Congenital Malformations of the Aortic Arch and Isthmus

A retrospective study of 588 patients undergoing surgery for Aortic Coarctation or Interrupted Aortic Arch at Rikshospitalet from 1971 to 2001

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Abstract

Bakcground: This quality-control study includes patients operated for Coarctation of the Aorta or Interrupted Aortic Arch at Rikshospitalet between 1971 and 2001 to give a comprehensive presentation of the material and identify predictors for death and for re-operation free survival

Methods: 588 patients were identified, information was obtained from databases, registries and patient records, then analyzed with Kaplan-Meier, univariate and multivariate regression analysis to identify risk factors.

Results: Fwup completeness was (99,3%), median fwup time was 19,15 years. There were 348 boys (59,2%) and 240 girls (40,8%), 425 had isolated CoA (72,2%), 108 had hypoplasia (18,4%), 55 had IAA (9,4%) Age at initial repair was <1 month in 244 (41,5%), between 1 month and one year in 126 (21,4%), >1 year in 218 (37,1%). 330 was considered to be in comorbidity group I (56,1%), 130 in group II (22,1%), 128 in comorbidity group III (21,8%) There were 59 early deaths (9,4%) and a total mortality of 20,6%. Operation in early time period, comorbidity group III, median sternotomy approach and surgery in the neonatal period predicted death. 113 patients (19,2%) were re-operated at a median time of 8,09 years after initial surgery. Re-operation free survival was 55% 30-35 after inital repair. Risk factors for death or re-operation was early time period, hypoplasia, interrupted arch, group III comorbidity and repair at neonatal age.

Conclusions: Mortality after surgical repair of Coa and IAA is linked to coexisting cardiac malformations. Hypoplasia of the aortic arch strongly predispose for re-operation.

Preface

Malformations of the aortic arch and isthmus aortae is quite common congenital heart defects connected to coarctation of the aorta or interrupted aortic arch, and more generally linked to cardiac malformations with decreased left ventricular output, creating less than normal flow in the aortic arch and isthmus. The spectre of malformation stretching from Coarctation of the aorta with a nearly normal aortic arch, via the hypoplastic arch to the total interruption of the aortic arch, the main fraction being those with coarctation. In the treatment of the coarctation there has traditionally been and still are a great diversity of operative techniques to choose among, and quite a few subjects of conflict when it comes to what is the optimal treatment. One topic of controversy and extensive disagreement is whether or not to directly address the concomitant arch underdevelopment, and to what extent theese malformations repairs itself when normal bloodflow is restored. Hence, the focus of the background chapter is on Coarctation and the hypoplastic arch, and not to the same extent the interrupted arch.

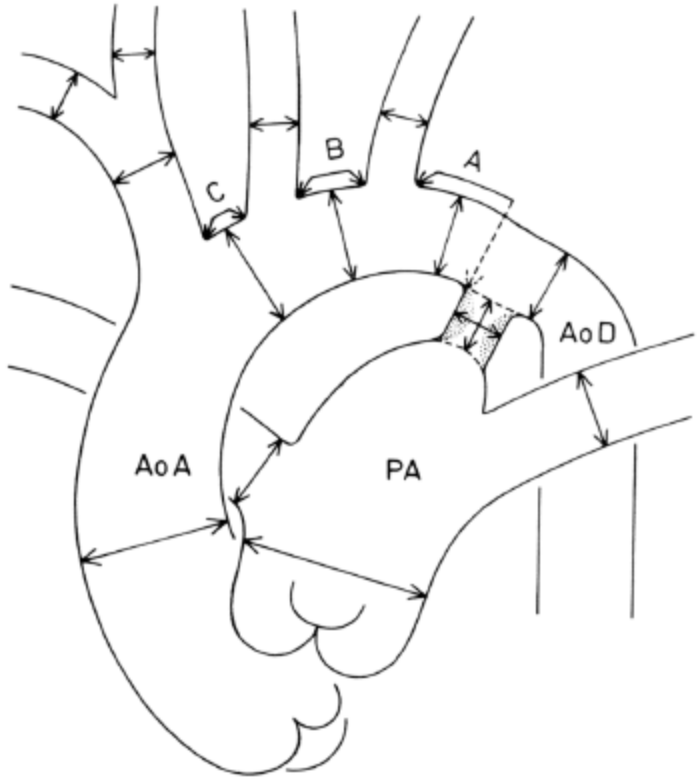
The main part of this medical student project is a study of 588 patients operated for Coarctation of the aorta or Interrupted aortic arch in the time period between 1971 and 2001, undergoing a total of 720 operations. As it spans thirty years of surgery with great progress in pre-, per- and post-operative care, much of the purpose of the study is to sum up theese differences evolvingh throughout the time period, and look for factors associated with decreased survival and the risk or re-operations, using survival and re-operation free survival as end-points. Due to the ongoing debate about those patients with aortic arch hypoplasia, this is one of the main topics of focus in this study as well.

Contents

1 Background

1.1 Proximal Aortic Anatomy

The aortic arch consists of an ascending part of the arch, which starts at the level of the aortic valve, and ends at the origin of the innominate artery, also known as the brachiocephalic artery. The transversal part of the aortic arch consists of a proximal segment (C on figure 1), which is between the innominate artery and the left carotid artery, and a distal segment (B on figure 1) that refers to the segment between the left carotid artery and the left subclavian artery. The aortic isthmus is defined as the part of the aorta lying between the left subclavian artery and the ductus arteriosus (A on figure 1).(1) Anatomical variations may occur, such as a double arcus aortae or the right subclavian artery being the last to leave the arch (arteria lusoria)(2)



Figur 1 A = aortic isthmus, B = distal aortic arch, C = proximal aortig arch. Arrows indicate sites of measurement in section 1.3.1. Figure from Moulaert(1)

1.2 Definitions

Coarctation of the aorta is the presence of a hemodynamic significant narrowing of the descending part of the thoracic aorta distal to the subclavian artery, usually where the ligamentum arteriosum attaches to the aorta, or in close proximity to its origin.(3) The typical lesion is a discrete narrowing consisting of a shelf or a ridge protruding into the lumen(4). To be hemodynamically significant, the lumen needs to be reduced with about 50% in the typical lesion, but in longer and more tubular lesions, the lumen reduction may be hemodynamically significant with less narrowing.(5)

In some cases, the coartctation could be located in the aortic arch between the left carotid and the left subclavian artery, in lower parts of the thoracic aorta or even in the abdominal aorta (midaortic syndrome, not included in this study). (4)In the most adverse form the aortic lumen might be completely occluded without blood flow, but with continuous aortic outer walls above and below the stenosis. If there is absence of continuity, the lesion is classified as an interrupted aortic arch. If there is a small fibrous strand as the only connection between the proximal and distal segment, the lesion is also classified as an interrupted arch (5)

1.3 Epidemiology and associations

Coarctation is one of the commonest congenital heart defects, representing 6-8% of all inborn cardiac defects. The lesion is two to five times more common in males than in females.(6) The isolated form accounts for about 80% of the cases, the rest having co-existing cardiac pathology.(7) Coarctation with or without concomitant ventricular septal defect or other types of left sided obstructions is associated with chromosomal abnormalities such as Turner's syndrome, Trisomy 18 or microdeletion of 22q11 (diGeorge syndrome), with some reporting chromosomal anomalies in as many as 30%.(8) Patent ductus arteriosus is present in nearly all neonates presenting with CoA, and is believed to be a part of the coarctation, not an additional anomaly. Having a hypoplasia of the aortic arch is also considered as a part of the normal picture.(5) Coarctation is associated with having a bicuspid aortic valve in 30-40% of the cases, maybe more.(6)

1.4 Classification

Coarctation of the aorta has been classificated in different ways throughout history, with each classification serving the purpose of different medical professions, as one makes more sense for the pathologist than for the epidemiologist etc.

1.4.1 Classification according to age or localization

Coarctations was originally categorized by means of the typical ages of presentation, namely an infant and an adult type. The age of presentation was then linked to the topographical relationship between of the coarctation and the ductus arteriosus/ligamentum arteriosum, as the infantile type was named preductal and the adult type became known as postductal. The main difference being that the preductal (or infantile) form reveals its presence as the duct closes soon after birth, while closure of the duct does not alter the bloodflow across a postductal lesion. However, this classification is somewhat inaccurate as most coarctations is shown to be juxtaductal.(3)

Even if the correlation between the obstruction's physical relation to the duct is not consistent between adult and infantile types, there are still pragmatic aspects of a subdivision based on debut age. The infantile type is assosciated with patency of the arterial duct, underdevelopment of the aortic arch (hypoplasia) and simultaneous intracardiac defects, while the adult type is more of a localized narrowing with well developed collateral blood supply, with typically less of arch or isthmus hypoplasia.(8)

1.4.2 Surgical classification

Amato et al stated a classification specificly designed to simplify the surgical decision-making. Based on the anatomical and pathological variations encountered during their surgical experience they found it pragmatic to separate coarctation into three types:

Type I – primary coarctation with or without patent ductus arteriosus

Type II – coartation with isthmus hypoplasia with or without patent ductus arteriosus

Type III – coarctation with tubular hypoplasia involving isthmus and distal transverse arch

Each of those categories could then be subgrouped A if there was coexistence of ventricular septal defect, or B if other major cardiac defects were present.(9)

An another common surgical classification is to split coartation into three groups according to cardiac comorbidity, group I being isolated coarctation, group II coarctation with ventricular septal defect and group III being coarctation with complex intracardiac anomalies. In an attempt to establish a common nomenclature, Backer and Mavroudis used comorbidity as second level in the hierarchy and a third layer consisting of the presence of isthmus, arch or combined arch and isthmus hypoplasia.(3) Instead of the classical adult or infantile type, the latter surgical classification consists of 27 possible combinations/categories.

1.5 Etiology, patophysiology

There are two major theories for development of congenital coarctation, namely the Skoda theory and the Clarke theory, the Skoda theory more suitable for adult type, and Clarke's theory better fit to explain infantile/neonatal.

1.5.1 Skoda's theory

The shelf of ductal tissue in the distal aortic arch at the intersertion site of ductus arteriosus to the aorta, or just proximal to it, consists of anomalous ductal tissue or residual fibrous derived from ductus. This then causes the coarctation to appear at the time of ductal closure. A counter-argument to this theory is that coarctation is shown to be present in utero in some, as fetal echocardiography shows narrowing of the arch with the ductus still patent, and fetal specimens at autopsy is found to have an already existing coarctation shelf.(8)

1.5.2 Clarke's theory of flow-mediated remodeling

Coarctation with hypoplasia is related to the amount of blood flow through the aortic arch during fetal life. Increased left ventricular afterload will re-route blood through foramen ovale, and decreases blood flow through the aortic arch. This increased flow through the ductus arteriosus may give an altered angle between the ductus and aorta, which can predispose for the formation of a localized shelf opposite the ductus. This further decrease the flow in the arch, then developing a hypoplastic aortic arch.(5;8)

1.5.3 **Defining Aortic Arch Hypoplasia**

A great deal of the relevant literature refers to the classical article by Moulaert when defining hypoplasia of the aortic arch. This definition partially relies on the relative proportions between different parts of the aorta, in addition to the observation that the brachiocephalic artery, left carotid and left subclavian arteries should arise from the aortic arch quite close to each other, and no more than 5 mm apart in infants. The proximal part of the transverse aortic arch is considered hypoplastic if the external diameter is less than 60% of that of the ascending aorta at a given point.(see figure 1 for indicated site of measurement) The criteria for distal transverse arch hypoplasia is an external diameter less than 50% of the ascending aorta, while the aortic isthmus is not labeled hypoplastic until its external diameter falls below 40% of the diameter of ascending aorta. Tubular hypoplasia is defined as the presence of a greater distance than 5mm between the arterial branches leaving the aortic arch, in addition, one or more hypoplastic segments needs to fulfill its criteria for hypoplasia as mentioned. (1)

A problem with applying Moulaerts definition is the fact that definitions of hypoplasia is based on comparative ratios with the ascending aorta as reference. Instead of Moulaerts single ascending aorta measurement, Myers et al used the average of three measurements to get a comparable dimension of the ascending part(10). Nevertheless, Elgmal et al argues that decreased bloodflow across the coarctation site or an hypoplastic aortic arch also would affect the dimensions of ascending aorta, making comparison with the descending part of the aorta at the level of the diaphragm a better reference for defining hypoplasia, a point of view also shared by Morrow et al.(11;12)

Karl and collegues uses an formula which relates arch dimensions to body weight, as the aortic arch is considered hypoplastic if the transverse arch diameter was less than the patient's weight in kilograms plus one (<BW+1), based on this formula they argue that such hypoplasia of the aortic arch is an indication for extended arch repair instead of simple coarctation repair.(13)

As an another approach to the problem of standardizing values and making them more comparable inter-individually, Liu et al(14) uses a Z-score, which relates the dimensions of the aortic arch to body surface area, a well-known strategy applicable on a diversity of cardiac measurements, as shown by Pettersen et al(15). Confusingly enough, Z-value (not Z-score) is also used to express hypoplasia, defined as the number of standard deviations from the mean

normal expected arch size, with a cut-off for hypoplasia when Z-value is below -2 standard deviations away from “normal”.(11)

The diversity of different definitions for aortic arch hypoplasia makes the different studies less comparable, and is one of the factors that maintains the controversy

1.6 Presentation and pre-operative management

The presentation is quite different between the adult and the infantile type, thus the choice of presenting them separately.

