Coarctation of Aorta: A Surgical Journey

Kasra Shaikhrezai

MD, MSc, MRCS, FETCS, FRCS (CTh)

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School of Medicine, College of Medical, Veterinary and Life Sciences, University of Glasgow

Abstract

Since my placement as a trainee at Royal Hospital for Children, I became interested in pathophysiology of coarctation of aorta. It may seem a simple pathology which narrow the aortic lumen in distal arch but the story behind this simple pathology is more complex. In fact I was fascinated by the surgical repair techniques and it did not take long after expressing interest to find out "which technique is the best?", I realised that this has been a historical question at least for the past 50 years. The review of coarctation repair in Scotland and evaluation of outcomes soon became operational while there was no previous such a regional study. Retrieving and reviewing of echocardiography images followed by measuring aortic parameters despite challenges soon became an exciting investigation. The systematic review of the literature was also a fascinating journey through the history where finding an answer for many questions on coarctation of aorta was challenged by a high degree of heterogeneity not only in the study design itself but also in the practice of the individual reporting institution. Apprising historical papers and studies from different part of the world was a rewarding experience; although the result of the search for the best technique was inconclusive. The "Future" Chapter is basically the conclusion of my journey with coarctation of aorta in this thesis. By observing current breakthroughs in technology and evolving computational modelling, the future of coarctation surgery has already been shaped. Maybe we have been looking for an answer for a historical question which probably should been made differently: "which technique is the best for which patient?"

Table of Contents

List of Tables

List of Figures

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Dedication

This work is dedicated to my beloved wife Haleh and our two wonderful boys, Nami and Radyn, who were patient and supportive while I was away working on this study.

Author’s declaration

“I declare that, except where explicit reference is made to the contribution of others, that this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.”

Printed Name: KASRA SHAIKHREZAI

Signature:

List of Abbreviations

AHA	American Heart Association
ANOVA	One-Way Analysis Of Variance
ASD	Atrial Septal Defect
BAV	Bicuspid Aortic Valve
BCA	Brachiocephalic Artery
BP	Blood Pressure
CDSR	Cochrane Database of Systematic Reviews
CFD	Computational Fluid Dynamic
CHF	Congestive Heart Failure
CoA	Coarctation of Aorta
CORE	The Collaborative Research group
CPB	Cardio-Pulmonary Bypass
CPR	Cardiopulmonary Resuscitation
CT-scan	Computed Tomography Scan
DA	Ductus Arteriosus
DHCA	Deep Hypothermic Circulatory Arrest
ECMO	Extra-Corporeal Membrane Oxygenation
EDLVP	End-Diastolic Left Ventricular Pressure
EEA	Resection of coarctation and End-to-End Anastomosis
EEAA	Resection of coarctation and Extended End-to-End Anastomosis
ENT	Ear, Nose and Throat
ESA	Resection of coarctation and End-to-Side anastomosis
HLHS	Hypoplastic Left Heart Syndrome

HTN	Hypertension
LBW	Low Birth Weight
LCCA	Left Common Carotid Artery
LSA	Left Subclavian Artery
LVF	Left Ventricular Function
LVH	Left Ventricular Hypertrophy
LVOT	Left Ventricular Out-flow Tract
MDT	Multi-Disciplinary Team
MRI	Magnetic Resonance Imaging
NEC	Necrotising Enterocolitis
OSI	Oscillatory Shear Index
PACS	Picture Archiving and Communication System
PDA	Patent Ductus Arteriosus
PFO	Patent Foramen Ovale
PGE_1	Prostaglandin E_1
PICU	Paediatric Intensive Care Unit
RAAS	Renin-Angiotensin-Aldosterone System
RCT	Randomised Clinical Trial
RLN	Recurrent Laryngeal Nerve
ROC	Receiver Operating Characteristic curve
PTFE	Polytetrafluoroethylene
SA	Subclavian Artery
SF	Subclavian Flap
SIMD	Scottish Index of Multiple Deprivation

STJ	Sino-Tubular Junction
TAWSS	Time-Averaged Wall Shear Stress
TGA	Transposition of Great Arteries
TGF	Transforming Growth Factor
Vmax	Peak velocity
VEGF	Vascular Endothelial Growth Factor
VSD	Ventricular Septal Defect
WHO	World Health Organisation

1. Introduction

1.1 Definition and history

Coarctation of aorta (CoA) is defined as the stenosis of proximal descending aorta and/or distal aortic arch which may be of haemodynamic significance causing symptoms in patients. CoA is a discrete lesion however it can be associated with another cardiovascular congenital anomaly. Giovanni B Morgagni (1682 – 1771) an Italian anatomist and the professor of anatomy at the University of Padua was first who described the narrowing of proximal of the descending aorta in an autopsy (Morgagny 1760). Few years later Meckel and Paris more elaborately explained the CoA physiopathology (Jarcho 1961). For the first time they examined the haemodynamic impact of CoA on the heart as well as body vasculature. The initial attention and exploration of CoA was not focused on symptomatic neonates who were exposed to a high risk of mortality. It did not take long that early intervention was recognised as the gold standard treatment of CoA in neonates. Clarence Crafoord (1899 – 1984) a Swedish surgeon was the first who performed CoA repair in Sabbatsberg Hospital in Stockholm (Kvitting 2009). The patient was an 11-year-old male patient who underwent resection of coarctation with an end-to-end anastomosis in October 1945. The operation revolutionised the surgical management of coarctation which previously was limited to animal experiments. Seven years later Lynxwiler and his team performed the first operation on a neonate through left thoracotomy with satisfactory results (Lynxwiler 1951). The operation performed by Lynxwiler was reproducible and soon became the main approach for the surgical management of CoA which is still currently practiced.

1.2 Anatomy and Embryology

The third week of gestation is an important time for the development of aorta. Pharyngeal arch arteries which are also called aortic arches are six pairs of bilateral arteries from which the future aorta and its head and neck branches are derived. The fourth pair plays an important role in the formation of the arch and associated anomalies such as CoA (Kau 2007). It is possible to see the CoA by ultrasonography at 21 weeks of gestation. CoA is a variant of arch obstruction which morphologically cane be Tubular (narrow lumen), Shelf lesion (infolding) and Waist lesion (severe ring-shape stenosis) (Joshi 2017). The

