a slower metabolism, this is why the sympathetic activity is more slowly mediated, but with longer lasting effects on the heart rate and heart rate variability compared with parasympathetic control (112).

Figure 5. The autonomic innervation of the heart.



The heart in a posterior view. Note dense populations of ganglia in relation to the SVC= superior vena cava, and the IVC= inferior vena cava.

Under normal conditions, there is little efferent sympathetic neural input to the sinoatrial node, however, there is substantial efferent parasympathetic input via the vagal nerve which slows the sinus node rate. Thus, resting heart rate is determined by both sympathetic and parasympathetic tone. Baroreceptors register blood pressure and send this information to the medulla oblongata. Medulla oblongata will respond through a change in the autonomic tone, in order to maintain pressure. Increased activity of the sympathetic nervous system is an important mechanism of the body to compensate altered hemodynamics due to heart disease. However, chronic sympathetic activation cause maladaptive and even detrimental effects to the cardiovascular system and the heart (113). Chronically increased sympathetic activity with elevated plasma catecholamines can be found in the setting of myocardial dysfunction (114). Elevated levels of catecholamines change electrophysiological properties of the myocardium and promote arrhythmia, through different mechanisms; i.e., enhanced automaticity, triggered activity, or re-entry (115). When there is sympathetic dominance the risk for arrhythmia and sudden death is increased (115-117). The parasympathetic nervous system may have important antiarrhythmic effects by reducing the heart

rate and counteracting the pro-arrhythmic effects of the sympathetic nervous system (118). On the other hand, excessive vagal tone is undesirable since excess vagal tone can result in SA-block and syncope.

Autonomous regulation, specifically of the cardiac ganglia, seems to be of importance for the protection from arrhythmic events. Cases of sudden cardiac death associated with arrhythmias in which no apparent pathology was present in the myocardium, coronaries, nodal tissue or conductive tissue of the heart, but where localised inflammation of cardiac ganglia was seen, have been described (119).

Surgical trauma to cardiac ganglia may also lead to withdrawal of cardio-protective vagal influences and predisposition toward arrhythmogenesis. When creating the bidirectional cavopulmonary connection (BDG), the SVC is transected, with the proximal end oversewn and the distal end anastomosed end-to-side to the pulmonary arteries. This might affect the ganglia located on the posterior surfaces of SVC near the junction of the right atrium. During cardiac surgery for the creation of the extracardiac conduit, the IVC is transected which could damage the ganglia located close to the IVC-atrial junction or at the medial and posterior surface of the IVC. In particular, the region on the SVC near the junction of the right atrium and inferior to the SA node is densely populated with ganglia (110).

Chronic changes appear in the cardiac autonomic control in order to compensate for hemodynamic alterations due to the single ventricle malformation itself, or to the different hemodynamic situations before and after BDG and after TCPC, or due to the surgery-related damage to the autonomic innervation of the heart. Assessment of cardiac autonomic function may provide insights to future disease progression. Increased sympathetic activity and decreased parasympathetic activity is strongly associated with myocardial dysfunction. A dominance in sympathetic activity plays a significant role in the progression of ventricle dysfunction and may contribute to long term sequelae, including fibrosis, after Fontan surgery (120).

Thus, to a certain extent the problem with the interpretation of low HRV is like that of the chicken and the egg. During the interpretation of low HRV one must keep in mind that increased sympathetic activity and decreased parasympathetic activity may not only be caused by autonomic dysfunction but also be caused by a physiological response to a decreased ventricular function, related to worse prognosis.

Heart rate variability (HRV)

A healthy heart does not perform as a metronome, i.e. it does not beat with a fixed rate. The oscillations in heart rate in a healthy heart are complex since the cardiovascular system constantly adjusts to physical inputs to keep homeostasis. Thus, the interval of heart beats is not constant but varies in certain patterns. HRV measures these beat-to-beat fluctuations in the RR intervals of the ECG. Analysis of HRV patterns allows the identification and measurement of underlying physiologic rhythms. One such rhythm is associated with breathing. Breathing gives rise to variations of thoracic blood pressure, which mainly affect the venous return to the heart. The baroreflex loop will then via the parasympathetic nervous system give rise to compensatory modulations of the heart rate. In 24 hour-ECG recordings, the predominant physiologic rhythm that accounts for the most HRV is the circadian rhythm, with relatively increased sympathetic activity associated with higher heart rates during the daytime and increased vagal activity associated with lower heart rates during the night (121). The strength of these rhythms is expressed by the magnitude of various frequency-domain and time-domain HRV measures. However it is important to observe that HRV, apart from reflecting the normal cardiac autonomic control (normal sinus rhythm), also reflects random variations due to underlying abnormalities in cardiac control (erratic rhythm).

How to measure HRV

HRV parameters normally are determined based on long-term recordings during daily activities over 24-hour periods, or as short-term (5 to 30 minutes) ECG recordings. A 24-hour registration better represent processes with slower fluctuations (e.g., circadian rhythms) and the cardiovascular system's response to a wider range of environment stimuli, than short-term recordings (123). Short term ECG recordings are reliable under controlled conditions; lying supine or standing position, and restrictions of drugs including coffee some hours before testing (124). However, the use of very short HRV recordings (10 seconds) has also been suggested. These very short recordings do not test the ability to change heart rate, but can detect markedly reduced HRV; in particular, if performed on multiple occasions (125).

Before HRV analysis is performed, ECG recordings are evaluated using regular procedures for analysis of standard 24-hour ambulatory ECG recordings. Assessment of underlying rhythm, cardiac conduction disturbances and the presence and frequency of arrhythmic beats carried out. RR intervals are normally automatically detected in the ECG recordings. Therefore, even after careful manual editing, additional error correction is often necessary before HRV analysis, by using automatic computerised filters to remove arrhythmic beats,

noise and or artefacts that interfere with the analysis of HRV (122). In children, with sinus arrhythmia, the filtering process has to allow a wider range in RR intervals, since the choice of the threshold is a trade-off between the ability of removing ectopic beats and the risk for removing normal sinus beats in subjects with pronounced respiratory sinus arrhythmia (122).

Spectral analysis

Overall HRV is normally characterized by the variance of the RR intervals over a given time interval, which is equivalent to the power of the signal. Spectral analysis works like a mathematical prism that divides the total power of HRV into components with different frequency and amplitude. The spectral analysis is graphically represented by a plot of the power spectral density (PSD), which shows the distribution of power into a large number of frequency components (123) (Figure 6). The definition of three HRV spectral components is based on the different underlying rhythms that the HRV signal is assumed to reflect. The area within each frequency region is then calculated representing the power of the spectral components. The PSD is expressed in milliseconds squared (ms^2) divided by cycles per second (ms^2/Hz) (121). Thus, the spectral components are expressed in ms^2 . In this thesis, the mathematical method used to calculate the power spectral density (PSD) is Fast Fourier transformation(124). The following frequency domain indices are determined:

- Total power (P_{tot}) in ms^2 – P_{tot} is the total variance in HRV.
- Very low frequency power (VLF, P_{VLF}) in ms^2 – VLF: (0.003 to 0.04 Hz). VLF is assumed to reflect parasympathetic activity related to heat control and the renin-angiotensin system. The VLF band cannot be analyzed from shorter (< 5 min) ECG recordings since the periods of oscillation measured have very low frequencies. Twenty-four-hour ECG registrations are preferred (121). The most low-frequent fluctuations in the VLF region are strongly associated with increased mortality (125-127) in the adult populations with cardiac disease, however there is uncertainty regarding the physiological mechanisms responsible for activity within this band. The heart's intrinsic nervous system appears to contribute to the VLF rhythm (121). The thermoregulation and the renin-angiotensin system may also influence VLF power (128). Moreover, parasympathetic activity may contribute to VLF power since parasympathetic blockade decreases VLF significantly (129).
- Low-frequency power (LF, P_{LF}) in ms^2 – LF: (0.05 to 0.15 Hz). Represents the parasympathetic modulation of the heart rate in combination with sympathetic modulation of the peripheral vasculature. The rhythm is

believed to arise because of modulations of the blood pressure via the baroreflex. The LF band is produced by both the parasympathetic and the sympathetic nervous systems in combination with regulation of blood pressure by baroreceptors (123).

- High-frequency power (HF, P_{HF}) in ms^2 – HF: (0.15 to 0.50 Hz). Represents the parasympathetic modulation of the heart rate. The variations are synchronous with the breathing. The HF band is produced by the parasympathetic nervous system alone (130). HF corresponds to the heart rate variations related to the respiratory cycle (129).
- LF/HF ratio – Often used to estimate the "sympathovagal" balance. However, this term is something of a misnomer since lower frequency fluctuations may be related to both sympathetic and parasympathetic activity. The LF/HF ratio should be based on 24 hour ECG recordings. The assumptions underlying the LF/HF ratio is that LF power is generated mainly by the sympathetic nervous system, while HF power is produced by the parasympathetic nervous system. A low LF/HF ratio reflects parasympathetic dominance and a high ratio reflects a sympathetic dominance (130).

Note that, if HRV is very irregular or even completely random (as in atrial fibrillation), then power is distributed over a wide frequency range, with nearly the same amplitude at all frequencies in the PSD; also referred to as white noise. Compare with white light with a uniform mixture of all colours.

The Poincaré diagram

The spectral analysis presumes that the HRV signal consists of different oscillating rhythms within different frequency regions. To describe more complex systems, non-linear methods, such as the Poincaré diagram can be used. In the Poincaré diagram each RR interval is plotted against the following RR interval. To quantify the variability an ellipse is fitted around the points in the plot a two-dimensional vector analysis of a Poincaré plot is used to measure separately the standard deviation in two perpendicular directions (131) (Figure 6):

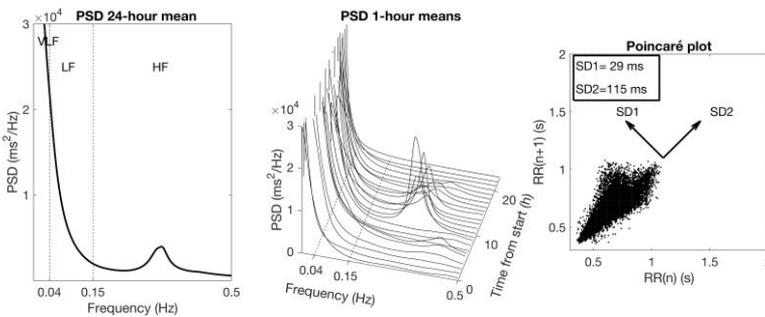
- **SD1** representing the instantaneous beat-to-beat RR interval variability which is influenced by the parasympathetic mediated incautious action on the sinus node.
- **SD2** representing the continuous long-term variation in mean RR interval, which is influenced by sympathetic innervation.

- **SD1/SD2** the SD1/SD2 ratio is often increased during arrhythmia. It has also been considered as a marker of the autonomic balance during absence of arrhythmia, since it correlates with the LF/HF ratio (132).

This plot is useful to detect if arrhythmia is affecting the HRV signal (133). A Poincaré plot in a subject with normal HRV and not affected by arrhythmias, will look like an ellipse in 5-minutes recordings and as a comet in 24-hour recordings (Figure 6). If there are arrhythmias, the plot will have a V-shaped or a more complex pattern with clusters of points within particular areas on both sides of the diagonal of the diagram.

