Coarctation of the Aorta
Register and imaging studies

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“With magic, you can turn a frog into a prince. With science, you can turn a frog into a Ph.D. and you still have the frog you started with.”

— Terry Pratchett, The Science of Discworld
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Abstract

Background Coarctation of the aorta (CoA) constitutes 5-8% of all congenital heart disease (CHD) and is associated with long-term complications such as hypertension (HTN) and left ventricular hypertrophy (LVH). Factors associated with HTN, LVH, and diffuse myocardial fibrosis, are not yet fully explored in this population.

Methods Papers I-III: The Swedish national register of congenital heart disease (SWEDCON) was used to identify adult patients with repaired CoA.

Paper IV: Data on 2,424 adult patients with CHD was extracted from SWEDCON and compared to controls (n = 4,605) regarding height, weight and body mass index (BMI).

Paper V: Adults with CoA (n = 21, age 28.5 (19.1-65.1) years, 33.3% female) referred for CMR were investigated with T1 mapping to determine left ventricular extracellular volume fraction (ECV).

Results Papers I-II: Out of 653 patients, 344 (52.7%) had HTN. In a multivariable model, age (years) (OR 1.07, CI 1.05-1.10), sex (male) (OR 3.35, CI 1.98-5.68) and BMI (kg/m²) (OR 1.09, CI 1.03-1.16) were associated with having HTN, and so was systolic arm-leg blood pressure (BP) gradient where an association was found at the ranges (10, 20] mmHg (OR 3.58, CI 1.70-7.55) and > 20 mmHg (OR 11.38, CI 4.03-32.11), in comparison to the range [0, 10] mmHg.

When investigating 243 patients with diagnosed HTN, 127 (52.3%) had elevated BP (≥ 140/90 mmHg). Age (years) (OR 1.03, CI 1.01-1.06) was associated with elevated BP, and so was systolic arm-leg BP gradient in the ranges (10, 20] mmHg (OR 4.92, CI 1.76-13.79), and > 20 mmHg (OR 9.93, CI 2.99-33.02), in comparison to the reference interval [0, 10] mmHg.

Patients with elevated BP had more classes of anti-hypertensive medication classes prescribed (1.9 vs 1.5, p = 0.003).

Paper III: Out of 506 patients, 114 (22.5%) were found to have LVH. Systolic BP (mmHg) (OR 1.02, CI 1.01-1.04), aortic valve disease, (OR 2.17, CI 1.33–3.53), age (years) (OR 1.03, CI 1.01–1.05), and HTN (OR 3.02, CI 1.81-5.02), were associated with LVH, while sex (female) (OR 0.41, CI 0.24-0.72) was negatively associated with LVH.

Paper IV: There was no difference in height, weight, or BMI between patients with CoA (n = 414) and the reference population.

Paper V: In the population of 21 patients, an increased left ventricular myocardial ECV was found in 6 cases (28.6%). Of the patients with increased ECV, 5/6 (83.3%) were female (p = 0.002). Patients with increased ECV did not otherwise differ from the rest of the study population.
Conclusions In adults with repaired CoA, HTN and LVH were common, and many patients with HTN had elevated BP despite treatment. The potentially modifiable factors BMI and systolic arm-leg BP gradient were associated with HTN, and the gradient was also associated with elevated BP among patients with diagnosed HTN. The gradient’s significance remained even within what the current guidelines consider acceptable ranges. Potentially modifiable factors associated with LVH were systolic BP and aortic valve disease. We found no general difference in height, weight, or BMI between patients with CoA and the reference population. While LVH was more common among men, increased myocardial ECV was more common among women.
Abbreviations

ASD atrial septal defect
ASVD atrioventricular septal defect
BAV bicuspid aortic valve
BMI body mass index
BP blood pressure
BSA body surface area
CHD congenital heart disease
CMR cardiovascular magnetic resonance
CoA coarctation of the aorta
ECG electrocardiography
ECV extracellular volume fraction
EF ejection fraction
GUCH grown-up congenital heart disease
HLHS hypoplastic left heart syndrome
HTN hypertension
IAA interrupted aortic arch
ICD implantable cardioverter-defibrillator
LVEDV left ventricular end-diastolic volume
LVH left ventricular hypertrophy
LVM left ventricular mass
LVMVI left ventricular mass volume index
MDCT multi-detector computed tomography
PDA persistent ductus arteriosus
SILC Statistics on Income and Living Conditions
SSFP steady-state free-precession
SWEDCON the Swedish Registry of Congenital Heart Disease
ToF Tetralogy of Fallot
ULF Untersökningarna av Levnadsförhållanden
VSD ventricular septal defect
List of original papers

This thesis is based on the following papers which are referred to by their Roman numerals in the text:


III. Rinnström D, Dellborg M, Thilén U, Sörensson P, Nielsen NE, Christersson C, Johansson B. Left ventricular hypertrophy in adults with previous repair of coarctation of the aorta; association with systolic blood pressure in the high normal range. *Int J Cardiol.* 2016;218:59-64


V. Rinnström D, Sörensson P, Johansson B, Ugander M. High prevalence of increased left ventricular myocardial extracellular volume fraction in adult women with coarctation of the aorta. *Manuscript.*
Sammanfattning på svenska

**Bakgrund** Coarctatio aortae (CoA) är förhållandevis vanligt bland de medfödda hjärtsjukdomarna och innebär att ett segment av stora kroppspulsådern är förträngt i närheten av ductus arteriosus. CoA åtgärdas vanligtvis i unga år och de flesta patienterna kan därefter leva väsentligen normala liv, men även efter ingreppet kvarstår en ökad risk för långtidskomplikationer som hypertoni och hjärtförstoring i form av ökad vänsterkammarmassa.

**Metod Delarbete I-III:** Det nationella registret för medfödd hjärtsjukdom (SWEDCON) användes för att identifiera vuxna (≥ 18 år gamla) med åtgärdad CoA och de respektive studiepopulationerna selekterades därefter utifrån övriga tillgängliga data.

**Delarbete IV:** Data rörande 2 424 vuxna med olika typer av medfödd hjärtsjukdom, däribland CoA, extraherades ur SWEDCON och analyserades med avseende på längd, vikt och BMI.

**Delarbete V:** Tjugoen vuxna personer med CoA remitterade för kardiovaskulär magnetisk resonanstomografi (CMR) genomgick en specialiserad undersökning med intravenöst kontrastmedel, i syfte att bestämma andelen extracellulärvolym (ECV) i vänster kammars hjärtmuskelvävnad. Detta gjordes eftersom ökad ECV kan tyda på diffus bindvävsinlagring, vilket i sig kan ses som ett förstadium till hjärtförstoring och funktionsstörning i vänster kammare.

**Resultat Delarbete I-II:** Av 653 patienter hade 344 (52,7 %) hypertoni definierat som antingen en registerdiagnos, blodtryckssänkande läkemedelsbehandling, eller förhöjt blodtryck (≥ 140/90 mmHg) vid den senast registrerade kliniska undersökningen. I en flervariabelmodell var ålder (år) (OR 1,07; CI 1,05–1,10), manligt kön (OR 3,35; CI 1,98–5,68), och BMI (kg/m²) (OR 1,09; CI 1,03–1,16) associerade med hypertoni, och det var även den systoliska blodtryckssgradienten mellan arm och ben, där associationer hittades för intervallen (10; 20] mmHg (OR 3,58; CI 1,70–7,55) och > 20 mmHg (OR 11,38; CI 4,03-32,11), i jämförelse med det valda referensintervallet [0; 10] mmHg.

När endast de 243 patienter som hade hypertoni baserat på registerdiagnos eller läkemedel analyserades, så visade sig 127 av dessa (52,3 %) ha förhöjt blodtryck (≥ 140/90 mmHg) vid den senast registrerade mätningen. Ålder (år) (OR 1,03; CI 1,01-1,05) och systolisk blodtryckssgradient mellan arm och ben (mmHg) (OR 1,08; CI 1,04-1,12) visade sig associerade även med detta. Gradienten delades därefter upp i intervall, varpå associationer med förhöjt blodtryck sågs för intervallen (10;
20] mmHg (OR 3,41; CI 1,31-8,85) och > 20 mmHg (OR 6,63; CI 2,12-10,73) jämfört med referensintervall [0; 10] mmHg.

Patienter med förhöjt blodtryck hade i genomsnitt fler typer av blodtryckssänkande läkemedel förskrivna än de vars blodtryck låg inom behandlingsmålen (1,9 vs. 1,5; p = 0,003).

Delarbete III: Av 506 patienter inkluderade i studien hade 114 (22,5 %) hjärtförstoring. Faktorer oberoende associerade med hjärtförstoring var systoliskt blodtryck (mmHg) (OR 1,02; CI 1,01-1,04), aortaklaffsjukdom (OR 2,17; CI 1,33–3,53), ålder (år) (OR 1,03; CI 1,01–1,05), och känd hypertoni (definierat som antingen en registerdiagnos eller blodtryckssänkande läkemedelsbehandling) (OR 3,02; CI 1,81-5,02), medan kvinnligt kön visade sig vara negativt associerat med hjärtförstoring (OR 0,41; CI 0,24-0,72). En univariat post hoc-analys utfördes där det systoliska blodtrycket visade sig vara associerat med hjärtförstoring för intervallen [130; 140] mmHg (OR 2,23; CI 1,05-4,73) och > 140 mmHg (OR 8,02; CI 3,76–17,12) i jämförelse med referensintervallet < 120 mmHg.

Delarbete IV: Där fanns ingen skillnad i vare sig längd, vikt eller BMI mellan de 414 patienter som hade CoA, och referenspopulationen.

Delarbete V: Hos 6/21 patienter (28,6 %) hittades ECV över det normala referensintervallet. Av patienterna med ökad ECV var 5/6 (83,3 %) kvinnor. Patienter med ökad ECV skilde sig däremot inte från den övriga studiepopulationen med avseende på ålder, ålder vid den första interventionen mot CoA, blodtryck, eller vänsterkammarmassa. Inte heller fanns där någon skillnad vad gäller funktionella parametrar som vänsterkammarvolym eller ejektionsfraktion.

1. Introduction

1.1 Congenital heart disease

In a definition proposed by Mitchell et al., the term congenital heart disease (CHD) is characterised as “a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance.” Thus, CHD represents a broad spectrum of defects in the structure and function of the heart due to abnormal heart development in utero, but this definition excludes abnormalities that are essentially functionless in daily life, such as persistent left superior vena cava. Congenital arrhythmias, such as long QT or Wolf-Parkinson-White syndrome are usually also excluded, as are lesions such as hypertrophic or dilated cardiomyopathy, since those conditions generally develop over time, even though the underlying genetic abnormalities are present at birth. On the other hand, Marfan syndrome, which is also a genetically determined condition, is sometimes included among the CHDs, even though cardiovascular lesions may not appear for many years, so the exact interpretation of the definition can vary.