usual location of CoA is at aortic isthmus which by anatomical definition is an area distal to the origin of the left subclavian artery (LSA). This area is in close relation to the ductus arteriosus (DA) which in fetal circulation offloads the lungs' blood flow by directing the blood flow from pulmonary artery (PA) to descending aorta i.e. from right-to-left, which is a physiological shunt. Therefore CoA can be located before, after or in front of DA. This anatomical relation is crucial with regard to patients' symptoms as well as clinical presentation. The aortic isthmus lumen becomes abnormal in CoA where the media layer infolds into the intima layer creating a shelf-like hypertrophic irregularity inside the lumen which resembles the brain gyrus. The proximity of the CoA and DA has led to assumptions that ductus tissue migration to the isthmus area triggers the stenosis. The DA intima as compared to adjacent major vessels is not smooth and contains an irregular intima. This irregularity allows the intima to be more sensitive to after birth pressure and oxygenation signals which triggers activation of vascular endothelial growth factor (VEGF) and transforming growth factor (TGF). These factors enhance intimal cells proliferation which narrows the lumen (Matsui 2008). DA is a peculiar vessel whose media layer lacks elastic component while the muscle fibres are abundant. These fibres are positioned circular and longitudinal resembling oesophagus muscular layer. This property is important for DA function as after birth this structure requires to be occluded by a strong constriction to seal the right-to-left physiological shunt. Mutations in VEGF which increase its activity has been recognise as a possibility for causing a haphazard intimal proliferation and lumen narrowing (Cleaver 1998). Scientists in rabbit model have demonstrated that over expression of genes which upregulate the production of collagen type I and III is associated with high blood pressure (BP) and luminal narrowing (Xu 2000).

In fetal circulation the blood flow through the isthmus is lower than of after birth. This physiological difference has speculated that low flow may trigger intimal changes. This becomes more notable when there is a considerable discrepancy between the sizes of the ascending/descending aorta with the arch. This means that at the junction of distal arch and proximal descending aorta a sudden change in lumen size has direct impact on flow pattern which eventually alters the isthmus intima (Rudolph 1972).

1.3 Classification

From early days CoA classification has been controversial. After discovery of CoA and explaining the pathology Bonnet was first who offered classification for CoA. He initially categorised them into two major groups of infantile and adult (Bonnet 1903). Although it is clear that from a scientific point of view the Bonnet classification may not be adopted, ironically many clinicians still use the similar classification on the basis of early and late presentation. As CoA is closely related to the DA it is sensible to adopt a classification which consider the relationship between CoA and DA. Therefore one of mostly adopted classifications is:

1- Pre-ductal: Stenosis proximal to DA

2- Ductal: Stenosis at the level of DA (most common)

3- Post-ductal: Stenosis distal to DA

This classification does not have a strong clinical relevance despite being anatomically accurate. For example a neonate born with ductal CoA can be severely symptomatic or asymptomatic depending on DA patency. Therefore for Ductal CoA there are three sub-classifications (Joshi 2017):

A) DA patent with non-restrictive CoA: patient can be asymptomatic with normal post ductal oxygen saturation, peripheral pulses can be either normal or weak, presence of bidirectional flow through DA
B) DA patent with restrictive CoA: patient can be symptomatic with low post ductal oxygen saturation, peripheral pulses can be either normal or weak, presence of right-to-left shunt i.e. PA to descending aorta
C) DA closed with restrictive CoA: patient is symptomatic with normal post ductal saturation however with poor trace, peripheral pulses can be either absent or weak, no presence of flow through DA

The classification can be summarised as: Ductal dependent and non-ductal dependent. It is also common to classify the CoA as isolated versus concomitant which latter entails more complex group of patients in which it is difficult to label the CoA as the primary anomaly.

1.4 Physiology

Physiologically any stenosis in the aorta, increases the pressure gradient across the narrowing as well as the afterload which in return leads to an augmented end-diastolic left ventricular pressure (EDLVP). While the heart is working against a stenosis, left ventricular hypertrophy (LVH) is also a consequence of long-term CoA. Interestingly coronary arteries are also affected in CoA where there is more demand for heart blood supply, dilatation and even atherosclerotic changes in prolonged CoA is not uncommon. However recent studies have cast doubt on the hypothesis that CoA is the culprit for coronary artery disease (Roifman 2012). Development of collateral vessels and at a later stage formation of aneurysm are strongly associated with long-term CoA. Reduction of flow after coarctation may activate renin-angiotensin-aldosterone system (RAAS) which after a series of hormonal positive feedback, sodium and water are re-absorbed from the nephron collecting ducts to maintain a higher BP. Although this physiologic event is well associated with low BP, explaining hypertension (HTN) in upper limbs is complex and requires further attention to pre-coarctation function of the aorta. The narrowing itself may also influence the blood flow and pressure before coarctation. Patent ductus arteriosus (PDA) plays and important role in the physiology and haemodynamics of CoA. Many symptoms which are attributed to the CoA is fundamentally related to the function of the DA. In asymptomatic ductal CoA where PDA is regulating the blood flow into the descending aorta high BP is still recorded in the upper limbs. This means that stenosis alone as a mechanical obstruction may not be the only cause of flow and pressure abnormalities. It is now hypothesised that the aorta and its associated major branches prior to coarctation are not normal. The smooth muscle in the media layer of the aorta are responsible for contraction as well as relaxation. This property which governs the wall tension is modulated by baroreceptors located on the aortic arch. Baroreceptors are sensitive to changes in wall tension caused by a high BP. The stimulated baroreceptor induces relaxation of aortic wall smooth muscle which leads to an increased aortic compliance and a drop in BP. Although baroreceptors are regulated by positive feedback, their activity is limited by chronic BP. Figure.1 demonstrates the sigmoid curve of baroreceptors' activity in relation to an increasing BP. The chronic HTN shifts the curve to the right meaning baroreceptors for activation require a higher BP than usual (Chapleau 2012). However baroreceptors are still capable of preventing acute increase of BP in the context of chronic HTN. While this sensory adaptation may explain the failure of reducing BP in patients with CoA, the abnormality of entire aortic wall prior to

coarctation is one of the key factors in coarctation haemodynamics. It is demonstrated that the aorta and its major branches respond differently and rather abnormally to baroreceptors as compared to the post coarctation aorta. The isometric force per each gram of entire aorta before coarctation which is stimulated by a contractile agent is lower than of post coarctation aorta. The aortic reactivity is also shown to be lower in pre coarctation zone which means that baroreceptors in the context of an ongoing high BP are not able to regulate the aortic compliance and wall tension (Sehested 1982). This is an important phenomenon while after coarctation repair no matter which technique has been deployed the abnormal haemodynamics as well as high BP still persists. The pathology of proximal aorta has also been demonstrated on computational fluid dynamic (CFD) studies where time-averaged wall shear stress (TAWSS) and oscillatory shear index (OSI) are entirely abnormal in proximal aorta and not just the coarctation region (Rinaudo 2015).

