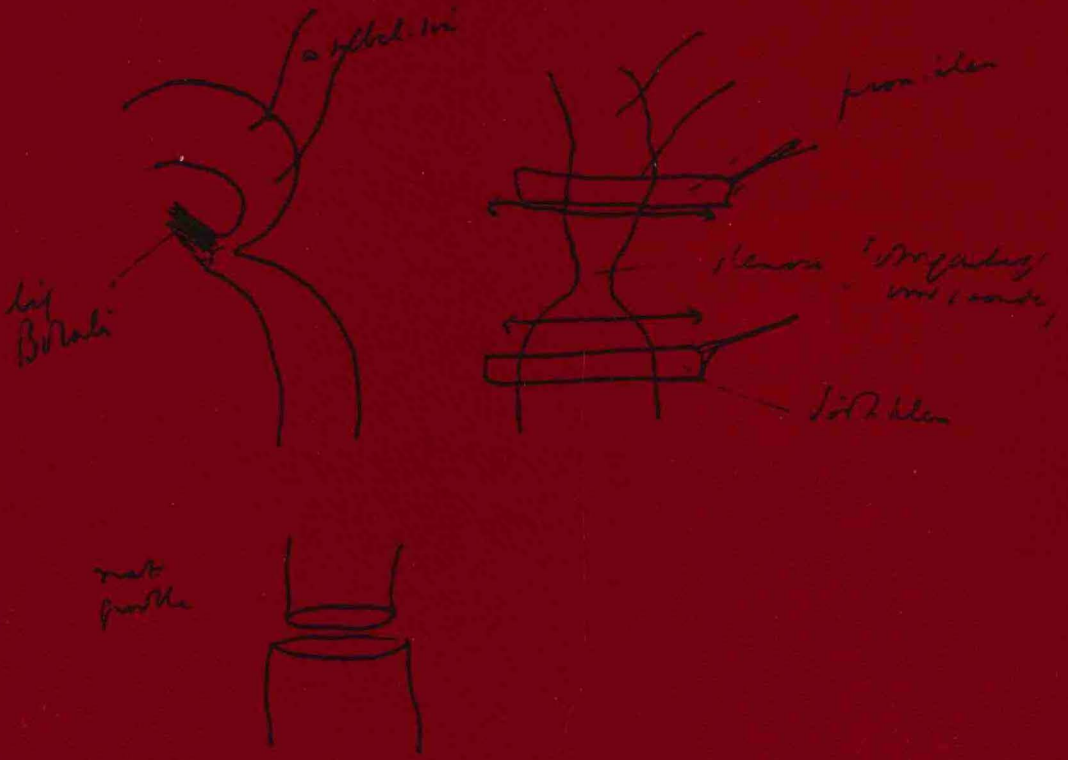
SURGICAL CONSIDERATIONS OF THE AORTIC COARCTATION



HANDTEEKENING OPERATEUR:

M.H.J. Brouwer

SURGICAL CONSIDERATIONS OF THE AORTIC COARCTATION

Stellingen behorende bij het proefschrift

SURGICAL CONSIDERATIONS OF THE AORTIC COARCTATION

M.H.J. Brouwer
Groningen, 19 oktober 1994

I

Gewicht ten tijde van de coarctatio aortae resectie én de gradient over de anastomose, uitgedrukt als een percentage van de op dat moment bestaande systolische bloeddruk, bepalen de kans op recoarctatie. *(proefschrift)*

II

Coarctatio aortae met een hypoplastische aortaboog dient behandeld te worden middels eenvoudige resectie van de coarctatio aortae en end-to-end anastomose. *(proefschrift)*

III

De noodzaak een ventrikelseptumdefect, als bijkomende intra-cardiale afwijking van de coarctatio aortae in één tempo te sluiten, wordt bepaald door de grootte van de preoperatief gemeten totale links-rechts shunt en de morfologie van het ventrikelseptumdefect. *(proefschrift)*

IV

De diameter van de aortaboog bij coarctatio aortae geassocieerd met een ventrikelseptumdefect, is omgekeerd evenredig met de shuntgrootte van het ventrikelseptumdefect. *(proefschrift)*

V

Electieve chirurgische behandeling van de coarctatio aortae dient rondom de leeftijd van 1 1/2 jaar te worden uitgevoerd. *(proefschrift)*

VI

De lengte van de isthmus aortae hangt af of een "korte" dan wel een "lange" rochade heeft plaatsgevonden.

VII

Multivariabele logistische regressie analyse wordt steeds vaker toegepast om risikoverhogende factoren op te sporen. Daarmee wordt de leer van het probabilisme in de medische wetenschap steeds belangrijker.

VIII

Een wetenschappelijk artikel is niet langer alleen een manier om met vakgenoten te communiceren, doch dient ook om de eigen status te verhogen.

IX

Het is juister te spreken over "ijzer prime" dan over "quick prime".

X

Vanwege de dubbele vergrijzing van onze samenleving én het feit dat leeftijd geen absolute contra-indicatie meer is voor open hart chirurgie, zou geriatrische cardiopulmonale chirurgie een erkend subspecialisme moeten worden.

XI

Hart- en longtransplantaties zijn ingrepen die het daglicht niet kunnen verdragen.

XII

Colitis ulcerosa is chirurgisch te genezen.

XIII

De overeenkomst tussen de eerste vrije val bij parachutespringen en het voor het eerst uitvoeren van een open hart operatie wordt gekenmerkt door angst vooraf, afgrijzen tijdens en opluchting nadien.

XIV

Indien men de aanbeveling "sta even stil bij het werk op de weg" te letterlijk neemt, zal het file probleem in Nederland nooit opgelost worden.

XV

Gezien de vruchtbare grondsoort löss, de typische geografische vorm en ligging ten opzichte van de rest van Nederland, kan met recht gesteld worden dat Zuid-Limburg het scrotum van Nederland is.

XVI

Een arts dient zijn patient zó te behandelen zoals hijzelf behandeld zou willen worden.

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SURGICAL CONSIDERATIONS OF THE AORTIC COARCTATION

PROEFSCHRIFT

ter verkrijging van het doctoraat in de Geneeskunde
aan de Rijksuniversiteit Groningen
op gezag van de Rector Magnificus Dr. F. van der Woude
in het openbaar te verdedigen op woensdag 19 oktober 1994
des namiddags te 4.00 uur
door

Marinus Hendrikus Josephus Brouwer

geboren op 12 juli 1957 te Hoensbroek

1994

Drukkerij Van Denderen
Groningen

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Voor Anette,
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Table of Contents

Repair of Aortic Coarctation in infants.

A retrospective study

The Journal of Thoracic and Cardiovascular Surgery 1991;6:1093-1098

Growth of the Hypoplastic Aortic Arch after simple Coarctation resection and End-to-End Anastomosis.

A prospective study

The Journal of Thoracic and Cardiovascular Surgery 1992;2:426-433

Decision making for the surgical management of Aortic Coarctation associated with Ventricular Septal Defect.

A retrospective study

The Journal of Thoracic and Cardiovascular Surgery (submitted)

Chapter I

Introduction

Chapter I

I 1 Introduction

Aortic coarctation is a congenital narrowing of the upper descending thoracic aorta, which is sufficiently severe that there is a pressure gradient across the area. The typical anomaly is a shelf-like protrusion which develops most directly opposite the arterial duct and fades away on either side, anteriorly and posteriorly. The result is an eccentric, localized narrowing of the aorta that externally corresponds to a notch in the aortic wall (Fig.I-1).

Aortic coarctation is likely to cause symptoms during infancy either because of associated cardiac anomalies and severe obstruction or during adolescence and adulthood because of the sequelae of systemic hypertension.

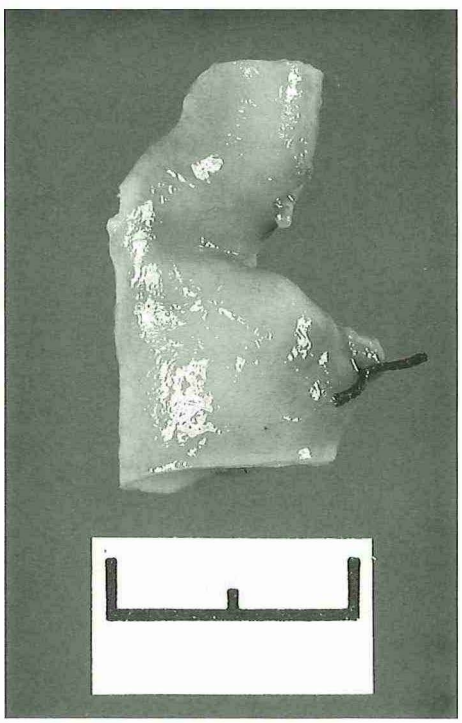


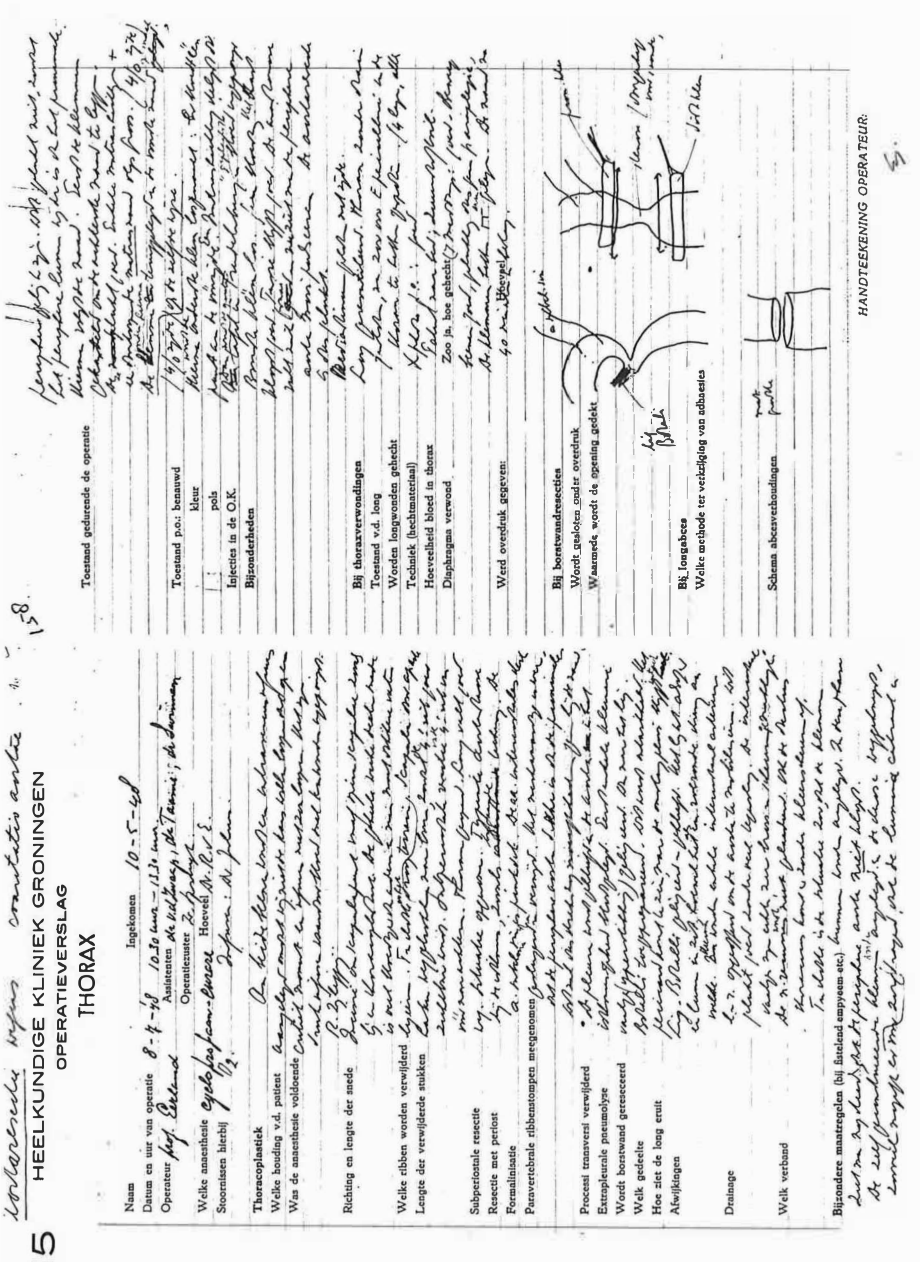
Figure I-1 *Autopsy specimen showing a juxtaductal aortic coarctation due to a localized shelf with a typical external deformity of the aorta at the site of the narrowing.*

Among all neonates born alive with isolated aortic coarctation and that are untreated surgically, about 10% die of acute cardiac failure during the first month of life. Another 40% may be expected to die between 1 and 4 years of age, usually from chronic heart failure. About 50% of the original group die between 14 and 50 years of age, of bacterial endocarditis, aortic rupture, intracranial hemorrhage or from heart failure secondary to systemic hypertension, coronary artery or valvar disease. As a consequence, about 90% of the original group has died before 50 years of age.[1]

The first aortic coarctation repair was performed by Crafoord on ***October 19, 1944*** at the Sabbatsberg Hospital in Stockholm.[2] The publication of Crafoord's article was recieved by the Journal of Thoracic Surgery on June 1, 1945 having undoubtedly taken many months during World War II to come from Sweden and was published in the autumn of 1945. Meanwhile, Gross publised his experimental article concerning the surgical correction of the aortic coarctation on September 6, 1945 together with an addendum briefly summarizing the two operations done on June 28 and July 6, 1945. Thus, Gross' article was the first one published in the English language documenting repair of aortic coarctation although Crafoord's patient had been operated on 8 months earlier. The first aortic coarctation repair in Groningen was performed July 8, 1948 in a 14 year old boy by Prof. Dr. L.D. Eerland (Fig.I-2). Since then till 1994, 590 patients have undergone aortic coarctation repair at the Division of Cardiopulmonary Surgery of the University of Groningen (Fig.I-3).

After 5 decades of experience with aortic coarctation repair, one might expect consensus regarding the ideal management of this congenital anomaly. The ideal management must include early referral, effective resuscitation if required, accurate comprehensive and atraumatic diagnosis of the congenital anomaly and any presenting complications. Formulation of a flawless plan that takes into account all the patient's presenting problems, and timely and flawless execution of the management plan. Furthermore, careful follow-up to allow identification of residual or emerging problems, which are to be handled by a further ideal management package.[3]

However, aortic coarctation embraces a wide spectrum of anatomic variations and concomitant intracardiac defects. So, the ideal management still remains controversial. For this reason, it is unlikely that a single surgical method will be appropiate for all types. In 50 years, much has changed regarding the treatment and results of primary aortic coarctation repair and one should see these changes in their perspective: before 1944, there was no definitive therapy, in the seventies, the original surgical procedure was generally accepted and the mortality was more than halved in neonates and children. Currently, there is discussion how to relieve the obstruction with no mortality and without opening the chest![4]


15 HEELKUNDIGE KLINIEK GRONINGEN
OPERATIEVERSLAG
THORAX

Naam
Ingekomen 10-5-48
Datum en uur van operatie 8-7-48 10.30 uur – 13.30 uur
Operateur Prof. Eerland
Assistenten
Operatiezuster
Welke anaesthesie
Hoeveel
Stoornissen hierbij
Thoracoplastiek
Welke houding v.d. patient
Was de anaesthesie voldoende
Richting en lengte der snede
Welke ribben worden verwijderd
Lengte der verwijderde stukken
Subperiostale resectie
Resectie met periost
Formalinisatie
Paravertebrale ribbenstompen meegenomen
Processi transversi verwijderd
Extrapleurale pneumolyse
Wordt borstwand gereseceerd
Welk gedeelte
Hoe ziet de long eruit
Afwijkingen
Drainage
Welk verband
Bijzondere maatregelen (bij fistelend empyeem etc.)
Toestand gedurende de operatie
Toestand p.o.: benauwd
kleur
pols
Injecties in de O.K.
Bijzonderheden
Bij thoraxverwondingen
Toestand v.d. long
Worden longwonden gehecht
Techniek (hechtmateriaal)
Hoeveelheid bloed in thorax
Diaphragma verwond
Zoo ja, hoe gehecht
Werd overdruk gegeven:
Hoeveel
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Wordt gesloten onder overdruk
Waarmede wordt de opening gedekt
Bij longabces
Welke methode ter verkrijging van adhaesies
Schema abcesverhoudingen
HANDTEEKENING OPERATEUR:

Figure I-2 *Report of the first operation for aortic coarctation performed by Prof. Dr. L.D. Eerland (Academic Hospital of Groningen)*

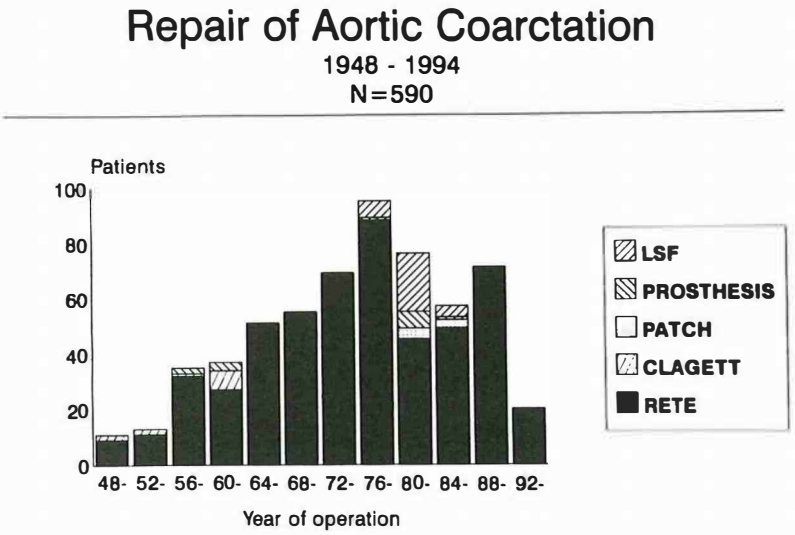

Figure I-3 *Number of aortic coarctation repairs from 1948 till 1994 at the Division of Cardiopulmonary Surgery of the University Hospital Groningen. Note that in this period, the resection and end-to-end anastomosis (RETE) has been the surgical technique predominantly performed. After 1985, the left subclavian flap angioplasty (LSF) has been abandoned. (Glagett; subclavian artery - descending aorta end-to-end anastomosis)*

I.2 References

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Chapter II

General Information

Chapter II

II 1 Historical Note

Aortic coarctation at autopsy was described first by the Prussian anatomist Johann Friederich Meckel in 1750 and later by Joannes Baptista Morgagni, professor of anatomy in Padua, in 1760.[1] In 1791, Paris, anatomist of the Hôtel-Dieu in Paris, was the first to describe the pathologic features fully in a female.[1] He observed that the thoracic arteries were larger and more tortuous than usual, and that the part of the aorta beyond its arch, between the remains of the arterial duct and the first inferior intercostal artery, was so contracted that its diameter was no more than a writing-quill.

In 1814, Graham, a clinician in Glasgow, was the first who envisioned the problem of aortic coarctation in clinical terms. His report was an attempt to establish diagnostic criteria for the disease.[2] Two other cases were published by Otto and Bertin in 1824.[3] In 1827, Meckel published a case report, which included a diagram illustrating the extensive collateral circulation and the presence of erosion of the ribs (Fig. II-4).[4]

In 1903, Bonnett suggested to divide the aortic coarctation into two groups, describing the infantile (preductal) type, as a tubular narrowing of the aortic isthmus and the adult (postductal) type. This classification, which has tended to persist ever since has become obsolete because most infants have more or less juxtaductal aortic coarctations in which the critical factor is hypoplasia of the aortic arch.[5,6]

The natural fate of the patients with unrepaired aortic coarctation was subsequently revealed by Campbell in his review of 304 necropsy cases in the combined series of Abbott and Reifenstein.[7-9] He discovered that, without repair, patients with aortic coarctation were subject to premature death at a mean of 34 years, caused most commonly by heart failure, aortic rupture, bacterial endocarditis, and intracranial hemorrhage.

The fact that aortic coarctation was frequently a cause of death in infancy, was reported by Calodney and Bahn in 1951.[10,11] Animal experiments designed to develop surgical treatment were published in 1944 by Blalock and Park.[12] They divided the left subclavian artery and turned it down onto the aorta. In 1938, Gross and Hufnagel commenced experiments involving resection and end-to-end anastomosis.[13]

However, the first aortic coarctation repair in a patient was reported by Crafoord and Nylin in October 1944.[14] Gross and Hufnagel were able to duplicate this success in June 1945.[15] The operation consisted in resection of the constricted portion and end-to-end anastomosis of the aorta. In 1947, Clagett reported the first successful anastomosis of the left subclavian artery to the aorta.[16] Extension of the repair into the infant group began in the 1950's: after an unsuccessfully repair in an infant using an arterial graft, successful resection and end-to-end anastomosis in infancy was reported by Calodney, Lynxwiler, Kirklin and Mustard.[10,17-19] Clinical studies revealed that prompt correction of the aortic coarctation and division of the arterial duct was the only rational form of treatment for these patients.[20] Furthermore, the optimal age for surgery

was thought to be between 8 and 20 years of life.[21] Since then, modifications in surgical repair have been developed. Prompted by the incidence of recoarctation, Vosschulte in 1957 introduced the prosthetic patch aortoplasty and the simple vertical incision and its transverse closure.[22] Subclavian flap aortoplasty was introduced by Waldhausen and Nahrwold in 1966 as an alternative surgical procedure.[23]

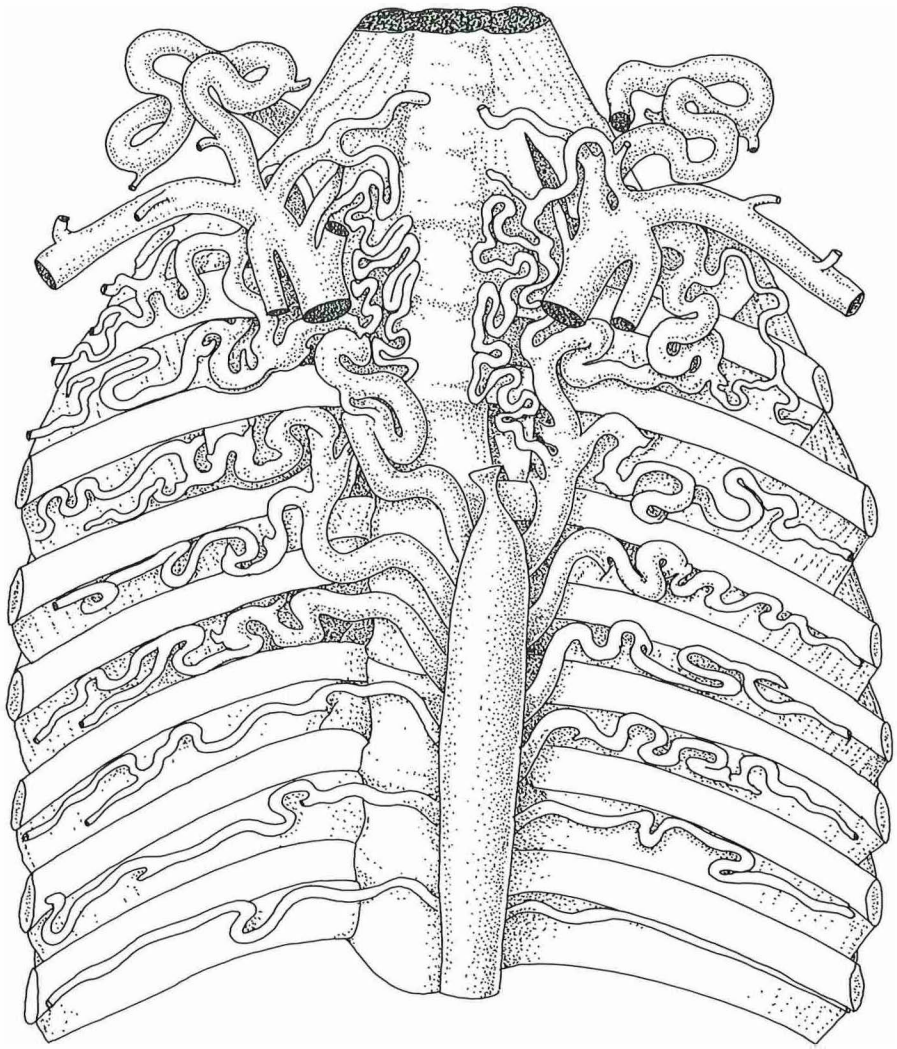

Figure II-4 *The extensive collateral channels and the presence of erosion of the ribs. (Redrawn after Meckel)*

II 2 Embryology

All mammals, including our own species, postnatally have an aortic arch system that consists of the aortic arch, the brachiocephalic trunk, the carotid and subclavian arteries, the pulmonary artery and arterial duct. Description of the aortic arch and its embryologic development and the development of the pulmonary artery, are based on the studies of Congdon.[24] The first pair of aortic arch arteries is formed when the basic body form of the embryo is established at an ovulation age of 3 weeks. As additional pharyngeal arches develop, each acquires its own aortic arch artery. Eventually six aortic arch arteries will develop, but at no point all six arteries are simultaneously present. By the time the third and fourth aortic arch arteries are established, the first two have been reduced to a portion of the maxillary and stapedial artery respectively (Fig.II-5a). At an ovulation age of 35 days, the aortic arch has lost its originally symmetrical pattern. The segments of the dorsal aorta between the third and fourth arch arteries have disappeared, and the third pair of aortic arch artery elongates as the heart descends further in the thorax. The dorsal portion of the right sixth aortic arch artery disappears and the right recurrent laryngeal nerve courses around the right fourth aortic arch artery which will become the origin the right subclavian artery. The seventh intersegmental artery has migrated craniad and gives rise to the left subclavian artery. The origin of the left subclavian artery is located distally to the pulmonary artery and shifts upward as the arterial duct moves downwards. This simultaneous up-and downward migration ('the Rochade') eventually determines the future aortic isthmus.[25,26]

At an ovulation age of 38 days, the part of the right dorsal aorta between the left dorsal aorta and the origin of the right seventh intersegmental artery disappears and the remainder with the right fourth aortic arch artery forms the proximal part of the right subclavian artery. The origin of the site of the isthmus is related to the left fourth and sixth branchial arches and the dorsal aorta.

The early development of the pulmonary artery differs as opposed to the earlier arches which arise from ventral and dorsal sprouts. According to Congdon, the aortic sac gives rise to a ventral sprout, which elongates caudally to form a large plexus. The plexus is situated ventral to the pharynx and extends caudally beyond the level of the dorsal sprout. The 'pulmonary arch artery' becomes continuous by the subsequent extension of the dorsal aorta, which joins the ventral plexus midway. The distal portion of the ventral vessel is formed by the primitive pulmonary artery, while the proximal portion becomes, together with the dorsal sprout from the dorsal aorta, the definitive pulmonary arch artery.(Fig.II-5a).[24] Additionally, Congdon noticed no other connections between the dorsal aorta and the ventrally situated pulmonary plexus other than this pulmonary arch artery. In contrast however, renewed studies of the development of the branchial arch system, performed by the Leiden group, clearly show that both the pulmonary arch arteries and the pulmonary arteries develop from a pre-existing plexus consisting of endothelial cells and precursors. Initially this plexus communicates with the dorsal aorta. When the pulmonary arteries develop ventrally in the plexus these connections disappear, except for the most cranial pair which give rise the definitive pulmonary arch arteries.[27,28] After birth the distal part of the left sixth aortic arch which

is the arterial duct, obliterates and is converted to the ligamentum arteriosum.

