From
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Karolinska Institutet, Stockholm, Sweden

CONGENITAL HEART BLOCK
A STUDY OF DIAGNOSTICS,
PATHOGENESIS, PROGNOSIS AND
TREATMENT

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Stockholm 2014
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Wir haben wenig Zeit, lasst uns deshalb langsam voran gehen

Ruth Cohn

To my beloved
ABSTRACT

Congenital heart block (CHB) is a rare condition with considerable mortality. In most patients the disease is associated with fetal exposure to maternal SSA-Ro and/or SSB-La autoantibodies (AB) and develops in fetal life. Accuracy in fetal diagnostics is important to distinguish benign from life threatening conditions. Transplacental steroid treatment to improve survival has been tried but the effect is unclear. The majority of exposed children do not develop CHB, but sometimes transitory conduction abnormalities, normalizing at birth, with unknown outcome in childhood. Pacemaker (PM) therapy to CHB patients is lifesaving, but does not always prevent development of heart failure.

The aims of this thesis were to study: The differential diagnostics in fetal bradycardia (paper I), the effect of transplacental steroid treatment and risk factors associated with a poor outcome (paper II), the clinical pathogenesis of antibody exposure (paper III) and PM treatment in young patients with complete atrioventricular block (CAVB) (paper IV)

In paper I, the diagnostic accuracy with Echo Doppler techniques was studied retrospectively in a regional cohort of 65 patients with fetal bradycardia. We found that the bradyarrhythmic mechanism was identified correctly in all but one patient. Benign blocked atrial bigeminies showed close resemblance to second-degree AVB in a few cases, but could be differentiated with meticulous measurements.

In paper II, the effects of exposure to transplacental treatment with fluorinated steroids in fetal second- and third degree AVB were studied retrospectively in a multicenter, multinational setting of 175 patients. Ninety-one percent were alive at birth and survival rate in the neonatal period was 93%, similar in treated and untreated fetuses. Risk factors (RF) associated with a poor outcome were gestational age < 20 weeks, ventricular rate ≤50, hydrops and impaired left ventricular function (LVF) at diagnosis. The presence of ≥1 RF was associated with a 10-fold increase in mortality before birth and a 6-fold increase in the neonatal period, independent of treatment.

In paper III, the effects of prenatal exposure to maternal autoantibodies on heart function and conduction properties were investigated in a cross-sectional follow-up of pre-school children who did not develop fetal complete heart block. Sixteen patients who developed AV time interval prolongation in utero (group A) were compared with 41 who did not (group B). Ten percent (6/57) exposed to maternal autoantibodies in fetal life had developed first-degree AVB at follow-up, in spite of a normal ECG at birth or at 1 month of age. All 6 had prolonged AV-time intervals in utero. LVF in terms of M-mode, was normal in all patients, but myocardial performance index was slightly higher in group A.

In paper IV, the outcome of young patients with CAVB and PM was studied retrospectively in a national cohort of 127 patients. Survival rate after 9 years of PM treatment was 96% and 8% developed LV dysfunction. There was a gender difference in cardiac status prior to PM but not at FU. Exposure to antibodies did not change the outcome significantly, but diagnosis <1 month of age and LV dysfunction before PM were associated with a poor outcome.
I. Eliasson H, Wahren-Herlenius M, Sonesson SE
Mechanisms in fetal bradyarrhythmia: 65 cases in a single center analyzed by Doppler flow echocardiographic techniques.

Isolated atrioventricular block in the fetus: A retrospective, multinational, multicenter study of 175 patients.

III. Bergman G*, Eliasson H*, Mohlkert LA, Wahren-Herlenius M, Sonesson SE
Progression to first-degree heart block in preschool children exposed in utero to maternal anti-SSA/Ro52 autoantibodies.

Outcome in young patients with isolated complete atrioventricular block and permanent pacemaker treatment: A nationwide study of 127 patients
In manuscript
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1 INTRODUCTION

Congenital heart block (CHB), or congenital atrioventricular block (AVB) is a disease which in the absolute majority of patients develops after exposure in utero to maternal autoantibodies (SSA/Ro-SSB/La) passing the placenta to the fetus during the second trimester. The mothers of these children often, but not always, have a connective tissue disease like Sjögren’s syndrome or Systemic Lupus Erythematosus.

CHB is a rare disease with a considerable mortality, especially in fetal life and the neonatal period. Practically all children surviving the neonatal period will eventually need to have a pacemaker implanted. This is a lifesaving therapy but not without problems for the child. When complete CHB has developed it is usually resistant to treatment and therefore current strategies aim at intervening before or at the onset of disease. The time span from onset of disease until development of the apparently irreversible complete heart block is sometimes short. The recognition and diagnostics of intermediate disease stages (first- or second-degree AVB) could therefore be lifesaving. On the other hand, diagnostics need to be able to distinguish these conditions from benign ones, avoiding unnecessary and potentially harmful treatment. Not all exposed fetuses develop the disease; with some showing only transitory conduction abnormalities in fetal life, normalizing at birth. These children are considered as having no risk for later disease progress, even if studies confirming this hypothesis are largely lacking.

This thesis encompasses four aspects of the disease where, in my opinion, a knowledge gap in one form or another was present; diagnostics, pathogenesis, treatment and prognosis. We aimed to evaluate the diagnostic aspects in a regional cohort of fetal bradycardia focusing on the accuracy of differential diagnostics. The pathogenesis in clinical expression was studied in a similar cohort, focusing on the outcome of previously antibody exposed pre-school children who never developed complete CHB, in order to see if heart function and conduction properties were still normal at follow-up. The treatment aspect was studied in the context of a multinational, multicenter format looking at the outcome of fetuses with second- or third-degree AVB with respect to treatment or non-treatment with transplacental fluorinated steroids. Possible risk factors associated with a poor outcome were identified. Finally, the outcome or prognosis of pacemaker treated patients with CHB was studied in a national cohort of young patients with antibody associated heart block and compared with those with heart block due to other reasons.
2 BACKGROUND

2.1 HISTORICAL REMARKS

In 1901, Morquio described the first case of a presumed congenital complete heart block (CHB) in the absence of major structural heart disease. The case was reported in the context of a familial condition with a permanently slow pulse, repeated attacks of syncope and sudden death. The first known case where ECG was included to beyond any doubt confirm the diagnosis of a CHB, was published in 1908 by van den Heuvel. In the following years only sporadic reports of new cases appeared. The first initiative to an original study was taken within the European Association of Pediatric Cardiologists in 1964 and a preliminary report on 244 cases was published in 1967. This study was later extended and “merged” with a North American study, forming the basis for the now classic study by Michaëlsson et al, describing the natural history of this disease.

2.2 DEFINITIONS AND CLASSIFICATION

Although a congenital heart block (CHB) may initially appear as first- or second-degree atrioventricular block (AVB), it is often generally understood and synonymously described as a (1) congenital complete heart block (CCHB), (2) congenital complete atrioventricular block (CAVB), or (3) third-degree AVB. For readability reasons, this is the definition intended whenever the term congenital heart block (CHB) is used in the context of this thesis; unless otherwise specified.

Complete AVB implies complete absence of conduction from atrium to ventricle in the presence of normal atrial activation and a slower dissociated ventricular rhythm with regular QRS-complexes.

Until around a decade ago, there was some confusion regarding how to define congenital complete AVB in terms of its temporal limitation, but in accordance with the proposal by Brucato and Rosenthal in 2003, the now universally accepted definition is: “an AVB is defined as congenital if it is diagnosed in utero, at birth or within the neonatal period (0-27 days after birth)”. A CHB can be associated with structural heart disease, but in this context, CHB is synonymous with isolated CHB, i.e. in absence of any structural heart disease associated with the heart block.

2.3 INCIDENCE

The measures of incidence in rare diseases are often inaccurate, and this is most likely the case also for CHB. Several studies have provided numbers of incidence measures but if one looks closer at the calculations behind these figures they are often based on approximate data. Beginning with the incidence cited in the absolute majority of the articles concerning CHB, Michaëlsson et al where one of the calculations were made by referring to a study in which 27 cases of CHB were found among 3,000 cases with congenital heart disease. Assuming an incidence of congenital heart defects of 1/100 live-born infants, an incidence of 1/15,000 was estimated. In the same paper referral was made to incidence calculations by another group, of around 1/22,000 (3 CHB in
67,000 deliveries in a Boston cohort from 1936 to 1962), and finally the authors concluded that taking these figures together with “various centers participating in this study indicate an average figure around 1 CHB per 20,000 live-born infants”. These incidence calculations from the early 1970s gave a first approximate number of the incidence of CHB, including those with structural heart disease. They were however not the results of estimations in a national cohort or similar.

So which is the “true” incidence for isolated CHB? A reasonable approximation using the best data available so far, is probably to use the calculated “average” incidence of 1/20,000, assuming that about 50-70 % of live-born children with CHB are isolated CHB. This would give an approximate incidence of isolated CHB of 1/30,000-40,000 live-born. Julkunen et al\textsuperscript{8} had a different result in a Finnish study, where their estimate in the Finnish population was 1/17,000 (1:14,000-1:21,000), and even 1:11,000 (1:8,000-1:17,000) in the 1990s. They did, however, include CAVB patients diagnosed up to 5 years of age in their figures. The strength of their study was that calculations were based on data from a national cohort. The authors speculate that the reasons behind the increased incidence could be that an increasing number of women with connective tissue disease manage to get pregnant due to improved treatment of their disease or that fetal treatment with IVIG, steroids, or plasmapheresis has increased survival in the group of CHB in recent years. There are to date no studies that can confirm such a hypothesis.

2.4 CARDIAC CONDUCTION SYSTEM

Embryology

Some basic knowledge of the development of the heart and the conduction system is indispensable in order to understand the arising pathologies in connection with the disease progress of congenital heart block. An attempt at a brief summary will follow below.

The development of the human heart starts around day 19, through the formation of the primary heart tube. In this early undifferentiated state, its walls consist of a primary myocardium already capable of slow conduction, slow contraction and spontaneous depolarization\textsuperscript{9}. With the subsequent formation of the chamber myocardium, the conduction gets more rapid and it is already possible to record a relatively normal ECG, including a period of AV delay\textsuperscript{10}. Within the primary heart tube a remodeling takes place, allowing for a separation of the atria and ventricles as well as the left- and right ventricular outflow tracts.

At around week 7 of the development of the human fetus a gradual separation of the atria and ventricles begins at the AV canal, forming an insulating layer of connective tissue: the annulus fibrosus\textsuperscript{11}. The process is thought to be completed at around week 12 of gestation\textsuperscript{12}. Animal studies have demonstrated the presence of multiple myocardial AV connections even in late stages of the development of the heart\textsuperscript{11}. A subsequent immunohistochemical study of fetal and neonatal sectioned hearts from 4 to 36 weeks of gestation, confirmed that the isolation of the AV junction is a gradual
process completing at between 10 and 20 weeks, but with thin persisting AV muscular connections up to 20 weeks\textsuperscript{13}.

The sinus node (SN) is recognizable already at 5 weeks of gestation, initially as a U-shaped structure comprising the definitive right sided SN and a transitory, temporary left sided SN; where the latter appears earlier in development and is larger than the right sided SN\textsuperscript{14,15} but disappear in the course of normal maturation and development of the heart. In early development, a “double” AV node with a posterior and anterior node is present, later fusing to a single AVN primordium\textsuperscript{16,17}. The posterior node subsequently connects to the His bundle, eventually forming the definitive AVN\textsuperscript{18}. The final maturation of the AVN is thought to be completed during the first year of life\textsuperscript{19}.

**Function of the cardiac conduction system**

The cardiac conduction system (CCS) consists of the sinus node (SN), the atrioventricular (AV) conduction axis (comprising the AV node), the left and right bundle branches and the Purkinje network. The entire system is made of highly specialized cells with the unique properties of electrical conduction. The SN generates impulses, rapidly spread over both atria. The atria and ventricles are electrically isolated from each other by a stratum of connective tissue, which is penetrated by the AV conduction axis along which the impulse from the atrium is propagated, constituting the only atrioventricular connection of the normal heart.

The function of the SN is distinctly different from the working myocardium in that the action potential (AP) has a slow upstroke because it is not generated by an increased Na-current into the cell but instead by smaller and slower T- and L-type Ca\textsuperscript{2+} - currents\textsuperscript{10}. Interestingly, in a study by Qu et al\textsuperscript{20} on human fetal heart cells, the alpha-1D L-type (Ca\textsubscript{v}1.3) calcium channel, considered a key player in the SN function and the generation of the diastolic depolarization, was demonstrated to be blocked by CHB Ig G. This finding could support clinical observations of sinus bradycardia appearing in antibody exposed fetuses and children.

The normal and fastest route for the AP from the SN to reach the AVN is through a pathway along the interatrial septum\textsuperscript{10}. It is located at what is known as the base of the triangle of Koch, which is in turn located at the base of the atrial septum. The main function of the AV node is basically to conduct the AP from the atria to the ventricles, decreasing the velocity and by doing so, allowing for the atrial systole to take place before the ventricular systole, enabling an adequate filling of the ventricles. Its capacity of reducing AP frequency to the ventricle protects the heart from very fast rhythms, while its capacity to act as a secondary pacemaker has a savior function in case of sinus node dysfunction or a complete heart block\textsuperscript{10}. There is a vast difference in the morphology of APs within the AVN, believed to reflect the difference in ionic currents and ion channel expression\textsuperscript{21}. As in the SN, Ca -currents rather than Na-currents are thought to be responsible for the upstroke of the AP and just like in the SN, the subunit of the L-type Ca\textsubscript{v}1.3 is upregulated in the AVN\textsuperscript{22}. This is interesting as one of the hypothesis of the cross reacting effect of Ro/SSA AB suggests an interaction with this channel. Another important function of the AVN is the ability for automaticity of the so called junctional P cells which hence not only act as conductors of the AP from the SN,
but are also capable of “producing” an effective escape rhythm in case of failure of the SN or appearance of complete AVB\(^{19}\).

**Disease progress**

The exact mechanisms of the progressive development from normal cardiac conduction to end stage CHB are not clear. The assumption is a gradual development through all intermediate steps, possibly over days or weeks in some cases. The leading hypothesis (see Pathogenesis) is an interaction between SSA/Ro autoantibodies and maybe the above described Ca-channels Ca\(_{v}1.3\) and Ca\(_{v}3.1\) shown to be important for the automaticity of AVN cells. Another important player is the HCN-channel, shown to cause SB and AVB in in a knock-out mouse model\(^{23}\). How these ion channels are influenced on a molecular level at the different stages of AVB is not known. The different stages of AVB are usually categorized in first- second- and third-degree AVB.

**First-degree atrioventricular block**

In first degree atrioventricular block (AVB), the impulse or action potential (AP) generated in the sinus node (SN) and travelling down to the AV node, is delayed causing a prolonged PR interval on ECG.

**Second-degree atrioventricular block**

In second degree AVB (AVB II), at least one (but not all) of the impulses generated in the SN is not conducted to the ventricles. There are mainly two types of AVB II; Mobitz type 1 where, after a progressive delay of the impulse conduction, one impulse is not conducted and Mobitz type 2 where the impulses are intermittently not conducted, without a previous prolongation of the delay in the AV node. Mobitz type 2 AVB II is considered a more advanced AVB and less stable in its form. There is often a fixed number of non-conducted impulses for every normally conducted impulse to the ventricle per cycle.

**Third-degree atrioventricular block**

In third degree or complete AVB there is a complete dissociation between the rhythm in the atria and the ventricles, with a slower ventricular rhythm, regular QRS-complexes and resulting bradycardia.

### 2.5 ETIOLOGY

**Congenital heart block as a part of Neonatal lupus syndrome**

Neonatal lupus syndrome (NL) is an uncommon autoimmune disease and represents a model of passively acquired autoimmunity\(^{24}\). The serum of the pregnant woman contains maternal autoantibodies to soluble, intracellular ribonucleoproteins 48kD SSB/La, 52 kD SSA/Ro or 60 kD SSA/Ro\(^{25,26}\). Half of the mothers are asymptomatic carriers of these antibodies, whereas the other half have Sjögren’s Syndrome, Systemic Lupus Erythematosus (SLE) or Mixed Connective Tissue Disease. In the newborn child a skin rash is often present, but the most serious manifestation is congenital heart block.

Congenital heart block is strongly associated with exposure to these maternal autoantibodies which are present in 85-90% of the mothers to children with CHB diagnosed in the perinatal period. Even if it is now common to categorize prenatally
diagnosed CHB and those diagnosed in the first month after birth in the same group, it seems that nature does not comply with this categorical definition, as cases diagnosed in fetal life have a higher percentage of exposure to maternal autoantibodies, around 95-98%27,28.

Until the beginning of 1970s, the etiology and pathogenesis of CHB was largely unknown and thought to be associated with infectious agents or unknown hereditary factors. Following single observations of offspring with CHB to mothers with connective tissue disease, the first systematic reports showing this association appeared in 197729,30 and 197931. In 1983, Scott et al32 showed that > 80% of the mothers to children with CHB had antibodies to a soluble tissue ribonucleoprotein antigen called Ro (SSA); a finding that has been confirmed repeatedly in later studies.

**Non immunologic congenital heart block**

In about 5-15% of patients, the heart block has developed without exposure to maternal autoantibodies. In the clinical context of a negative test with respect to presence of maternal autoantibodies, the preexistence of a clearly recognizable underlying disease is rare.

**Association with extracardiac disease or cardiomyopathies**

Neuromuscular disorders are sometimes referred to be connected with CHB, but they seem rather to develop and progress in childhood, being extremely rare at birth 33. In a similar way, certain subtypes of familial dilated cardiomyopathies are associated with various degrees of AVB, but practically always appearing in childhood or later34,35.

**Infectious agents and congenital heart block**

Infectious agents - sometimes present at the time of diagnosis of AVB in childhood - could theoretically cause myocarditis and AVB through maternal-fetal transfer of viral antigens inducing conduction disorders. Reviewing the literature there are, however, only single cases diagnosed before one month of age36 and no published cases with a CHB, and myocarditis verified by heart biopsy, in the absence of maternal autoantibodies. One could also mention the fact that certain viral antigens have been suggested to in some way facilitate the development of CHB in antibody-exposed patients, there is however no evidence supporting that hypothesis.

**Hereditary components**

A recent multicenter study showed that parental conduction disease was present in about half of the cases of non-immune isolated AV block presenting in utero, in the neonatal period or in childhood 37,38. Eighteen percent of the cases were CHB. The cohort included patients from 13 different centers, making prevalence and incidence difficult to estimate, but this highly interesting finding suggests that the so far unexplained remainder of CHB not associated with maternal autoantibodies, to a substantial extent could have a hereditary/genetic background.
2.6 PATHOGENESIS

From association to explanation?