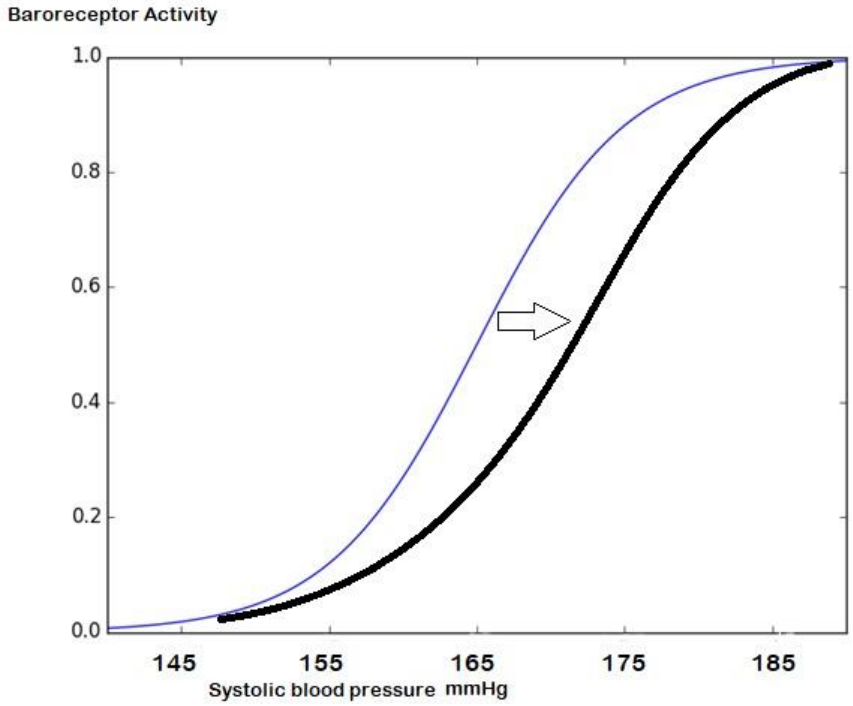

Figure 1. Baroreceptors activity (the arrow demonstrates a shift to the right)

1.5 Multifactorial aetiology

Although there are multiple theories on aetiology of CoA none of them individually can justify the formation of coarctation during fetal development. This is more pronounced in

mutation theories while coarctation is isolated to a discrete lesion with totally normal vasculature in the whole body. This demonstrates the complexity of CoA pathology where a multifactorial aetiology seems more logical to explain the insidious narrowing of aorta.

1.6 Associated anomalies

CoA is not always isolated and mostly (60%) is associated with another cardiovascular anomaly as well as other congenital diseases. As CoA is a part of a wider spectrum of arch/aorta anomaly, it is common to see both pathologies together. Isolated CoA is seen frequently in Turner syndrome. It is also evidenced that high BP in neurofibromatosis type-1 is secondary to coexisting CoA with this syndrome (Mavani 2014). The most common congenital heart disease coinciding with CoA is ventricular septal defect (VSD) which can be of haemodynamic significance or not. Other cardiac congenital anomalies seen with CoA are listed below (Quaegebeur 1994):

- Bicuspid aortic valve (BAV)
- Atrial septal defect (ASD)
- Transposition of great arteries (TGA)
- Anomalies with single ventricle (examples: Mitral valve atresia, double outlet left or right ventricle)
- Taussig-Bing heart

1.7 Clinical Manifestation

Patients with CoA can be asymptomatic however they can be diagnosed incidentally at a later stage with a murmur or high BP. The murmur related to the isolated CoA is usually systolic ejection murmur which is best heard at the left sub-clavicle or left sub-scapular area. Antenatal diagnosis of CoA is difficult and challenging with high false negative reports (Matsui 2008). After birth the early diagnosis is important to prevent catastrophic outcomes. This mainly includes paediatric intensive care support and infusion of Prostaglandin E_1 (PGE_1). PGE_1 which is on the list of World Health Organisation (WHO) essential medications has been widely used since 1981 to prevent early DA closure. It fundamentally works by dilating the DA following relaxation of smooth muscles

(Heymann 1979). The neonates may present with failure-to-thrive, low peripheral (lower limbs) saturation, feet cyanosis, acidosis, decompensated heart failure, cardiogenic shock, oliguria and a higher systolic BP in upper limbs vs. lower limbs (> 20 mmHg). Development of collateral vessels is predominantly seen in patients who present at a later stage and is uncommon in neonates.

1.8 Surgical Repair

Untreated CoA with haemodynamic significance leads to a wide spectrum of complications which entails heart failure and mortality. Although the role of non-surgical approach and percutaneous balloon aortoplasty in the treatment of CoA in older patients has been explored (Walhout 2009), surgery in neonates and younger patients is the gold standard in the management of CoA. The ultimate aim for the management of CoA in neonates is to remove the obstruction. Generally the older the patient the more challenging the operation and this is mainly due to development of a complex collateral system. Surgery in neonates is usually performed via left posterolateral thoracotomy approach. The incision and surgical access to the left pleural cavity is through the fourth or fifth intercostal space (Figure 2.).

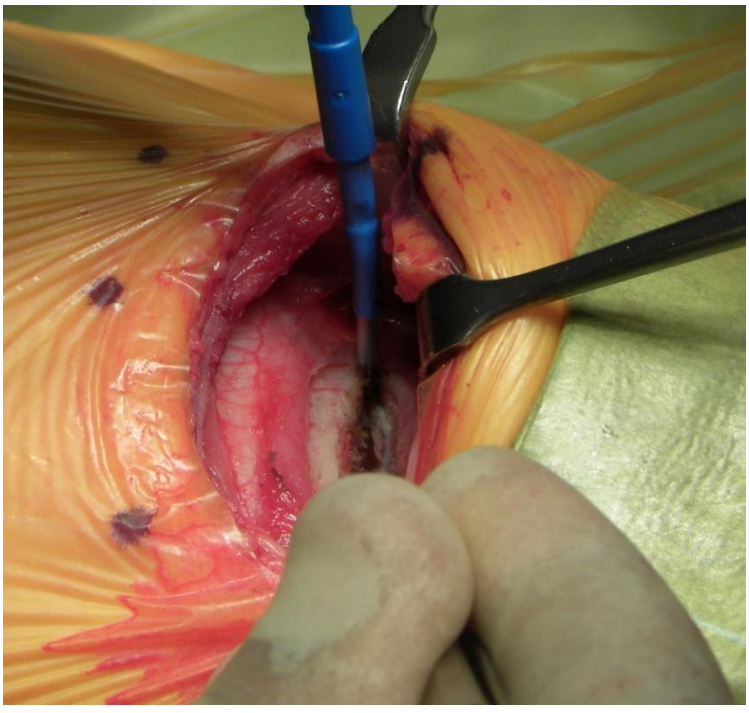

Figure 2. Posterolateral thoracotomy through the fourth intercostal space

The retractor is applied between the ribs with caution as over spreading may cause future scoliosis. Left lung is held away from the mediastinum by a wet swab. Then the pleura over mediastinum is opened to expose the arch, coarctation and DA. The major structures of the arch including DA are isolated by using an elastic loop as demonstrated in Figure 3. Almost all surgical techniques via thoracotomy share the abovementioned steps. In resection of coarctation and end-to-end anastomosis (EEA), two clamps are applied on the proximal aorta to include the origin of the subclavian artery (SA) and on the distal aorta after the third intercostal arteries. The DA is ligated on the PA side and then the coarctation with associated DA is resected (Figure 4.). Mobilisation of the arch and descending aorta is important as this prevents traction forces on the suture line. The two ends of aorta are then anastomosed together by continuous sutures. Figure 5 shows the conclusion of EEA operation. Figure 6 demonstrates the steps of EEA operation.