1.6.1 Neonates and infants

The newborn might be symptom-free as long as the ductus arteriosus remains open, but as it close the presentation is that of heart failure, with tachypnoea, feeding difficulties and sweating. On examination the femoral pulses might be absent or delayed compared to brachial, a left sternal edge systolic murmur might be audible, as well as radiation to the posterior between the scapulae. There is often a gallop rhythm, and they might have hepatomegaly.Blood pressure differences between arm and leg is also present.(5;6;8) Due to the influence of ductal closure, the femoral pulses might be normal at birth but absent at 1 week.(5) This clinical picture may also be accompanied by loss of urine production, loss of sphlanchnic circulation, leading to circulatory collapse and subsequent death if diagnosis and adequate treatment is not established promptly. (2) Therefore, to stabilize before repair, intravenous prostaglandin E1 infusion should be started in suspected neonatal coarctation if there are significant blood pressure differences between arm and leg or if there is heart failure.(8)

1.6.2 Children and adults

In those diagnosed after one year of age, almost all are asymptomatic. If symptomatic, the commonest are cold extremities or claudication at exercise, while heart failure is rare beyond neonatal period. Routine examination may reveal absent of delayed femoral pulses, hypertension, murmurs from collaterals or coarctation and blood pressure differences between

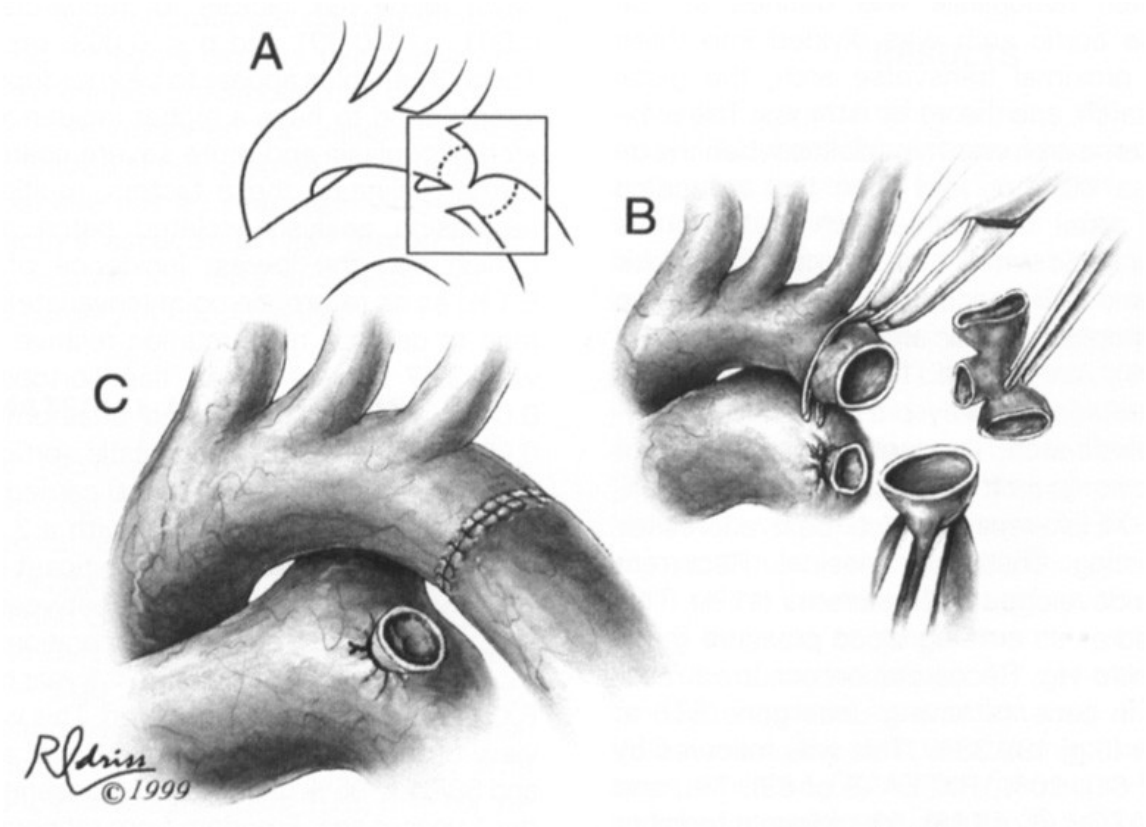
upper and lower extremities. The condition could also be suspected by an abnormal chest radiograph, with “figure 3-sign” or rib-notching.(5;6)

1.6.3 Timing of repair

Due to development of hypertension, coarctation repair should be performed in infancy or early childhood. If the condition is detected later, immediate repair is the recommandation. If repaired after infancy or early childhood, there is a risk of persistent and irreversible hypertension.(16)

1.7 Types of repair

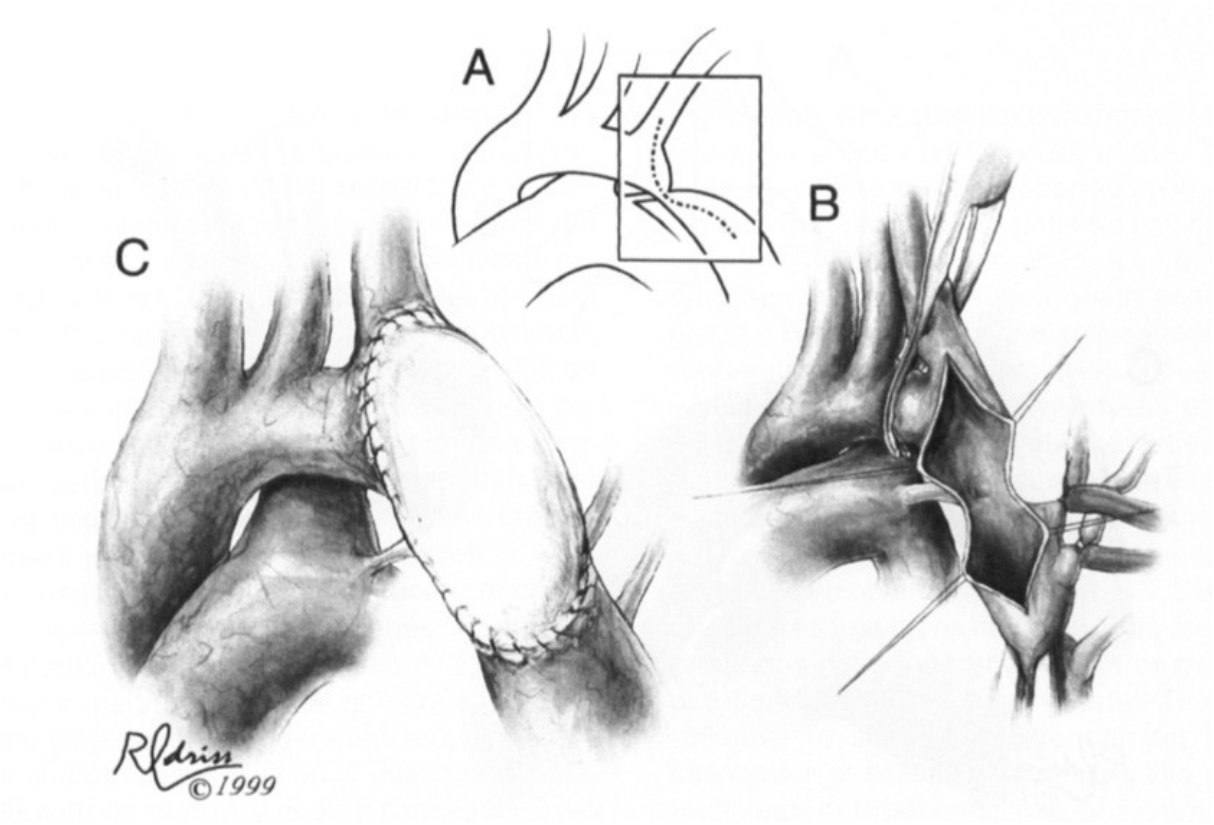
1.7.1 End-to-end-anastomosis



Figur 2 from Dodge-Khatami(17)

In addition to lack of consensus with regards to definitions of hypoplasia, there is also no consensus when it comes to choice of operative technique. The first successfull surgery for coarctation was described in 1944 by Crafoord and Nylin, and consisted of a simple resection of the coarctation site and an end-to-end anastomosis. (7). This procedure is made through a left posterolateral thoracotomy usually in the fourth intercostal space. The proximal left subclavian artery, the distal transverse aortic arch, the aortic isthmus, the coarctation site, the ductus arteriosus or ligamentum arteriosus are dissected in addition to aorta beyond the coarctation site, with precaution not to damage intercostal arteries. Aorta is cross-clamped proximally at the level of the origin of the left subclavian artery, allowing flow in the left carotid artery. Second clamp is placed with good distal margin to the coarctation site. The ductus is ligated and divided, the coarctation site is resected and the proximal and distal parts of aorta brought together and anastomosed.

1.7.2 **Patch angioplasty**

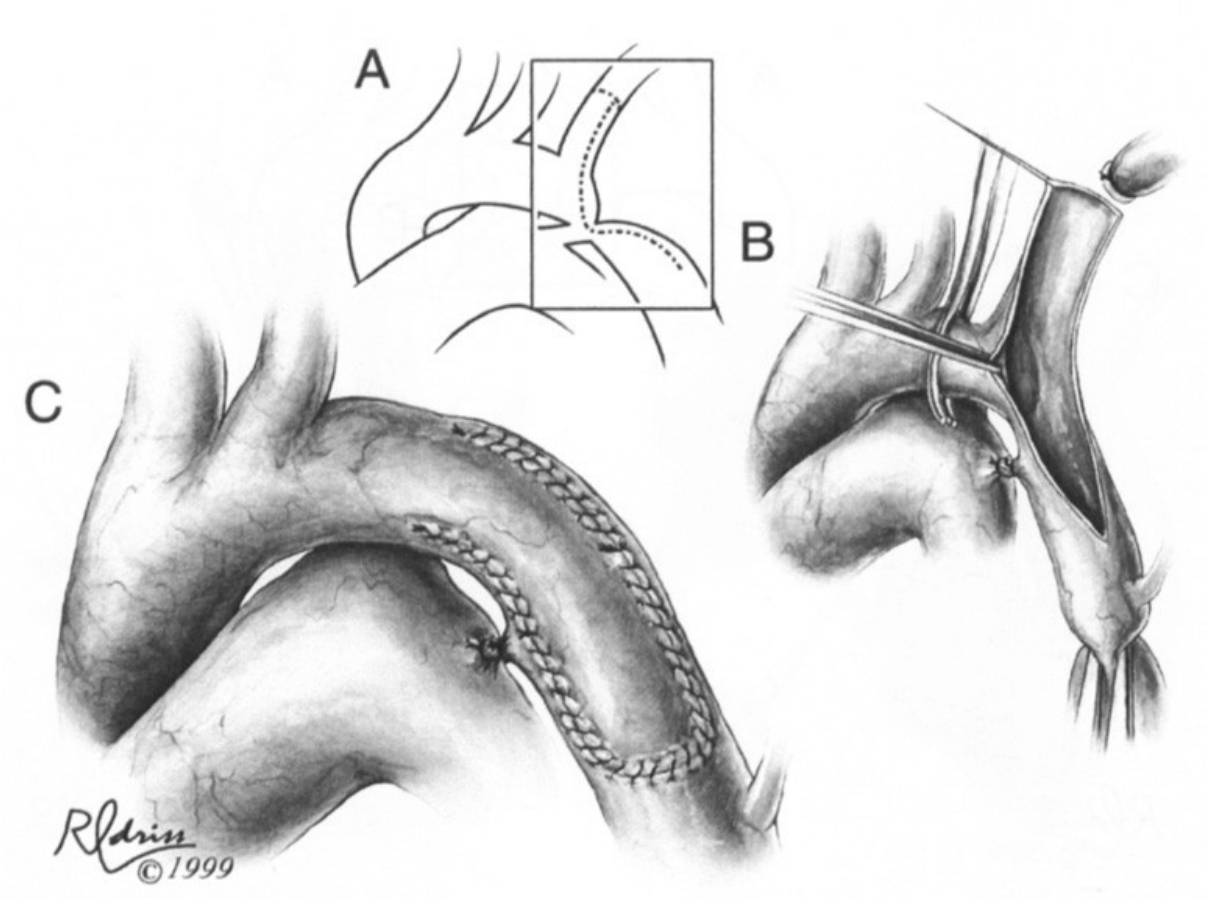


Figur 3 from Dodge-Khatami(17)

In 1961, a new technique was introduced by Vosschulte – the indirect isthmusplasty operation, later known as patch angioplasty. It was said to have several advantages, with limited vessel mobilization and therefore subsequent saving of intercostal vessels and the avoidance of a circumferential suture, believed to sustain a better growth potential.(18) The access of choice is the posterolateral thoracotomy, using a single, large side-biting clamp. The aorta is opened longitudinally, usually on the lateral side, from the level of the origin of the left subclavian artery, downwards to below the ductus arteriosus. A prosthetic material is trimmed into a suitable shape and sutured, making sure to create suficcient dimension of the new lumen . (4) Examples of prosthetic material are polytetraflouroethylene (PTFE/gore-tex), Dacron polyester, autologous pericard patch or even bovine pericardium. The technique soon became popular and was utilized for several years, and showed improved survival and reduced morbidity, especially almost eliminating the problem of paraplegia after aortic cross clamping, due to its shorter cross clamp time.(7) At Rikshospitalet, Dacron patch was used from 1976 until 1980, later the PTFE patch was the treatment of choice.(19) An unfortunate late complication is that of those who underwent Dacron patch angioplasty, many are prone to

develop late aneurisms, with a reported incidence between 4-38% in some series, and up to 51% in a series by Parks and collegues.(20) There has also been reported aneurisms after patch angioplasty at Rikshospitalet.(21) It is believed that the material's inherent compliancy, with bulging of the patch and excessive pulswave stress on the aortic tissue opposite to the patch contributes to the aneurism formatiln, in addition to the prosthetic material's ability to induce inflammatory response that weakens the adjacent wall. Total resection of the intimal shelf of the coarctation ridge or retention of abnormal aortic tissue after repair is also believed to predispose.(22) (23)

1.7.3 Subclavian flap angioplasty

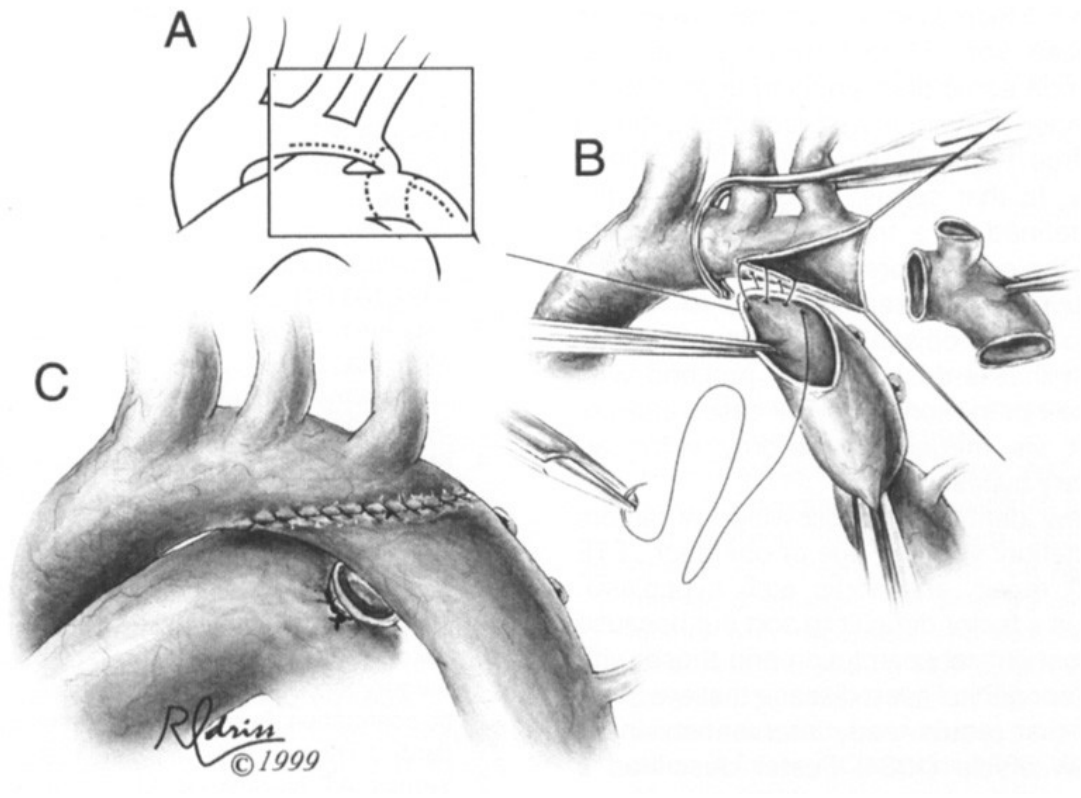


Figur 4 from Dodge-Khatami(17)

Waldhausen and Nahrwold reported on a new technique for operative repair in 1966, the subclavian flap angioplasty. Through a posterolateral thoracotomy, the aortic arch, subclavian artery, aortic isthmus, ductus arteriosus/ligamnentum arteriosum and descending aorta is dissected free. Aorta is clamped between the left common carotid and left subclavian artery

and distal to the coarctation site, but usually proximal to the third intercostal vessels. The subclavian artery is dissected and ligated distally just before its first branch, then split longitudinally at its posterior margin and down to about 1cm distal to the coarctation site. The intimal shelf of the coarctation ridge is then dissected away, the subclavian artery is then cut, turned down and trimmed, then sutured. (5;24) This technique was adapted method of choice at many centers, as there are advantages with use of autologous tissue with growth potential and the avoidance of circumferential suturing, but on the other hand some potential disadvantages as it sacrifices the major blood supply to the left arm. Significant differences of blood pressure between the upper extremities has been reported.(7) There has also been reported examples of gangrene of the upper extremity, with an estimated incidence of 0,2% in a classic report by Geiss and William.(25) Sacrificing the left subclavian artery does normally involve only minor side-effects, with shortening of the left limb as the most common, present in all subjects in a report by Todd et al(26) Using the procedure in newborns and infants less than three months old is shown to give significant risk of early recurrence, and is therefore best avoided.(27;28)

1.7.4 **Extended end-to-end**



Figur 5 from Dodge-Khatami(17)

To better address the problem of transverse arch hypoplasia, the extended end-to-end technique was developed (29;30). The arch and the main vessels are dissected in the same fashion as for the previously described procedures, with proximal dissection including the brachiocephalic trunk. The arch is cross-clamped just distal to the innominate artery, the distal part of the aorta is mobilized by ligating intercostal vessel, usually three sets. The duct is ligated, and the descending aorta clamped well beyond the coarctation site. The arch is incised at the undersurface, the coarctation site resected, and the ends are brought together and anastomosed, leaving a long oblique suture line and an adequate enlargement of the hypoplastic segment of the arch.(31) In a 2009 report by Kaushal and Backer, the extended repair shows good results with low mortality and low rate of reintervention for recurrent coarctation.(32)

1.7.5 **End-to-side anastomosis**

Another approach to treat concomitant hypoplasia is the use of the end-to-side technique, which is applied when there is an exceptionally long and narrow posterior arch.(33) It is quite

similar to the extended- end to end, but differs somewhat as the aortic isthmus is ligated, and the line of incision lies completely on the undersurface of the aorta, being dimensioned to correspond to the circumference of the descending aorta, with the anastomose at the level of the innominate and left carotid artery.(5;13) This procedure may preferably be performed via a median sternotomy.