CHD is the most common form of all structural birth defects, with a reported prevalence varying between 4 and 10 per 1,000 live births, and CHD is an important cause of childhood mortality.

The various conditions that fall under CHD can be broadly classified into three categories: cyanotic heart diseases, left-sided obstruction defects, and septation defects.

Cyanotic heart diseases are conditions that result in deoxygenated blood bypassing the lungs and entering the systemic circulation, either by shunting of blood from the right to the left side of the heart, by malposition of the great arteries, or by increased pulmonary vascular resistance such as in Eisenmenger syndrome. Examples of cyanotic CHD are Tetralogy of Fallot (ToF), and tricuspid or pulmonary atresia. A blue tint to the skin is a common sign of cyanotic heart disease in infants—a condition in the past referred to as “blue baby syndrome”.

Left-sided obstructive lesions are conditions which, as the name suggests, obstruct the left-sided circulation, and include conditions such as mitral or aortic stenosis, hypoplastic left heart syndrome (HLHS), interrupted aortic arch (IAA), and coarctation of the aorta (CoA).

Septation defects are conditions in which abnormal connections exist between the atria and/or ventricles. These CHDs include atrial septal defects (ASDs), ventricular septal defects (VSDs), and atrioventricular septal defects (AVSDs).

These three groups cover most types of CHD, but there are also a few conditions such as patent ductus arteriosus (PDA) which do not quite fit
into any of the main categories, and bicuspid aortic valve (BAV) which is common enough to generally be regarded as an anatomical variation rather than a CHD, despite frequent long-term complications. CHDs can also be classified by severity or complexity, but though various systems of classification have been applied, there is no general consensus in the matter.

Due to advancements in paediatric cardiovascular care, with regards to interventions, imaging, and treatment, mortality from CHD has decreased, and most patients with CHD now reach adulthood. The global prevalence of adult CHD—also known as grown-up congenital heart disease (GUCH)—was estimated to be around 3,000 per million adults (0.3%) in 2012, and expected to increase even further with time.

1.2 Coarctation of the aorta
The word coarctation or coarctatio means tightening and is derived from the Latin coartare, to constrict, in turn stemming from co- and arctare, to fix firmly, from artus, close, tight.

Coarctation of the aorta (CoA) is a relatively common CHD, accounting for about 5 to 8% of all structural CHDs with a 1.3-2.0:1 male to female ratio. In CoA, a segment of the artery narrows, typically in proximity to the ductus arteriosus, or the ligamentum arteriosum after closure, but the constricted area of the aorta can vary in location, as well as in shape, diameter and length.

1.2.1 Symptoms, findings and diagnosis
The symptomatology of CoA varies over a wide spectrum. Severe cases induce considerable upper-body hypertension (HTN) and can lead to congestive heart failure and death soon after birth if not corrected. However, mild cases of CoA can be asymptomatic, and sometimes remain undiagnosed for years. Symptoms, when present, include breathing difficulties and failure to thrive in infants, while older children and adults may develop headache, nosebleeds, dizziness, tinnitus, cold feet, abdominal angina, exertional leg fatigue, leg claudication, and even intracranial haemorrhage.

Routine examinations in children generally include palpation of the femoral pulses as a way of screening for previously undiagnosed cases of CoA. Even so, the diagnosis is sometimes not established until adulthood, typically when investigating HTN. At that point, adjacent arteries may have developed an extensive collateral circulation, bypassing the site of coarctation, and partially compensating for the obstruction (figure 1).
Figure 1. CMR image showing extensive collateral circulation in an adult patient with untreated CoA. The arrow indicates the site of coarctation.

1.2.2 History
The first known post-mortem report of CoA dates back to 1760\textsuperscript{21, 22} but the condition was not clinically diagnosed with any regularity until the 1930s\textsuperscript{23}, and its history is therefore incomplete, being largely derived from available post-mortem records and selected case series\textsuperscript{23}.

Historically speaking, CoA has often been viewed as a unique and localised pathology restricted to the main artery, but it has since been shown that the condition is associated with several other congenital abnormalities such as BAV, VSD, and PDA\textsuperscript{24}.

1.2.3 Treatment
The first successful surgical treatment of CoA was performed in Sweden by Crafoord and Nylin in 1944\textsuperscript{25-27}.

At the time, several physicians were working on possible surgical methods for correcting CoA, and experimental procedures had already been performed, primarily on dogs\textsuperscript{28}. While promising, these experiments had led to some concern that cross-clamping of the aorta during surgery risked
exposing the subject to spinal cord ischemia with varying degrees of gait disturbances as a result. However, Crafoord reasoned that the well-developed collateral circulation to the lower body, seen in patients with CoA, would provide protection from spinal ischemia during aortic cross-clamping.

The first interventional surgery for CoA took place on October 19, 1944, and lasted for 6 hours. The patient was an 11-year-old boy with upper-body HTN, who, after the procedure, had an uneventful postoperative course. Two weeks later, Crafoord repeated the procedure on a second patient, and on a third in the spring of 1945, both cases successful.

Since then, several different techniques have been developed for the treatment of CoA, both surgical and catheter-based, the latter sometimes including the positioning of intravascular stents.

1.2.3.1 End-to-end anastomosis
The original principle for repairing CoA is still applied today, especially in older children and adults. This technique involves the placement of vascular clamps, and subsequent transection of the aorta above and below the site of coarctation, excising the abnormal aortic tissue before reconnecting the proximal and distal parts of the aorta (figure 2). The original procedure involved a circumferential suture line, but a more recent variant—coarctation resection with extended end-to-end anastomosis—involves an oblique suture line with extension to the underside of the transverse aortic arch.

![Figure 2. End-to-end anastomosis. The constricted section of the aorta is surgically removed, and the proximal and distal ends of the aorta are then reconnected.](image-url)
1.2.3.2 Subclavian flap

Also known as the Waldhousen procedure after its author, subclavian flap angioplasty involves transection of \textit{a. subclavia sin.} and its use as a flap to enlarge the site of coarctation (figure 3). Though rarely associated with severe left arm ischaemia, long-term arm length discrepancy, and claudication during exercise have been described. Blood pressure in the left arm might become lower than the systemic pressure as a result of the procedure, stressing the importance of bilateral blood pressure registrations in clinic.

![Figure 3. Subclavian flap procedure. A. subclavia sin. is transected and used as a flap to enlarge the constricted part of the aorta.](image)

1.2.3.3 Percutaneous interventions

In the past three decades, percutaneous transcatheter therapies have become available as an alternative to surgical repair of CoA. Transcatheter balloon angioplasty (figure 4) was first described by Singer in 1982, and involves inserting a catheter into the aorta, advancing it to the site of coarctation, and using an inflatable balloon to expand the constricted segment. Intraluminal blood pressure subsequently causes remodelling and expansion of the coarctation post intervention. Studies have shown the procedure to be quite safe compared to surgical alternatives, but with a higher rate of recoarctation.

In cases with longer constricted segments, expandable intravascular stents are sometimes used to prevent recoarctation. The results are generally favourable, but aneurysm formation is sometimes seen after the procedure. Also, cardiovascular magnetic resonance imaging (CMR) of patients with implanted stents is complicated by artefacts, limiting the use of CMR as an imaging modality in these cases.
Figure 4. Balloon angioplasty. A balloon is passed into the aorta using a catheter, then inflated in order to open up the constriction. Alternatively, an intravascular stent can be placed in the area of coarctation using a similar technique.

1.2.4 Associated cardiovascular anomalies
CoA is associated with several other congenital cardiovascular lesions. The most common is BAV, but VSD and PDA also occur together with CoA. Furthermore, there is an association between CoA and intracranial aneurysms, most commonly berry aneurysms of the circulus arteriosus Willisi\textsuperscript{19, 24}. CoA occurs in approximately 35 % of women with Turner’s syndrome\textsuperscript{24}.

1.2.4.1 Ventricular septal defect
In VSD, there is a defect in the ventricular septum with shunting of blood from the left ventricle via the right ventricle, and into a. pulmonalis, thus causing volume overload of the left side of the heart and the pulmonary circulation.

Small, restrictive VSDs are usually left without treatment unless other cardiac surgery is performed, but large VSDs must be detected early and closed, otherwise irreversible pulmonary HTN develops, resulting in cyanosis, marked limitation of physical capacity, and a high risk of complications including mortality. The treatment of VSD is usually surgical, with favourable prognosis if treated in time\textsuperscript{24}. 
1.2.4.2 Persistent ductus arteriosus
The ductus arteriosus normally closes spontaneously early in life, but in some patients there remains a persistent flow in the vessel, with various degrees of left-to-right shunting.

In PDA, as in VSD, small shunts are often left untreated unless other cardiac surgery is performed, but larger shunts must be closed to protect the pulmonary circulation. The treatment is either surgical or catheter-based. If treated before irreversible pulmonary HTN develops, the prognosis is favorable24.

1.2.4.3 Bicuspid aortic valve
BAV—meaning that the aortic valve is composed of only two leaflets instead of three—is the most common congenital heart abnormality, occurring in 1-2 % of the general population47 and in approximately 60-85 % of patients with CoA48-50. The earliest known description of BAV is attributed to Leonardo da Vinci who, in his numerous drawings of the human circulatory system, sketched what is believed to be the bicuspid variant of the aortic valve47. Several subtypes of BAV have since been described51-54, as well as several systems of classification55, 56, though no golden standard currently exists.

The condition may be sporadic or familial, and is associated with an increased risk of developing further aortic valve complications57-60, as well as dilatation of the aorta ascendens61.

1.2.5 Long-term complications from coarctation of the aorta
Before surgical treatment was introduced, the leading cause of death in adults with CoA was congestive heart failure, typically in the third decade of life62. Though surgical treatment of CoA has been possible since the mid-forties25, 27, 49, late complications such as aortic valve disease, aortic dilatation, HTN, and left ventricular hypertrophy (LVH) still pose significant risks to the patients’ health after intervention63-69.

1.2.5.1 Aortic valve disease
Patients with both CoA and BAV are at increased risk of developing long-term complications such as aortic valve disease and ascending aortic dilatation70, 71. Aortic valve disease, both stenosis and regurgitation, is strongly related to the high prevalence of BAV among these patients50, and aortic valve disease with need for aortic valve replacement is a common reason for reoperation in patients with CoA. In a cohort reported by Brown et al, this procedure made up approximately 30 % of all performed reinterventions72.
1.2.5.2 Aortic dilatation
Ascending aortic dilatation may occur in patients with CoA, especially in the presence of BAV\(^5^0\). Coarctation repair in patients with BAV may provide some protection\(^7^3\), but for patients with CoA, evaluation of aortic diameter remains an important aspect of periodic follow-up\(^7^4\).