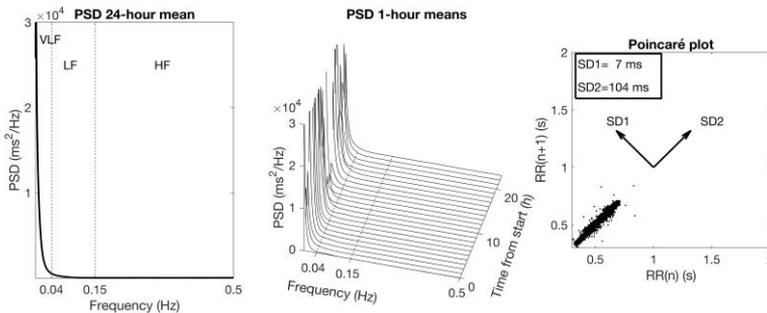
Low HRV (Figure 7) is associated with worse outcomes in numerous settings including; increased mortality and a greater risk of cardiac events in population studies (125, 134), increased mortality after myocardial infarction (127, 135), increased mortality in patients with heart failure (136) and increase mortality in patients with atrial fibrillation (137). Increased HRV is not always better since pathological conditions such as arrhythmia, and cardiac conduction abnormalities elevate HRV and elevated HRV has been found to be strongly linked to increased risk of mortality in adults (138). Patients with normal HRV measures, even if they have suffered an acute myocardial infarction, are at very low risk of mortality (117).

Figure 6. Examples of normal HRV



Examples of normal HRV; (left and middle) Power spectrum with a marked day-night variation in the respiratory-related peak near 0.3 Hz. The Poincaré plot (right) shows a “comet” pattern, where the variability increases with increasing R-R interval.

Figure 7. Examples of low HRV



Examples of low HRV; (left and middle) Power spectrum. The Poincaré plot (right) shows a “torpedo” pattern, with very little variability.

Age- and gender dependency of HRV

In childhood, HRV does not differ between females and males (139). During childhood, there is a positive correlation between age and HRV. HRV increases most rapidly during infancy and continues to increase, though at a slower rate, in early childhood and late childhood (140). After puberty HRV gradually decrease.

Clinical application of HRV

The most widely spread clinical use of HRV is in the monitoring of labour (cardiotocography, CTG). The variability of the fetal heart beats correlates with fetal viability. The postulated mechanism for this observation is that the fetal heart rate is modulated on a beat-to-beat basis by the parasympathetic and sympathetic nervous systems. Depression of the central nervous system secondary to anoxia leads to a loss of this fine beat-to-beat modulation of the heart rate and, hence, to a more metronome-like heartbeat (112). HRV is also used in clinical practice in patients with diabetes mellitus and familiar amyloidosis for detection and quantification of autonomic neuropathy (141).

HRV in congenital heart disease

Pre-operatively, patients with atrial septal defects have reduced HRV, but HRV normalizes post operatively (142-144). Also, in neonates with early repair of coarctation of the aorta, HRV was reduced compared to healthy babies. At five

years age, HRV in these children was at the same level as the healthy controls (145). Furthermore HRV studies in infants with transposition of the great arteries (TGA) demonstrated significantly lower P_{HF} and P_{LF} preoperatively, when compared with healthy infants (146). In patients with tetralogy of Fallot, Butera et al found a significant reduction in HRV, particularly in patients with non-sustained ventricular tachycardia (147). In a large cohort of 258 patients with congenital heart disease of different types the association between the New York Heart Association (NYHA) functional classes I–IV and HRV was studied. HRV parameters were decreased compared to controls in NYHA class II-IV, but not in NYHA class I (148). Impaired autonomic nervous activity is associated with an increased risk of sudden cardiac death in patients with congenital heart disease (116).

HRV in univentricular heart defects and Fontan circulation

Already in fetal life, HLHS is associated with reduced HRV (149). Until now, there is only one published study that compares HRV during operations to complete Fontan circulation. HRV was analysed in 900-second ECG recordings. The study found a higher root mean square of successive RR interval difference (RMSSD) and a lower P_{LF} in the BDG group (150). After Fontan surgery HRV is reduced (151-153) and HRV continues to decrease over time after TCPC surgery (154). Bossers et al found no differences in HRV parameters between LT and EC except for a higher LF/HF ratio in EC group (71).

HRV and arrhythmia

Reduced HRV is also associated with a higher risk of arrhythmias such as supraventricular and ventricular arrhythmias (137, 155). In adults, reduced HRV implies a shift of the sympatho-vagal balance toward sympathetic dominance, and reduced vagal tone has been shown to precede onset of arrhythmia (156). There is also evidence that the HRV is reduced in children with idiopathic ventricular tachycardia (155), and that HRV correlates negatively to the extent of disease in patients with arrhythmogenic right ventricular cardiomyopathy (157). Our group has previously shown a change in HRV in Fontan patients who develop arrhythmias, compared with non-arrhythmic patients, even before the onset of arrhythmia (158).

Specifically, in studies by Bergfeldt et al and Sosnowski et al, HRV has been described to be significantly higher in adult patients with SND than in controls (159, 160). It was shown that patients with SND had an abnormal pattern using Poincaré plots for HRV-analysis (159). Furthermore, measures of HRV were highly predictive of high-degree atrioventricular (AV)-block after acute myocardial infarction in adults (161).

Overall Aim

The overall aim of this thesis was to study heart rate variability, arrhythmia and pacemaker treatment in children with Fontan circulation, with the purpose of contributing to the reduction of long term complications in this patient group.

Specific Aims

- To investigate HRV in ambulatory 24-hour ECG recordings (Holter-ECG) in a large cohort of children with TCPC and to compare patients operated with LT with EC (Paper I).
- To study HRV in between surgical stages to study the temporal profile of HRV changes in relation to the surgical steps (Paper II).
- To investigate whether handheld ECG monitoring could be useful for the detection of silent arrhythmias and as a screening tool and for detection of changes in HRV in patients with Fontan circulation (Paper III).
- To examine the prevalence of and risk factors for pacemaker treatment in a large national cohort of patients with Fontan circulation (Paper IV).
- To study if changes in HRV could be detected on 24-hour ECG recordings in patients with Fontan circulation and SND (Paper V).

Overview of included studies

Study	Aims	Study group
I	To investigate HRV in ambulatory 24-hour ECG recordings in a large cohort of children with TCPC and to compare patients operated with LT with EC	<ul style="list-style-type: none"> Swedish patients with Fontan circulation, (n= 112) Healthy controls (n=66)
II	To investigate HRV in ambulatory 24-hour ECG recordings in a cohort of children with TCPC, focusing on the effect of HR and HRV in relation to surgical steps	<ul style="list-style-type: none"> Swedish patients with univentricular heart defects (n=89) Healthy controls (n=38)
III	To investigate whether handheld ECG monitoring in patients with Fontan circulation could be useful for two purposes: <ul style="list-style-type: none"> Detection of silent arrhythmias and As a screening tool for detection of cardiac autonomic dysfunction 	<ul style="list-style-type: none"> Patients with Fontan circulation from the northern part of Sweden (n=27) Healthy controls (n=41)
IV	To examine the prevalence of and risk factors for pacemaker treatment in a national consecutive national cohort of patients with Fontan circulation	<ul style="list-style-type: none"> All cases in Sweden with Fontan circulation operated on between 1982 and 2017 (n=599)
V	To study if changes in HRV could be detected in 24-hour electrocardiogram (ECG) recordings in patients with Fontan circulation and SND	<ul style="list-style-type: none"> Patients with TCPC and pacemaker treatment due to severe SND (n=12) Patients with TCPC and SND without pacemaker treatment (n=11) Healthy controls (n=66) TCPC controls (n=90)

METHODS	RESULTS
<ul style="list-style-type: none"> • Structured review of medical records • Ambulatory 24-hour ECG • HRV: Power spectral analysis • Comparisons between Fontan patients and healthy controls; EC and LT • Statistical methods: Chi2-test, one-way ANOVA, multiple linear regression 	<ul style="list-style-type: none"> • Clinical characteristics, findings of arrhythmia • TCPC vs controls: Longer RR (bradycardia in 14%), Lower HRV • LT vs EC: no difference in HRV, LT longer RR • Multivariate analysis showed low HRV in: <ul style="list-style-type: none"> ◦ Older age at time for Fontan operation: P_{tot}, P_{VLF}, P_{HF} ◦ Multiple medications: P_{tot}, P_{LF}, P_{HF}
<ul style="list-style-type: none"> • Enrollment of patients from the two operating centers in Sweden • Study of medical records • Ambulatory 24-hour ECG • HRV: Power spectral analysis, Poincaré plots • Statistical methods: Comparison of HRV (z-scores) The linear mixed effects models, the non-parametric Wilcoxon test 	<ul style="list-style-type: none"> • Pre-BDG vs Post-BDG: increased RR interval and SD2 • Pre-BDG vs controls: reduced P_{tot} • Post-TCPC vs pre-TCPC: reduction in P_{HF} • Post-TCPC vs controls: reduced P_{tot}
<ul style="list-style-type: none"> • Enrollment of patients from local registers • Study of medical records • Handheld intermittent ECG recordings • HRV: Poincaré analysis • Statistical methods: Paired T-test, ANOVA, (cross-correlation analysis) 	<ul style="list-style-type: none"> • In a study of ECG-registrations performed intermittently with a hand-held ECG arrhythmia was found in 2/27, and reduced HRV in 7/27 cases
<ul style="list-style-type: none"> • Identification of patients in four registers: • Study of medical records in patients with Fontan circulation and pacemaker implantation • Statistical methods: Chi2-tests, Kaplan-Meier analysis 	<ul style="list-style-type: none"> • 13% (78/599) pacemaker • EC<LT • SND main indication: 64% • High prevalence: MA (44%), DORV (24%), DILV (20%) • Low prevalence: PA/IVS (3%), HLHS (6%)
<ul style="list-style-type: none"> • Identification of patients- see above, paper IV • Study of medical records • Import of 24-hour ECG registered before pacemaker implantation • HRV: Power spectral analysis and Poincaré analysis • Statistical methods: ANOVA 	<ul style="list-style-type: none"> • TCPC/SND with or without PM had higher HRV compared with both healthy controls and TCPC without SND ($p<005$) • SD2 and VLF tended to decrease again in SND patients with pacemaker compared to TCPC/SND no PM ($p=006$)

Materials and Methods

Identification of the patients

Patients with Fontan circulation were identified through the cardiothoracic surgery databases at the two operating centers in Sweden: Children's Heart Centers at The Queen Silvia Children's Hospital in Gothenburg and University Hospital in Lund (paper I-V), as well as the Swedish registry for congenital heart disease (SWEDCON) and the Swedish ICD and Pacemaker registry (paper IV-V).

Data collection

Clinical data

Clinical records were reviewed for date of birth, gender, anatomical diagnoses, type and date of surgical interventions, late complications (arrhythmia, thromboembolism, PLE, heart failure or plastic bronchitis). We noted type of arrhythmia/s and symptoms of arrhythmia and medications at the time of 24-hour ECG recordings. Moreover, data on ventricular function and AV valve regurgitation assessed by echocardiography were collected. Data concerning anatomical diagnose, and surgical procedures were extracted from the four registers mentioned above and confirmed with the patient's records.

Ambulatory 24-hour electrocardiogram (Holter)

Patients and controls underwent standard 24-hour ambulatory ECG monitoring during daily activity (Study I, II and V). In paper I all Holter ECGs were collected using a DL 700 Digital Holter Recorder (Braemar Inc, Burnsville, USA). In order to retrospectively study pre-pacemaker 24-hour ECG recordings in patients who later had a pacemaker implantation Holter data stored at local hospitals was imported for HRV analysis (manuscript II and V). Holter recordings were manually analysed by a PC-based Holter System (Aspect Holter System, GE Healthcare, Borlänge, Sweden). One of the two channels (V2 or V5) was analysed. (Paper I, II and IV).

Hand-held ECG

A small hand-held device, Zenicor-ECG® (Medical system AB, Stockholm, Sweden), was used to record 30-second ECG traces in paper III. The device has a display and two thumb sensors, providing a bipolar extremity lead I. The subjects were instructed to perform ECG recordings for 14 days by putting their thumbs on the sensors for 30 seconds twice a day, once in the morning and once in the evening. The participants were told to perform extra recordings upon occurrence of symptoms such as palpitations, dizziness, nausea, pre-

syncope/syncope, or any chest discomfort. They were also asked to perform at least one additional recording after exercise. After having recorded each 30-second ECG, the subject was instructed to push a send button to send the ECG to a database, using the built-in mobile phone. If the recording was prompted by symptoms the participant was instructed to press an additional event button. Patients treated with beta-blockers, with a pacemaker, or with very frequent episodes of arrhythmia were excluded from the comparison with controls.