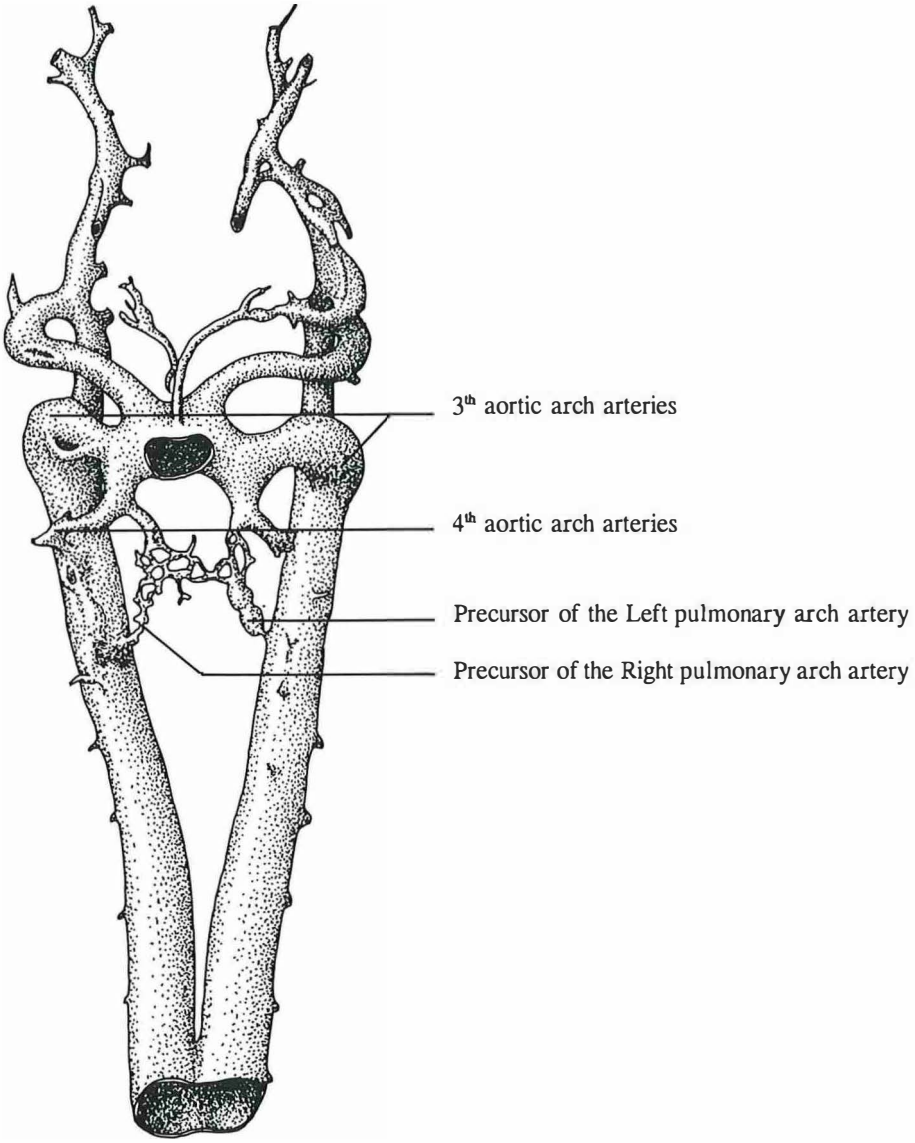

Figure II-5 *Ventral view of an embryo in which the first aortic arch artery has gone, the second is much reduced, and the third arch artery has well developed. Dorsal and ventral outgrowths for the fourth and the pulmonary arch artery are present. (Redrawn after Congdon)*

II 3 Morphology

Coarctation derives from Latin 'coarctatio', which literally means a 'drawing together', and is one of the more common forms of congenital cardiac disease reported to occur in 4-8% of newborns born with a congenital cardiac anomaly. In fact, aortic coarctation is an extracardiac defect, but its frequent association with cardiac anomalies justifies its inclusion in any account of congenital heart disease. It is a shelf-like protrusion or infolding of the aortic media into the lumen, which is most prominent in that portion of the circumference opposite the arterial duct and fades away on either side, anteriorly and posteriorly. This inward protrusion is absent on the ductal side. The result is an eccentric, localized narrowing of the aorta. It is marked externally by an localized indentation or notch of the left aortic wall, pulling the aorta toward the arterial duct like a string (Fig.I-1).[29,30]

The depth of the notch does not necessarily correspond to the severity of the coarctation, and may be absent in the neonate.[31] The aorta beyond the aortic coarctation shows poststenotic dilatation and the wall beyond the aortic coarctation is usually thicker. Almost always, in addition to the infolding of the aortic media, there is a localized hypertrophy or intimal veil producing a pinhole meatus, representing the only communication between the ascending and descending aorta (Fig.II-6).[32] A circumferential sling of ductal tissue is always identified. Moreover, tonguelike prolongations of ductal tissue extend distally from the circumferential sling and occupy constant positions in the aortic wall; one tonguelike prolongation extends distally below the insertion of the arterial duct and the other from the circumferential sling opposite the entrance of the arterial duct.[31,33-35]

From the anatomic point of view, **discrete** aortic coarctation, the commonest form, and **tubular hypoplasia** can be distinguished. The **discrete** aortic coarctation descibes a shelf-like lesion frequently with a tapering of the aortic arch upstream and hypoplasia of the isthmus, while tubular hypoplasia describes a narrowing of a part of the aortic arch. Currently, the classification of aortic coarctation is based on the location of the protrusion relative to the entrance on the arterial duct (pre-, post-, or juxtaductal). Preductal coarctation with or without a patent arterial duct, is the most common type and generally presents itself in young infants. There is nearly always isthmal hypoplasia with tapering down to the isthmus-ductal junction to produce a 'waist' lesion (Fig.I-1). The aortic coarctation itself is produced by a 'shelf lesion' superimposed upon the waist. The shelf is composed of ductal tissue which completely encircles the isthmic orifice. Preductal coarctation is associated with other major cardiovascular anomalies such as subaortic perimembranous ventricular septal defect with or without extension into the inlet or outlet septum, bicuspid aortic valve or mitral valve anomalies. Paraductal and postductal coarctations are uncommon and often seen in older children in which the arterial duct is generally converted to a ligament.

It has become fashionable to consider the pre- and paraductal as well as postductal coarctations simply to be juxtaductal. However, this term is inadequate and confusing: if it is meant to indicate that the lesion is exactly opposite the mouth of the arterial duct, then such lesions do exist. But, almost all lesion are in the environs of the

arterial duct, be they pre- para- or postductal in position. Therefore, the choice of 'paraductal' might be a better adjective to describe the obstructions which occur opposite the mouth of the arterial duct.[34-36]

During the first 3 months of life, the isthmic aortic coarctation is associated with hypoplasia of the aortic arch in at least 60% to 70% of patients.[37-40] The aortic arch comprises the transverse arch and the isthmus. The transverse arch lies between the brachiocephalic artery and the left subclavian artery; the isthmus lies between the left subclavian artery and the patent arterial duct. The hypoplasia is most usually a gradual narrowing down from the origin of the left subclavian artery to the site of the coarctation. This arrangement is called **tubular hypoplasia** and can affect the segment of the aortic arch between the left common carotid and left subclavian artery, or rarely between the brachiocephalic and left common carotid artery.[25]

According to Moulaert[41], a segment of the aortic arch is hypoplastic if its diameter is less than 50% of the diameter of the ascending aorta and if its length exceeds 5 mm. However, from the hemodynamic point of view, the ascending aorta is more liable to display an abnormal blood flow pattern than the descending aorta due to obstructions in the left ventricular outflow tract.[42] Therefore, it seems to be more accurate to choose the descending aorta instead of the ascending aorta as the reference point as will be discussed in chapter VI. Furthermore, blood flow seems to determine the number of elastin lamellae in the hypoplastic arch, which is significantly lower than in the corresponding segments of normal specimens.[43] This finding implicates that decreased blood flow through the left ventricular outflow tract has a detrimental effect on the normal development of the aortic arch and ascending aorta.

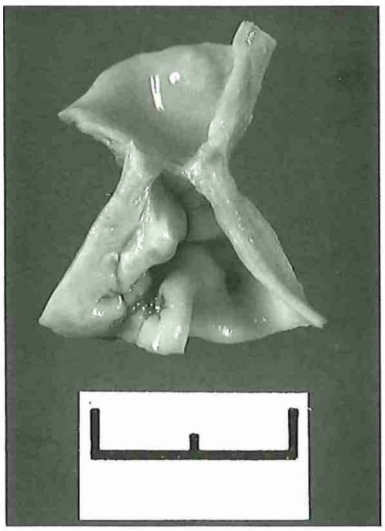

Figure II-6 *Autopsy specimen showing a juxtaductal aortic coarctation due to a localized shelf with a typical external deformity of the aorta at the site of the narrowing. Note the localized hypertrophy or intimal veil producing a pinhole meatus, representing the only communication between the ascending and descending aorta.*

II 4 Pathogenesis

The mechanism of formation of the aortic coarctation is still disputed. Several theories have been proposed. The first theory, proposed by Craigie[44] in 1841 and restated by Skoda[45] in 1855, is supported by histologic studies of the region of the arterial duct and the aortic coarctation. Abnormal extension of contractile ductal tissue into the aorta and forming a sling around the infolded wall, is thought to be a significant pathogenetic factor in the creation of the intra-aortic shelf with further accentuation of the obstruction when the arterial duct closes.[31,46,47] In normal hearts, ductal tissue may extend around the normal aorta for up to 30% of its circumference and has a very discrete junction with the aorta, not extending around the isthmus-aortic junction. In contrast, in arches with aortic coarctation, the isthmus inserts into a sling composed of ductal tissue. Moreover, the self lesion becomes converted from ductal tissue in the young hearts into fibrous tissue in older hearts.[46]

In contrast to the role of the arterial duct as a mechanism of development of aortic coarctation, Clagett[48] speculated that the proximal movement of the left seventh intersegmental artery (left subclavian artery) beyond the junction of the arterial duct with the aorta was involved, a phenomenom which was recognized by Bruins as well. In her work, Bruins pointed at the important rearrangement of the left subclavian artery relative to the arterial duct during development, an event she compared to the castling movement in chess ('the Rochade').[26] More recently, Kantoch confirmed this subclavian artery involvement in the pathogenesis of the aortic coarctation by echocardiography. He found that a more distal displacement of the subclavian artery was associated with aortic coarctation as compared to normal anatomy and that the subclavian artery and the proximal segment of the aortic arch formed an acute angle of less than 90 degrees.[49]

The theory about abnormalities of blood flow has much recent support. Any anomaly that causes prenatal obstruction to aortic arch flow, can cause greater than normal ductal flow and produce aortic coarctation. Under these conditions, the site of entrance of the arterial duct into the aorta becomes a branch point of the arterial duct.[50] The hypothesis is that if there is relatively greater pulmonic than aortic flow, there would be a predisposition to aortic coarctation when the ductal flow divides into proximal and distal streams. Rudolph et al promoted this concept based on inequality of flow through the aortic and pulmonary pathways during fetal life.[6] They argued that diameters of vessels were proportional to flow through them and that almost always when the arterial duct is patent, a lesion is found within the heart itself which diverts blood away from the aorta and into the pulmonary arterial system and thence to the arterial duct. Furthermore, they hypothezised that any lesion that further reduced aortic flow during fetal life would potentiate to the development of significant isthmal hypoplasia.

Finally, Elzenga et al proposed that in the presence of a left-sided obstruction, there is an increase in right-to-left flow through the arterial duct during in utero development. This results in migration of ductal tissue into the adjacent aorta wall. Conversely, if there is a right-sided obstructive lesion such as tetralogy of Fallot or pulmonary atresia with a ventricular septal defect, left-to-right flow through the arterial

duct results in migration of ductal tissue into the left pulmonary artery potentially causing juxtaductal pulmonary artery coarctation.[51-53]

Thus, the patterns of flow are important in the setting of the aortic coarctation, however the protagonists of the flow hypothesis overstep the mark when they suggest that ductal tissue itself has no involvement in the aortic coarctation lesion. Furthermore, they do not explain all examples of aortic coarctation, nor rule out the additional factor of retraction of ductal tissue during closure of the arterial duct. So, it should be remembered, that many infants with aortic coarctation do not have anatomical evidence of lesions which have reduced aortic flow during development.[32,43]

Recently, studies have shown that abnormalities of the cranial neural crest play a role in the pathogenesis of the aortic coarctation.[54] The cranial neural crest gives rise to ectomesenchym from which the pharyngeal arches III, IV and VI originate. Lesions of cranial neural crest at time of the development of the pharyngeal arches III, IV and VI may explain the anomalies with structures deriving from the arches.

Elastic lamellae contribute markedly to the internal diameter and strength of the aorta. Patients with an aortic coarctation and hypoplastic aortic arch, show a lower number of elastic lamellae in the wall of the isthmus and proximal aortic arch. In contrast to Becker[43], the Leiden group believes that this phenomenom cannot be explained by the reduced blood flow. In the setting of an aortic coarctation and a closed arterial duct, they found that the number of elastic lamellae in the ascending aorta turned out to be reduced despite a normal blood flow. Apparently, a developmental error is likely to play a more important role in the pathogenesis of the divergent structures of the aortic wall than blood flow. Therefore they conclude that the elastogenic matrix of the aortic wall and the formation of the outflow tract of the heart itself are influenced by cells from the cardiac neural crest. Developmental errors of the aortic arch might therefore, be associated with outflow tract anomalies such as the outlet ventricular septal defect or subaortic narrowing.[55]

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Chapter III

Interventions for Aortic Coarctation

III 1 Non Elective Procedure
III 1.1 Resection and end-to-end anastomosis
III 1.2 Prosthetic patch angioplasty
III 1.3 Subclavian flap angioplasty
III 1.4 Extended resection and end-to-end repair
III 1.5 Alternative surgical procedures
III 1.6 Balloon dilation angioplasty

III 2 Elective Procedure
III 3 References

Chapter III

General Remarks

The diagnosis of aortic coarctation is an indication for treatment, since the probability of survival and resting upper body normotensive state are greater after repair than in the natural history of the condition. In the past era, the ideal age for elective aortic coarctation repair was supposed to be between 4 years and adolescence (Chapter VIII). Currently, the presence of congestive heart failure in infants with an aortic coarctation plays an important role in the clinical decision whether to operate promptly or not. Therefore, the treatment of aortic coarctation can be divided in an non-elective and elective procedure, depending on the clinical condition of the infant.

III 1 Non-elective procedure

The non-elective procedure for neonates with aortic coarctation is determined by morphology of the aortic coarctation, associated intracardiac defects, pathophysiology, nonsurgical and surgical options, and potential postoperative complications. About half of all neonates born with an aortic coarctation develop within the first month of life symptoms of congestive heart failure attributed to a number of pathophysiological factors and therefore require a non-elective intervention.[1] The first factor is the natural closure of the arterial duct which begins on the side of the nearest to the pulmonary artery and progresses to the aortic end at the end of the second week of age.[2,3] As long as the arterial duct is still patent, pulmonary overcirculation may produce right ventricular enlargement and failure in patients with an aortic coarctation. After closure of the arterial duct, sudden loss of flow into the descending aorta precipitates left ventricular hypertrophy and congestive heart failure. Graham found that abnormalities of left ventricular pump function is common in the setting of an aortic coarctation. Left ventricular stroke volume and ejection fraction are depressed. These pathophysiologic events are primarily related to afterload mismatch brought about by the sudden and rapidly developing aortic coarctation as the arterial duct closes. Moreover, retraction of ductal tissue, fibrous change and intimal proliferation all contribute to further development of the aortic coarctation.[4-6] Furthermore, these morphologic and hemodynamic changes possibly precipitate alterations in the renin-angiotensin system [7-18], mechanical properties of the left ventricle and the aorta, the setting of the baroreceptors, upper segment arterial vessel wall changes, and reflex activity to the heart.[19-32] All these events may compound each other to the development of congestive heart failure and proximal systemic hypertension. Furthermore, the presence of associated anomalies, frequently a ventricular septal defect, is one of the most common causes of congestive heart failure, renal failure, metabolic acidosis, and pulmonary overcirculation during the first 2 weeks of life.[33-35]

In the early 1960s, surgical mortality was extremely high for neonates with an aortic coarctation, particularly in the setting with associated cardiac anomalies, and surgery was justified only because of the devastating outcome of medical management

alone. Since then, there has been progressive reduction of the early mortality to about 18%-21% by the middle of the past decade due to improved preoperative preparation, better surgical and anesthetic techniques, and enhanced postoperative management.

After the introduction of prostaglandin in the 1980s, mortalities as low as 0% -14% have been reported, the majority of deaths related to the severity of the associated defects. Prostaglandin E_1 (PGE_1), given as a continuous intravenous infusion at 0.025-0.1 ug/kg/min, re-opens the arterial duct and so provides a better systemic flow to the lower extremities. For this reason, PGE_1 restores vital functions, permits surgery under hemodynamically improved conditions, thereby reducing the early hospital mortality in these neonates.[36-44] Besides digoxine and furosemide, dopamine, dobutamine, isoproterenol or epinephrine can be administered by continuous infusion to increase ventricular contractility. Slowly administration of sodium bicarbonate will correct acidosis due to a 'surge' of lactate into the general circulation. The critically ill neonate does not tolerate oral feeding: calories should be maintained at 120-150 cal/kg/day by nasogastric route or by hyperalimentation. Finally, pulse oximetry should be used to monitor the oxygenation status.[44]

Improvement in diagnostic methods, e.g. two-dimensional echocardiography now provides the surgeon with a clear and precise description of the anatomy. Comprehensive imaging of the entire aortic arch and the anatomy of the aortic coarctation, may require a combination of suprasternal, high left parasternal, parasternal and subcostal echocardiographic views to obtain all information on the anatomy of the left ventricle, ascending aorta, aortic arch, vessels to the head, isthmus and aortic coarctation. However, false-negative diagnosis of the aortic coarctation may occur, when the hypoplastic isthmus is associated with a widely patent arterial duct that obscures the presence of the aortic coarctation. The posterior shelf of the aortic coarctation may not be seen in the suprasternal notch long-axis view due to the usually parallel course of the isthmus and the ultrasound beam. On the other hand false-positive diagnosis of an aortic coarctation may occur if an anterior shelf formed by the entry of the arterial duct into the descending aorta is mistaken for luminal narrowing, or if the echo beam projects the inferior wall of the left carotid artery over the distal aortic arch, giving the impression of an luminal narrowing.[45,46] Nevertheless, two-dimensional echocardiography has proven extremely useful and accurate with a high sensitivity and specificity for assessing either significant or subtle forms of left ventricular inflow disease and in confirming the diagnosis of neonatal aortic coarctation.[47-59]

In addition, Doppler ultrasound turnes out to be an accurate noninvasive adjunct to two-dimensional imaging. The principle is that volumetric flow of fluid in a vessel is equal to the velocity of the flow x the cross-sectional area of the tube. As the vessel narrows, the flow velocity across the obstruction must increase in order for the fluid volume to cross the narrowing. The pressure drop across the obstruction can be described by the simplified Bernoulli equation: $P_1 - P_2 = 4 (V_2^2 - V_1^2)$, where P_1 = pressure proximal to the obstruction; P_2 = pressure distal to the obstruction; V_1 = flow velocity proximal to the obstruction; and V_2 = flow velocity in the jet distal to the obstruction.[60,61]

More recently, Color Doppler flow mapping allows new observations of aortic coarctation flow diameter, spatial aortic acceleration, and turbulence in the proximal descending aorta, thereby assessing the severity of the aortic coarctation. These non-

invasive methods are essential in the decision making for acute medical or surgical management of these ill neonates and usually eliminate the need for invasive catheterization.[62-77] The clinical justification for cardiac catheterisation therefore turns on whether it will alter subsequent decision about surgery. Thus, in these ill neonates, invasive investigation is only justified if it will help the surgeon to decide whether to perform a single-stage repair (e.g. concomitant closure of the VSD) or multi-stage repair if necessary (Chapter VII).

Up to the present, most of the debate about surgical management of these ill neonates with aortic coarctation, has focused on two issues; ***first, which technique is best to repair the aortic coarctation, and second, are associated anomalies (e.g. a VSD) amenable to primary definitive repair.***

The technical debate is driven by a relatively high prevalence of ***recoarctation***. Recoarctation is mostly defined as a resting peak systolic gradient exceeding 20 mmHg across the repaired area. The usefulness of this definition however, is limited. It does not consider the background hemodynamics because the absolute value of the gradient has more importance in the setting of a low systolic arm pressure than in the setting of a high pressure. The prevalence of recoarctation appears to be related to operative technique, age at operation and even more strongly to small weight at operation. The smaller the weight, the higher the probability of recoarctation (Chapter V). Additionally, the gradient as a ratio of the systolic arm pressure and the weight at operation exert an amplifying effect on each other.[78]

General Remarks

The classic resection of the aortic coarctation and end-to-end anastomosis was introduced in 1944. Because of early unsatisfactory results in infants with end-to-end anastomosis, different other surgical approaches, such as the prothetic patch aortoplasty and later the subclavian flap aortoplasty have been heralded as the operation of choice in order to reduce the incidence of recoarctation and early mortality. In the following sections, these different surgical techniques and other alternative surgical approaches will be discussed.

III 1.1 Resection and end-to-end anastomosis

The classic surgical approach to aortic coarctation is through a left posterolateral thoracotomy with the patient in a full lateral position. Blood pressures are monitored in the right arm by the cuff method, or by an indwelling radial and/or femoral catheter. A curving incision is made around the angle of the scapula and mostly it is not necessary to incise the trapezius muscle. The chest is entered through the fourth intercostal space. Whatever the type of surgical technique will be, it is of utmost importance to mobilize the mediastinal pleura widly over the aortic coarctation and then retracted medially, carrying with it the recurrent laryngeal and vagus nerve. Then the subclavian artery, the arterial duct, the distal aortic arch, the left carotid artery, and the descending aorta are mobilized. Tapes are placed around the aorta beyond the aortic coarctation, the aortic arch and subclavian artery. The possibility of damage to the thoracic duct and the presence of Abbott's artery, an anomalous vessel arising from the medial aspect from the isthmus, should be remembered.[79,80] Collateral intercostal vessels should be spared as much as possible, although in some cases it is necessary to divide one or more bronchial, oesophageal and intercostal arteries medially. The arterial duct or ligament is divided. When the aortic coarctation is beyond the origin of the subclavian artery, the proximal clamp is placed across the distal aortic arch and the subclavian artery so as to leave ample length for the proximal cuff. The distal clamp is placed on the descending aorta. Then, the aortic coarctation as well as the isthmus are resected. The left subclavian artery is incised over a short distance and the resected end of the descending aorta may be beveled to increase the anastomotic diameter. The clamps are brought together, and the end-to-end anastomosis is begun at the deep angle in a continuous, running fashion both posteriorly and anteriorly or interrupted anteriorly, with a monofilament suture, whereby an absorbable suture is optimal (Fig.III-7a-c). Reported benefits of the absorbables monofilament include minimal scarring, growth potential and viability in all parts of the anastomosis.[81-83]

The advantages of this original surgical technique include removal of all abnormal ductal and aortic coarctation tissue, avoidance of prosthetic material, which is particularly important in infants, and preservation of the normal vascular anatomy. In the past however, the reported prevalence of recoarctation after resection and end-to-end

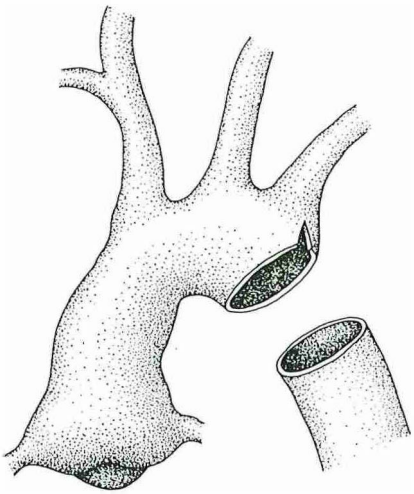

Figure III-7a *Resection and end-to-end anastomosis for the repair of aortic coarctation. The aortic coarctation has been excised, getting back to a wide orifice proximally and distally. The left subclavian artery has been incised over a short distance to increase the anastomotic diameter.*

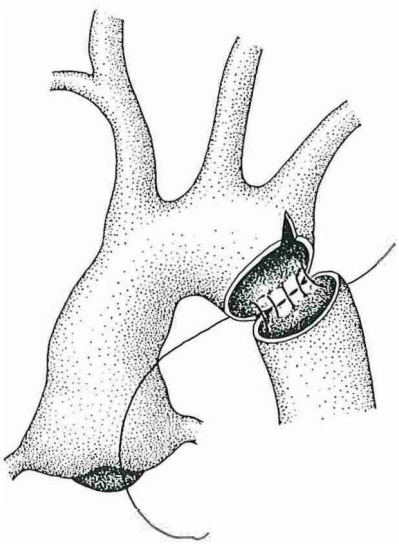

Figure III-7b *A monofilament suture (7-0) is used in a continuous, running fashion both anteriorly and posteriorly.*

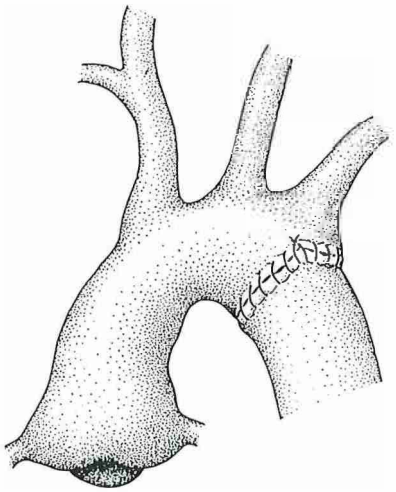

Figure III-7c *The end-to-end anastomosis has been completed*

anastomosis varied widely, ranging from 5-50%.[78,84-91] Too much tension on the suture line and lack of adequate growth potential were considered to be major drawbacks of this technique. However, due to recent advances in absorbable monofilament sutures (PDS^{R}) and microvascular technique, the results have improved dramatically.

Aortic coarctation resection and end-to-end anastomosis is from a certain point of view easiest in the neonate. Firstly, the tissues are relatively pliable so that radical excision of the aortic coarctation in order to excise abnormal ductal tissue and even resection of a hypoplastic isthmus do not add a substantial risk to the operation. Secondly, the subclavian artery is preserved and maintenance of growth potential with absorbable monofilament sutures has been demonstrated.[81,83,92-95]

Therefore, the improved technique and results concerning mortality and incidence of recoarctation for resection and end-to-end anastomosis, have created a wave of renewed enthusiasm for the original procedure (Fig.I-2).

III 1.2 **Prosthetic patch angioplasty**

The preparation for operation, the approach, the incision and the dissection are as described for the resection and end-to-end anastomosis. After clamping, the aorta is incised well below the aortic coarctation and opened longitudinally through the aortic coarctation. Then, the incision is extended several millimeters into the subclavian artery. If hypoplasia of the isthmus is present, the incision can be extended into the transverse arch. The shelf-like protrusion may be excised with care not to injure the aortic wall.[96,97] A tubular prosthetic graft, made of Dacron or expanded polytetrafluorethylene (PTFE) is cut to the same length as the aortotomy and opened longitudinally. Then, it is sutured in place with a continuous monofilament suture. The patch must billow to ensure longterm adequacy because it has no growth potential.(Fig.III8a-b)

Due to the high mortality and recoarctation in older infants after resection of the aortic coarctation and end-to-end anastomosis in the past, prosthetic patch angioplasty was introduced as an alternative surgical procedure by Vosschulte [96]. The advantages of this technique were manifold. Minimal dissection and operative time, preservation of the normal vascular anatomy, concomitant enlargement of the hypoplastic isthmus and tension-free repair argue strongly for this surgical approach. With regard to arm-to-leg pressure gradients in rest and after excercise, no difference was found between prosthetic patch angioplasty and resection and end-to-end anastomosis.[98-103]

However, the initial enthusiasm for this technique was tempered by mid- and longterm reports showing several major drawbacks: first, there is an increased risk of recoarctation, and more strongly an increased risk of aortic aneurysm formation opposite to the prosthetic patch with a 5% to 38% incidence rate. Etiologic possibilities for this aneurysm formation include congenital abnormality of the aortic wall, surgical interruption of the vasa vasorum, intimal disruption due to extensive excision of the shelf-like protrusion and finally, rigidity of the prosthetic patch. In contrast to these reports, the Freiburg group could not find any evidence of aneurysm in their longterm follow study. They believe that this contrast is likely related to the surgical technique they employed in which the integrity of intimal membrane was vigilently respected to avoid changes in the structure of the aortic wall. Furthermore, other concerns include lack of growth and potential for infection.[104-120]

Finally, prosthetic patch angioplasty should be avoided in infants with a tubular hypoplasia of the isthmus for several reasons, including the stiffness of the material compared to the friability of the posterior wall. Furthermore, the patch then becomes the majority of the aortic segment which is less satisfactory with respect to recoarctation.