Ever since the first reports and observations in the 1970s and -80s and the apparently convincing link between SSA/Ro exposure and development of AVB, there has been continuous work to form hypotheses and explain underlying mechanisms in the pathogenesis. To date, it has not been able to explain why only 1-2% of children exposed to SSA/Ro autoantibodies develop CHB \(^{39} 40\). However, the fact that the recurrence rate in subsequent pregnancies is 12-20% \(^{41} 41-44\) indicates that other factors - maternal, fetal or both - play a role in the evolution of CHB.

**Passive immunization through anti-SSA/Ro antibodies**

At the outset of the research in this field, a bystander effect had to be excluded and a possible causal effect of the antibodies investigated, for which reason animal models were developed to study the role of the SSA/Ro-SSB/La antibodies in the pathogenesis. A passive model of CHB was developed where pregnant mice were injected with SSA/Ro-SSB/La antibodies from mothers of children with CHB. The offspring developed first-degree AVB to a high extent as well as sinus bradycardia but none developed CHB \(^{45}\). Several active mouse models (female mice and rabbits immunized with Ro 52, Ro60 and La 48 antigens) could subsequently show a range of conduction abnormalities developing, including CHB in a few cases \(^{46}-48\). The acute effect of anti-Ro/La antibodies was studied in Langendorff perfused mouse and human fetal hearts showing a progressive development from sinus bradycardia to first-, second- and finally third-degree AVB \(^{47}, 49-51\). These animal- and in vitro -models thus gave further evidence for the central role of SSA/Ro-SSB/La autoantibodies in the pathogenesis.

The presence of immunoglobulin deposits in the heart of human fetuses who died due to CHB, for the first time linked maternal SSA/Ro autoantibodies to the development of CHB on a cellular/molecular level. Deposition of immunoglobulin, fibrosis and calcification, not only at the AV node but throughout the myocardium, suggest a link to tissue damage, as seen in the clinical picture of CHB \(^{52}, 53\).

One question that has still not been completely answered is how the Ro/La antigen exert their effect as they are intracellular proteins, unable to penetrate the cell membrane of the cardiomyocyte. I will below briefly mention some of the current hypotheses and research results that attempt to constitute an explanatory link between the molecular- and clinical observation level.

**Apoptosis-Inflammation-Fibrosis hypothesis**

It has been proposed that translocation of the intracellular SSA/Ro antigen to the cell surface, making it accessible to interaction and binding with antigens, becomes possible through apoptosis of the cardiomyocytes \(^{46}\). A fairly recent study has shown that it is mainly the Ro60 Ag component, and to a lesser extent, in late apoptosis, the La component, that are expressed on the cell surface, not Ro52 \(^{54}\). But if apoptosis is a normal phenomenon in the fetal heart, why should it provoke a cascade of inflammation and fibrosis \(^{55}\)?
One hypothesis is that anti Ro60 antibodies bind to apoptotic cardiac cells, thereby blocking the normal non-inflammatory pathway, diverting instead to an inflammatory pathway and subsequent ingestion by macrophages leading to an exaggerated apoptosis. This process is further suggested to contribute to the transdifferentiation of cardiac fibroblasts to a scarring phenotype; thus providing an explanation for the “endstage” of CHB with fibrosis of the AV-node.56-58

Furthermore, impaired clearance of apoptotic cardiomyocytes, resulting in accumulation of apoptotic cells, promoting inflammation and formation of subsequent scarring, are thought to play a role in the process59. This hypothesis still does not explain the role of Ro52, showed to be more common than Ro60 in children with CHB60, so it has been suggested that Ro52 acts in a later phase of the process, binding to the necrotic cardiomyocytes and promoting a process towards calcification and fibrosis.

Research focusing on the role of anti-Ro52 antibodies, has shown that levels of maternal antibodies to the amino acid p200 of the Ro52 protein were significantly higher in mothers of children with CHB compared with in mothers of those who did not develop heart block61. This finding has been further supported in that high levels of p200 were seen to be correlated with AV time interval prolongation in exposed fetuses, in a study by Salomonsson et al62. The same group reported that p200 antibodies bind to the cell surface and dysregulate calcium homeostasis in cardiomyocytes, leading to cell death; shown in cardiomyocyte cultures from neonatal rat. The above studies have led to formulation of the hypothesis that anti-Ro52 antibodies mediate their effect on the fetal heart by cross-reacting with another molecule on the cell surface, possibly involved in the regulatory system of the cardiac excitation-contraction system55. The so-called L- and T-type calcium channels have been suggested to be involved in this system, and contain subunits involved in cardiac contractility as well as in AV-node conduction and sinus node activity62,63.

The results presented thus far led the group of Wahren-Herlenius and other leading researchers in the field64 to launch a hypothesis or explanatory model55, briefly recapitulated below.

A cross-reaction of passively transferred anti Ro52-antibodies with one or several molecules, possibly involving the aforementioned L-type Ca-channels, induces disturbance of the calcium homeostasis, calcium overload and apoptosis. La- and anti-Ro60 autoantibodies may then bind to the apoptotic cells. This could lead to conduction impairment at the AV node affecting the cardiac excitation-contractionility process on the cell surface of the cardiac myocyte in early pregnancy; hypothetically corresponding to the AV time interval prolongation seen in anti Ro antibody exposed fetuses. It could also explain the signs of impaired cardiac performance seen in a study of antibody-exposed fetuses without subsequent development of CHB65. Depending on the presence of certain fetal susceptibility genes, the inflammation is then suggested to take either of two directions: resolving or becoming chronic. The latter pathway would then lead to an exaggerated inflammatory response with increased cell apoptosis and initiation if the inflammatory cascade, eventually leading to irreversible damage with fibrosis and calcification of the AV-node and as a consequence: complete heart block.
This model of pathogenesis, although providing convincing evidence regarding the mechanisms, takes us back to where we started: Why do only 1-2% of the antibody exposed fetuses develop heart block? And why is there a recurrence rate of 12-20% in already affected families? Furthermore, with the assumption that CHB is a progressive disease: why do some fetuses only develop discrete signs of disease, in form of transitory first-degree AVB whereas others die of heart failure already in fetal life? The level of antibodies have been suggested to play a role in disease expression but there has not been convincing evidence supporting this hypothesis, apart from a recent study by Jaeggi et al where cardiac complications appeared only in the presence of moderate or high maternal titers of anti-Ro levels, regardless of the anti-La antibody titers.66

Other factors have been explored and suggested to play a role in the process of disease expression:

**Genetic contributors**
A study looking at genetic polymorphisms in two different genes, encoding TNF-alpha and TGF-beta, indicated that the genotype of the fetus could be of importance for the development of CHB. In a more recent study, focusing on variation at the Major Histocompatibility Complex (MHC), it was shown in a rodent model that maternal MHC determine both the maternal ability to form pathogenic antibodies and the fetal susceptibility to develop CHB. Finally, in a study by Meisgen et al, HLA-DRB1*04 and HLA-Cw*05 alleles were identified as novel fetal HLA allele variants associated with susceptibility to CHB in response to Ro/SSA autoantibody exposure, whereas DRB1*13 and Cw*06 seemed to be protective alleles. A paternal contribution to susceptibility was also shown for the first time.

**Environmental factors**
Fetal as well as maternal factors possibly associated with the development of CHB were studied in a Swedish nationwide cohort. Older maternal age was shown to be associated with CHB development, as well as pregnancies with gestational weeks 18-24 occurring in January to March, giving rise to a hypothesis connected with a decrease in light exposure, possibly leading to lowered vitamin D levels.

To summarize, there has been an incredible development and increased insight in the pathogenesis of this disease over the last decades, but nevertheless important parts of this puzzle are missing in order for us to understand the enormous spectrum of disease expression as well as the low penetrance of the disease.

### 2.7 DISEASE EXPRESSION

**CHB as a part of Neonatal lupus syndrome**
Transfer of antibodies is thought to begin as early as 11 weeks of gestation but the heart block is usually diagnosed in week 18-24, a period often referred to as the susceptibility period, when maximum antibody passage is thought to take place. The earliest observation of a CHB is around week 16 of gestation. The heart block is thought to evolve progressively from normal sinus rhythm to first- second- and eventually a third-
degree heart block. This is a reasonable assumption as there are now several published cases where these different stages have been observed in a single patient. There is, however, no timetable for when these events occur and the time intervals from the earliest stages of disease onset to development of CHB seem to vary considerably between individuals. In some cases a complete AVB does not develop until after birth.

With improved diagnostic techniques and surveillance of pregnancies at risk, first- and second-degree AVB are increasingly often diagnosed already in fetal life. The total impact of the antibody exposure is not dependent exclusively on the development of CHB, but also on the degree of myocardial affection with a possible myo- and/or pericarditis, hydrops or development of endocardial fibroelastosis (EFE). The latter is a feared consequence of antibody exposure, often leading to fetal or early neonatal death. There are even cases with EFE without affection of the conduction system with a poor outcome, suggesting that CHB and EFE are two different but associated manifestations of neonatal lupus. The clinical expression of antibody associated CHB is hence highly variable, from cases of early fetal demise in heart failure to others with a stable ventricular HR, a normal left ventricular function and excellent long term prognosis. The reasons for this spectrum of disease expression are to date unknown.

If the outcome at birth is a normal left ventricular function and a stable nodal escape rhythm with a sufficiently high ventricular heart rate without sudden pauses, a PM implantation is often not immediately necessary. The absolute majority will, however, eventually receive a PM. At the age of 1 year about two thirds of the CHB patients in the American neonatal lupus registry had a PM implanted. Neonatal extracardiac manifestations as a result of the antibody exposure include skin rash, elevated liver enzymes, and cytopenia. In contrast to the cardiac manifestations, they resolve spontaneously as the maternal autoantibodies are cleared from the maternal circulation. Curiously, it seems to be more common that girls are affected by skin rash than boys.

Even if sinus bradycardia (SB) has occasionally been reported in antibody exposed children with CHB, other studies suggest that the atrial heart rate is normal in the majority of patients with CHB. One of the studies reported on a range of disease expression connected with SB, from asymptomatic cases without CHB to severe heart failure with EFE. In a cohort of antibody exposed individuals, 4% were found to have SB, whereas no difference in HR was seen compared with unexposed individuals in another cohort. This has been proposed to be a result of the effect of the maternal autoantibodies on the sinus node (SN), but the mechanism has not yet been elucidated. Recent hypotheses, however, suggest an interaction with calcium channels at the SN. Even if there may be an interaction at a molecular/cellular level, the clinical impact seems to be very limited with the absolute majority of CHB patients having a sufficiently normal SN function.

At least one study has reported on QT interval prolongation in patients exposed to SSA/Ro- SSB/La autoantibodies who did not develop CHB, but the findings could not be confirmed in a subsequent study where exposed children were compared with unexposed without showing any difference in QTc interval. QTc prolongation in CHB patients has been reported in two studies from the same group and was
considered to be a risk factor of a poor outcome and the implantation of a pacemaker was recommended. In the latest European guidelines for PM implantation QT interval prolongation is not mentioned as an indication for pacing.

2.8 DIAGNOSTICS OF FETAL HEART BLOCK

Whereas postnatal diagnoses of incomplete and complete AVB are uncomplicated and very straightforward, diagnostics of AVB in fetal life can be much more complicated, especially when the degree of AVB is oscillating. Just like on a postnatal ECG, fetal rhythm diagnostics is based on the recognition and chronology of atrial and ventricular depolarization. For obvious reasons, a regular ECG of the fetus is not available and diagnostics therefore have to rely on other techniques.

Fetal ECG
The first published attempt of monitoring fetal heart rhythm was undertaken more than a century ago using a so called string galvanometer electrocardiograph, obtaining records by placing one lead on the abdomen and one in the vagina of a nine months pregnant woman. The recording showed low voltage deflections superimposed on the maternal ECG. Further technical development was achieved by various researchers in the decades following. In spite of development of more refined techniques with low-noise measurements and digitized systems in the last decade, the initial problem with a relatively low signal to noise ratio (SNR) has not yet been completely solved, at least not to the point where various arrhythmic substrates can be reliably differentiated. More recent studies have shown that in about 25-40 % of the cases, not all atrial depolarization (P-wave) are detected, although single groups have compared Echo Doppler-derived mechanical intervals with fetal ECG, claiming the latter to be superior in differentiating normal from prolonged PR intervals. The lack of new reports or studies in the last years, underlines the fact that this method has still not gained ground in the clinical practice, although it has potential.

Magnetocardiography
Magnetocardiography (MCG) is a non-invasive technique for recording magnetic fields generated in the heart. By using high sensitivity sensors, the weak signals emitted in the fetal heart are amplified, resulting in an ECG of a quality much superior to a fetal ECG, providing information on all important elements of the electrical cardiac cycle, and enabling measurements of different time intervals. The method has been and is still, an important source of information and has given new insights in fetal electrophysiology. Unfortunately, the method has considerable disadvantages in that the examination is time consuming, takes place in a magnetically shielded room and is expensive; all contributing to the fact that very few hospitals around the world are equipped with a fetal MCG.

Fetal echocardiography and Doppler techniques
Given the various drawbacks of the above methods as simple and reproducible tools in the diagnostics of fetal arrhythmias, echocardiography with M-mode and Doppler techniques remain the modalities of choice for most fetal cardiologists and obstetricians in the diagnostics of arrhythmia in clinical practice. Whichever method used (M-mode,
Doppler flow techniques or Tissue Doppler imaging (TDI), it is not the cardiac electrical activity per se that can be measured, but its mechanical consequences. This must be kept in mind, even though it in most cases, and using the appropriate method, is sufficient to reveal the underlying arrhythmia.

**Classification of the bradyarrhythmic substrate**
The M-mode approach, the first method used in fetal arrhythmia diagnostics, is based on the simultaneous recording of atrial- and ventricular wall movements, reflecting atrial and ventricular depolarization. The first reports from the early 1980s showed that many underlying arrhythmic substrates could be diagnosed correctly by using M-mode, though the precision or accuracy of the method was not evaluated. A complete heart block can normally be diagnosed with a high precision, whereas measurements of cardiac time intervals are usually impracticable due to the sometimes unclear onset and peak of the atrial and ventricular contractions.

Doppler flow techniques use the principle of detection of the initial phase of blood flow velocity alterations within the vessels as a mechanical result of previous cardiac electrical activity. The benefits of this method were shown by Strasburger et al. in a report from 1986, comparing M-mode and Pulsed Doppler echo. Several studies have shown the superiority of the latter method compared with M-mode in measuring the mechanically derived AV intervals, corresponding to the PR intervals on ECG.

Over the years, techniques using different Doppler methods and approaches have developed based on simultaneous recordings from (1) Mitral valve and left ventricular aortic outflow (MV-Ao), (2) Superior vena cava and ascending aorta (SVC-Ao) and (3) a pulmonary vein and a pulmonary artery. The methods are complementary and used for different purposes. In addition to this, they are all angle dependent and the position of the fetus at the time of examination will therefore influence the choice of method. Recordings from the pulmonary trunk and ductus venosus seem to be less used, even though the latter method was described more than two decades ago. However, these methods have been among the standard methods used at our institution for many years, for reasons that will be further elucidated below. I will briefly describe the usefulness and disadvantages of the mentioned methods in the diagnostics of fetal bradyarrhythmia, including incomplete AVB.

**AV- interval measurements and diagnostics of first-degree AVB.**
The probably most frequently used methods of measuring Doppler derived time intervals are the MV-Ao and VCS-Ao methods; especially the former, as it is usually fairly easy from a technical point of view to obtain good quality recordings (see figure 2.8.1). AV time interval measurements have, as mentioned above, been used for many years as a substitute for the postnatal PR interval to describe and evaluate conduction properties in the fetus. Reference values are established and several studies have validated the method.
Figure 2.8.1. Doppler recording from the left ventricular inflow (mitralis) and left ventricular outflow (aorta). The hemodynamic results of the atrial contractions (A wave) are marked with a. The Atrioventricular (AV) time interval is measured from the intersection of the E- and A waves to the beginning of the ejection wave of the aortic outflow.

How good or relevant is the method in predicting PR interval prolongation after birth? It is not as easy as it may seem to answer that question. Theoretically, AV interval prolongation as a result of intrauterine exposure to SSA/Ro autoantibodies could be transient, thus normalizing at birth and “failing” to prove its predictive value. In fact, in a study by Sonesson et al\textsuperscript{110} one third (8/24) of antibody-exposed fetuses developed AV time prolongation, exceeding +2 z-score of published reference intervals\textsuperscript{107} in at least two consecutive examinations, persisting at birth in 4/8. This study not only supported the hypothesis of CHB as a progressive disease, but also raised questions regarding the normal reference intervals and predictive value, challenged by the PRIDE-study where a value of 3 z-scores above the mean was used as a cut-off, and hence reporting a smaller percentage of individuals with prolonged AV interval\textsuperscript{111}. If fetal MCG is to be used as the gold standard, a prospective comparison between fMCG and Doppler-derived AV time interval measurements would probably be valuable. However, in the view of many fetal cardiologists, these Doppler methods are good alternatives to a fetal ECG or fMCG and can be used in the surveillance of conduction properties in this patient group. As a matter of fact, there is an additional value in that ICT interval measurements could reveal a prolongation, possibly representing early signs of cardiac involvement in exposed patients, see below.

AV time intervals are consistently longer than PR intervals on postnatal ECG\textsuperscript{112} as well as in a comparison with signal averaged fetal ECG\textsuperscript{98}. The explanation for this is that the AV interval includes the early systolic time interval (ICT; isovolumetric contraction) that precedes the opening of the aortic valve. Therefore, the proposal has been made, to exclude the ICT interval from the AV interval measurements but as was shown in a study by Bergman et al\textsuperscript{65} this could lead to a failure in registering the prolonged ICT that has been seen in SSA/Ro antibody exposed fetuses, hypothesized to be a sign of decreased cardiac performance.