1.7.6 Other procedures

Some other procedures have also been applied at some centers and in some cases, with Arrieta and Martinez presenting the left carotid artery flap as a surgical alternative for treating complex coarctation with severe hypoplasia of the transverse arch.(34) Caliani et al presents a different approach with a wide resection of the hypoplastic segment involving the distal arch,and reimplantation of the subclavian artery onto the carotid artery.(35)Zannini et al used a combination of subclavian flap angioplasty and end-to-end anastomosis to treat coarctation with a coexisting long and hypoplastic isthmus.(5;36)In the rare rare cases of pre-subclavian coarctation, the subclavian-turn-up procedure can be used, or it could be combined with end-to-end anastomosis. In older patients and adults, there is also a possibility of using of a tube interposition graft, or in some special situations using the simpler procedure of inserting a by-pass graft. (5)

1.7.7 Operative access

The traditional operative access has been the posterolateral thoracotomy, but alternatively the median sternotomy is used when simultaneously addressing intracardiac defects. Lately the strategy has changed with a trend towards treating arch hypoplasia more aggressively, using a midline incision and cardiopulmonary bypass. The standard thoracotomy access gives poor exposure of the proximal arch, and also makes treating coexisting anomalies such as VSD, TGA, subaortic or aortic stenosis difficult.(13;37). On the other hand, the risk of suboptimal surgical repair through a thoracotomy needs to be counter-weighed against the disadvantages and risks associated with cardiopulmonary bypass, DHCA and cardioplegia via a midline incision. Thus, the median approach is mainly used on patients with long, proximal and severe hypoplasia.(13;14;36)

1.7.8 **Balloon Angioplasty**

Catheter intervention as a treatment for isolated coarctation was reported the first time in 1983(7), and from early on it was considered a safe and effective less invasive procedure (38), with reported results not differing significantly from those of surgery with.(39) The balloon angioplasty is performed via the femoral artery, alternatively by access from the carotid artery. The coarctation site is treated with a balloon measuring 120-150% of the size of aorta at the diaphragmatic level.(7) Despite being less invasive, there are some complications encountered, such as femoral artery thrombosis, cerebrovasular accidents (40) and aortic dissections during the procedure(7). One important long-term complication is that of restenosis, which is reported ranging from 8-60%, and even up to 75% when performed in neonates.(41) Another long-term drawback is the 10-15% risk of late aneurism formation, probably due to tears involving the lamina media created during the procedure.(7) Balloon aortoplasty also serves as an alternative to surgical intervention for recurrent coarctation.(42)

1.8 Re-coarctation and morbidity

1.8.1 Hypertension

The early presumtions that patients undergoing repair was cured, has been repelled by reports with long follow-up, with findings of surprisingly high morbidity and increased mortality. The prevalence of hypertension is found to be from 35% to 49%(43), and the probability of late hypertension increases drastically when repair is performed after one year of age (44), not necessarily associated with re-coarctation as shown by Presbitero, where 36% had hypertension without recoarctation, and 30 years after repair, only 32% was normotensive, which was significantly higher than in the normal popluation.(45) The cause of post coarctectomy hypertension is not fully understood. In a minority of cases, the hypertension might be due to residual stenosis after initial repair. It has also been hypothized that Coarctation is a manifestation of some generalized vascular abnormality, but it seems more likely that having a coarctation produce changes in the pre-coarctation vascular tree that not necessarily are fully reversible. The vascular response to noradrenaline in the forearm was three times higher in post-coarctectomy patients compared to a group of mildly hypertensive individuals, but with no difference in lower leg vessel response.(46) Also, histologic studies have shown vessel abnormalities with increased rigidity, more collagen, less smooth muscle but greater contractility in response to vasoconstrictors

1.8.2 Re-coarctation

Due to the possibility of irreversible vascular changes in the upper body, one cannot soley rely on measurements of blood pressure differences between upper and lower limbs when diagnosing a re-coarctation. Some have used arm-leg gradient of 20 mmHg as a cut off for intervention, but there is no way of making a certain diagnosis other than by clinical examination combined with diagnostic imaging. (5) A 25 mmhg gradient noted on transthoracic ecco or a diastolic tail to the doppler signal in descending aorta indicates re-coarctation (24), as do peak pressure gradient of 20 mmHg and/or collateral circulation on MRI. Blood pressure measurement during exercise testing could often reveal huger gradients than at rest, and in that case strengthen the indications for re-intervention, especially in physically active adolescents, as there is an increased risk of cerebrovascular accidents if stress-indused proximal hypertension is present.(2)

The best re-intervention modality is based on the pre-operative investigations, with balloon-angioplasty recommended for discrete recoarctation, but if there is a long segment of recoarctation, aortic arch hypoplasia, and especially aortic aneurisms or pseudoanerurisms, surgery should be the treatment of choice. Redo-surgery has a slightly higher mortality rate than initial repair(16), and the choice of technique is influenced by the prescene of intrathoracic scarring and the degree of collaterals, thus favoring techniques not requiring extensive aortic mobilisation(47) such as tube graft interposition technique. Some consider median sternotomy to be the best approach if obstruction is proximal to the former repair and the aortic arch is significantly hypoplastic, while if the obstruction is just proximal for, at, or distal to left subclavian artery, the posterolateral thoracotomy access should be preferred.(42) Extra-anatomic bypass with graft from ascending to descending aorta may be an alternative, especially when multiple repairs have been performed earlier.(2)

2 Material and methods

After enquiry to the regional ethical committee, this project was appreciated as a quality control study, which then gave permission to extract data from databases and patient files, both electronically and paper records.

2.1 The Datacor and Berte Database

The vast majority of paediatric thoracic surgery throughout history in Norway has been done at Rikshospitalet, and Datacor is a database containing selected information extracted from procedures done from 1971 until today. Due to the natural history of computer technology, a great extent of the procedures done in the early periods have therefore been manually typed into the database at a later stage. The database is organized by procedure, so patient oriented research means re-stacking information into a person-oriented fashion as a last step before analyzing the data. With regards to follow-up-data, cross- checkings of procedures, diagnoses and identification numbers, the paediatric cardiology database Berte was of great help, which is a patient oriented database.

2.2 From Procedures to Patients

Procedure data was extracted from the Datacor database at Rikshospitalet by filtering for patient categories (IAA-interrupted aortic arch, COA-Coarctation of the Aorta and COC complex coarctation) for those operated in the time interval 01.01.1971-31.12.2001. In addition, to identify those of these patients undergoing re-operations in the period after 31.12.2001, but before 01.07.2011(closing date), a filtered search for the relevant procedure codes for re-operations were done and double-checked manually.

All procedures were then grouped by operative access (posterolateral thoracotomy vs sternotomy), degree of coarctation, operation technique, co-morbidity and whether it was a re-operation or not. Other relevant per-operative parameters were also extracted.

2.3 Identifying Aortic Arch Hypoplasia

As one of the main purposes of the study was to identify the role of aortic arch hypoplasia, all patients needed to be grouped after the degree of coarctation. Ideally, those with pure Coarctation needed to be separated from those with aortic arch hypoplasia and those with interrupted aortic arch, respectively. The Datacor database contained two groups with information about the degree of arch interruption, namely COA and IAA. Due to the lack of a separate group for arch hypoplasia, those categorized as interrupted arch then consisted of a mix of patients with true IAA and coarctation with arch hypoplasia, and on the other hand, some of those categorized as COA were in fact coarctation with concomittant aortic arch hypoplasia. The study included over 730 procedures, and with regards to the time limitations set by the nature of this student assignment, searching through all patient record were not feasible. To identify those who might have an hypoplastic arch, those categorized as COA but containing IAA in the description of the procedure or in the diagnosis section, or those categorized as IAA but containing COA in procedure or diagnosis were checked either against patient records where possible, or matched against information in the Berte database to reveal those with an hypoplastic aortic arch.

To further identify those with arch hypoplasia, both the procedure entries and the diagnosis entries were analyzed, and those mentioned as hypoplastic, atretic or dysplastic categorized into same hypoplasia group. Descriptions of the surgical procedures of all those re-operated was gathered by searching the Datacor database, searching electronical patient records, and then supplemented by searching paper records from the archives for those not electronically available. The surgical procedure descriptions were then analyzed, and those with aortic arch described as hypoplastic were registered. Finally, for those re-operated, consistency in the categorization was assured by comparing database-exctracted procedure and diagnosis entries, surgical procedure descriptions and grouping (IAA/COA/COC) between the different records for each patient.

2.4 Surgical technique

With regards to operative technique, the Datacor database contained information consisting of procedure codes and a short entry-like description. Where description and procedure code mismatched, description overruled the procedure code, as mistyping dramatically changes the procedure code in contrast to the minor effect of simple mis-spellings. Where the description was missing, procedure code was used for classification. Where both were missing, the actual

procedure was identified by searching in Berte database, by looking the patient up in the electronic patient record system or by checking the surgical descriptions gathered.

Various peroperative parameters such as precence and type of extracorporal circulation, perfusion time, cardioplegia time, aortic cross clamp time, bleeding as a complication and total blood loss were exctracted from Datacor.

2.5 Post-operative information

Datacor also provided information about post-operative complications, the need for and time on respirator, and the rare but unfortunate cerebral accidents. Both length of stay at the intensive care unit and the time until discharge from the ward was registered.

2.6 Co-morbidity

Co-morbidity was identified by the diagnosis entries extracted from the database, in those procedures where information was missing, supplemented information was extracted from Berte. Then, co-morbidity was split into three categories, Group I containing patients diagnosed with Coarctation with or without hypoplasia, or interrupted arch, with or without co-excisting patent ductus arteriosus (PDA) and with or without simple atrial septal defect (ASD). Group two consisted of patients with Coarctation with or without hypoplasia, or interrupted arch, with ventricular septal defect with or without coexcisting ASD. Group three consisted of patients diagnosed with Coarctation with or without hypoplasia, or interrupted arch, with coexcisting cardiac anomalies other than VSD, PDA or ASD

Group I:	COA/HYPOPLASIA/IAA, +/- PDA, +/- ASD
Group II:	COA/HYPOPLASIA/IAA, + VSD, +/- ASD
Group III:	COA/HYPOPLASIA/IAA + COMPLEX CARDIAC DEFECTS

2.7 Re-operations

Re-operations were identified by sorting all procedures by date of birth, in addition to analyzing procedure codes and descriptions from the database. A handful of patients were registered as a re-operation even though there were no previous records in the Datacor database. Those were double checked against Berte database, patient records or later surgical procedure descriptions where available. Balloon angioplasties for re-coarctation were not recorded.

2.8 Other Parameters

Co-existing syndromes and the precense of prematurity was extracted from the diagnosis column in the database.

2.9 Follow-up

In the early years, the patients operated for aortic coarctation was considered cured when operated, hence it was believed that there were no need for a comprehensive follow up program. Some were followed up in the main unit or others in peripheral outpatient clinics or by general practictioners. Nevertheless, follow-up information is readily available in Norway due to the national death registry. Where follow-up information was missing, a search in the death registry was performed, slightly complicated by the fact that the national identity number was not registred in hospital records until 1989, and in those operated after 1989 a great deal recieved surgical treatment in the neonatal period and was registered in the database with a provisional identity number. Therefore, searching the national death registry was partly done by other available information such as date of birth, sex, forename, surname. Also, by searching the Berte database or electronical patient records for names or date of birth, updated national registry numbers was provided. All deaths was registered by date, and categorized into early and late mortality. Early mortality was defined as death until day 30 after the operative procedure, and late death beyond 30 days after the procedure. Early mortality was then sub-categorized into groups depending on whether it was attached to first operation or some of the re-operations, respectively. In-ward mortality was registered by using the parametres directly from Datacor, being those registered as dead at discharge. A small number of patients were registered to have left the country, for those individuals follow-up was defined to last until the registered date. First day of follow-up was defined as day of initial repair, and closing date for the study was set to first of July 2011.

2.10 Statistics

Statistical analysis was performed using SPSS 18.0 (inc.,Chicaco, Illinois, USA). The analysis was performed using Pearson's chi-square test, log rank test and Breslow test. To illustrate cumulative survival and re-operation free survival, the Kaplan-Meier plot was utilized. Univariate and multivariate logistic regressen were used to identify significant predictors for death and re-operation or death respectively. The parameters included in the multivariate model all had a p-value below 0,20 in the univariate analysis, the assumptions underlying multivariate logistivc regression analyses were checked and found to be adequately fulfilled. A p-value below 0,05 was considered signifigant, and a p-value less than 0,01 as highly significant.

3 Results

3.1 Patient charachteristics and procedures

The material consisted of 588 patients who recieved primary surgery because of coarctaion of the aorta or interrupted aortic arch in the time period between 1971 and 2001. Of those were 348 boys (59,2%) and 240 girls (40,8%). Four patients were lost to follow-up (0,68%), giving a follow-up completeness of 99,3%. The median follow-up time is 19,15 years (range:0-40,35 years), with a total of 11215 patient years.

Of the initial 588 patients, three hundred and thirty (56,1%) were classified to belong to comorbidity group I, 130 (22,1%) in group II and 128 (21,8%) in comorbidity group III. During the time period, the internal distribution of comorbidity groups has changed, as illustrated in the table.