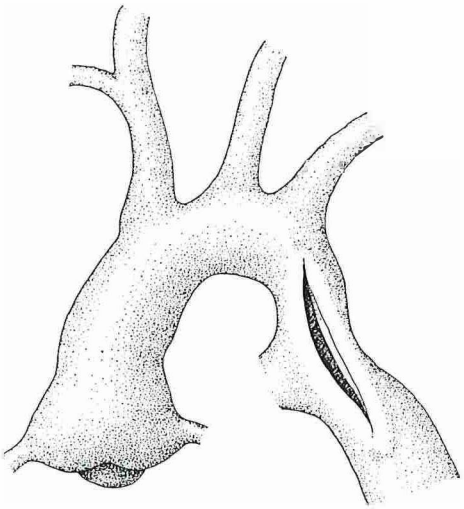

Figure III-8a *Prosthetic patch aortoplasty for the repair of aortic coarctation. The aorta is incised longitudinally through the coarctation and proximal several millimeters onto the left subclavian artery.*

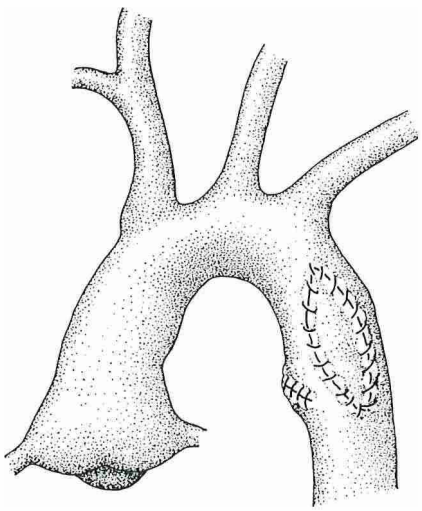

Figure III-8b *An elliptical prosthetic patch, made of Dacron or polytetrafluoroethylene (PTFE), is sutured in place along the edges of the aortotomy.*

Despite of these drawbacks, prosthetic patch angioplasty remains an good alternative in selected patients, in the treatment for recoarctation that does not respond well to balloon dilation angioplasty, in the treatment of aortic coarctation associated with intracardiac defects via an anterior midline approach (Chapter VII), or in infants with critical aortic coarctation and borderline sized left ventricles (left ventricular volumes of 20-25 ml/m^2). Use of prosthetic patch angioplasty in this category infants allows the arterial duct to be preserved and to be left open after aortic coarctation repair. This enables the infants to use the arterial duct to 'pop-off' the high pulmonary pressures untill the left ventricle demonstated its adequacy as a systemic pump.[121-122]

III 1.3 Subclavian flap angioplasty

The preparation for operation, the approach, the incision, and the dissection are as described as above. More than in the previous surgical techniques, the subclavian artery is mobilized distally to expose its branches.[123] The vertebral artery may be ligated to avoid a steal syndrome. If possible, the subclavian artery is ligated and divided proximal to the internal mammary artery and the thyrocervical trunk in order to preserve collateral circulation to the left arm. The subclavian artery is transected, split open longitudinally along the posterior margin and extended distally across the aortic coarctation into the descending aorta for at least 1 cm. Like as in the prostetic patch angioplasty, the shelf-like protrusion is excised as completely as possible without damaging the aortic wall. The subclavian artery is now transected and folded down into the incision where it may be tacked to the distal opened aorta using a monofilament suture. Then the continuous suture is carried proximally.(Fig.III-9a-c) In order to repair coarctation proximal to the left subclavian flap, a flap is created along the superior aspect of the divided left subclavian artery. The longitudinal incision is then extended through the hypoplastic segment of the distal aortic arch, to the origin of the left common carotid artery. The flap is folded up into the incision and approximated to the most proximal point of incision in the aortic arch.[124]

Due to the significant rate of recoarctation after resection and end-to-end anastomosis in infancy, the subclavian flap angioplasty subsequently gained popularity in the seventies and eighties, and was considered to be the optimal surgical approach for the treatment of aortic coarctation in infancy (Fig.I-2).[125-129] The advantages of this technique is its simplicity and avoidance of extensive dissection with a short cross-clamping time and more important, it allows potential for growth by utulizing autogenous, noncircumferential tissue.[130-137] Additionally, blood pressure response to exercise in infants following the subclavian flap angioplasty indicates that it is an effective form of treatment for the aortic coarctation with an expected low incidence of residual coarctation or recoarctation.[88,132-141] Furthermore, anatomopathological studies of the aortic coarctation suggest that the surgical procedures must be tailored to the precise anatomy present and that the subclavian flap angioplasty might offer the best chance of success in this morphological setting.[93]

However, inspite of these high expectations, rather disappointing late results of the subclavian flap angioplasty are published since 1985. The first drawback of the subclavian flap angioplasty is that it does not reduce the need for reoperation, due to an unexpected high incidence of early recoarctation especially in infants under 3 months of age (Chapter V). It seems that the recoarctation appears to be due to lumen obliteration by the shelf-like posterior wall tissue which is probably left behind after the subclavian flap angioplasty. The shelf is composed of smooth muscle of ductal origin and may further contract and fibrose, causing recoarctation.[86,102,142-153]

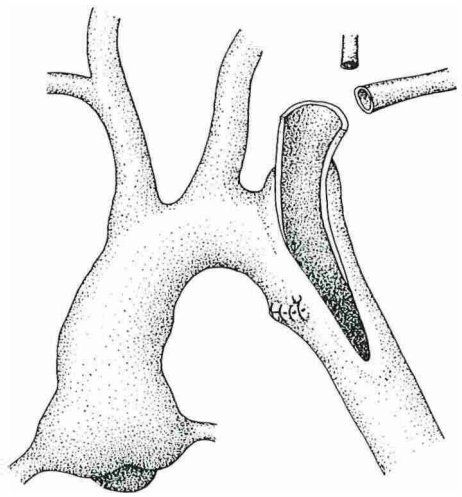

Figure III-9a *Subclavian flap aortoplasty for the repair of aortic coarctation. A longitudinal incision is made along the length of the subclavian artery and extended distally across the aortic coarctation.*

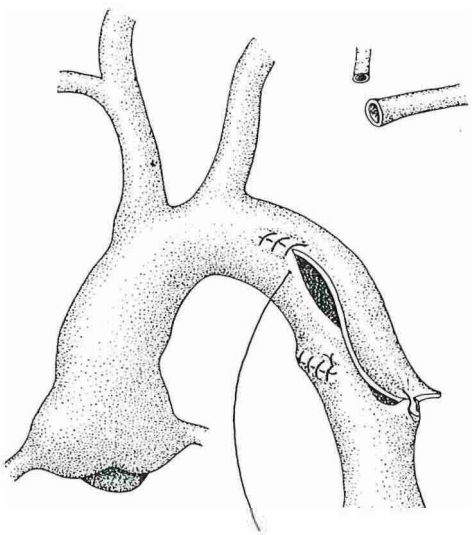

Figure III-9b *The subclavian vessel is then folded down into the incision and anastomosed to the edges of the aortotomy.*

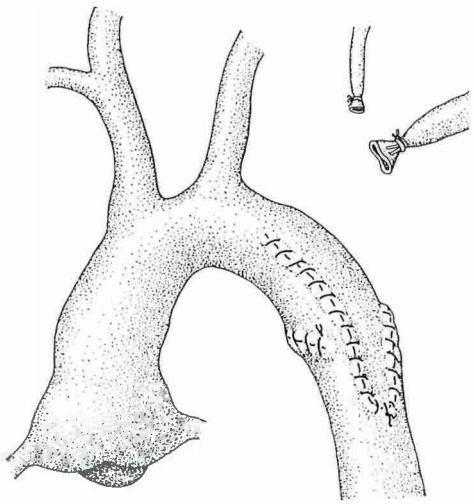

Figure III-9c *The anastomosis has been completed.*

A second drawback of the subclavian flap angioplasty is the potential of left upper extremity ischemia in rest and during reactive hyperemia, or even gangrene due to the sacrifice of the left subclavian artery. Hemodynamic analysis of the blood flow velocity in the left branchial artery during reactive hyperemia shows that the capacity of the physiologic augmentation after the subclavian flap angioplasty is marginal or absent. Furthermore, ligation of the subclavian artery causes diminution in the longitudinal growth of the long bones and diminution in the muscle thickness. Even cerebellar infarction secondary to the ligation of the vertebral artery has been reported. Therefore in order to avoid these sequalae, it is of paramount importance not to disturb branches of the subclavian artery in order to maximize the collateral flow.[154-161] In contrast, Todd and Shenberger refute these data, and report only minor shortening and decreased muscle mass of the left upper limb.[162,163] Surprisingly, late aneurysm formation is reported following left subclavian flap angioplasty. Its mechanism has not been clearly established. Stress exerted on abnormal tissue in that portion of the aorta, periductal tissue which is left behind in the subclavian flap procedure and hypoplasia of the aortic arch are possible factors in the development of the aneurysm.[164,165]

III 1.4 Extended resection and end-to-end anastomosis

The association of aortic coarctation with hypoplastic arch can be difficult to manage surgically. The hypoplastic arch can be enlarged either with resection of the aortic coarctation with either subclavian flap angioplasty or by carotid-subclavian angioplasty.[166,167] In 1984, the extended end-to-end technique, a modification of the classic resection and end-to-end anastomosis, was introduced by Lansman, in order to address specifically aortic coarctation with associated hypoplastic aortic arch.[168] This technique was further modified by Zannini and Elliott.[169,170] The preparation for operation, approach, and the dissection are as described as above. The aortic arch then is extensively dissected to expose the subclavian artery, the carotid artery, the innominate artery, and the left side of the ascending aorta. After the arterial duct is dissected, a large Castaneda or Cooley clamp is then applied, to include the left subclavian artery, the left carotid artery, and part of the innominate artery; the distal tip of the clamp is positioned down to the left wall of the ascending aorta.(Fig.III-10a-b) An angled straight aortic cross-clamp is then positioned on the mobilized descending aorta to provide a longer incision site on its lateral aspect. Then the arterial duct is ligated, divided and oversewn, and resected along with the aortic coarctation. The incision on the descending aorta is extended laterally to allow the proximal and distal segments to coincide when approximated. The two are then approximated, and the anastomosis is created using continuous 7-0 monofilament sutures beginning at the ascending aorta aspect of the arch incision. The anastomosis is then continued along the posterior aspect of the incision, finally completing it with the anterior layer. Surgical treatment of a hypoplastic aortic arch associated with an aortic coarctation is controversial. The controversy concerns the claimed need to enlarge surgically the diameter of the hypoplastic arch. Enlargement of the hypoplastic arch can be achieved by either retrograde subclavian flap or carotid-subclavian angioplasty.[171] Recently, reports have appeared on resection of the aortic coarctation with extended aortic arch anastomosis in order to increase the aortic arch instantaneously. The goal was to reduce early mortality and incidence of recoarctation.[172-174] The advantages of this technique were thought to be, complete excision of all ductal tissue, instantaneously correction of the distal and transverse hypoplastic aortic arch, no use of synthetic material and preservation of the left subclavian artery.

However, this technique is technically more demanding as compared to the classic resection or left subclavian flap for several reasons. First, a tension-free anastomosis and hemostatic control of the circumferential anastomosis are desirable but often difficult. Second, a large Castaneda or Cooley clamp must be placed proximally to occlude the left subclavian artery, the left carotid artery, and part of the left innominate artery. This means, that the cerebral perfusion can only be maintained in the setting of an intact circle of Willis. However, aortic coarctation can be associated with cerebral arterial occlusive disease or even hypoplasia of the left posterior communicating artery of the circle of Willis.[175,176] Thus, these anatomic variations in cerebral blood flow could be lethal when performing the extended resection and end-to-end anastomosis in this morphologic entity.

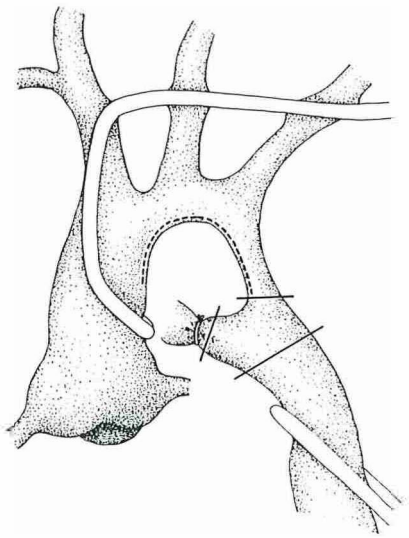

Figure III-10a *Extended resection and end-to-end anastomosis for the repair of aortic coarctation. Proximally, a long incision is made on the inferior surface of the aortic arch. Distally, the descending aorta is trimmed obliquely with a lateral linear incision to enlarge the anastomosis.*

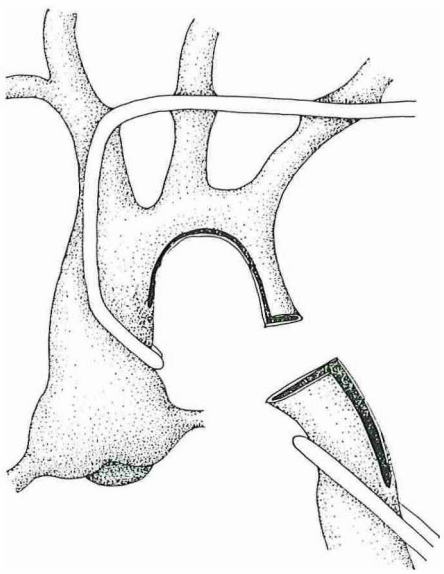

Figure III-10b *Approximation of the clamps, and the proximal and distal ends are then anastomosed in a continuous running fashion.*

Recently, questions have been posed concerning the potential for growth and development of the originally hypoplastic aortic arch after resection and end-to-end anastomosis or subclavian flap angioplasty. The hemodynamic molding theory predicts that growth of the aortic arch occurs when normal flow is established through the aortic arch and that a 'catch-up' can be expected.[5,177-181] Indeed, the Pittsburgh group found excellent growth of the transverse aortic arch after these conventional surgical techniques and stated that the extended resection repair should be reserved for the small group of infants with transverse aortic arch to ascending aorta diameter ratios of less than 0.25. Moreover, serial aortograms have shown progressive growth of the hypoplastic aortic arch after simple aortic coarctation repair, no doubt secondary to restoration of normal aortic arch blood flow.[180]

This phenomenon has been further corroborated by us (Chapter VI).[181] We found that even severly hypoplastic arch segments between the left common carotid and left subclavian artery increased to normal size within 6 months of **simple** resection and end-to-end anastomosis in young infants. In contrast to these findings, growth potential of the extensive resection and end-to-end repair is still speculative and up to the present, no longterm growth studies have been reported. Finally, another goal of the extended resection and end-to-end anastomosis was to lower the early mortality rate and the incidence of recoarctation. However, Vouhé et al reported an overall early mortality rate of 26%; 18% in the group infants with pure aortic coarctation associated with a hypoplastic aortic arch, and 17% in the group infants with additional ventricular septal defect, with a incidence of recoarctation of 10%.[172] The overall early mortality rate reported by Lacour-Gayet et al was 26% and the incidence of recoarctation was 12.5%.[173] Maehara also reported an unusually early recoarctation after extended end-to-end anastomosis in a neonate.[182]

In contrast, in the Groningen series, the early mortality rate after simple resection and end-to-end anastomosis for the treatment of the aortic coarctation and hypoplastic aortic arch was 0%, even in the presence of a ventricular septal defect and the incidence of recoarctation was comparable at 12.5%.[181] Considering the potential drawbacks of the extended resection versus the favorable results of the Pittsburgh and Groningen group, the question arises whether the extended resection and end-to-end repair really contributes to a better treatment of the aortic coarctation associated with a hypoplastic aortic arch. The answer to this question cannot be given yet, for it requires more longterm follow-up.

So, the use of this agressive surgical technique has become unsettled, for progressive growth of the severely hypoplastic arch segment between the left common carotid and left subclavian artery to normal size has been clearly demonstrated, no doubt secondary to restoration of normal blood flow (Chapter VI).

III 1.5 Alternative surgical procedures

In the last decade, different variations of the subclavian flap angioplasty have been reported. The main goal of these modifications was to preserve the arterial blood flow in the subclavian artery, thereby avoiding the potential sequelae of the classic subclavian flap angioplasty.

Reimplantation of the divided left subclavian artery following the subclavian flap angioplasty into the left carotid artery via a short vertical cervicotomy in a 17-year-old female was performed by Hvass.[183,184]

The subclavian-sparing advancement technique was introduced as an other technique for subclavian reimplantation in infancy. This technique consists of a complete mobilization of the left subclavian artery extending to the origin of its first branches. After clamping, the left subclavian artery is detached from the aorta at its origin and is opened longitudinally at its posterior aspect. The anterior wall of the aorta is then incised from the origin of the left subclavian artery to the descending aorta across the aortic coarctaton. The coarctation shelf is excised and the arterial duct is ligated and divided. The opened left subclavian flap is pulled down and sutured to the edges of the aorta, widening the aortic coarctation site and also preserving the blood flow to the left arm.(Fig.III-11a-c) This technique is feasible in the great majority of cases in which the classic subclavian flap angioplasty would have been an option, with the advantage of preservation of the blood flow to the arm.[149,185,186] So, this subclavian-sparing advancement technique is a promising addition to the surgical armamentarium for aortic coarctation in neonates.

An other alternative to the classic subclavian flap aortoplasty for long-segment aortic coarctation is the isthmus flap aortoplasty.[187] This technique avoids the limitations of the subclavian flap angioplasty; after resection of the arterial duct and the coarctation shelf, the posterior wall of the isthmus is opened longitudinally to the level of the transverse aortic arch. The descending aorta is mobilized and advanced to the level of the aortic arch, where the posterior half is sutured. The anterior flap of attached isthmus is then sewn into a longitudinal incision made in the anterior wall of the descending aorta.

Use of the left internal mammary artery for preservation of the circulation to the left arm after the subclavian flap angioplasty was reported by Fournier[188] and later by Henze and Nair.[189,190] Additionally, the Uppsala group modified this technique by using the internal mammary artery as a free end flap aortoplasty. They conclude that the left mammary artery flap reflects the basic principle of autogenous arterial grafting in situ; it allows circumferential widening of the aorta, and is a powerful conduit with extraordinary flow capacity provided the internal mammary artery is of good quality and calibre and the runoff is appropriate.[191-193](Fig.III-12a-c)

Finally, the combined resection-flap procedure (an end-to-end anastomosis enlarged with a subclavian flap angioplasty) is recently reported and seems to be effective in avoiding gradients and preventing recoarctation.[103]

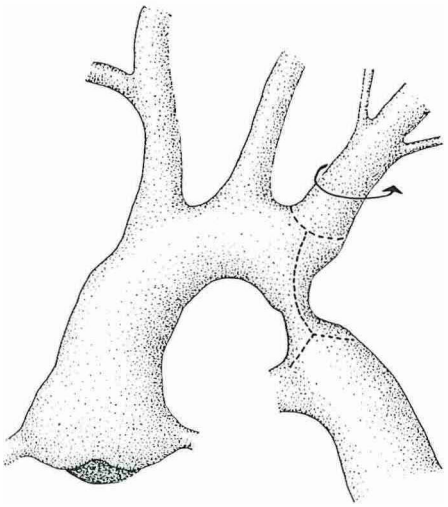

Figure III-11a *The left subclavian artery is detached from the aorta at its origin and an incision is then made in the anterior wall of the aorta.*

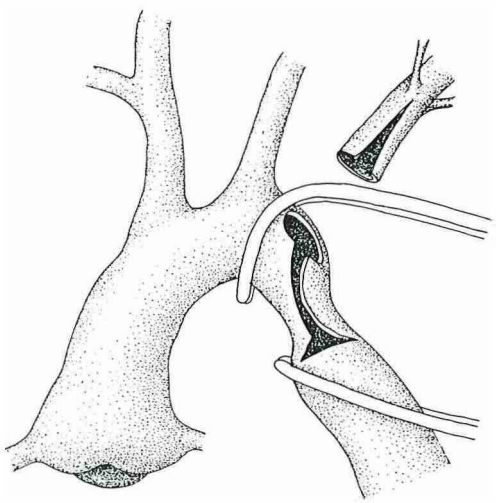

Figure III-11b *The posterior face of the left subclavian artery is opened longitudinally and the length of the incision should be about the same as the incision made on the anterior aspect of the aorta.*

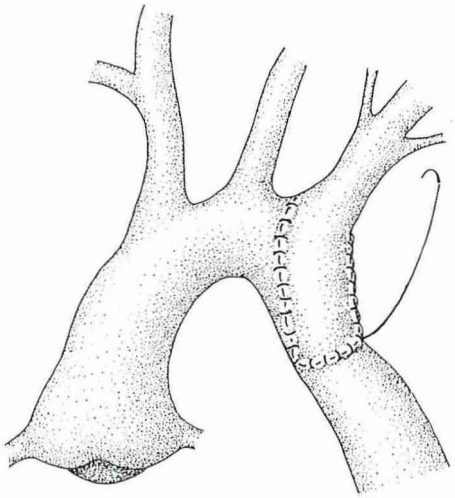

Figure III-11c *The edges of the left subclavian flap are then sutured to the distal end of the aortic incision.*

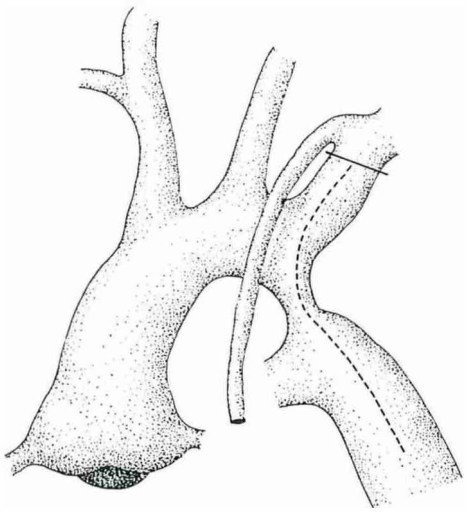

Figure III-12a *The mammary artery is dissected free from its origin on the left subclavian artery down to the fourth intercostal space.*

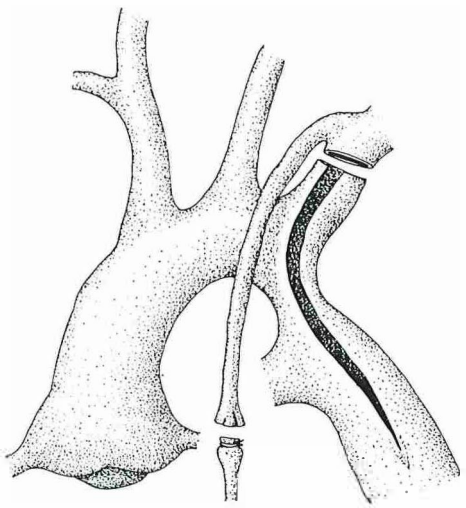

Figure III-12b *The aortic coarctation is corrected with the subclavian flap.*

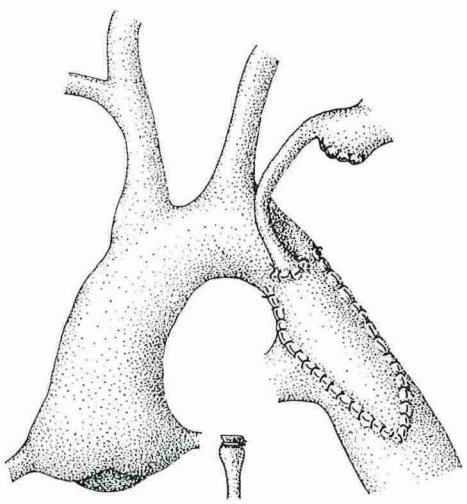

Figure III-12c *The mammary artery is anastomosed to the aorta at its junction with the origin of the subclavian flap.*

III 1.6 Balloon Dilation Angioplasty

In 1979, Castaneda and Amplatz demonstrated in an experimental model of balloon angioplasty in vessels from cadavers, that the dilation of a vessel was due to tears in the intima and media instead of remodeling of atheromatous material. The vessels then supposedly healed in the dilated position.[194,195]

In that same year, Sos enlarged succesfully a surgically resected neonatal aortic coarctation with a balloon dilation catheter.[196] In order to demonstrate the mechanism of the balloon dilation angioplasty, Lock performed dilation on excised aortic coarctation segments in vitro with a Gruntzig polyvynil chloride balloon catheter. He found that the key to successful dilation and tear (the controlled injury) was related to balloon size, inflation pressure and inflation duration and number of inflations.[197,198]

The first clinical applications were encouraging; in virtually all patients with recoarctation after resection and end-to-end anastomosis or with a native coarctation, shortterm follow-up showed a remarkable increase in diameter in the anastomosed area or coarctation diameter with a persistent gradient reduction. In the majority of cases, no serious morbidity occurred and mortality was rare.[199-207] Based on these shortterm benign results, balloon dilation angioplasty was considered to become the treatment of choice for the operated as well as for the unoperated patient with an aortic coarctation.[208-212]

However, in an editorial comment, Lock worried about effects of the controlled injury. Although no aneurysms had been described at that time, areas of medial thinning had been seen experimentally in the first year after dilation. In contrast to the recoarctation, which will have postoperative fibrous perivascular scar that may prevent aneurysm formation, the unoperated aorta is not 'protected' and therefore prone to aneurysm formation.[213]

Indeed, shortly thereafter, reports demonstrated aneurysm formation at or immediately distal to the primary balloon dilatation site in infants with isolated discrete aortic coarctation.[214-219] These data raised serious concerns about the longterm safety and efficacy of balloon dilation angioplasty. Histological examination revealed that cystic medial necrosis, defined as depletion and disarray of elastic tissue, was a consistent feature of aortic coarctation and provided the basis for the aneurysm formation.[220] This cystic medial necrosis combined with the controlled injury may lead to 'uncontrolled' damage of the aortic wall following balloon dilation angioplasty varying from small linear tears, creation of a false passage in the transverse aortic arch, to aneurysm formation or even fatal aortic wall dissection.[221-229] Therefore, recommendations for use of balloon dilation angioplasty as primary treatment procedure, were clouded by these reports and its role in the management of the aortic coarctation remains controversial.

In 1990 however, Tynan published the outcome of the multicenter prospective study of balloon angioplasty for ***aortic coarctation*** within the **V**alvuloplasty and **A**ngioplasty of **C**ongenital **A**nomalies (**VACA**) Registry which started in 1984.[230] Balloon dilation angioplasty was performed on 141 aortic coarctations in 140 patients between 3 days and 29 years of age. The mean peak systolic pressure gradient fell from 48 $\pm$ 18.6 to 12 $\pm$ 11.3 mmHg. The mortality was 1.4% and the morbitity 17%. The incidence of recoarctation was 16.4% with an incidence of aneurysm formation of 5.8%.

Currently the prevalence of recoarctation after balloon dilation angioplasty of aortic coarctation has been reported up to 35%.[231-236] Age less than 12 months, tubular hypoplasia, and an aortic coarctation segment smaller than 6 mm after balloon dilation angioplasty, seem to be risk factors for the development of recoarctation. Avoiding or minimizing the number of these risk factors may reduce the incidence of recoarctation after balloon dilation angioplasty.[237-239]

So, in the last decade, balloon dilation angioplasty as a non-elective procedure, seems to have obtained a place in the armamentarium of the interventional pediatric cardiologist. It can be performed effectivily and relatively safely in both neonates and older children, despite the concerns of recoarctation and the appearance of aneurysms.

III 2 **Elective procedure**

Almost all infants over 1 year of age with an aortic coarctation are asymptomatic unless they have significant associated lesions. Aortic coarctation is usually a chance finding at a routine physical examination, with findings of hypertension in the upper extremities and absent or weak pulses in the lower extremities. Normally, the systolic pressure in the femoral artery is 20 mmHg higher than in the brachial artery. Therefore, a femoral pressure less than or equal to the brachial pressure is suspicious for aortic coarctation.[240-250]

Predominant symptoms, if any, are fatigue, claudication, headaches or nose bleeds. On examination, an increased cardiac impulse is found at the apex and a palpable thrill over the suprasternal notch. Continuous bruits may be heard over collaterals in the back and intercostal arteries. The electrocardiogram shows predominantly left ventricular hypertrophy, which depends on the degree of hypertension. If there is pulmonary hypertension, signs of right ventricular hypertrophy will also be present. The chest X-ray shows cardiomegaly in about 33% and rib notching resulting from dilated collateral vessels in 15%, mainly older children.

Congestive heart failure has a bimodal distribution in aortic coarctation; it is common in infancy and uncommon between 1 and 30 years of age. It reappears in patients who have survived beyond 40 years as a sequela of the longstanding hypertension[1]. Congestive heart failure in adulthood is predominantly determined by associated valvar anomalies, mostly the aortic valve: a bicuspid aortic valve, which is reported in 42% of the hearts, is prone to aortic valvular stenosis and bacterial endocarditis in the fourth and fifth decade of life. Other sequelae from the aortic coarctation are aortic dissection, which occurs mostly in the second and third decades of life and involves the ascending aorta and the area beyond the aortic coarctation and, the prevalence of a subarachnoid hemorrhage from rupture of a Berry aneurysm on the circle of Willis. This incidence of hemorrhage is increased as compared to the normal population and due to longstanding hypertension.[251-253] In older infants with uncomplicated aortic coarctation, there is no justification for catheterisation. Two-dimensional echocardiography and Doppler assessment demonstrate the aortic coarctation and the decreased systolic and increased diastolic blood flow in the descending aorta. Recently, Magnetic Resonance Imaging (MRI) as a new diagnostic modality, provides a high-resolution image of coarctation anatomy with a dynamic visualization of blood flow, an excellent detail of vascular anatomy and information of the severity of the aortic coarctation. The anatomic delineation is comparable to the cineangiography and probably superior to echocardiography in pre- as well as postoperative patients.[254-263] (Fig.III-13)

Currently, there is consensus that the aortic coarctation should be treated in childhood and currently the classic resection and end-to end anastomosis seems to be the operation of choice.(Fig.I-2) However, the ***exact surgical timing*** of elective repair is a matter of current debate, particularly in those with an asymptomatic isolated aortic coarctation. In the past era, the ideal age for elective aortic coarctation repair was supposed to be between 4 years and adolescence in order to avoid the high operative mortality in neonates to minimize the incidence of recoarctation and to avoid the incidence of late cardiovascular complications.[264-268]

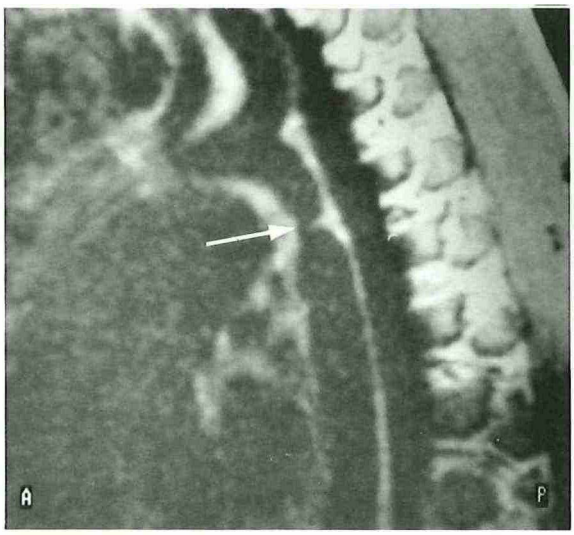

Figure III-13 *Magnetic Resonance Imaging (MRI) in the sagittal plane showing the aortic arch with a discrete aortic coarctation (arrow). A, anterior; P, posterior.*

These observations suggest that there is an age beyond which the benefit of waiting for repair is marginal. Since that time, a great deal of effort has gone into defining that age. Later studies of Shinebourne suggest the 'breakpoint' to be one year of age.[269] Currently, instead of age at time of operation, the presence of congestive heart failure plays an important role in the clinical decision whether to operate promptly or not. But, if congestive heart failure is not present, it is suggested to delay the operation to about 3 to 6 months of age, but not beyond.[270] This strategy is based on the apparently higher incidence of persistent and/or recurrent aortic coarctation in younger children, and on the absence of any demonstrable lower probability of longterm survival and resting upper body normotensive state. This philosophy is for the most part confirmed by the study presented in Chapter VIII. Longterm analysis of a cohort of patients with an isolated aortic coarctation, operated electivily between 1948 and 1965, shows that not all patients live healthily ever after the aortic coarctation repair as compared to an age- and era matched group, but remain at risk for premature death, predominantly caused by the late effects of hypertension. Indeed, age at time of the operation turns out to have a key-position in the optimal treatment for elective aortic coarctation repair, and determines the probability of recoarctation, late hypertension and premature death as well. But, in contrast to the current opinion, this study shows that the freedom from recoarctation, late hypertension and premature death has its peak around 1 1/2 years of age at the time of aortic coarctation repair. The cause for this is that the risks for late hypertension and premature death are almost constant in this age range, while the risk for recoarctation drops rapidly and levels off at 1 1/2 year (Chapter VIII, fig. VIII-6).