Controls in paper III

In paper III we randomly selected 15 non-overlapping 30-second sections of 24-hour-ECG recordings from 41 healthy control children. Data from the 30 segments was pooled and SD1, SD2, and the SD1/SD2 ratio were calculated. These results were compared to the HRV data obtained from the handheld ECG system.

To evaluate the agreement between the handheld ECG system and the 30-second segments of a Holter recording, five patients and five healthy controls performed simultaneous recordings of Holter ECG and handheld ECG with a 30-second duration. HRV was quantified in both the simultaneous recorded 30 seconds of ECG. A cross-correlation analysis of the series of RR intervals from the two devices was made.

Moreover, supplementary control material was collected. In this control material one female and one male at every year of age 0-18 years were asked to make 15 30-second registrations with the hand-held -ECG device in the morning and 15 in the evening. The controls group consisted of healthy children who underwent echocardiography with normal findings.

ECG analysis

Whether ECG data was extracted from 24-hour ECG recordings or pooled data from intermittent Zenicor® recordings: heartbeats were classified as: normal, supraventricular extra systolic beats, ventricular extra systolic beats, or beats of uncertain origin. Supraventricular arrhythmia was defined as four or more consecutive supraventricular beats. Bradycardia on the 24-hour ECG recordings was defined as a heart rate below the 5th percentile and tachycardia as a heart rate above the 95th percentile for gender and age(162) (paper I) and in paper II and V, z-score for of mean RR and age for controls >2 was defined as bradycardia and mean RR <2 as tachycardia.

HRV analyses

Before HRV analysis all data were reviewed and carefully edited by one experienced analyst. Data was also filtered in a recursive filtering procedure.

In this thesis, the automatic filtering process is a recursive procedure where RR intervals are removed if they differ from the mean of the surrounding RR intervals more than a predetermined limit (ranging from 35% to 50%). The threshold was selected to allow the removal of errors in the series of RR intervals, such as ectopic beats and false detections due to noise, without removing normal sinus beats in children with pronounced respiratory sinus arrhythmia.

Power spectral analysis

Spectral analysis of HRV was performed in paper I, II and IV. Fast Fourier transformation was used to perform a power spectral analysis of the beat-to-beat fluctuations in R-R intervals. Spectral power was determined in three frequency regions: very low frequency region (VLF: 0.003-0.04 Hz), low-frequency region (LF: 0.04-0.15 Hz), and high-frequency region (HF: 0.15-0.70 Hz). In paper I and V, the upper limit for HRV was 0.50 Hz. In paper II the age group investigated was younger, thus the limit 0.70 Hz was used. The total power (TP) was also determined in the region 0.003-0.70 Hz. Finally, the LF/HF-ratio was calculated. In the 24-hour recordings (manuscript I and IV) spectral indices were calculated as average data over the complete recording period.

Poincaré plots

Poincaré analysis of HRV was performed in paper II, II and V. Poincaré analysis was performed on data from 24-hour-ECG recordings (paper II and V) and on pooled data from all 30-second episodes for each patient (paper III).

Statistical methods

Continuous variables were presented as mean with standard deviation or median with range. Categorical variables were presented as the number of subjects or as a percentage. Frequency domain HRV parameters were log-transformed due to their skewed distribution.

The age-dependency in HRV had to be taken in to account. As previously discussed, HRV increases linearly with age up until puberty, thereafter there is a gradual reduction in HRV. In paper I, we used Analyses of variance ANOVA with age as a covariate in a linear regression model; thus both controls and the patients will have an influence on the inclination of the regression line. In papers II and V, age related differences in HRV was adjusted for by using z-scores.

Z-scores

Z-scores, i.e. age-adjusted reference ranges for HRV parameters were calculated. The z-scores were based on the age-dependency in controls. In paper II the study group was young (range 0-9 years) and in patients and controls nearly all HRV

indices increased linearly with age. Therefore, the age-dependency in most HRV scores were modeled by linear regression, excluding LF/HF where a quadratic regression line (U-shaped) was used. In paper V, where the patient group was older, including teenagers, the HRV scores were modeled by quadratic regression. Data were age-corrected by subtracting the regression line, and then divided by the standard deviation of the age-corrected data for controls. Thus, a z-score of 0 is equivalent to the mean for controls of the same age, and a z-score of 1 is equivalent to one SD above the mean of the controls. Reduced HRV was defined as a z-score less than -2, and high HRV as a z-score more than +2.

In paper V elliptic confidence intervals were constructed using principal component analysis of the bivariate distribution of z-scores for controls and TCPC patients without SND, respectively.

Comparisons between groups

The comparison of patients and control subjects (paper I) was made using independent T-tests. Paired T-tests were used to determine the agreement between measures obtained from 24-ECG recordings and from the hand-held ECG device (paper III). ANOVA, adjusted for age was used to compare HRV parameters in comparisons between patients with Fontan circulation and healthy controls, and between LT and EC (paper I and III). Post-hoc analysis was performed based on confidence intervals (CI) for different groups, where a significant difference was considered to be present if the CI's for two groups did not overlap. In paper V, z-scores for the four groups; healthy controls, patients with Fontan circulation without SND (TCPC), patients with Fontan circulation with SND without pacemaker treatment (TCPC/SND) and patients with Fontan circulation with a pacemaker implantation because of SND (TCPC/SND/PM), were used to adjust for age. The z-scores for the groups were compared using ANOVA, followed by post-hoc analysis with group-wise t-tests.

In paper II we compared HRV parameters in patients from 24-hour-ECG recordings between the different surgical steps towards complete Fontan circulation: 1) before BDG (pre-BDG), 2) after BDG/ before TCPC (post BDG) and 3) after TCPC (post-TCPC) with each other and with healthy controls. Z-scores for the three different recordings in patients were compared to each other and controls, using linear mixed effects modeling. Differences between different stage recordings and recordings of controls were modeled using a nominal categorical variable with four levels. The linear mixed effects models also included random effects for each subject since the included patients, due to loss-to-follow-up, had a different number of recordings (1-3). In all patients with one or both of the two pairs of 24-hour-ECG recordings the changes between (pre-BDG) and (post-BDG), and between post-BDG and (post-TCPC) were analyzed using the non-parametric Wilcoxon signed rank test. In paper IV the Mann-Whitney U-test was used to compare ventricular function and AV valve regurgitation in patients who

later had a pacemaker implanted to patients without pacemakers and the Wilcoxon signed-rank test was used to compare ventricular function and AV valve regurgitation before and after pacemaker implantation.

Comparisons between the number of subjects in different groups in paper I and IV were evaluated by the chi square test. For analysis of anatomical diagnoses in paper IV, a chi square test was first used to compare pacemaker prevalence among all diagnoses, and then the prevalence in one anatomical diagnosis was compared to all other diagnoses. Fischer's exact test was used if a group was smaller than five.

Kaplan-Meier analyses was performed to compare the frequency of pacemaker implantation in patients operated with the two surgical variants of TCPC (LT and EC), (Paper IV).

Multiple linear regression analysis

A multiple linear regression analysis was used to study the relationship between the HRV parameters and gender, age at Holter assessment, age at TCPC, ventricle function, AV-regurgitation, multiple medication and morphology of the single ventricle (paper I).

In all tests, the level of statistical significance was defined as p-value <0.05. All data and statistical analyses were performed with Matlab R2017b, R2018b (Mathworks Inc, Natick, Ma) and IBM SPSS Statistics for Windows, Version 17.0, 18.0, 24.0 (Chicago, IL/ IBM Corp. Armonk, NY, USA).

Results

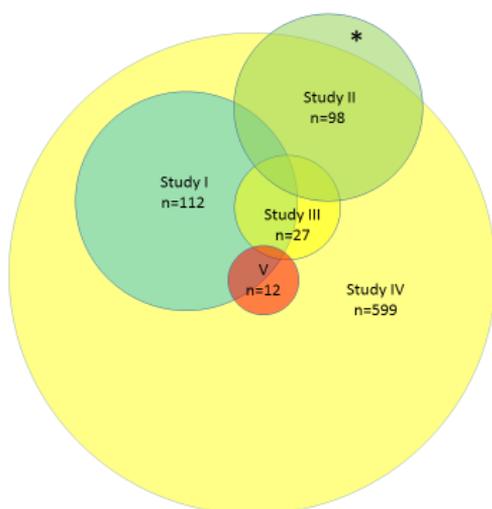
Main findings

- *Paper I*; In a cohort of 112 patients with Fontan circulation HRV (P_{tot} , P_{VLF} , P_{LF} and P_{HF}) was significantly reduced compared to healthy controls. No significant difference in HRV was seen between patients operated with LT or EC.
- *Paper II*; During the stages to complete Fontan circulation, HRV was reduced compared to controls, already before BDG with further reductions after TCPC. Heart rate was reduced after BDG compared with before BDG, and heart rate was also reduced after BDG and after TCPC compared with healthy controls.
- *Paper III*; In ECG-registrations performed intermittently, with a hand-held ECG device, patients with Fontan circulation showed arrhythmia in 2/27 cases and reduced HRV in 7/27 cases.
- *Paper IV*; Thirteen percent of Swedish patients with Fontan circulation have a pacemaker. Pacemaker treatment was more common among patients operated with LT. Patients with MA, DORV and DILV had the highest prevalence of pacemaker implantations, and SND was the most common indication for pacemaker treatment.
- *Paper V*; In Fontan patients with SND, the HRV was significantly higher compared to controls and Fontan patients without SND. However, in patients with severe SND, requiring a pacemaker, HRV-parameters SD_2 and P_{VLF} tended to be lower than in patients with SND without pacemaker.

Patients

In total 599 Swedish patients with Fontan circulation were identified through four different registries. In paper I, 112 of these patients underwent a 24 hour-ECG- recording. HRV from these recordings was compared to HRV from 24-hour ECG recordings in 66 controls. In paper II a total of 89 patients and 38 controls were included. In paper III 27 of the patients (all from the northern part of Sweden) underwent repeated intermittent hand-held-ECG (Zenikor®) recordings. The recordings were pooled and compared to short sections of 24-hour ECG recordings from 41 controls. In paper IV we described 78 of the 599 patients with Fontan circulation who also had a permanent pacemaker. Twenty-four-hour ECG data from the period before pacemaker implantation was stored and could be imported in 18 cases and out of these 12 patients had SND as the main indication for pacemaker implantation. In paper V, HRV from the pre-implantation ECGs in these 12 patients was compared to HRV from the 66 controls and 102 patients with Fontan circulation who had not had a pacemaker implantation during follow-up (Figure 8 and 9.)

Figure 8. Overview of participating Fontan patients.