Co-morbidity	**Time period**						
	1971-75	**1976-80**	**1981-85**	**1986-90**	**1991-95**	**1996-01**	**Total**
Group I	39 (66,1%)	74 (74,7%)	53 (56,4%)	47 (47,5%)	71 (60,7%)	46 (38,3%)	**330 (56,1%)**
Group II	6 (10,2%)	12 (12,1%)	28 (29,8%)	24 (24,2%)	19 (16,2%)	41 (34,2%)	**130 (22,1%)**
Group III	14 (23,7%)	13 (13,1%)	13 (13,8%)	28 (28,3%)	27 (23,1%)	33 (27,5%)	**128 (21,8%)**
Total	**59**	**99**	**94**	**99**	**117**	**120**	**588**

3.1.1 Initial operation

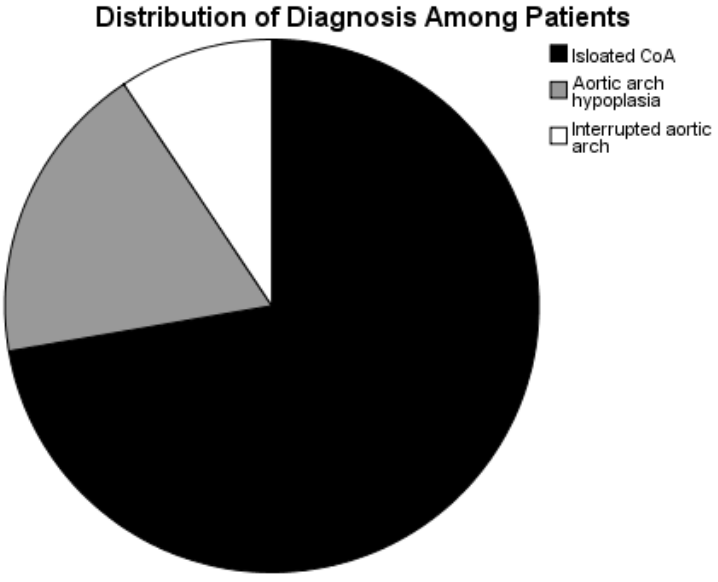
Median age at the initial repair was 0,186 years (68 days), with a range from 0 to 18,79years. The distribution in the respective decades is shown in table 1.

Time period	**Individuals operated**	**Median age at operation (yrs)**	**Range**	**Standard deviation**
1971-1980	158	3,908	0-17,01	4,58
1981-1990	193	0,096	0-18,35	4,15
1991-2001	237	0,082	0-18,79	3,32
Overall	588	0,186	0-18,79	4,18

244 patients (41,5%) underwent surgery in the neonatal period (0-30 days old), whereas 126 (21,4%) were operated as infants. The rest were operated in childhood and adolescent age (218 patients, 37,1%). The tendency of operating a greater share of the patients in the neonatal period throughout the later decades of the study period is shown in the table, where 71 out of 120 (59,1%) underwent surgery in the neonatal period in the latest time period, whilst only 11 out of 59 (18,6%) did so in the first five-year period.

Age at repair	**Time period**						
	1971-75	**1976-80**	**1981-85**	**1986-90**	**1991-95**	**1996-01**	**Total**
Neonate (<1 m)	11 (18,6%)	20 (20,2%)	40 (42,6%)	53 (53,5%)	49 (41,9%)	71 (59,2%)	**244 (41,5%)**
Infant (>1m,<1y)	13 (22,0%)	10 (10,1%)	20 (21,3%)	25 (25,3%)	30 (25,6%)	28 (23,3%)	**126 (21,4%)**
Child/adolescent (>1y)	35 (59,3%)	69 (69,7%)	34 (36,2%)	21 (21,2%)	38 (32,5%)	21 (17,5%)	**218 (37,1%)**
Total	**59**	**99**	**94**	**99**	**117**	**120**	**588**

Of the five hundred and eighty-eight patients included in the study, 425 (72,2%) were diagnosed with an isolated coarctation, 108 (18,4%) were labeled to have coarctation with a concomitant hypoplastic aortic arch, while 55 (9,4%) of the patients had an interrupted aortic arch. Of those with coarctation (total 533 patients) 20,3% had an hypoplastic aortic arch.



This distribution of diagnosis is a bit skewed, with a higher incidence of hypoplacia among those diagnosed with CoA during the later periods, especially the latest, where 35,8% was labelled as hypoplastic.

Diagnosis	Time period						
	1971-75	**1976-80**	**1981-85**	**1986-90**	**1991-95**	**1996-01**	**Total**
Isolated Coa	49 (83,1%)	89 (89,9%)	79 (84,0%)	64 (64,6%)	89 (76,1%)	55 (45,8%)	**425 (72,3%)**
Hypoplastic arch	6 (10,2%)	7 (7,1%)	14 (14,9%)	22 (22,2%)	16 (13,7%)	43 (35,8%)	**108 (18,4%)**
Interrupted arch	4 (6,8%)	3 (3,0%)	1 (1,1%)	13 (13,1%)	12 (10,3%)	22 (18,3%)	**55 (9,4%)**
Total	**59**	**99**	**94**	**99**	**117**	**120**	**588**

Five hundred and eleven of the total five hundred and eighty eight had their initial repair through a posterolateral thoracotomy (86,9%), the remaining 77 being accessed via a midline sternotomy (13,1%).

The procedure of choice was mainly patch angioplasty (57%) and end-to-end anastomosis (38,1%), while the remaining proportion underwent other procedures such as subclavian flap angioplasty, tube grafts or bypass grafts or procedures not specified in the database material.

Procedure	No of procedures	Percentage
End-to-end	224	38,1
Patch	335	57,0
Other	29	4,9
Total	588	100

The distribution of the operation types throughout the time periods is reflected in table below. As one can see, the end to end procedure underwent its renessiance in the nineties, partly because of the evolvement of the extended technique.

Operative procedure	Time period						
	1971-75	**1976-80**	**1981-85**	**1986-90**	**1991-95**	**1996-01**	**Total**
EEA	47 (79,7%)	26 (26,3%)	2 (2,1%)	6 (6,1%)	34 (29,1%)	109 (90,8%)	**224 (38,1%)**
Patch	7 (11,9%)	69 (69,7%)	85 (90,4%)	82 (82,8%)	83 (70,9%)	9 (7,5%)	**335 (57,0%)**
Other	5 (8,5%)	4 (4,0%)	7 (7,4%)	11 (11,1%)	0	2 (1,7%)	**29 (4,9%)**
Total	**59**	**99**	**94**	**99**	**117**	**120**	**588**

3.1.2 Per-operative parameters

Of the 588 initial repairs, 522 was performed without extracorporal circulation, of those with bypass (66 patients, 11,2%) were 56 performed in deep hypothermia (84,8%), the rest not specified or in mild or moderate hypothermia. Aortic cross clamp time was not registered in the database in those undergoing surgery through the posterolateral thoracotomy, but according to prof. Lindberg it has been a median time of approximately 20 mins. Of those undergoing bypass, the median perfusion time was 78 minutes (range:31-317mins), median aortic cross-clamp time was 21 minutes (range:2-43).

3.1.3 Re-operations

113 of 588 needed re-operation during the follow-up period (19,2%). The median time interval from initial repair to re-do was 8,09 years (range 5 days to 29,3 years). 26 of the 113 (23%) had their re-operation less than a year after the initial repair. The median age at re-operation was 9,24 years, with a range from 0,36 to 34,1 years. Of those re-operated, 70,8% were accessed through a thoracotomy, while the remaining 29,8% were operated via an median sternotomy.

Operative access	No of procedures	Percentage
Posterolateral thoracotomy	80	70,8
Median sternotomy	33	29,2
Total	113	100

While the predominant technique of choice for the initial repair was EEA and Patch, a relatively great proportion of those reoperated had a tube-graft inserted (23%), and just a small number of End-to-end procedures, as illustrated in the table.

Procedure	No of procedures	Percentage
End-to-end	10	8,8
Patch	74	65,5
Tube-graft	26	23,0
Other	3	2,7
Total	113	100

3.1.4 Co-existing syndromes

Out of the total 588 patients, 55 (9,4%) were registered in the database with a co-existing syndrome. The distribution of those most frequently encountered is listed in the table below:

Syndrome	Number of patients	Percent of total (n=588)
Down's syndrome	15	2,6
Di George syndrome	11	1,9
Turner's syndrome	8	1,4
Shone's complex	2	0,3
Other syndromes	19	3,2
Total	55	9,4

3.1.5 Complications

Two of the 588 patients undergoing initial repairs were registered as having a major cerebral event in connection with the repair (0,14%). The first one in 1992, a three and a half month old girl with isolated coarctation and comorbidity group three, undergoing patch angioplasty accessed through a posterolateral thoracotomy and without cardiopulmonary bypass. She died 15 days later. The second incidence of cerebral insult was a two and a half month old girl who underwent an end-to-end anastomosis for an hypoplastic aortic arch in 1999. She was also in comorbidity group 3, and was operated through a midline sternotomy, with total cardiopulmonary bypass in deep hypothermia for 96 minutes, and cardioplegia for 27 minutes. She was alive and not re-operated for her hypoplastic aortic arch at closing date.

Of the 113 patients re-operated, there were two incidents of cerebral events (1,8%), the first one being a 4 year old boy formerly operated in the neonatal period in 1978 with a patch angioplasty for his isolated coarctation without significant comorbidity. He underwent re-do surgery in 1983 through a thoracotomy. The procedure of choice was patch angioplasty without by-pass. He later underwent a second re-do, receiving a tube graft in 2006, and was alive at closing date. The second cerebrovascular accident in the re-do-group was a 14 year old boy recieving a tube-graft via a midline sternotomy in 2005, with cardiopulmonary bypass in deep hypothermia for 94 minutes, aortic cross clamp time of 25 mins and circulatory arrest

for 15 minutes. He was formerly operated neonatally in 1990 with an unspecified procedure. He was labelled with an hypoplastic aortic arch, and categorized in comorbidity group II.

Out of a total of 720 operations, those 4 incidents gives a risk of 0,56%

Of a total 720 operations, only 16 patients was registered with excessive bleeding as a complication (2,2%)

3.1.6 **Post-operative management**

The median time of ventilatory support is 24 hrs, with a range from 1 to 840 hrs. The 25th and 75th percentiles being 8 hrs and 48 hrs respectively. During initial repair, the median stay at intensive care unit was three days, with a range from 0 to 40 days, the 25th and 75th percentiles being 2 and 5 days. The median length of stay in the ward was 5 days, (range:0-40), percentiles was 2 and 8 days, illustrating that discharge most often is to another ward in the hospital or an another hospital.

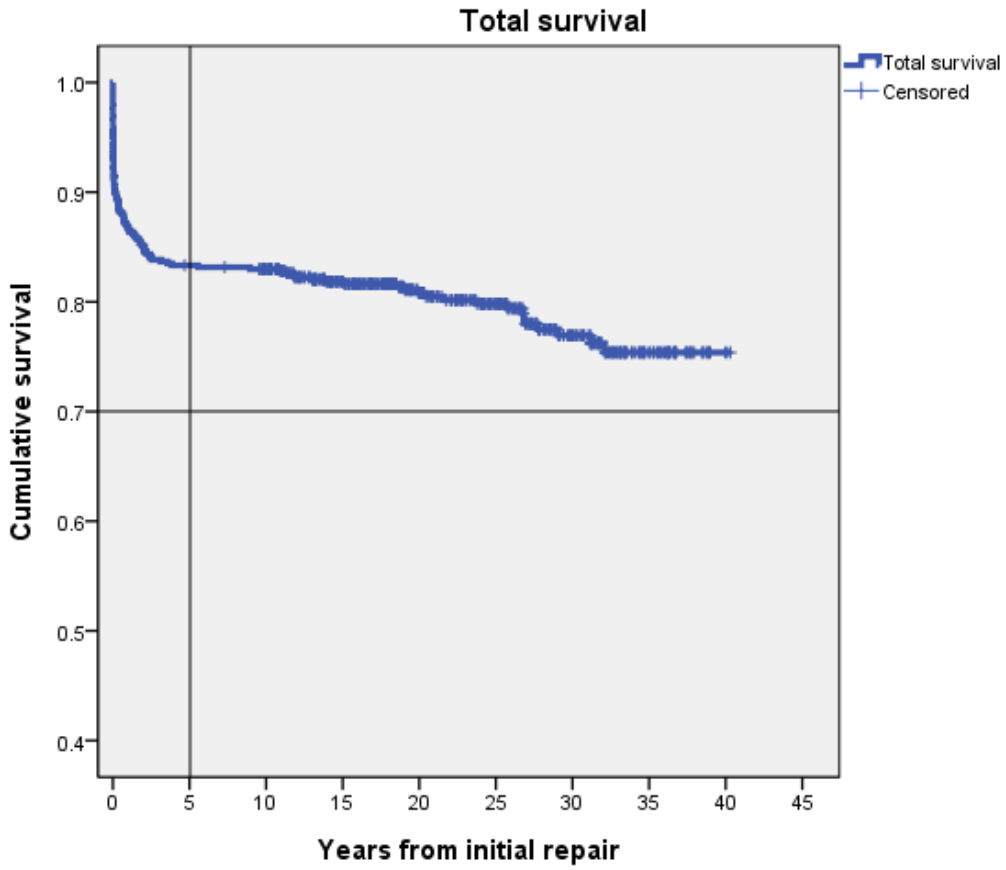
3.2 Mortality

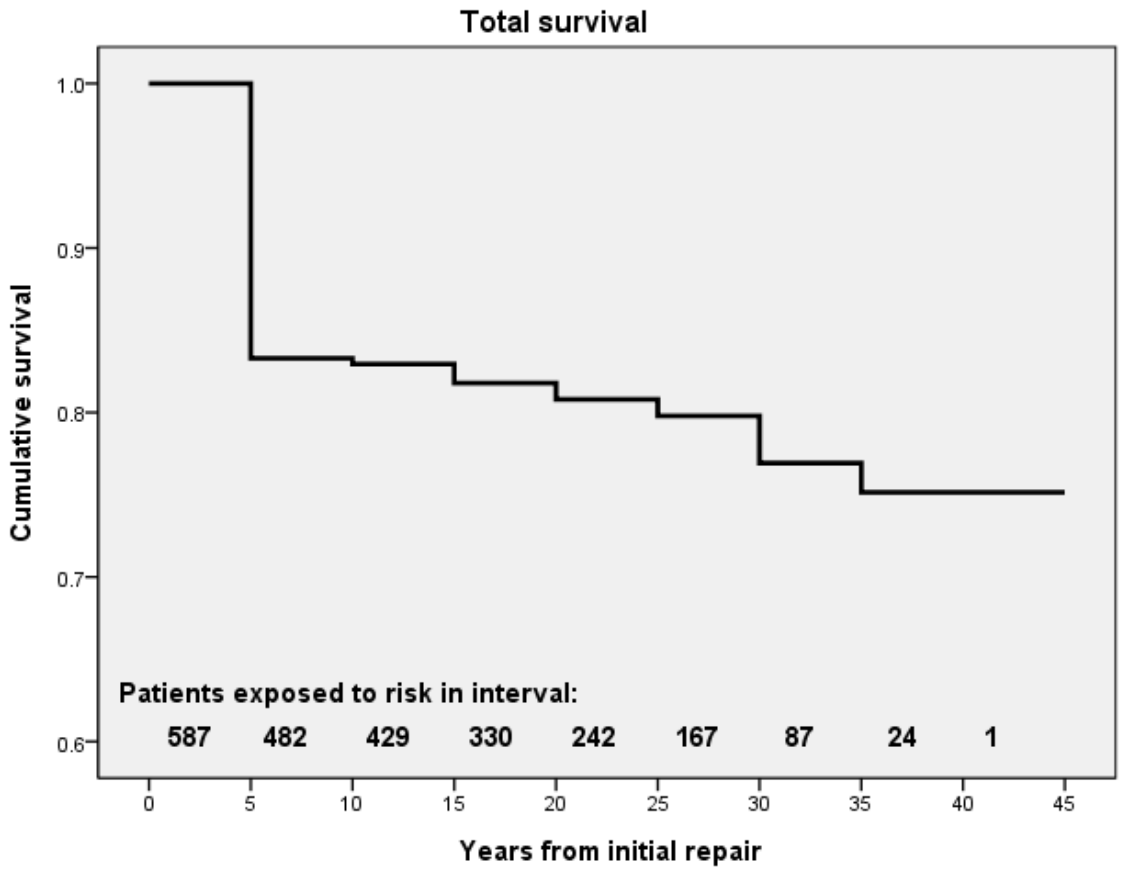
Out of the 588 initial repairs, 39 patients were registered as in-ward mortality (6,6%), but pursuant to the death registries, the total early mortality rate within 30 postoperative days was 9,4% (59 patients). The early mortality after initial repair shows quite a development throughout the time stratas, with a decrease from 18,6% in the earliest period, but with a rebound peak in the period between 1986 and 1990, before the early mortality rates lowers to a diminishing 2,5% in the latest period.