Therefore, it seems that at this age, the combined risk is lowest and the repair can be safely undertaken at age 1-2 years with minimal risk of late hypertension and premature death.[271]

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Chapter IV

IV 1 Aims of the Study

Due to year-long experience of aortic coarctation repair and the development of fine-tuning surgical skills, we now know at least some truths insofar the aortic coarctation is concerned: patients with aortic coarctation benefit from operation in terms of decreased mortality and lowering of blood pressure and surgery offers repair or relief but not total correction, so that these patients should continue under longterm follow-up.[1,2]

Moreover, the prevalence of recoarctation remains a concern and the problem of the hypoplastic aortic arch is attracting increasing attention. One should weigh the benefit of new surgical techniques to reconstruct the hypoplastic aortic arch towards aortic coarctation repair alone. Proximal narrowing can widen by growth if adequate relief of obstruction is accomplished downstream.

The question arises, whether associated anomalies e.g. a ventricular septal defect (VSD) are amenable to single-stage repair. Little specific information other than survival is available in this group of patients. The VSDs in this pathophysiologic setting seem to have the same tendency to close spontaneously as when the aortic coarctation is not present.[3] In the period 1960-1980, hospital mortality after aortic coarctation repair in these patients has been significantly higher than in the group with aortic coarctation alone.[4] This may not be the case in infants operated on in the current era, although data from the multi-institutional study of the Congenital Heart Surgeons Society 1990-1991, suggest that the initial risks are still higher in infants with coexisting VSD; the hazard functions for death levels off 6 months after aortic coarctation repair and become similar as for infants without coexisting VSD.[5]

When aortic coarctation coexists with a VSD in a neonate with congestive heart failure, the size of the VSD and, if large, the probability of its spontaneous closure are the major determinants of the treatment protocol. These neonates may be treated by one of the following stategies; 1) by only aortic coarctation repair with initial conservative treatment of the VSD, 2) by initial aortic coarctation repair with banding of the pulmonary artery when high pulmonary blood flow is a factor, or 3) single-stage total repair.[3-10] Most centers adopted a multi-stage repair in which the aortic coarctation was repaired initially and the postoperative course followed; if the neonate cannot not be weaned off the ventilator, banding of the pulmonary artery or secondary closure of the VSD was performed.

The specific morphology of the VSD's was studied by Anderson, who studied hearts from the Heart Museum of Children's Hospital of Pittsburgh and found that almost always the VSD was perimembranous and that it could extend into all parts of the muscular ventricular septum.[11] Additionally, deviation of the outflow septum was found to an extent to obstruct the left ventricular outflow tract which diverts blood flow from the aortic arch into the pulmonary system.[12-14]. This phenomenon is reflected by an increased incidence of hypoplasia of the aortic arch. One might speculate that aortic coarctation, hypoplasia of the aortic arch and the presence of a VSD forms an unique

pathophysiologic entity, in which the size of the aortic arch is inversely proportional to the size of the shunt through the ventricular septal defect (Chapter VI, Fig. VI-3). Furthermore, it seems that particularly the VSD's in the perimembranous position, have a high tendency to close spontaneously or become hemodynamically insignificant. But, if the VSD is large and not in the perimembranous position, or large and in the outlet of the right ventricle, the probability that it will spontaneously narrow appreciable or close is thought to be small.[15,16]

So, besides the controversy of the technique best to repair aortic coarctation in this pathophysiologic entity, the second controversy deals with the therapy of coexisting VSD. Therefore, the optimal surgical management of the aortic coarctation associated with a VSD forms another matter of debate in these neonates.

Finally the optimal age for elective aortic coarctation repair as well as the best method of repair for aortic coarctation repair still remain controversial.[17-24]

So, inspite of the tremendous achievement in the treatment of aortic coarctation in the last decades, the cardiac surgeon still encounters surgical, anatomical and pathophysiological problems.

The aims of this thesis was to deal with these problems from the **cardiac surgeon's point of view**. Are there any pre- or peroperative guidelines which might help him to choose the ideal management of the aortic coarctation?

The problems, which will be discussed, are the following:

1. Is it possible to prevent the prevalence of recoarctation; e.g. are there pre- and/or peroperative incremental risk factors which predict an increase of the probability of recoarctation?
2. How should the cardiac surgeon define and interprete the hypoplastic aortic arch as a concomitant anomaly and what are the surgical implications?
3. Does the presence of a VSD as an associated anomaly always justify an single-stage repair?
4. What is the optimal age for elective aortic coarctation repair in an asymptomatic infant with isolated aortic coarctation?

These features are the subjects of the chapters V, VI, VII, VIII of this thesis.

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Repair of Aortic Coarctation in Infants

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V 1 Abstract

Fifty-three consecutive infants younger than 2 years underwent coarctation repair. A recoarctation occurred in eleven infants (21%). To determine variables associated with recoarctation, preoperative and operative data were entered into a multivariate stepwise logistic regression analysis.

Patient weight was an incremental risk factor for recoarctation instead of age, in contrast to previously published studies. Furthermore, the residual gradient after the operation was a strong incremental risk factor. This risk factor was even more significant when expressed as a ratio of the systolic arm pressure, thus taking background haemodynamics into account.

Because weight is a more significant risk factor than age, we conclude that deferring operation is only indicated when the infant gains weight. Furthermore, a residual gradient is of more importance in the haemodynamic setting of a lower systolic arm pressure.

V 2 Introduction

Repair of aortic coarctation in infants younger than 2 years of age continues to carry the risk of recoarctation in 10%-60% of cases.[1-5] Several longterm studies have shown the subclavian flap angioplasty to have similar long term results for recoarctation as has the classic resection and end-to-end anastomosis in contrast to initial expectations.[1,6-9] Furthermore, incremental risk factors for recoarctation are reported to be: young age at the time of operation, morphology of the coarctation, and suture material.[10-13]

The purpose of this study was to determine risk factors for recoarctation.

V 3 Patients and methods

Between January 1, 1975 and July 1, 1988, 53 consecutive infants less than 2 - years of age, underwent repair of aortic coarctation at the division of Thoracic surgery of the University of Groningen. Of these 53 infants, 18 were girls (34%) and 35 were boys (66%). The median age at operation was 83 days, and the median weight at time of operation was 4000 gr. The predominant symptom at the time of operation was severe congestive heart failure. Other symptoms were failure to thrive, hypertension and cardiogenic shock (table V-1).

Table V-1 *Coarctations in infants less than 2 years of age*

Initial symptoms	N	%
CHF	29	55%
Failure to thrive	8	15%
Hypertension	8	15%
CHF, hypertension	5	9%
Cardiogenic shock	3	6%

Key: *CHF = congestive heart failure*

Diagnosis of aortic coarctation was made by history and physical examination, and confirmed by cross-sectional echocardiography. All patients underwent preoperative cardiac catheterization in order to evaluate the type of the coarctation, to exclude other cardiac malformations and to measure the systolic pressure gradient across the coarctation. Two types of coarctation were found: a discrete juxtaductal lesion in 34 infants (64% CL*: 56%-72%) and a preductal tubular isthmic narrowing in 19 infants (36% CL: 28%-44%). Associated anomalies are tabulated in table V-2.

Table V-2 *Coarctations with associated cardiac anomalies in infants less than 2 years of age*

Associated Cardiac Anomaly	N	%
None	28	53%
VSD	10	19%
VSD and ASD	10	19%
Congenital aortic stenosis	2	4%
DORV and TGV	2	4%
Aortic and mitral stenosis	1	1%

Key: *VSD, ventricular septum defect*
ASD, atrial septum defect
DORV,double outlet right ventricle
TGV, transposition of the great vessels

Additionally, in all patients, oxymetry was performed. Twenty infants were proven to have a left-to-right shunt, all caused by a ventricular septal defect (38% CL: 30%-46%). Ten of these 20 infants also had an atrial septal defect.The mean pulmonary

*CL; 70% confidence limits

to systemic flow ratio was 2.8 (SD** ± 1.5). In all 53 infants a left posterolateral thoracotomy was performed. Collateral vessels were spared as much as possible. In most patients arterial pressure tracings in the right radial and in a femoral artery were recorded simultaneously in order to measure a pressure gradient before and after the coarctation repair. Introduction of a pressure line into a femoral artery was not accomplished in 6 infants (11%).

Resection and end-to-end anastomosis was performed in 32 patients (60%). Patch angioplasty was performed twice (4%), and subclavian flap angioplasty was performed in 19 patients (36%) (Table 3).[14,15] Operative technique was chosen according to personal preference and fashion. The mean pressure gradient between the radial and femoral artery dropped significantly from 57.0 mmHg (SD ± 23.8 mmHg, range 30 mmHg-110mmHg) to a mean of 6.0 mmHg (SD ± 11.3 mmHg; range: 0 mmHG-65 mmHg; $p<0.05$ paired T-test; N=47).

Banding of the pulmonary artery to a predetermined diameter was performed in 4 infants within the same operation.[16] Banding was performed as a secondary procedure in 3 infants, because the infant could not be weaned off the ventilator due to pulmonary overflow.

V 3.1 Mortality

A total of 4 out of 53 infants (8%; CL:4%-13%) died in our series. A 17 days old infant died 3 days after resection and end-to-end anastomosis due to cardiac arrest of unkown origin. Two infants died on the day of operation due to congestive heart failure: a 38 days old infant with an isolated coarctation and a 10 days old infant after an abortive attempt at banding for a large ventricular septal defect. Finally a 4 month old patient had signs of a recoarctation 3 months after a successfully performed subclavian flap angioplasty. One day before reoperation he died suddenly of severe congestive heart failure. The autopsy showed myocardial hypertrophy and signs of severe restenosis of the isthmus.

V 3.2 Morbidity

Paraplegia or other neurologic complications were not seen in our series. Chyle drainage and a left sided Horner syndrome occurred once; both complications disappeared spontaneously. Postoperative hypertension without signs of a residual coarctation occurred in 3 patients. They were successfully treated medically and are now normotensive but still on medication. Differential left arm growth rate due to the subclavian flap angioplasty has not been observed during the follow-up period.[17]

**SD; Standard Deviation

To follow up on the infants, we saw them 2 weeks after hospital discharge, after 3 months and then yearly. One patient was lost to follow-up (2%). Mean follow up was 5.6 years (SD $\pm$ 3.5 years, range 0.6-13.2 years). Special attention was paid to systolic blood pressure in arms and legs and femoral arterial pulsations. X-ray of the chest and an electrocardiogram were performed to evaluate left ventricular hypertrophy. If these data suggested a recoarctation, cross-sectional echocardiography and eventually cardiac catheterization was performed. Recoarctation was defined by a arm-to-leg systolic pressure gradient exceeding 20 mmHg across the repaired area.

V 3.3 Statistical analyses

All data were summarized in contingency tables and statistically analysed by using the Chi-square test, and the Student't test. Seventy percent confidence limits of binomial distributions were calculated.

In order to determine variables associated with recoarctation, the following variables were entered into a multivariate stepwise logistic regression analysis: age, and weight at time of operation, surgeon, year of operation, arm-to-leg peak systolic pressure gradient before and after the operation, the decrement in pressure gradient due to the operation, the ratio between the gradient after operation and the peak systolic arm pressure (gradient ratio), the morphology of coarctation, the type of operation, suture material, shunt size if any, banding of the pulmonary artery, presence and repair of a ventricular septum defect. P-values of less than 0.05 were considered to be significant, while p-values between 0.05 and 0.1 were considered to be probably significant.

A time related analysis according to the Kaplan Meier method was done to depict the 'freedom from recoarctation' for the group as a whole, and stratified into those who had a resection of the coarctation tissue, and those who had no resection. A Wilcoxon (Breslow) analysis was done to assess the significance of differences if any.

V.4. Results

Recoarctation was found in 11 of the 53 patients (21%; CL:15% - 28%). Recoarctation was found in 4 of the 32 patients that underwent resection and end-to-end anastomosis (13%; CL 6%-22%). Recoarctation was found in 7 of the 21 patients (33%; CL 22%-47%) that underwent either subclavian flap angioplasty (N=19) or patch angioplasty (N=2). Univariate analysis showed this difference to be associated with a p-value of 0.067 (Chi-square; Cramer's V= 0.2513), however, these groups also differ significantly in weight at operation (Table V-3).

Table V-3 *Incidence of recoarctation*

Type of* operation	number of patients N	recurrent coarctation N %	weight** (gr)	gradient*** ratio
Resection	32	4 13%	5985 ± 3368	4% ± 6%
No resection	21	7 33%	4240 ± 2412	10% ± 17%
Subclavian flap	19	6 32%		
Patch angioplasty	2	1 50%		

* $p(x^2)$ *resection vs.no resection 0.067*
** $p(x^2)$ *weight (resection vs no resection) 0.0328*
*** $p(x^2)$ *gradient ratio (resection vs no resection) 0.1474*

The Kaplan Meier time related analysis showed that the group of patients having had a resection had a freedom from recoarctation of 75% at 11 years follow-up. But the patients with a subclavian flap repair had a 49% freedom from recoarctation at 7.5 years follow-up (Fig V-1a and V-1b). The generalized Wilcoxon (Breslow) test showed that the probability that this difference was due to chance is 10.9%.

Initial multivariate analysis showed the year of operation to be an incremental risk factor for recoarctation. However we decided to exclude this variable from the multivariate logistic regression because there was a strong negative correlation between the year of operation and the interval between the operation and occurrence of recoarctation (-0.73; $p < 0.01$). This would result in a bias, favoring recently operated children, since they did not yet have a 'chance' to develop a recoarctation. Therefore recently operated children would only seem to have a lesser risk of recoarctation. Furthermore, although the hazard for recoarctation was highest in the first three postoperative months in those having a subclavian flap repair, thereafter the hazard remained fairly constant. This gave us extra concern about the date of operation in the logistic regression analysis. The subsequent multivariate logistic regression analysis that followed leaving out the date of operation, produced weight at operation and the gradient ratio as significant incremental risk factors for recoarctation (Table V-4).

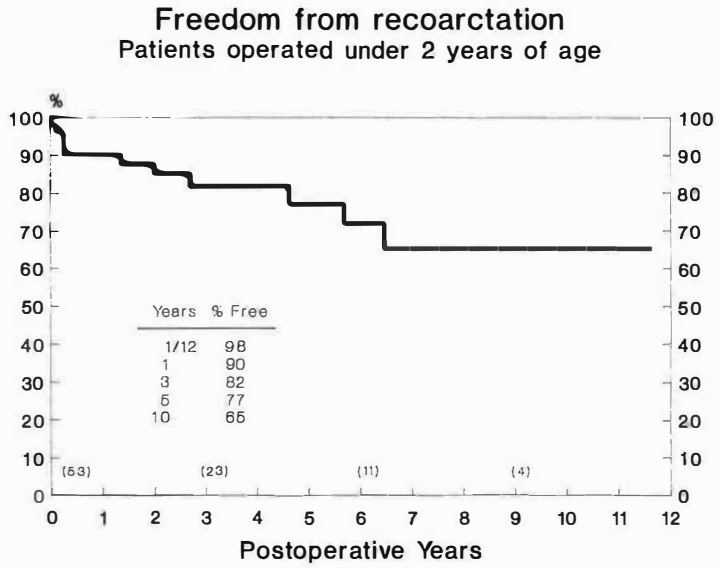

Figure V-1a *Actuarial freedom from recoarctation for the group as a whole (N=53).*

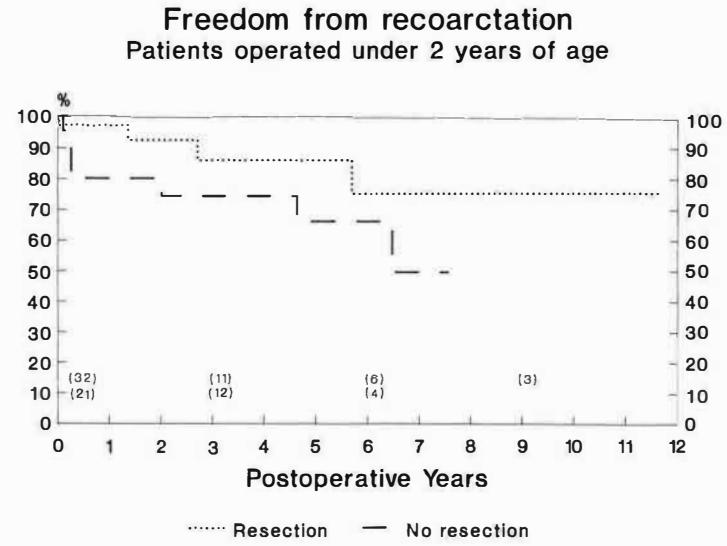

Figure V-1b *Actuarial freedom from recoarctation stratified into those who had resection versus no resection operation.*

Table V-4 *Logistic regression analysis for recoarctation.*

Incremental risk factor	Logistic coefficient ± SE	p value
Gradient ratio (%)	0.145 ± 0.062	0.001
Weight at operation	-0.375 ± 0.286	0.096
Intercept	0.6498 ± 1.313	

Key: *gradient ratio: ratio between the post-operative gradient across the anastomosis and the peak systolic arm pressure.SE, Standard Error*

Leaving operative variables such as the postrepair gradient out of the analysis did not produce different risk factors.

V 5 Discussion

The purpose of this study was to find risk factors associated with an increased risk of recoarctation. These factors were the ratio between the gradient across the anastomosis after operation and the systolic arm pressure and furthermore, weight at time of operation.

Recoarctation is usually defined as a postoperative arm-to-leg peak systolic pressure gradient exceeding 20 mmHg across the repaired area.[18] This definition does not consider the background hemodynamics, because the absolute value of the gradient obviously has more importance in the setting of a low systolic arm pressure than in the setting of a high pressure. Therefore division of this gradient by the systolic arm pressure produced a systolic gradient ratio, which proved to be a more significant incremental risk factor than the gradient itself, thus underscoring the importance of the background hemodynamics (Fig.V-2).

That the gradient ratio is a more useful variable than the arm-to-leg systolic pressure gradient to predict the probability of recoarctation is a novelty of this study.

Age at time of operation is reported to be a major incremental risk factor for recoarctation.[8,19] However, in this study, weight at operation turned out to be a more significant incremental risk factor for the probability of recoarctation than age. After weight was included in the model, age did not separately have a significant effect on the probability of recoarctation. The smaller the weight, the higher the probability of recoarctation. The finding that weight and not age is a more significant incremental risk factor for recoarctation is new but not surprising. Because children that fail to thrive become older while not gaining weight. Tissue properties change through growth, probably less through age by itself. This discrepancy between age and weight is further illustrated by the linear but less than perfect correlation (0.94; $p < 0.001$) (Fig.V-3).

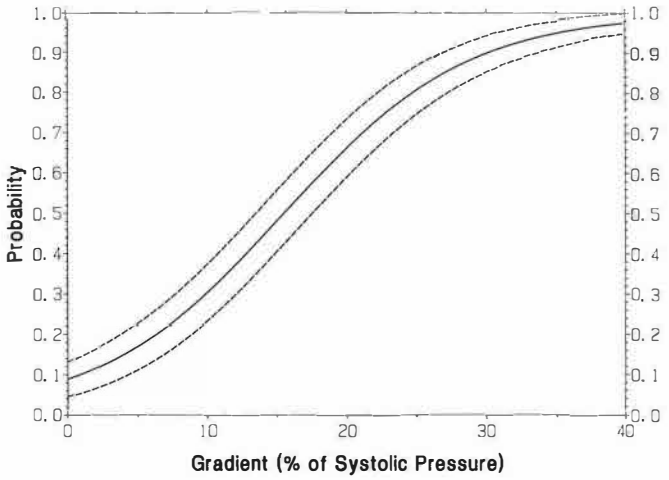

Figure V-2 *Nomogram of the multivariate equation (table 4) for the incremental risk factor for recoarctation according to the gradient as percentage of the systolic blood pressure. The dashed lines enclose the 70% confidence limits. p (gradient %) = 0.001*

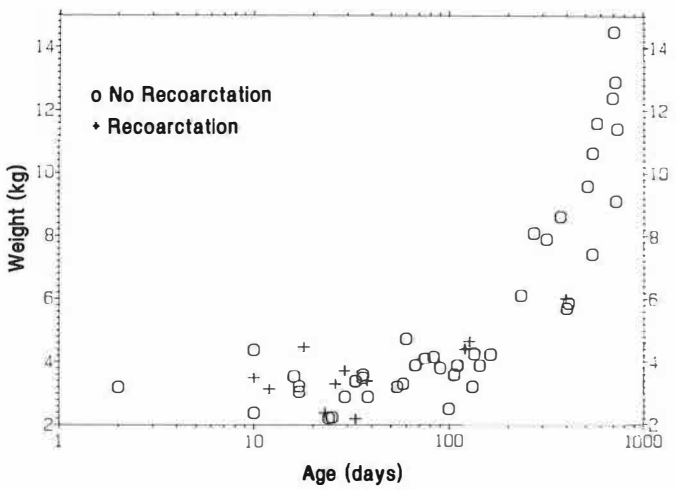

Figure V-3 *The distribution between weight and age at time of operation and the incidence of recoarctation (+). Note that 10 out of 11 infants with recoarctation were less than 5 kg of weight. The horizontal axis has a logarithmic scale.*

Subclavian flap repair carried a slightly higher risk of recoarctation which occurred primarily in the first 3 postoperative months. However, because of the relatively constant hazard of recoarctation during the rest of the follow-up, this difference could be due to chance.

In summary, weight and gradient ratio together determine the risk of recoarctation in our study. The gradient ratio and weight at operation exerted an amplifying effect on eachother: at a certain ratio, the probability of recoarctation was much higher in an infant with a low weight compared to an infant with a higher weight (Fig.V-4).

It is our opinion that these new findings are of clinical relevance. If a low weight infant with a coarctation of the aorta is in distress, the coarctation should be removed. The primary goal is a gradient ratio as low as is possible, for even small gradients have a strong incremental effect on the probability of recoarctation in the setting of a low weight infant. We now prefer resection and end-to-end anastomosis although this study does not indicate that this method decreases the risk of recoarctation. However, if a low weight infant with a coarctation is not in distress, we will preferably not remove the coarctation while the body weight is below 5 kg.

In conclusion, we found that the weight at operation and the gradient ratio to be the only incremental risk factors for the occurrence of recoarctation.

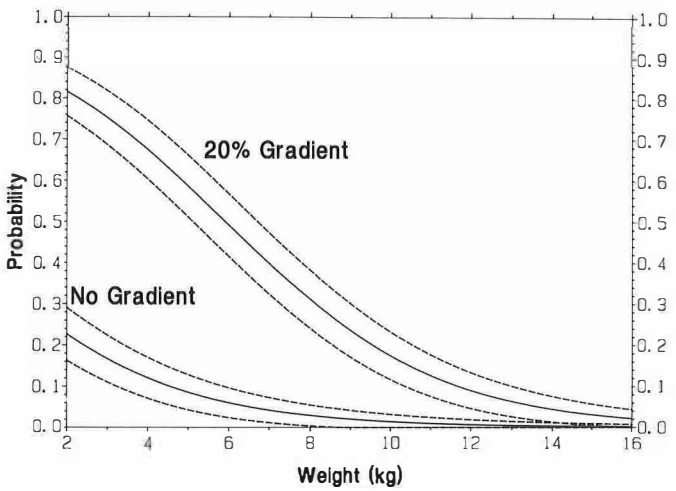

Figure V-4 *Nomogram of the multivariate equation (table V-4) for the incremental risk factors weight at operation and the gradient ratio for recoarctation. The dashed lines enclose the 70% confidence limits. p (weight)=0.096 p (gradient %) = 0.001*

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V 7 Appendix

Probability estimates (P) were obtained from the logistic regression equation, according to the following formulas:

$$p = \frac{1}{1 + e^{-z}}$$

$$z = b_0 + b_1x_1 + \ldots\ldots + b_kx_k$$

which e is the base of the natural logarithm, b_0 is the intercept of the logistic equation and b_1 - b_k are logistic regression coefficients associated with the values for the incremental risk factors x_1 - x_k

Growth of the Hypoplastic Aortic Arch after simple Coarctation Resection and End-to-End Anastomosis.

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VI 1 Abstract

Surgical treatment of a hypoplastic aortic arch associated with an aortic coarctation is controversial. The controversy concerns the claimed need to enlarge surgically the diameter of the hypoplastic arch, in addition to resection and end-to-end anastomosis. The purpose of this prospective study is to determine the fate of the hypoplastic aortic arch after resection of the aortic coarctation and end-to-end anastomosis. Between July 1, 1988 and January 1, 1990 in 15 consecutive infants less than 3 months of age with an aortic coarctation, were evaluated echocardiographically. A Z-value was calculated, being the number of standard deviations the aortic arch differs from the expected value, derived from a control group. Eight of these 15 infants had a hypoplastic aortic arch with a mean Z-value of -7.14 ± 1.39. The other 7 infants had a 'normal' aortic arch with a mean Z-value of -1.85 ± 1.08. All 15 infants underwent simple coarctation resection and end-to-end anastomosis. Six months after operation the mean Z-value increased significantly in those with a hypoplastic arch to -1.08 ± 0.69 ($p<0.0001$) and in those with a 'normal' aortic arch to 0.106 ± 0.99 ($p=0.004$). No infant died in our series (0% CL 0%-12%) and once a recoarctation was found (12.5% CI 2%-36%).

Therefore we believe that simple resection and end-to-end anastomosis is the operation of choice for aortic coarctation associated with a hypoplastic aortic arch despite the presence of a ventricular septal defect and that enlargement of the hypoplastic aortic arch is not necessary.

VI 2 Introduction

Surgical treatment of a hypoplastic aortic arch with an invariably associated aortic coarctation is controversial. The controversy concerns the claimed need to enlarge surgically the diameter of the hypoplastic aortic arch, in addition to resection of the coarctation. Enlargement of the hypoplastic aortic arch can be achieved by either retrograde subclavian flap or carotid-subclavian angioplasty.[1-3] Recently, reports have appeared on resection of coarctation with extended aortic arch anastomosis in order to increase the diameter of the aortic arch instantaneously.[4-8]

In contrast to the extended surgical procedures, simple resection of the aortic coarctation and end-to-end anastomosis has been our operation of choice, regardless of the diameter of the aortic arch and associated anomalies. Our philosophy being, that a hypoplastic vessel will grow under the influence of increased flow. The purpose of this prospective study is to determine the fate of the hypoplastic aortic arch after simple resection of the aortic coarctation and end-to-end anastomosis.

VI 3 Patients and Methods

Between July 1, 1988 and January 1, 1990 an aortic coarctation was repaired by simple resection and end-to-end anastomosis in 15 consecutive infants less than 3 months of age at the division of Cardiothoracic Surgery at the University Hospital of Groningen. All 15 infants were critically ill and treated with prostaglandin E_1, diuretics and some with inotropic medication. The diagnosis of aortic coarctation was based on physical examination and echocardiography. Twenty-seven infants less than 2 years of age without any intra- or extracardiac anomaly served as a control group.