**Diagnostics of second – and third degree AVB**

In complete AVB, there is a constant dissociation between atrial and ventricular depolarization. Unless the atrial rhythm happens to be exactly twice that of the ventricular escape rhythm at the time of examination, thus mimicking a 2:1 second-
degree AVB, the diagnosis can usually be made, irrespective of the chosen method, even with M-mode. A second-degree AVB with a varying degree of block, behaving in a Mobitz type I or II manner, or even oscillating between the two, makes diagnostics more complicated. Occasionally, even a predominantly complete AVB can vary between a second- and third-degree block. In these more complex situations simultaneous recordings of venous and arterial profiles can increase the possibilities of a correct diagnosis.\textsuperscript{113-115} Many fetal cardiologists would still use MV-Ao Doppler to assess the arrhythmia, probably because it is more easily accessible, but as can be seen in an example in fig 2.8.2 below, the events occurring in the atrium are less clearly visible even in complete AVB, compared with the SVC-Ao (figure 2.8.3) or in recordings from the pulmonary trunk.

![Figure 2.8.2](image1.png)

Figure 2.8.2. A Doppler recording from the left ventricular in- and outflow tract (MV-Ao) showing a complete heart block and atrioventricular dissociation with the superiorly directed slower ventricular outflow and the faster, inferiorly directed inflow, with the A waves marked (a), sometimes not clearly visible during ventricular systole

![Figure 2.8.3](image2.png)

Fig 2.8.3. Doppler recording from vena cava superior (above the baseline) and aorta (flow directed inferiorly) showing a complete heart block with a slower ventricular rhythm and the clearly visible atrial contractions (a) even during ventricular systole.
Why is it important to differentiate between second- and third-degree AVB?
A third degree AVB is usually irreversible whereas single reports indicate that a second degree AVB can be reverted or at least prevented from progressing to a higher degree of AVB if treated with fluorinated steroids\textsuperscript{116-118}. It appears that the window of treatment is narrow, making a fast and accurate diagnosis is of uttermost importance.

Benign atrial bigeminies and second-degree AVB- a potential diagnostic dilemma?
At our institution, we had occasionally observed difficulties in differentiating second-degree AVB from mid gestational blocked atrial bigeminies (BB). These sustained BB, resulting in a temporary reduction of the ventricular heart rate, are well tolerated by the fetus, frequently resolve spontaneously and require no treatment\textsuperscript{115,119,120}. For obvious reasons, high quality differential diagnostics are crucial in order to distinguish this benign condition from a potentially lethal condition that could possibly be prevented from evolving if treated in time.

Recognizing that this diagnostic dilemma was experienced by others\textsuperscript{121}, we decided to study the underlying mechanisms in fetal bradycardia and to study the ability of Echo Doppler techniques in differentiating between them (Paper I).

2.9 NATURAL COURSE

Natural history of CHB- fetal and neonatal outcome
If natural course is taken to mean that no interventions that could possibly alter the course of the disease have been undertaken, none of the studies below describe the natural course. Some of the patients were treated with transplacental fluorinated steroids or were given a PM immediately after birth. Even in the study by Michaëlsson et al\textsuperscript{4}, a few of the more diseased patients were paced just after birth.

One of the first groups to describe the outcome in CHB detected prenatally was Schmidt et al who found that 85% of the cases with isolated CHB survived the neonatal period\textsuperscript{122}. Another single-center study reported on the outcome of 36 fetuses with 1/3 dying in fetal life or immediately after birth. Hydrops and low heart rates were associated with a poor outcome\textsuperscript{123}. In a Finnish cohort of 91 patients where around 90% were diagnosed in fetal life, the perinatal mortality was surprisingly low at 7\%\textsuperscript{124}. Given the fact that patients diagnosed as far back as 1950 were included, there is a considerable risk of not having included some cases of intrauterine demise. Finally, in a study on fetal, neonatal and childhood diagnosis of complete AVB, 41\% of those diagnosed in fetal life did not survive to 1 week of age. Taken this and other studies together, survival to 1 month in fetal CHB is around 60-90\%. Reasonable explanations to the variation in mortality rates are: (1) some of the most diseased patients not being included, (2) multicenter studies with unclear selection procedures, (3) studies spanning over several decades with changing treatment strategies including early pacemaker treatment.

In the now classic publication by Michaëlsson et al from 1972, the natural history of congenital heart block- including cases with associated disease- was described extensively in an inimitable way; a great part of our knowledge comes from that single
publication. A few problems emerge, however, when we try to extrapolate and generalize the outcome on a larger population, especially regarding the fetal perspective. The study included patients born in the 1940s and onwards and for obvious reasons we have only limited knowledge of fetal outcome from the study. As the authors conclude, the fact that the average age at death was lower in those diagnosed in more recent years could be attributed to the fact that many children from the earlier period never had a chance to be diagnosed in the first place. With sampled cases from many centers all over Europe, and limited control over selection bias (patients with an early/fetal diagnosis and a poor outcome are more likely not to have been included), make the mortality figures less reliable.

Another issue relates to the diagnosis. The study group was divided into those diagnosed < 1 week, < 1 year and < 15 years. In all, 122/418 patients were diagnosed in fetal life or at birth and would by the current definition correspond more closely to the group of “real” congenital heart block. The follow-up time is not explicitly mentioned, but half of the 122 patients had reached the age of 5 years by the end of the study. The mortality rate was 15% in those diagnosed at birth; all deaths occurring before the age of five. Four of the 42 patients diagnosed at > 1 week but < 1 year of age died. Five of the 122 patients had a PM implanted and all died; 2 of 5 supposedly as a result of the implantation itself.

Taking the results of these early studies together, they all confirm that most of the patients at risk of a poor outcome present in fetal life or at birth, whereas those who survive the neonatal period generally have a good outcome. There is little doubt that PM therapy has improved the outcome, both in those needing early pacing and in the apparently asymptomatic patients who nowadays will receive a PM, acknowledging the risk of sudden death even in this group\textsuperscript{90}.

\section*{2.10 TREATMENT}
\paragraph*{2.10.1 Fetal treatment approaches}
We know that fetuses and neonates with congenital heart block have a considerable risk of a poor outcome with a high perinatal mortality. As a consequence, studies and evaluations of therapeutic interventions have been a high priority in the research community around CHB, possibly finding a curative or prophylactic treatment; or at least a treatment that could mitigate the effects and improve the outcome in terms of morbidity. Considering the widely adopted hypothesis of pathogenesis and disease progress, with inflammation as a possible intermediate step towards a definitive calcification and fibrosis of the conduction system, there is intrinsic logic to a therapy aiming at diminishing the consequences of inflammation and/or lowering the titers of the circulating maternal autoantibodies. Accordingly, many therapeutic attempts at reducing the degree of AVB in cases of fetal complete AVB, have been undertaken, above all transplacental treatment with fluorinated steroids (dexamethasone or betamethasone)\textsuperscript{116, 125-127, 118}, only partly inactivated or metabolized in the placenta. Another consequence of the inflammatory process following fetal exposure to maternal autoantibodies is the presence of hydrops or ascites/pleuropericardial effusions which has been reported to resolve after steroid treatment\textsuperscript{118, 128, 129}. There are, however, no
randomized studies to support these observational reports. Treatment of EFE cases has also been tried with no apparent beneficial effect. Other treatment strategies have also been explored. Plasmapheresis lowers the levels of SSA/Ro- and SSB/La levels in maternal blood, and could thereby theoretically prevent or diminish the damage induced by the maternal autoantibodies in the fetus. This treatment has practically always been combined with steroids, making its individual contribution to possible treatment effects difficult to assess. There are reports of single cases in combination with steroids where treatment seemed to be of no benefit in cases of complete AVB but with a possible effect on myocarditis or pericarditis in some cases. Intravenous immunoglobulins (IVIG) are thought to exert their effect by inhibiting or reducing the transplacental passage of maternal autoantibodies, accelerate their clearance and reduce the inflammatory response in the fetus. This hypothesis is supported by an animal study where IVIG treatment inhibited the transfer of maternal autoantibodies across the placenta in a murine model, according to the researchers most likely by blocking the Fc-receptors of the placenta. Maternal betamimetic therapy has also been tried, with the objective to increase HR and survival to birth, with limited benefit in most reports.

2.10.2 Fetal treatment based on indications

2.10.2.1 Treatment to improve survival

Transplacental steroid treatment has been proposed to improve the outcome of complete AVB, in terms of both morbidity and mortality. However, there are no trials on a larger scale supporting such a strategy, only a few smaller studies, of which only the one by Jaeggi et al showed a better survival in the steroid treated group than in the untreated historical “control group”. The unexpectedly low survival in the untreated group compared with that in other studies, combined with the fact that the study compares patients from two different eras, has not convinced the profession of fetal cardiologists that steroid treatment is beneficial. Accordingly, there is currently no consensus as to if the treatment is efficient or not and hence, therapy traditions seem to vary between centers around the world.

2.10.2.2 Treatment to improve AV conduction

When a complete AVB has evolved it is usually permanent and resistant to any form of intervention aiming at restoring normal cardiac conduction. There are sporadic reports of fetal interventions claiming to have restored normal conduction, but published cases with sound proof are to date lacking. Several reports combined single doses of IVIG with combination therapy with steroids, showing no effect on the heart block but resolution of myocarditis in a few cases. All different therapeutic approaches have so far been shown to be inefficient in treating a complete AVB.

There are reports of small series or single cases where incomplete AVB reverted to 1:1 conduction or sinus rhythm within weeks after initiation of transplacental steroid treatment in some but not all fetuses. In a small study of 3 patients with second-degree AVB and 3 with CAVB, a combination therapy consisting of IVIG,
plasmapheresis and fluorinated steroids throughout the pregnancy was attempted, with reversion to SR from second degree AVB in 2 cases, but no effect on the CAVB\textsuperscript{148}.

2.10.2.3 Treatment to prevent first-degree AVB to progress

First degree AVB is known to be present in up to 30% of prospectively followed fetuses exposed to maternal autoantibodies\textsuperscript{110}; the cut-off value for the upper normal limit deciding its incidence in larger cohorts. Even if little is known about the long-term outcome, it seems as if most patients with a fetal first-degree AVB, normalize the PR interval before or at birth\textsuperscript{110}. In the PRIDE study (PR Interval and Dexamethasone Evaluation prospective study), 2 of 95 fetuses exposed to maternal autoantibodies developed a PR interval exceeding 150 ms and were subsequently treated with dexamethasone. The PR interval normalized within a week after treatment started at 4mg/day. A similar attempt in a study with a different definition of AV-interval prolongation, showed that 6 of 70 fetuses developing first-degree AVB according to the study’s definition, normalized the AV intervals after dexamethasone treatment and remained in normal SR\textsuperscript{145}. In the light of spontaneous normalization in other cases of fetal AV interval prolongation before or at birth, the interpretation of the authors of a successful intervention has been questioned.

2.10.2.4 Treatment to prevent development of CHB

Attempting to prevent a subsequent development of CHB in fetuses of women with at least one previous pregnancy resulting in CHB, IVIG was given in early pregnancy in two studies. In the first study of 20 mothers, 3 children developed CAVB\textsuperscript{147} whereas in the second study 3/15 developed CAVB\textsuperscript{149}, which corresponds well to the expected outcome in an untreated cohort of risk pregnancies, indicating no preventive effect from the treatment.

2.10.2.5 Improved long-term survival or decreased morbidity with treatment?

The small retrospective studies claiming an effect on survival after transplacental steroid treatmen of CHB are not convincing. Considering the risk of both maternal and fetal side effects, further studies are needed. Regarding a possible effect on morbidity and development of dilated cardiomyopathy, we have no results thus far that support a preventive effect of steroid treatment

2.10.2.6 Side effects with steroid treatment

Side effects connected with transplacental steroid treatment are well known; in both mother and the fetus. In the mother all types of side effects connected with steroid treatment can occur, including hypertension, diabetes, adrenal insufficiency and even psychotic disorders. In the fetus the most commonly reported side effects include growth restrictions, oligohydramniosis, premature delivery and contraction of the ductus arteriosus\textsuperscript{116, 127, 133, 150}. It can however, in each specific case, be difficult to separate possible side effects from the consequences of the disease itself, which can be connected with growth restrictions and a poor general outcome including fetal demise. Worries have furthermore been expressed concerning a possible negative impact on the neuropsychological development in children who in fetal life were exposed to treatment with fluorinated steroids. Most studies have been performed in patients with other
treatment indications than CHB. In one study, a reduction in birth head circumference was seen\textsuperscript{151}, whereas, in another study, an increased risk of leukomalacia and neurodevelopmental abnormalities was seen in children previously treated with dexamethasone but not in those treated with betamethasone\textsuperscript{152}. In a small study on 11 children with CHB and previously exposed to transplacental steroid treatment, all had a normal neuropsychological development at follow-up\textsuperscript{153}. The study comparing dexamethasone and betamethasone has however made many fetal cardiologist more prone to using betamethasone.

2.10.2.7 **Summary- treatment**

Taking all these results together, there is no evidence in current knowledge supporting transplacental treatment of a developed CAVB. Randomized studies are however lacking and retrospective are small and not conclusive. Fetal first degree AVB generally seems to revert to normal SR at birth in most cases, with or without treatment. Long term follow-up studies are however lacking. Single cases of rapid progression from first degree AVB to CAVB within a week or less, suggest that there is a subgroup of patients with a more severe response to antibody exposure. The multiple case reports on a transitory or possibly long term response with reversion to SR or first-degree AVB after steroid treatment in cases of second-degree AVB, suggest that there is a time-window in which reversal is possible, supported by the fact that no cases of spontaneous reversal of antibody associated second-degree AVB have been reported.

As a natural consequence of the limited knowledge of the effect of fetal steroid treatment in CHB, the multinational, multicenter study on steroid treatment of isolated CHB was undertaken in 2008, after an initiative by the Fetal Working Group of AEPC (Paper II).

2.10.3 **Pacemaker treatment**

The first report of a pacemaker implanted in a child with a heart block was presented in 1962. It was a 7-year-old child with a postoperative complete AVB\textsuperscript{154}. Only small series of patients were reported in the following years, until a study in 1976 reported on 24 children with a PM implanted at age 9.7 years on average\textsuperscript{155}. Initially, the therapy was associated with a high risk of complications and the pacemakers were not designed for children, often pacing at a fixed rate. They were heavy and did not have the flexibility that modern pacemakers have. Complications were common. As a consequence, the strategy for a long time was to wait “as long as possible” which sometimes meant that some patients had developed dilated cardiomyopathy (DCMP) before they underwent PM implantation. Others may have experienced sudden death in spite of a seemingly good cardiac status. Following the study by Micha{"e}lsson et al\textsuperscript{90}, where it was shown that even asymptomatic patients over 15 years of age were at risk for sudden death, new treatment strategies were adopted almost universally and reflected in international guidelines of PM treatment in the young.

Class I indications for pacing in isolated CAVB include a low ventricular heart rate (< 55 in the newborn and <50 beyond first year of life), ventricular dysfunction,
instable or wide complex escape rhythm or abrupt pauses. While the community of pediatric cardiology more or less agree regarding the indications for pacing, the positions diverge on type (epicardial or endocardial) and mode (VVI or DDD) at what age. This is reflected in the latest consensus document from the European Association of Pediatric Cardiology (AEPC) and the European Heart Rhythm Association (EHRA). As an example, where for instance left ventricular epicardial VVI pacing would be the recommended approach in a CAVB patient weighing <10kg, an endocardial PM could also be recommendable due to “center preference”. This approach is probably supported by the concept that the outcome in a single case will depend on the skills and the experience of the surgeon or the implanting cardiologist, with respect to the chosen method.

Risks of complications connected with pacing are known to be substantial in children, even if only limited data on complications in the recent era are available. Complications following pacing depend on multiple factors. At least one previous study has shown that a young age at first PM implantation is associated with a higher number of complications. Lead related problems are the most common, reported to be more frequent in epicardial pacing, whereas obstructed veins and lead dislodgements are more frequent in endocardial pacing, as well as rare complications like cardiac perforation and tamponade. A relatively frequent and threatening complication is an infection of the pacing system, occurring in (1-8%) of pediatric patients, often necessitating explantation of the entire pacing system. One problem with most previous studies however, is that complications are compared in mixed patient groups, including postoperative heart block and patients with complex structural heart disease. Patients in such mixed groups may, on a group level, have a different risk of experiencing pacing-related complications than patients with isolated CHB. There are to date no studies evaluating risk factors for pacing-related complications exclusively in patients with isolated CHB.

Ever since the first reports on late development of DCMP after years of pacing, growing attention has been directed towards the possibility of pacing-induced cardiomyopathy, namely by right ventricular (RV) pacing, especially from the apex. The clinical reports have been accompanied by experimental studies showing the hemodynamically negative consequences compared with left ventricular (LV) pacing, assumed to be due mainly to pacing induced dyssynchrony. The results are theoretically convincing but is the type of pacing really to blame for all patients developing DCMP? If not, then to what extent?

There are several points to consider when evaluating this: RV pacing has been the dominant type of pacing for many years and most studies reporting on outcome of CAVB patients and pacemaker therapy have an overwhelming dominance of RV paced patients. For obvious reasons this makes a fair comparison between LV and RV pacing difficult, if not impossible. Many pediatric cardiologists would agree that RV apical pacing is not the optimal pacing site and should be avoided if possible. Left ventricular pacing may offer hemodynamic advantages compared with other pacing sites but to what extent can/should this be translated to a clinical context? Many cardiologists would probably opt for a LV epicardial pacing system in a patient <15 kg, but is there really evidence for LV pacing being superior to RV septal pacing for older patients? It
is a fact that most patients with RV pacing do not develop DCMP in spite of pacing for 10 years and more. Another problem with most studies is that the cardiac status prior to pacing is not taken into account when group comparisons are performed.

**How is life with a pacemaker?**

Carrying a pacemaker surely has an impact on young person’s life, even in the absence of particular problems connected with pacing or symptoms related to the heart condition. Although the general impression from clinical practice is that most children seem to cope rather well with the situation of being a pacemaker carrier, there are few studies in this group of patients. More is actually known about children and adults regarding psychosocial aspects in ICD carriers than in young patients with pacemakers. There are however a few recent publications investigating these aspects. In a study by Webster et al\(^{166}\) a group of adolescents with PM were compared with a group of patients with implantable cardioverter defibrillators (ICD). Standardized structured psychiatric interviews and self-report questionnaires were used. Patients with ICD and PM had similar psycho-social functioning but lower physical Quality of Life (QoL) scores compared with a normal reference population. Patients with an ICD had higher rates of anxiety disorders than did patients with a PM. In another study of patients with CAVB and Right ventricular pacing questionnaires assessing health-related quality of life (HRQoL) were used\(^{167}\). Possible associations with functional capacity were tested using the 6 minute walk -distance test (6MWDT). Almost all patients had received their PM in childhood but were adolescents or young adults (mean age 21.5 years) at the time of evaluation. The study showed that chronic RV pacing in this group did not seem to affect overall HRQoL. Female gender, decreased left ventricular function and cardiac drug therapy were associated with lower scores. A third study, also using HRQoL, included 27 children and adolescents with a mean age of 14 years, where the majority had isolated heart block\(^{168}\). The results showed that the studied group had lower overall levels of HRQoL compared with healthy norms, as indicated by both the so called proxy-report as the child self-report. So what do these studies tell us? In my view it is difficult to draw any general conclusions due to the different methods and varying study groups, as well as study design. Another question arising is if the study design- and approach really captures the whole picture? A qualitative research approach would perhaps be more useful as it could pinpoint the specific situation and possible problems connected with carrying a pacemaker.