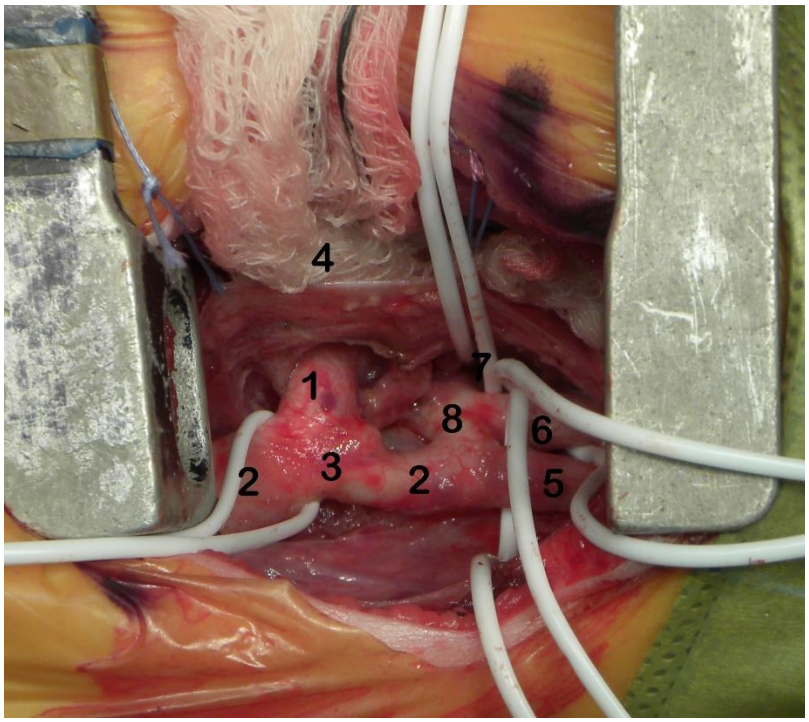

Figure 3. Exposure and mobilisation of major strictures, 1: DA, 2: Descending Aorta, 3: Coarctation, 4: Swab retracting the left lung, 5: SA, 6: Left common carotid artery (LCCA), 7: Brachiocephalic artery (BCA), 8: Arch

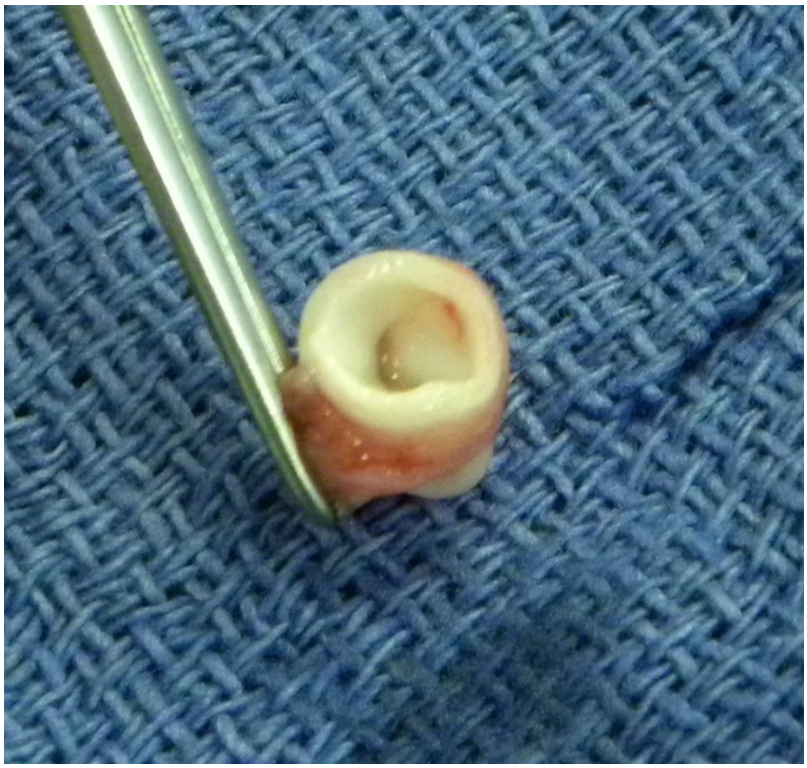

Figure 4. Resected coarctation

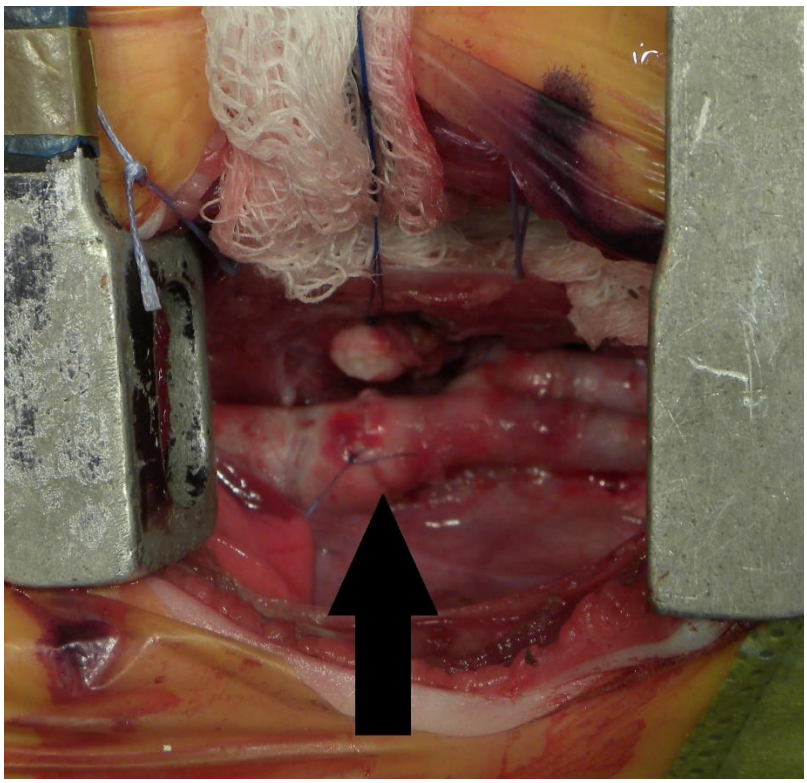

Figure 5. Conclusion of Coarctation resection and end-to-end anastomosis, demonstrating the suture line (black arrow)