Cross-sectional echocardiograms in all 42 infants were obtained using a Toshiba SS 65 colour-coded Doppler machine with a 5 MHz transducer. Intracardiac anatomy was established and the internal diameters of the great vessels were determined. The standard right high parasternal or the suprasternal long axis cut were found to be adequate for visualization of the internal diameter of the ascending aorta, the aortic arch, the isthmus and the aortic coarctation.[9-11] The internal diameter of the descending aorta was measured at diaphragm level. The diameter of the ascending aorta was measured proximal to the origin of the brachiocephalic artery, the aortic arch distal to the left carotic artery and the descending aorta distal to the coarctation (Table VI-1, Fig.VI-1).

In 7 of the 15 infants with a coarctation a cardiac catheterization was performed because the cross-sectional echocardiography was not entirely conclusive. The catheterization included oximetry, ventriculography and aortography. In all 15 infants with an aortic coarctation a left posterolateral thoracotomy was performed. The aortic coarctation was resected and an end-to-end anastomosis was made with PDS ^{R} 6-0 (polydioxanon). The arterial duct was oversown with Prolene ^{R} 6-0. The left subclavian artery was incised over a short distance to adapt the diameter of the proximal end of

Table VI-1 *Aortic coarctation with hypoplastic and 'normal' aortic arch: Raw data (N=15)*

Pt	Age	BSA	Ao asc	Arch	Ao desc	Z value
t = 0 (at time of operation)						
1	37	0.194	6	3	7	-5.72
2	14	0.23	6	2	6	-5.85
3	12	0.196	7	2	6	-5.85
4	37	0.215	9	3	8	-6.94
5	18	0.22	8	2	8	-8.28
6	14	0.23	9	3	9	-8.16
7	31	0.23	10	3	8	-6.94
8	70	0.215	8	2	9	-9.50
9	68	0.195	8	6	7	-1.69
10	35	0.21	7	8	9	-1.44
11	16	0.20	7	7	7	-0.35
12	50	0.20	8	7	7	-0.35
13	10	0.22	8	7	8	-1.57
14	18	0.25	6	5	6	-1.82
15	25	0.15	8	7	7	-0.35
t = 0.5 year after operation						
1	217	0.26	9	9	11	-2.53
2	194	0.29	10	8	8	-0.23
3	192	0.25	8	7	7	-0.35
4*	217	0.37	11	7	8	-1.57
5	198	0.29	9	6	8	-2.91
6	194	0.37	10	7	9	-2.78
7	211	0.285	10	6	7	-1.69
8	250	0.36	11	7	9	-2.78
9	248	0.39	10	9	9	-0.10
10	215	0.35	11	10	10	0.02
11	196	0.36	9	9	8	1.11
12	230	0.37	13	12	11	1.49
13	190	0.36	12	10	10	0.02
14	198	0.36	8	7	8	-1.57
15	210	0.34	9	8	8	-0.23

Key: *Ao asc (mm), Ascending aorta; Ao desc (mm), descending aorta; BSA, body surface area (m^2). * Recoarctation*

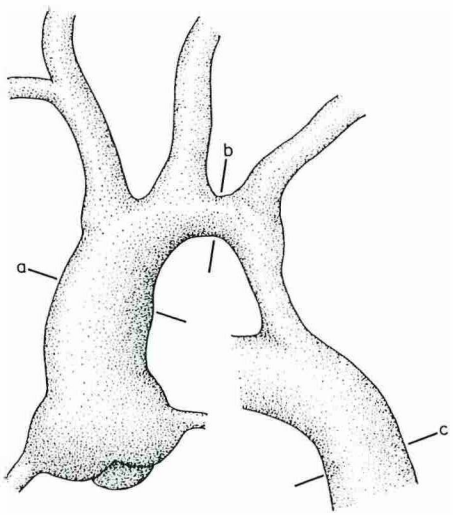


Figure VI-1 *Diagram of aortic coarctation with hypoplasia of aortic arch and isthmus. Diameter of ascending aorta is measured proximal to origin of brachiocephalic artery (a), aortic arch distal to left carotic artery (b), and descending aorta distal to coarctation (c)*

the aorta to the diameter of the descending aorta. Collateral vessels were spared as much as possible. In all infants arterial pressure tracings in the right radial artery were recorded during operation. In 12 of the 15 infants a femoral artery pressure was as well recorded simultaneously in order to measure pressure gradients before and after coarctation repair. Introduction of a pressure line into a femoral artery was not accomplished in 3 infants. No banding of the pulmonary artery or closure of a ventricular septal defect were performed. Postoperatively all infants could be weaned off the ventilator within 48 hours without any further surgical intervention. No infant died in our series (0%; CL* 0%-12%). No paraplegia or other neurologic complications, nor postoperative hypertension were seen. In follow up, the infants were seen 2 weeks after hospital discharge and again after 6 months. Special attention was paid to systolic blood pressures in arms and legs and femoral arterial pulsations. Recoarctation was defined as an arm-to-leg systolic pressure gradient exceeding 20 mmHg. Six months after operation all infants underwent cross-sectional echocardiography to determine the arch ratio and to exclude a possible recoarctation. If these data suggested a recoarctation, cardiac catheterization was performed.

Comparisons of all continuous variables between the groups were made by an one-way-analysis of variance. Regarding possible growth of the aortic arch, the null hypothesis was that no growth would occur. In the control group, correlations between aortic arch, ascending aorta, descending aorta and body surface were made (table VI-2).

*CL; 70% confidence limits

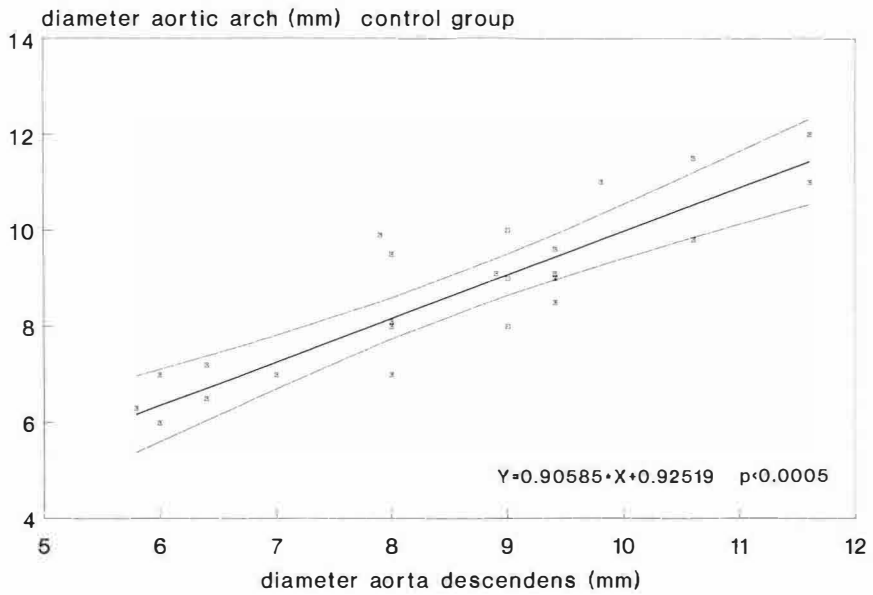


Figure VI-2 *Nomogram presenting linear regression in control group between interval diameters of aortic arch and descending aorta and 99% confidence limits.*

Table VI-2 *Correlation analysis*

	Correlations			
N=27	Arch	Ao asc	Ao desc	BSA
Arch	1.0000	0.8811*	0.8925*	0.7711*
Ao asc	0.8811*	1.0000	0.8592*	0.8401*
Ao desc	0.8925*	0.8592*	1.0000	0.7799*
BSA	0.7711*	0.8401*	0.7999*	1.0000

Key: *Ao asc, Ascending aorta; Ao desc, descending aorta; BSA, body surface area. *1-tailed significance: -0.001.*

The correlation coefficient between aortic arch and descending aorta was with 0.8925 the largest, thus this parameter was chosen as a reference. In order to assess the growth of the hypoplastic aortic arch, independently of the growth of the infant, the internal diameter of the aortic arches of the control group were normalized by relating them to the internal diameter of the descending aorta. The nomogram representing the linear regression and the 99% confidence limits, is shown in Fig.VI-2. The internal diameter of the aortic arch relative to the internal diameter of the descending aorta was expressed as a Z-value, which is the number of standard deviation that the aortic arch differs from the expected value. P values of smaller than 0.05 was considered to be significant.

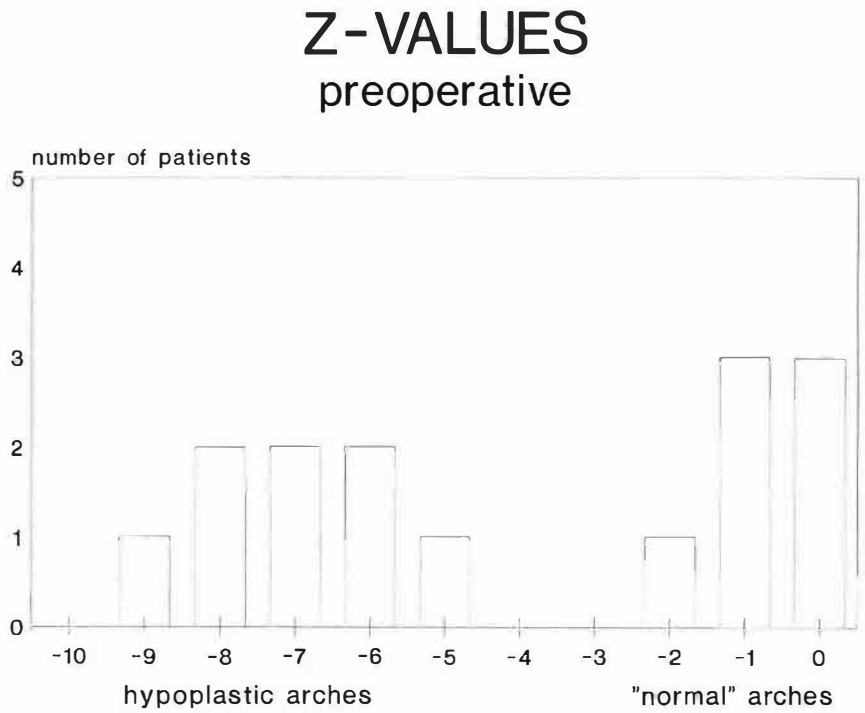


Figure VI-3 *Distribution of preoperative Z-values for aortic arch diameter in 15 consecutive infants with aortic coarctation. Two groups can be clearly identified: those with a hypoplastic arch and those with a relatively 'normal' arch.*

VI 4 Results

The Z-value of the aortic arch diameters at the time of operation divided the total of 15 infants with an aortic coarctation in two distinctly separate groups, each having approximately a normal distribution (Fig. VI-3). Eight of these 15 infants had a hypoplastic aortic arch; the mean Z-value in this group was -7.14 SD** ± 1.39. Six of these eight infants had concomitant perimembranous ventricular septal defect and one had an atrial septal defect. Seven of the 15 infants had a 'normal' arch; the mean Z-value of this group was significantly larger: -1.85 SD ± 1.08 ($p < 0.001$). Two of these seven infants had concomitant perimembranous ventricular septal defect and one had a atrial septal defect associated with aortic valve stenosis. Of note is that in these 15 consecutive infants with an aortic coarctation, no other co-existing major cardiac anomalies were found. The difference in presence of an associated cardiac lesion in the two groups of patients was associated with a p-value of 0.23 (Fisher's exact test). Length, nor weight nor the diameter of the ascending aorta and the descending aorta in the 2 groups did differ significantly, nor did they differ significantly from the control group (table VI-3).

Table VI-3 *Comparison between hypoplastic and 'normal' arches at time of operation*

	hypoplastic arch N=8	'normal' arch N=7
Length (cm)	52.6 ± 2.00	51.7 ± 4.3
Weight (gm)	3357 ± 464	3576 ± 912
Ao asc	7.88 ± 1.46	7.71 ± 0.99
Arch	2.50 ± 0.5 *	6.93 ± 0.83
Ao desc	7.62 ± 1.19	7.36 ± 1.01
Z	-7.14 ± 1.49 *	-1.85 ± 1.08
SPDbef	39.3 ± 9.3	47.1 ± 20.5
SPDaft	11.0 ± 9.0 **	9.8 ± 7.6
Systpr	95.0 ± 10.4	107.0 ± 15.6

Key; *Ao asc, Ascending aorta (mm); Ao desc, Descending aorta (mm); Z;Z value;SPDbef, systolic arm-to-leg pressure difference before repair (mmHg);SPDaft, systolic arm-to-leg pressure difference after repair (mmHg);Systpr, systolic pressure in right radial artery after repair (mmHg). Values are mean ± SD *: $p < 0.001$;**: $p < 0.0001$*

The systolic arm-to-leg difference before and after the coarctation repair between group with a hypoplastic and 'normal' arches did also not differ significantly. After operation, the systolic arm-to-leg pressure difference in both groups decreased significantly ($p<0.0001$). Postrepair growth of the hypoplastic aortic arches was quantitated by comparing the Z-values (Fig.VI-4). Six months after operation the mean Z-value in the group with a hypoplastic arch had increased significantly from -7.14 (SD $\pm$ 1.49) to -1.85 (SD $\pm$ -1.08) and in the group with a 'normal' arch from -1.85 (SD $\pm$ 0.69) to 0.106 (SD $\pm$ 0.99). The null hypothesis that there was no growth was rejected for both groups ($p<0.0001$ and $p<0.004$). Two of the 8 hypoplastic aortic arches were in range of the 99% confidence limits of the control group (Fig.VI-5).

At that time no significant difference was found between the internal diameter of the ascending aorta, descending aorta and the length of both groups, however the infants with a hypoplastic arch weighed significant less than those with a 'normal' arch ($p=0.007$) (table VI-4).

Table VI-4 *Comparison between hypoplastic and 'normal' arches 6 months after operation*

	hypoplastic arch N=8		'normal' arch N=7
Length (cm)	64.5 $\pm$ 4.9		68.0 $\pm$ 1.3
Weight (gm)	5893 $\pm$ 1334	*	7725 $\pm$ 619
Ao asc	9.88 $\pm$ 1.13		10.3 $\pm$ 1.8
Arcus	7.13 $\pm$ 0.64	**	9.29 $\pm$ 1.6
Ao desc	8.25 $\pm$ 1.28		9.14 $\pm$ 1.21
Z	-1.08 $\pm$ 0.69	***	0.106 $\pm$ 0.99

Key; *Ao asc, ascending aorta (mm); ao desc, descending aorta (mm). Z, Z value*
**: p= 0.007 **: p= 0.038 ***: p= 0.009 Values are mean $\pm$ SD*

**SD; standard deviation

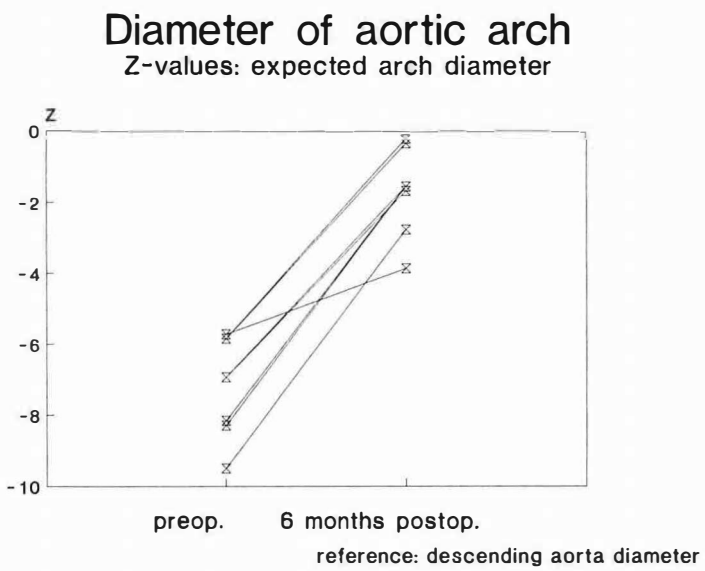


Figure VI-4 *Preoperative and 6-month postoperative diameters of aortic arch expressed by Z-value in eight infants with aortic coarctation associated with hypoplastic aortic arch. Growth of all hypoplastic arches can be observed.*

Four of the 8 perimembranous ventricular septal defects had closed spontaneously six months after coarctation resection, whereas the other 4 ventricular septal defects were considered to be of minor haemodynamic importance.

One residual gradient was found in one infant with a hypoplastic arch 6 months after operation (12.5%; CL: 0%-36%). Cardiac catheterization showed a systolic pressure gradient of 25 mmHg across the repaired area. A percutaneous transluminal balloon angioplasty was succesfully performed and no pressure gradient was found afterwards. In those with a 'normal' arch no recoarctation was found.

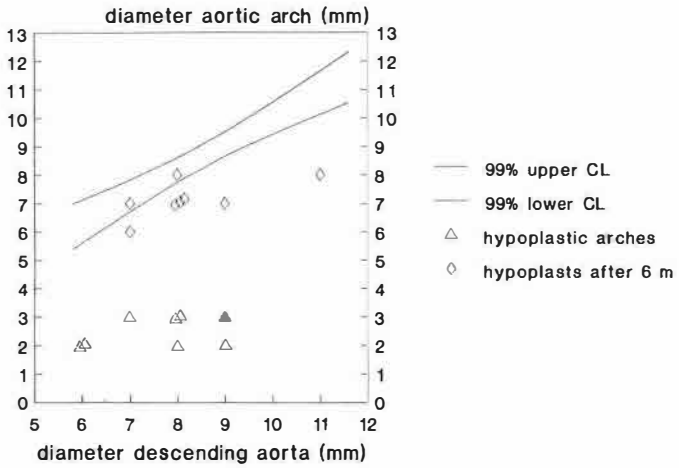


Figure VI-5 *Preoperative and postoperative diameters of hypoplastic aortic arches. Note that after 6 months two of the eight hypoplastic arches had come into the range of the 99% confidence limits (CL)*

VI 5 Discussion

This study demonstrates that infants with an aortic coarctation can be divided into two separate groups according to their Z-value. The empirical cutpoint is a Z-value of -4. Our data suggest that these groups represent separate anatomical entities, because of their respective normal distribution and because they do not overlap. The developmental reason for the existence of the two groups can be twofold. The difference in association of a hypoplastic aortic arch with a ventricular septal defect in this small series could well be due to chance, because the p-value of 0.23. Nevertheless, in the setting of an aortic coarctation and concomitant ventricular septal defect, blood flow through the left ventricular outflow tract is conceivably diminished from the early developmental stage onwards. It is imaginable that the difference in aortic arch size is inversely proportional to the size of the shunt through the ventricular septal defect.

Blood flow seems to be a major factor in development of the aortic arch: it determines the amount of elastin lamellae in the media of the aorta.[18] These elastin

lamellae are considered to be essential in the development of a normal aortic diameter. Becker found that the number of elastin lamellae in the hypoplastic aortic arch was significantly lower than in the corresponding segments of normal specimens. This finding implicates that decreased blood flow through the left ventricular outflow tract has a detrimental effect on the normal development of the aortic arch.[12-18]

The question addressed by the present study was to determine the fate of the hypoplastic aortic arch after only simple resection of the aortic coarctation and end-to-end anastomosis. The main finding of this study is that after simple resection of the coarctation a relatively rapid growth of the aortic arch can be observed (Fig. VI 6a and 6b). This growth is more pronounced in the hypoplastic arch than in the 'normal' arch. The reason for this rapid growth can only be the increased blood flow through the aortic arch. This confirms the concept, that a hypoplastic vessel will grow under the influence of increased flow.

Body weight has also been reported to be an important variable of vessel growth in the course of development.[19] At the time of operation no significant difference was found between the body weight of infants with hypoplastic and relative normal aortic arches. However, 6 months after operation the infants with hypoplastic aortic arches weighed significantly less than the infants with relative normal aortic arches. In spite of the lower body weight, the growth of the aortic arch in these infants was impressive. Therefore, it seems to us that growth of the hypoplastic aortic arch is more related to increased blood flow than to body weight.

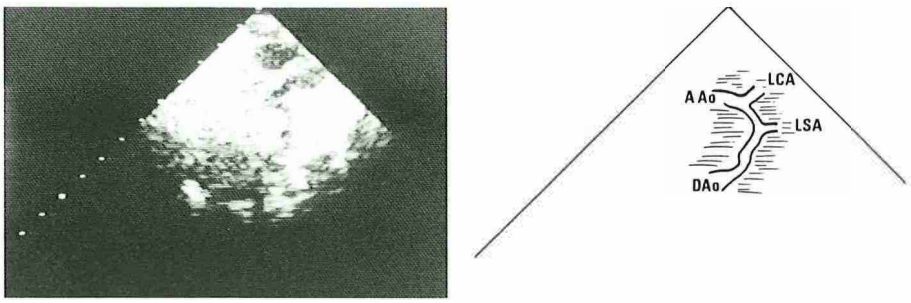
In the past an attempt has been made to define the hypoplastic aortic arch: in an autopsy study measurements were taken of the external diameter of the different aortic segments and an arch ratio was expressed as a fraction of the ascending aorta. Moulaert considered an aortic arch to be hypoplastic when the ratio between the aortic and external diameter of the descending aorta was less than 0.5.[20]

Since the correlation coefficient of the descending aorta to the aortic arch in our control series turned out to be larger as compared to the correlations of the ascending aorta and body surface, we believe that the aortic arch should be related to the **internal** diameter of the **descending** aorta. Additionally, from the haemodynamic point of view, it seems to us that the ascending aorta is more liable to display an abnormal blood flow pattern than the descending aorta in the setting of an aortic coarctation and arterial duct.[21]

Furthermore, the Z-value should be used to express the size of the hypoplastic aortic arch. We believe that this sort of normalization is more comprehensible and gives a clear impression of size and growth.

The early mortality after coarctation resection and aortic arch enlargement for pure aortic coarctation varies from 13.3% to 18% and from 0% to 17% for aortic coarctation with concomitant ventricular septal defect. The recurrent coarctation rate varies from 10.5% to 12.5%.[7,8] Our series, showing an early mortality of 0% (70% CL 0%-12%) for both groups with a recurrent coarctation rate of 12.5% (70% CL 2%-36%), compares favorably to these studies. Therefore, we feel confident that simple resection of the coarctation without aortic arch enlargement is a quite adequate operation in these children.

a



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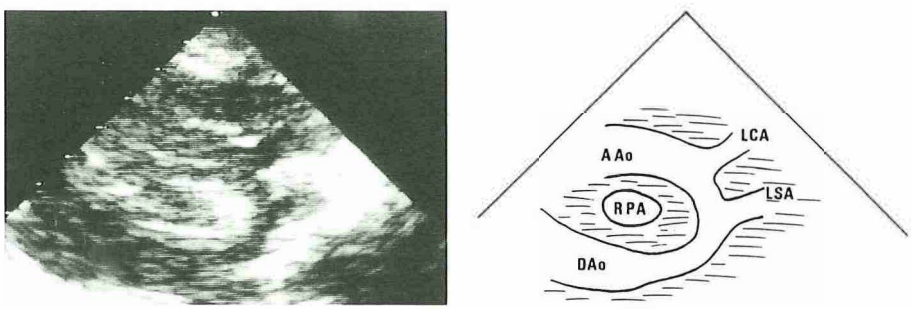

Figure VI-6. *a, Suprasternal two-dimensional echocardiogram at time of operation in an infant with aortic coarctation associated with hypoplastic aortic arch. b, Suprasternal two-dimensional echocardiogram in same infant 6 months after resection of aortic coarctation. AAo, Ascending aorta; DAo, descending aorta; RPA, right pulmonary artery; LCA, left carotid artery; LSA, left subclavian artery.*

A residual pressure gradient after resection of the coarctation and end-to-end anastomosis remains a potential problem in an infant with a hypoplastic aortic arch. The question arises whether this pressure gradient is due to inadequate resection of ductal tissue, decreased aortic elasticity or due to the disparity between the proximal and distal side of the end-to-end anastomosis.[12,22] This disparity causes local blood flow disturbances and could mimic a recoarctation. However, a residual pressure gradient may disappear in short time because widening of the lumen of the aortic arch and the anastomosis is to be expected. Therefore, based on our current experience, it seems safe to wait and monitor on the development of the pressure relations as well as the development of the aortic arch ratio in the postoperative period.

In conclusion, after simple resection of the aortic coarctation without any aortic arch enlargement, a significant growth of the hypoplastic aortic arch has been observed and this grow correlated best to the growth of the descending aorta. Furthermore, the Z-value can well be used to express the size of the hypoplastic aortic arch. Finally, we believe that simple resection of the aortic coarctation and end-to-end anastomosis is the operation of choice for aortic coarctation associated with a hypoplastic aortic arch despite the presence of a concomitant ventricular septal defect and that enlargement of the hypoplastic aortic arch in this morphological entity is not necessary.

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Decision making for the Surgical Management of Aortic Coarctation associated with Ventricular Septal Defect.

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Submitted for publication

VII 1 Abstract

Coarctation of the aorta (CoA) associated with a ventricular septal defect (VSD) may be repaired simultaneously, or by initial CoA repair with ot without banding of the pulmonary artery. The question arises, whether there are specific preoperative criteria which enable the surgeon to make the decision for the optimal surgical management. Between 1980 and 1993, 80 infants with a CoA and VSD less than 3 months of age were treated surgically. In 64 infants (multi-stage group), simple CoA repair was performed via a posterolateral approach with concomitant banding of the pulmonary artery in 10 infants. Twenty VSDs were closed as a secondary procedure and 4 as a tertiary procedure. Sixteen infants (single-stage group) underwent one-stage repair via an anterior midline approach. The total hospital mortality was 7.5%. The left-to-right shunt and extension of the perimembranous VSD into the inlet and/or outlet, were risk factors for prolonged postoperative ventilation time and more strongly for the probability of eventual surgical VSD closure after initial CoA repair. Freedom from recoarctation in the multi-stage group after 5 years was 91.3% versus 60.0% in the single-stage group ($p=0.018$). Freedom from secondary VSD treatment in the multi-stage group after 5 years was 40.7% versus 100% in the single stage group ($p=0.016$). Thirty-seven VSDs (46.2%) in the multi-stage group closed spontaneously. In conclusion, the indication for cardiac catheterization could be extended to calculate the L-R shunt, particulary in infants with an perimembranous VSD with extension into the inlet and/or outlet septum. This policy offers a well-considered choice between single-stage versus multi-stage repair, weighing the risk of secondary VSD treatment versus the risk of recoarctation. Finally, the number of surgical procedure/infants will be as low as possible.

VII 2 Ultramini Abstract

The optimal treatment of aortic coarctation and VSD remains debatable. The purpose of this study was to find criteria to optimize surgical decision making. Analyses showed the preoperative L-R shunt and the morphology of the VSD to be risk factors for the probability of eventual surgical closure of the VSD after initial CoA repair.

VII 3 Introduction

The optimal surgical management of the aortic coarctation (CoA) associated with a ventricular septal defect (VSD) remains a matter of debate in infants presenting with cardiac failure. These infants may be treated by different therapeutic stategies; single-stage total repair, initial CoA repair with concomitant banding of the pulmonary artery, or by only CoA repair with initial conservative treatment of the VSD.[1-4]

The question has arisen whether there are specific preoperative criteria which enable the surgeon to make a decision for the most optimal surgical management in this pathophysiological setting.

Therefore, the purpose of this retrospective study was to find preoperative criteria in order to optimize surgical decision making in infants with CoA and VSD.

VII 4 Patients and Methods

Between 1980 and 1993, 80 infants less than 3 months of age with CoA associated with a VSD were operated upon at the Divisions of Cardiothoracic Surgery of the University Hospital Groningen and the Dijkzigt University Hospital Rotterdam. The therapeutic strategies in the two hospitals were different, changed over time and were subject to the personal preference of 6 different surgeons.

There were 48 boys (60%) and 32 girls. The mean age at operation was 29 days (SD* $\pm$ 23 days) with a mean weight of 3386 gm (SD $\pm$ 646 gm). All infants were treated with diuretics, digitalis; 30 infants (39%) were critically ill and needed prostaglandin E_1 or inotropic medication. The diagnosis of CoA, the morphology of the VSD and coexisting associated anomalies were made by physical examination, cross-sectional echocardiography and/or cardiac catheterization. In the last few years, cardiac catheterization was performed only then when the echo diagnosis was not conclusive. Coexisting associated anomalies were hypoplastic aortic arch in 27 (33.8%) and aortic valve stenosis in 7 (8.8%). The hemodynamic and oximetric data of those who underwent cardiac catheterization are tabulated in table VII-1.

In 64 infants, the CoA was operated only, leaving the VSD to be treated at a later stage, if necessary; thus this constitutes the multi-stage group. Through a left posterolateral thoracotomy the CoA and the isthmus were resected and an end-to-end anastomosis was performed in 30 infants (46.9%), a left subclavian flap angioplasty in 28 (43.8%), a subclavian artery-descending aorta anastomosis in 3 (4.7%), and a patch angioplasty in 3 (4.7%). Banding of the pulmonary artery (PAB) at the time of CoA repair, was performed in 10 infants (15.6%).[5,6] Four of them eventually underwent debanding and closure of the VSD as a secondary procedure, whereas 4 other infants only needed debanding because the VSDs had become hemodynamically insignificant. Finally, the last 2 infants are planned for debanding, without closure of the VSD, for the same reason.