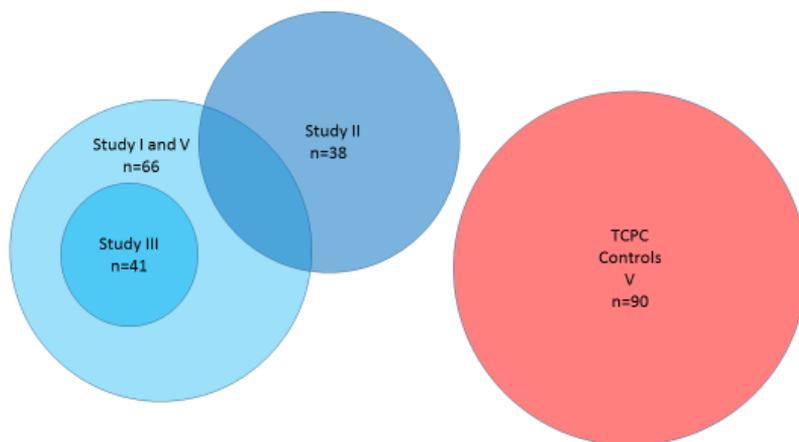


*The same patients were included in more than one study. Fourteen patients participated both in study I and II, seventeen participated both in study I and III. All patients in study I, III and V were included in study IV. Seven patients in study I did also participate in study V. Twelve patients in study II were also included in study III, 65 patients in study II were included in study IV. Two of the patients in study III were also included in study V. * 24 patients with univentricular heart defects had not complete Fontan circulation at time for enrollment in study IV.*

Controls

In study I and V, the control material consisted of 66 healthy children and youths (33 females and 33 males, median age of 9.7 (1.1-17.6) years) who underwent 24-hour ECG recordings and a baseline echocardiography, all with normal findings. In study II, we required younger controls therefore another 21 infants underwent echocardiography and 24-hour ECG recordings, also with normal findings. In addition, the youngest 17 children from the original control group were used, making a control group of 38 children, (24 females and 14 males, median 20 (0-65) months). In study III, since repeated hand-held ECG recordings only were performed in patients, we used randomly selected 30 second segments from the morning and evening periods of the 24-hour-ECG recordings from the 41 subjects in the original control group (Figure 9). After study III was published, a new control group was created, consisting of hand-held ECG recordings in 34 healthy children, 17 females and 17 males performing. One female and one male in every one-year group from ages 1 to 17 was included, thus, median age was 9.0 (range: 1.1-17.4) years. All children and youths had normal findings on echocardiography. The two control groups were compared, and the results were coherent (Figure 9). Finally, in study V patients with TCPC and SND were compared to both 66 controls and to 90 patients with TCPC (from study I) without arrhythmia (including SND) or pacemaker treatment (Figure 12).

Figure 9. Overview of participating controls



In study I and V the controls were 66 healthy children, median age of 9.7 years. In study II, the controls were 38 children, median age 20 months. In study III, 41 24-hour-ECGs from the original control group were used (study I and V). Finally, in study V patients with TCPC and SND were compared to 90 patients with TCPC but without SND (from study I).

ECG findings (paper I, III)

Conventional analysis of 24 hour-ECG recordings, from 112 patients with Fontan circulation (paper I) showed that the majority of the patients (81%) were in normal sinus rhythm. Fourteen patients (12%) showed sinus rhythm with intermittent episodes of nodal rhythm. One patient had episodes of supraventricular tachycardia, two had nodal tachycardia and two had sinus arrests/ SA-blocks. Fourteen patients (12%) showed bradycardia, defined as mean heart rate less than the 5th percentile for age. The proportion of bradycardia using this definition did not differ significantly between patients with LT (12%) and EC (14%). Thus, in a comparison of RR intervals in patients, the mean RR interval adjusted for age was significantly longer in the LT group than in the EC group.

In paper III, 27 patients with Fontan circulation performed 30-second-long ECG registration twice a day and extra registration during symptoms. This resulted in 22-43 (mean 27) registrations per patient and a mean observation time of 13.5 minutes. Sinus rhythm was seen in 22 patients (82%), one patient showed ectopic atrial rhythm and another patient a nodal rhythm and two intermittent pacemaker induced rhythm periods. Five patients showed frequent nodal replacement beats. One patient who experienced palpitations showed a previously undiagnosed supraventricular tachycardia. One asymptomatic patient showed frequent ventricular extra systolic beats, paired and in bigeminy.

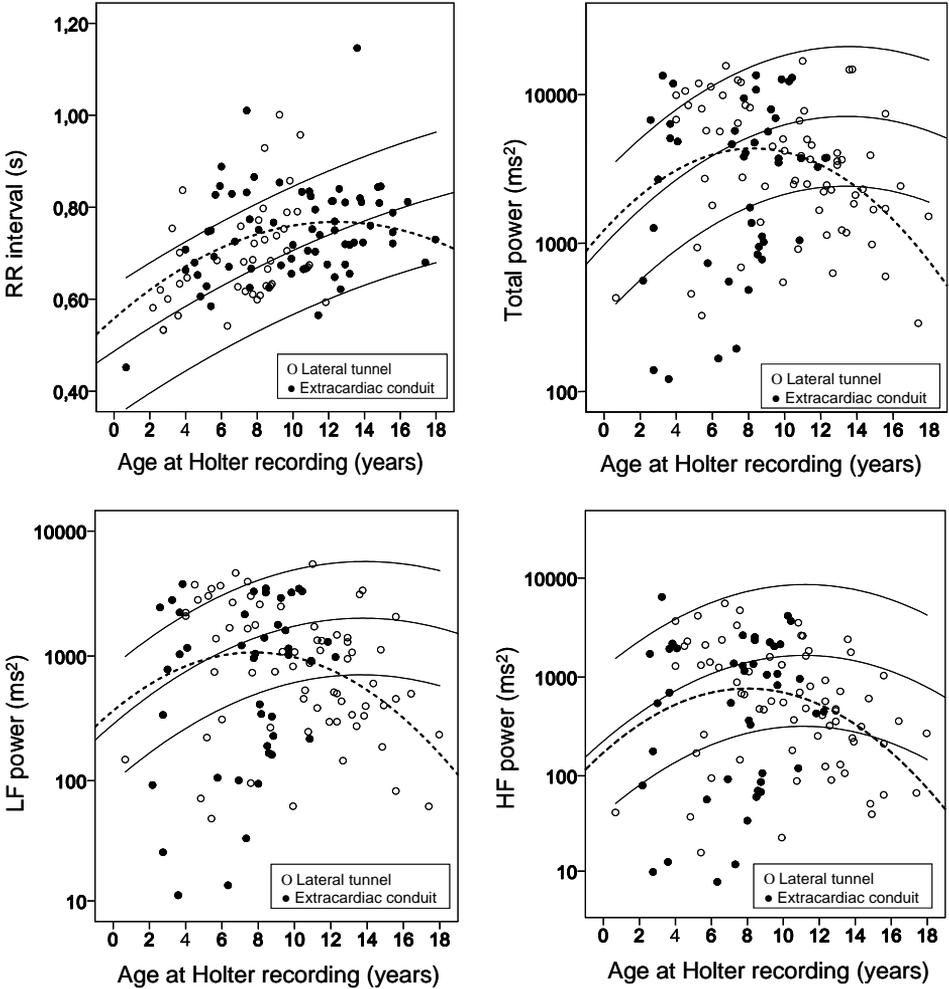
Heart Rate Variability (study I, II, III, V)

In paper I we showed that patients with Fontan circulation (n=112) had a significantly reduced HRV in all spectral indices compared to healthy controls (Figure 10). HRV was extremely reduced in four patients (Figure 10). At the time of the Holter ECG, none of these patients had reduced ventricular function or large AV valve regurgitation. No patients were on beta-blocker medication.

Lateral tunnel (LT) versus extracardiac conduit (EC) (paper I)

We found no difference in HRV parameters between the LT and the EC type of TCPC when we compared HRV from 24-hour-ECG recordings in 50 LT patients, 44 EC patients, and 46 controls (Figure 10).

Figure 10. HRV in patients with lateral tunnel (LT) and extracardiac conduit (EC).



Solid lines indicate the best-fit quadric regression lines for controls and 95% confidence intervals. Dashed lines show the corresponding regression lines for Fontan patients.

Using linear multiple regression analysis, we studied the relationship between HRV and gender, morphology of the single ventricle, age at Holter-ECG registration, age at Fontan surgery, type of TCPC (LT or EC), ventricle function and AV-regurgitation assessed with echocardiography and multiple medication.

We found an association between older age at Fontan surgery and reduced spectral indices; P_{tot} ($p=0.03$), P_{VLF} ($p=0.04$) and P_{HF} ($p=0.03$). P_{HF} was significantly reduced in patients with a morphologic right single ventricle compared to patients with a morphologic left ventricle ($p=0.03$). Furthermore, we found a reduced HRV; P_{tot} ($p=0.028$), P_{LF} ($p=0.035$), P_{HF} ($p=0.032$) in patients with multiple medication (two or more different medications). The $P_{\text{LF}}/P_{\text{HF}}$ ratio was higher in older patients than in younger patients ($p=0.043$).

HRV through surgical stages to TCPC (Paper II)

HRV was analysed from Holter 1 obtained before BDG (pre-BDG) in 47 patients, aged 4.5 (0.6-53.4) months, Holter 2 obtained after BDG/ before TCPC (post-BDG) in 47 patients, aged 25 (7-40) months, and Holter 3 after TCPC (post-TCPC) in 45 patients, aged 3.7 (2.2-8.8) years. Repeated Holter recordings were available for 39 patients; all three ($n=11$), Holter 1+2 ($n=8$), Holter 1+3 ($n=7$), Holter 2+3 ($n=13$). Patients were unavailable for Holter-ECG recordings for multiple reasons. During follow-up 10 patients had a heart transplant or died (3 after TCPC). In 18 cases the final TCPC stage was not performed because of age (too young, $n=7$), operation not possible due to hemodynamic parameters or small size of the pulmonary arteries ($n=3$).

Z-scores for heart rate (RR) and HRV were based on the corresponding age-dependency in controls. Marked sinus bradycardia ($RR > 2$ Z-score) was found in 6% (3/47) of the pre-BDG-, 30% (14/47) of the post-BDG- and 31% (14/45) of the post-TCPC-recordings. In the HRV analysis via the mixed model analysis method, in which means of Z-scores for HRV-parameters from spectral power analysis and Poincaré analysis were compared, a significantly lower HRV was found in pre-BDG recordings compared to controls. The RR interval was significantly increased post-BDG compared to pre-BDG. The SD2 was significantly increased post- compared to pre-BDG. Compared to controls, the post-BDG recordings had a significantly longer RR-interval, and decreased P_{tot} and P_{LF} . In patients' post-TCPC recordings, HRV parameters (P_{tot} , P_{VLF} , P_{LF} , P_{HF} , $P_{\text{LF}}/P_{\text{HF}}$) and in Poincaré analysis SD2, and SD1/SD2 ratio were decreased compared to before TCPC (post-BDG) (Table 2). Compared with controls, patients post-TCPC showed longer RR intervals and reduced HRV in P_{tot} , P_{VLF} , P_{LF} , and P_{HF} , and in SD1, and SD1/SD2 ratio calculated via Poincaré analysis (Table 1).

In a subgroup of patients with repeated Holter-ECG recordings, paired analyses were carried out using Wilcoxon test and the same pattern of results was noted; increased RR interval and SD2, and reduced SD1/SD2 post-BDG as compared with pre-BDG. A significant reduction of P_{tot} , P_{LF} , and P_{HF} and in Poincaré analysis the SD1, and SD1/SD2 compared to before TCPC (post-BDG) was also

found. Reduction of P_{VLF} , $SD2$ and the ratio P_{LF}/P_{HF} was not statistically significant.

Table 1. Comparisons of Z-scores for HRV between Holter recordings.

	Pre-BDG (n=47)	Post-BDG (n=47)	Post-TCPC (n=45)
RR	0.21 (0.21)	1.47 (0.22)* †	1.35 (0.22)*
P_{tot}	-1.40 (0.29)*	-0.93 (0.29)*	-1.46 (0.30)*
P_{LF}	-1.81 (0.36)*	-1.42 (0.36)*	-2.02 (0.37)*
P_{HF}	-0.78 (0.21)*	-0.43 (0.21)	-1.36 (0.22)* #
P_{LF}/P_{HF}	-0.97 (0.22)*	-0.44 (0.22)	0.36 (0.23) #
SD1	0.01 (0.22)	-0.06 (0.22)	-1.05 (0.22)* #
SD2	-1.32 (0.23)*	0.22 (0.23) †	-0.14 (0.23)
SD1/SD2	1.40 (0.29)*	-0.16 (0.29) †	-0.96 (0.30)*

Values are estimated marginal means of Z-scores (SE) from controls. P-values are derived from linear mixed effect models with random effects to adjust for repeated observations. Tot= total, VLF= very low frequency, LF= low frequency, HF= high frequency, SE= standard error. $p < 0.05$ is statistically significant.