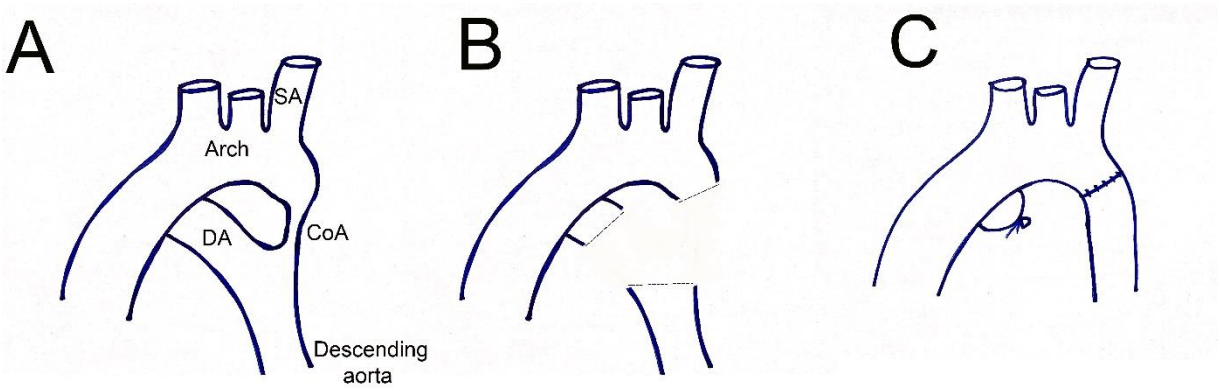

Figure 6. The steps of EEA operation: A) CoA and relevant structures B) DA and CoA are resected C) the proximal end of DA is tied off and the two ends of aorta are anastomosed in an end-to-end fashion (The incisions are shown by dotted lines)

In subclavian flap (SF) technique the SA is ligated distally and after applying clamp across the arch proximal the origin of SA and descending aorta, the SA is incised longitudinally to include the isthmus as well as the coarctation. Then the flap is reversed to cover the incised aorta. With this technique coarctation is not resected. DA ligation and transection if the plan is not to preserve it, is similar to those of EEA. Figure 7 demonstrates the steps of SF operation.

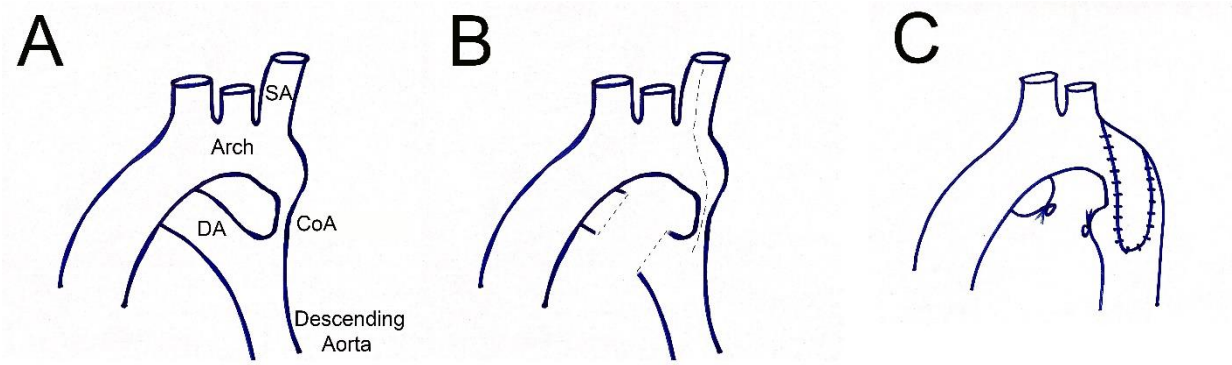

Figure 7. The steps of SF operation: A) CoA and relevant structures B) DA is resected and a longitudinal incision is performed on the SA covering the CoA C) the proximal and distal ends of DA are tied off ,the subclavian flap is brought down and sewn to the incised area (The incisions are shown by dotted lines)

In situations where the size of aorta distal to the origin of SA is small there are different techniques available to address the size of proximal descending aorta. One of them is a combination of SF and EEA technique. The other techniques are resection of coarctation and extended end-to-end anastomosis EEEA as well as resection of coarctation and end-to-side anastomosis. Figure 8 demonstrates the steps of EEEA operation.

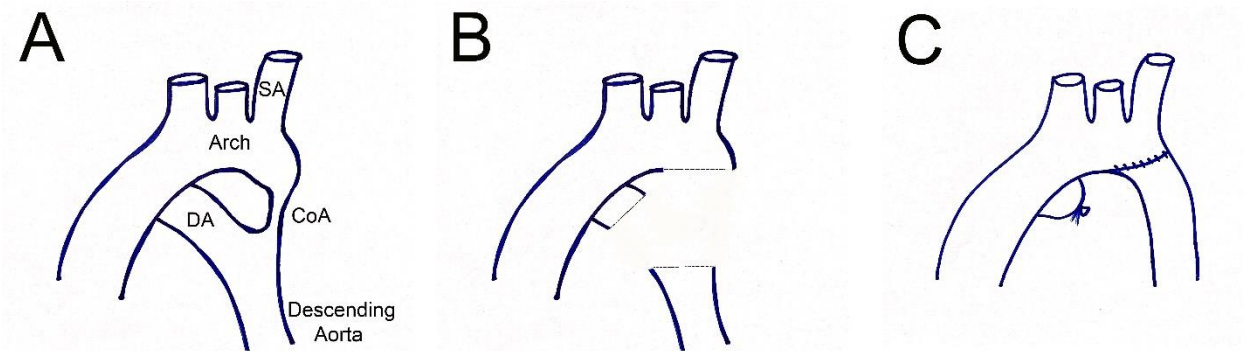

Figure 8. The steps of EEEA operation: A) CoA and relevant structures B) DA and CoA are resected then the proximal end of aorta is spatulated towards the arch i.e. extended incision C) the proximal end of DA is tied off and the two ends of aorta are anastomosed in an end-to-end fashion (The incisions are shown by dotted lines)

The same technique can be used for similar group of patient with end-to-side anastomosis which means that the anastomosis line is located in inferior distal arch and the isthmus will be ligated. In extended techniques it is required to incise the distal arch proximally towards ascending aorta. Figure 9 demonstrates the conclusion of similar operation with end-to-side anastomosis.