Aortic dilatation is a severe vascular pathology since the incidence of life-threatening complications such as aortic dissection and rupture appear directly related to the diameter of the aorta\(^7^5, 7^6\). It has also been demonstrated that aortic root diameter is a general predictor of mortality in elderly patients regardless of other cardiovascular risk factors\(^7^7\).

HTN has been shown to be a major factor in aortic dissection\(^7^8, 7^9\), but while HTN is commonly regarded as a predisposing condition for the development of thoracic aortic aneurysms, the link between HTN and ascending aortic dilatation is still somewhat controversial\(^7^5, 8^0\).

1.2.5.3 Hypertension
HTN affects approximately one billion adults worldwide\(^8^1\), and is an important risk factor for coronary events, stroke, heart failure and end-stage renal disease\(^8^2-8^9\).

Of the many long-term complications associated with CoA, HTN is the most common, with a prevalence ranging from 25 to 68 % depending on the definition of HTN, the studied population, and differences in diagnostic method\(^9^0\). It has also been shown that HTN is associated with early mortality in patients with repaired CoA\(^6^7, 9^1\).

The underlying pathophysiology of HTN after coarctation repair is likely multifactorial, but several studies have shown that CoA is associated with vascular abnormalities not limited to the site of coarctation. In particular, CoA has been shown to be associated with cystic medial necrosis\(^9^2\) and decreased aortic distensibility\(^9^3-9^5\), as well as with a general vascular bed pathology\(^9^6-9^8\), and impaired baroreceptor reflex\(^9^9\), subsisting after the lesion itself has been repaired. Thus, there may be several factors that differ between HTN in CoA and essential HTN, but the exact mechanisms are still unknown, and a recent study from 2014 found no clinically significant difference in endothelial function between patients with repaired CoA and healthy controls\(^1^0^0\).

Several studies have previously identified risk factors associated with the development of HTN in patients with repaired CoA. Male sex, age, age at intervention, type of interventional procedure, residual systolic arm-leg blood pressure gradient, and high preoperative blood pressure have all, at some point, been found associated with HTN in patients with CoA\(^5^7, 9^0, 1^0^1-1^0^5\). However, the outcome of anti-hypertensive treatments, and factors associated with response to treatment, among patients with CoA and HTN are largely unknown.
1.2.5.4 Left ventricular hypertrophy

Increased left ventricular mass (LVM), known as LVH, is common in several heart diseases and may also be a physiological response to exercise training. Pathological LVH—i.e. not resulting from ventricular remodelling as a response to training—is an important long-term complication in CoA\textsuperscript{106, 107}. LVH is highly related to cardiovascular morbidity\textsuperscript{108}, and is considered an adaptive response to chronically increased afterload\textsuperscript{109}. Furthermore, it has been shown that treatments reducing left ventricular mass in patients with HTN also decrease the risk of future complications\textsuperscript{110}.

It has previously been shown that patients with repaired CoA are at risk of developing increased LVM due to impairment of vascular mechanics and abnormal blood pressure regulation\textsuperscript{111-113}, but little is known about how other factors interact with blood pressure and LVM in this particular population.

1.2.5.5 Recoarctation

Recoarctation is a term used to describe narrowing at the site of the previously repaired coarctation. A study from 2014, including 247 patients with repaired CoA, found recoarctation in 31 % of the patients, but not all recoarctations are considered clinically significant\textsuperscript{114}. Still, intervention for recoarctation is a common procedure in patients post repair of CoA\textsuperscript{72}.

Common signs of recoarctation are upper body HTN, increased arm-leg blood pressure gradient, and weak or delayed femoral pulses. The narrowing can be visualised using CMR or multi-detector computed tomography (MDCT), and CMR or echocardiography may reveal increased flow velocities over the recoarctation. At present, reintervention may be indicated when the invasively measured gradient over the recoarctation is 20 mmHg or more\textsuperscript{78}.

1.3 Body mass index

Body mass index (BMI) is a value derived from weight and height, expressed in units of kg/m\textsuperscript{2}, and can be used to classify underweight, overweight and obesity. The same classification is generally applied for both sexes, with BMI ≤ 18.5 classified as underweight, BMI ≥ 25 as overweight, and BMI ≥ 30 as obesity\textsuperscript{115}. Being overweight or obese is a risk-factor for cardiovascular disease including mortality\textsuperscript{116, 117}, but little is known of BMI in adults with CHD. As acquired heart disease may complicate the course of CHD, it is of importance to know the risk factor profiles in this population. In patients with CoA, risk factors related to HTN and atherosclerosis are a concern, as HTN is common and early atherosclerotic disease development has been reported\textsuperscript{98}.

The present data on BMI in patients with CHD is somewhat conflicting as both higher and lower prevalence of overweight/obesity have been reported\textsuperscript{118, 119}. 

9
1.4 Imaging Techniques
While physical examinations and electrocardiographic data can often provide some basic information regarding heart function, the clinical benefits of advanced cardiovascular imaging techniques cannot be overstated. Today, cardiovascular imaging is routine in most hospitals, and many different imaging modalities are available.

1.4.1 Echocardiography
Echocardiography is a form of medical ultrasonography—an imaging technique using pulsed ultrasound to generate images from the echoes created when emitted high-frequency soundwaves pass between materials with different acoustical impedance\(^\text{120}\).

The first successful cardiac ultrasonography was performed in 1953 by Swedish cardiologist Inge Edler and Hellmuth Hertz who was, at the time, a graduate student at the department of nuclear physics at Lund University. The investigation was performed using a supersonic reflectoscope originally developed for use in mechanical engineering\(^\text{121}\). Since then, echocardiography has become a staple of cardiovascular investigations.

As an imaging modality, ultrasonography is especially useful for imaging muscle, soft tissues, and the interfaces between solid and fluid-filled spaces. The equipment is also portable, and relatively inexpensive in comparison to other imaging techniques. However, ultrasonography has limited depth perception, and difficulty imaging tissues behind bone or gas. Furthermore, the quality of an echocardiographic examination is highly dependent on the skill of the operator.

In clinical practice, echocardiography is a quick, noninvasive examination that can identify LVH, as well as provide an assessment of heart function, including details on systolic and diastolic function, cardiac output, regional wall motion, and valvular function.

1.4.2 Cardiovascular magnetic resonance imaging
Magnetic resonance imaging is an imaging modality based on a quantum mechanical phenomenon called nuclear magnetic resonance. Within an external magnetic field, atomic nuclei with nuclear spin are able to absorb and emit radio frequency photons, and in magnetic resonance imaging, this property is utilised to image tissues by sending pulses of radio waves into the subject and detecting returning signals. Due to gradients in the strong, external magnetic field provided by the scanner, the origin of these returning echoes can be localised and translated to images\(^\text{122}\).

The first successful attempt at magnetic resonance imaging was performed by Paul C. Lauterbur, with the results published in 1973\(^\text{123}\). Since then, CMR imaging has become a valuable asset in the cardiac diagnostic
arsenal, complementing or, at times, replacing echocardiography as the preferred imaging modality.

Using CMR, both cardiac and extracardiac anatomy can be visualised. Steady state free precession (SSFP) sequences visualise the moving heart and ventricular volumes, allowing both EF and ventricular mass to be calculated with high accuracy and precision. Furthermore, blood flow can be measured, allowing for estimation of valve function, cardiac output and shunts. After injection of intravenous gadolinium-based contrast agents, angiograms can be obtained, and late after injection of contrast—typically 10-20 minutes after injection—focal myocardial fibrosis such as post-infarction or non-ischemic scars can be visualised. This technique has been further developed for estimation of myocardial extracellular volume fraction (ECV) and thereby indirect assessment of diffuse myocardial fibrosis (see Material and Methods).

As an imaging modality, CMR is useful for long-term follow-up of patients with repaired CoA, since it provides extensive details on both cardiac function and morphology, but patient-related factors such as claustrophobia, implanted devices (e.g. cardiac pacemakers) and severely impaired renal function (which is a contraindication for gadolinium-based contrast) may limit its use.
2. Aims

The general aim of this thesis was to further the knowledge of long-term complications in patients with CoA. The specific aims were as follows:

**Paper I** To investigate the prevalence of HTN in adults with repaired CoA, and identify associated factors.

**Paper II** To investigate the prevalence of elevated blood pressure (≥ 140/90 mmHg) among adult patients with repaired CoA who have been diagnosed with HTN, and identify associated factors.

**Paper III** To investigate the prevalence of LVH in adults with repaired CoA, and identify associated factors.

**Paper IV** To investigate height, weight and BMI, as well as the distribution of different BMI classes, in adults with various forms of CHD, including CoA.

**Paper V** To investigate the prevalence of increased left ventricular myocardial ECV in adults with CoA, and to assess the relationship between increased ECV and LVH.
3. Materials and methods

3.1 SWEDCON

Papers I-IV are based on data extracted from the Swedish national register of congenital heart disease (SWEDCON, www.ucr.uu.se/swedcon/). Since 1998, SWEDCON has covered all seven health care regions in Sweden, but registration started even earlier in some centres.

Data collected by each centre contain information on diagnoses, interventions, functional class, symptoms, quality of life (EQ-5D), social variables, electrocardiographs (ECGs), exercise tests, self-reported level of physical exercise, echocardiographies, and medication, as well as on pacemakers/implantable cardioverter-defibrillators (ICDs). At the first entry in the register, information is usually retrospective and based on access to relevant medical records such as surgical notes. After the first entry in the database, further data collection from clinic visits and investigations is prospective.

In the beginning of 2013, the register’s section on GUCH contained data on 9,864 patients. All data collected up to February 17, 2013 were searched in order to obtain data for papers I-IV.

3.2 Study population

Below follows a brief description of the study population for each paper in this thesis.

3.2.1 Papers I-III

The study populations for papers I, II, and III were selected from the same database, originally extracted from SWEDCON (figure 5).

3.2.2 Paper IV

In paper IV, adult patients (≥ 18 years of age) were selected from SWEDCON, grouped by diagnosis. Patients with genetic syndromes, heart transplant recipients, and those with Eisenmenger syndrome were excluded. Subsequently, the diagnoses were further classed as either complex or simple. Upper age limits of 40 and 50 years were applied for complex and simple lesions, respectively. Of the 9,864 patients in the original database extracted from SWEDCON, 2,424 remained for analysis, the majority excluded due to diagnosis and/or age criteria, with only 10 % excluded due to missing data on height and/or weight. Data on 6,849 persons regarding age, weight, height and BMI from the ULF/SILC 2012 survey, were obtained from Statistics Sweden. After stratification for age, data from 4,605 persons remained for use as controls. All data analyses were performed remotely on a server located at Statistics Sweden.
Data on 9,864 GUCH patients were extracted from SWEDCON.