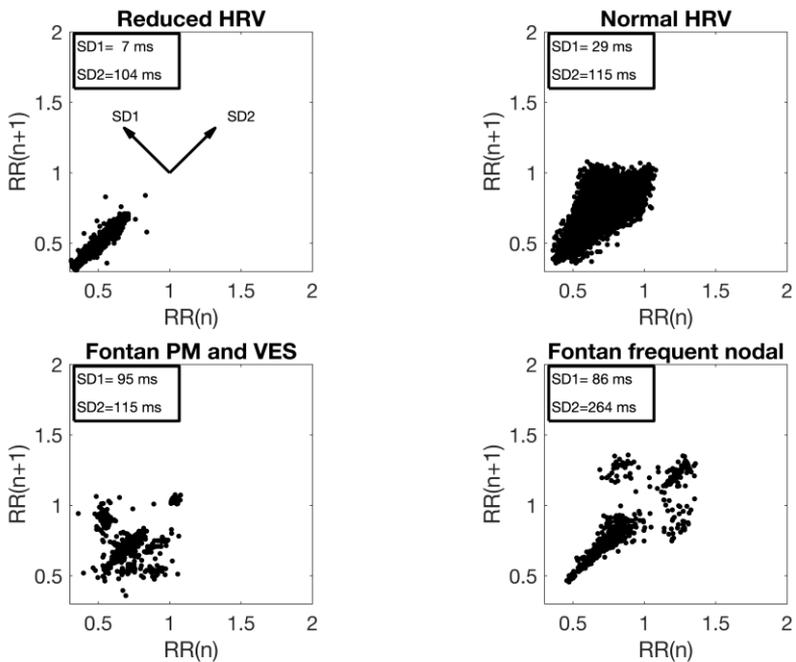
* $p < 0.05$ versus controls, † $p < 0.05$ versus pre-BDG, # $p < 0.05$ versus post-BDG/pre-TCPC

Intermittent short-term ECG findings (paper III)

ECG data showed that the patients with Fontan circulation (n=27) performed a mean of 27 30-second ECG recordings from the hand-held ECG device during the 14-day study period. This data was pooled and analyzed with Poincaré plots. The Poincaré plots showed different types of normal and abnormal Poincaré patterns (Figure 11). The plots showed the classic patterns seen in subjects with reduced HRV, i.e. the “torpedo” pattern, and with high HRV, i.e. the “comet” pattern. More complex patterns were seen in patients with arrhythmias (Figure 11). Quadratic regression lines were determined based on Holter-ECG data from controls. Before filtration of the data 4 out of 27 patients with Fontan circulation showed markedly reduced HRV ($SD1$ or $SD2 < 2$ z-score), and 4 additional patients showed HRV parameters above the 95% confidence interval. After filtration, when arrhythmic beats were removed of reduced HRV was found in 7 of the 27 patients.

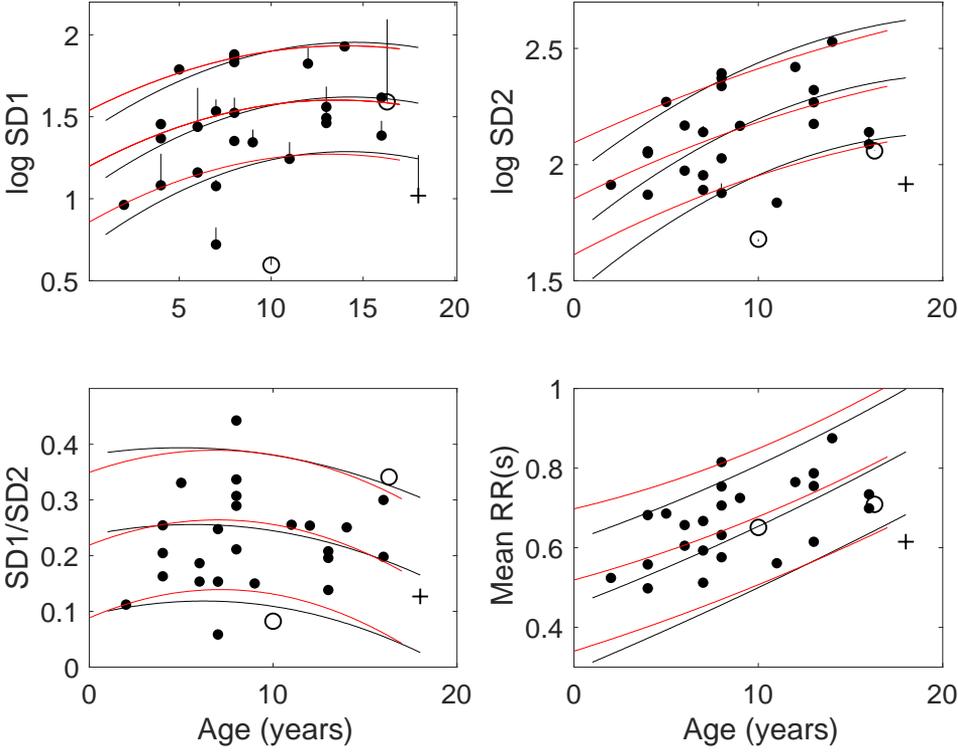
A comparison, performed simultaneously, of the HRV data from Holter monitors with the HRV data from the handheld ECG device in the 5 patients and 5 controls revealed no significant difference in the results. The Pearson correlation coefficient was 1.0 for both SD1 and SD2 ($p < 0.001$). Moreover, the newly recorded control material based on hand-held-ECG recordings agreed with the control material published in paper III (Figure 12).

Figure 11. Examples of Poincaré plots.



Top, left: classic Poincaré pattern seen in subjects with reduced HRV resembled by a torpedo pattern. Top, right: Comet shaped Poincaré pattern seen in subjects with normal HRV. Bottom left and right: More complex patterns of the Poincaré plot was seen in patients with arrhythmia.

Figure 12. Comparison of HRV from the controls used in Study III (based on 24-hour ECGs) vs. the new control group (based on hand-held-ECG registrations).

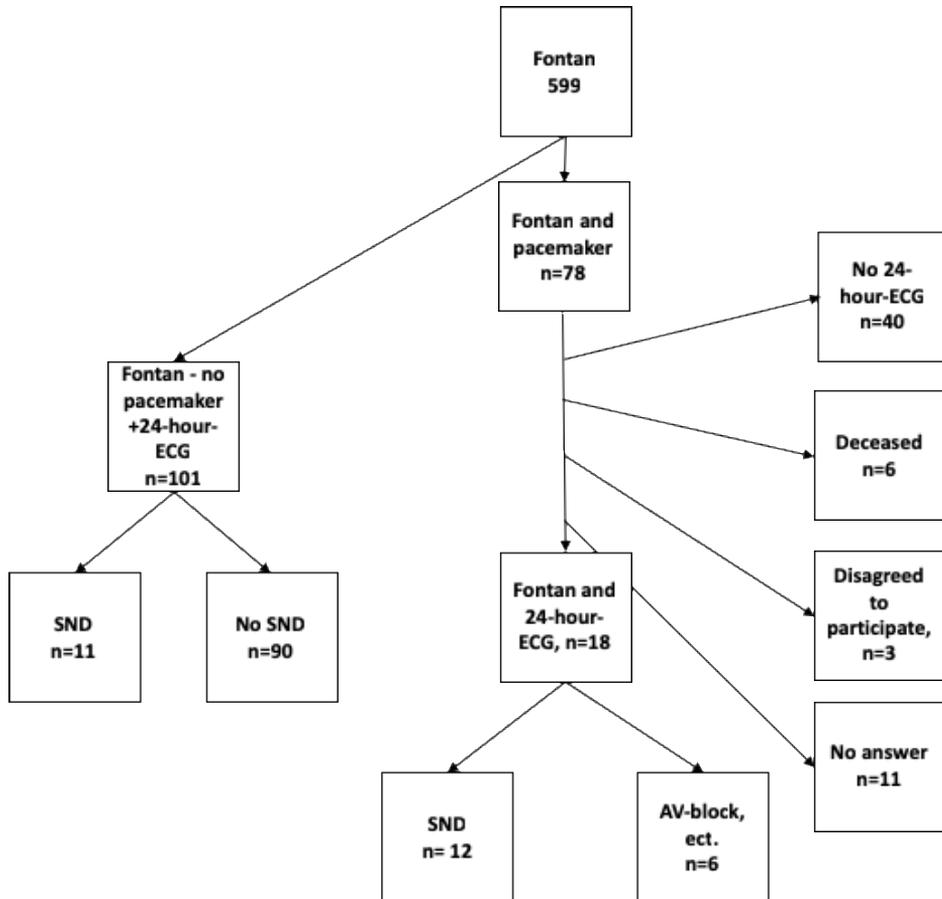


The two variants of normal limits are shown: from Holter (black), by Zenicor® (red). Normal ranges of HRV were calculated from short sequences from a single 24-hour ECG in 41 controls, and by pooled intermittent hand-held-ECG registrations in 34 new controls.

HRV in patients with SND (Paper V)

Retrospective 24-hour ECG data could be collected from 12 patients before they had a pacemaker implantation due to severe SND (Figure 13). Data was compared with 24-hour ECG recordings from 66 healthy controls, 11 TCPC patients with evidence of SND on one of the 24-hour-ECG recording and 90 TCPC patients without SND.

Figure 13. Flow-chart (paper V)



Paper V. Pre-implantation 24-hour ECG was available in 12 patients with Fontan circulation and pacemaker treatment. Among 101 Fontan patients without a pacemaker who performed a 24-hour ECG recording, 11 fulfilled criteria for SND.

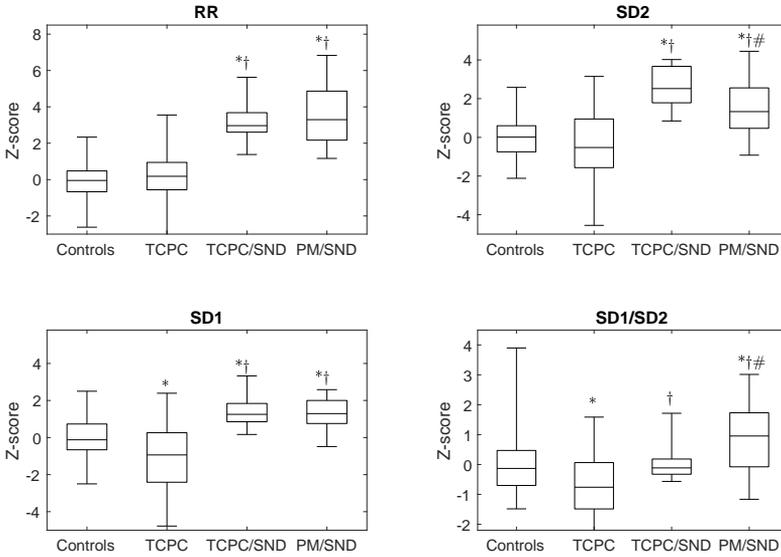
All Poincaré indices (except SD₁/SD₂) and all spectral indices (except the P_{LF}/P_{HF}) were significantly higher in the SND group compared to controls. All HRV indices were significantly higher in the SND group than in patients with TCPC without SND (Figure 14).

HRV in Fontan patients before pacemaker implantation due to SND

Among the 12 Fontan patients with 24-hour ECG recordings before pacemaker implantation and SND as the indication for a pacemaker, SD₁, SD₂, SD₁/SD₂ and P_{VLF} were significantly higher compared to controls. Moreover, all HRV indices

were significantly higher in the TCPC/SND/pacemaker group than in patients with TCPC and no SND. Two HRV indices; SD2 and P_{VLF} , and SD1/SD2 showed a tendency to be reduced in TCPC patients with SND who required a pacemaker compared to TCPC patients with SND without pacemaker ($p=0.06$) (Figure 14).