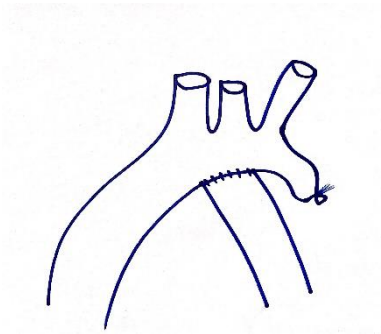

Figure 9. The conclusion of CoA resection with end-to-side anastomosis

Use of patch augmentation and rarely interpositional grafts have been reported however they are not common in routine practice as they are associated with aortic growth impairment as well as development of aortic aneurysm (Parks 1995).

The gradient across the repaired descending aorta is checked intra-operatively prior to transfer of patient to paediatric intensive care unit (PICU).

Post-operative possible complications include: bleeding, pneumothorax, wound infection, damage of thoracic duct and chylothorax, injury of left recurrent laryngeal nerve, scoliosis, injury of phrenic nerve, arrhythmia, persistent HTN, re-coarctation (early and late presentation), heart failure and mortality.

Immediate surgical outcomes for aortic coarctation are satisfactory and in-hospital mortality has been reported to be between 2% to 10% (Trinquet 1988); however this has significantly improved by evolving technology and technical skills. Today early mortality rate following operation for repair of isolated CoA is as low as 0.5 – 1% (Tulzer 2016). Generally the mortality rate is directly proportional to the complexity of the anomaly and concomitant congenital heart disease.

1.9 Aim of Thesis

Isolated CoA seems a simple pathology which can be treated safely with excellent immediate results. In practice the pathophysiology of this anomaly is more complex than a simple narrowing of proximal descending aorta. One of the striking complications of CoA repair is re-coarctation or recurrence of narrowing. Re-coarctation is associated with poor outcomes and persistent post-operative symptoms. Persistent HTN is also a mystery while it does occur in patients with satisfactory repair and no re-stenosis. Although the impact of surgical techniques on the outcomes have been frequently studied, it is still interesting to examine the common surgical techniques through a large systematic review. The question about the different surgical strategies particularly regarding EEA vs. SF is an old concern which dates back to as early as the very first operations to repair the CoA (Clagett 1948).

An extensive literature review which is explained in details in the next Chapter, did not reveal any randomised clinical trial (RCT) performed to date to compare the two main surgical techniques and their impact on re-coarctation. Another interesting aspect of post-operative outcome is aortic growth and remodelling. This can be studies alone and also in the context of different surgical techniques. Analysis of echocardiography images to obtain the aortic dimensions and parameters can allow the study of post repair growth.

Paediatric cardiac surgery practice in Scotland has been centralised for almost the past two decades. This allows the access to a unique population in the region where the operations are performed in a single centre. Reviewing the post-operative follow-up has led to recommendations in the form of an audit which can be used for service improvement. The epidemiology and geographical distribution of coarctation in Scotland is also an interesting aspect of current thesis which has been discussed in the third Chapter.

The evolving technology has allowed advances in the field of congenital heart surgery. 3D modelling and CFD has opened new horizons in surgical techniques and pre-operative strategy making. Virtual surgery is the future, particularly with regard to isolated CoA where the surgery itself does not have much complexity however the post-operative haemodynamics and flow changes need more subtle attention. This can be calculated by a programmed software to choose the best surgical technique and approach for different anatomical variations.

The aims of this thesis are summarised as follows:

- To run a systematic review to investigate the outcome of different surgical repairs for CoA and to explore the evolving surgical techniques in the past 50 years.
- To run a retrospective cohort to examine the impact of surgical techniques on the outcomes of CoA repair in Scotland
- To evaluate the role of technology in the future of CoA surgical repair

2. Systematic Review

2.1 Methods

The structure and methodology of systematic review is based on the previous study performed by the author of current thesis as the former member of the Collaborative Research (CORE) group (Phan 2014). The summary of methodology has been demonstrated on Figure 10.

2.1.1 Primary search

The search was performed electronically using initially the Ovid Medline interface. The time frame for the search was from 1945 up to 2016. Then to strengthen the search PubMed, Cochrane Database of Systematic Reviews (CDSR) and Database of Abstracts of Review of Effectiveness (DARE) was also searched in the same fashion with the same time frame. The primary search retrieved 369 papers. All abstracts' of these papers were downloaded for the next stage. The primary search was independently performed twice. First the author of current thesis performed the search and then a congenital heart disease registrar (acknowledged on the acknowledgement page) with an academic background performed the second search. Combination of both was considered as the primary search.

2.1.2 Primary filtration

Following the review of abstracts, 108 papers were excluded. These papers were case reports, editorial comments and non-English language articles. This process allowed 261 papers to enter the next phase.

2.1.3 Secondary filtration

The full manuscripts were obtained and reviewed in details. The papers which did not have the minimum clinical data were also excluded. If multiple papers were reported from one institution with time overlap, the largest study was included. Geographical distribution of literatures was also considered to obtain different studies from different countries across the world.

2.1.4 Eligibility criteria

- Age < 18 AND
- EEA AND/OR SF surgical technique AND

- Re-coarctation AND/OR re-stenosis

Seventy-three papers were excluded after applying the eligibility criteria.

2.1.5 Final papers

The final 56 papers which were chosen for systematic review analysis, were critically appraised. All data were retrieved from the manuscripts, figures and tables. All studies were retrospective cohorts. The qualitative analysis of the final papers is discussed on this Chapter. The geographical distribution of final appraised papers is demonstrated on Figure 11.