*SD; standard deviation

Table VII-1 *Preoperative Hemodynamic Profile in Infants Undergoing repair of Coarctation associated with a VSD.*

	Pressure*	Sat.O_2 *
Left Atrium	11 ± 4	94 ± 5
LV (syst)	91 ± 19	94 ± 4
LV (diast)	9 ± 5	
Right Atrium	6 ± 3	76 ± 10
RV (syst)	82 ± 19	83 ± 10
RV (diast)	8 ± 13	
PA (syst)	81 ± 20	85 ± 8
PA (diast)	32 ± 9	
Ascending Aorta		91 ± 8
Descending Aorta		91 ± 6

Key:*: *mm Hg, mean ± Standard Deviation, LV, left ventricle; RV, right ventricle; PA, pulmonary artery.*

Twenty-three infants could not be weaned off the ventilator after simple CoA repair as a result of persistent pulmonary overflow: 20 of them underwent subsequent closure of the VSD whereas the other 3 underwent PAB as a secondary procedure. Two other infants, who were weaned off the ventilator successfully, needed PAB as a secondary procedure 3 and 7 days after extubation because of persistent dyspnea. Of the 5 infants, who underwent PAB as a secondary procedure, finally 3 were debanded and the VSD was closed, whereas the other 2 only needed debanding without closure of the VSD. So, in total 35 of the 64 VSDs (54.6%) needed surgical treatment of the VSD, whether secondary or tertiary closure of the VSD or banding of the pulmonary artery as a primary or secondary procedure (Fig.VII-1).

The other group of 16 infants underwent an anterior midline approach and were operated upon with extra-corporeal circulation, under deep hypothermic circulatory arrest and crystalloid cardioplegia to correct the CoA and the VSD in a single-stage procedure. The CoA was resected and an end-to-end anastomosis was performed in 15 infants (93.7%) and once a patch angioplasty. All 16 VSDs were closed via the right atrium. This constitutes the single-stage group.

Aortic Coarctation and VSD

Procedures

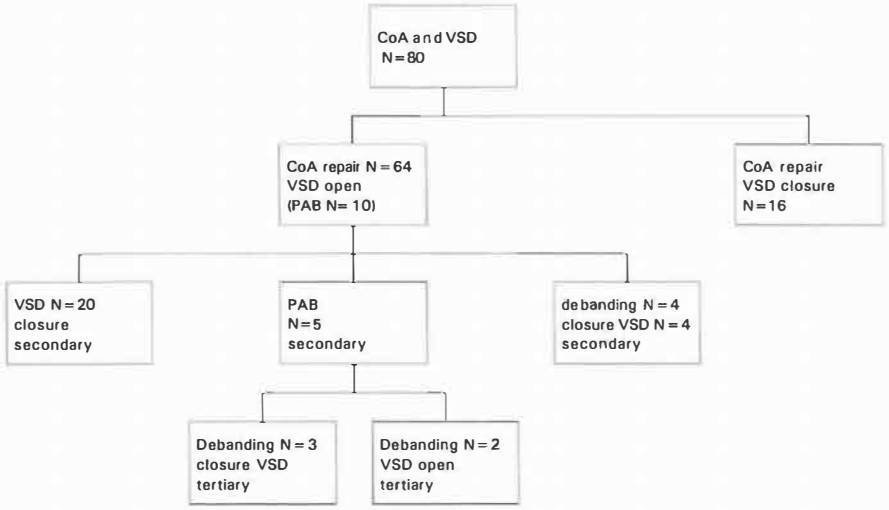


Figure VII-1 *Diagram showing all the procedures for VSD after the initial aortic coarctation repair.*

VII 5 Follow up

To follow up on the infants, we saw them 2 weeks after hospital discharge, 3 months later and then yearly. No patient was lost to follow up. Mean follow up was 6.0 years (SD $\pm$ 4.3, range 1 day-14.6 years). Special attention was given to systolic blood pressure in arms and legs and femoral pulsations. X-ray of the chest and electrocardiography were performed to exclude left ventricular hypertrophy or signs of pulmonary overflow. Cross-sectional echocardiography was performed to exclude recoarctation and to evaluate the hemodynamic importance of the VSD, if any. If these data suggested a recoarctation, cardiac catheterization was performed. Recoarctation was defined by an arm-to-leg systolic pressure gradient exceeding 20 mmHg across the repaired

VII 6 Statistical analysis.

All data were summarized in contingency tables. Seventy percent confidence limits (CL 70%) of binomial distributions were calculated. One way analysis of variance was performed. To determine incremental risk factors, multivariate stepwise logistic regression analysis were performed. P values of less than 0.05 were considered significant. Time-related analysis were performed according to the Kaplan-Meier method.

VII 7 Results

VII 7.1 Mortality and Morbidity.

In total 8 infants (10%) died in our series. The hospital mortality (< 30 days) concerned 6 infants (7.5%): 3 infants died in the multi-stage group (4.7%, CL**:2.1%-9.2%), and 3 infants (18.8%, CL: 8.4%-34.2%) died in the single-stage group. This difference in hospital mortality was not statistically significant. All these 6 infants died due to right ventricle failure.

Late mortality concerned 2 infants of group 1: they died 42 days and 1 year after CoA repair due to right ventricle failure and lung embolism respectively. Paraplegia or other neurologic complications were not seen in our series. Permanent heart block was seen in 1 infant.[7-9]

VII 7.2 Hemodynamic characteristics of the VSD

Fifty-three infants underwent cardiac catheterization prior to CoA repair. In order to quantify the hemodynamic characteristics of the VSD, the total Left-to-Right shunt (L-R shunt) as a percentage of total pulmonary flow and the ratio between the right ventricular peak systolic pressure and the left ventricular peak systolic pressure (RV/LV ratio) as a parameter for pressure loading between the ventricles, could be calculated in 50 infants.In the other 3, hemodynamic data were missing. The mean L-R shunt of these 50 infants was 60.4% (SD $\pm$ 16.2%, range 22%-89%), and the mean RV/LV ratio was 0.94 (SD $\pm$ 0.165, range 0.37-1.4).

In 40 of these 50 infants, the VSD was large: the L-R shunts were more than 50%, and the RV peak systolic pressures were almost equivalent to or even exceeded the LV peak systolic pressure. In 7 infants the VSD was moderate-sized: the L-R shunt was almost 50%, the RV peak systolic pressure was raised approximately half the LV pressure. Finally, in 3 infants, the VSD was small. The L-R shunt was less than 30% and there was no raise of the RV peak systolic pressure.

**CL; 70% confidence limits

Twenty-seven infants underwent two-dimensional echocardiography and Doppler flow mapping. The modified Bernoulli equation was used to calculate a pressure drop across the VSD between the left and right ventricle (pLVRV): gradient (mmHg) = $4(V_2^2 - V_1^2)$, where the gradient was the pressure drop between the left and right ventricle; V_1 was the flow (m/s) in front of the VSD ; and V_2 was the flow velocity in the jet behind the VSD. The mean pLVRV was 7.0 mmHg (SD $\pm$ 15, range 0 mmHg-81 mmHg). Twenty of these 27 infants (74%) had a pLVRV less than 10 mmHg and their VSDs were considered to be non-restrictive. Finally, 13 of the 27 infants in our series underwent cardiac catheterization as well as two-dimensional echocardiography. In this group the RV/LV ratio as well as the pLVRV could be calculated. Correlation analyses between these variables was almost perfect at 0.93 ($p<0.001$). The nomogram representing the linear regression and the 95% confidence limits, is shown in Fig. VII-2. This regression equation enabled us to calculate the missing pLVRV of the catheterized infants and vice versa, the missing RV/LV ratio of the infants who underwent echocardiography only. By doing this, eventually in 77 infants the RV/LV ratio as well as the pLVRV was present either by direct measurement or by calculation.

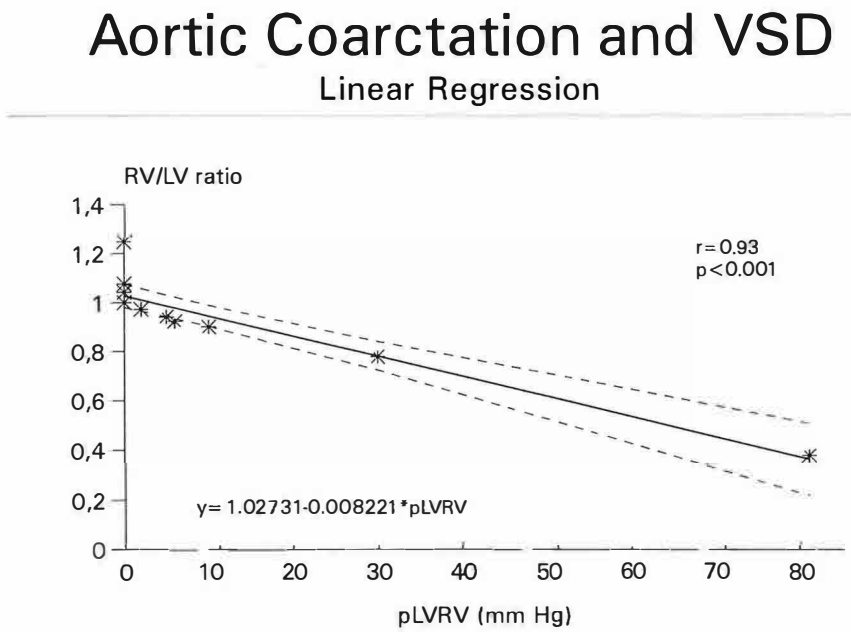


Figure VII-2 *Nomogram representing the linear regression between the pLVRV and the RV/LV ratio and the 95% confidence limits.*

VII 7.3 Morphology of the VSD

The division of the VSDs was into defects in which part of the rim of the defect abuts on area of continuity between atrioventricular and aortic valves (perimembranous defect) and defects which have entirely muscular rims (muscular defects). The extension of the perimembranous VSDs in our studies varied markedly, due to deficiency of the adjacent muscular septum: some perimembranous VSDs had an extension into the inlet of the right ventricle, others had an extension into the outlet of the right ventricle and finally some extended in both directions. The muscular VSDs in our studies, were found anywhere in the septum and could be divided into those in the inlet, trabecular, or outlet septum. Moreover, some were multiple or coexisted with malalignmentof septal structures.

VII 7.4 Morphology of the VSD, Surgery and Follow-up

Of the 80 VSDs, 48 were perimembranous defects (60%); 28 subaortic, 10 extending into the outlet septum, 7 into the inlet septum and 3 into both the inlet and outlet septum. Twenty-one defects were muscular, 8 were multiple and 3 were malaligned and situated in the outlet septum.

Twenty defects were closed as a secondary procedure after CoA repair. Seven of them were subaortic perimembranous defects; an other 7 were perimembranous with extension into both the inlet and outlet septum and 3 into the inlet septum. Two defects in this group were muscular and 1 defect was multiple.

Sixteen VSDs were closed in the single-stage group as a concomitant procedure at the time of CoA repair. Five of them were subaortic perimembranous defects; another 3 were perimembranous with extension into both the inlet and outlet septum; 3 into the outlet septum and 1 into the inlet septum. Two defects were muscular and 2 were malaligned and situated in the outlet septum.

Four VSDs were closed as a secondary procedure with concomitant debanding of the pulmonary artery. A subaortic perimembranous, a muscular, a muscular malaligned outlet VSD, and multiple VSDs were all found once. Finally, 3 VSDs were closed as a tertiary surgical procedure: twice an inlet and once a perimembranous VSD were found.

So, 21 of the 37 perimembranous defects (56%, CL:46%-66%) in the **multistage group**, needed surgical closure after the initial CoA repair. Of the 27 muscular VSDs, 6 defects needed surgical closure (22%, CL:13%-33%). Univariate analysis showed this difference between the perimembranous and muscular VSDs to be associated with a p value of 0.005.

Of the 37 perimembranous VSDs, 23 defects (68%, CL:52%-71%) were described as subaortic. Ten of these 23 VSDs eventually needed surgical closure of the VSD. Of the other 14 VSDs which extended into the inlet and/or outlet septum, 11 defects (78% CL:61%-90%) needed surgical closure eventually. Univariate analysis showed this difference between the different morphology of the perimembranous VSDs to be associated with a p value of 0.036.

In summary, in total 43 defects of the 80 (53.8%) were closed surgically

(Fig.VII-1). The other 37 VSDs (46.2%), including those in 4 infants with primary or secondary banding of the pulmonary artery, closed spontaneously or became small and hemodynamically insignificant.

VII 7.5 Hemodynamics of the VSD and Postoperative Ventilation Time (PVT) in relation to Surgery.

VII 7.5.1 Hemodynamics of the VSD in relation to Surgery

The mean L-R shunt of the multi-stage and single-stage group was 58% (SD* ± 16%) and 68% (SD ± 14%) respectively (p=0.108). The mean RV/LV ratio was 0.91 (SD ± 0.18) and 0.97 (SD ± 0.92) (p=0.07). However, the mean pLVRV of the single-stage group was significantly lower at 5 mmHg ± 8 versus 10.5 mmHg ± 18 in the multi-stage group (p=0.027).

Thirty infants of the multi-stage group (46.8%) needed treatment of the VSD, either primary PAB (N=10) or secondary closure of the VSD (N=20)(Fig.VII-1). The mean L-R shunt and the mean pLVRV at time of operation of the 10 infants with PAB did not differ significantly as compared to those who underwent CoA repair alone. However, the RV/LV ratio in these 10 infants was significantly higher (p=0.015).

In the other 20 infants, the VSD was closed as a secondary surgical procedure at a mean period of 5.5 months (SD ± 10.1) after the initial CoA repair. Seven of them within 1 month after the initial CoA repair because they could not be weaned off the ventilator due to persistent pulmonary overflow without signs of recoarctation. The other 13 infants could be weaned off the ventilator successfully, but the VSD was closed at an interval ranging from 35 days to 3.6 years after the initial CoA repair. Recurrent pulmonary infections and failure to thrive were the main reasons for closure. The hemodynamics of the VSD **before** the initial CoA repair in these 20 infants did not differ significantly as compared to the hemodynamic in those in whom the VSD was left open.

VII 7.5.2 Postoperative Ventilation Time (PVT) in relation to Surgery

In 77 of the 80 infants (96.2%), the mean postoperative ventilation time (PVT) after the initial operation was 7.0 days (SD ± 12.5, range 0-61 days). In the other 3 infants, data concerning the ventilation time were missing. The policy concerning extubation was virtually uniform for all infants. The mean PVT in the multi-stage group was 7.0 days (SD ± 12) versus 6.9 days (SD ± 9.3) in the single-stage group (p=NS).

The mean PVT of the 10 infants of the multi-stage group who underwent concomitant PAB was 4.5 days (SD ± 9.7) versus 7.4 days (SD ± 12.0) of those who underwent CoA repair alone (p=NS). The mean PVT of the 20 infants in the multi-stage group who underwent secondary closure of the VSD after the initial CoA repair was 13.2 days (SD ± 17.8) versus 5.0 days (SD ± 8.1) in those in whom the VSD was left open (N=44) (p=NS).

*SD; standard deviation

Fourty-four out of the 77 infants (55.5%) could be weaned off the ventilator within 24 hours. In order to find incremental risk factors for the PVT of longer than 24 hours, age and weight at operation, body surface area (BSA), the RV/LV ratio, the L-R shunt, and the pLVRV were entered into a multivariate logistic regression analysis. The analysis produced the L-R shunt as the only incremental risk factor for the probability of PVT > 24 hours (Fig.VII-3a). Additionally, the influence of the morphology of the VSD on the probability of PVT > 24 hours, in particular the perimembranous VSD with extension into the inlet and/or outlet septum, is illustrated in Fig.VII-3b. Note that at a L-R shunt of 60%, the probability of prolonged PVT in the setting of a perimembranous VSD with extension into the inlet and/or outlet is 35% versus 0% in a simple subaortic perimembranous VSD.

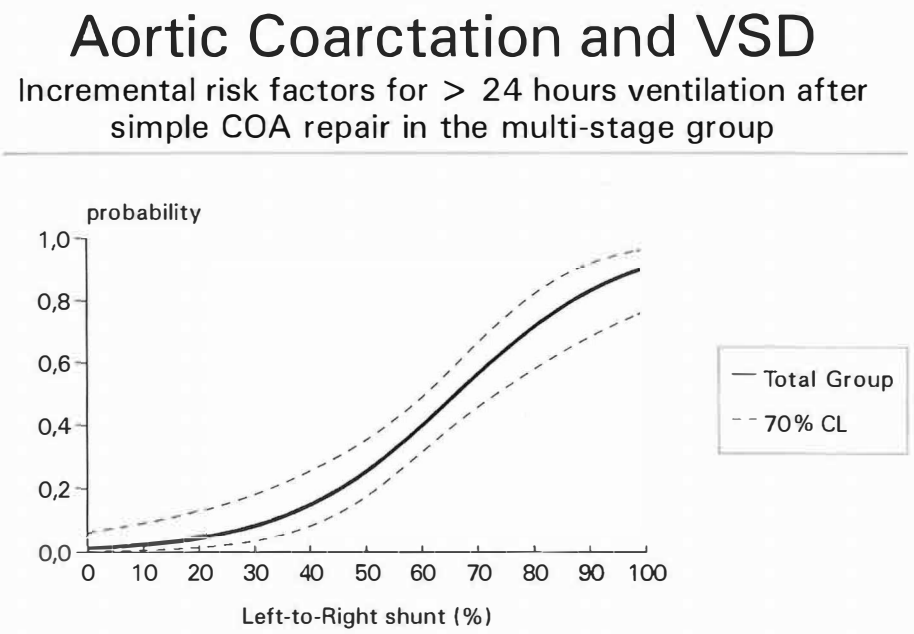


Figure VII-3a *Nomogram of the multivariate equation for the incremental risk factors for postoperative ventilation time of > 24 hours according to the L-R shunt in the total group. (Intercept -4.1873, Log.Coef: 0.0643, p=0.0072) (70% CL = 70% confidence limits)*

Aortic Coarctation and VSD

Incremental risk factors for > 24 hours ventilation after simple CoA repair in the multi-stage group

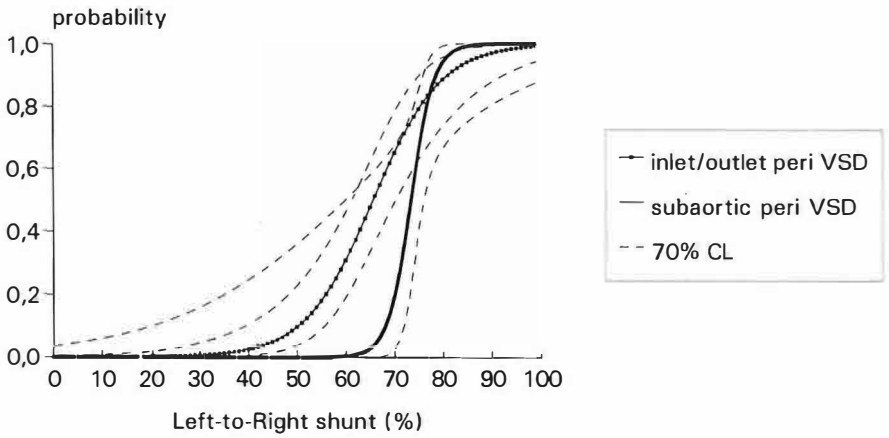
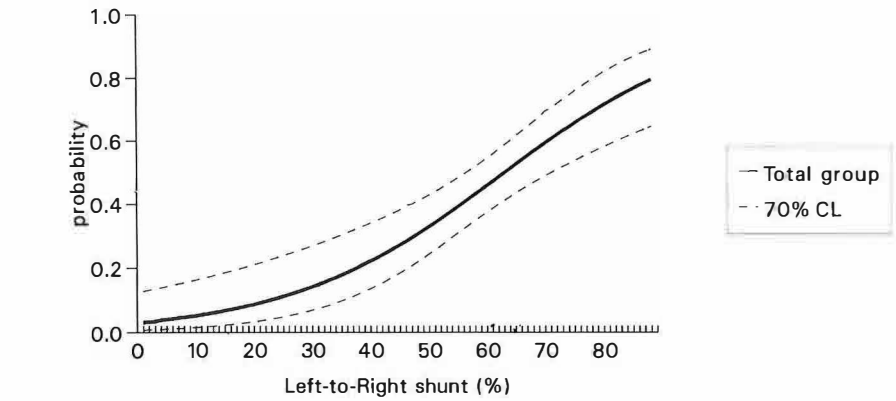


Figure VII-3b *Nomogram of the multivariate equation for the incremental risk factors for postoperative ventilation time of > 24 hours in relation to the L-R shunt and the morphology of the VSD. Note the influence of the perimembranous VSD with extension into the inlet and/or outlet ventricular septum. (70% CL; 70% confidence limits, peri; perimembranous)*

VII 7.6 Incremental Risk Factors for the probability of Surgical Treatment of the VSD in the multi-stage group.

In order to find incremental risk factors for the probability of surgical treatment of the VSD in the multi-stage group, we entered the following variables into a multivariate stepwise logistic regression analysis: age and weight at operation, the BSA, the L-R shunt, the RV/LV ratio, the pLVRV and the PVT. The analysis produced the L-R shunt as the only incremental risk factor for the probability of surgical closure of the VSD after the initial CoA repair (Intercept: -3.2704, Log.Coef: 0.0521, p=0.0027)(Fig. VII-4a). The influences of the morphology of the VSD, in particular the perimembranous VSD with extension into the inlet and/or outlet septum, are illustrated in (Fig.VII-4b). Note that at a L-R shunt of 50%, the probability of surgical closure of the VSD after initial CoA repair in the perimembranous VSD with extension into the inlet and/or outlet septum, is more than double as compared to a simple subaortic perimembranous VSD.



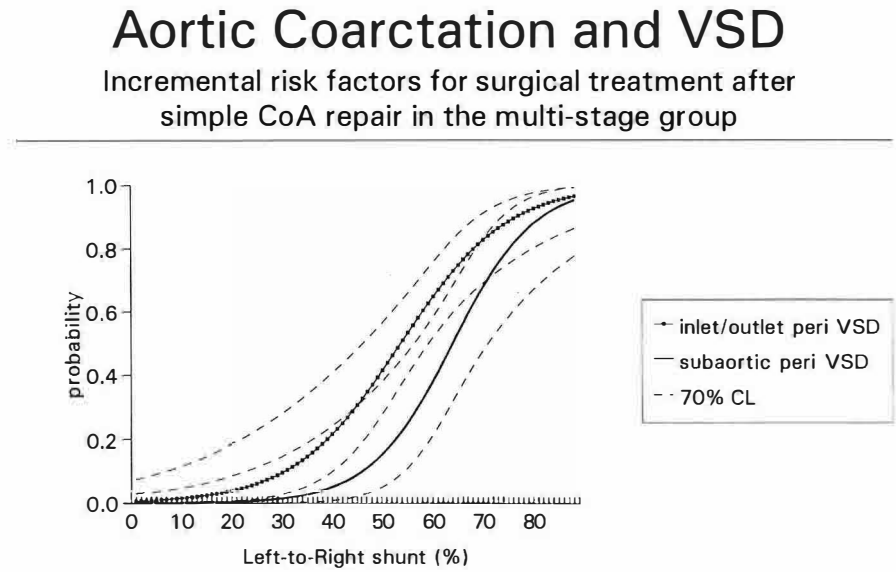


Figure VII-4a and 4b *Nomograms for the incremental risk factors for VSD treatment (closure VSD, PAB and debanding and closure VSD) after CoA repair according to the L-R shunt in the total group. Note the influence of the inlet and/or outlet perimembranous VSD.(70% CL; 70% confidence limits, peri; perimembranous)*

VII 7.7 Primary and following Procedures

VII 7.7.1 Freedom from Recoarctation

Recoarctation was found in 13 of the 80 patients (16.3%, CL**:12-22%): 9 times in the multi-stage group and 4 times in the single-stage group. Six of the 45 infants (13.3%, CL:8-21%) after resection and end-to-end anastomosis, 5 of the 28 infants after subclavian flap angioplasty (17.9%; CL:10-28%), and 2 of the 4 infants after patch angioplasty (50%: CL:18-82%). The difference for the prevalence of recoarctation between resection and end-to-end anastomosis and subclavian flap angioplasty was not significant. Furthermore, age and weight at operation between the group with and without recoarctation did not differ significantly either. Ten times a percutaneous balloon angioplasty (PTBA) for recoarctation was performed, and thrice a reoperation.

In order to depict the freedom from recoarctation in the multi-stage and single-stage group, a time-related analysis was performed. It showed that the freedom from recoarctation in the multi-stage group after 5 years was 91.3%, whereas the freedom from recoarctation in the single-stage group for the same period was significantly lower at 60.0% (p=0.018)(Fig.VII-5).

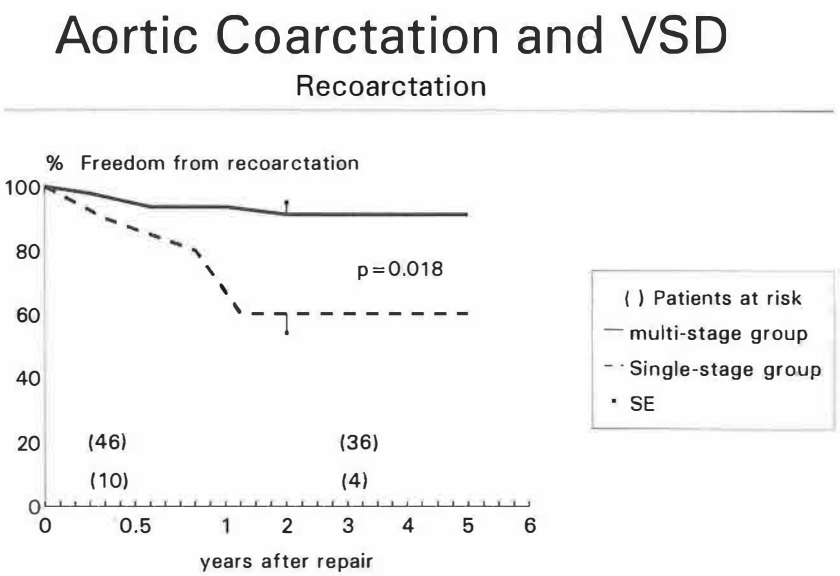


Figure VII-5 *Actuarial freedom from recoarctation stratified into the multi-stage and single-stage group. (SE; standard error)*

**CL; 70% confidence limits

VII 7.7.2 Freedom from Surgical Events.

In order to depict the freedom from secondary treatment in relation to the VSD in the multi-stage and single-stage group, a time related analysis was performed. It showed that the freedom from secondary treatment in relation to the VSD (including secondary VSD closure, secondary PAB and debanding and surgical closure of the VSD) in the multi-stage group after 5 years was 40.7%, versus 100% in the single-stage group (p=0.016)(Fig. VII-6).

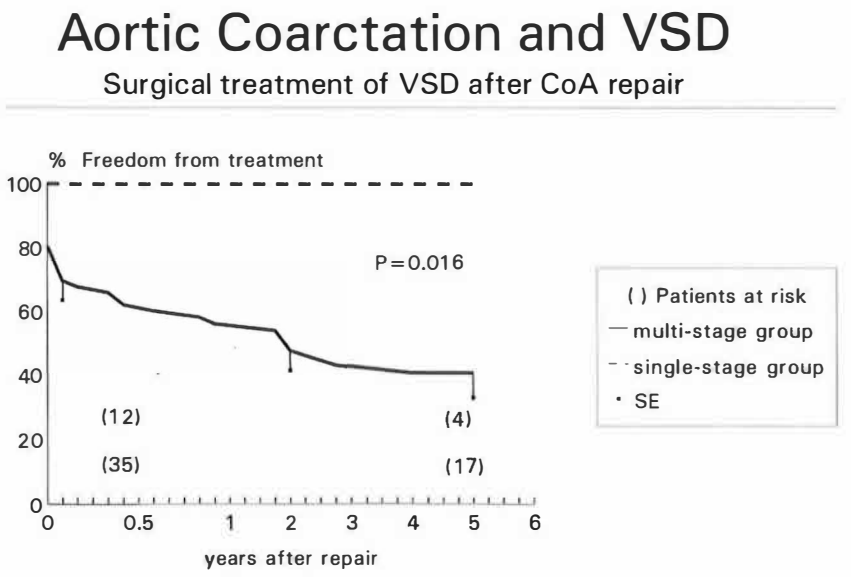


Figure VII-6 *Actuarial freedom from secondary surgical treatment of VSD, secondary PAB, and debanding and surgical closure of the VSD stratified into the multi-stage and single-stage group. (SE; standard error)*

So, in the multi-stage group (N=64), in total 111 procedures were performed: 54 times a CoA repair and 10 times CoA repair and concomitant PAB. Thirty-three infants needed a secondary surgical procedure (52%, CL: 44%-59%): 20 times secondary surgical closure of the VSD, 5 times secondary PAB, 4 times secondary surgical closure of the VSD and debanding, and 4 times secondary debanding. Five infants needed a tertiary surgical procedure (8%, CL: 4%-13%): 3 times debanding and surgical closure of the VSD and twice debanding. Six infants underwent a percutaneous balloon dilation angioplasty (PTBA), and 3 a reoperation for recoarctation. So, 17 of the 64 (26.5%) infants had only 1 procedure. Five infants died in this group, so at the latest follow-up, 59 infants (92%) are well after 1.73 procedure per infant.