	Time period						
	1971-75	**1976-80**	**1981-85**	**1986-90**	**1991-95**	**1996-01**	**Total**
Patients operated	59	99	94	99	117	120	588
Early mortality	11 (18,6%)	9 (9,1%)	8 (8,5%)	18 (18,2%)	6 (5,1%)	3 (2,5%)	55 (9,4%)

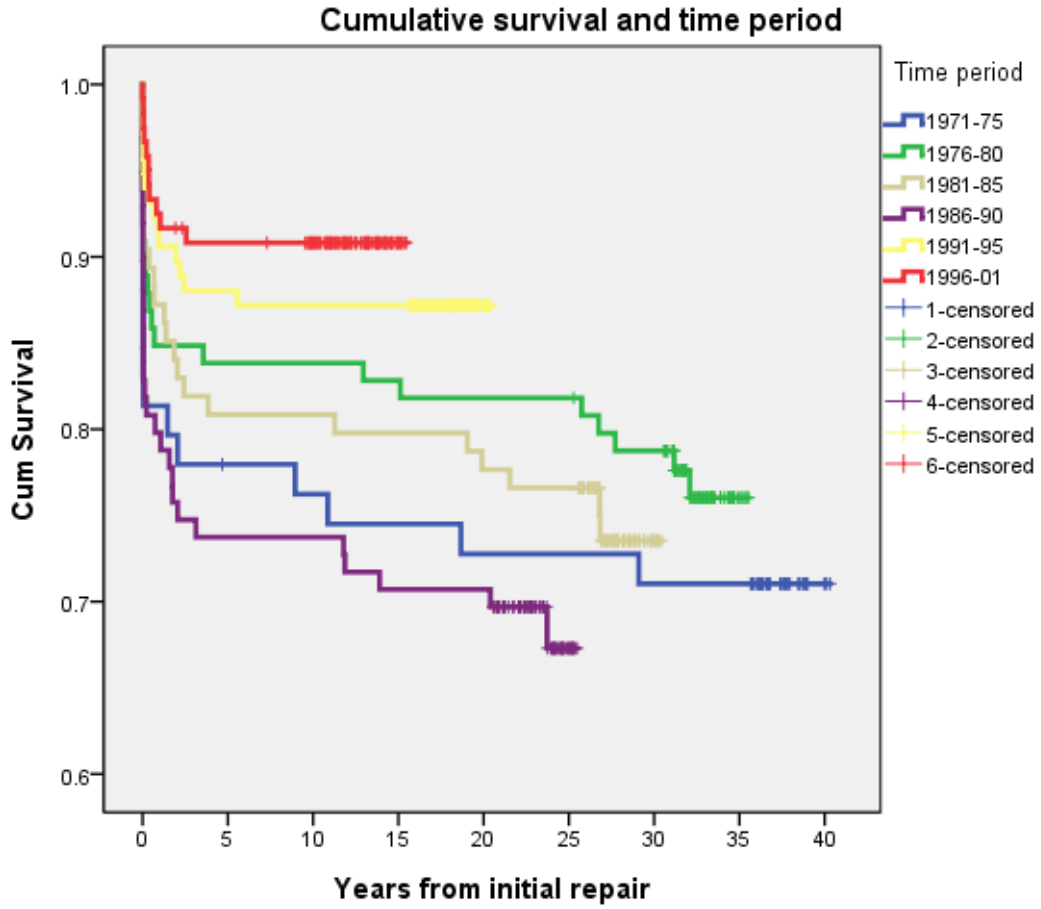
Three of the patients surviving initial repair were later registered as early mortality after re-operation, and one patient died short time after the third re-operation. Overall late mortality was 10% (59 patients). When including those registered as early mortality after initial repair, those who died within 30 postoperative days after re-do surgery, and including those lost to follow-up dead, the total mortality rate was 20,6% (121 patients). The over all median age at death was 17,9 years (range: 0,48-40,1 yrs, 25th and 75th percentiles:10,3;23,2), while median age at death for those surviving initial repair was 21,2 years (range:2,3-40,1 yrs, 25th and 75th percentiles:14,6;27,2)

Survivial is shown in the Kaplan-Meier plot and in the time period survival analysis. The cumulative survival drops quite abruptly the first years, stabilizing from about third until tenth postoperative year, then steady declining with a new plateu phase at approximately 33-40 years after surgery. The time period survival analysis illustrates that the further away from initial repair, the less patients are exposed to risk, hence one should be careful when interpreting the results of 40 year survival, unless the overall trend is stable.


Total survival
Total survival
Censored
Cumulative survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
5
10
15
20
25
30
35
40
45
Years from initial repair


Total survival
Cumulative survival
1.0
0.9
0.8
0.7
0.6
Patients exposed to risk in interval:
587 482 429 330 242 167 87 24 1
0
5
10
15
20
25
30
35
40
45
Years from initial repair

3.2.1 **Time period and survival**



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	19.047	5	.002
Breslow (Generalized Wilcoxon)	19.530	5	.002

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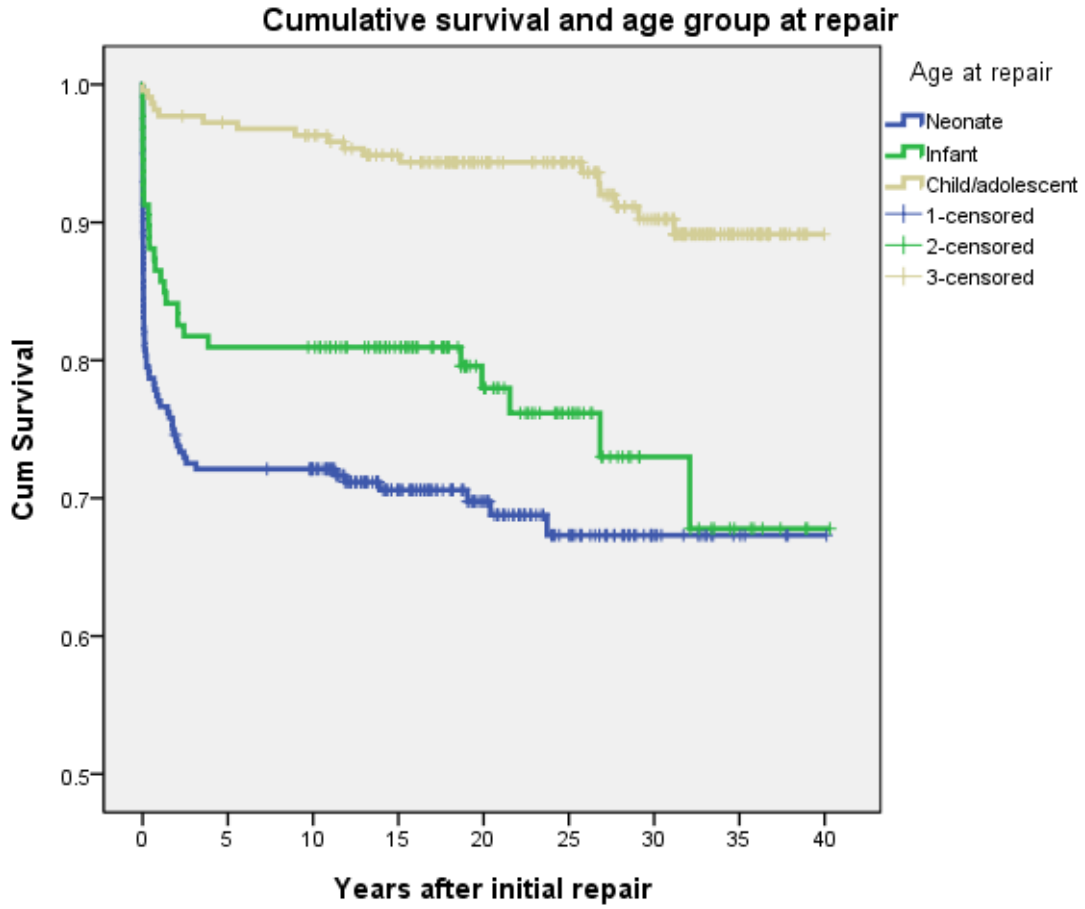
The Kaplan-Meier plot illustrates the differences between the strata based on time period of initial repair. Comparisons of groups showed significant difference sith a p value of 0,002. This coincide with the formerly commented difference in early mortality, this time with the lowest cumulative survival in the group repaired between 1986 and 1990, as an exception from the tendency of higher cumulative survival the later the time period of initial repair.

3.2.2 **Age at primary repair and survival**

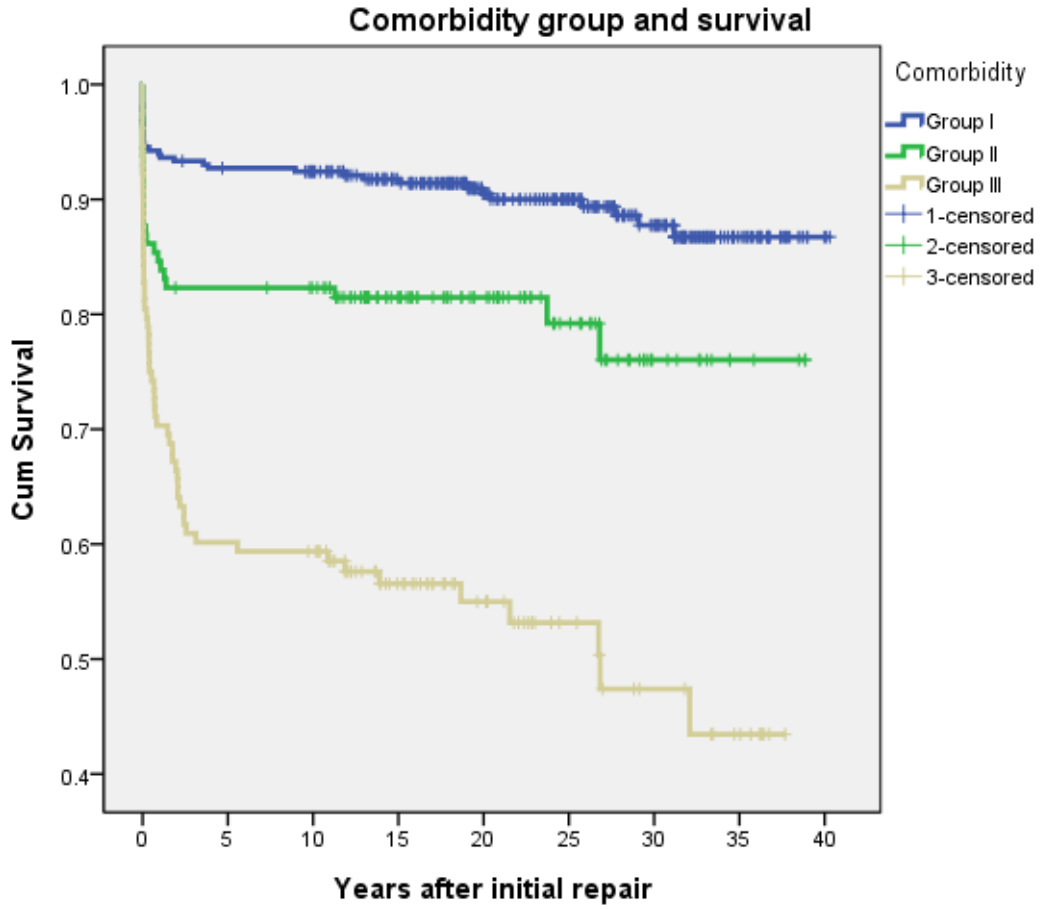


Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	45.857	2	.000
Breslow (Generalized Wilcoxon)	50.167	2	.000

The age at primary repair is shown to influence survival in this Kaplan-Meier plot, being a higher cumulative survival in the group operated beyond 1 year of age, whilst the neonate group has got the lowest cumulative survival. There seems to be a difference between the neonatal and the infancy group, but the two curves seems to converge after 32 to 40 years beyond initial repair. Comparison of age at repair shows a significance level of <0,001.

3.2.3 **Comorbidity and survival**



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	85.718	2	.000
Breslow (Generalized Wilcoxon)	77.405	2	.000

This Kaplan-Meier plot shows the heavy influence of comorbidity on survival, with a significance level below 0,001, the group without significant comorbidity showing a cumulative survival of nearly 90% in contrast to group III, with complex cardiac comorbidity showing a cumulative survical of just above 40% after 35 years. Of the 128 patients in group III, seventy patients (54,7%) was alive at the closing date, while twenty two died during the firste 30 postoperative days (17,2%) after initial repair, three patients died postoperatively after first re-do surgery (2,3%), and one patient shortly after third re-do, as previously described. The late mortality of those in co-morbidity group III was 25% (32 patients)

3.2.4 **Risk factors for death**

To further investigate survival after initial repair, logistic regression analysis was used to highlight risk factors for death. The results are presented in the table below, each parameter consists of different values, and the risk of death is compared agains the referance value (bolded and ref in brackets)

Parameter	Value	Univariate analysis			Multivariate analysis		
		Sig.	**OR**	**95% CI for OR**	**Sig.**	**AOR**	**95% CI for AOR**
Sex	**Male (ref)**						
	Female	.056	1,49	0,99-2,24	.359	1,26	0,77-2,04
Time period	**1971-1975(ref)**						
	1976-1980	.471	0,76	0,36-1,60	.983	1,01	0,42-2,41
	1981-1985	.615	0,83	0,39-1,75	.175	0,54	0,22-1,32
	1986-1990	.623	1,20	0,59-2,45	.038	0,39	0,16-0,95
	1991-1995	.018	0,39	0,18-0,85	.000	0,11	0,04-0,30
	1996-2001	.002	0,27	0,11-0,62	.000	0,018	0,005-0,067
Diagnosis	**Isolated CoA (ref)**						
	Hypoplasia	.780	0,92	0,53-1,62	*.252*	*0,68*	*0,33-1,39*
	Interrupted arch	.000	3,57	1,98-6,43	*.290*	*1,47*	*0,52-4,13*
Comorbidity	**Group I (ref)**						
	Group II	.013	2,03	1,16-3,54	.557	1,22	0,63-2,33
	Group III	.000	7,07	4,30-11,61	.000	7,48	4,11-13,61
Access	**Thoracotomy (ref)**						
	Sternotomy	.276	1,37	0,78-2,40	.000	7.30	2,71-19,67
Op.technique	**EEA (ref)**						
	Patch	.790	1,06	0,68-1,65	*.633*	*0,84*	*0,41-1,72*
	Other	.000	6,68	2,96-15,11	*.466*	*1,47*	*0,52-4,17*
Age at repair	**Neonate (ref)**						
	Infant	.063	0,62	0,37-1,03	.013	0,47	0,26-0,85
	Child/adult	.000	0,20	0,11-0,34	.000	0,14	0,07-0,29

OR – odds ratio, AOR – adjusted odds ratio. Univariate and multivariate analysis, factors contributing to death. The results in italics is omitted from the final multivariate analysis, as they were shown not significant. Sex as a variable was included in the multivariate analysis as a forced variable.