**Cardiac resynchronization therapy**

The basic goal and principle of Cardiac resynchronization therapy (CRT) is to restore synchrony of the left ventricle in patients who have developed dilated cardiomyopathy in combination with dyssynchrony of the LV. Limiting the discussion to patients with isolated CHB and pacemaker treatment, the problem of dyssynchrony after RV pacing in some patients has been described above. Data supporting this therapy in children are much more limited than in adults. In the pediatric group, the best responders seem to be patients upgraded from RV pacing to CRT\(^{169,170}\). There is, however, a spectrum from non-responders to a completely normalized LVF in single cases. Long-term follow-up of patients with exclusively isolated CHB and CRT are to date missing.
2.11 PROGNOSIS

As mentioned earlier, the course of this disease has changed in a positive way over the last decades, mostly thanks to the introduction of pacemaker therapy at an early age. As a whole, mortality is still high if we include fetal demise, usually 15-30%. For a child who survives the neonatal period without early development of dilated cardiomyopathy, the outlook is much better. Several studies have indicated that a small proportion of patients may, however, develop late onset left ventricular (LV) dysfunction, in spite of pacing therapy compliant with guidelines and international recommendations. The risk factors associated with development of LV dysfunction are not clear, although exposure to maternal autoantibodies is suggested to be one of them. Another suggested risk factor is RV pacing.

Children who in fetal life were exposed to maternal autoantibodies without developing complete AVB are considered out of risk for subsequent disease development. Long-term follow-up of both this group and individuals who developed transitory conduction abnormalities in fetal life, are lacking.

Complications to pacemaker treatment are unfortunately relatively common even in the short-term, mainly pacing lead-related complications, but also infections, and smaller risks for serious complications, such as perforation of the myocardium in connection with implantation of endocardial pacemakers. We still have relatively limited knowledge about the long-term outcome for patients with isolated CHB; most studies so far do not separate this group from other groups with complex structural heart disease. While pacemakers were implanted in children already during the 1960s, the receivers were almost exclusively very diseased and most of them died. It is only in the last few decades that children without symptoms more systematically undergo PM treatment. This means that we have relatively little long term data as grounds for what the consequences will be like in terms of complications and clinical symptoms as a whole.
3 AIMS

The general aims of this thesis were to increase knowledge of the clinical consequences of fetal exposure to maternal SSA-Ro and/or SSB-La autoantibodies, focusing on those individuals who develop complete heart block.

The specific aims were:

- To study the underlying substrates in fetal bradyarrhythmia and the accuracy of Echo Doppler techniques in differential diagnostics, specifically in distinguishing benign conditions from potentially lethal ones.

- To compare the outcome in fetuses with second- and third degree AVB given vs not given transplacental treatment with fluorinated steroids, in respect to morbidity and mortality and to identify risk factors associated with a poor outcome.

- To study cardiac- function and conduction properties in pre-school children who had been exposed to maternal SSA-Ro autoantibodies in utero, without developing complete heart block.

- To study the outcome after pacemaker therapy in children exposed to maternal autoantibodies compared with unexposed, with specific focus on heart function at follow-up and to identify risk factors of a poor outcome.
4 METHODS

4.1 STUDY SUBJECTS AND METHODS

4.1.1 Paper I

4.1.1.1 Patients and study design

In a single center, retrospective study, all patients referred to Astrid Lindgren Children’s Hospital for evaluation of fetal bradycardia between 1990 and 2007 were identified through a search of the local database. Data from 75 pregnant women were retrieved. Three additional cases of fetal bradycardia, detected during echocardiographic surveillance of anti-Ro52 antibody positive pregnancies, were also included for further evaluation. The reports from fetal and neonatal cardiac examinations performed on these 78 cases were analyzed and video and/or digital records re-evaluated.

4.1.1.2 Definitions and inclusion criteria

Bradycardia was defined as a heart rate ≤ 110 bpm; classified as sustained only if the fetus remained in bradycardia for the entire 45 minutes of examination. Cases with an irregular heart rhythm were not included.

4.1.1.3 Echocardiographic recordings

M-mode echocardiograms and Doppler recordings from the mitral valve/aorta were used from the beginning of the study period. Doppler recordings from the superior vena cava/aorta, as well as from a pulmonary vein and a peripheral pulmonary artery came into use around 2000, whereas recordings from the pulmonary trunk and the ductus venosus have been used from 2003 and onwards. Recordings from the pulmonary trunk were obtained from any view with a narrow angle of insonation and the sampling volume adjusted to the flow in or just above the pulmonary valve. Besides typical systolic outflow profiles these recordings also comprised very sharp late diastolic antegrade flow profiles, corresponding to atrial contractions. Doppler recordings of the ductus venosus were obtained in a midsagittal or transverse section.

4.1.1.4 Classification of arrhythmias

Identification of the electrophysiological mechanism generating the bradycardia was based on recognition of the chronological relationships between atrial (A) and ventricular (V) depolarization, which were in turn identified by their mechanical (M-mode) or hemodynamic (Doppler) consequences. Fetuses with a regular ventricular rhythm and 1:1 AV relationship were considered to be in sinus rhythm. In case of a regular ventricular rhythm and 2:1 AV relationship, the AA time interval was further analyzed. If every second atrial contraction was premature, resulting in a pattern where a shorter AA interval was systematically alternating with a longer interval, the fetus was diagnosed to have BB. If AA time intervals were constant, a second recording was made to compare the AV intervals with those from the first recordings. When the AV intervals remained unchanged between these two examinations, the diagnosis of second-degree AVB was made. In case of AV dissociation at the first or second
recording the fetus was diagnosed as having third-degree AVB. To more meticulously investigate the AA intervals in fetuses with BB and second-degree AVB, a ratio was constructed by dividing the time interval between the conducted and consecutive blocked atrial contraction (a_{cb}) with the time interval between two conducted atrial beats (a_{cb}/a_{cc} ratio). Heart rate was assessed from any of the Doppler tracings with arterial flow profiles. All measurements were made on three consecutive velocity waveforms, using the electronic calipers on the ultrasound machine, and averaged.

4.1.2 Paper II

4.1.2.1 Patients and study design

In a retrospective, multicenter, multinational study, all members of the Fetal Working Group (FWG) of the European Association of Pediatric Cardiology were invited to contribute data of fetuses diagnosed with isolated second-degree AVB (AVB II) or third-degree AVB (AVB III) from 2000 to 2007. Data on 189 patients from 28 contributing centers in 15 countries were submitted.

4.1.2.2 Criteria for exclusion and inclusion

Fourteen fetuses were excluded after data evaluation. In 10 cases no birth outcome data was available and in 4 cases, claimed to have reverted from AVB II or III, documentation was lacking (n=2) or the initial diagnosis of AVB could not be retrospectively confirmed (n=2). The resulting final study population consisted of 175 fetuses diagnosed with isolated AVB II or III and a minimum follow-up time from diagnosis until birth or intrauterine death. Cases of AVB demonstrating improved atrioventricular conduction were only included if accompanied by M-mode or Doppler recordings confirming the diagnosis.

4.1.2.3 Data collection and methods

All cases had been diagnosed by a fetal cardiologist at each center using standard fetal echocardiographic techniques. The examination diagnosed the arrhythmia, evaluated cardiac function and hemodynamics and excluded major cardiac malformations known to be associated with heart block. Data were collected retrospectively through review of the clinical charts and echocardiographic examinations at each of the participating centers and sent to the study coordinator. The collected data included: (1) maternal data; age, presence of autoimmune disease and autoantibodies (SSA-Ro/SSB-La), steroid treatment at time of conception, parity and previous fetuses with AVB, (2) fetal data; gestational age, degree of AVB, atrial and ventricular rate, left ventricular function and presence of hydrops, (3) pharmacological treatment; steroids (type, dose, duration), betamimetics (type, dose, duration) and documented fetal and/or maternal complications; (4) fetal outcome: survival and cardiac status; (5) the child at birth/ follow-up: date of birth, gestational age, birth weight, degree of AVB, ventricular rate, age at last follow-up or death. Pacing and development of cardiomyopathy were documented. Transplacental steroid treatment was only considered present when the pregnant mothers were given fluorinated steroids. Hydrops was defined as serous effusions in at least two compartments.
4.1.2.4 Methods and group comparisons

Cases were divided into groups based on placental treatment (steroid treated or untreated) and outcome at birth and 1 month of age (survival or death), respectively. All patients alive at birth, except 11 patients lost to follow-up, were assessed for neonatal mortality. These analyses were also performed on the subgroups of patients defined by (1) a positive anti-Ro/SSA- and/or anti-Ro/SSB test and (2) a positive test further restricted to AVB II-III/III.

4.1.3 Paper III

4.1.3.1 Patients and study design

This was a single center, cross-sectional follow-up study of children exposed in utero to maternal anti-SSA/Ro52 autoantibodies. During 1999-2007, 83 fetuses (82 pregnancies) in 63 anti-SSA/Ro52 autoantibody positive women followed a protocol for fetal echocardiography surveillance and an outcome ECG during the first week after birth. With the exception of five families not living within our region, one case with an umbilical cord complication resulting in intrauterine death and two cases of CAVB, all families going through our surveillance protocol were invited to let their child participate in a follow-up study. Parents declined participation in 18 cases, resulting in a final study population of 57 children.

4.1.3.2 Methods

The children of the cohort were divided into two groups: AV time interval prolongation (group A) and normal findings (group B) in utero, and compared on a group basis as well as individually to published reference data. The study protocol included basic demographic data as well as clinical history, physical examination, ECG at rest, 24-hour Holter ECG and echocardiographic studies.

4.1.3.2.1 Prenatal echocardiographic studies

The protocol of weekly fetal echocardiographies, from 18 to 24 weeks of gestation, used for surveillance of fetuses at risk for CAVB has been described elsewhere. Briefly, Doppler flow recordings from left ventricular in- and outflow (MV-Ao) and superior vena cava and ascending aorta (SVC-Ao) were used to measure mechanical AV time intervals as an indirect estimate of electrical AV conduction. Both methods have been validated and reference values have been established. For comparison with the PR interval on ECG, all fetal AV time measurements were categorized in respect to 95% and 99% reference ranges, and considered abnormal if exceeding their respective upper cut off limits at two consecutive examinations. Individual AV time intervals were calculated by averaging the two highest measurements. For all other analyses, the MV-Ao time interval with a 95% reference range was used to assign cases to the group with prolonged AV time intervals in utero (group A) or the group with normal recordings (group B).

4.1.3.2.2 ECG recordings and 24 hour Holter ECG

From a standard 12 lead ECG, measurements of heart rate (HR), QRS-duration, PR- and QTc intervals (using Bazett’s formula), were obtained and compared with age
related reference values, defining the 98th percentile as the upper normal limit\textsuperscript{172}. All 24-hour ECG recordings were analyzed by a single investigator blinded to the grouping of patients at time of analysis. HR was analyzed by defining its 24-hour mean, standard deviation, range and maximum RR interval. To standardize measurements of AV conduction, the PR interval was averaged over three consecutive beats, during a period where the HR matched the average over the whole 24-hour period.

4.1.3.2.3 Pediatric echocardiographic studies

A complete echocardiographic study was performed to rule out structural abnormalities. Systolic left ventricular function was studied with M-mode\textsuperscript{173} and diastolic function was investigated using mitral Doppler flow velocity recordings, where early (peak E) and active (peak A) filling velocities were measured and E/A ratio calculated\textsuperscript{174}. The myocardial performance index (MPI), assessing combined systolic and diastolic function of the left ventricle, was obtained by measuring the isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT) and ejection time (ET) intervals on recordings of mitral valve inflow and left ventricular outflow profiles, and calculated using the formula; MPI = (IVCT+IVRT)/ET\textsuperscript{175}. Tissue Doppler imaging (TDI) for evaluation of longitudinal function of the left ventricle was performed using two sample sites: the lateral mitral valve annulus and the basal ventricular septum. At each site 6 variables (peak E’, A’ and S’ velocities, IVCT’, IVRT’, ET’) were measured as previously described\textsuperscript{176}. TDI derived myocardial performance indices (MPI’) were calculated as described above. IVCT’ and IVRT’ were corrected for HR (IVCT’c, IVRT’c) by division with the square root of the RR interval. All Doppler registrations were performed using a 4-chamber view and an angle of insonation within 30°. In all measurements, the average of 3 recorded complexes was used.

4.1.4 Paper IV

4.1.4.1 Study design and patients

This was a nationwide, retrospective cohort study where all patients in Sweden with pacemaker (PM) treatment and isolated complete AVB (CAVB) diagnosed before the age of 15 years, were identified by searching the following registers: (1) Swedish ICD-and Pacemaker Registry, (2) Swedish National Patient Registry and (3) local clinical patient registries, as well as through a network of pediatricians, cardiologists and rheumatologists at six university hospitals in Sweden. All patients were cross-matched to the Swedish Malformation Registry as well as the Swedish Heart Surgery Registry in order to exclude patients with CAVB due to a cardiac malformation or as a result of heart surgery. To evaluate mortality among patients with isolated CAVB and PM, the Swedish Cause of Death Registry was searched. Heart transplantation was in the context of this study equated with death.

A total of 168 pacemaker treated patients with a diagnosis of AVB <15 years of age, born 1980 to 2011 were identified. Eleven patients were excluded as they did not respond to at least two letters (n=5), or declined participation (n=6).
Patient records were collected and examined for assessment of eligibility. Thirty of the patients did not meet the inclusion criteria and were excluded. Patients with advanced second to third degree AVB and permanent pacing, were classified as CAVB and included in the study. Permanent pacing was defined as ventricular pacing >99% of the time.

4.1.4.2 Methods

The final study population consisted of 127 patients and observational data were collected retrospectively by review of the clinical charts. Briefly, the collected data included information on presence of maternal autoimmune disease and exposure to autoantibodies (SSA-Ro/SSB-La), gestational age (GA), degree of AVB, transplacental treatment with steroids or betamimetics and status at fetal presentation. Neonatal- and childhood data included: cardiac status, signs of extracardiac disease or symptoms, treatment with beta-adrenergic agonists.

Electrocardiography (ECG): Tracings were reviewed and analyzed for rhythm and heart rate at diagnosis. Echocardiographic examinations: Data were collected and registered regarding heart function and presence of structural heart disease. Patients with associated structural abnormalities were only included if the defect was not considered causal of the heart block. Data on left ventricular function (LVF) at birth and at FU were collected: (1) left ventricular end diastolic dimensions (LVEDD), (2) left ventricular fractional shortening (FS) values. In cases where these data were not documented, the qualitative description of the LVF by the examiner was used and classified as normal, borderline or impaired. To enable comparisons across age groups, LVEDD values were transformed to a body surface related z-score (LVEDD z-score)\textsuperscript{177} and FS values were transformed to an age related z-score (FS z-score)\textsuperscript{178}. Ejection fraction (EF) values were reported when present. To enable categorical comparisons, LVF was additionally classified as normal (LVEDD z-score < 2 and FS z-score > -2), borderline (LVEDD z-score > 2 or FS z-score < -2) or impaired (LVEDD z-score > 2 and FS z-score < -2), or according to the classification by the examiner whenever either of the values were missing. Most patients had been examined using echocardiography (echo) at several occasions but the data presented in the study are: echo before PM treatment and echo at last FU and, if appropriate, echo at diagnosis of impaired LVF.

Pacing data were collected through the Swedish ICD- and Pacemaker Registry or the patient records, including age and date of PM implantations, type and mode of pacing, characteristics of pacemakers and electrodes as well as data on complications. A complication was defined as any occurring event leading to an unforeseen re-intervention of the pacing system. The events were further classified as early (< 3 months) or late (> 3 months) with respect to time from previous intervention. To evaluate possible changes over time in mode or type of pacing, the cohort was divided arbitrarily into an early period (1983-2000) and a late period (2001-2011).
4.2 STATISTICAL ANALYSES

Overall
In all papers, comparisons of normally distributed continuous variables were performed using two sample t-test and measures presented as mean and standard deviation. Continuous variables with a skewed distribution were compared using Wilcoxon’s two sample test or Mann-Whitney U-test when appropriate; variables presented as median and range. Comparisons of frequencies with respect to categorical variables were performed using Fisher’s exact tests or Pearson Chi square test as appropriate. The level of statistical significance was set at p<0.05 in all papers.

4.2.1 Paper I
Comparisons with respect to gestational age or fetal heart rate between patients with different arrhythmia substrates were performed using one-way ANOVA with Tukey HSD test.

4.2.2 Paper II
Cases were divided into groups based on placental steroid treatment (treated vs untreated) and outcome at birth and 1 month of age (survival or death), respectively. Intrauterine mortality and neonatal mortality with respect to steroid treatment were analyzed separately, where all patients were assessed for intrauterine mortality. All patients alive at birth, except 11 patients lost to follow-up, were assessed for neonatal mortality. Both these outcomes were analyzed by exact logistic regression including only steroid treatment and an adjusted model conditioned on gestational age at diagnosis (categorized as <20, 20-24, 25-29, ≥30 weeks). These analyses were also performed on the subgroups of patients defined by a positive anti-Ro/SSA- and/or anti-Ro/SSB test (1), and a positive test further restricted to AVB II-III/III (2). Results of the logistic regressions are presented as odds ratios with exact 95% confidence limits.

The analysis of the effect of betamimetics on heart rate included only patients with data on ventricular rate both prior to initiation of treatment and within two weeks after initiation. Follow-up of the cohort beyond the neonatal period is incomplete with missing information about the time-points when patients were lost to follow-up. Data on long-term outcomes and characteristics are therefore purely descriptive.

4.2.3 Paper III
Linear regression was used to analyze relationships between flow velocity and tissue Doppler variables on one hand, and the PR interval on the other hand. For analysis of sensitivity, specificity, positive and negative predictive value (PPV and NPV), positive and negative likelihood ratio (LR+ and LR-) with their 95% confidence intervals, the Vassar Stats Clinical Research Calculator 1 was used179.