In the single-stage group (N=16), 21 procedures were performed. Sixteen times a CoA repair and concomitant closure of the VSD and once an implantation of a VVI pacemaker as a secondary procedure because of a permanent heart block. Four times a PTBA for recoarctation was performed. Three patients died in this group. So, 13 infants (81%) are well after 1.31 surgical procedure per infant. No statistical difference was found between the surgical procedures per infant in the multi-stage versus the single-stage group (p=0.11).

VII 8 Discussion

About half of all neonates with a CoA and VSD develop symptoms of congestive heart failure within the first month of life attributed to a number of pathophysiological factors or associated anomalies. The severity of the CoA, the morphology and hemodynamics of the VSD are all factors which contribute to this hemodynamic situation.

From the morphologic point of view, the CoA is almost always in an juxtaductal position and its position seems to be age dependent.[10] Though, in very young infants, as in our series, the hemodynamics might display all characteristics of a preductal position of the CoA. The right ventricle supplies blood to the lower body through the arterial duct while also pumping blood to the lungs at systemic pressure. In order to reach adequate systemic circulation, the pulmonary circulation is overloaded. Therefore, the right ventricle must cope with a large preload and afterload at a systemic level.

In the setting of a CoA and VSD, blood flow through the left ventricle is probably diminished from the early developmental stage onwards and the presence of hypoplasia of the aortic arch or isthmus is caused by a paucity of aortic blood flow during fetal development. As a result, these obstructions will further contribute to the right ventricular preload by diverting left ventricular blood flow into the pulmonary trunk.[10-16]

Nowadays, it is an established fact that the CoA, which is considered to be the dominant lesion in this morphological setting, should be repaired promptly. However the discussion centers on the question whether it is reasonable to repair the CoA alone and then follow the postoperative course or perform CoA repair and VSD closure as a single-stage procedue.[17-28] It would be ideal if one could predict, which VSD would require immediately surgical closure and which VSD can be treated conservatively. The multivariate logistic regression analysis produced the preoperative L-R shunt as the only hemodynamic risk factor. The nomogram of the multivariate equation shows the relation between the pre-operative L-R shunt and the probability of eventual surgical treatment of the VSD (including secondary closure of the VSD, PAB and debanding and closure of the VSD (Fig. VII-4a).

Currently, less is known whether there is a specific morphologic type of VSD associated with the CoA that should be considered a surgical risk factor. Anderson found that the majority of these hearts had a particular form of perimembranous defect which could extend into all parts of the muscular ventricular septum with aortic overriding. Furthermore, this necropsy study suggested that perimembranous defects are

undergoing spontaneous closure in most cases, a phenomenon also confirmed by the necropsy study of Moene. [11,29] In contrast, we found that the incidence of surgical VSD closure after the initial CoA repair, was highest in the 'perimembranous' group. Furthermore, the influence of the morphology was even more strongly marked as we stratified the perimembranous VSDs into different locations: the nomogram shows that the probability of surgical closure of a simple subaortic perimembranous VSD with a L-R shunt of 50%, is 18%, whereas a perimembranous VSD with extension into the inlet/or outlet septum, has a probability of 42% for the same L-R shunt (Fig. VII-4b). So, it seems that in particular the perimembranous VSD with extension into the inlet and/or outlet septum, should be considered another risk factor for the need of surgical closure after initial CoA repair.

Surprisingly, the freedom from recoarctation in the multi-stage group after 5 years was significantly higher than in the single-stage group (Fig. VII-5). Age and even more strongly, weight at time of operation are reported to be incremental risk factor for the prevalence of recoarctation[30]. However, these variables did not differ significantly between the two groups and therefore cannot explain this difference of the freedom from recoarctation. It appears that mobilization of the descending aorta and excision of the ductal tissue via an anterior midline approach to such an extent that all ductal tissue is removed, is technically more difficult than via a posterolateral approach. Therefore, it may be so, that an anterior midline approach for this morphological entity imposes an extra risk factor for recoarctation in a group infants, which are already prone for recoarctation because of their young age and low weight.[18,30-32] Nevertheless this may be taken as a calculated risk, within the argumentation that balloon dilation of recoarctation is a procedure that is to be preferred over an extra operative procedure.[33,34]

In summary, these clinical findings are of utmost importance, for they offer the surgeon new perspectives in the surgical decision making for CoA associated with a VSD. The preoperative L-R shunt and the perimembranous VSD, particularly those extending into the inlet and/or outlet septum, are risk factors for a prolonged PVT and more strongly for eventually surgical VSD closure after initial CoA repair. Currently, two-dimensional echocardiography provides the surgeon the precise description of the anatomy. If the diagnosis is not conclusive, cardiac catheterization is then performed to rule out coexisting anomalies. But, based on this study, it seems to us that the indication for cardiac catheterization might be extended to all infants in order to calculate the L-R shunt, particularly in those infants with a perimembranous VSD which is located in the inlet and/or outlet ventricular septum. Knowing these two risk factors, the probability of eventually surgical treatment of VSD after the initial CoA repair can be calculated.

This policy offers the surgeon different advantages: first, a well-considered choice for the single-stage or multi-stage repair, second, weighing the risks of secondary or tertiary surgery of the VSD versus the risk of recoarctation, and third, the amount of procedures per infant will be as low as possible.

In conclusion we believe that these data might help the surgeon to make a well-considered surgical decision for the optimal treatment of the CoA associated with a VSD.

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VII 10 Appendix

Probability estimates were obtained from the logistic regression equation according to the following formulas:

$$p = \frac{1}{1 + e^{-z}}$$

$$z = b_0 + b_1 + \ldots\ldots + b_k x_k$$

where e is the base of the natural logarithm, b_0 is the intercept of the logistic equation , and b_1 and b_k are the logistic regression coefficients associated with the values for the incremental risk factors x_1 and x_k.[18]

Influence of Age on Survival, late Hypertension and Recoarctation in Elective Aortic Coarctation repair.

Including longterm results after elective aortic coarctation repair with a follow up from 25 to 44 years.

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VIII 1 Abstract

The optimal age for elective aortic coarctation repair is controversial. The optimal age, should be associated with a minimal risk of recoarctation, risk of late hypertension and other cardiovascular disorders. The purpose of this retrospective study is to determine the actuarial survival rate after aortic coarctation repair 25 years or more after operation, and to calculate the optimal age for elective aortic coarctation repair. From 1948 to 1966, 120 consecutive patients underwent aortic coarctation repair. There were 87 men (72.5%). The mean age at operation was 15.5 years (SD ± 9.1). Resection and end-to-end anastomosis was performed in 103 patients (85.8%). Early mortality occurred in 6 patients due to surgical problems, whereas late mortality in 15 patients was predominantly due to cardiac causes. The mean follow-up period was 32 years (range 25y-44,2y). Ninety-two patients (96.8%) were in NYHA class I. The probability of survival 44 years after operation was 73%. Patients younger than 10 years at operation had the highest probability of survival at 97%. Multivariate analysis produced age at operation as the only incremental risk factor for the occurrence of recoarctation, of late hypertension as well as for premature death. In order to avoid these sequelae, elective aortic coarctation repair should be performed around 1.5 years of age. At that age, the probability of recoarctation will have decreased to less than 3%, and the probability of upper body normotensive state and longterm survival will be optimal.

VIII 2 Ultramini-abstract

The optimal age for elective aortic coarctation repair is controversial, and should be associated with a minimal risk of recoarctation and late hypertension. In order to avoid these sequelae, elective repair should be performed around 1.5 years of age. Then the probability of recoarctation is less than 3%, and the probability of normotensive state and survival will be optimal.

VIII 3 Introduction

Unrepaired aortic coarctation is known to have a detrimental effect on survival. Survival is jeopardized by heart failure, rupture of the aorta, intracranial hemorrhage, endocarditis, hypertension or coronary artery disease. Ninety percent of untreated patients die before the age of 50 years due to these complications.[1-3] The first clinical surgical repair for this anomaly was performed by Crafoord in 1944.[4]

Ever since, different studies have revealed early success of the repair in terms of decreased mortality and lowering of blood pressure. However, the success of elective repair diminishes with an increasing age at repair.[5-14]

On the other hand, however, aortic coarctation repair in infancy carries an increased risk of recoarctation.[15-19] Therefore, in order to calculate the optimal age for elective repair, one should steer a course between the risk of recoarctation and the risk of late hypertension and other cardiovascular disorders.

The purpose of this retrospective study is to determine the actuarial survival rate after aortic coarctation repair in patients with a follow up of more than 25 years, and to calculate the optimal age for elective aortic coarctation repair.

VIII 4 Patients and Methods

From 1948 to 1966 120 consecutive patients underwent surgical repair of an aortic coarctation at the division of Cardiothoracic Surgery of the University Hospital of Groningen. There were 87 men (72.5%) and 33 women. The mean age at operation was 15.5 years (SD* $\pm$ 9.1, range 0.5 year- 48.0 years): 37 patients (30.8%) were less than 10 years old at operation (group 1); 57 patients (47.5%) were between 10 and 20 years old at operation (group 2) and 26 patients (21.7%) were older than 20 years at operation (group 3). Preoperatively, 61 patients (50.8%) had one or more symptoms (table VIII-1). In the other 59 patients, the aortic coarctation was found by chance during a medical examination. On auscultation, 108 patients (90%) had a systolic murmur over the precordium. The mean systolic blood pressure in the left arm was 169 mmHg (SD $\pm$ 60, range 120 mmHg-240 mmHg), and the mean systolic blood pressure in the left leg was 37 mmHg (SD $\pm$ 56, range 0 mmHg - 170 mmHg). Femoral pulsations were found to be absent in 77 patients (64.1%). Left ventricular hypertrophy was found on the electrocardiogram in 78 patients (65.5%). Rib notching was found on the chest roentgenogram in 33 patients (27.5%) and a dilated ascending aorta in 9 patients (7.5%). In all patients, the aortic coarctation was confirmed by angiography. Aortic valve stenosis as a concomitant anomaly was seen in 5 patients (4.1%), aortic valve regurgitation was found in 5 other patients, ventricular septal defect was found in 4 patients (3.3%) and a mitral valve regurgitation was found in another 2 patients (1.6%).

*SD; standard deviation

Table VIII-1. *Preoperative symptoms in 61 patients (50.8%)*

Symptoms	N	%
Dyspnea	29	47.5%
Fatigue	26	42.6%
Headache	23	37.7%
Palpitations	18	29.5%
Cold feet	11	18.0%
Angina pectoris	9	14.8%
Vertigo	7	11.5%
Claudication	6	9.8%
Syncope	5	8.2%
Miscellaneous	2	1.6%

Resection and end-to-end anastomosis was performed in 103 patients (85.8%), a Glagett's operation (end-to-end anastomosis of the left subclavian artery to the descending aorta) in 12 patients (10%) in the period 1951-1962[20], and insertion of a prosthetic vascular graft in 5 patients (4.2%). Thoracic aneurysms were identified during operation in 6 patients and resected during the same surgical procedure: 4 of an intercostal artery, 1 of the left subclavian artery, and 1 of the descending aorta.

Recent follow up data were collected by two questionnaires: one held with the patient and one with the family physician. The questionnaire included several demographic and current health status data as well as questions concerning cardiac-related events, symptoms, and medications. Additional information was obtained from the cardiologist or other specialist if necessary. Hypertension was defined when the diastolic blood pressure in the right arm exceeded 90 mmHg at regular blood pressure measurements. The mean follow-up period was 32 years (SD $\pm$ 4.8, range 25 years-44.2 years). Four patients (3.8%) were lost to follow up.

VIII 5 Statistical analysis

All data were summarized in contingency tables. A time related analysis according to the Kaplan-Meier method was done to depict the probability of survival of the whole group and stratified into different age groups. Comparisons of all continuous variables between the groups were made by one-way-analysis of variance. The null hypothesis, being that there is no difference between the groups, was rejected at a P value ≤ 0.05. In order to determine incremental risk factors for survival a stepwise multivariate logistic regression analysis was performed additionally. P-values ≤ 0.05 were considered to be significant.

VIII 6 Results

VIII 6.1 Clinical course

A total of 21 out of 120 patients (17.5%) died in our series. Six patients (5%) died within 48 hours after coarctation repair: 5 due to tear of the suture line and 1 due to an unexplained sudden death. Late postoperative mortality occurred in 15 patients (12.5%) at a mean of 17.8 years (SD ± 11.7 y) after operation. The mean age at operation of these 15 patients was significantly higher at 18.7 years (SD ± 7.4 y) as compared to the survivors (14.3, SD ± 8.2 y, p=0.036). The mean age at time of death was 37 years (SD ± 11.7y, range 13.2y-57.5y). Cardiovascular causes were predominant: myocardial infarction in 5 patients (4.2%), rupture of a true aneurysm of the ascending aorta in 2 patients (3.4%), cerebrovascular accident and bleeding of the pulmonary artery both in 1 patient (1.7%) and sudden death in 6 patients (5.2%).

Late morbidity occurred in an additional 55 patients (45.8%): hypertension in 29 patients (25%); valvar anomalies in 13 patients (11.2%); four of them underwent an aortic valve replacement because of aortic valve stenosis and 2 underwent a mitral valve replacement because of mitral valve regurgitation. Nine patients (7.7%) suffered from angina pectoris; 4 of them eventually developed a myocardial infarction. Recurrent coarctation was found in 2 patients (4.5%) who had undergone initial repair at an age of 4 and 8 years respectivily: one patient underwent a reoperation 16 years after the initial repair and the other is treated medically. Finally, a cerebrovascular accident and a carcinoma of the lung both in one patient (1.7%).

At most recent follow-up 95 patients (79.2%) were alive with a mean age of 46.6 year (SD ± 10.2, range 31y-79y). Ninety-two (96.8%) were in NYHA class I, 2 patients in NYHA class II and 1 patient in NYHA class III.

VIII 6.2 Survival

The probability of survival (Kaplan Meier) in our series was 93% at 1 year after operation, 89% at 10 years, 88% at 20 years, 81% at 30 years and 73% at 44 years (Fig. VIII-1). However, it appeared that the survival of an age-and era matched group based on cohort life tables of the normal population after 40 years differed significantly at 93% (p=0.026).[21]

The influence of age at operation on survival is shown in Fig. VIII-2. In group 1 (<10 y) the probability of survival was 97%. In group 2 (10y-20y) and group 3 (>20y), the probability of survival differed significantly at 69% and 70% respectively (p=0.027)

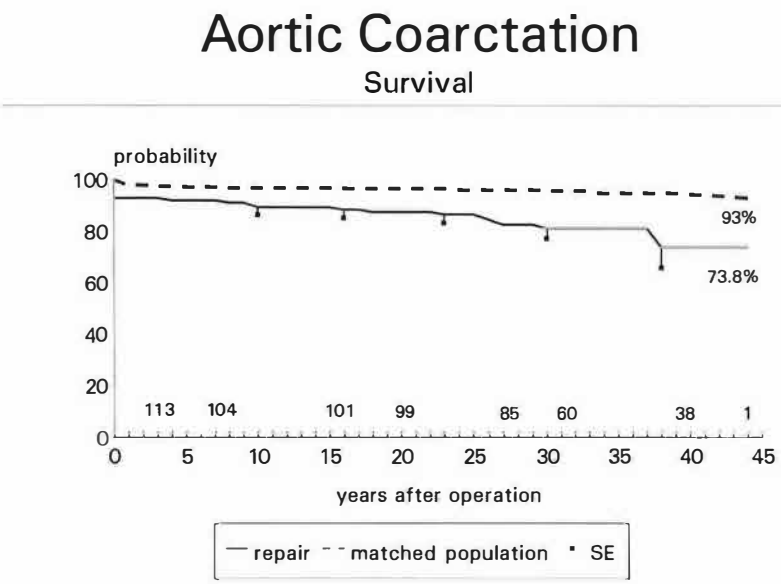


Figure VIII-1 *Survival after coarctation repair versus a matched population.*

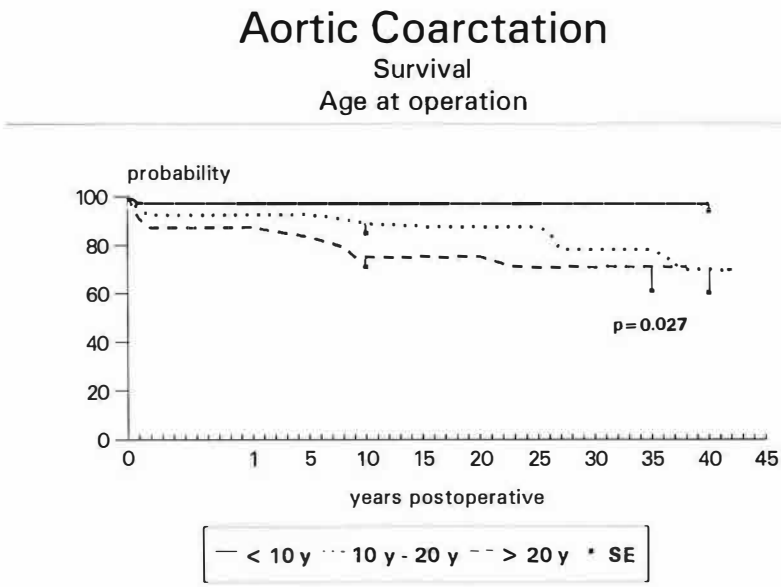


Figure VIII-2 *Survival after coarctation repair statified into different ages.*

The outcome of the one-way analysis of variance for survival is tabulated in table VIII-2. The null hypothesis being that there was no difference between the groups was rejected for age at operation and the pre-operative systolic bloodpressure (p=0.0124 and p=0.0254, respectivily). The multivariate analysis that followed produced age at operation as the only incremental risk factor for survival (Log.coef = -0.0710, p=0.03).

Table VIII-2. *One-way-analysis of Variance for Survival*

Variable	p
Age at operation	0.0124
Pre-op syst press*	0.0254
Post-op syst press**	0.7810
Gender	0.8344
Surgical procedure	0.96

Key:* *pre-operative systolic blood pressure > 140 mmHG or > 90th percentile for blood pressures defined by the American Task Force.*[42]
** *postoperative systolic blood pressure > 140 mmHg*

VIII 7 Discussion

The follow up of our group of patients for aortic coarctation is one of the longest published until now, with a probability of survival at 44 years after elective coarctation repair of 73%.[5-14,22] These results are in contrast to the survival rate of the unoperated patient: nearly 90% of those patients die before reaching the age of 50 years.[23] However, the course of the actuarial survival curve, shows a striking phenomenon: it declines more from the second postoperative decade onwards as compared to the natural course of a matched population. This phenomenon indicates that despite the early apparent success after elective aortic coarctation repair, not all patients live healthily ever after but remain at some risk of premature death. It must be borne in mind, though, that the age at operation of our group of patients is old in the light of the current practise.

Premature death long after successful aortic coarctation repair is an alarming event. Seventy-one percent of the mortality in our series was of a cardiovascular nature. The explanation for this can be manifold. Left ventricular hyperkinesia and increased ventricular mass are found even in normotensive patients long after successful aortic coarctation repair: increased ventricular mass can provoke rythm disturbances and could cause an imbalance between muscle and coronary vessel growth with subsequent decreased oxygen reserve[24-26]. Moreover, hypertension and coronary sclerosis as normal aging processes, will further accelerate the effects of these haemodynamic changes and may explain the increased incidence of sudden death and myocardial infarction.[27-29]

Therefore, even long after successful elective aortic coarctation repair, patients appear to remain at risk for premature death mainly due to cardiovascular disorders.

The age at operation has a key position in the optimal treatment for elective aortic coarctation repair. In the past era, the ideal age for elective aortic coarctation repair was supposed to be between 4 years and adolescence in an attempt to avoid the high operative mortality in neonates, to minimize the occurrence of recoarctation and to avoid the incidence of late cardiovascular complications.[30-33] Gradually the timing for elective aortic coarctation repair has shifted towards infancy. Currently, instead of age at time of operation, the presence of congestive heart failure in infants with an aortic coarctation plays an important role in the clinical decision whether to operate promptly or not. If congestive heart failure is present, prompt surgical repair is generally accepted to be mandatory. However, the issue remains when to operate electively on the asymptomatic infant with isolated aortic coarctation.

In order to calculate the optimal age for elective aortic coarctation repair, 3 potential problems should be taken into account: first, young age at operation and even more strongly low weight at operation are incremental risk factors for the prevalence of recoarctation. In a previous study we demonstrated that in infants less than 2 years of age with an aortic coarctation the prevalence of persisting coarctation or recoarctation was strongly related to low weight at operation: the lower the weight, the higher the probability of recoarctation.[15] The linear correlation between weight and age at operation in that study was almost perfect ($r=0.94$, $p<0.001$). After exclusion of weight at operation from the multivariate analysis, the subsequent analysis, produced age at operation as an incremental risk factor for recoarctation. The younger the patient at operation, the higher the probability of recoarctation. This probability is 22%-33% when the repair is performed in neonates, about 15% at six months of age and less than 3% when the infant is older than 1.5 years of age. Thus these findings, which concur strongly with those reported by Kirklin[23], suggest the optimal age for elective coarctation repair beyond **3 years** to avoid recoarctation (Fig.VIII-3).

However, the prevalence of late hypertension after aortic coarctation repair is another problem to take into consideration. Late hypertension is an incremental risk factor for premature death after aortic coarctation repair at older age and its prevalence in the literature varies from 12%-66%.[6,12] Older age at operation, endocrine factors, abnormal compliance of upper body small blood vessels, stiffness of the aorta proximal to aorta coarctation repair or persistent recoarctation are associated with the occurrence of late hypertension.[34-41] Currently, less is known about the influence on this prevalence by performing the operation very early in life. Therefore, age at operation, the preoperative systolic bloodpressure and follow-up as independent variables were included in this present study into a multivariate analysis for late hypertension: the analysis produced age at operation as the only incremental risk factor for the prevalence of late hypertension (Log.Coef: 0.0685 $p=0.016$): even if the aortic coarctation repair is performed in neonatal life, the probability for late hypertension is more than 10% (Fig.VIII-4).

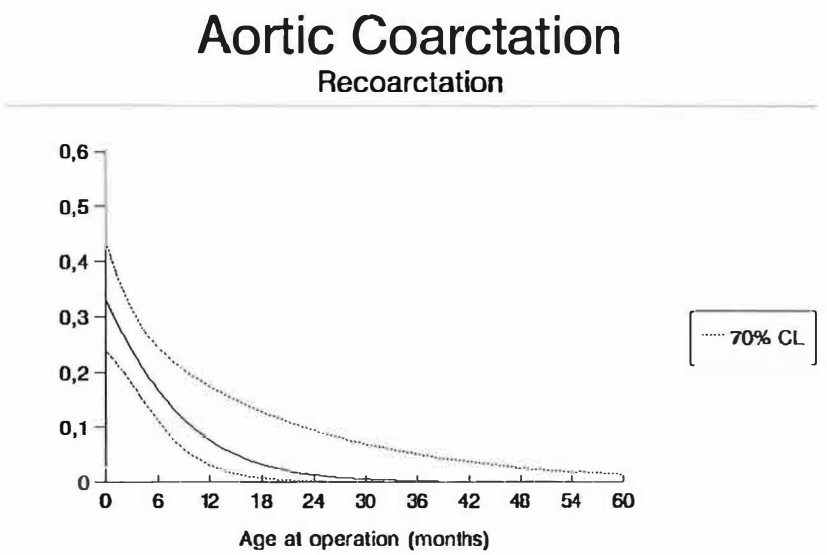
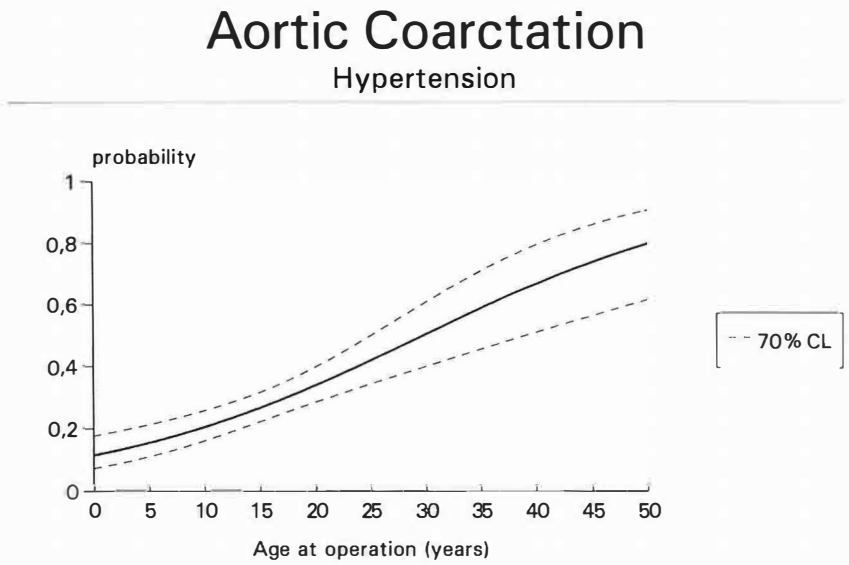


Figure VIII-3 *Nomogram of the multivariate equation for the incremental risk factor for recoactation. Note that if the aortic coarctation is repaired at an age of 3 years, the risk for recoarctation is nil (Logistic coefficient = -0.0049, p=0.02)(CL 70%; 70% confidence limits).*

These findings concur with the study of Kappetein et al. in which they found that the risk for late hypertension even in infants less than 6 months of age at time of repair was significantly higher as compared to the normal population.[42]

Finally, age at operation for aortic coarctation repair also turns out to be an incremental risk factor for premature death (Logistic coefficient : 0.071, p=0.03): it superimposes a risk factor above the 'normal' risk for death found in the normal population. The risk for premature death remains fairly constant up to 9 years of age, but increases beyond (Fig.VIII-5).

In summary, age at operation is an incremental risk factor for the probability of recoarctation, late hypertension as well as for premature death. In order to determine the most optimal age for elective aortic coarctation repair, we combined the results of the previous study on recoarctation[15] and the present study on late hypertension and premature death. A major problem though, is that these results come from different patient populations, operated upon in different time frames. However, it is impossible to use other data sets, because nobody would nowadays operate patients electively at an age that was common several decades ago. The composite nomogram, combining the nomograms for the risk for recoarctation, late hypertension and premature death after aortic coarctation repair, shows the most optimal freedom of the sequelae around 1 1/2



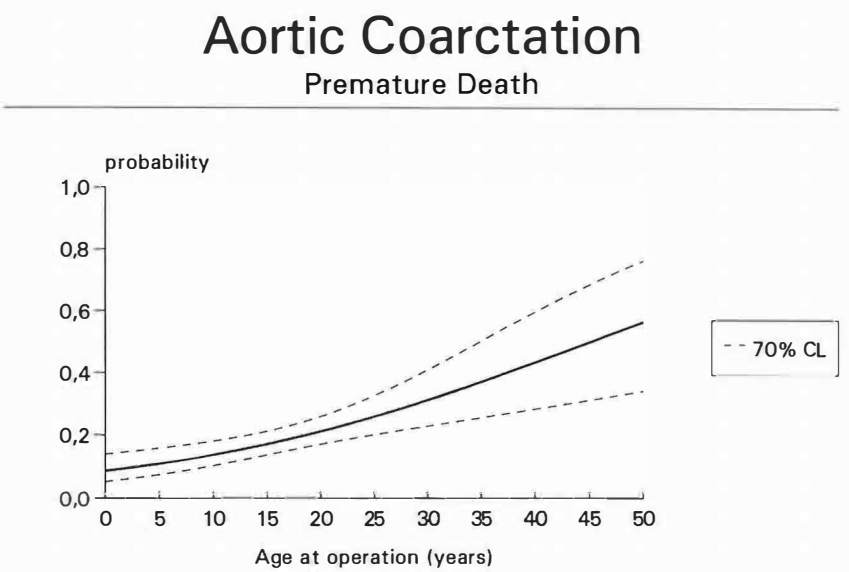


Figure VIII-4 and VIII-5 *Nomograms of the multivariate equations for the incremental risk factor for late hypertension and for premature death. (70% CL).*

year of age. The cause for this is that the risks for late hypertension and premature death are almost constant in the age range, while the risk for recoarctation drops rapidly and levels off at 1 1/2 year of age. Therefore, we come to the conclusion that at this age, the combined risk is lowest (Fig. VIII-6).

In conclusion, even long after successful aortic coarctation repair, patients remain at risk for cardiovascular disorders. Age at time of operation determines the prevalence of recoarctation, late hypertension and premature death. Therefore, in order to avoid these sequelae, we suggest that elective aortic coarctation repair should be delayed to 1.5 year of age, but should then not be delayed much longer.