1,026 patients had been diagnosed with CoA.

810 patients remained after those with genetic syndromes such as Turner, and/or complex pathologies such as single ventricle physiology had been excluded.

916 patients were ≥ 18 years old at the last clinic visit with a registered systolic BP.

677 of the remaining patients had previously undergone interventions for CoA.

666 patients remained after excluding 11 patients with their first CoA interventions within 6 months before their clinic visits.

656 patients had sufficient data for determining whether or not they had been diagnosed with HTN.

628 patients were ≥ 18 years old at their last registered echocardiographic examination.

677 of the remaining patients had previously undergone interventions for CoA.

573 patients remained after excluding 55 patients with their echocardiographic examinations within 6 months before the clinic visits.

653 patients remained in the study population for paper I, after excluding 3 patients with insufficient diastolic BP data.

506 patients had echocardiographic data on LVH. These constituted the study population for paper III.

656 patients had sufficient data for determining whether or not they had been diagnosed with HTN.

506 patients had echocardiographic data on LVH. These constituted the study population for paper III.

243 patients had been diagnosed with HTN. These constituted the study population for paper II.

Figure 5. Flow chart of the inclusion and exclusion process generating the study populations for papers I-III. GUCH denotes grown-up congenital heart disease. SWEDCON is the Swedish national register of congenital heart disease. CoA denotes coarctation of the aorta. BP denotes blood pressure. HTN denotes hypertension. LVH denotes left ventricular hypertrophy.

3.2.3 Paper V
The study population for paper V consisted of 21 adult (≥ 18 years old) patients with CoA, referred for CMR with T1 mapping from October 2013 to April 2015.

3.3 ULF/SILC
The national living condition survey (ULF) is performed by Statistics Sweden (www.scb.se), and was initiated in 1975, on behalf of the Swedish Parliament. Since 2008 the ULF and the European Union Statistics on Income and Living Conditions (SILC) are integrated in the survey
ULF/SILC. Telephone interviews are performed annually with 12,000–13,000 randomly selected persons aged 16 and older. The areas covered in the interviews are housing, income, health, leisure, civic activities, social relationships, employment and security.

3.4 Definition of hypertension, diagnosed hypertension and elevated blood pressure
Cases of HTN were defined as (A) previously diagnosed HTN identified by register diagnosis and/or by anti-hypertensive prescription medication—in SWEDCON grouped as beta blockers, ACE-inhibitors, calcium blockers, diuretics, angiotensin II antagonists, or other medications prescribed for systemic HTN; or (B) blood pressure ≥ 140/90 mmHg at the last clinic visit. This broad definition of HTN was chosen to ensure that undiagnosed cases would not be excepted, but since a single increased blood pressure registration is not clinically diagnostic, a more restrictive variable was also created describing diagnosed HTN, i.e. only cases identified by register diagnosis and/or anti-hypertensive prescription medication. In paper I, two sets of logistic regression analyses were performed; identifying factors associated with HTN and diagnosed HTN respectively.

It is generally recommended that blood pressure be measured in both arms in patients with CoA, registering the highest value. The last registered office blood pressures were compared to the recommended target values (i.e. < 140/90 mmHg) and thus defined as being within or above the recommended limits. If either systolic or diastolic blood pressure was found to exceed the currently recommended limits (i.e. being ≥ 140/90 mmHg), the blood pressure was classified as elevated. In cases where only one of the pressures—systolic or diastolic—was available, the blood pressure was classified as elevated if the available pressure exceeded the recommended limits. The comparison was otherwise considered indeterminate and thus classified as missing data.

3.5 Systolic arm-leg blood pressure gradient
The systolic arm-leg blood pressure gradient—the difference between upper and lower extremity blood pressure—was calculated using the registered office data. Negative values, i.e. higher blood pressure in the lower extremity may be expected, and were mainly assumed to signify pulse-wave reflections. Negative values were therefore interpreted as no fall in pressure over the coarctations, i.e. zero gradients.

3.6 Definition of LVH
Data regarding LVH were extracted from echocardiographic examinations reported in SWEDCON. In the register, data on LVH are semi-quantitative and reported as none, mild, moderate, or severe. The classification is
performed at the discretion of the investigator, in line with local routines. In paper III, LVH was defined as the presence of any degree of LVH ranging from mild to severe.

3.7 Cardiovascular magnetic resonance investigations

The investigations described in paper V were performed at 1.5 T (Siemens Healthcare Sector, Erlangen, Germany) using a 32-channel coil. Patients underwent cine SSFP imaging generally including two-, three-, and four-chamber long axis images, and a short-axis stack covering the left ventricle from the apex to the base.

Calculation of left ventricular volumes and mass

Analysis of left ventricular (LV) volumes, ejection fraction (EF) and mass was performed using Segment v1.9 R1942. The delineation of left ventricular endocardial and epicardial borders was performed manually, with measurements of left LVM at end-diastole and end-systole, and expressed as the mean. A difference of less than 5% between end-systolic and end-diastolic mass was accepted, otherwise technical reasons were sought for and corrected. The resulting LVM measurements were indexed to body surface area (BSA) calculated using the Mosteller formula. The left ventricular mass volume index (LVMVI) was calculated using the formula LVMVI = LVM/LVEDV, where LVEDV denotes left ventricular end-diastolic volume.

Measurement of ECV fraction

Quantitative ECV maps were generated inline on the scanner using customized software from T1-maps acquired using a Modified Look-Locker Inversion-recovery (MOLLI) sequence acquired during end-expiratory apnoea before and 15–20 min after injecting 0.1 mmol/kg intravenous Dotarem (gadoterate meglumine) (Guerbet LCC, Villepinte, France) (figure 6). ECV maps were calibrated to blood ECV determined by venous sampling of haematocrit at the time of imaging.

The published upper normal limit for ECV is 30.4% and our own reference (95% upper limit) based on normal subjects is 30.6%. In the study, we decided to use the latter reference derived from the facility where the patients were investigated.
Figure 6. Representative examples of cardiovascular magnetic resonance images from two patients, with a short-axis cine image in end-diastole, and the corresponding myocardial extracellular volume (ECV) image. The top row shows the results from a female patient with a left ventricular mass index of 75 g/m$^2$ and a myocardial ECV of 34 %. The bottom row shows the results from a male patient with a left ventricular mass index of 95 g/m$^2$ and a myocardial ECV of 24 %.

3.8 Statistics
In papers I-III, differences in means and ratios between groups were tested with the Student’s $t$-test, chi square test, or one-way ANOVA as appropriate. Variables for multivariable analysis were selected from those significant in univariate logistic regression, and multivariable logistic regression was performed in a manual backward manner, excluding the variable with highest $p$-value in each step.

In paper IV, differences in means, ranks, and ratios were tested by one-way ANOVA, Kruskal–Wallis test or multifrequency cross-tables. In post hoc mode, the Student’s $t$-test, Mann–Whitney $U$ test, or chi square test were used as appropriate. For multiple-group comparisons, the Bonferroni correction was applied. The effects of variables were tested by univariate and multivariable linear regressions vs. BMI run in a manual backward mode.

In paper V, continuous variables were described in terms of medians and ranges due to the relatively small study population, with differences in rank between groups investigated using the Mann-Whitney $U$ test. Possible correlations were investigated with Spearman’s rank-order correlation.
All calculations in the studies were performed using SPSS 20-23 (IBM, Armonk, NY, USA).

The null hypothesis was rejected for $p$-values < 0.05. Confidence intervals (CIs) are listed at a 95% confidence level.

3.9 Ethics
Papers I-IV are based on register data analyses approved by the Regional Ethical Review Board in Umeå, Sweden (Dnr 08-218 M and 2012-445-32 M).

Paper V describes an investigation approved by the Regional Ethics Review Committee in Stockholm (approval number 2011/1077-31/3). All included patients gave their informed written consent to participate in the study.
4. Results

4.1 Paper I

Of the 653 patients included in the study, 414 (63.4 %) were male. The mean age at the last registered clinic visit was 36.9 ± 14.4 years, the mean age at intervention was 9.5 ± 11.0 years, and the average time between intervention and follow-up was 27.4 ± 12.8 years (table 1). In the entire study population, 344 patients (52.7 %) met the criteria for HTN, and 97/649 patients (14.9 %) had blood pressure exceeding the recommended upper limit (≥140/90 mmHg) despite not having been previously diagnosed with HTN.

Table 1. Patient characteristics in paper I. aTime to follow-up denotes time from first intervention to last clinic visit. bIn the study population, 108 patients had undergone at least one reintervention for CoA, with a total of 131 reinterventions performed. Of these, 34 (26.0 %) were end-to-end anastomoses, 13 (9.9 %) were subclavian flap procedures, 34 (26.0 %) were percutaneous interventions, and 50 (38.2 %) were classified as other reconstructions. cBMI denotes body mass index. dBP denotes blood pressure. Systolic and diastolic blood pressures were measured in the arm. eBP gradient denotes the systolic arm-leg blood pressure gradient as a continuous variable, with negative values defined as no gradient.

The prevalence of HTN was greater among men, and increased with age (figure 7).
To identify factors associated with HTN, variables that were significant in univariate logistic regression were subsequently selected to be included in a multivariable logistic regression. In the final model age (years) (OR 1.07, CI 1.05-1.10), sex (male) (OR 3.35, CI 1.98-5.68) and BMI (kg/m²) (OR 1.09, CI 1.03-1.16) were independently associated with HTN, and so was systolic arm-leg blood pressure gradient, where an association with HTN was found at the ranges (10, 20] and > 20 mmHg, in comparison to the interval [0, 10] mmHg (OR 3.58, CI 1.70-7.55; and OR 11.38, CI 4.03-32.11) (Table 2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Wald</th>
<th>OR</th>
<th>95 % C.I. for OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>414/653</td>
<td>20.28</td>
<td>3.35</td>
<td>1.98</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>653</td>
<td>45.92</td>
<td>1.07</td>
<td>1.05</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>495</td>
<td>7.66</td>
<td>1.09</td>
<td>1.03</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Arm-leg BP gradient ↑</td>
<td>-</td>
<td>28.74</td>
<td>-</td>
<td>-</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>[0, 10] mmHg</td>
<td>347/436</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>[10, 20] mmHg</td>
<td>54/436</td>
<td>11.26</td>
<td>3.58</td>
<td>1.70</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt; 20 mmHg</td>
<td>35/436</td>
<td>21.11</td>
<td>11.38</td>
<td>4.03</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Table 2. Final multivariable logistic regression model, with hypertension as dependent variable. The model includes 377 patients, p < 0.001. BMI denotes body mass index. Arm-leg BP gradient denotes the systolic arm-leg blood pressure gradient as a continuous variable, with negative values defined as no gradient.