Sex is borderline significant in the initial univariate analysis with an apparent increased odds ratio (OR 1,49; CI:0,99-2,24) for female sex compared to male, but when included in the multivariate calculation, the results shows to be insignificant (p=0,359).

Time period as a predictor for death shows to be significant, being operated in the time period 1986-1990 seems to be a possible (but not significant) risk factor for death when analyzed alone (OR=1,20;CI:0,59-2,45), but when analyzed as a part of the total picture, it shows that having initial repair in this time period is significantly connected to a decreased odds compared to that of the referance period 1971-1975. (OR=0,39; CI:0,16-0,95, p=0,038). The

latest two time periods shows highly significant less risk of death (p<0,001) with respectively OR of 0,39 (CI:0,01-0,30) and 0,018(CI:0,005-0,067).

When comparing isolated CoA with those with hypoplastic aortic arch or interrupted arch, the univariate analysis reveals a highly significant OR of 3,57 (CI:1,98-6,43), indicating that interrupted arch was a considerable risk factor, but as the multivariate analysis displays – the effect is not significant when encountered as a variable in the multivariate analysis.

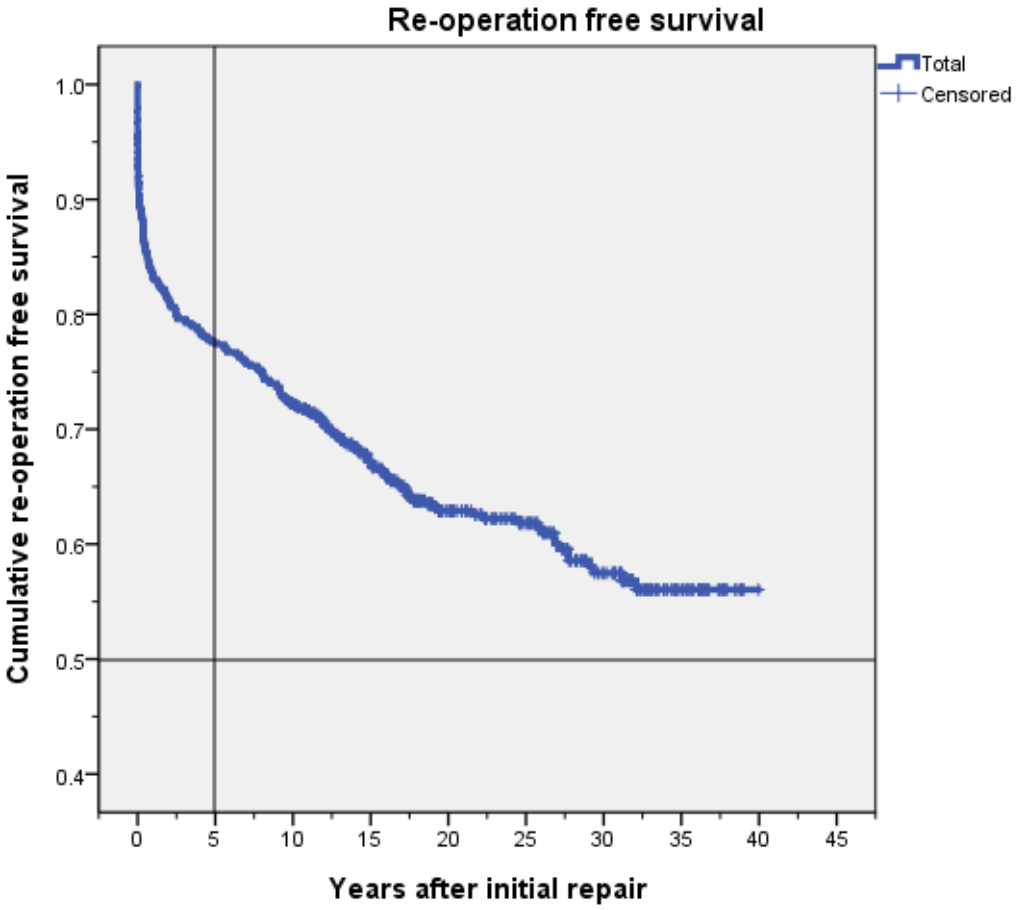
In concomitance with results presented in the Kaplan-Meier plot in 3.1.3, comorbidity group III is shown to be a highly significant (p<0,001) risk factor for death (OR 7,48; CI:4,11-13,61). Being categorized in comorbidity group II on the other hand, follows the same pattern as mentioned above, with significant increased risk when univariately analyzed, but without significance as a part of the multivariate analysis

When the influence of operative access is compared, the opposite pattern emerges, as it shows no significant difference in the univariate analysis, then a rather distinct difference reveals itself in the multivariate analysis, as the sternotomy group has marked increased risk but a quite wide confidence interval. (OR 7,30;CI:2,17-19,67).

The technique of choice seem to play a minor role, and shows no significance as a predictor of death, while age group at repair on the other hand shows that undergoing initial repair during neonatal period is more assiciated with death than undergoing surgery as neonate or child/adolescent.

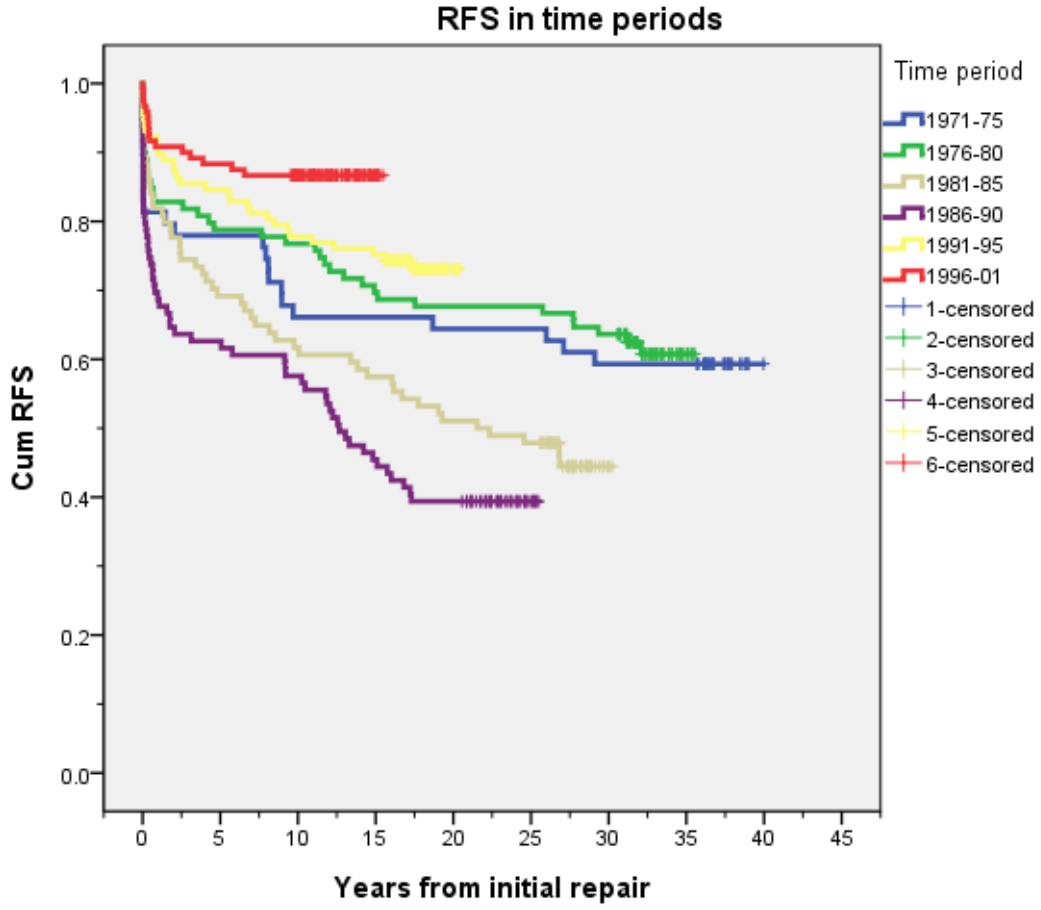
3.3 Re-operation free survival

It is of substantial interest to investigate how big fraction of those who underwent repair who are alive, and who has been without need for subsequent re-operations. This is illustrated in the Kaplan-Meier plot below, where the cumulative re-operation free survival (RFS) is shown.



The overall pattern for this parameter seems to mimic the one of survival, with a quite steep incline in the curve the first couple of years, illustrating early mortality and early re-operations. There is a quite stable incline in RFS from about two and a half year after initial repair and the next fiftheen years, then incline decrease, then finally stabilize at about 32,5yrs postoperatively at a cumulative RFS of approximately 55%.

3.3.1 **RFS and time period**



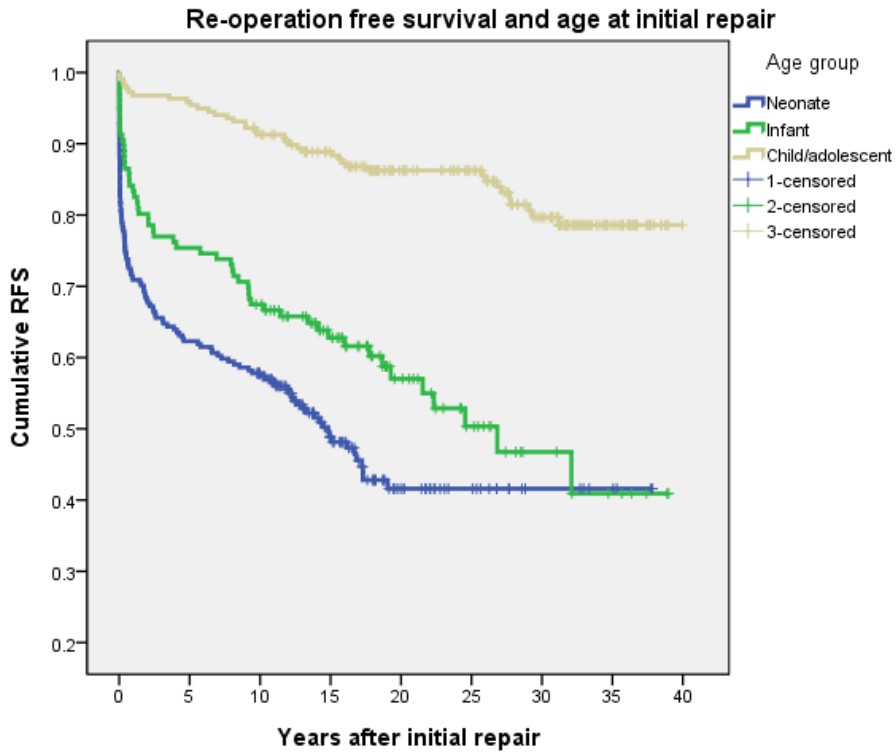
Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	54.745	5	.000
Breslow (Generalized Wilcoxon)	48.678	5	.000

When comparing the re-operation free survival in the different time periods, the difference shows to be highly significant (p<0,001). All periods shows the same trend of steep decline in the curve the first years, representing early mortality and early re-operations Those who underwent surgery in the latest period seems to stabilize at just below 90% after approximately 5 years postoperatively, those operated in the time period between 1991-95 have a greater decline, and seems to stabilize about 20 years after initial repair. Those operated in the time interval 1976-80 does not differ greatly from those operated in the earliest time period, both seems to a have a fairly stable phase from 27 years on, with approximately 60% having an uneventful follow-up after coarctation repair. The former group shows a more gradual decline from the first couple of years, via a plateau phase 15-25 years

after initial repair, while the latter also shows a plateau from the first years until about 8 years postoperatively, then abruptly decreasing from about 80% RFS down to mid 60s, then stabilizing before slowly dropping down to the same level as for the interval between 1976-80. The two groups having the lowest cumulative RFS is those operated in the eighties, with the 1981-85 group steadily declining down to about 45% cumulative RFS, then stabilizing after 27 years. Those operated in late eighties shows the lowest re-operation free survival, with a steep and tall first drop the first years, then steadily decline until about 17, years postoperatively at a cumulative RFS of 40%.

3.3.2 **RFS and age at primary repair**



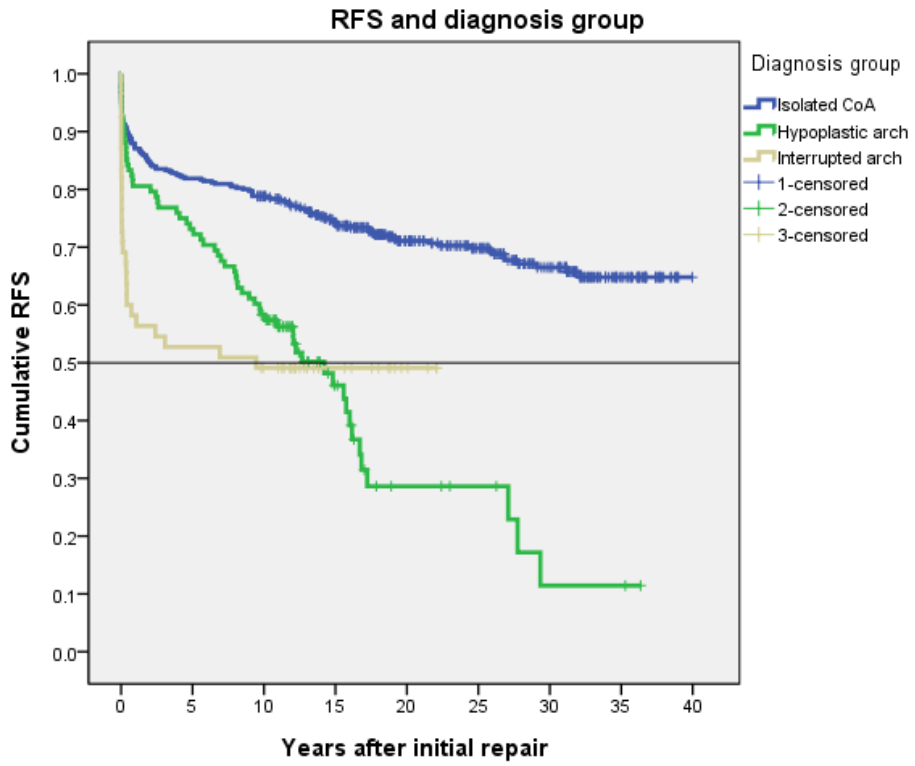
Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	92.066	2	.000
Breslow (Generalized Wilcoxon)	91.279	2	.000

Observing the Kaplan-Meier plot separated on age group of primary repair, quite clearly separates the trend of those operated as children and adolescents from those operated neonatally of during infancy. With a significance level of below 0,001, the trend for those operated beyond first year of life is a stable decline with low rate of early mortality and early re-operations, on the other hand showing a steadily declining curve, stabilizing at a high eighties RFS in the approximate interval between fifteen and twenty five years postoperatively, then a new decline 25-30 years after initial repair, finally stabilizing at about 80% re-operation free survival.