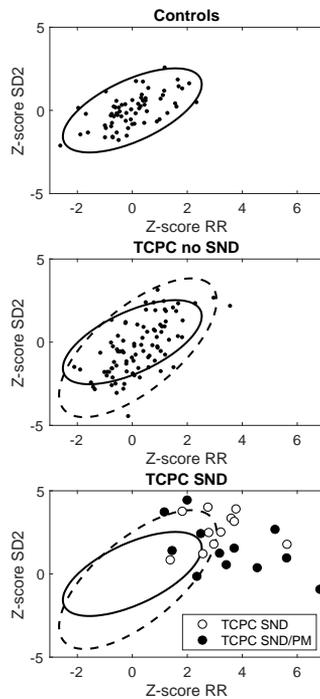
Figure 14. Poincaré indices presented as z-scores based on controls.



Boxes represent median and interquartile range, whiskers show range. *P*-values were derived from post-hoc tests after analysis of variance. TCPC=total cavopulmonary connection, SND= sinus node dysfunction, PM=pacemaker. * $p<0.05$ versus controls. † $p<0.05$ versus TCPC. # $p=0.06$ TCPC/SND vs TCPC/PM /SND.

Figure 15 shows the relationship between the changes in mean heart rate (mean RR interval) and the Poincaré parameter SD2. SD2 will increase when the diurnal variability in mean heart rate increases. This will be the case if there are of episodes of bradycardia but still a normal maximal heart rate. Possibly, with progression of SND, and a failing chronotropic competence, the diurnal variability (SD2) will decrease. At this point, the SD2 parameter may appear to be normal, but the mean heart rate will further decrease. In this case a bivariate graphical analysis of RR and SD2, the pathology can better be visualised (Figure 15).

Figure 15. Relations between RR interval and Poincaré indices.



Top: Relation between z-scores for SD1 and SD 2, resp. RR and SD2 in healthy controls.

Middle: As above, in patients with Fontan circulation without SND. TCPC=Total Cavo Pulmonary Connection, SND=sinus node dysfunction.

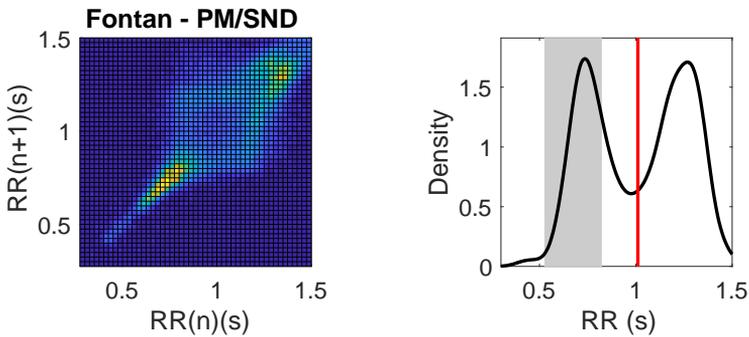
Bottom: As above, HRV changes in patients with TCPC/SND have no pacemaker treatment. TCPC/SND/PM are patients with severe SND, later requiring pacemaker treatment are visualized. Ellipses show 95% confidence intervals based on a principal component analysis of data from controls (thick solid lines) and from TCPC patients without SND (dashed lines), respectively. Note two of the patients with SND who subsequently had a pacemaker implantation, showed high SD2 but relatively normal mean RR, which could reflect the presence of episodes of pronounced bradycardia in between times with more normal heart rates.

Case presentation - HRV and clinical findings

Figure 16 shows the distribution of RR intervals in an eight-year-old child born with tricuspid atresia and a ventricular septal defect who had symptoms of fatigue.

Regarding clinical characteristics, the child complained of not being able to dress as fast as his/her mates in school, and the child’s hands and feet were often cold. A 12-lead ECG showed sinus rhythm, with a heart rate of 51 beats/minute. Echocardiography showed good ventricular function and minor mitral regurgitation. During an exercise test, the child’s maximum heart rate was 126 beats/minute (at max 20 W) and the respiratory frequency increased from 20 to 48 per minute. 24- Hour Holter monitoring showed sinus arrhythmia, with a mean heart rate of 67 (min: 41, max 128) beats/min. After a pacemaker was implanted, the child gained strength. According to the parents, the child was much more active and alert and the hands and feet were also warmer. During an exercise test, the child’s maximum heart rate was 162 beats/min (at max 60 W), and the maximum respiratory frequency was 44 per minute.

Figure 16. Examples of Poincaré (left) and density (right) plots of RR intervals



The Poincaré plots is colour coded where yellow colour corresponds to regions with the highest number of values, which also corresponds to the location of peaks in the density plots. The Poincaré plot shows a rhomboid shape due to changes between nodal and sinus rhythm. The right panel shows the corresponding density plot for all RR intervals, where the mean RR interval of the patient is shown as a red line and the grey area corresponds to the 95% CI for the expected mean RR at the age of the patient.

Pacemaker implantation in patients with Fontan circulation (paper IV)

In a retrospective study of all patients who were discharged from hospital after completion of Fontan circulation (n=599) in Sweden between 1982 and 2017, 13% (78/599) had a permanent pacemaker implanted after a mean follow-up time after Fontan surgery of 12.2 ± 7.3 years. Mortality data was available in 596 of 599 cases. There was no significant difference in mortality between patients with (8%) and without pacemaker implantation (5%). In 61 of the 78 patients who received their pacemaker after complete Fontan surgery, the mean time from Fontan procedure to pacemaker implantation was 3.9 ± 4.5 years (Figure 17). The mean age at pacemaker implantation in the whole group (n=78) was 6.2 ± 4.9 years. Seventeen of the 78 patients (22%) received a pacemaker within 30 days after Fontan surgery.

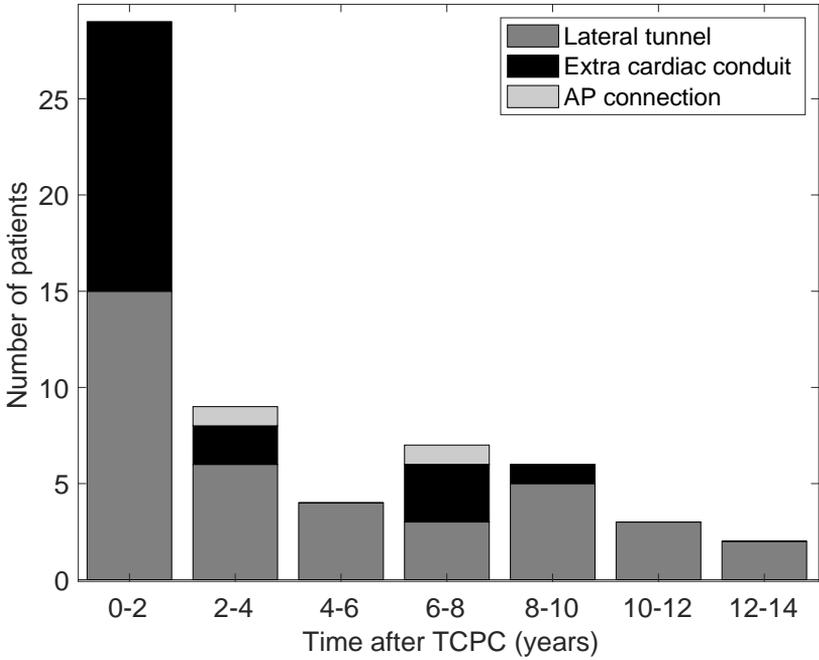
In the cohort of 599 patients 224 (37%) were female and 375 (63%) were male. The largest anatomical diagnose groups were TA 117 (19.5%), HLHS 103 (17.2%) and DILV 97 (16.2%). Data about the morphology of the single ventricle was available in 573 cases. In 307 (54%) of the cases the dominant ventricle was a morphological left ventricle and in 248 (43%) of the cases it was a right ventricle. Eighteen (3%) patients had both a left and a right ventricle.

Most patients had their first cardiac surgery in the neonatal period and Glenn-surgery was performed in median at 7 months age. Data concerning staged Fontan surgery was available in 474 (79%) cases. Of these 406 patients (68%) had staged Fontan surgery, whereas 68 (11%) had the SVC and IVC connection made in the same operation.

Indication for pacemaker implantation

Data concerning indications for pacemaker implantation were available in 76 of 78 patients (97%). The most common primary indication for pacemaker implantation was SND in 49/76 (64%). High degree AV block was the second most common indication in 24/76 (32%), and in 3/76 (4%) the indication was protection against bradycardia due to treatment with anti-arrhythmic drugs for tachy-arrhythmias. The origin of the AV blocks was in 7/23 (30%) postoperative, and in 9% (2/23) AV blocks developed at heart catheterization.

Figure 17. Time from Fontan surgery to pacemaker implantation.



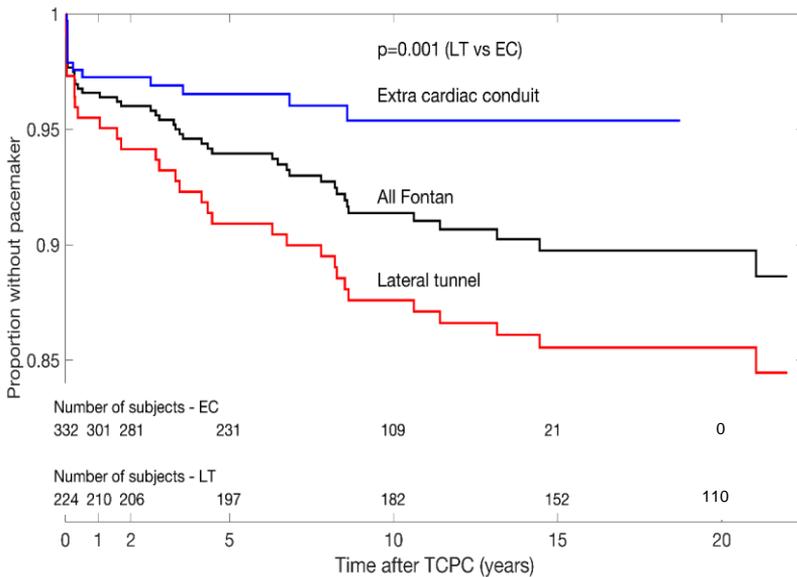
AP=atriopulmonary. TCPC= total cavopulmonary connection.

LT versus EC

In a Kaplan-Meier analysis, patients with EC showed a significantly lower prevalence of pacemaker implantation compared to patients with LT (p=0.004). At five years follow-up, 4% of the patients with EC and 11% of the patients with LT had a permanent pacemaker implanted. At 10 years of follow-up 7% of patients with EC compared to 14 % of patients with LT had pacemaker treatment. The mean follow-up time was 18.7 years in the LT group; however, since EC has not been performed as long in Sweden mean follow up time was 8.1 years.

In a separate Kaplan-Meier analysis of patients with SND as an indication for pacemaker implantation after TCPC (LT =31, EC =13), we found that pacemaker dependency because of SND was less prevalent among patients with EC than patients with LT (p=0.001, Figure 18).