Subsequently, the procedure was repeated, excluding all patients who had blood pressure out of range without having been diagnosed with HTN. This
resulted in a similar final model containing the same variables as before (table 3).

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Wald</th>
<th>OR</th>
<th>95 % C.I. for OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>341/552</td>
<td>13.46</td>
<td>3.09</td>
<td>1.69</td>
<td>5.66</td>
</tr>
<tr>
<td>Age (years)</td>
<td>552</td>
<td>51.07</td>
<td>1.09</td>
<td>1.06</td>
<td>1.12</td>
</tr>
<tr>
<td>BMI (kg/m²)¹</td>
<td>424</td>
<td>4.21</td>
<td>1.08</td>
<td>1.00</td>
<td>1.15</td>
</tr>
<tr>
<td>Arm-leg BP gradient²</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>[0, 10] mmHg</td>
<td>300/374</td>
<td>30.71</td>
<td>4.21</td>
<td>1.08</td>
<td>1.15</td>
</tr>
<tr>
<td>(10, 20] mmHg</td>
<td>44/374</td>
<td>11.77</td>
<td>4.36</td>
<td>1.88</td>
<td>10.12</td>
</tr>
<tr>
<td>&gt; 20 mmHg</td>
<td>30/374</td>
<td>23.82</td>
<td>15.15</td>
<td>5.09</td>
<td>45.13</td>
</tr>
</tbody>
</table>

Table 3. Final multivariable logistic regression model, with diagnosed hypertension as dependent variable, excluding all undiagnosed patients with blood pressure ≥ 140/90 mmHg. The model includes 325 patients, p < 0.001. ¹BMI denotes body mass index. ²Arm-leg BP gradient denotes the systolic arm-leg blood pressure gradient as a continuous variable, with negative values defined as no gradient. BP gradient [0, 10] mmHg is used as reference.

### 4.2 Paper II

Of a study population consisting of 243 patients, 27.2 % were female; the mean age was 45.4 ± 15.3 years, with an average of 31.1 ± 16.3 years from first intervention to follow-up, and a total of 7,557 patient years post intervention (table 4). At the last registration, 127 (52.3 %) patients had elevated blood pressure, defined as ≥ 140/90 mmHg.

The prevalence of elevated blood pressure was greater among men. Figure 8 shows the distribution of elevated blood pressure across different age groups.

Figure 8. Percentage of patients with elevated (≥ 140/90 mmHg) blood pressure (BP) in the study population of paper II, grouped by age. The cutoff values for the age quartiles are 32.8, 46.4, and 57.0 years.
Table 4. Patient characteristics in paper II. ¹Time to follow-up denotes time from first intervention to last clinic visit. ²In the study population, 56 patients had undergone at least one reintervention for CoA, with a total of 68 reinterventions performed. Of these, 15 (22.1 %) were end-to-end anastomoses, 5 (7.4 %) were subclavian flap procedures, 19 (27.9 %) were percutaneous interventions, and 29 (42.6 %) were classified as other reconstructions. ³BP gradient denotes the systolic arm-leg blood pressure gradient as a continuous variable, with negative values defined as no gradient.

Patients with elevated blood pressure had, on average, more types of anti-hypertensive medication classes prescribed than those with blood pressure reaching the recommended treatment goals (1.7 ± 1.1 vs 1.5 ± 0.9, p = 0.003). Beta-blockers were the most common anti-hypertensive medication class, prescribed to 144/242 patients (59.5 %), followed by ACE-inhibitors that were prescribed to 92/242 patients (38.0 %) (table 5). In the study population, 16/242 patients (6.6 %) had no pharmacological treatment for HTN, eight of whom had elevated blood pressure.

Table 5. Anti-hypertensive medication in the study population. ¹BP denotes blood pressure.
To identify factors associated with elevated blood pressure, variables that were significant in univariate logistic regression were subsequently included in a multivariable logistic regression analysis. The initial regression included age (years), weight (kg), body mass index (kg/m$^2$), and systolic arm-leg blood pressure gradient (mmHg), but to avoid interactions between weight and body mass index, the multivariable logistic regression analysis was repeated twice with each of these two variables allowed to take precedence over the other. All analyses yielded the same final multivariable model, including age (years) (OR 1.03, CI 1.01-1.06), and systolic arm-leg blood pressure gradient in the ranges (10, 20] mmHg (OR 4.92, CI 1.76-13.79), and $>20$ mmHg (OR 9.93, CI 2.99-33.02), in comparison to the reference interval [0, 10] mmHg (table 6).

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Wald</th>
<th>OR</th>
<th>95 % C.I. for OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>243</td>
<td>7.05</td>
<td>1.03</td>
<td>1.01-1.06</td>
<td>0.08</td>
</tr>
<tr>
<td>Arm-leg BP gradient (mmHg)$^1$</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>[0, 10]</td>
<td>107/156</td>
<td>19.22</td>
<td>-</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(10, 20)</td>
<td>25/156</td>
<td>9.20</td>
<td>4.92</td>
<td>1.76-13.79</td>
<td>0.002</td>
</tr>
<tr>
<td>$&gt;20$</td>
<td>24/156</td>
<td>14.04</td>
<td>9.93</td>
<td>2.99-33.02</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 6. Final multivariable logistic regression model, with blood pressure $\geq 140/90$ mmHg as dependent variable. The model includes 156 patients, $p < 0.001$. $^1$Arm-leg BP gradient denotes the systolic arm-leg blood pressure gradient as a continuous variable, with negative values defined as no gradient. BP gradient [0, 10] mmHg is used as reference.

4.3 Paper III
Within the population of 506 patients, 187 (37.0 %) were female, and the mean age was 35.7 ± 13.8 years with an average of 26.8 ± 12.4 years post coarctation repair (table 7). 114 patients (22.5 %) had LVH (mild 18.4 %, moderate 4.2 %, no severe cases). Patients with LVH were, on average, older, included more men and the interventions on their coarctations had been performed later in life.

Among the patients with diagnosed HTN, beta-blockers were the most commonly prescribed medication type, followed by ACE-inhibitors (table 8). The variable describing the number of anti-hypertensive medication classes prescribed was included in the univariate logistic regressions to show differences in treatment between groups, but not considered an explanatory factor.

Based on univariate analyses, a multivariable logistic regression analysis was performed, yielding a final model in which age (years) (OR 1.03, CI 1.01-1.05), diagnosed HTN (OR 3.02, CI 1.81-5.02), systolic blood pressure (OR 1.02, CI 1.01-1.04), and aortic valve disease (OR 2.17, CI 1.33-3.53) were independently associated with LVH, whereas female sex was negatively associated with LVH (OR 0.41, CI 0.24-0.72) (table 9).
### Table 7. Patient characteristics in paper III.

1. Time to follow-up denotes time from first intervention to last clinic visit.
2. End-to-end anastomosis is used as reference category for type of intervention.
3. BP denotes blood pressure. Systolic and diastolic blood pressures have been measured in the arm.
4. BP arm-leg gradient denotes the systolic arm-leg blood pressure gradient, with negative values defined as no gradient.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>% or mean ± SD</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>187/506</td>
<td>37.0 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>506</td>
<td>35.7 ± 13.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first intervention (years)</td>
<td>506</td>
<td>8.6 ± 10.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to follow-up (years)</td>
<td>506</td>
<td>26.8 ± 12.4</td>
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<tr>
<td>Type of intervention</td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>End-to-end anastomosis</td>
<td>331/506</td>
<td>65.4 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subclavian flap</td>
<td>109/506</td>
<td>21.5 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous intervention</td>
<td>21/506</td>
<td>4.2 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other reconstruction</td>
<td>45/506</td>
<td>8.9 %</td>
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<td>Height (cm)</td>
<td>450</td>
<td>173.8 ± 9.9</td>
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<td>Weight (kg)</td>
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<td>74.4 ± 15.5</td>
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<td>BMI (kg/m²)</td>
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<td>24.5 ± 4.1</td>
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<td></td>
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<tr>
<td>Diagnosed arterial hypertension</td>
<td>175/498</td>
<td>35.1 %</td>
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<tr>
<td>Systolic BP (mmHg)</td>
<td>506</td>
<td>130.3 ± 16.0</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>501</td>
<td>74.7 ± 9.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP arm-leg gradient (mmHg)</td>
<td>367</td>
<td>6.0 ± 9.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of anti-hypertensive medication classes</td>
<td>497</td>
<td>0.6 ± 1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other heart defects</td>
<td>258/506</td>
<td>51.0 %</td>
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</tr>
<tr>
<td>Atrial septal defect</td>
<td>27/506</td>
<td>5.3 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>75/506</td>
<td>14.8 %</td>
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</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>104/506</td>
<td>20.6 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic valve disease</td>
<td>155/506</td>
<td>30.6 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 8. Anti-hypertensive medication among patients with diagnosed arterial hypertension.

<table>
<thead>
<tr>
<th>Anti-hypertensive medication</th>
<th>All patients</th>
<th>Patients without LVH¹</th>
<th>Patients with LVH¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blockers</td>
<td>103/174</td>
<td>59.2 %</td>
<td>58/99</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>63/174</td>
<td>36.2 %</td>
<td>37/99</td>
</tr>
<tr>
<td>Calcium blockers</td>
<td>46/174</td>
<td>26.4 %</td>
<td>20/99</td>
</tr>
<tr>
<td>Diuretics</td>
<td>37/174</td>
<td>21.3 %</td>
<td>18/99</td>
</tr>
<tr>
<td>Angiotensin II antagonists</td>
<td>26/174</td>
<td>14.9 %</td>
<td>8/99</td>
</tr>
<tr>
<td>Other medications prescribed for systemic hypertension</td>
<td>4/174</td>
<td>2.3 %</td>
<td>2/99</td>
</tr>
</tbody>
</table>

### Table 9. Final multivariable logistic regression model, describing factors associated with left ventricular hypertrophy in the entire study population of paper III.

The model includes 498 patients, p < 0.001. BP denotes blood pressure. Systolic blood pressure has been measured in the arm.
Among patients with diagnosed HTN, only systolic blood pressure proved significantly associated with LVH in the final multivariable logistic regression model (OR 1.03, CI 1.01–1.05) (table 10).

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Wald</th>
<th>OR</th>
<th>95 % C.I. for OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)¹</td>
<td>175</td>
<td>8.80</td>
<td>1.03</td>
<td>1.01</td>
<td>1.05</td>
</tr>
</tbody>
</table>

Table 10. Final logistic model describing factors associated with left ventricular hypertrophy among patients with diagnosed arterial hypertension. The model includes 175 patients, \( p = 0.002 \). ¹BP denotes blood pressure. Systolic blood pressure has been measured in the arm.