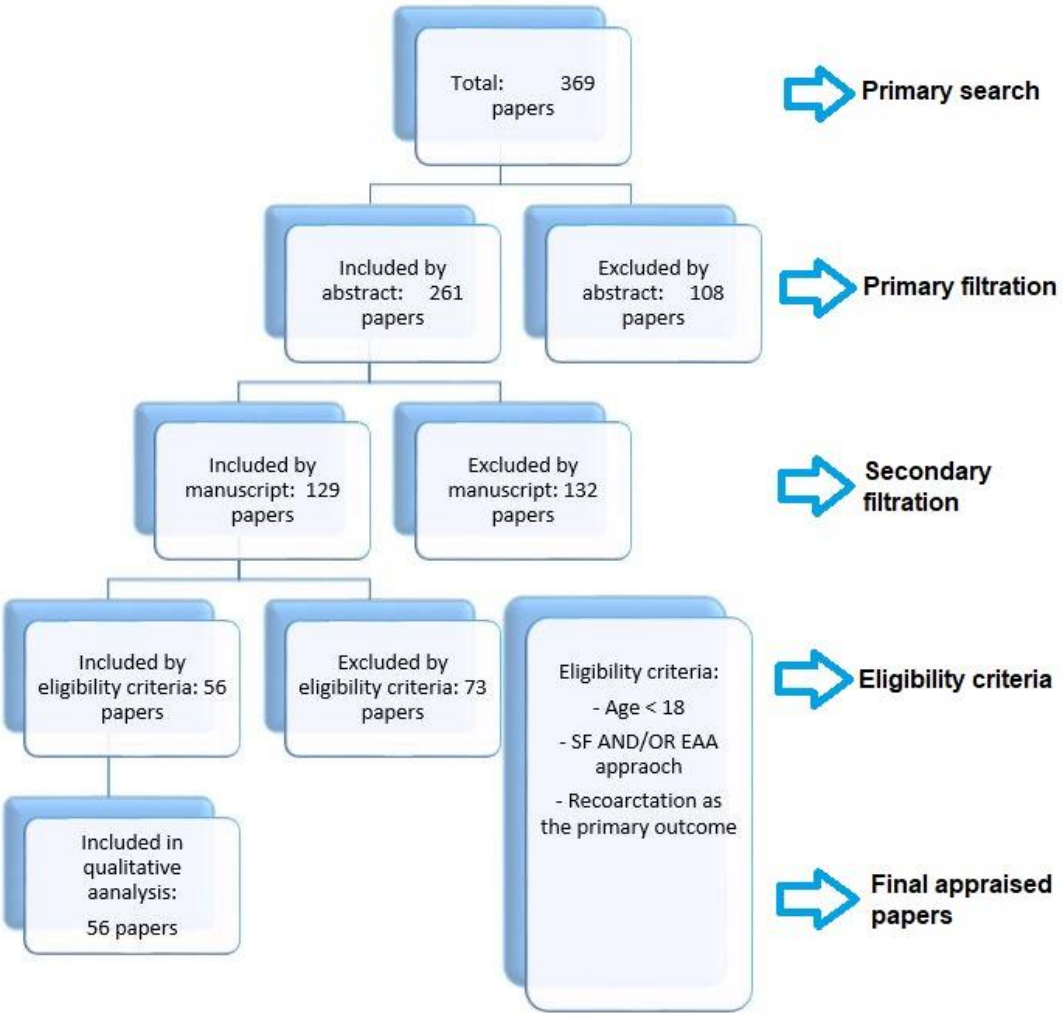

Figure 10. Summary of literature search methodology

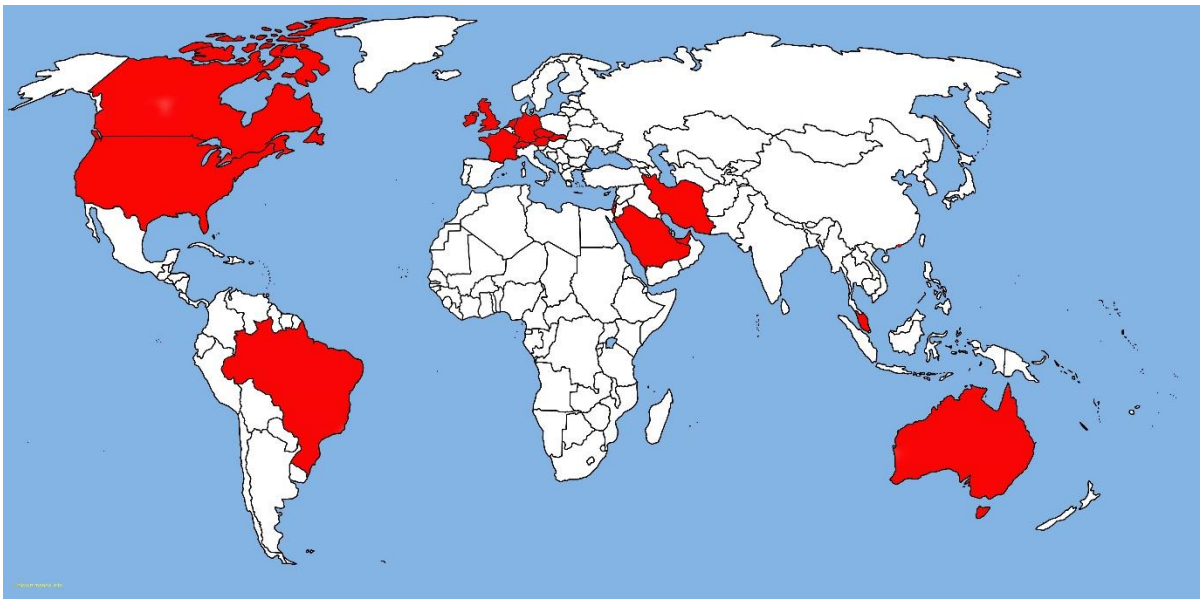

Figure 11. Geographical distribution of final appraised papers

2.1.6 Primary and secondary endpoints

The primary endpoint is defined as reoccurrence of coarctation after the surgical repair or re-coarctation. The secondary endpoint is a composite endpoint which includes in-hospital mortality and post-operative complications (chylothorax, Horner's syndrome, respiratory failure, necrotising colitis, vocal cord palsy, cardiac arrest, wound infection, seizure, neurological events, re-exploration for bleeding, sepsis and scoliosis)

2.2 Literature review and results

The final studies included in the systematic review are discussed in chronological order from the oldest to the most recent. The studies are divided in time to examine the evolution of repair techniques and transformation of patients' characteristics through the past 50 years of CoA surgical practice. The impact of different surgical techniques on the outcome of CoA is examined by analysing the selected literature. The evolution of surgical approach in half a century of CoA surgical practice has also been studied. The summary of literature review is demonstrated on Tables 3, 14, 33 and 60 and Figures 12, 13, 14 and 16 as per year of publication.

2.2.1 Year 1970 – 1979

2.2.1.1 Hamilton et al

Hamilton et al reported one of the first cohorts of patients who underwent CoA repair exclusively by SF technique (Hamilton 1978). Retrospective review of patients who were operated during 70s identified 45 consecutive infants younger than 6-month-old. Coexisting congenital heart disease which required surgical intervention at the same time with CoA repair was also included in 58% of population. Therefore the sample from a surgical point of view was heterogeneous. Patients had a mean follow-up of 3 years. Authors have emphasised that they have used non-absorbable sutures for anastomosing the SA flap to the descending aorta which is in contrast with similar studies from 80s that have been discussed in this Chapter. It is of note that all patients presented with heart failure and in a critical condition which reflects an era of without PGE_1 infusion. In-hospital mortality was 24% including the complex cases. However there were no early mortalities in isolated CoA group. In isolated CoA group there was no report of re-coarctation. The definition of re-coarctation is not described so it was not clear what methodology has been used to monitor the patients. Authors have mentioned about angiography but the criteria for this invasive diagnostic tool was also not clarified. There was no mention of arch study and its hypoplasia. The study did not have any statistical analysis or test of significance. In discussion section authors have advocated SF technique as the operation of choice for CoA; however the study design and multiple bias as well as poor analysis of confounding factors , made this paper as an institutional case report which may not be applied to current practice.