4.2.4 Paper IV
Kolmogorov-Smirnov test was used to test continuous variables for normality. Uni- and multivariate Cox regression analyses were performed in the comparison of possible event (complication) predictors. Hazard ratio with 95% confidence intervals were calculated for each covariate. A p-value <0.05 was considered significant.
4.3 ETHICAL CONSIDERATIONS

Studies I, III and IV were evaluated and approved by the Ethics Committee at Karolinska University Hospital. The multinational, multicenter study (study II), was evaluated by the National Research Ethics Committee (Hammersmith and Queen Charlotte’s and Chelsea research Ethics Committee, 2007) and considered to not require review by a National Health Service Research Ethics Committee. In practice, this study was also locally approved by the Ethics Committee at Karolinska University Hospital, as Stockholm data for study II was extracted from study I.
5 RESULTS

General remark: The central and most important results of each paper are presented in this section. For complete results, please see published papers (I-III) and the final paper in manuscript form (paper IV).

5.1 PAPER I

The aims of this study were to assess the underlying mechanisms in fetal bradyarrhythmia and the diagnostic accuracy of Echo Doppler techniques.

Sixty-five patients had a HR< 110/min; table 5.1 details the underlying arrhythmic substrates. Forty-two patients had sustained bradycardia; in 20 cases the underlying rhythm was a complete AVB, in 5 cases a second-degree AVB, in 6 blocked bigeminies (BB) and sinus bradycardia (SB) was seen in a further 11 patients. All 23 patients with intermittent bradycardia had BB and 4 of them developed supraventricular tachycardia. Patients with constantly blocked BB were diagnosed earlier than those with intermittent tachycardia and 7 of 11 patients with SB had a potentially serious underlying condition.

Table 5.1. Diagnosis and clinical characteristics in 65 pregnancies with fetal bradycardia (Heart rate ≤ 110 bpm).

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>No</th>
<th>GA</th>
<th>CHD</th>
<th>LQTS</th>
<th>SVT</th>
<th>TOP</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3°) AVB</td>
<td>20</td>
<td>23.2±4.4</td>
<td>7</td>
<td>3/4</td>
<td>56.9±10.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2°) AVB</td>
<td>5</td>
<td>20.8±2.5</td>
<td>1</td>
<td>1</td>
<td>67.4±6.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained BB</td>
<td>6</td>
<td>19.3±4.8</td>
<td>1</td>
<td>1/0</td>
<td>75.7±5.3b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent BB</td>
<td>23</td>
<td>31.1±5.7b, d, h</td>
<td>1</td>
<td>4</td>
<td>77.3±7.2b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>11</td>
<td>29.4±6.3a, c, g</td>
<td>3</td>
<td>3</td>
<td>105±2.7b, c, h, i</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± 1 SD. a, p < 0.05, b, p < 0.001 (vs. 3°AVB), c, p < 0.05, d, p < 0.01, e, p < 0.001 (vs. 2°AVB), f, p < 0.05, g, p < 0.01, h, p < 0.001 (vs. Sustained BB), i, p < 0.001 (vs. Intermittent BB). n, number of fetuses; AVB, atrioventricular block; BB, blocked atrial bigeminy; CHD, congenital heart disease; LQTS, long QT syndrome; SVT, supraventricular tachycardia

Diagnostic Accuracy

A correct prenatal diagnosis was made in all cases but one; a case with sustained fetal bradycardia where a postnatal ECG verified an ectopic rhythm. In one further case, the correct diagnosis was considered at the second examination but confirmed only
postnatally. This was a case of functional second-degree AVB due to long QT syndrome where 1:1 conduction was intermittently restored at the second examination.

Visual validation of the Doppler recordings was usually sufficient to determine the arrhythmic substrate. In 7 cases a recording from the pulmonary trunk clearly differentiated between second- and third degree AVB. Good quality recordings from the ductus venosus were available in 12 cases, making a differentiation between BB and second degree AVB feasible. Meticulous measurements of time intervals were needed only in a few midgestational cases of sustained BB, with a constant 2:1 relation between atrial and ventricular beats. Five of 6 cases with sustained BB, diagnosed in early gestation, had surprisingly long \( a_{ch} \) intervals and \( a_{ch}/a_{cc} \) ratios, similar to the cases of second degree AVB, illustrated in figure 5.1. Heart rates < 65 bpm were not seen in BB and a HR<60 bpm was seen only in complete AVB. The cases with SB all had a stable HR between 100 and 110.

![Fetal heart rate and Doppler time interval](image)

**Figure 5.1.** Fetal heart rate (left panel) and the Doppler time interval between the conducted and following blocked atrial contraction divided by the time interval between two conducted atrial beats (\( a_{ch}/a_{cc} \) ratio, right panel) plotted against the gestational age at the first echocardiographic examination. 3°AVB, complete atrioventricular block; 2°AVB, second-degree AVB; BBs, sustained blocked atrial bigeminy; BBi, intermittent blocked atrial bigeminy; SR, sinus rhythm.

### 5.2 PAPER II

The overall aims of this study were to investigate prognostic factors associated with a poor outcome and the effect of transplacental steroid treatment in fetal second- and third- degree AVB.

Eighty percent of the patients were exposed to maternal autoantibodies (Anti-Ro/SSA-positive) and maternal collagen disease was present in 46%. Eighty-three percent had AVB III, 9% AVB II and 8% AVB II-III at the time of diagnosis.
Transplacental treatment
Sixty-seven fetuses (38%) were treated with fluorinated steroids; 52 were given dexamethasone at a median starting dose of 4 mg/day (2-12 mg) and 15 received betamethasone at 4 mg/day (3-5 mg). In two cases, fluorinated steroids were given in combination with prednisolone. The duration of treatment was median 10 (1-21) weeks and remained unchanged in most cases. Side effects in the child were reported in 11 pregnancies (oligohydramniosis, growth restriction and constriction of the arterial duct) whereas only one mother was reported to have side effects from the treatment (diabetes mellitus, adrenal insufficiency and psychosis). Betamimetics were given to 41 fetuses (23%) at median gestation 25 weeks (19-33) for a median duration of 8 weeks (2-18). Ventricular heart rate (VHR) increased from 50.1±3.8 to 55.1±3.7 bpm (p=0.001) in the 15 patients where data were available prior to as well as after two weeks of treatment. Betamimetics were more frequently given in combination with steroid treatment than as a single therapy (23/67 vs 18/108; p=0.01).

Overall outcome

Figure 5.2.1 The overall outcome of the patients included in the study.

Survival at birth and in the neonatal period
Ninety-one percent (159/175) were alive at birth and a further 10 of these patients died during the first month (=neonatal death). There were no differences in survival at birth or at 1 month of age with respect to steroid-treated and untreated fetuses (Table 5.2.1). Restricting the comparison to antibody exposed fetuses did not influence the results significantly. Steroid treatment in the group with at least one risk factor associated with a poor outcome at the time of diagnosis, did not have any significant effect on outcome. Adjusting for the small difference between the groups in gestational age at diagnosis
did not have any significant effect on the results. There were no differences between steroid-treated and untreated in the following variables at the time of diagnosis; Anti-Ro/SSA exposure: 86 vs 76% (p=0.25), Ventricular HR: 61.3 ± 11.3 vs 58.9 ± 11.5 (p=0.19), Impaired left ventricular function: 13 vs 12% (p=0.84), Hydrops: 7 vs 10% (p=0.54).

Table 5.2.1 Transplacental steroid treatment and outcome of all 175 included fetuses (at birth) and the 148 live born neonates with known outcome at one month of age.

<table>
<thead>
<tr>
<th>Categories</th>
<th>All patients</th>
<th>Steroid treated</th>
<th>Untreated</th>
<th>OR- crude</th>
<th>OR-adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At birth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All fetuses</td>
<td>91% (159/175)</td>
<td>91% (61/67)</td>
<td>91% (98/108)</td>
<td>0.96 (0.27-3.10)</td>
<td>0.79 (0.21-2.67)</td>
</tr>
<tr>
<td>AB+</td>
<td>91% (119/131)</td>
<td>91% (51/56)</td>
<td>91% (68/75)</td>
<td>0.95 (0.22-3.72)</td>
<td>0.85 (0.20-3.41)</td>
</tr>
<tr>
<td>AB+ and AVB III</td>
<td>90% (109/121)</td>
<td>90% (44/49)</td>
<td>90% (65/72)</td>
<td>1.05 (0.25-4.15)</td>
<td>0.97 (0.22-3.96)</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1 month</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All neonates</td>
<td>93% (138/148)</td>
<td>95% (53/56)</td>
<td>92% (85/92)</td>
<td>0.69 (0.11-3.18)</td>
<td>0.58 (0.23-1.79)</td>
</tr>
<tr>
<td>AB+</td>
<td>95% (103/108)</td>
<td>96% (44/46)</td>
<td>95% (59/62)</td>
<td>0.89 (0.07-8.16)</td>
<td>1.00 (0.08-10.2)</td>
</tr>
<tr>
<td>AB+ and AVB III</td>
<td>95% (96/101)</td>
<td>95% (39/41)</td>
<td>95% (57/60)</td>
<td>0.97 (0.08-8.92)</td>
<td>1.04 (0.08-10.7)</td>
</tr>
</tbody>
</table>

AB+: Anti-Ro/SSA and/or La/SSB positive, OR-crude; unadjusted odds ratio, OR-adjusted; odds ratio adjusted for gestational age (categorized as <20, 20-24, 25-29, ≥30 weeks). OR is presented with 95% confidence limits; all other results as percent and number of cases.

**Risk factors associated with a poor outcome**

Gestational age (GA) at diagnosis was higher in survivors at birth and at 1 month compared with non survivors. Ventricular HR was higher in survivors than non-survivors at birth; 60.8 ± 10.9 vs 49.9 ± 11.8 (p=0.0002), whereas no significant difference was seen in survivors vs non-survivors at 1 month of age; 61.0 ± 10.8 vs 59.6 ± 14.6 (p=0.70). Intrauterine mortality was around 4 times higher in fetuses diagnosed with AVB diagnosed at GA< 20 weeks compared with > 23 weeks and 5 times higher in fetuses with a VHR ≤50 bpm compared with >55 bpm. The presence of impaired LVF and hydrops increased both intrauterine - and neonatal mortality by a factor of 4 and 6, respectively.
Figure 5.2.2. below shows the effects of the presence of at least one of these risk factors on survival outcome.

![Figure 5.2.2](image)

Figure 5.2.2. Intrauterine (panel A, n=107) and neonatal (panel B, n=90) mortality in fetuses with known presence or absence of risk factors (RF) at diagnosis, AVB II-III/III and fetal exposure to maternal anti-Ro/SSA and/or La/SSB antibodies. Mortality is shown by treatment group in the figure legend. High risk denotes the presence of at least one risk factor; GA <20 weeks, ventricular rate ≤50 bpm, presence of hydrops or impaired LV-function. Low risk are those without any risk factor. Numbers on top of bars are number (n) of cases. Comparisons are treated vs untreated patients.

**Steroid treatment and atrioventricular conduction**

Nine percent (15/175) of the fetuses had AVB II, diagnosed at GA 22 weeks (19-29) of which 10 were exposed to maternal antibodies, 4 were unexposed and in 1 case there was no information on exposure. Eight percent were reported to have AVB II-III, diagnosed at 21 weeks (19-31); 10 were exposed to maternal antibodies, 3 unexposed and 1 unknown. Briefly, of the 7 fetuses with AVB II, 3 reverted to 1:1 conduction within 1-2 weeks after treatment and were in sinus rhythm (SR) at birth. At FU, only one was known to be in SR (1 year of age), whereas one had progressed to AVB I-II (5 years of age) and in one there was no information. Six of 14 fetuses with AVB II-III were treated with steroids, of whom one reverted to 1:1 conduction within weeks after initiation of steroid treatment. The patient had however progressed to AVB III at FU (4 years of age). Another patient (unexposed to antibodies) reverted from AVB I-III to SR after steroid treatment at 21 weeks of GA and remained in SR at FU (2.7 years of age).

**Postnatal outcome**

One hundred and thirty-eight patients were alive at FU (Figure 5.1.1) at an average age of 3.3 years. Two infants died between 1 month and 1 year of age and 2 died after 1 year of age. Eight patients (6/8 exposed to antibodies) developed dilated cardiomyopathy. A permanent pacemaker (PM) was implanted in 102 patients of whom 60 (43%) of the children alive at 1 month were paced. Eighty-one percent had an epicardial PM system implanted at a median age of 10 days (1 day-7.9 years) and 19% an endocardial system at median 2 months (1 day-2.2 years).
5.3 PAPER III

The overall aim was to study the outcome of fetal exposure to maternal anti-SSA/Ro antibodies in children who did not develop complete atrioventricular block (CAVB).

Of the 16 children with AV time interval prolongation in utero (group A), 9 had first-degree AVB (AVB I) on ECG at birth and 8/9 had a normal ECG at 1 month of age; one was lost to follow-up. Two of the 8 patients had a fetal history of transient second-degree AVB reverting to 1:1 conduction after transplacental treatment with betamethasone. Of the 41 children with normal findings in utero (group B), only one had a transient first-degree AVB on ECG at birth. The age at postnatal FU was median 4 (0.8-8) years; 26 boys and 31 girls. None of the children had any cardiac symptoms. Two children with a fetal history of AV time interval prolongation and a skin lesion after birth, also had AVB I at FU. There were no differences between the groups in respect to gender, age, height or weight.

Electrical conduction at FU

ECG

Table 5.3.1 details ECG characteristics at follow-up. Six of the 57 patients (10.5%) had AVB I on ECG. All 6 had prenatal AV time interval prolongation exceeding the 99% reference range for both the MV/Ao- and SVC/Ao Doppler methods (Figure 5.3). Three of 6 had AVB I at birth, normalized at FU at 1 month of age; the other 3 had normal ECG at birth. Of the 2 steroid treated patients with transient prenatal AVB II, 1 had AVB I at FU and 1 had a normal ECG.

Figure 5.3. Prenatal AV time intervals, measured using the MV-Ao (left panel) and SVC-Ao (right panel) Doppler methods against PR intervals on ECG at follow-up. Triangles denote individuals with prenatal atrioventricular (AV) time intervals exceeding the upper 95% (pointing up) or 99% (pointing down) confidence limits for normal fetuses. Diamonds represent the two cases with fetal second-degree AV block, reverted to first-degree AV block during transplacental betamethasone treatment, while circles represent cases with normal prenatal findings. Filled symbols are individuals with age related PR intervals defined as first-degree AV block at follow-up.
24-hours Holter ECG
Fifty-three of 57 children underwent a Holter registration and the registration was interpretable in 50; 12 in group A and 38 in group B. The PR interval was approximately 25 ms longer in group A compared with group B (Table 5.3.1). Four of the 6 children with AVB I where a Holter registration could be performed, had long PR intervals (160-220 ms). One child (aged 5.6 years) with transient AVB II in fetal life and AVB I at FU, had episodes of AVB II (Mobitz type 2) at night, whereas the other child (aged 1.9 years) with transient fetal AVB II had a normal ECG at FU but a highly variable PR interval (120-180 ms) on the Holter registration. QTc was normal in all patients.

Table 5.3.1. ECG and Holter at follow-up grouped in accordance with presence of prenatal signs of first-degree AV block (group A) or not (group B).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A</th>
<th>Group B</th>
<th>p-level</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR, bpm</td>
<td>105±28</td>
<td>105±19</td>
<td>NS</td>
</tr>
<tr>
<td>PR, ms</td>
<td>140±24</td>
<td>121±13</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>401±21</td>
<td>405±17</td>
<td>NS</td>
</tr>
<tr>
<td>Holter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR mean, bpm</td>
<td>105±17</td>
<td>104±11</td>
<td>NS</td>
</tr>
<tr>
<td>HR min, bpm</td>
<td>76±17</td>
<td>75±11</td>
<td>NS</td>
</tr>
<tr>
<td>PR at HR mean, ms</td>
<td>155±35</td>
<td>129±15</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

Values are mean ± SD. HR, heart rate; PR at HR mean, PR interval at 24 hour mean heart rate

Myocardial performance at FU

M-mode of the left ventricle: All measurements were within normal limits\(^{173}\) without any differences between the groups. MV doppler: All measurements were within normal limits\(^{174, 175}\), MPI was slightly higher in group A; see Table 5.3.2 below:).

Table 5.3.2. Mitral valve Doppler findings at follow-up grouped in accordance with presence of prenatal signs of first-degree AV block (group A) or not (group B).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A</th>
<th>Group B</th>
<th>P-level</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV-Doppler</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak E, m/s</td>
<td>0.84±0.14</td>
<td>0.86±0.12</td>
<td>NS</td>
</tr>
<tr>
<td>Peak A, m/s</td>
<td>0.53±0.09</td>
<td>0.55±0.08</td>
<td>NS</td>
</tr>
<tr>
<td>E/A</td>
<td>1.61±0.32</td>
<td>1.57±0.23</td>
<td>NS</td>
</tr>
<tr>
<td>IVCT, ms</td>
<td>38.4±7.4</td>
<td>35.7±5.9</td>
<td>NS</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>48.2±5.7</td>
<td>46.5±5.0</td>
<td>NS</td>
</tr>
<tr>
<td>MPI</td>
<td>0.35±0.03</td>
<td>0.33±0.02</td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>

Values are mean ± SD; E and A, early and active filling waves of the mitral valve; IVCT, isovolumetric contraction time; IVRT, isovolumetric relaxation time; MPI, myocardial performance index
**Tissue Doppler:** Table 5.3.3 details the outcome. One child, with a prenatal history of transient AVB II and intermittent AVB II on Holter ECG at FU, had an abnormal MPI (z-score 2.7), owing to prolongation of the IVCT interval. On a group level, MPI values were higher in group A, remaining so even after correction for heart rate, but individual values were within normal limits in both groups. With the assumption that the mechanical cardiac performance in some way could be different in the 2 patients with more advanced impairment of AV-conduction in fetal life, the analyses were repeated after exclusion of those 2 patients. A significant difference between groups could still be seen for MPI (p<0.01), IVCT’ and IVCT’c from the mitral annulus and MPI’ from the basal septum (p<0.05), but not in MPI’ from the mitral annulus and basal septum IVCT’ and IVCT’c. In order to evaluate a possible influence of impaired AV-conduction on MPI, both mitral valve and TDI measurements were related to PR interval on ECG; the 2 cases with a prenatal history of AVB II were excluded in this analysis also. There was no correlation between mitral valve MPI and the PR interval, whereas a weak correlation between the PR interval and MPI’ estimates was seen from the mitral annulus (r²=0.10; p<0.05) as well as from the basal ventricular septum (r²=0.19; p<0.01).