Among the patients with diagnosed HTN, those with LVH had, on average, more classes of anti-hypertensive medication simultaneously prescribed than those without LVH (1.81 ± 1.05 vs. 1.44 ± 0.87, \( p = 0.015 \)). Patients on beta-blockers, as single or combined treatment, did not differ from other patients with diagnosed HTN, regarding blood pressure (data not shown).

The multivariable logistic regression analysis of factors associated with LVH for patients without diagnosed HTN yielded a final model including female sex (OR 0.22, CI 0.09–0.54), age (OR 1.04, CI 1.01–1.07), and aortic valve disease (OR 3.00, CI 1.47–6.11) (table 11).

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Wald</th>
<th>OR</th>
<th>95 % C.I. for OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>137/323</td>
<td>10.62</td>
<td>0.22</td>
<td>0.09</td>
<td>0.54</td>
</tr>
<tr>
<td>Age (years)</td>
<td>323</td>
<td>5.70</td>
<td>1.04</td>
<td>1.01</td>
<td>1.07</td>
</tr>
<tr>
<td>Aortic valve disease</td>
<td>89/323</td>
<td>9.10</td>
<td>3.00</td>
<td>1.47</td>
<td>6.11</td>
</tr>
</tbody>
</table>

Table 11. Final multivariable logistic model describing factors associated with left ventricular hypertrophy among patients without diagnosed arterial hypertension. The model includes 323 patients, \( p < 0.001 \).

Post hoc, a univariate logistic regression analysis was performed, with the variable describing systolic blood pressure divided into quartiles. It was shown that, compared to the first quartile (< 120 mmHg), both the third ([130, 140] mmHg) and forth quartile (> 140 mmHg) were associated with LVH (OR 2.23, CI 1.05–4.73; and OR 8.02, CI 3.76–17.12, respectively) (table 12).
### Table 12. Logistic regression describing the association between left ventricular hypertrophy and systolic blood pressure, with the blood pressure divided into quartiles based on rank. The lowest quartile (< 120 mmHg) is used as reference. The model includes 506 patients, p < 0.001. p-values indicating significant outcomes are typed in bold.

<table>
<thead>
<tr>
<th>Systolic blood pressure</th>
<th>n</th>
<th>Wald</th>
<th>OR</th>
<th>95 % C.I. for OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 120 mmHg</td>
<td>100/506</td>
<td>43.73</td>
<td>1.70</td>
<td>0.76-3.82</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>[120, 130) mmHg</td>
<td>126/506</td>
<td>1.64</td>
<td>2.23</td>
<td>1.05-4.73</td>
<td>0.020</td>
</tr>
<tr>
<td>[130, 140) mmHg</td>
<td>176/506</td>
<td>4.40</td>
<td>8.02</td>
<td>3.76-17.12</td>
<td>&lt; 0.036</td>
</tr>
<tr>
<td>&gt; 140 mmHg</td>
<td>104/506</td>
<td>28.95</td>
<td>-</td>
<td>-</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**4.4 Paper IV**

There were no differences in height, weight and BMI between patients with CoA and controls, stratified for sex (table 13).

Men with complex heart lesions had higher prevalence of underweight, and lower prevalence of underweight compared with controls. This pattern was not seen in women with corresponding congenital heart disease.

In regression analysis, age was associated with higher BMI both for patients with complex and simple congenital heart disease.

<table>
<thead>
<tr>
<th></th>
<th>Controls Mean ± SD</th>
<th>CoA Mean ± SD</th>
<th>t-test</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>180.7 ± 6.8</td>
<td>179.6 ± 6.8</td>
<td>0.13</td>
<td>0.50</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.0 ± 13.5</td>
<td>81.2 ± 15.9</td>
<td>0.50</td>
<td>0.99</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.4 ± 3.8</td>
<td>25.2 ± 4.6</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.6 ± 6.6</td>
<td>165.1 ± 7.2</td>
<td>0.054</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.2 ± 12.3</td>
<td>65.5 ± 13.6</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9 ± 4.2</td>
<td>24.0 ± 4.6</td>
<td>0.99</td>
<td></td>
</tr>
</tbody>
</table>

**Table 13. Height, weight, and body mass index (BMI) among men and women aged 18-50 years.** A reference population is compared to patients with coarctation of the aorta (CoA). All p-values have undergone Bonferroni correction for multiple comparisons.

**4.5 Paper V**

In the study, 7 of the 21 included patients (33.3 %) were female, and the median age in the population was 28.5 (19.1-65.1) years. The median myocardial ECV was 29.0 (22.0-35.0), and 6 patients (28.6 %) were found to have an ECV exceeding the previously determined upper normal limit (30.6 %). Eighteen patients (85.7 %) had previously undergone surgical repair of CoA, with the median age at repair being 4.8 (0.0-31.4) years (table 14).

Patients with increased myocardial ECV did not differ from the rest of the study population in terms of age, age at intervention, blood pressure, or functional parameters such as left ventricular volumes or EF (p > 0.05 for all), whereas there were more women than men in the group with increased
ECV (83%, $p = 0.002$). The median ECV was 32.0 (27.0-35.0) % for women, and 29.0 (22.0-33.0) % for men ($p = 0.026$). Myocardial ECV did not correlate with LVM (r = -0.224, $p = 0.357$), and left ventricular function was predominantly normal in the study population, with only one patient having impaired left ventricular function, and this impairment being classified as mild.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>% or median (interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General medical demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (female)</td>
<td>7/21</td>
<td>33.3 %</td>
</tr>
<tr>
<td>Age (years)</td>
<td>21</td>
<td>28.5 (19.1-65.1)</td>
</tr>
<tr>
<td>Repaired CoA</td>
<td>18/21</td>
<td>85.7 %</td>
</tr>
<tr>
<td>Age at repair (years)</td>
<td>18</td>
<td>4.8 (0.0-31.4)</td>
</tr>
<tr>
<td>Type of repair</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Subclavian flap</td>
<td>3/18</td>
<td>16.7 %</td>
</tr>
<tr>
<td>End-to-end anastomosis</td>
<td>10/18</td>
<td>55.6 %</td>
</tr>
<tr>
<td>Graft</td>
<td>2/18</td>
<td>11.1 %</td>
</tr>
<tr>
<td>Balloon angioplasty with stent implantation</td>
<td>3/18</td>
<td>16.7 %</td>
</tr>
<tr>
<td>Reintervention</td>
<td>4/18</td>
<td>22.2 %</td>
</tr>
<tr>
<td>Age at reintervention (years)</td>
<td>4</td>
<td>14.8 (3.2-50.1)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>21</td>
<td>171.0 (152.0-196.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>21</td>
<td>71.0 (50.0-112.0)</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>21</td>
<td>22.2 (18.4-31.0)</td>
</tr>
<tr>
<td>Systolic BP, arm (mmHg)$^3$</td>
<td>19</td>
<td>141.0 (89.0-198.0)</td>
</tr>
<tr>
<td>Diastolic BP, arm (mmHg)$^3$</td>
<td>19</td>
<td>80.0 (54.0-116.0)</td>
</tr>
<tr>
<td>Systolic arm-leg BP gradient (mmHg)$^3$</td>
<td>21</td>
<td>10.0 (0.0-55.0)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>13/21</td>
<td>61.9 %</td>
</tr>
<tr>
<td>Signs of LVH on ECG$^4$</td>
<td>3/21</td>
<td>14.3 %</td>
</tr>
<tr>
<td>Smoking$^5$</td>
<td>2/21</td>
<td>9.5 %</td>
</tr>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired left ventricular function$^6$</td>
<td>1/21</td>
<td>4.8 %</td>
</tr>
<tr>
<td>Mechanical aortic valve prosthesis$^7$</td>
<td>2/21</td>
<td>9.5 %</td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>10/21</td>
<td>47.6 %</td>
</tr>
<tr>
<td>Maximum velocity in aorta descendens (m/s)</td>
<td>18</td>
<td>2.7 (1.3-3.6)</td>
</tr>
<tr>
<td>Peak gradient over the aortic valve (mmHg)</td>
<td>18</td>
<td>28.0 (7.0-51.0)</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
<td>7/21</td>
<td>33.3 %</td>
</tr>
<tr>
<td><strong>CMR examination</strong></td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>LVEDV (ml)$^9$</td>
<td>20</td>
<td>176.5 (106.0-261.0)</td>
</tr>
<tr>
<td>LVESV (ml)$^{10}$</td>
<td>20</td>
<td>73.0 (40.0-121.0)</td>
</tr>
<tr>
<td>EF (%)$^{11}$</td>
<td>20</td>
<td>58.2 (49.4-69.0)</td>
</tr>
<tr>
<td>LVM (g)$^{12}$</td>
<td>19</td>
<td>128.0 (64.0-235.0)</td>
</tr>
<tr>
<td>LVM/BSA (g/m$^3$)$^{13}$</td>
<td>19</td>
<td>71.5 (44.0-99.6)</td>
</tr>
<tr>
<td>LVMVI (g/ml)$^{14}$</td>
<td>19</td>
<td>0.8 (0.6-1.1)</td>
</tr>
</tbody>
</table>

Table 14. Patient characteristics in paper V. $^1$Age denotes age at CMR examination. $^2$BMI denotes body mass index. $^3$BP denotes blood pressure. $^4$ECG denotes electrocardiography. $^5$No previous smokers were present in the study population. $^6$The term impaired left ventricular function only describes mild disease, as no moderate or severe cases were present in the study population. $^7$No biological aortic valve prostheses were present in the study population. $^8$The term aortic regurgitation includes mild (6 patients) and moderate (1 patient) cases, but no severe. $^9$LVEDV denotes left ventricular end-diastolic volume. $^{10}$LVESV denotes left ventricular end-systolic volume. $^{11}$EF denotes ejection fraction. $^{12}$LVM denotes left ventricular mass. $^{13}$BSA denotes body surface area. $^{14}$LVMVI denotes left ventricular mass volume index.
In post hoc analyses, male and female patients were compared with regards to LVM, both in absolute terms and indexed to BSA and end-diastolic volume, respectively. Men were found to have greater LVM in all three cases. Without indexation, the median LVM was 141.0 (123.0-235.0) g for men vs. 105 (64.0-127.0) g for women ($p = 0.001$); indexed to body surface area, the median LVM/BSA was 73.5 (64.0-99.6) g/m² for men vs. 62.4 (44.0-74.9) g/m² for women ($p = 0.035$); and, with the mass indexed to end-diastolic volume, LVMVI was 0.8 (0.6-1.1) g/ml for men vs. 0.7 (0.6-0.8) g/ml for women ($p = 0.028$).