Those operated in the neonatal period shows quite a drop down to 60% during the first five years postoperatively, then steady decline until the curve seems to reach full stagnation at about 18 years until 37 years, at just above 40% RFS. Those operated as infants seem to perform a bit better with regards to RFS, but after 30 years of decline, joining the neonatal group, stabilizing at the same level of above 40% RFS.

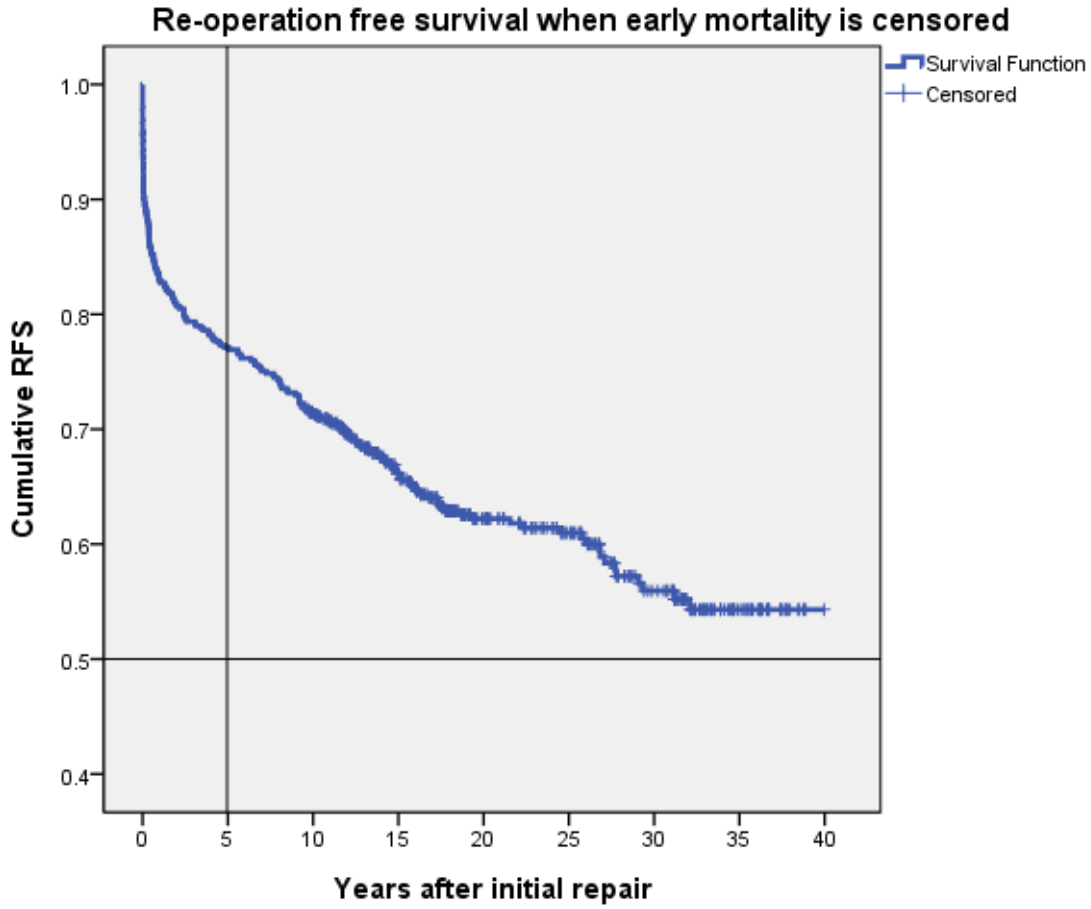
3.3.3 **RFS and Diagnosis**



	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	55.064	2	.000
Breslow (Generalized Wilcoxon)	45.772	2	.000

By separating the patients with regards to their diagnosis, the Kaplan-Meier plot reveals some interesting differences with high significance ($p<0{,}001$). Those diagnosed with isolated CoA showing the highest level of re-operation free survival, with gentle decline until about the thirtieth postoperative year, stabilizing at about 65% RFS. Those with an interrupted arch shows a high rate of re-operation or death the first years, but the decline quite abruptly levels out after about 5 years after initial repair, then stabilizes at 50% re-operation free survival. A diagnosis of a hypoplastic aortic arch seems gives a intermediate early decline, placing itself below the CoA group, but a great deal above the IAA group initially, but in contrast to the other groups, the curve continues to decline steadily, crossing below the IAA group after about 15 years, then reaching a plateau phase 17-27 years postoperatively at just below 27%, then decreasing down to 10% at 30 years after repair.

3.3.4 **Censoring early mortality**



This Kaplan-Meier plot shows that by excluding those who died during the first post-operative days after initial repair, the overall pattern does not differ from the one presented in the beginning of chapter 3.3. When running similar plots in the different categories under chapter 3.3.1 through 3.3.3, the new curves shows the same pattern as those presented when early mortality is included.

3.3.5 **Risk factors for re-operation or death**

As for survival, a logistic regression analysis was performed to investigate which factors predicted re-operation or death in this material. The results are presented in the table below, each parameter consists of different values, and the risk of death is compared against the referance value (bolded and ref in brackets)

Univariate and multivariate analysis, factors contributing to re-operation and death

Parameter	**value**	**Univariate analysis**			**Multivariate analysis**		
		Sig.	**OR**	**95% CI for OR**	**Sig.**	**AOR**	**95% CI for AOR**
Sex	**Male (ref)**						
	Female	.094	1,34	0,95-1,88	.538	1,15	0,74-1,77
Time period	**1971-1975(ref)**						
	1976-1980	.814	0,92	0,47-1,80	.466	1,35	0,60-3,04
	1981-1985	.106	1,73	0,89-3,34	.611	1,24	0,54-2,82
	1986-1990	.012	2,34	1,21-4,54	.731	0,87	0,38-1,98
	1991-1995	.078	0,55	0,28-1,07	.000	0,19	0,08-0,44
	1996-2001	.000	0,23	0,11-0,49	.000	0,02	0,01-0,06
Diagnosis	**Isolated CoA (ref)**						
	Hypoplasia	.000	3,32	2,14-5,13	.000	8,57	4,42-16,62
	Interrupted arch	.002	2,46	1,39-4,34	.001	3,91	1,72-8,89
Comorbidity	**Group I (ref)**						
	Group II	.000	2,15	1,41-3,27	.744	1,10	0,62-1,96
	Group III	.000	3,03	1,98-4,65	.002	2,45	1,40-4,282
Access	**Thoracotomy (ref)**						
	Sternotomy	.103	0,65	0,38-1,09	*.293*	*0,57*	*0,20-1,63*
Op.technique	**EEA (ref)**						
	Patch	.000	2,04	1,41-2,97	*.330*	*1,38*	*0,72-2,64*
	Other	.000	18,64	6,22-55,88	*.087*	*3,20*	*0,85-12,10*
Age at repair	**Neonate (ref)**						
	Infant	.078	0,68	0,44-1,05	.036	0,56	0,33-0,96
	Child/adult	.000	0,19	0,12-0,29	.000	0,12	0,06-0,21

OR – odds ratio, AOR-adjusted odds ratio. Univariate and multivariate analysis, factors predicting death or re-operation. The results in italics is omitted from the final multivariate analysis, as they were shown not significant. Sex as a variable was included in the multivariate analysis as a forced variable.

Sex do not seem to predispose for re-operation or death, showing the same tendency as in the analysis under section 3.1.4, with decreasing significance as more variables are included in the analysis.

Time period on the other hand shows a different pattern, the first three periods not being significantly different from each other, neither in the univariate nor the multivariate analysis. Rather interestingly, being operated in the interval of 1986-1990 shows the opposite pattern of that of the survival analysis, from being significant in the univariate analysis (OR:2,34;CI1,21-4,54) to not significant in the adjusted OR from the multivariate analysis

(p=0,73). Thus, the only time periods significantly predicting re-operation or death is the latest two, where the adjusted analysis show a highly significant result – being operated 1991-95 giving a OR of 0,19 (CI:0,08-0,44), and being operated during the latest period involves a OR of 0,02(CI:0,01-0,06) when compared to the reference period.

As one might suspect from the Kaplan-Meier plot seen in 3.2.3, being labelled with a hypoplastic arch is quite a strong predictor for re-operation or death, with an univariate OR of 3,32(CI:2,14-5,13) at p<0,001, then adjusted to an OR of 8,57(CI:4,42-16,62) when included in the multivariate analysis. Having an interrupted arch at the initial repair is also a significant predictor (adjusted p=0,001) with an adjusted OR of 3,91 (CI:1,72-8,89) compared to isolated coarctation.

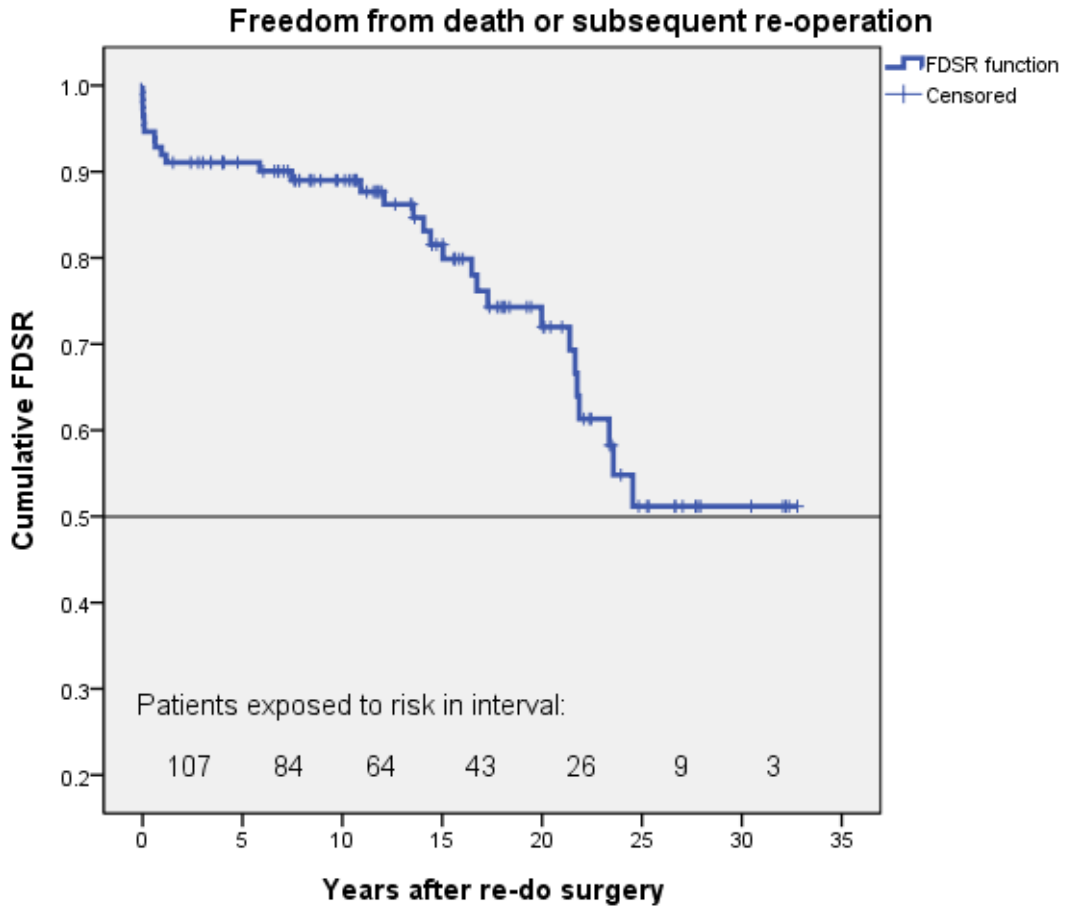
Co-morbidity group II shows the same tendency as in 3.1.4, this time going from highly significant (p<0,001, OR:2,15;CI1,41-3,27) when counted for as single variable, then turning insignificant with a p value of 0,74 in the adjusted analysis. Conversely, being categorized as group III is associated with a increased risk of re-operation or death, with highly significant OR both univariate and adjusted. (AOR:2,45;CI:1,40-4,28)

Concerning operative access, being operated via a sternotomy as the initial repair does not significantly influence the risk of re-operation or death, neither do the choice of operative technique – even though both patch angioplasty and the "other technique" group shows significant increase in risk when treated univariately.

Age at initial repair does also here stand out as a useful predictor, with undergoing repair after one year of age being protective compared to neonatally (AOR:0,12;CI:0,06-0,21). Repair during infancy also turns out to be protective when compared to neonatal repair when included in the multivariate analysis, the p value decreasing from 0,078 to 0,036, with an AOR of 0,56 with confidence interval of 0,33-0,96.

3.4 Subsequent re-operations

Eighteen of the 113 being re-operated needed a second redo session (15,9%), with a median time from initial operation to second re-operation of 16,5 years (range:0,8-28,3). The median time from first re-operation to second re-operation was 15,4 years (range:0-24,5), which indicates the tendency of proximity between initial repair and first re-operation for those re-operated a second time. The median time interval between initial repair and first re-do for this group was 0,68 years (range:0,02-9,2). However when running a univariate regression analysis, having short interval between initial repair and first re-operation does not predict a second re-operation.



The cumulative freedom from death or subsequent repairs seems to be stable at about 90% for about 10 years, then declining with increasing steepness, before stabilizing just abouve 50%. One should bear in mind the small number of patients exposed to risk when interpreting this Kaplan-Meier plot.

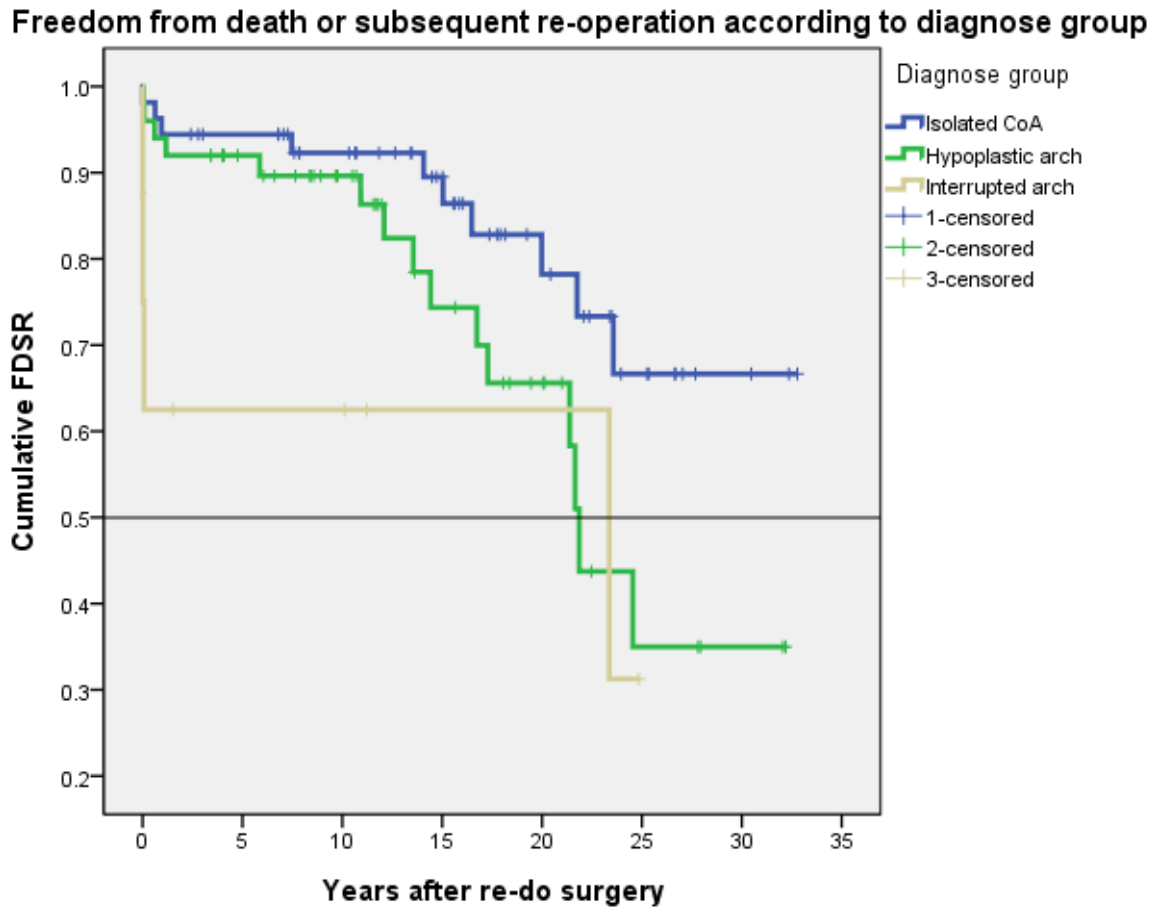
The distribution of choice of operative access at second re-operation is shown in the table below.At second re-do, a higher percentage had their repair from a midline approach than at the first re-do (61,1% vs 29,2%).