Table 5.3.3. Tissue Doppler findings at follow-up grouped in accordance with presence of prenatal signs of first-degree AV block (group A) or not (group B).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A</th>
<th>Group B</th>
<th>P-level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mitral annulus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E’/A’</td>
<td>2.64±0.97</td>
<td>2.34±0.72</td>
<td>NS</td>
</tr>
<tr>
<td>IVCT’, ms</td>
<td>64.0±23.6</td>
<td>47.5±7.7</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>IVCT’c, ms</td>
<td>77.7±25.3</td>
<td>61.2±9.1</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>IVRT’, ms</td>
<td>47.8±7.4</td>
<td>45.2±5.0</td>
<td>NS</td>
</tr>
<tr>
<td>IVRT’c, ms</td>
<td>59.0±10.4</td>
<td>58.3±7.8</td>
<td>NS</td>
</tr>
<tr>
<td>MPI’</td>
<td>0.42±0.09</td>
<td>0.37±0.03</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td><strong>Basal septum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E’/A’</td>
<td>2.16±0.44</td>
<td>1.92±0.39</td>
<td>NS</td>
</tr>
<tr>
<td>IVCT’, ms</td>
<td>59.0±19.1</td>
<td>47.6±9.2</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>IVCT’c, ms</td>
<td>72.5±17.6</td>
<td>60.6±8.8</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>IVRT’, ms</td>
<td>47.9±6.6</td>
<td>43.6±4.3</td>
<td>NS</td>
</tr>
<tr>
<td>IVRT’c, ms</td>
<td>59.0±10.4</td>
<td>58.3±7.8</td>
<td>NS</td>
</tr>
<tr>
<td>MPI’</td>
<td>0.40±0.05</td>
<td>0.36±0.03</td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Abbreviations as in table 5.3.2. c, correction for heart rate by division with the square root of the RR interval.
5.4 PAPER IV

The main objectives with this study of patients with complete atrioventricular block diagnosed <15 years of age and pacemaker treatment, were to compare the outcome in patients exposed versus unexposed to maternal auto antibodies, identify risk factors associated with a poor outcome and describe pacing characteristics.

Of 127 patients, 112 (88%) were tested for exposure to anti- SSA-Ro/SSB-La antibodies and 69 (62%) were exposed (AB+) while 43 (38%) unexposed (AB-). Table 5.4.1 details the clinical characteristics. The FS z-score before PM- therapy was lower in AB+ than in AB- but no difference was seen in LVEDD z-score. In patients diagnosed in the earliest period (1981-1989) the time from diagnosis to PM implantation was significantly longer compared with in the later period (1999-2007); median 5.8 vs 0.2 years. (p=0.0003)

Table 5.4.1. Comparison of clinical characteristics in children with isolated complete AVB (CAVB) who were exposed (AB+) or unexposed (AB-) to maternal autoantibodies.

<table>
<thead>
<tr>
<th></th>
<th>All cases</th>
<th>AB+</th>
<th>AB-</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender M/F</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=127</td>
<td>55/72</td>
<td>34/35</td>
<td>17/26</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Age at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal</td>
<td>63/127 (50)</td>
<td>55/69 (80)</td>
<td>5/43 (12)</td>
<td>0.001</td>
</tr>
<tr>
<td>Neonatal</td>
<td>9 (7)</td>
<td>6 (9)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>&gt;1 month</td>
<td>55 (43)</td>
<td>8 (12)</td>
<td>36 (83)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Minor cardiac malformations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echo before PM</td>
<td>120/127 (94)</td>
<td>64/69 (93)</td>
<td>42/43 (98)</td>
<td>0.40</td>
</tr>
<tr>
<td>FS z-score</td>
<td>0.91±3.2</td>
<td>-0.14±3.6</td>
<td>2.03±2.3</td>
<td>0.006</td>
</tr>
<tr>
<td>LVEDD z-score</td>
<td>2.19±1.8</td>
<td>2.48±2.1</td>
<td>1.81±1.4</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Values are number of cases (%), the mean ± 1 SD or the median with range

**Gender and characteristics prior to pacemaker implantation**

The time from diagnosis to PM implantation was shorter in boys compared to girls; 0.2 vs 1.0 years (p=0.03). The difference was still significant when the comparison was restricted to AB+ and age at diagnosis < 1 month, respectively. Median heart rate was lower in boys than in girls; 50 vs 60 (p=0.02), FS z-score before PM implantation was lower in boys; -0.19 ±3.38 vs 1.42±2.98 (p=0.02) and LVEDD z-score was higher in boys; 2.68 ±1.41 vs 1.74 ±1.4 (p=0.02).

**Pacemaker therapy**

A first PM was implanted in 127 patients at a median age of 3.2 (0.01-16.9) years. Fifty-five patients receiving an epicardial pacing (epi) system were significantly younger than 72 patients receiving an endocardial pacing (endo) system (median 0.2 vs 7 years; p<0.0001). Ventricular single-chamber pacemakers (VVI) were implanted in 52% (67/127); 37 vs 30 epi/endo. Twenty percent (25/126) were paced from the left
ventricle. At the last FU of 122 living patients at median age 15.4 years, 30% had an epi-system, 68% an endo-system and 2% cardiac resynchronization therapy (CRT).

**Pacing system revision**
In 30 patients (24%) a re-intervention was necessary due to complications or failure of the pacing system. There was a total of 42 events leading to re-interventions. Twenty-six percent (11/42) of the events occurred < 3 months after the intervention. The risk of an event in connection with the first implantation was almost 5 times greater for those who received a PM < 1 month of age than for those with pacing > 1 month of age.

There were no significant differences in risk between epicardial vs endocardial pacing and DDD vs VVI pacing mode, respectively (Table 5.4.2). The year of implantation did not have a significant impact, although there was a possible trend towards a higher risk of complication the earlier a PM was implanted (in the era from 1983 to 2011); p=0.055. The most important reasons for a re-intervention were: pacing lead related complications in 22 cases (dysfunction or lead fracture in 18; dislodgement of the electrode in 4), infection in 11 cases, obstructed veins or fibrotic attachment of the leads in 3 cases and pacing leads passing foramen ovale to the left atrium or -ventricle in 3 cases.

**Table 5.4.2. Cox proportional hazard model comparing potential risk factors for developing a complication in connection with the first operation. Multivariate analyses.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>P-value</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 1 month at first operation</td>
<td>4.635</td>
<td>0.002</td>
<td>1.722</td>
<td>12.474</td>
</tr>
<tr>
<td>Endocardial PM</td>
<td>0.878</td>
<td>0.747</td>
<td>0.399</td>
<td>1.932</td>
</tr>
<tr>
<td>DDD PM mode</td>
<td>1.339</td>
<td>0.554</td>
<td>0.509</td>
<td>3.526</td>
</tr>
<tr>
<td>Year of operation*</td>
<td>0.948</td>
<td>0.055</td>
<td>0.898</td>
<td>1.001</td>
</tr>
</tbody>
</table>

*Decreased risk per year for developing a complication compared to reference year 1983 if the year of implantation was delayed by one year

**Clinical outcome and echocardiographic data**
Of the 127 patients included in the study 4 died at the age of 1.2 3.8 0.7 and 17.5 years respectively. In the first two cases the cause of death was progressive heart failure, in the third case a combination of respiratory insufficiency (possibly pulmonary hypertension) and heart failure. In the fourth case the cause of death was sudden but unclear. One further patient had a heart transplant at the age of 16 years, after progressive heart failure which commenced before PM implantation at the age of 14.5 years. There were no significant differences in any of the comparisons regarding left ventricular function between AB+ and AB- at FU (Table 5.4.3). Eight patients (6%) reported symptoms connected with effort and 4 patients were on medication (beta-blockers n=1, a combination of ACE-inhibitors, betablockers or spironolactone n=3). None of the patients with a normal LVF before PM implantation developed LV dysfunction.
Table 5.4.3. Echocardiographic data of 122 survivors* at last follow-up. Comparison of exposed (AB+) or unexposed (AB-) to maternal autoantibodies.

<table>
<thead>
<tr>
<th></th>
<th>All n=122</th>
<th>AB+ n=67</th>
<th>AB- n=42</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>15.5 (1.3-19)</td>
<td>14.7 (1.3-19)</td>
<td>15.6 (1.9-19)</td>
<td>0.92</td>
</tr>
<tr>
<td>Pacing, y</td>
<td>8.8 (0.5-18.1)</td>
<td>10.6 (0.9-18.1)</td>
<td>7.2 (0.5-15.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>LVF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>83/117 (71)</td>
<td>48/67 (71)</td>
<td>28/42 (67)</td>
<td>0.67</td>
</tr>
<tr>
<td>Borderline</td>
<td>30/117 (26)</td>
<td>16/67 (24)</td>
<td>13/42 (31)</td>
<td>0.51</td>
</tr>
<tr>
<td>Impaired</td>
<td>4/117 (3)</td>
<td>3/67 (4)</td>
<td>1/42 (2)</td>
<td>0.50</td>
</tr>
<tr>
<td>FS, z-score</td>
<td>0.16 ±2.41</td>
<td>-0.01 ±2.33</td>
<td>0.14 ±2.53</td>
<td>0.75</td>
</tr>
<tr>
<td>LVEDD, z-score</td>
<td>1.13 ±1.49</td>
<td>1.24 ±1.60</td>
<td>1.0 ±1.40</td>
<td>0.45</td>
</tr>
</tbody>
</table>

Values are number of cases (%), the mean ± 1SD or the median with range. *4 patients dead and 1 patient transplanted; last echocardiographic values not included in the comparison of these patients.

**Left ventricular dysfunction and predisposing factors**
Nine patients (8%) developed LV dysfunction. None of these patients had normal LVF before PM implantation. All patients were diagnosed at < 1 month of age, 6/7 tested were AB+ and the gender distribution was 2:1 male to female. Three patients (33%) had an epicardial left ventricular (VVI) pacing system as a first system (Table 5.4.4). At FU 2 patients were dead, 2 had a CRT device and 1 had a heart transplant.

Table 5.4.4 Characteristics of patients who developed impaired left ventricular function (LVF) compared with cases with normal function at follow-up

<table>
<thead>
<tr>
<th></th>
<th>Impaired LVF n=9</th>
<th>Normal LVF n=83</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender M/F</td>
<td>6/3</td>
<td>34/49</td>
<td>0.17</td>
</tr>
<tr>
<td>Diagnosis &lt; 1 month</td>
<td>9/9</td>
<td>47/83 (57)</td>
<td>0.01</td>
</tr>
<tr>
<td>AB- exposure</td>
<td>6/7 (86)</td>
<td>47/75 (63)</td>
<td>0.41</td>
</tr>
<tr>
<td>Normal echo before PM</td>
<td>0/8</td>
<td>52/81 (64)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Age at PM</td>
<td>1.2 (0.01-14.5)</td>
<td>2.5 (0.01-14.9)</td>
<td>0.50</td>
</tr>
<tr>
<td>LV pacing</td>
<td>3/9 (33)</td>
<td>17/83 (20)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Values are given as number of cases (%) or the median with range.
Variables influencing the left ventricular function
To evaluate the influence of AB exposure, age at diagnosis, gender, pacing duration and age at PM implantation on left ventricular function, LVEDD z-score and FS z-score were compared in these groups at FU or when (if) LV dysfunction developed (before death or interventions like CRT, medication or heart transplant); see Table 5.4.5. Except for a higher LVEDD z-score in patients diagnosed < 1 month of age as compared with those diagnosed at a later age, no significant differences were observed. Patients with LV dysfunction vs normal LVF prior to pacing were not equally distributed between groups (epi/endo, VVI/DDD, LV/RV) making a meaningful evaluation of the impact of type or mode of pacing on LVF impossible.

Table 5.4.5. Effects of clinical characteristics and PM treatment on left ventricular function

<table>
<thead>
<tr>
<th>Variables</th>
<th>Yes</th>
<th>No</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis &lt; 1 month</td>
<td>LVEDD</td>
<td>1.73±2.08</td>
<td>0.87±1.06</td>
</tr>
<tr>
<td></td>
<td>FS</td>
<td>-0.67±3.52</td>
<td>0.29±2.55</td>
</tr>
<tr>
<td>Male</td>
<td>LVEDD</td>
<td>1.32±2.05</td>
<td>1.25±1.51</td>
</tr>
<tr>
<td></td>
<td>FS</td>
<td>-0.70±3.49</td>
<td>0.1±2.90</td>
</tr>
<tr>
<td>AB-exposure</td>
<td>LVEDD</td>
<td>1.39±1.82</td>
<td>1.00±1.40</td>
</tr>
<tr>
<td></td>
<td>FS</td>
<td>-0.59±3.10</td>
<td>0±2.88</td>
</tr>
<tr>
<td>PM&lt; 1 month</td>
<td>LVEDD</td>
<td>1.29±1.80</td>
<td>1.20±1.70</td>
</tr>
<tr>
<td></td>
<td>FS</td>
<td>-0.90±3.43</td>
<td>0.03±3.06</td>
</tr>
<tr>
<td>Pacing duration &gt;10 years</td>
<td>LVEDD</td>
<td>1.48±1.76</td>
<td>1.07±1.76</td>
</tr>
<tr>
<td>(versus &lt; 5 years)</td>
<td>FS</td>
<td>-0.29±3.35</td>
<td>0.16±3.60</td>
</tr>
</tbody>
</table>

LVEDD and FS are expressed as z-scores (mean ± 1 SD). PM; pacemaker.
6 DISCUSSION

The overarching aims of this thesis were to investigate diagnostics, pathogenesis, treatment and prognosis in individuals with congenital heart block. Specifically, the following research questions were asked:

1. Can present Echo Doppler techniques correctly diagnose and differentiate between benign and potentially lethal causes of fetal bradyarrhythmia?

2. Does transplacental steroid treatment of fetuses with isolated second- or third-degree atrioventricular block affect outcome and what are the risk factors for perinatal death?

3. Are conduction properties and heart function affected in preschool children, previously exposed to anti-SSA/Ro antibodies?

4. What is the outcome after pacing therapy in children with isolated complete atrioventricular block and what are the risk factors associated with a poor outcome?

6.1 DIAGNOSTICS OF BRADYARRHYTHMIA (PAPER I)

We studied the accuracy of Doppler flow Echocardiography in diagnosing the underlying arrhythmia substrates in fetal bradycardia and showed that a correct diagnosis could be made in nearly all cases. This underlines the importance and usefulness of the method in the diagnostics of fetal bradyarrhythmia.

The prevalence of the different underlying arrhythmic substrates compared well with a previous study where about half of the patients with sustained bradycardia had a second- or third-degree AVB and 20-30% had BB and SB, respectively\textsuperscript{115}.

The majority of our cases with sustained sinus bradycardia had a significant underlying cardiac condition that needed intervention after birth. This has been seen in previous studies \textsuperscript{115,119,180} and our study confirms the need for caution in managing these patients.

With this retrospective study design, it was not possible to perform quantitative comparisons between the different Doppler flow recordings, but from a qualitative point of view we could see that they are complementary. Recordings from the pulmonary artery turned out to be very useful in differentiating between second- and third degree AVB, where sharp late-diastolic flow profiles, presumably reflecting atrial depolarization, are clearly visible. It is unclear if these profiles actually reflect flow activity in the pulmonary trunk or in the left atrium. The ductus venosus approach was found to be effective in distinguishing between second-degree AVB and sustained BB in mid-gestation. Even if an ocular examination of the registration was sufficient to differentiate between these conditions in most cases, meticulous measurement by
applying the constructed ratio was helpful in the few cases where the intervals between a blocked and a conducted beat were similar. A study by Wiggins et al.\textsuperscript{181} aimed at comparing magnetocardiography and Echo Doppler techniques in their ability to distinguish between BB and 2:1 AVB, concluding that diagnostics can be difficult using echocardiography. The Echo Doppler method they used, however, was the MV/Ao approach which we recognize to be inadequate in analyzing the atrial activity in these conditions. In a recently published study by our group we investigated to what extent measurements of isovolumetric time intervals could improve differential diagnostics in distinguishing between BB and isolated 2:1 AVB\textsuperscript{182}. Interestingly, we could see that the isovolumetric contraction time (ICT) interval was consistently shorter in BB than in 2:1 AVB.

Surprisingly, mid-gestation seems to be a period where the coupling interval of supraventricular extrasystoles are longer than normal, compared with both late-gestation and the postnatal period. There are however few previous published reports confirming this observation. With the assumption that these BB are resulting from a retrograde conduction over accessory pathways (AP), one could speculate that the conduction properties of the APs in midgestation are different from later in gestation or after birth. An equally intriguing phenomenon is the fact that in four of the five cases with BB in mid-gestation where it was possible to measure the interval between a conducted and a non-conducted atrial depolarization, the coupling interval was 325-380 ms. This coupling interval would under normal circumstances be sufficiently long to result in a ventricular contraction. A possible explanation to this phenomenon, suggested by Zhao et al.\textsuperscript{183}, is a prolonged repolarization in the AV-node or in the ventricle causing a prolonged QT-interval with a resulting BB.

### 6.2 ISOLATED FETAL AVB AND STEROID TREATMENT (PAPER II)

There are very few previous studies regarding transplacental steroid treatment to fetuses with congenital heart block, especially concerning possible treatment effects. We described the outcome in the largest reported data set of fetuses with isolated second- and third-degree AVB. The main objectives were to compare the outcome in steroid-treated versus untreated patients, identify risk factors associated with a poor outcome and describe treatment practices.

The results of our study confirmed the impression that there is no consensus regarding treatment with fluorinated steroids to fetuses with second- or third-degree AVB. Almost all patients were treated at some centers, whereas at others no patients received treatment, independent of the fetal status at diagnosis. At the outset, we expected that the more diseased fetuses would be more likely to get steroid treatment but that did not seem to have been the case. Apart from a small difference in GA at time of diagnosis the groups were comparable, allowing us to analyze the effect of steroids on outcome, adjusting only for the difference in GA at diagnosis in a logistic regression model. We could see no significant differences in survival at birth or at 1 month of age, not even
when the comparisons were restricted to the group of antibody exposed fetuses; a group that, at least theoretically, would be most likely to benefit from treatment.