In the study population, LVM/BSA exceeded the normal reference intervals for sex and age in 3/19 cases (16%). However, myocardial ECV did not correlate with LVM/BSA ($r = -0.184$, $p = 0.450$), nor was increased ECV associated with increased LVM/BSA when analysed as nominal variables ($p = 0.943$).
5. Discussion

5.1 Hypertension and elevated blood pressure

In paper I we showed that more than half of the included patients had HTN and HTN was associated with age, sex, BMI, and systolic arm-leg blood pressure gradient. This result was valid both when we included patients with only elevated blood pressure—i.e. patients that were not diagnosed or treated for HTN but had elevated blood pressure in clinic—and when these patients were excluded from the analyses. In epidemiologic investigations, single blood pressure measurements are often included in the definition of HTN\textsuperscript{90}, while a single elevated blood pressure recording is not sufficient to clinically diagnose a patient with HTN. We found that both sets of analyses led to the same final model, suggesting a similarity between the patients with diagnosed HTN and the undiagnosed patients who nevertheless had elevated blood pressure. It seems likely that many of the undiagnosed patients have since been diagnosed with HTN and treated, but no such data was available in the study. Nevertheless, our data confirm the strong association between CoA and HTN, and also indicate that a significant proportion of patients may have undiagnosed HTN.

In paper II we further analysed the control of blood pressure among patients with diagnosed HTN. Approximately half of the patients had blood pressure exceeding the treatment goals, despite the majority being prescribed anti-hypertensive medication. On average, they were treated with more types of anti-hypertensive medication classes than the patients with blood pressure within the target range. This indicates that they were under more intense treatment, but still did not reach the target blood pressure. It might be that the form of HTN observed in these patients differs from essential HTN in patients without CoA, but the data is still limited.

The large prevalence of elevated blood pressure is especially noteworthy, given that elevated blood pressure, in a relatively young population such as this, can act upon the cardiovascular system over long periods of time. The relative youth of the studied population, but long follow-up time from the first intervention, might in part explain why systolic blood pressure in paper III was found to be associated with LVH even within the current normal range.

As shown, HTN is an important reason for close monitoring of patients with CoA after successful intervention. There may be many patients at risk, and suboptimal treatment results appear to be common. Groups at risk can be identified, i.e. men, older patients, those with a residual systolic arm-leg blood pressure gradient, and patients with higher BMI. This information can therefore be used for risk stratification, and possibly also for intervention.
5.2 Left ventricular hypertrophy
Before the introduction of surgical techniques for correcting significant CoA, patients often died from left ventricular failure secondary to increased afterload. Even though treatments for CoA have been available for more than seven decades, LVH remains a concern for approximately one quarter of all patients with CoA. The long-term clinical significance of such hypertrophy in young and middle-aged patients is largely unknown, but treatments targeting and preventing development of increased LVM are likely justifiable, in order to prevent cardiovascular morbidity. Similarly, a reduction in LVM is an identified favourable prognostic marker during treatment of essential HTN, where LVH is considered a target organ injury.

The prevalence of LVH found in paper III (22.5 %) is essentially consistent with previous findings in similar populations, i.e. adults with repaired CoA, where the prevalence of LVH has varied between approximately one fourth and one half of the patients, depending on patient selection and the definition of LVH used. Our study was multi-centre in its design, had no obvious selection bias of patients and, importantly, represented a large number of patients with long follow-up; 13,561 patient-years after intervention. Based on the acquired data, every fourth to fifth patient in this young population is exposed to the long-term risks associated with established LVH.

We found that age, male sex, diagnosed HTN, systolic blood pressure and aortic valve disease all were independently associated with LVH in the total study population. However, among patients with diagnosed HTN, only the systolic blood pressure was associated with LVH. Finally, when the systolic blood pressure was stratified into quartiles, the association with LVH remained in the range [130, 140] mmHg, i.e. within the current target range. This analysis was performed post hoc in univariate mode, but a similar direction in target levels of blood pressure has recently been observed in a large randomised clinical trial. Lower target levels may be recommended in the future, but, at present, 140/90 mmHg applies for uncomplicated essential HTN and CoA alike.

5.3 Extracellular volume fraction
As shown in paper V, increased left ventricular myocardial ECV was common among adults with CoA. Over one quarter (28.6 %) of the patients included in the study had ECV exceeding the normal limits, and among these, there was an overrepresentation of women. However, no associations were found between increased left ventricular myocardial ECV and other tested variables, such as age or HTN, even though an association between ECV and age has previously been observed in patients with “normal-appearing” myocardium. 

It is known that increased ECV is a sign of diffuse fibrosis in the myocardium, which in itself has been found in several cardiovascular pathologies including ischemic heart failure\textsuperscript{38}, aortic stenosis\textsuperscript{39}, idiopathic dilated cardiomyopathy\textsuperscript{40}, and hypertrophic cardiomyopathy sarcomere mutation carriers without LVH\textsuperscript{41}. It has also been shown that myocardial ECV tends to be increased in unspecified adult congenital heart disease\textsuperscript{42}, suggesting a similar diffuse extracellular remodelling process as seen in acquired heart failure. Associations have also been found between increased ECV in CHD, and functional parameters such as end-diastolic volume index and EF\textsuperscript{42}. However, in our study population, functional parameters were predominantly normal, and we found no association between increased ECV and left ventricular dysfunction. Also, we did not find any association between increased ECV and LVH despite 16 % of the included patients having an indexed LVM exceeding the normal reference range for their age and sex.

One might speculate that our findings suggest a high prevalence of preclinical myocardial disease in women with CoA, but due to the cross-sectional nature of the study, this possibility could not be investigated further, as no follow-up data was available.

5.4 Age
There was a relationship between increasing age and HTN, but it is noticeable that age at the first intervention for CoA was not associated with HTN in the multivariable models of paper I, despite showing an association in the univariate analyses. Previous studies have reached varying conclusions regarding the importance of age at intervention, with some studies having suggested that late intervention is an important, or even the most important, predictor for the development of HTN in patients with CoA\textsuperscript{67, 91, 102, 104, 105}; and others having provided models in which age at intervention is not significantly associated with HTN\textsuperscript{101, 103}.

Our data suggest that age at intervention is indeed less important than age at follow-up. Since the patients in paper I had been followed for three decades after their original interventions, the results might suggest that an early intervention provides a beneficial effect in the years immediately following intervention, but that this effect eventually fades with increasing age.

In paper II it was shown that among patients with diagnosed HTN, age was one of two identified factors independently associated with elevated blood pressure. Importantly, HTN in the study population of paper I was much more prevalent at younger ages, compared to cohorts of essential HTN\textsuperscript{137, 143}.

Age was also found to be associated with LVH in paper III, which is interesting, considering that it has previously been shown that LVM in
healthy subjects generally tends to decrease with increasing age\textsuperscript{131}. However, since LVH can be regarded as a physiological response to long-term myocardial strain, one might speculate that the age variable in this case represents the time needed for elevated intracardiac pressure to affect the myocardium, despite the statistical independence from both blood pressure and aortic valve disease.

5.5 Sex
As shown in paper I, not only were there more men in the study population of adults with repaired CoA, but male patients also had a greater prevalence of HTN.

Additionally, men were more likely to have LVH, as shown in paper III. In some part, this is likely due to the greater prevalence of HTN in men, but it is worth noting that sex and HTN were both independently associated with LVH in the entire study population. Also, when excluding patients with diagnosed HTN from the analysed population, male sex still proved associated with LVH, suggesting that sex is indeed relevant for LVH in these patients regardless of other factors.

Since we found greater prevalence of both HTN and LVH in male patients, it might have been reasonable to also expect a greater prevalence of increased left ventricular ECV in men rather than in women, but, as paper V shows, that was not the case. Increased ECV was more common in women, with five out of seven women in the study having increased ECV, and the mean ECV of the female patients consequently being above the upper normal limit.

Of all the various factors included in the analyses for paper V, only female sex was associated with increased ECV, and the reason for this is not apparent. It might be speculated that the difference in ECV between male and female patients in the study could be related to the fact that women, on average, have thinner ventricular walls than men, which can affect the outcome of the ECV measurement. However, in this population, we found no correlation between LVM and ECV.

5.6 Aortic valve disease
Aortic valve disease may cause LVH by increasing the intracardiac systolic pressure, or by causing volume overload. Aortic valve disease is also common in patients with BAV, which, in turn, is found in 60-85 % of the patients with CoA\textsuperscript{48-50}.

In the relatively young population studied in paper II, aortic valve disease was common, but generally mild or moderate, which does not usually meet intervention criteria for long periods of time. However, when valve dysfunction is present, lesser severity does not necessarily protect the left ventricle from developing signs of pressure or volume overload. In a young
patient, the pressure or volume overload may act over long periods of time, with the aortic valve’s function deteriorating until the criteria for aortic valve repair are eventually met.

Repair of the aortic valve is usually performed when the patient has symptoms, and/or based on left ventricular size, functional criteria, or degree of aortic stenosis. It has been shown that moderate aortic lesions, not yet requiring intervention, are associated with LVH in patients with repaired CoA.

In addition, the presence of a valve prosthesis may still be a factor associated with LVH, as mechanical valves, usually offered to young patients, still tend to yield some transvalvular gradient. Also, a patient with aortic valve prosthesis may have remaining LVH, originally developed before the prosthesis was implanted.

5.7 Systolic arm-leg blood pressure gradient
The systolic arm-leg blood pressure gradient was associated with both HTN, and elevated blood pressure in patients with diagnosed HTN. This association was seen even for gradients within the range (10, 20] mmHg, and there was no difference in the prevalence of HTN between patients with recorded gradient data and those without. These findings are consistent with a previous study that shows an independent association between mild residual descending aortic narrowing in patients with repaired CoA, and mean daytime blood pressure.

It is tempting to suggest a causal relationship between gradient and HTN resistant to treatment, but it is also important to remember that we do not yet know whether the gradient itself is the culprit or merely the result of unfavourable vascular mechanics. Furthermore, we do not have data on collateral circulation.

5.8 Body mass index
In paper I, we found an association between increased BMI and HTN, but despite the high prevalence of HTN in adults with CoA, paper IV showed no difference in BMI between patients with CoA and the reference population. Thus, the previously reported increased BMI in patients with CoA could not be confirmed. Also, the average BMI in the study population for paper I was only 24.9 kg/m², which is generally classified as being within the normal range. It might be speculated that adults with repaired CoA are even more sensitive to increased BMI than the general population.
5.9 Limitations

Papers I-IV are based on data from a national register. As with most register data, there is concern on how well the register covers the population, and, in incomplete coverage, which patients/conditions/events might not be accurately represented.

The number of adults with CHD in SWEDCON’s section on GUCH was somewhat lower than expected, considering that the global prevalence of CHD has been estimated at approximately 0.3 % of the adult population\textsuperscript{16}, but this may be a result of some relatively uncomplicated lesions, such as VSD, being followed elsewhere, if at all.

In its current form, the register has expanded outside the university hospitals, but there is no obvious reason to suspect any relevant selection bias, except for a possible underrepresentation of the most uncomplicated lesions and corrected shunts. Most patients with more complicated lesions are expected to be followed in a university hospital, and the catch areas of the Swedish university hospitals are relatively small, from an international perspective.