Operative access	No of procedures	Percentage
Posterolateral thoracotomy	7	38,9
Median sternotomy	11	61,1
Total	18	100

The operative technique of choice was either patch aortoplasty (44,4%) or insertion of a tube graft (38,9%). At first re-do only 2,7% had a tube graft, while 65,5% recived a patch.

Procedure	No of procedures	Percentage
End-to-end	0	0
Patch	8	44,4
Tube-graft	7	38,9
Other	3	16,7
Total	18	100

3.4.1 **Diagnosis group and freedom from DSR**



	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	7.087	2	.029
Breslow (Generalized Wilcoxon)	9.256	2	.010

When separating the plot into different stratas based on the diagnosis group, there seems to be a significant difference between the groups. Isloated CoA stabilizes at well above 90% for the first 15 years or so, then declining over the next ten years, gaining a new level of about 65% freedom from death of subsequent repair the rest of the timeline. The hypoplasia group seems fairly close to the isolated CoA group in the first years, but starts to decline approximately five years before those with Isolated CoA, and appears to decline way further, stabilizing at 35% after twenty five years past re-do. The interrupted arch plot shows characteristics indicating a too small number of patients, hence it is not trustworthy. Once again, the number of patients at risk in the later time periods is small.

3.4.2 Risk factors for death or subsequent re-operation

Neither diagnosis group, nor initial comorbidty group showed to be significant risk factors for DSR, and when running an multivariate regression including age, time group of initial repair, age group of initial repair, diagnosis group, comorbidity group, operative access at re-do-surgery or operative technique at re-do-surgery, none were significant as predictors.

4 Discussion

4.1 Patients and procedures

4.1.1 Comparability

In this material, both those diagnosed with coarctation and interrupted arch was included, on the same basis as argued by Karl et al., since there is a floating transition from those with hypoplastic arch to those of true interruption, with similar physiology (increased pulmonary blood flow and ductal dependency), presentation (heart failure) and to a certain extent same surgical repair technique.(13) Other retrospective studies, on the other hand, tends to focus on or exclude a special diagnosis or comorbidity group, such as Cohen et al (included only those who underwent isolated coa repair)(44) or Presbitero (excluding early mortality in their analysis)(45) This extensive changeability in inclusion criterias and parameters analyzed makes direct comparison to other series difficult, or at least less meaningful.

4.1.2 Follow-up

With 588 patients and a follow up of 99,3% (584 patients) and a median follow-up of 19,15 years (or 11 215 patient years), this is one of the biggest single institution materials analyzed. Cohen et al performed a study with 646 patients, but long-term follow-up was availiable in 571 patients (mortality status available in 588), other have included from 109 to 362 patients, with a follow-up percentage of 52-97,3% and a median follow-up time of 5,2-27 years (17;22;43;45;48;49) Even though Høimyr et al have fwup time of 27 years, the total amount of patient years is 51,2% of those observed in this study.(49)

4.1.3 Re-operations

The re-operation rate after initial surgery was 19,2%, with a median time to re-do of 8,09 years. The observed median time interval between initial repair and re-do surgery may perfectly well explain why some other studies with shorter follow-up-time have lower re-operation rates. This implication might remind us to interpret reports with extremely low re-operation-free rates or studies presenting unsurpassed success of new surgical approaches with some expectancy. In genereal, the reported prevalence of re-coarctation after end-to-end

anastomosis is about 20% when performed in neonates, 15% if performed at 6 months of age, and below 5% if operated after infancy, whereas reports for patch aortoplasty have been variable, with some reporting recoarctation rates of 18%, and no difference from that of end-to-end anastomosis.(5) Thus, the re-operation rate of 19,2% in this material seems to be in the upper part of the range.

4.1.4 **Mortality**

The reported in-ward mortality rates after initial repair was 6,6%, the total early mortality was 9,4%, which is somewhat higher than the findings of others (2,89-6,0%)(44;48;50) When separated in time periods, the trend is towards less early mortality, with only 2,5% in the last time period, the same trend also seen in other reports(5).

Late mortality was 10%, and total mortality rate was 20,6% when those lost to fwup was considered in the mortality group. These percentages might be attributed to the long follow-up period and the completeness of follow-up. In a danish retrospective study by Høimyr et al with up to 40 year follow-up after EEA and Patch repair, the early mortality was 6%, the late mortality was 15,3% and the total mortality 22,7%(49) Similar findings of total mortality is reported by Cohen et al (17,6%)(44), both being studies with follow-up time of over 20 years, while Presbitero et al reports similar late mortality numbers as do we (11,5%), but has excluded those suffering from early death in their analysis.(45)

Overall survival seems to be quite influenced by the time period of repair (with significantly less risk of death when operated after 1986), the age at initial repair (neonates running the greatest risk, significantly different from both infants and children/adolescents), comorbidity group III and the operative access. There is seemingly a higher risk of being approached from a median sternotomy when analyzing all patients together, while diagnosis group or operative technique do not seem to influence the outcome. In a report by Jahangiri et al, the year of operation had similar influence on survival as in our material, in addition to decreased chance of survival for those having persistent arch hypoplasia after the operation. However, they failed to find a significant difference between neonates and infants.(24) Høimyr found that early decade of surgery did predispose for late mortality, so did age below 1 year of age at surgery as well as class III comorbidity (slightly different classification to the one used in this study). Similar to our results presented in 3.2.4, the danish study showed that surgical technique was insignificant as a predictor of late mortality, so was sex.(49)

4.1.5 Re-operation free survival

By investigating the Kaplan-Meier plot of re-operation free survival, it seems clear that undergoing initial repair does not imply curation, with about 45% of patients either dead, reoperated or both after 40 years, with even lower percentage if repair was done at early age or if concomitant hypoplasia or interruption was present. These results are not directly comparable to those of other studies, but Høimyr et al states that the probability of avoiding -1: death, -2: reintervention(reCoA or aortic surgery, coronary artery intervention or valve surgery) or -3: cardiovascular accidents (myocardial infaction or stroke) at 40 years post-repair is 39%.(49)

In the multivariate analysis, being operated in the latest two time periods seems to be protective, whereas hypoplasia, comorbidity group III and neonate age at repair predicts re-operation or death. In the danish study, event free survival was negatively affected by both comorbidity class II and III.(49)

When looking at death or subsequent re-operations in those undergoing first-re-do, there seems to be a difference between the diagnosis groups, but due to few patients at risk in the later time periods of the Kaplan-Meier plot, the difference remains a bit unclear. None of the variables checked for were significant predictors for death or subsequent re-operations after first re-do.

4.1.6 Hypoplastic aortic arch

One of the great topics of discussion and disagreement when it comes to coarctation and aortic arch surgery, is whether or not to address the hypoplastic aortic arch at initial repair. According to the haemodynamic molding theory, the aortic arch is believed to adapt its proportions according to the amount of blood flow passing through it, thus normalizing its size when normal flow is established(10), but this concept does not seem to have indefinite reach, as some hypoplastic arches does not grow after repair. This heated discussion is further complicated by the lack of consensus when it comes to defining aortic hypoplasia, as seen in the background chapter.

In this material, 18,4% of the infants was labelled as hypoplastic when including those with interrupted arch, and 20,3% when IAA was excluded. In other studies, the reported incidence in neonates is 65-81% (11), whereas if you look at incidence first three months of life it is

reported to be 60-70%(36). Siewers et al report an incidence of 32%, but refers to others who reports from 20-50%(51). In a study of fairly comparable patient population, the incidence of isthmus hypoplasia, arch hypoplasia or both was 32,5%, using the Moulaert criteria(22), while another comparable study revealed an incidence of 14% using the same criteria.(17) The distribution of hypoplastic arch as a diagnosis during the different time periods (as shown in 3.1) in this material could very well explain some of the discrepancy in incidence between what seen in Rikshospitalet's database and in other reports. An another possible contributor to this observable fact, is that the phenomenon of the hypoplastic aortic arch has become more into focus the later decades, thus underlining that you tend to be finding more of what you are looking for. Skeweness in hypoplasia diagnosis during time periods might also reflect the preoperative care development and the age group of repair, since reported incidence is higher among neonates and with the ability of maintaining ductal patency by PGE infusions, neonates that in the early period would have died before reaching the operating room could safely undergo repair in the latest period of time.

Being labelled as having an hypoplastic aortic arch did most significantly affect the freedom of death or reintervention, as shown in the Kaplan-Meier plot in 3.3.3, as well as being identified as the strongest and most powerful predictor variable for death or reintervention in the multivariate analysis, with an AOR of 8,57 compared to Isolated CoA, and even greater than the interrupted arch (AOR 3,91). In contrast, having an aortic arch hypoplasia did not significantly predict death, neither in the univariate nor the multivariate analysis, which further supports the trend of being a strong predictor for re-operations. The same trend has been shown to by Walhout et al in a study of 262 children operated with patch angioplasty or end-to-end anastomosis between 1973 and 2000, but then only significant for transverse arch hypoplasia, not isthmus hypoplasia(22). Hypoplasia as predictor for re-operation is also confirmed by Dodghe-Khatami et al and Jahangiri et al(17;24), but was found not significant when included in multivariate analysis by Kappetein et al(43). It should be noted that in other studies, transverse arch hypoplasia significantly predicted mortality in univariate analysis(32) as did persistent arch hypoplasia after the initial repair in a multivariate analysis of 185 patients undergoing surgery in neonatal or infant age.(24)

To establish a reliable association between aortic arch hypoplasia and risk of re-operation is a powerful contributor to the debate wheather or not to address the hypoplasia at initial repair or not, and to what extent process of haemodynamic molding takes care of an underdeveloped

aortic arch after simple repair. Both the optimal choice of technique and surgical access are debatable. According to Myers et al, most hypoplastic arches will grow after SFA repair, but those of tubular hypoplasia were not included in that study, (10) Siewers et al does also state that extensive repair of a hypoplastic segment with an arch index of 0,30-0,50 seems to be unnecessary, but considers those with an index less than 0,25 as candidates for extended repair.(51) Jahangiri et al states that the arch hypoplasia regresses after subclavian flap repair(24), whereas Poirier studied 37 patients with persisting arch hypoplasia, 30 of them formerly receiving conventional repair, of those 16 with SFA(23). Liu et al states that arch growth after repair rests on studies with relatively short follow-up, with poor definition of the studied anatomy and with insufficient definitions of what is optimal growth. They report that the proximal and distal transverse arch should be analyzed separately due to findings of lack of proximal growth compared to distal growth, and that most patients with moderately hypoplasia demonstrate growth after conventional repair (SFA, EEA, extendedETE). An interesting contribution to the debate of hypoplasia definitions, was that by using Z-score, 35% had small proximal arch at last follow-up (z-score<-2), whereas by using ascending to transverse ratio the 15 year ratio was 0,81+/-0,10, illustrating the influence of choice of hypoplasia definition on the outcome.(14)

4.2 Limitations

Several limitations is apparent in this study. By being a retrospective study spanning thirty years of development within surgical technique, pre-, per-, and post-operative management, the patient material consists of quite a heterogenous group. Secondly, the limitations of database as source of information manifest itself in several aspects. First of all, there was a need for supplemental information sources to gather information missing, or to rule out possible mistypings or misplaced codes. The completeness and progress of the amount of the content in the database is readily observed, as the amount of completed parametres has increased dramatically over the years, which also means that some of the per- and postoperative parameters are missing in the earlier years, making direct comparison impossible. Another weakness is created by the fact that both the coding system for the diagnoses and the procedures did change in 1999, with the new nomenclature not being directly compatibe with the old. For instance, by merging all those categorized as having patch repair into one big group, one would miss out on whether the patch was used as for arch

augumentation or just relief of coarctation, the same as for end-to-end anastomosis – where the degree of hypoplasia relief might differ substantially between classic end-to-end and the extended-end-to-end.

As for the rest of the litterature in this field, the lack of precice definition and consensus about definition of hypoplasia weakens the results. The database did not contain any parameters applicable to calculate ratios, z-scores or z-values, neither did it say wheather hypoplasia was isthmal, distal, proximal or tubular when encountered, and by only controlling the surgical procedure descriptions for those re-operated, one might miss out on those considered hypoplastic but not coded so in the database, hence there is quite a possibility of selection bias in the categorization of diagnosis groups that may favor the impact of aortic arch hypoplasia on re-operations. An another factor that strengthens the impact of hypoplasia is that balloon angioplasties was not included in the analysis. The same analysis might be significantly altered if BA were included to the multivariate risk calculations for re-operation or death analysis as the success rate for BA is higher in those not having hypoplastic arch, thereby possibly avoiding surgical correction in those, but not intervention for re-coarctation.

An another potential weakness of the study is the use of repoeration free survival as a criterion for outcome. Kappetein et al(43) argues that the impact of other concomitant problems such as hypertension, or if there is poor out-patient follow-up in the study population, one migh be missing out those having recoarctaition without knowing. Due to the nature of the study, re-operation free survival was the best availiable end-point in this case.

5 Conclusion

The patient who undergoes operative repair has through the time periods become younger of age at initial repair, and is more likely to have severe cardiac comorbidity. Surgery seems to have become safer the latest three time periods (1986-2001), with an low early mortality despite the tendency to treat more complex cases than in the early periods. It does also seem to be less of a risk for re-operation when operated in a late time period (1991-2001) Neonatal repair is linked to higher risk for death when analyzed all periods together. Being accessed through a median approach does also seem to increase mortality risk compared to lateral thoracotomy, but when looking at re-operation free survival as final outcome, the operative access seems to play a minor role, in contrast to when analyzed as predictor soley for death.

The operative technique seems to play a minor role when analyzed all time periods together.

Mortality is most of all linked to the comorbidity group of the patient with the most severe cardiac comorbidity. Being classified as group III comorbidity also predicts re-operation or death.

In this study, being labelled as having an hypoplastic aortic arch is a strong predictor for re-operation in particular, but not for death.

To further conclude how to best address hypoplasia at initial operation, there is first of all a need for a consensus of the diagnostic criteria and classification, next there is ideally a need for prospective randomized studies to determine the ideal operative technique.

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