**Our results in perspective**

Given the rarity of the disease, there are unfortunately no prospective, blinded studies comparing treatment effects and very few retrospective studies. Our results do, however, contrast with those of Jaeggi et al.\(^{125}\), who described a treatment effect in comparison with an untreated historical cohort. The most surprising result of their study was a mortality rate close to 50% among the untreated, whereas 1-month survival in the treated group was similar to the overall survival in our study. Examining the data by Jaeggi et al, demonstrated that risk factors shown in our study to be associated with a poor outcome, were more frequent in the untreated group; thus perhaps explaining some of the difference. In another study by Lopez et al.\(^{184}\), the largest single-center study so far, 51/57 (89%) of fetuses with isolated second- or third degree AVB, not receiving steroid treatment, had a 1-month survival of 80%. Half of the steroid treated patients (3/6) died before 1 month, in contrast to the high survival rate in our study.

**Transplacental steroids - effective or not?**

Even if our results do not indicate a beneficial effect of transplacental steroid treatment, the retrospective and multicenter design cannot rule out a possible effect in subgroups of patients. A simple power calculation tells us that we would need > 500 patients to detect a 50% reduction in mortality at a 5% significance level with 80% power. This means that there is a risk that we have failed to detect smaller differences between the groups, as this study is “underpowered” in that sense. Furthermore there was a considerable variation in dosage, gestational age at initiation of therapy as well as treatment duration, which could not be controlled for in the comparisons.

In agreement with previous reports\(^ {116-118}\) reversion from incomplete AVB to 1:1 conduction after steroid treatment was observed in a few cases, namely in 3 of 7 antibody exposed second-degree AVB, and in a further 2 of 6 (5 antibody exposed) cases with AVB II-III. However, only 2 of those with known outcome were still in sinus rhythm at FU. There are to our knowledge no reports of spontaneous reversion of an incomplete AVB exposed to maternal autoantibodies. This could, in our opinion, indicate a possible beneficial effect of maternal steroids in this restricted group.

**Risk factors associated with a poor outcome**

*Gestational age*

We found a correlation between low GA at the time of diagnosis and the risk of intrauterine and/or neonatal death in our study. In the study of Jaeggi et al, with comparable average GA at diagnosis, there was no significant difference between survivors and non-survivors. Patients in the Lopez study were diagnosed later than our patients (average 29 vs 24 weeks). Obviously, gestational age cannot be a risk factor per se (a part from a possible difference as to when the heart block will actually develop), but the earlier the detection, the larger the proportion of fetuses at risk. Hence, some of the differences will likely depend on differences in ultrasound screening programs and midwife surveillance.
Other risk factors

Fetal hydrops, impaired left ventricular function and low heart rate are all variables previously shown to be associated with a poor outcome, findings consistent with the results of our study. In addition to the contribution of increased risk by each of these factors, we studied the impact of having at least one risk factor, including low gestational age at time of diagnosis. Intrauterine and neonatal mortality was 22 and 18% respectively, if at least one risk factor was present, but only 2 and 3% in those without risk factors. This has, to best of our knowledge, not been studied before but could be useful in the counseling and management of this patient group, enabling a better risk stratification.

Due to patient loss to FU as well as a substantial variation in FU time, long term outcome in terms of morbidity, could not be evaluated on a group level. The proportion of dilated cardiomyopathy (DCMP) in our study may therefore be underestimated. Other studies report, however, a varying prevalence of DCMP; from 28% in the study by Villain to around 5-10% in others.

Study limitations

As mentioned above, the retrospective study design, gave limited control over especially details regarding exposure to treatment. Dosage, duration and GA when treatment started varied in the group and could hence not be controlled for. There is a non-negligible risk that we have failed to detect small differences between the groups, due to the relatively small study group, the presence of missing data in some of the variables and the retrospective study design. A multicenter format also complicates data control.

6.3 CLINICAL PATHOGENESIS AND ANTIBODY EXPOSURE (PAPER III)

Little has been known about the long term outcome of fetal exposure to maternal anti-Ro/SSA autoantibodies in individuals who do not develop heart block early in life. Previous studies are small with a limited number of patients and limited follow-up.

In this study of preschool children, previously exposed in utero to maternal autoantibodies, we found that the group with prenatal AV time interval prolongation (group A), also had longer PR intervals on ECG compared to those with normal prenatal findings (group B). About 10%, all belonging to group A, had progressed to first-degree AVB at follow-up, in spite of a normal ECG at birth and/or 1 month of age. It was unexpected to find this fluctuation in PR intervals, with a normalization at birth or at 1 month of age in all subjects, and a progression in some patients later in life. The findings on ECG were confirmed by very similar results in the Holter recordings, where one additional patient with clear but intermittent PR interval prolongation had a normal PR interval on ECG, showing that conduction abnormalities can fail to be detected unless a Holter ECG is included. These are, to the best of current knowledge, new findings that could support a hypothesis claiming that exposure to maternal autoantibodies, causing only a minor injury, can be subtle and easily escape detection.
A previous prospective controlled study of anti SSA/Ro exposed newborn infants showed a 10% (5/51) prevalence of AVB I at birth. Three of these patients remained in AVB I and 2 normalized the PR interval at FU at 1 year of age. In another prospective, multicenter study, nine percent (4/46) of anti-SSA/Ro exposed children had PR interval prolongation (>140 ms) at 20-90 days of age and 0/26 patients at FU at 1 year of age. In the PRIDE study of 98 antibody exposed fetuses, 2 developed AV time interval prolongation between GA 16 and 26 weeks (upper limit set to > 150ms), both were treated with dexamethasone and were said to “reverse” to normal AV intervals within 1 week after treatment was given. Both had normal PR intervals at birth and 1 year of age. In contrast, another patient from the same study who had normal AV intervals throughout the gestation, had AVB I at 3 years of age. In a study by Costedoat-Chalumeau et al, 58 patients were exposed to anti-SSA/Ro antibodies and in the 20 of these cases where an ECG was performed at FU, all had a normal ECG without PR interval prolongation. Possible explanations for the discrepancy between the results of our study compared with those of others could be: (1) smaller sample sizes and/or (2) loss to FU in the above studies or (3) a longer FU in our study. Moreover, it is always hypothetically possible that our results appeared by chance. This is in my opinion unlikely, as we know that antibody exposure can cause impaired AV conduction both in fetal life and after birth. There are, however, only a few previously documented examples of postnatal progression from normal sinus rhythm at birth to first-degree AVB in cases associated with exposure to maternal antibodies.

Is it important to diagnose first-degree AVB in these children?

Even if we have good reasons to believe that the majority of the children will not progress to complete AVB, a follow-up of this patient group was lacking and our results provide clinical evidence to the pathogenesis of development of AVB. It furthermore confirms that the outcome analyses of antibody exposure cannot be simplified to a categorical outcome in terms of did/did not develop CAVB, but should rather be seen as a broad continuum from a barely perceptible affection (like first-degree AVB) to fulminant disease. In a study by Bergman et al, a subgroup of antibody exposed individuals were diagnosed with complete AVB after the perinatal period (aged 4 months to 43 years), supporting the hypothesis of a late and gradual progression to complete AVB. It must be said however, that to date no cohort of antibody exposed individuals have been followed prospectively into adult age.

Myocardial performance

In order to detect even subclinical impact on cardiac function by exposure to maternal autoantibodies, a complete echocardiographic study was performed on our patients. We could see that almost all observations were within normal limits. There was, however, a small difference between groups, in that patients from group A had higher MPI, possibly reflecting a reduction in the ventricular function as a consequence of a more pronounced impact of antibody exposure in some patients. The observed difference in MPI only showed a weak correlation with PR interval prolongation. These minor differences in MPI are most likely not very relevant from a clinical point of view, but they are interesting from a pathophysiological perspective as they are in line with our previous observations where the isovolumetric contraction time (ICT) interval was prolonged in antibody exposed fetuses. There are also other clinical observations...
supporting a hypothesis of a myocardial process following antibody exposure, without a concomitant advanced degree of AVB. These clinical observations are in turn supported by a previous study in an animal model where pups exposed to antibodies to the p200 stretch of Ro52 developed first-degree AVB. These specific cloned autoantibodies were furthermore shown to bind to cardiomyocytes causing dysregulation of the calcium balance with subsequent loss of contractility. However, we still need to elucidate the long term outcome of having been exposed to maternal autoantibodies in fetal life, for those developing only a minor conduction abnormality persisting into pre-school age.

**Study limitations**

The sample size in this study was relatively small, although larger than most similar previous studies. Another limitation is the lack of an unexposed control group.

### 6.4 PACEMAKER TREATMENT AND COMPLETE AVB (PAPER IV)

We performed a nationwide, retrospective study describing the outcome in one of the largest datasets of young patients with isolated complete AVB and PM treatment.

As this cohort only included patients who survived to pacing therapy, it excluded potential non-survivors who did not benefit from therapy and the study therefore does not estimate survival and early morbidity in congenital or complete AVB as a whole.

Survival was 96% at FU after approximately 9 years of pacing. Overall, this result compares well with previous studies. In a comparable single center study by Villain et al., 105/111 underwent PM treatment for > 6 months with a survival rate of 95% after median 10 years of PM treatment. In a study by Kim et al. all 63 patients were alive after PM treatment for a median duration of 10 years, but patients with cardiac dysfunction prior to PM implantation were not included. Udink ten Cate et al. studied 111 patients with CAVB and PM treatment in a retrospective multinational, multicenter setting. Three patients died and 2 received a heart transplant, giving a survival rate of 95% at 10 years of FU; however, 3/5 did not survive to 6 months of PM treatment.

Apart from a shorter duration of pacing in the AB- group we could not detect any differences in LVF between AB- and AB+ at follow-up. This was, however, after any intervention (CRT or medication) due to development of LV dysfunction. Patients who died were excluded in the comparison, meaning that the comparison did not evaluate antibody exposure per se.

Looking at variables with a possible influence on LVF, only age at diagnosis had a significant impact on LVF with a higher LVEDD z-score in age< 1 month at diagnosis, whereas time of exposure to pacing, AB-exposure, and gender had no significant impact on outcome. To the best of our knowledge, only Villain et al have previously compared the outcome of AB+ vs AB-, showing that only AB+ patients developed LV dysfunction; however they did not compare the impact on LVF at a group level. The advantage of their study was that information on AB exposure was present in all cases,
compared with in 88% of our cases. Given the close relationship between AB-exposure and age at diagnosis, our finding of an increased LVEDD z score in those diagnosed < 1 month of age, points to a possible impact of either AB exposure or diagnosis at an early age. In agreement with the study by Kim et al194, no difference in LVF between long- term and short- term pacing at FU could be seen in our study.

Dilated cardiomyopathy and predisposing factors

Study cohort size
The problem of identifying predictors of a poor outcome in a rare disease like CAVB is obvious; not even the largest studies like the one of Villain et al, will have more than around 5-15 patients in each cohort developing DCMP. In our study nine patients (8%) developed LV dysfunction (equivalent to DCMP in other studies); a result that compares well with previous studies188,194-200 Interestingly, none of our patients had a normal echo before PM implantation and none of those with a normal echo before PM therapy developed LV dysfunction. Furthermore, all were diagnosed in fetal life or just after birth and 6/7 tested, were associated with autoantibody exposure. The gender distribution was 2:1 male to female.

Exposure to maternal autoantibodies and early diagnosis
Other studies have shown that patients developing DCMP are predominantly diagnosed before 1 month of age186,195. Combined with the fact that 80- 90% of those early-diagnosed are exposed to maternal autoantibodies39,124,186,201; this means it is a difficult and maybe even less important task to “prove” the causality between AB exposure and development of DCMP. Most studies have a retrospective design and encompass several decades. Consequently, information on AB-status will often be lacking and sometimes even incorrect, due to lower precision in detecting antibodies in the past, whereas information on age at diagnosis often will be present. This leads to a “dilution” of the data set and contributes, in our opinion, to a stronger correlation between age of diagnosis and outcome than between antibody exposure and outcome. However, the fact that the majority of individuals with early diagnosis/antibody exposure do not develop DCMP indicates that these characteristics may be a prerequisite in most cases but other factors are needed to develop DCMP.

Cardiac status prior to PM implantation
None of our patients who developed DCMP had a normal LVF before PM implantation, but only 3/8 had developed LV dysfunction, as defined in this paper. Information on the cardiac status prior to implantation was often lacking in previous studies but Villain et al reported that 12/16 of their DCMP- cases had this diagnosis before a PM was implanted. Applying the age correlated FS z-score on the data presented by Moak et al202, 12/16 had z-score values below –2. These results indicate the importance of thoroughly evaluating the pre-intervention LVF when predicting the outcome and analyzing the impact of other variables.

Gender
We found, unexpectedly, that the time from diagnosis to PM implantation was significantly shorter in boys than in girls, especially in the AB+ as well as those
diagnosed < 1 month of age. With the assumption that this could reflect a gender difference in the pre-implantation status we compared LVF measures and found that LVEDD z-scores were higher and FS z-scores lower in boys. Furthermore, HR at birth was lower in boys. This could indicate a gender difference in the degree of disease in our study group and a possible interpretation of these findings is that the boys were given a pacemaker at an earlier age simply because they were in a more compromised cardiac situation than the girls.

In the few studies where data on AB exposure and gender are present, there seems to be a rather equal gender distribution among the AB exposed. Regarding a possible difference in morbidity or mortality, the picture is less clear, but in a study by Eronen et al\textsuperscript{124} where 91 patients with CAVB were diagnosed in fetal life or as neonatal, only 31/91 (34\%) were males but 12 (39\%) had a poor outcome vs 22\% of the females. In a further two reports, 75 and 100\% of patients developing DCMP\textsuperscript{188, 203} were males, without this having been particularly discussed or highlighted. In an effort to see if a Medline search could give some indication in this matter, we performed a search for studies reporting on young patients diagnosed with DCMP. We found 13 studies and 1 case report\textsuperscript{124, 186-189, 194, 195, 197, 199, 200, 203-205}, the present study included, where the definition of DCMP was acceptably transparent and unequivocal with a total of 107 patients meeting the criteria. Surprisingly, information on gender was presented in only about half of the studies. Looking closer at the studies containing data on gender distribution, 38 males versus 16 females had developed DCMP. Taking these data into consideration, it is difficult to exclude a possible gender effect on morbidity or mortality. A Medline search is obviously not comparable to a regular study and hence the results must be interpreted with caution. It is furthermore impossible to exclude the risk that the data of some patients have been published in more than one study. It would however be interesting to put the hypothesis of a gender component involved in the development of the clinical picture in the context of a larger prospective and blinded study.

**Pacing**

We investigated the time from diagnosis to PM implantation and discovered that there has been a shift towards a considerably shorter time interval between diagnosis and PM implant over the last decades. This has to our knowledge not been studied previously and the results support the general impression that guidelines advocating pacing therapy at an earlier age than before are being implemented. Our data also support the hypothesis that patients who were paced in the early period were more diseased, in that they had significantly higher LVEDD z-scores and lower FS z-scores than patients in the late period and our interpretation is that asymptomatic patients were given a PM at a later age in the early period.

It is an ongoing debate as to whether and to what extent the type of pacing, and especially right ventricular pacing, plays a role in the development of DCMP. About 20\% in this cohort had LV pacing as a first system and we aimed at studying the importance of pacing mode/type and site with respect to outcome. There were, however, differences in the baseline characteristics between the groups, which made a fair comparison impossible. Several studies have shown that impaired LV function and intra-ventricular dyssynchrony, is mainly observed in pacing from the RV apex\textsuperscript{163, 206}. 
In the multicenter study by Janusek et al\textsuperscript{207} where LVF- and LV dyssynchrony measures were important outcome variables, LV function and LV synchrony was superior in individuals paced at the LV apex or the LV midlateral wall. FS values were, however, compared without taking into account a significant difference in age between the groups. Correcting the EF and FS values for age, creating a FS a-score or a similar EF correction for age or body surface, could in our opinion have given a more correct picture of the differences, even if the data as a whole support the concept of more favorable hemodynamics in LV pacing, at least compared with RV apical pacing. More importantly however, there is a problem of translating these observations into clinical practice, knowing that around 90\% of the CHB patients do not have LV dysfunction at FU, irrespective of type of pacing, making it obvious that other factors than pacing site plays a role in the development of DCMP in selected groups of patients. Many cardiologists would however, if possible, probably avoid RV apical pacing.

**Complications to pacing therapy**

Most previous studies did not compare endocardial and epicardial pacing in isolated CAVB, but mixed study groups with postoperative AVB and/or CAVB associated with congenital heart disease. Age span, definitions of complications/re-interventions and time of FU also varied considerably, making a direct comparison with our study difficult.

At least one re-intervention was necessary due to PM system related complications in 24\% of our patients, compared with 42\% (11/26) in a study by Balmer et al\textsuperscript{208}; one of the few previous studies of exclusively isolated CAVB with information on PM related complications. As in previous studies\textsuperscript{208-210}, lead related problems (fracture, insulation break or dislodgement) were the most common causes for re-interventions in our study, followed by infections. We found that PM implantation before 1 month of age was strongly associated with procedure related complications. This is line with at least one previous study on pacing related complications\textsuperscript{156}, though this was in a group where the majority had CHD or postoperative CHB. The occurrence of complications necessitating a re-intervention was not significantly different between the epicardial- and endocardial groups, as opposed to results in the majority of previous studies on mixed populations where epi-pacing was less favorable\textsuperscript{157, 209, 210}. A possible reason for this could be the non-separation of isolated CAVB and structural heart disease when comparing the systems in previous studies. Another study focusing only on lead related problems failed to show any differences between the groups\textsuperscript{211}.

**Strengths and Limitations**

The retrospective study design is obviously a disadvantage, especially regarding the lack of control of data and maybe most importantly, of the outcome variables. It is well known that measuring FS and LVEDD does not tell the whole truth about left ventricular function. A prospective FU with a more sophisticated evaluation of LVF (3D echo, spackle tracking, and diagnostics of dyssynchrony) as well as a control group would of course have been a better alternative. We aimed at comparing the possible impact of different kinds of pacing modes and types but a non-randomized study like this does not permit controlling for differences in morbidity (LVF) prior to PM therapy.
This would make comparisons non-meaningful. Furthermore, we could not study the impact of pacing site on LVF, as information of the exact position of the pacing electrode in the ventricle was present in less than half of the patients. Missing values in some outcome variables can have affected the precision of the estimates. Recognizing the difficulties in ruling out a possible importance of non-significant results in a multifactorial context and a retrospective study design, it is possible that we have underestimated the importance of one or more tested variables when evaluating their impact on outcome. The strength of the study is above all its character of a national cohort where in our opinion the process of identification and selection of patients is transparent. Through use of the unique personal identification numbers used in Sweden, we have minimized the risk of not having identified patients meeting the inclusion criteria.