Figure 18. Patients who received a pacemaker because of sinus node dysfunction



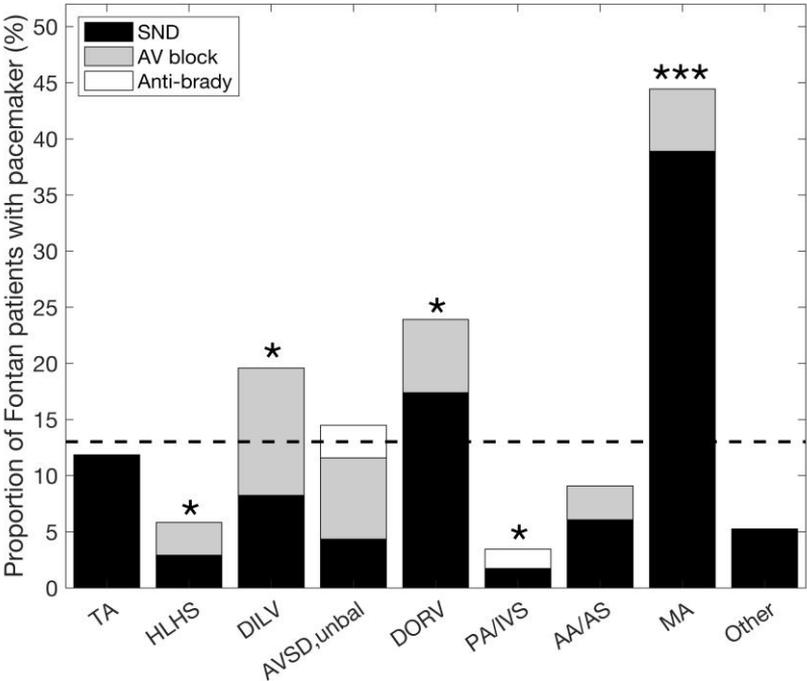
The proportion of patients that were free from pacemaker treatment at different times after total cavopulmonary connection (TCPC) is shown.

Numbers refers to the remaining number of EC/LT patients 0, 1, 2, 5, 10, and 15, 20 years after TCPC. LT= lateral tunnel, EC= extracardiac conduit.

Pacemaker implantation in different anatomical diagnoses

There was a significant overall difference in the proportion of pacemaker implantation between patients with different underlying anatomical diagnoses ($p < 0.001$). Pacemaker implantation was significantly more prevalent among patients with MA (44%, 8/18, $p < 0.001$), DORV (24%, 11/46, $p = 0.022$) and DILV (20%, 19/97, $p = 0.036$) compared to the other anatomical groups. In contrast, patients with HLHS, had a significantly lower prevalence of pacemaker implantation than in the other groups (6%, 6/103, $p = 0.017$). Pacemaker implantation was significantly lower (3%, 2/58, $p = 0.023$) in patients with PA/IVS (Figure 19).

Figure 19. The proportion of pacemaker treatment within anatomical diagnoses.



Shows the proportion of pacemaker treatment within anatomical diagnoses, including the indication for pacemaker treatment. Dashed line shows the average proportion (13%) within the Fontan cohort.

Indications: SND=sinus node dysfunction, AV-block=atrioventricular block, anti-brady= protection for bradycardia when treating with anti-arrhythmic drugs.

Anatomical diagnoses: TA= tricuspid atresia, HLHS= hypoplastic left heart syndrome, DILV= double inlet left ventricle, AVSD= atrioventricular septal defect, DORV=double outlet right ventricle, PA/IVS=pulmonary atresia with intact ventricular septum, AA= aortic atresia, AS= aortic stenosis, MA= mitral atresia.

Pacemaker implantation was significantly more prevalent among patients with heterotaxia syndrome, 22% (12/54, $p=0.035$). Among patients with heterotaxia syndrome three patients (9%) had right isomerism and nine (41%) had left isomerism. Patients with left isomerism had a significantly higher prevalence of pacemaker implantation ($p<0.001$). In this cohort only 5% of patients with double discordance as a part of their anatomical diagnosis had a pacemaker. Data

concerning morphology of the single ventricle was available for 96% of the patients. The prevalence of pacemaker implantation was 14% (44/307) in patients with dominant left ventricle, and 13% (33/248) in patients with a dominant right ventricle. In patients with DILV, unbalanced AVSD, and HLHS we found a relatively high proportion of AV block as the indication for pacemaker, 58%, 50%, and 50%, respectively.

Symptoms related to pacemaker implantation

Study of medical records allowed for data to be collected regarding symptoms before pacemaker implantation, was only available in 59% (46/78) of the patients. Symptoms varied from none (n=8) to circulatory instability/impaired hemodynamics (n=8). Fatigue was the most commonly reported symptom (n=22). Two patients had experienced syncope, four had palpitations or chest discomfort, and two reported headaches. Other symptoms reported were sleeping disorders, failure to thrive, edema and ascites, and dizziness. A history of paroxysmal supraventricular tachycardia before pacemaker implantation was reported in 19% of patients and ventricular tachycardia in 3% of patients.

Discussion

The Fontan surgical procedure, first described in 1971 is offered as a palliative treatment for a wide range of univentricular heart defects (10). The overall outcomes for patients with Fontan circulation have improved over the years. However, these patients still suffer from long-time complications.

Arrhythmia

Arrhythmia is one of the main causes of postoperative morbidity in Fontan patients (163). Supraventricular tachycardia in patients with Fontan circulation, should be treated urgently since this is strongly associated with venous thromboembolism, syncope, and rapid development of congestive heart failure (37, 164). Quality of life studies have shown that physical function, mental health, and general health perception is significantly lower in patients with Fontan circulation compared with controls. In particular, re-operations and arrhythmias have been shown to significantly compromise quality of life (165). Risk factors for development of arrhythmias in Fontan patients include; older age at surgery, longer duration of follow up and worse NYHA class symptoms (166). Furthermore, in patients with Fontan circulation, low physical functional status has been independently associated with history of arrhythmia (167). Although atrial re-entry tachycardia and SND are the most common types of arrhythmias, asymptomatic ventricular tachycardia also occurs in children and adolescents with Fontan circulation (71), emphasising the need for adequate rhythm surveillance in patients with Fontan circulation. For this reason Holter monitoring is recommended as a routine outpatient follow-up investigation for all patients with Fontan circulation (99, 164).

ECG registration

In clinical practice, arrhythmias are usually diagnosed with either a resting 12-lead ECG or ambulatory 24-hour-Holter ECG monitor, with intermittent patient- or event-activated trans-telephonic monitors gaining popularity. In children, trans-telephonic event recordings are significantly better at detecting subjective symptoms of arrhythmias compared to Holter recordings, however Holter monitoring was more effective in detecting asymptomatic arrhythmia among high-risk children (168). In adults, intermittent ECG traces, recorded by a hand-held-ECG device during a 30-day period, were superior in providing diagnosis of paroxysmal atrial fibrillation when compared to continuous 24-hour ambulatory ECG recorded during a single 24-hour period. This suggests that this type of device can be used to easily diagnose asymptomatic arrhythmia in adults (103). On the other hand, the handheld ECG monitors and other types of post-event recorders have obvious disadvantages; if the ECG recording is initiated upon

symptoms the start of the arrhythmia will not be recorded. Another disadvantage is a risk of failure to record an event when an arrhythmia episode terminate before thumbs are put on the device to activate a recording. In paper III, we focused on screening for silent arrhythmias and on HRV analysis. The disadvantages mentioned above were not relevant in this study because we focused on asymptomatic arrhythmia. We performed HRV analysis on these recordings by summarising an average of 27 30-second recordings and the results were presented in a single Poincaré plot (Figure 11). Intermittent monitoring by hand-held device revealed significant arrhythmias including; frequent and complex ventricular extra systoles and intermittent paroxysmal atrial tachycardia. This study suggests that a hand-held intermittent ECG recording device may be a useful and user-friendly tool for arrhythmia surveillance and HRV measures.

In studies I and III, we found a low incidence of rhythm abnormalities on 24-hour-Holter ECG recordings and on intermittent hand-held ECG recordings, compared to earlier studies (58, 163). However, more recent studies of patients with Fontan circulation show a similar, relatively low incidence of atrial tachycardia, indicating that the more recent surgical and medical treatment may have decreased the development of arrhythmias in this group (71, 169). As the surgical technique developed from LT to EC, one of the expected advantages was a reduction in post-operative arrhythmias due to avoidance of atrial surgery (170). For this reason, from the beginning in 1998, EC is now the preferred Fontan procedure in Sweden.

Bradycardia

We found significantly longer RR intervals in patients with Fontan circulation compared to controls (paper I, II, and V). This is in line with earlier work by Blafox et al. who found that 27% of Fontan patients had a resting heart rate below the fifth percentile for their age (169). A lower heart rate may be beneficial, since diastolic filling time increases, which is of relevance in the Fontan circulation where reduced pre-load is a major hemodynamic problem, however cardiac output may be significantly reduced if bradycardia is pronounced.

In the longitudinal study (paper II) we found that after BDG surgery the RR intervals on 24-hour ECG were significantly increased (heart rate reduced) compared to before BDG surgery. This suggests that the BDG procedure contributes to the overall decrease in heart rate seen in patients post-TCPC completion. Interestingly, pre-BDG heart rate were within normal range in patients when compared to controls, indicating that the reduction in heart rate post-BDG is not related to a decrease of ventricular volume overload alone. It has been suggested that the low heart rate in Fontan patients may be the result of surgical or functional autonomic derangements due to the surgical procedure,

with selective reduction of cardiac sympathetic activation rather than sinus node dysfunction (169).

A high mean heart rate (Z-score >2) was extremely rare between the surgical stages and after completed Fontan circulation. Only one patient showed increased mean heart rate before BDG. This is somewhat unexpected since in low cardiac output states, increased sympathetic stimulation with a concomitant increased heart rate would be expected. However, the majority in our study population throughout the surgical steps showed good (grade III-IV) ventricular function assessed with echocardiography (Paper I-V).

Sinus node dysfunction (SND)

Even though more recent studies show lower incidence of tachyarrhythmias than previously, the incidence of SND remain high, around 30% (59, 71, 169). Cardiac output may be limited in patients with SND if bradycardia is pronounced. Furthermore, in junctional escape rhythms, stroke volume will be reduced due to reduced ventricular filling as a consequence of AV dyssynchrony (57, 171). Pacemaker treatment in patients with SND is indicated when the patient has symptoms related to bradycardia, provided that other causes of the symptoms have been excluded (83). In a study from the Netherlands only a minority of patients with SND received pacemaker treatment (71). Close surveillance of patients with asymptomatic SND is of major importance since patients with SND can become symptomatic over time. Symptoms are non-specific and therefore it is possible that the patient and, or doctors do not recognise the slowly developing symptoms such as fatigue as be related to the heart rhythm. Moreover, SND in patients with Fontan circulation is associated with the development of atrial flutter (166). Thus, a method for predicting progressive symptomatic SND requiring pacemaker treatment would be helpful to clinicians caring for these patients.

In study I we showed significantly longer RR intervals in patients with LT compared to EC. However, we found no difference between LT- and EC-operated patients regarding the prevalence of bradycardia. This is in line with findings by Cohen et al where no difference in SND between LT and EC were identified (57). Other studies show a lower frequency of SND in patients operated with EC (29, 87), however another study found a lower frequency in patients with LT compared to EC (58). It has been suggested that patients operated with LT may have a higher risk of developing SND because the surgery is performed close to the sinus node.

Pacemaker treatment

In our Swedish national cohort of 599 patients who had Fontan surgery between 1982 and 2017, 13% were identified as having had pacemaker treatment after a mean follow-up time after Fontan completion of 12.2 years. Previous studies of patients with Fontan circulation reported a prevalence of pacemaker implantation of 7-25% (59, 61, 71, 74, 92). In our study, a large proportion of the patients had their permanent pacemaker implantation within the first two years after Fontan completion.

The most common indication for pacemaker treatment in the Swedish Fontan cohort was SND, and the second most common indication was AV block. This finding is in contrast with a study by Pundi et al., in which the main indication was late arrhythmias such as atrial re-entry tachycardia (61). One reason for the relatively low incidence of late tachy-arrhythmias in our cohort may be that the cohort consisted of fewer patients with atrio-pulmonary Fontan surgery. This surgery is often complicated by atrial enlargement, and is correlated to a higher risk of late arrhythmias (62). Pacemaker implantation is indicated if the patient fulfills the SND ECG criteria and has related symptoms (83). In paper IV we studied symptoms documented in medical records. The most common symptom among Swedish Fontan patients with SND was fatigue. Fatigue is however a difficult symptom to study objectively, there is a possibility both of over- and under-identification of such a subjective, non-specific symptom. "Normal" fatigue during puberty could be misinterpreted as a significant symptom, or severe fatigue interfering with the daily activities of the child could be blamed on the severe heart defect. Overestimate of the possibly SND-related symptoms entails an obvious risk of unnecessary complications, whereas underestimate carries risks of unnecessary impaired quality of life for the patient (165, 172).