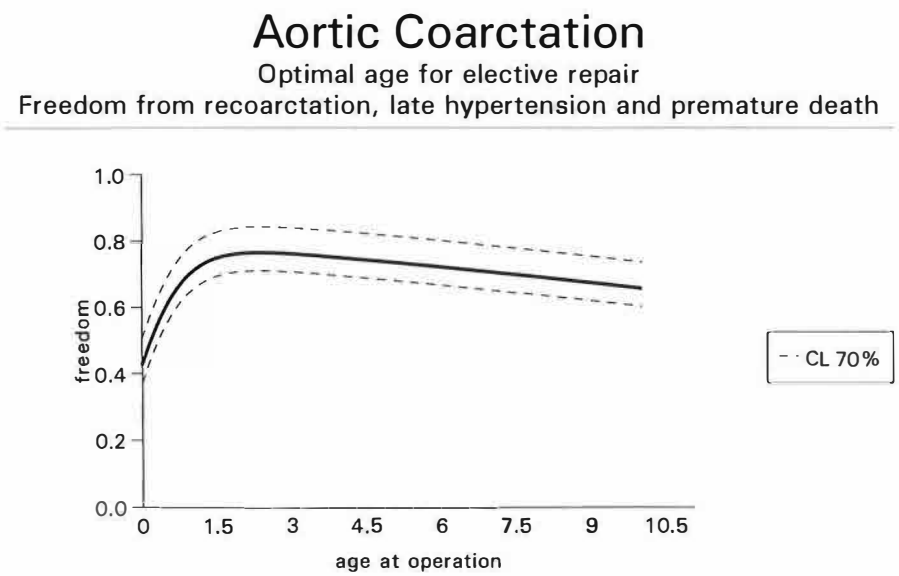


Figure VIII-6 *Composite nomogram showing the freedom from recoarctation, late hypertension and premature death. Note that the optimal age for repair is around 1 1/2 year of age (CL 70%; 70% confidence limits).*

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VII 9 Appendix

Probability estimates were obtained from the logistic regression equation according to the following formulas:

$$p = \frac{1}{1 + e^{-z}}$$

$$z = b_o + b_1 + \ldots\ldots + b_k x_k$$

where e is the base of the natural logarithm, b_0 is the intercept of the logistic equation, and b_1 and b_k are logistic regression coefficients associated with the values for the incremental risk factors x_1 and x_k .

Summary and Conclusions

Samenvatting en Conclusies

Summary

In **chapter I**, the definition of the aortic coarctation, the natural outcome and the current controversies about its surgical treatment are outlined.

Aortic coarctation is a congenital narrowing of the upper descending thoracic aorta, which is sufficiently severe that there is a pressure gradient across the area. The typical anomaly is a shelf-like protrusion which develops most directly opposite the arterial duct and fades away on either side, anteriorly and posteriorly. The result is an eccentric, localized narrowing of the aorta that externally corresponds to a notch in the aortic wall.

Aortic coarctation is likely to cause symptoms during infancy either because of associated cardiac anomalies and severe obstruction or during adolescence and adulthood because of the sequelae of systemic hypertension. Among all neonates born alive with isolated aortic coarctation and that are untreated surgically, about 10% die of acute cardiac failure during the first month of life. Another 40% may be expected to die between 1 and 4 years of age, usually from chronic heart failure. About 50% of the original group die between 14 and 50 years of age, of bacterial endocarditis, aortic rupture, intracranial hemorrhage or from heart failure secondary to systemic hypertension, coronary artery or valvar disease. As a consequence, about 90% of the original group has died before 50 years of age.

After 5 decades of experience with aortic coarctation repair, one might expect consensus regarding the ideal management of this congenital anomaly. However, aortic coarctation embraces a wide spectrum of anatomic variations and concomitant intracardiac defects. Therefore, the best method of repair for aortic coarctation repair is still controversial.

In **chapter II**, a historical survey of the aortic coarctation is presented. The development of the aortic arch system is reviewed. Subsequently, the morphology of the aortic coarctation, the ductal tissue as well as the relation between the arterial duct and the aortic arch system are discussed. Furthermore, the influence of the blood flow on the development of the aortic arch is outlined. Various mechanisms of formation of the aortic coarctation are discussed such as the abnormal extension of contractile ductal tissue; the proximal movement of the left 7th intersegmental artery; abnormalities of the blood flow pattern and the role of the neural crest.

In **chapter III**, the non-elective procedure in neonates with aortic coarctation is discussed. About half of all these neonates within the first month of life, develop symptoms of congestive heart failure due to a number of pathophysiological factors or associated anomalies. In the early 1960s, surgical mortality was extremely high in this group of patients. However due to improved preoperative preparation (prostaglandin E_1), better surgical, anesthetic and postoperative management, the mortality has decreased dramatically to 0%-14%.

Two-dimensional echocardiography has proven extremely useful in confirming the diagnosis of the aortic coarctation and is essential in the armamentarium of the pediatric cardiologist and cardiac surgeon. Additionally, Doppler ultrasound, Color

Doppler flow mapping and Magnetic Resonance Imaging contribute to new observations of aortic coarctation flow patterns, thereby assessing the severeness of the aortic coarctation more precisely. Furthermore, different surgical procedure are presented.

Currently, most of the debate about surgical management of these ill neonates concerns the prevention of recoarctation and the optimal treatment of the coexisting VSD.

Traditionally, aortic coarctation was managed by resection and end-to-end anastomosis. However, due to a significant high rate of recoarctation after the classic resection and end-to-end anastomosis between 1950 and 1970, the prosthetic patch angioplasty was introduced to overcome this problem. However, mid-and longterm reports show several major drawbacks. Recoarctation and an increased risk of aortic aneurysm formation tempered the initial enthuisiasm for this technique. Later the subclavian flap aortoplasty was introduced and heralded as the operation of choice. In contrast to the high expectations of the subclavian flap, recent studies have reported a high incidence of recoarctation as well due to failure of resection of all ductal tissue. Furthermore, the occurrence of postoperative limb ischemia and late growth retardation of the left upper limb are other potential drawbacks of this technique.

The best surgical technique for neonates with aortic coarctation and concomitant hypoplasia of the aortic arch is still controversial. For this group infants, the extended resection and end-to-end anastomosis was introduced. The main goal was to enlarge the aortic arch instantaneously. However, this technique is technically more demanding, may jeopardize the cerebral circulation, and does not lower the incidence of mortality and recoarctation as compared to the simple resection and end-to-end anastomosis. Furthermore, growth potential of the reconstructed aortic arch is still speculative.

In the last decade, alternative surgical techniques have been reported such as the subclavian-sparing advancement technique and the use of the left internal mammary artery.

Furthermore, a historical survey is presented of the balloon dilation angioplasty. This alternative technique has obtained a place in the armamentarium of the interventional pediatric cardiologist, in the relief of the aortic coarctation and postoperative recoarctation.

Finally, the exact surgical timing of elective repair particularly in those infants with an asymptomatic isolated aortic coarctation is discussed.

In **chapter IV**, the aims of the thesis are outlined:

1. Is it possible to prevent the prevalence of recoarctation; e.g. are there pre- and/or peroperative incremental risk factors which predict an increase of the probability of recoarctation?
2. How should the cardiac surgeon define and interprete the hypoplastic aortic arch as a concomitant anomaly and what are the surgical implications?
3. The optimal treatment of aortic coarctation with coexisting VSD is still controversial. Does the presence of a VSD as an associated anomaly always justify an single-stage repair?
4. What is the optimal age for elective aortic coarctation repair in an asymptomatic infant with isolated aortic coarctation?

In **Chapter V**, incremental risk factors for recoarctation are discussed. From a retrospective study in 53 infants with aortic coarctation, weight at operation and the residual gradient after the aortic coarctation repair expressed as a ratio of the systolic arm pressure, turned out to be incremental risk factors for recoarctation. It is concluded that the gradient ratio after repair should be as low as possible, for even small gradients will have a strong incremental effect on the probability of recoarctation in the setting of a low weight infants. Therefore, if the infant is not in distress, the aortic coarctation should not be removed while the weight is below 5 kg and the gradient ratio should be as low as possible.

In **Chapter VI**, the fate of the hypoplastic aortic arch after simple resection of the aortic coarctation and end-to-end anastomosis is presented. In this prospective study, 15 neonates with an aortic coarctation were evaluated echocardiographically. A Z-value, being the number of standard deviations the aortic arch differs from the expected value derived from a control group, was calculated. Eight neonates had a hypoplastic aortic arch with a mean Z value of -7.14 ± 1.39. The mean Z value of the other 7 neonates was -1.85 ± 1.08. All 15 neonates underwent simple aortic coarctation repair. Six months after repair, the Z values of the hypoplastic aortic arches increased significantly to almost normal values. Based on this study, the hemodynamic molding theory is confirmed, being that growth of the hypoplastic aortic arch occurs when normal blood flow is established, and that a 'catch-up' growth really takes place. Therefore, simple resection and end-to-end anastomosis should be the operation of choice for aortic coarctation associated with a hypoplastic aortic arch.

Currently, the optimal surgical management of the aortic coarctation associated with a ventricular septal defect (VSD) remains a matter of debate. The question has arisen whether there are specific preoperative criteria which enable the surgeon to make the most optimal decision for this pathophysiological setting. The purpose of the retrospective study presented in **Chapter VII**, was to find preoperative criteria in order to optimize surgical decision making in infants with an aortic coarctation associated with a VSD. The preoperative left-to-right shunt as a percentage of pulmonary flow, and the morphology of the VSD, in particular the perimembranous defect with extension into the inlet and/or outlet septum, are incremental risk factors for prolonged postoperative ventilation time and more strongly for the probability of eventually surgical closure of the VSD after the initial aortic coarctation repair. Knowing these two factors, a well-considered choice between single-stage versus multi-stage repair can be made.

In **Chapter VIII**, the longterm results after elective aortic coarctation repair with a follow up from 25 to 44 years, and the influence of age on survival, late hypertension and recoarctation in elective aortic coarctation repair, are presented. The longterm results indicate that despite the early apparent success after elective aortic coarctation repair, not all patients live healthily ever after but remain at risk of premature death. Age at operation has a key position in the optimal treatment for elective aortic coarctation repair: it is an incremental risk factor for the probability of late hypertension, and premature death. Based on the study presented in chapter V, we found that age at operation is an incremental risk factor for the probability of

recoarctation as well. Therefore, the impression arises that the optimal age for elective aortic coarctation repair is around 1 1/2 year. At that age, the probability of recoarctation will have decreased to less than 3%, and the probability of longterm survival and upper body normotensive state will be nearly optimal.

Conclusions

1. Weight at operation and the residual gradient, expressed as a ratio of the systolic arm pressure after the aortic coarctation repair, are incremental risk factors for the probability of recoarctation.

2. Simple resection and end-to-end anastomosis is the operation of choice for aortic coarctation associated with a hypoplastic aortic arch despite the presence of a VSD. Surgical enlargement of the hypoplastic aortic arch is not necessary.

3. The preoperative L-R shunt and the perimembranous VSD, in particular those extending into the inlet and/or outlet septum, are risk factors for eventually surgical VSD closure after the initial aortic coarctation repair. These two factors might help the cardiac surgeon to make a well-considered surgical decision for the optimal treatment of the aortic coarctation associated with a VSD.

4. Elective aortic coarctation repair should be performed around an age of 1 1/2 year. At that time the probability of recoarctation will have decreased to less than 3%, and the probability of longterm survival and upper body normotensive state will be optimal.

Samenvatting

De coarctatio aortae, een van de meest voorkomende aangeboren afwijkingen, is een vernauwing van de thoracale aorta en komt voor in 4%-8% van alle aangeboren hartafwijkingen. Hoewel aangeboren ontwikkelt deze vernauwing zich in de eerste levensdagen op een zodanige wijze, dat er een verschil in bloeddruk kan ontstaan tussen de bovenste en onderste lichaamshelft. De typische pathologische bevinding is een vooruitstekende verdikte rand in de aortawand, meest gelegen tegenover de ductus arteriosus. Deze rand verdwijnt geleidelijk in craniale en caudale richting. Het resultaat is een eccentrisch gelocaliseerde vernauwing van de aorta, hetgeen zich weerspiegelt in een inkeping aan de buitenkant van de aortawand. De verdikte rand in de aortawand bevat vrijwel altijd ductaal weefsel. Dit weefsel, feitelijk een uitloper van de ductus arteriosus, omcirkelt de aortawand volledig of kan naar craniaal en/of caudaal uitbreiden. De relatie tussen de coarctatio aortae en de ductus arteriosus is een bijzondere en uit zich in obstructies van de linker en rechter uitstroombanen van het hart. Zo kan bij een coarctatio aortae, een ductus afhankelijke lichaamscirculatie ontstaan en bij een pulmonalis atresie, een ductus afhankelijke longcirculatie. Opvallend is dat bij deze uitstroombaanobstructies de vaatafwijkingen zich vaak rondom de plaats bevinden waar de ductus arteriosus en de grote vaten op elkaar aansluiten, namelijk de isthmus en de bifurcatie van de longslagader.

Coarctatio aortae veroorzaakt vaak symptomen op zuigelingen leeftijd en in de eerste kinderjaren. Deze symptomen worden veroorzaakt door de nadelige hemodynamische effecten van de vernauwing en door de eventueel bijkomende intracardiale afwijkingen zoals het ventrikelseptumdefect, open ductus arteriosus, ernstige aortaboogafwijkingen en aorta en mitralis klepafwijkingen. Het is dan ook in dit verband juister om over een "coarctatiesyndroom" te spreken. Bij oudere kinderen, in de adolescentie en op volwassen leeftijd, waarbij de coarctatio aortae meestal een toevalsbevinding is, worden de symptomen toegeschreven aan de gevolgen van de langdurig bestaande hypertensie.

De prognose van de onbehandelde coarctatio aortae is niet goed. Van alle niet-behandelde zuigelingen met een coarctatio aortae sterft 10% in de eerste levensmaand door acuut hartfalen (**Hoofdstuk I**). Tussen het eerste en vierde levensjaar zal ongeveer 40% van de niet behandelde kinderen komen te overlijden door chronische hartfalen. Ongeveer 50% van de oorspronkelijke groep sterft tussen 14 en 50 jaar als gevolg van een bacteriële endocarditis, aorta ruptuur, intracraniële bloeding of door hartfalen secundair aan de langbestaande hypertensie, kranslagaderverkalking of hartkleppen-afwijkingen. Uiteindelijk zal ongeveer 80%-90% van de oorspronkelijk niet behandelde groep zuigelingen met een coarctatio aortae komen te overlijden vóór het 50ste levensjaar.

Na 50 jaar chirurgische ervaring met de coarctatio aortae, zou men consensus verwachten ten aanzien van de behandeling van deze afwijking. Echter, de coarctatio aortae omvat zo'n breed scala aan anatomische variaties en bijkomende intracardiale afwijkingen, dat een enkele ideale behandeling niet mogelijk lijkt.

In **Hoofdstuk II** wordt een historisch overzicht gegeven van de coarctatio aortae. Vervolgens wordt de embryonale ontwikkeling van het aortaboog complex, de morfologie van de coarctatio aortae en de relatie tussen de ductus arteriosus en het aortaboog complex uiteengezet. Voorts wordt de invloed van de bloedstroom op de ontwikkeling van de aortaboog beschreven. Tenslotte worden verschillende theorieën ten aanzien van de ontstaanswijze van de coarctatio aortae uiteengezet zoals de contractiliteit van het ductale weefsel, de invloed van de proximale beweging van de 7de intersegmentale slagader tijdens de embryonale fase, afwijkende patronen van de bloedstroom en de rol van de neurale buis.

De non-electieve en electieve behandelingsprocedure van de coarctatio aortae worden beschreven in **Hoofdstuk III**. Ongeveer de helft van het aantal zuigelingen met een coarctatio aortae, ontwikkelt in de eerste levensmaand symptomen van hartfalen veroorzaakt door een aantal pathofysiologische factoren, zoals het sluiten van de ductus arteriosus, de acute afname van de bloedstroom naar de onderste lichaamshelft en de verminderde pompfunctie van de linker ventrikel door de toegenomen weerstand veroorzaakt door de coarctatio aortae. Bijkomende intracardiale afwijkingen versterken het acute hartfalen, hetgeen zich weerspiegeld in een overbelaste longcirculatie, overbelaste linker en rechter ventrikel, metabole acidose en nierinsufficientie. Deze zuigelingen dienen dan ook met spoed medicamenteus en chirurgisch behandeld te worden.

In het begin van de zestiger jaren waren de resultaten van deze behandelingen bij zuigelingen erg slecht. De mortaliteit bedroeg 40%-100%. Echter door verbeterde diagnostiek (twee-dimensionele echocardiografie) en preoperatieve zorg (o.a het gebruik van Prostaglandine E_1), chirurgische techniek, anesthesie en postoperatieve zorg, daalde de mortaliteit in de tachtiger jaren naar 0%-14%. Twee-dimensionele echocardiografie is momenteel onmisbaar voor het vaststellen van intra- en extracardiale afwijkingen en behoort nu tot het standaard onderzoek van de kindercardioloog. Vervolgens dragen Doppler flow onderzoek en MRI (Magnetic Resonance Imaging) bij tot gedetailleerde observaties van abnormale bloedstroompatronen en evaluatie van de ernst van de coarctatio aortae.

Voorts worden verschillende operatietechnieken beschreven. De discussie omtrent de chirurgische behandeling, wordt grotendeels bepaald door recoarctatie en bijkomende intra-en extracardiale afwijkingen zoals ventrikelseptumdefect en hypoplastische aortaboog. De klassieke resectie van de coarctatio aortae en end-to-end anastomosis zoals beschreven door Crafoord, was traditioneel gezien de eerste operatiekeuze. Echter, vanwege de hoge incidentie van recoarctatie bij kinderen, werd in 1957 door Vosschulte de "prosthetic patch angioplastiek" geintroduceerd. Het aanvankelijk enthousiasme voor deze operatietechniek werd getemperd door de midden- en lange termijnresultaten: naast de wisselende incidentie van recoarctatie, vormden ware en valse aneurysmata van respectievelijk de aortawand en de hechtnaad andere bijkomende problemen.

In 1966 introduceerde Waldhausen de "subclavian flap angioplastiek". Deze operatietechniek werd ingeluid als dé operatiekeuze ter voorkoming van de recoarctatie. Echter, midden- en lange termijnresultaten rapporteren een incidentie van recoarctatie tot 25%. Onvoldoende groei van de hechtnaad en achterblijven van ductaal weefsel

lijken belangrijke oorzaken te zijn voor recoarctatie. Ischemie en groei- achterstand van de linker arm zijn andere nadelen zijn van deze operatietechniek.

De beste chirurgische benadering voor zuigelingen met een coarctatio aortae en een hypoplastische aortaboog blijft controversieel. Voor deze groep patientjes werd in 1985 de "extended resection en end-to-end anastomosis" geintroduceerd. Het doel van deze operatietechniek is, naast de resectie van de coarctatio, het direkt verwijden van de hypoplastische aortaboog. Echter, deze benadering is technisch moeilijker en kan, door het ruim afklemmen van de aortaboog, een bedreiging vormen voor de cerebrale circulatie. Bovendien laten de vroege termijnresultaten zien dat de mortaliteit en de kans op recoarctatie niet lager zijn dan na eenvoudige aortae coarctatio resectie en end-to-end anastomosis, waarbij de hypoplastische aortaboog grotendeels ongemoeid wordt gelaten. Tenslotte is, in tegenstelling tot de groei van de aortaboog na eenvoudige resectie van de coarctatio aortae, nog niet aangetoond of de verwijde aortaboog na de "extended resection" wel voldoende mee groeit.

Recentelijk zijn er alternatieve chirurgische technieken beschreven, zoals de "subclavian-sparing advancement technique" en het gebruik van de linker arterie mammaria interna. Deze technieken zijn ontwikkeld om de kans op recoarctatie te verminderen en een adequate bloedstroom naar de linker arm te waarborgen.

Mede door de bijkomende complicaties van de "prosthetic patch angioplasty", "subclavian flap angioplasty" en de "extended resection" aan de ene kant en de introductie van micro-chirurgische technieken en nieuwe ontwikkelingen op het gebied van hechtmaterialen aan de andere kant, lijkt er een herniewde belangstelling te bestaan voor de klassieke resectie van de coarctatio aortae en end-to-end anastomosis.

Voorts wordt een historisch overzicht gegeven over het gebruik van de ballon dilatatie techniek. Deze alternatieve techniek waarbij een vernauwing in een bloedvat kan worden opgerekt, heeft een vaste plaats verworven in het armamentarium van de kindercardioloog ter behandeling van de coarctatio aortae en met name de postoperatief optredende recoarctatie. Tenslotte wordt in het laatste deel van hoofdstuk III, het tijdstip voor electieve chirurgische behandeling van de coarctatio aortae bij asymptomatische kinderen bediscussieerd.

In **Hoofdstuk IV** worden de doelstellingen van dit proefschrift uiteengezet.

1. Is het mogelijk recoarctatie te voorkómen, met andere woorden, zijn er pre- en/of peroperatieve risiko factoren die een verhoogde kans op recoarctatie kunnen voorspellen?
2. Hoe moet de hypoplastische aortaboog als bijkomende afwijking gedefinieerd worden en wat zijn de chirurgische consequenties?
3. Wat is de optimale chirurgische behandeling van de coarctatio aortae gepaard gaande met een hemodynamisch belangrijk ventrikelseptumdefect?
4. Wat is de optimale leeftijd voor electieve chirurgische behandeling van de coarctatio aortae bij asymptomatische kinderen?

In **Hoofdstuk V**, worden de risikofactoren voor recoarctatie uiteengezet. Uit een retrospectieve studie bij 53 kinderen onder 2 jaar met een coarctatio aortae bleek dat het gewicht ten tijde van de operatie én de gradient over de gemaakte anastomose,

uitgedrukt als een ratio van de op dat moment bestaande systolische bloeddruk, risiko factoren zijn voor het optreden van recoarctatie. Een geringe stijging van de gradient ratio, heeft een sterk risiko verhogend effect op de kans op recoarctatie. Dit effect wordt nog meer geaccentueerd wanneer het gewicht ten tijde van de operatie laag is. Dus, wanneer er geen aanwijzingen zijn voor acuut hartfalen, is het beter de chirurgische behandeling van coarctatio aortae uit te stellen opdat het gewicht kan toenemen. Voorts moet er dan gestreefd worden naar een zo laag mogelijke gradient ratio.

In **Hoofdstuk VI** wordt het beloop van de hypoplastische aortoboog na resectie van de coarctatio aortae en end-to-end anastomosis beschreven. In deze prospective studie, werden preoperatief 15 zuigelingen met een coarctatio aortae echocardiografisch geevalueerd. De Z waarde, zijnde het aantal standaard deviaties dat de hypoplastische aortoboog verschilt met de verwachte waarde verkregen uit een controle groep zuigelingen, werd berekend. Acht zuigelingen hadden een hypoplastische aortaboog met een gemiddelde Z waarde van -7.14 $\pm$ 1.39. De gemiddelde Z waarde van de andere 7 zuigelingen bedroeg -1.85 $\pm$ 1.08. Bij alle 15 zuigelingen werd een eenvoudige klassieke resectie van de coarctatio aortae en end-to-end anastomosis verricht. Zes maanden na operatie, bleken de Z waarden significant te zijn toegenomen tot bijna normale waarden. Deze studie bevestigt de hypothese dat, na eenvoudige coarctatio aortae resectie, de bloedstroom in de hypoplastische aortaboog wordt hersteld en dientengevolge de groei van de aortaboog zal bevorderen, zodanig dat er een inhaal-effect ontstaat. Om deze reden lijkt de eenvoudige resectie van de coarctatio aortae en end-to-end anastomose dé operatiekeuze te zijn voor de coarctatio aortae met een hypoplastische aortaboog.

Momenteel is de optimale chirurgische behandeling van de coarctatio aortae met een ventrikelseptumdefect controversieel. De vraag doet zich voor of er specifieke preoperatieve criteria bestaan, die de hartchirurg instaat stellen een weloverwogen beslissing te nemen ten aanzien van de optimale chirurgische benadering van deze pathofysiologische afwijking. Uit de retrospectieve studie uiteengezet in **Hoofdstuk VII**, blijkt dat de preoperatief gemeten absolute links-rechts shunt, als een percentage van de longdoorbloeding én de morfologie van het ventrikelseptumdefect, in het bijzonder het perimembranous ventrikelseptumdefect met uitbreiding naar het inlet en/of outlet septum, risikofactoren zijn voor respectievelijk de postoperatieve beademingsduur en secundaire chirurgische behandeling van het ventrikelseptumdefect na de initiële coarctatio aortae behandeling. Rekeninghoudend met deze twee risikofactoren, kan er een weloverwogen keuze gemaakt worden tussen een single-stage benadering, waarbij naast de coarctatio aortae behandeling het ventrikelseptumdefect meteen gesloten wordt, versus een multi-stage benadering waarbij alleen de coarctatio aortae wordt behandeld en een afwachtende houding wordt aangenomen ten opzicht van het ventrikelseptum-defect. Bij deze laatste benadering wordt er vanuit gegaan dat het ventrikelseptumdefect spontaan zal sluiten of hemodynamisch onbelangrijk wordt.

In **Hoofdstuk VIII**, worden de lange termijn resultaten na electieve chirurgische behandeling van de coarctatio aortae met een follow-up van 25 tot 44 jaar én de invloed

van leeftijd op de overleving, het vóórkomen van late hypertensie en recoarctatie uiteengezet. Uit dit retrospectief onderzoek blijkt dat, ondanks de succesvolle korte termijn resultaten na coarctatio aortae chirurgie, de patienten in vergelijking met een leeftijd overeenkomstige groep mensen uit de normale populatie, een verhoogde kans hebben op vroegtijdig overlijden. Leeftijd ten tijde van de operatie vervult een sleutelpositie bij de optimale electieve chirurgische behandeling van de coarctatio aortae: het is een risikofactor voor de kans op het vóórkomen van late hypertensie en vroegtijdig overlijden. Gebaseerd op de gegevens verkregen uit de studie van Hoofdstuk V, blijkt dat leeftijd ten tijde van de operatie ook een risikofactor is voor de kans op recoarctatie. De indruk ontstaat nu, dat de optimale leeftijd voor electieve chirurgische behandeling van de coarctatio aortae, rond de 1 1/2 jaar is. Op deze leeftijd is de kans op recoarctatie minder dan 3% en de kans op maximale overleving en het normotensief blijven, het grootst.

Conclusies

1. Gewicht ten tijde van de operatie en de gradient over de anastomose, uitgedrukt als een ratio van de op dat moment bestaande systolische bloeddruk, zijn risikofactoren voor recoarctatie.

2. Eenvoudige resectie van de coarctatio aortae en end-to-end anastomose is de operatiekeuze voor de coarctatio aortae met een hypoplastische aortaboog.

3. De preoperatief gemeten absolute links-rechts shunt en het perimembranous ventrikelseptumdefect, in het bijzonder die met uitbreiding naar het inlet en/of outlet septum, zijn risikofactoren voor eventueel chirurgische behandeling van het ventrikelseptumdefect ná de initiële coarctatio aortae behandeling.

4. Electieve chirurgische coarctatio aortae behandeling moet uitgevoerd worden rondom de leeftijd van 1 1/2 jaar. Op die leeftijd is de kans op recoarctatie minder dan 3% en de kans op maximale overleving en het normotensief blijven het grootst.

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Curriculum Vitae

De schrijver van dit proefschrift werd op 12 juli 1957 geboren te Hoensbroek. In 1975, na het behalen van het eindexamen Atheneum B aan het St. Janscollege te Hoensbroek studeerde hij Geneeskunde aan de Rijksuniversiteit Limburg te Maastricht. In 1980 was hij werkzaam als student-assistent bij de vakgroep Algemene Heelkunde, St. Annadal ziekenhuis te Maastricht en op de Department of Surgery, State University Cincinatti, USA (hoofd: Prof.Dr. J.M. Greep, Prof.Dr. J. Fischer). Na het behalen van het artsexamen in juli 1981, werd hij arts-assistent Algemene Heelkunde in het St. Jozef ziekenhuis te Kerkrade (hoofd: Dr. J. Tantua). Van maart 1982 tot maart 1983 volgde hij de opleiding Huisartsgeneeskunde aan de Rijksuniversiteit Limburg te Maastricht en Haelen, gevolgd door huisartswaarnemingen tot juni 1983. Van april tot juli 1983 volgde er een stage op de afdeling Cardiopulmonale Chirurgie van het Catharina ziekenhuis te Eindhoven (hoofd: Dr. J.J. Bredée). Van juli 1983 tot juli 1986 was hij arts-assistent in opleiding Algemene Heelkunde in het Stadsmaten ziekenhuis te Enschede (opleider: Dr. F.J. Voorhuis), waarna begonnen werd met de opleiding tot cardiopulmonaal chirurg in het Academisch Ziekenhuis Groningen (opleider: Prof. Dr. J.N. Homan van der Heide). Vanaf juli 1990 is hij als cardiopulmonaal chirurg werkzaam in het Thoraxcentrum van het Academisch Ziekenhuis Groningen en lid van het Harttransplantatieteam Academisch Ziekenhuis Utrecht - Academisch Ziekenhuis Groningen.