**Conclusion**

Our study confirms previous results of showing an excellent outcome in this group of patients with complete AVB and PM treatment. Interestingly, we could see that none of the patients who developed LV dysfunction/DCMP had a normal LVF prior to PM treatment, indicating the importance of taking into account the cardiac status prior to pacing when predicting the long term outcome. We also report on a gender difference in time from diagnosis to PM treatment as well as more impaired LVF values in males than females prior to PM treatment. Given the retrospective character of the study, these findings need to be further elucidated, preferably in a prospective setting.
7 CONCLUSIONS

With current Echo Doppler techniques underlying substrates of fetal bradycardia can be differentiated with accuracy and precision; even in mid-gestation when there was a high resemblance between benign atrial bigeminies and second-degree AVB. Sinus bradycardia had a high prevalence of associated disease, emphasizing the importance of postnatal follow-up in this group.

Transplacental treatment of fetuses with third-degree AVB did not improve survival, nor did it affect AV-conduction. Risk factors of a poor outcome were identified and the presence of at least one of them at the time of diagnosis, had a substantial impact on mortality, with a 10-fold increase at birth and a 6-fold increase at 1 month of age. The results do, however, not exclude a treatment effect in subgroups of patients. Furthermore, we observed a possible treatment effect in terms of improved conduction properties in second-degree AVB, although numbers are small.

Pre-school children exposed in utero to maternal SSA-Ro autoantibodies and who developed fetal AV time interval prolongation but not complete AVB, could develop first-degree AVB even if ECG was normal at birth or 1 month of age. Discrete signs of impaired left ventricular function in this group could be an effect of antibody exposure. The results demonstrate the variable disease expression as a result of exposure to maternal autoantibodies and give new insights in the clinical pathogenesis of congenital heart block. The implications of the findings are, in my opinion, a follow-up restricted to individuals with conduction abnormalities.

Children with complete AVB who survive the perinatal period have a very good prognosis with an excellent survival rate of 96% after 9 years of pacemaker treatment. The majority had no complications from pacing therapy during this period. Impaired left ventricular function before pacemaker treatment as well as diagnosis < 1 month of age, were risk factors for a poor long term outcome with development of left ventricular dysfunction. The results indicate that patients with congenital heart block may have a different outcome compared with patients who develop heart block later in life, but also that cardiac status before treatment is an important predictor.
Medfött hjärtblock är en ovanlig sjukdom som i de flesta fall drabbar barn till kvinnor som bär på vissa antikroppar vilka under graviditeten överförs till fostret och i en del fall innebär att hjärtat angrips. Ibland kan även andra organ påverkas, men dessa effekter är oftast övergående och ofarliga. Av hittills okända anledningar är det bara ca 2% av barnen vars mödrar bär på antikroppar som utvecklar hjärtblock; de övriga tros vara friska även om en del forskningsresultat tyder på lindrigare påverkan i vissa fall. Medfött hjärtblock utvecklas oftast redan i fosterlivet och leder till att de impulser som uppstår i sinusknutan i hjärtats övre del inte kan fortledas till hjärtats kammare på vanligt sätt utan blockeras i övergången mellan förmak och kammare, i den s k AV-knutan, som är ett slags omkopplingsstation i hjärtats impulsspridningssystem.

Om ett hjärtblock uppstår leder det till att pulsen sänks kraftigt; från ca 110-150 till 50-70 slag per minut. Graden av påverkan avgör fostrets och barnets framtid. Det är emellertid inte bara hjärtats impulsspridningssystem som kan påverkas, även själva hjärtmuskeln kan utsättas för angrepp (inflammation) och i värsta fall uppstår hjärtsvikt och fosterdöd. De barn som överlever (ca 70-85%) kommer förr eller senare att behöva få en pacemaker (PM); en behandling som är livslång.

I en del fall ställs diagnosen genom screeningundersökningar av gravida som man vet bär på antikroppar och därför har en viss risk att födda barn med hjärtblock. I andra fall sker upptäckten efter att man på mödravårdscentralen uppmätt misstänkt låg puls hos fostret. Den slutgiltiga diagnosen ställs med hjälp av ultraljud av fostrets hjärta. Diagnostiken ställer höga krav på precision och noggrannhet; en felaktigt ställd diagnos kan aningen leda till onödig behandling, som kan vara skadlig för fostret eller en missad chans till -i vissa fall- livsviktig behandling av ett s k andra gradens hjärtblock; ett mellansteg på väg till komplett hjärtblock.

Många försök har gjorts att ge kortison- (steroid) behandling till den gravida kvinnan med avsikten att medicinen via moderkakan skall nå fostret och sedan dämpa den inflammation man vet kan drabba hjärtat. Med dagens kunskap finns dock ingen effektiv behandling att erbjuda när ett komplett hjärtblock väl har utvecklats, även om en del forskare tycker sig ha sett en förbättrad överlevnad med steroidbehandling. Resultaten bygger dock på enstaka studier med låga patientantal och professionen är inte enig i om behandling bör användas eller ej. Behandlingen kan nämligen ge oönskade effekter hos såväl mor som barn. Man tror att de allra flesta barn som exponerats för antikroppar i fosterlivet utan att utveckla hjärtblock ej heller kommer att
göra det senare i livet. Dock har en del studier visat att barn kan utveckla en lindrig störning och fördröjning av impulsspridningen (hjärtblock av första graden) under fosterlivet, vilket emellertid verkar vara ett övergående tillstånd i de flesta fall. Pacemakerbehandling är visserligen livräddande i många fall, samtidigt har man sett från tidigare studier att en del barn drabbar av hjärtsvikt trots PM-behandling. Det är oklart vilka faktorer som påskyndar en sådan utveckling.

**Mitt avhandlingsarbete belyser huvudsakligen fyra frågeställningar:**
- Kan man med nuvarande ultraljudsteknik på ett tillfredsställande sätt ställa diagnos hos foster med långsam hjärtrytm?
- Påverkas överlevnad och sjuklighet hos foster med hjärtblock av steroidbehandling och vilka är riskfaktorerna för dödlig utgång?
- Hur mår barn i förskoleåldern som under fosterlivet utsattes för antikroppar från modern men ej utvecklade komplett hjärtblock? Finns några kvarvarande tecken till påverkan hos den minoritet som uppväxta hjärtblock av första graden i fosterlivet?
- Hur går det för barn med medfött hjärtblock och pacemakerbehandling? Har de ett annat utfall än de som utvecklar hjärtblock senare?

**Metoder och Resultat:**
I studie I analyserades ultraljudsundersökningar av 65 barn från upptagningsområde Stockholm-Uppsala och vi fann att en korrekt diagnos hade ställts i samtliga fall utom ett samt att man i samtliga fall kunde skilja godartade från potentiellt farliga och behandlingskrävande rytmrubningar.

I studie II jämfördes 175 fall av hjärtblock diagnostiserade under fosterlivet; data kom från 28 centra i 15 länder. Nittio procent var levande födda. Ingen skillnad i överlevnad kunde ses mellan dem som fått behandling med steroider jämfört med obehandlade. Riskfaktorer kopplade till dödlig utgång kunde identifieras.

I studie III undersöcktes 57 barn med ultraljud av hjärtat, ekg samt långtids-ekg och resultaten visade att ca 10% hade en begränsad påverkad på impulsspridningen i hjärtat. Det fanns också tecken till en mycket diskret påverkan av hjärtfunktionen. Alla barn var i övrigt hjärtfriska.

I studie IV jämfördes data från samtliga unga personer med hjärtblock i Sverige, diagnostiserade mellan 1980 och 2011. Knappt två tredjedeler hade medfött hjärtblock och av dessa var 90% kopplade till antikroppar. Överlevnaden var 96% efter i genomsnitt nio års pacemakerbehandling. Åtta procent utvecklade nedsatt hjärtfunktion och av dessa hade samtliga medfört hjärtblock.

Sammanfattningsvis visar studie I att det med en tillfredsställande precision gick att ställa rätt diagnos på barn med långsam hjärtrytm. I studie II sågs ingen effekt på överlevnad av steroidbehandlande hjärtblock under fosterlivet men riskfaktorer kopplade till död kunde identifieras. Tioprocent av de barn som hade exponerats för antikroppar från modern hade utvecklat hjärtblock av första graden vid uppföljning i förskoleåldern (studie III). Barn och unga med pacemakerbehandling hade en utmärkt prognos, dock fanns en koppling mellan tidig diagnos och påverkan av hjärtfunktionen (studie IV).
9 FUTURE PERSPECTIVES

Although congenital heart block is clearly associated with the passive transplacental transfer of maternal autoantibodies and studies of the pathogenesis have made great progress over the last years, we are still far from understanding why only 2% of fetuses exposed to antibodies develop CHB. Current hypotheses involve fetal and maternal factors as well as environmental and genetic components. Further studies are, however, needed to elucidate the mechanisms involved in “transforming” a status of exposure to autoantibodies, without apparent impact on the fetus, to the development of CHB and neonatal lupus syndrome, with all its components. Successful therapeutic interventions will depend on a profound understanding of the mechanisms leading to disease.

The ideal scenario would of course be to prevent heart block from occurring, possibly by blocking the transfer of autoantibodies to the fetus during pregnancy, or impeding their effect on the fetus by identifying the key players in that process. Current therapeutic interventions have not been successful thus far. Treatment strategies aiming at intervening when the fetuses show signs of impaired AV conduction, i.e. developing first-degree AVB, have been tried. The problem is that we do not know if the treatment is useful, as only about 10% of those with fetal exposure to maternal autoantibodies had developed first-degree AVB at follow-up, whereas AV time interval prolongation appears to be transitory in the majority of cases, as our study (III) showed.

Furthermore, we have no evidence to support a hypothesis that these pre-school children with first-degree AVB are at risk of progressing to complete AVB later in life. This, combined with the fact that there is clear evidence for a sometimes very rapid progress of conduction disease from normal SR to complete AVB in less than a week, but possibly even much faster than that, suggests that those who develop complete AVB do so at a higher “speed” and therefore may be out of reach for treatment.

So, a challenge for the near future is to individuate the best methods for identifying individuals who really are at risk of progressing to a complete and irreversible heart block and to distinguish these individuals from those who will “only” experience AV time interval prolongation, transitory or not. One of the problems is that we do not know which prolongation of the AV interval, irrespective of methods used, is too long. Is an extreme first-degree AVB too long and should this always require treatment? A research project monitoring fetuses at risk in the critical period from around 15 to 26 weeks would probably provide new insights and knowledge. Such an approach is obviously connected with possible risks of interfering psychologically with normal pregnancies in a group where around 98% will give birth to a child without CHB.

Once a CHB has developed through exposure to autoantibodies, it is considered irreversible and the affected individuals will need lifelong pacemaker treatment. As we have seen from our study (IV) and others, the absolute majority have a very good prognosis. However, we need to further study the subgroup of patients who, in spite of PM treatment, will develop dysfunction of the left ventricle. Is early diagnosis a risk factor and is the association with antibody exposure just as strong? Is there a gender difference involved? While most patients seem to tolerate RV pacing well, is there a subgroup of patients, maybe with impaired LV function prior to PM treatment, who
would benefit from LV pacing? It is very unlikely that we will ever have blinded, randomized studies comparing different types of pacing, but even with a retrospective study design with a cross-sectional follow-up and a multicenter approach (such as the one by Janousek et al\textsuperscript{207}), we could gain knowledge. The quality of the dataset must however improve, in the sense that full information on exposure to autoantibodies, gender and, above all, echocardiography prior to pacing must be present to qualify for inclusion in future studies. In order to evaluate current treatment strategies in young patients with isolated CHB, we also need to evaluate the adult population. Apart from single smaller studies, more systematic data on outcome are lacking.

**Future pacing strategies**

*Leadless pacing*

Pacing in children is still technically challenging and entails a considerable risk of intervention-related complications, many of which are due to pacing lead problems. A recent study in an adult population with self-contained leadless cardiac pacemakers showed promising preliminary results with few early complications\textsuperscript{212}. It is, however, still far from being an accessible tool in the pediatric population as the delivery device and catheters are not adapted for children. Furthermore, the device in its actual form is tailored for implantation in the RV apex, which is a pacing site we wish to avoid in children. With further technical development, this device may be adapted to alternate pacing sites and to a pediatric population.

*Biological pacing*

Research in the field of human biological pacing has been increasing over the last years, with interesting results from animal studies. The current understanding of the method implies the usage of gene- and cell-therapy for delivery and introduction of pacemaker function to the heart\textsuperscript{213}. However, there is a long way to go before problems connected with safety and efficacy can be resolved and biological pacing becomes a reality for the pediatric population.
10 ACKNOWLEDGEMENTS

Många har på ett eller annat sätt- känslomässigt eller materiellt- bidragit till mitt avhandlingsarbete. Alldeles särskilt skulle jag dock vilja tacka följande personer:

Sven-Erik Sonesson, min huvudhandledare, som jag lärt mig så mycket av under dessa år; inte minst ett strukturerat förhållningssätt till forskning. Du är en sann forskare i ordets allra bästa bemärkelse. Din lägsta nivå vad gäller kvalitet och noggrannhet är något för oss andra att sträva efter. Din oerhörda generositet med allt ifrån akututryckningar för att kompensera mina tillkortakommanden till att på alla sätt ha skapat bästa möjliga förutsättningar för min forskning, kan jag inte nog tacka för.

Marie Wahren-Herlenius, min bihandledare, en forskare ut i minsta cell, med en naturlig nyfikenhet och entusiasm inför alla upptäcktliga, nybakade hypoteser och infall. Din förmåga till kristallklara och hyperlogiska reflektioner på luddigt formulierade tankar och frågor upphör aldrig att förvåna. Tack för att du alltid så generöst har delat med dig av tid och kunskap

Fredrik Gadler, min andra bihandledare, blixtsnabb och intuitiv med känsla för det viktiga. Dina kunskaper kring pacemakerbehandling har varit ovärderliga och en förutsättning för tillkomsten av det fjärde arbetet i avhandlingen. Jag har uppskattat din generösa och omedelbara tillgänglighet oerhört.

Bo Lundell, min före detta chef, nuvarande kollega och tyvärr snart pensionsaktivist, som inte bara varit en förebild som barnkardiolog och kliniker men också en tydlig inspiratör till att jag slutlig, om än lite tveksamt, hoppade i forskarvaken. Jag har alltid känt mig oerhört stöttad och buren av din entusiasm och ditt engagemang.

Maria Lindström Bagge, min chef på Barnkardiologen, som tålmodigt väntat in min långsamma vandring mot disputationen och därmed skapat de förutsättningar som var nödvändiga för att jag till sist skulle kunna nå ända hit, om än med obeintliga marginaler.

Gunilla Hedlin, min mentor, som det har känts så tryggt att ha i bakgrunden, som klok rådgivare och samtalspartner.

Mina medförfattare samt forskarkompisar i CHB-gruppen; alldeles särskilt: Gunnar Bergman för fetala kunskaper samt att du så generöst bidrog med den vackra teckningen till ”summanfattningen på svenska”; Lilly-Ann Mohlkert, som med sina högkvalitativa ultraljudsundersökningar gjorde tredje arbetet möjligt; Amanda Skog, för hjälp med struktur och datainsamling, Stina Salomonsson, högoktanig och entusiasmerande primus motor i nätverket; Anders Jonzon, en föregångare inom svensk barnarytmologi som alltid så generöst delat med sig av kunskap och hjälp.

Anna-Karin Hamnarstedt- mitt infrastrukturella högkostnadsskydd på Barnkardiologen, som inte bara hanterat och skött mina patienter under min allt tätare
bortavaro -så att de förmodligen inte ens märkt att jag varit frånvarande- utan dessutom alltid varit hyperflexibelt fixar-allt-ig. Grazie mille!

**Gunnar Sjöberg**- min trogne rumskamrat som inte bara har en alldeles särskilt sällsynt tolerans för allehanda impulsgenombrott (mina) utan dessutom enkelt och lätt låter sig mutas (billigt) till att utföra i-sista-minuten-liv (avhandlings-)räddande åtgärder av allehanda slag.

**Felicia Nordenstam**- för glada, täta, uppbyggliga tillrop på distans samt alltför sällsynta men alltid lika välkomna ocensurerade skratt och andra känslottringar

**Linda Lagnefeldt**, utan din enastående, pilsnabba, organisatoriska förmåga i att hålla reda på (mig) och samla in patientdata, hade studie IV nog aldrig blivit klar.

**Anita Fredenson**, som på ett effektivt och högkvalitativt sätt hjälpt till att få in resterande delar av forskningsdata till studie IV

**Cecilia Pegelow-Halvorsen**, för kontinuerlig uppmuntran under kappaskrivandet och inte minst, generösa och akuta hjälpinsatser vid klippans och desperationens rand

**Mina oefterhärmliga arbetskamrater på barnkardiologen som utgör ett av de mest väl samarbetande individpräglade arbetskollektiv man kan tänka sig. Tack för att ni tagit hand om delar av mitt arbete när jag inte varit plats och att ni bara av födsel och ohejdad vana är sådana att man efter ett tag på annan plats längtar tillbaks till jobbet igen.

**Astrid Häggblad** vars administrativa noggrannhet gjorde att t o m jag hade –nästan-alla papper i ordning inför disputationens granskning

**Linnéa Holmén**, för att ha jagat bort språkliga grodor ur min ramberättelse

**Till mina fantastiska vänner**, i periferin av denna avhandling men i centrum av mitt hjärta. När jag nu kravlar mig ur mitt forskaride hoppas jag att ni fortfarande vill leka.

**Mina föräldrar**, Nils och Birgitta Eliasson, som har lärt mig så mycket mer än de någonsin kan ana och givit mig ett överflöd av kärlek

**Min syster Inger Tynn med Daniel, Johanna och Sara**- våra band är så starka att de tål att tänjas, även ut över landets gränser. När vi behöver varandra finns vi där.

**Stefano**, il mio compagno di vita. Senza di te, tutto questo lavoro non avrebbe avuto nessun senso. In fondo, l’ho fatto per noi. Adesso voglio passare più tempo con te. Ora e sempre.

**Följande generösa bidragsgivare:** Stiftelsen Samariten, Stiftelsen Frimurare Barnhuset i Stockholm, Hjärt-Lungfonden, Karolinska Institutet och Fonden för ALF-medel. Utan detta ekonomiska stöd hade ingen avhandling skrivits.
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