In our study we found no significant difference in mortality between patients with and without pacemakers. Future studies should look into more morbidity with subtle differences such as physical activity and quality of life. We compared the prevalence of pacemaker implantation in LT versus EC Fontan patients and found that pacemaker implantation was significantly less common after EC. This supports results presented by Downing et al. (93). On the other hand, others have not identified a difference regarding pacemaker implantation rates between LT and EC Fontan patients (74). Since the first EC procedure in Sweden was performed in 1998, the follow-up after TCPC surgery was shorter for the EC group than for the LT group. Our data does not allow us to predict the frequency of pacemaker implantation in a perspective beyond 15 years of age.

In paper IV we also investigated the risk of pacemaker implantation in each univentricular heart anatomical sub-group. We found that the prevalence of

pacemaker implantation was significantly higher in patients with DILV, MA and DORV, and significantly lower in patients with HLHS and PA/IVS. The findings of a high prevalence of pacemaker implantation in patients with DILV confirms earlier findings by Williams et al. (92). The proportion with AV block as the indication for pacemaker treatment was high among patients with DILV. DILV shares anatomic features with double discordance. Risk for pacemaker treatment has been shown to be increased in Fontan patients with ventricular L-looping (62, 92). The prevalence of pacemaker treatment was also high in patients with MA. We found no significant difference between LT and EC within the MA group, thus, type of TCPC did not explain the high prevalence of pacemaker implantation in the MA group. In our study the classification of the different anatomical diagnoses originated from the patients' medical records. In the case of MA or left AV valve atresia, the defect could be the primary diagnosis, be part of a complex anatomical diagnosis or be a secondary diagnosis; DILV with MA or DORV with MA (173). Among all patients in the Swedish cohort with MA as part of their cardiac malformation (primary or secondary), pacemaker implantation was significantly more common than among other Fontan patients. It has been described previously that, since there is a risk of development of left atrial hypertension in a heart with an absent or obstructive left AV valve, this could in turn contribute to progressive deterioration of the AV conduction (173). In our Swedish population, SND was the main indication for pacemaker implantation in patients with MA. A South Korean group reported an association between elevated LA pressure and increased LA size and SND in patients undergoing mitral valve surgery (174, 175). They proposed a mechanism of atrial fibrosis leading to SND. Thus, we speculated that a similar mechanism could be present in patients with MA, Fontan circulation, and SND.

In the DORV group, patients with left isomerism were found to have a high number of pacemaker implantations. As expected, the prevalence of pacemaker implantations in patients with left isomerism was high and SND was the indication for pacemaker treatment in all patients with left isomerism. This is also expected since normally located sinus node is absent in left isomerism, entailing a risk for development of both AV block and SND (18). In the HLHS group, pacemaker implantation was less prevalent compared to the other anatomical diagnoses. This is in contrast to a study by Williams et al., which reported a higher incidence of pacemaker implantation among patients with HLHS (92). Norwood surgery, complicated by AV-block or SND, have been shown to have a very poor prognosis in patients with HLHS (176, 177). In our study only Fontan survivors were included, thus it is possible that if we had included all patients born with, and operated (completed Fontan or not), univentricular heart defects in Sweden between 1982 and 2017, the frequency of pacemaker implantation among patients with HLHS may have been higher.

Heart rate variability (HRV)

HRV is normally used to study the autonomic nervous effect on the sinus node and in general, reduced HRV is associated with poor outcomes in patients with cardiac disease. HRV also mirrors the heart rate fluctuations caused by cardiac arrhythmias and thus minor increases HRV could reflect subtle arrhythmias (178). Analysis of HRV from 24-hour ECG recordings, has obvious advantages in the study of the power spectral analysis of HRV, allowing for assessment of HRV during both day and night. In paper III each ECG recording by a handheld ECG device was 30-seconds. A novel approach used in this study was to collect several intermittent recordings and pool them for each individual for use in HRV analysis. The Poincaré plots, used in study II, III and IV can be helpful in revealing autonomic dysfunction as well as subtle arrhythmias (178). A Poincaré plot provides a good graphic representation of HRV. Marked beat-to-beat variability, depicted as a “comet-shaped” pattern, suggests preserved cardiac autonomous nervous function and “torpedo shape” pattern suggests decreased HRV, indicating potential loss of cardiac autonomous nervous function. In this case, longer recordings and more detailed HRV analyses are recommended.

HRV and SND

We found in patients with Fontan circulation and SND, significantly higher HRV than both controls and patients with Fontan circulation without SND (paper V). HRV is known to be high in normal cardiac autonomic modulation when there is a parasympathetic predominance, however, HRV is also increased during arrhythmia. Previously in adults, HRV has been studied in patients without congenital heart disease and results from Poincaré analysis have shown significant differences between patients with SND and controls (159, 160). In agreement with the findings in the adult population, we found abnormal patterns of Poincaré plots in this pediatric population with SND. In the Poincaré plot, SD2 reflects diurnal variation of the mean heart rate; a low SD2 is seen when the diurnal variability is reduced, and a high SD2 when there is increased HRV over 24 hours. In the Poincaré analysis group means of SD1 and SD2 were higher in Fontan patients with SND (with- or without- pacemaker treatment) than in Fontan patients without SND. On comparison of SND patients with a pacemaker to those without, SD2 was slightly reduced ($p=0.06$) (paper V). This finding could indicate a reduced diurnal HRV in addition to severe bradycardia. We hypothesize that patients with SND initially have an elevated SD2 due to episodes of pronounced bradycardia. At this point, the mean heart rate is lower than in controls, but still there is good chronotropic competence with the ability to a relatively high maximal heart rate, resulting in an increased SD2. Possibly, at a later stage of more advanced SND, chronotropic competence will fail leading to a decrease in SD2 to normal values, whereas mean heart rate will further decrease.

In this case the Poincaré plot would appear more normal despite a more severe SND.

High SD1 reflects a high beat-to-beat variability, but is also seen in the presence of frequent large changes in mean heart rate. Thus, in the case of SND, an increased SD1 could be explained by repeated shifts in the heart rhythm between sinus rhythm and junctional rhythms. Another explanation to increased SD1 could be other forms of arrhythmia like atrial extra-systole or AV conduction disturbance, which also would contribute to increased beat-to-beat variability.

Other plausible reasons for low HRV in Fontan patients

In adults, HRV is reduced in patients with congestive heart failure (126, 179). However, in our cohort there were only few patients with poor ventricular function or severe AV valve regurgitation assessed on echocardiography. Thus, heart failure is therefore not the likely cause of reduced HRV found in our studies. Multiple medications may indicate previous impairment in ventricle function and more severe AV valve regurgitation, not still detectable in echocardiography. ACE-inhibitors and diuretics, used to treat these conditions were the most prevalent medication, (after acetyl-salicylic-acid) in our studies. In the multiple regression analysis we found that multiple medications were related to lower HRV in TP, HF and LF (paper I).

HRV related to surgical stages

Histological studies of the normal human heart, both in adults, children and fetuses, have shown large populations of autonomic neural ganglia located in fat pads on the posterior surfaces of the right atrium, near the SVC at the junction of the right atrium, and between the entrances of both caval veins. The IVC-atrial junction also contains populations of ganglia, and ganglia are also prevalent on the medial and inferior surface of the IVC (106, 109, 110). Thus, the anatomical location where the BDG and the TCPC surgery take place is densely populated with autonomic ganglia. The BDG procedure is performed by detaching the SVC, at the entrance to the heart and oversewing the cardiac end. The SVC and right pulmonary artery are then connected with an end to side anastomosis. During the surgical procedure for EC conduit the IVC is transected. This could damage the parasympathetic ganglia located close to the IVC-atrial junction or at the medial and posterior surface of the IVC. Hence, a plausible cause for reduced HRV in patients with Fontan circulation is damage to autonomic nerves, ganglia plexuses or to blood vessels supporting these structures, resulting in impaired cardiac autonomous nervous activity reflected as a reduced HRV (151, 153). Ganglionated plexuses are composed of sympathetic, parasympathetic and mixed nerves (108). This could explain the global reduction in HRV noted after cardiac surgery (151). Furthermore, in a study on sheep, which have hearts neuroanatomical similar to

human hearts, an area that contains about 40% of total epicardial ganglia was ablated using radiofrequency method. All sheep underwent a 24-hour ECG monitoring the day before the ablation, on the second day after the ablation and repeated every month throughout a twelve – month period. There was an instant reduction in HRV parameters LF and HF after the ablation and both components remained decreased twelve months after ablation (180).

In our research we have confirmed that Fontan patients have reduced HRV when compared with healthy controls (151, 154). We have found that, in patients with Fontan circulation, HRV was significantly reduced in the HF region compared with controls (paper I, II and V). HF represents the parasympathetic nervous regulation of the heart and a decrease in HF could be a sign of damage to the parasympathetic nervous innervation. We attempted to clarify the temporal development of the HRV changes during the staged surgery and if reduction of HRV was related to a particular type of surgery or stage of progression towards completion of Fontan circulation. In our longitudinal follow-up we found HRV parameters to be reduced already before BDG surgery, which could be interpreted as a pre-existing cardiac autonomic dysfunction in these patients. Another possibility is that the reduced HRV seen pre-BDG may be related to volume overloading of the single ventricle. Several studies in adult populations have shown reduced HRV in patients with dilated cardiomyopathy (181, 182). In children with a volume overloaded right ventricle due left- to-right-shunting over an ASD, HRV was reduced before, but normalised after transcatheter ASD closure (144). Thus, the reduction in HRV seen in patients before BDG may be explained by the volume overloading of the single ventricle.

In study II, we found a further reduction in HRV after completion of the TCPC procedure, with significantly lower P_{HF} and $SD1$ compared to before the TCPC, indicating a reduced parasympathetic action of cardiac autonomic innervation. In this study the majority of patients (96%) were operated with the EC conduit variant of TCPC surgery. During this surgical procedure the IVC is transected, and the parasympathetic ganglia to the IVC–atrial junction, or at the medial and posterior surface of the IVC, may be affected (106, 110). We found significant reductions in HRV which supports our findings in paper I. This indicates that the EC conduit surgery may also affect the cardiac autonomic innervation.

Conclusions

There is a growing population of patients with palliated univentricular heart defects. These patients are at risk of serious complications and thus represent a cohort in which systematic review and studies focusing on specific issues related to mortality and morbidity may contribute to important discoveries. Atrial arrhythmias and SND are frequent complications in patients with Fontan circulation, however it is still unclear if and how the onset of cardiac arrhythmia could be predicted and if the choice of conduit is responsible or contributes to development of complications.

It has been previously established that patients with Fontan circulation have significantly reduced HRV and mean heart rate compared to controls, however we have now shown that bradycardia is present already after BDG surgery and further significant reductions in HRV after completion of the final surgical intervention was also found. These changes indicate progressive alterations in the cardiac autonomic nervous system in patients with univentricular heart defects undergoing conversion to Fontan circulation. It could be speculated that the reduction in HRV is caused by the underlying pathophysiology of the congenital heart defect; a compensatory mechanism due to over- and under volume loading of the single ventricle and/or a result of damage to cardiac autonomous ganglia during surgical procedures. In any case our findings indicate that HRV analysis may be useful when following-up patients with Fontan circulation, contributing valuable information regarding the development of arrhythmia complications such as SND and the prediction for subsequent need of pacemaker treatment. It is interesting that autonomic modulation by electrical stimulation of the parasympathetic nervous system has emerged as a new therapeutic modality. In the future, strategies for stimulating epicardial ganglia might be included in the therapeutic arsenal for patients with Fontan circulation at risk for arrhythmias and sinus node dysfunction.

Our research has highlighted the importance of focusing and developing research in this area to prevent expected long-term complications and improve the future and quality of life for the growing population of patients with palliated univentricular heart defects.

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