In the register, the amount of missing data was relatively large, but while additional data is desirable from a scientific standpoint, making data entry into the register more demanding, might, in itself, introduce a selection bias to the process. In order to reduce missing data in this thesis, we decided to use data from the last visit with a systolic blood pressure recording, rather than the chronologically last visit.

Papers I-III describe retrospective register studies, analysing data from the last clinic visits where systolic BP measurements were available. The blood pressure measurements and medications prescribed were therefore those recorded at these visits. While single office blood pressure measurements are less reliable than 24-hour registrations, it has previously been shown that elevated office blood pressure is associated with LVH in patients with repaired CoA\textsuperscript{106}. The extracted database contained data regarding the number of anti-hypertensive medication classes, but there was no data available regarding dosage, or whether the treatment had recently been initiated or adjusted, and we did not have access to information pertaining to further attempts at treatment. Therefore, we chose to mainly focus our analyses on other factors than pharmacological treatment. However, the number of simultaneously prescribed antihypertensive medication classes still provides a rough measure of the intensity of the treatment, albeit not with details on actual dosage.

The register did not include data pertaining to anatomy of the aortic arch, which might otherwise have been included in the analyses since previous studies have shown an association between late HTN and an angulated aortic arch in patients with repaired CoA\textsuperscript{148}. However, while our studies did not include anatomical data regarding the area of the previously treated
coarctation, the systolic arm-leg BP gradient can be considered to indirectly provide some information regarding the post-interventional aortic anatomy. We did not have access to data regarding cardiovascular risk factors such as hyperlipidaemia or diabetes mellitus, and while the register did contain some information regarding smoking habits, the variable was excluded due to large amounts of missing data.

Since the classification of LVH in SWEDCON is performed at several sites with different local routines, there is no predefined method recommended. Furthermore, a register with the ambition of long-term follow-up must be designed to allow future developments of methods. Therefore, data on LVH are categorised to compensate for different methodologies, present and future.

A relatively small number of patients (n = 21) were included in the study population of paper V, limiting the statistical power of the analyses. Again, the study was cross-sectional, and it was therefore not possible to follow the patients over time. Consequently, no assessment could be made regarding whether increased ECV in these patients might provide prognostic information on development of decreased left ventricular function over time.

The patients included in the study detailed in paper V had all been clinically referred for CMR, and had no contraindications for either CMR or the use of intravenous contrast, possibly resulting in a selection bias.

5.10 Clinical implications
Several factors associated with adverse conditions in adult patients with repaired CoA have been identified in these studies. BMI and aortic valve disease are both potentially modifiable traits, but especially interesting are the factors that were relevant even within their current normal ranges, such as systolic arm-leg blood pressure gradient.

Current guidelines recommend that all patients with a non-invasive systolic blood pressure gradient > 20 mmHg between upper and lower limbs, regardless of symptoms but with upper limb HTN, pathological blood pressure response during exercise, or significant LVH should be considered for reintervention\textsuperscript{74}. It has been suggested that a lower threshold for reintervention of aortic narrowing might be desirable\textsuperscript{103}, and our findings lend support to this suggestion. Papers I and II showed that both HTN and elevated blood pressure in patients with diagnosed HTN, were associated with the systolic arm-leg blood pressure gradient, even for gradients within the range (10, 20] mmHg.

It is worth noting that the current guidelines were originally established at a time when most reinterventions for CoA were surgical in nature, with all the risks thoracic surgery entails, as well as uncertain effects on small gradients, and frequent need for prosthetic material. It is possible that a new
risk-benefit analysis in light of the new findings, and the current access to catheter-based techniques, may yield a different conclusion. There may therefore be reasons to consider reintervention at even smaller systolic arm-leg blood pressure gradients than currently recommended, although further studies are necessary before any such conclusions can be reached. Presently, we do not know if treating a small residual gradient will affect either the current blood pressure level or the future progression to HTN, especially since stent-based interventions may also contribute to aortic stiffness.

The current guidelines on blood pressure control recommend that the treatment of HTN should aim to keep the pressures below 140/90 mmHg. However, we found an association between systolic blood pressure in the high normal range and LVH, suggesting that adult patients with CoA and HTN may still be at an increased risk of developing LVH, even when considered adequately treated with regards to blood pressure. This is especially noteworthy considering that a recent randomised trial on patients ≥ 50 years old with HTN and high risk for cardiovascular events (but without diabetes) showed that targeting a systolic blood pressure of < 120 mmHg, in comparison to < 140 mmHg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause. Since a similar randomised trial with mortality as endpoint would likely be difficult to perform on patients with CoA on a large scale, it seems reasonable to assume that, should the target value for systolic blood pressure be lowered in high-risk patients with HTN, it might be beneficial to count patients with CoA among them.

The large number of patients with diagnosed HTN and elevated blood pressure in paper II further stresses the need for anti-hypertensive treatment in these patients, and suggests that current treatment regimens might not be entirely adequate.

We showed that BMI was associated with HTN in patients with CoA, although in paper IV, BMI did not differ from controls on a group level. Our cohorts of patients with repaired CoA were, on average, noticeably younger than those generally studied in HTN-trials. If not kept within acceptable levels, elevated blood pressure may therefore act on the cardiovascular system for large parts of the patients’ lives. Awareness of the potential risks with increased BMI, and targeted advice, may therefore be advised for patients with CoA.
5.11 Future studies

Based on the work in this dissertation, several suggestions for future studies have emerged:

- SWEDCON contains data on aortic measurements which could be used to investigate the prevalence of aortic dilatation in adults with repaired CoA, and identify associated factors.

- Algorithms for blood pressure monitoring and adjustment of treatment could be tested in randomised trials. Adjustment of treatment based on blood pressure recording at home, and support using mobile applications may be more successful than standard treatment.

- A randomised trial could be performed on adults with repaired CoA and HTN, investigating the effects of lowering the target value for systolic blood pressure. While it might not be feasible to use standard endpoints such as mortality or other major cardiovascular events as endpoints in a small population, changes in surrogate endpoints such as left ventricular function and mass could be studied, and the development or regression of LVH could be used as an observed outcome.

- In order to examine body composition, especially in males with complex cardiac lesions, studies with dual-energy x-ray absorptiometry have been initiated.

- An investigation of ECV similar to the study described in paper V could be performed on a larger study population of patients with CoA, as well as on populations with other forms of CHD. Such a study could also be longitudinal, investigating whether patients with increased ECV are at greater risk of developing left ventricular dysfunction or LVH.
6. Conclusions

**Papers I-II**  Hypertension (HTN) was common in adult patients with repaired coarctation of the aorta (CoA), and many patients diagnosed with HTN were found to have blood pressure exceeding the recommended limits, despite seemingly rigorous pharmaceutical treatment. Body mass index (BMI) and systolic arm-leg blood pressure gradient were associated with HTN—both factors potentially modifiable as a means of treatment or prevention—and the gradient was also associated with elevated blood pressure among patients with HTN. Systolic arm-leg blood pressure gradient was shown to be of significance, even within what the current guidelines consider an acceptable range.

**Paper III**  Left ventricular hypertrophy (LVH) was common in adult patients with repaired CoA. Potentially modifiable factors associated with LVH were systolic blood pressure and aortic valve disease. Systolic blood pressure was shown to be univariately associated with LVH in the high normal range.

**Paper IV**  We found no general difference in height, weight, or BMI between patients with CoA and a normal reference population.

**Paper V**  Increased myocardial extracellular volume (ECV) was common among adults with CoA, especially in women. There was no correlation between ECV and LVH.
7. Acknowledgements

This work was supported by the Swedish Heart and Lung Foundation, the Heart Foundation of Northern Sweden, the research foundation of The Swedish Heart and Lung Association, the research foundation of Healthcare Professions within Cardiology, Umeå University, Karolinska Institutet, the County Council of Västerbotten, and the Stockholm County Council.

I wish to express my deepest gratitude to all my friends and family, and to everyone who has helped make this thesis possible. You are far too many to list, but I would especially like to thank the following:

My main supervisor Bengt Johansson. No one could ask for a better mentor. Thank you so much for all the knowledge you have shared, for always being available when I've needed your help, and for your boundless support and enthusiasm on this journey. You are a true role model, both as a scientist and as a teacher.

My co-supervisors: Michael Henein for your support and encouragement while I was learning the ropes, and Martin Ugander for all your help with the papers and thesis, as well as your impressive knowledge of all things CMR. I truly admire your expertise.

My brilliant and very well-organised co-author Camilla Sandberg for all your invaluable help, both with the papers, and while writing this thesis.

My other co-authors Mikael Dellborg, Ulf Thilén, Peder Sörensson, Niels-Erik Nielsen, Christina Christersson, and Karin Wadell for all your contributions to the papers we have written together.

Jenny Rasck, Sofie Olsson, and Karin Bouma, for expert help with image acquisition for paper V.

Stefan Söderberg and Gunnar Engström for your assistance with the statistics when I was first starting out.

Eva Jonasson, Stina Jakobsson and all the other personnel at the fourth floor, for all your help.

Erling and the wonderful staff at the hospital’s coffee shop. Without you, this thesis would have taken twice as long to write.
All members of MESK and Umespexarna, past and present. Where would I be without you, my friends?

**Hanna Israelsson**, for support and sound advice on how to plan writing my thesis (advice that I, in retrospect, really should have followed more closely).

My dear friends and fellow gamers **Björn Sjöström**, **Cristian Brändström**, **John Gustafsson**, **Jonas Molin**, **Martin Kristiansen**, and **Tomas Häggström**. Keep on rolling!

My parents **Siv** and **Ove Rinnström** for believing in me, and for always being there. I have had a love for science for as long as I can remember, and it was your encouragement that set me on this path.

My sister **Helena**, my brother-in-law **Benny**, and their wonderful children **Ellen** and **Ebbe**. Thank you for all the dinners. I suspect that even I could not have survived on coffee alone.

And finally, I would like to thank my grandmother **Margit Hedlund**. It feels like it was only yesterday we stayed up all night watching action movies. I will miss you always.
8. References


19. Gatzoulis MA, Webb GD, Daubeny PEF. Aortic Coarctation and Interrupted Aortic Arch. In. Diagnosis and Management


21. Morgagni JB. *De sedibus et causis morborum. Epist. XVIII, Article 6*; 1760.


40. Beekman RH, Muller DW, Reynolds PI, Moorehead C, Heidelberger K, Lupinetti FM. Balloon-expandable stent treatment of experimental coarctation of the aorta: early


86. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies C. Age-specific relevance of usual blood


131. Maceira AM, Prasad SK, Khan M, Pennell DJ. Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance. Journal of