Patient group	Outcomes	Key results	Comments
- Infants	- Re-coarctation - Mortality	- low mortality and morbidity with SF	- Retrospective study - No comparison of repairs - No multivariate analysis

Table 1. Summary of Hamilton et al study

2.2.1.2 Pierce et al

Paediatric surgeons from Milton S.Hershey Medical Centre of Pennsylvania State University reported their experience in surgical treatment of CoA during 70s with SF technique (Pierce 1978). In this study which is mainly a case report on a novel surgical

technique, 12 patients from 14-day-old to 98-day-old were studied. These patients also underwent concomitant cardiac surgery such as PA banding for a staged operation. There were no early mortalities. As all patients presented with CHF, cardiac ratio on CXR was also investigated and demonstrated that after CoA repair and CHF treatment the ratio significantly reduced. Four (33%) patients underwent catheterisation with no mentioned reason from which none demonstrated a high gradient across the repaired site. There was no arch analysis in this study. Authors did not advocate SF technique while this paper was sharing an experience only; however they have suggested that for severe CoA where the distal arch might be involved SF technique may not address the distal arch pathology.

Patient group	Outcomes	Key results	Comments
- Infants	-Heart failure improvement - Gradient across the repaired site	-Reduction of cardiac index after repair	- Retrospective study - No comparison of repairs - No multivariate analysis - Heterogeneous population

Table 2. Summary of Pierce et al study

Author	Year	Location	Age (days)	Follow-up (years)	Total	Operation N (%)			Re-coarctation N (%)			In-hospital mortality N (%)			Superior technique
						EEA	EEEA	SF	EEA	EEEA	SF	EEA	EEEA	SF	
Hamilton	1978	UK	60 (4 - 180)	3 (0.5 - 7.5)	45	0	0	45 (100%)	0	0	0	Total = 0 (isolated CoA)			N/A
Pierce	1978	USA	(14 - 98)	(0.4 - 5.5)	12	0	0	12 (100%)	0	0	0	0	0	0	N/A

Table 3. Summary of published literatures 1970 – 1979: EEA: resection of coarctation and End-to-End Anastomosis; EEEA: resection of coarctation and Extended End-to-End Anastomosis; SF: no resection and Subclavian Flap; N/A: Not applicable (Study examines only one technique and there is no comparison of other techniques); Age: Median (range) or Mean ± Standard deviation or median alone (yrs: years, m: months, if not specified it is days); Follow-up: Median (range) or Mean ± Standard deviation or median alone, Number (%) for surgical techniques.

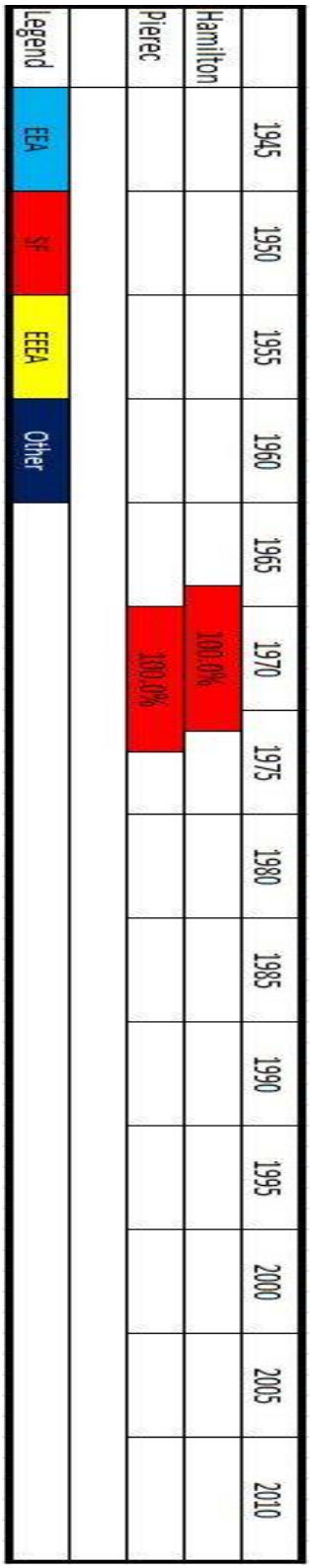

Figure 12. Published literatures 1970 – 1979. Horizontal bar shows the study period. The surgical techniques are demonstrated in different colours (legend) with the percentage of the used technique in the specified study period.

2.2.2 Year 1980 – 1989

2.2.2.1 Van Son et al

Paediatric cardiac surgeons from academic hospital Nijmegen in Netherlands studied 70 consecutive infants who underwent CoA repair between 1973 and 1987 (Van Son 1989). Their main focus was EEA technique; while in their population 51 (72%) patients underwent EEA and 19 (28%) underwent SF technique. Other cardiac anomalies requiring simultaneous intervention were also included. From schematic images by which authors have described their EEA technique it seems isthmus has been completely excised and the operation resembles EEEA rather than EEA. In-hospital mortality was 12 (23.2%) and 2 (10.5%) for EEA and SF patients respectively. Neonates were significantly more at risk of mortality as compared to patients who were older than 30-day-old. This is similar to contemporary studies when PGE_1 was not introduced into the practice. There were no difference between the two main surgical groups with regard to in-hospital mortality. PA banding was performed at the same time in 10 patients (15%) to facilitate a second stage operation. As stated previously this has created a bias particularly in follow-up as population is not homogeneous at all. In SF group one (5%) patient developed shorted left arm compared to right upper limb. Prior to surgery 39% of population were hypertensive and after surgery during the follow-up this number reduced to 17% among survivors. Re-coarctation which was defined as discrepancy between the systolic BP of upper and lower limb of more than 20 mmHg, was observed in 12 (23.2%) patients of EEA group and 2 (10.5%) patients of SF group. Statistically there were no difference between the surgical techniques in freedom from re-coarctation. Generally the sample size was small with a heterogeneous population not allowing to elicit a reliable result.

Patient group	Outcomes	Key results	Comments
- Infants	- Re-coarctation - Mortality	- No difference SF vs. EEA	- Kruskall-Wallis and Fisher's exact test for statistical analysis - Small sample size - Heterogeneous population

Table 4. Summary of Van Son et al study

2.2.2.2 Hopkins et al

Hopkins et al from the Hospital for Sick Children in London retrospectively studied the outcome of CoA repair by considering an individualised surgical approach (Hopkins 1988). Their study included 179 patients with an age of ranging from 31-day-old to 1-year-old. Follow-up was performed with a mean of 5.4 $\pm$ 3.2 years. This population included 32 (18%) patients who underwent EEA technique and 124 (70%) patients who received SF technique for the repair of CoA. Total early mortality was high and reported at 15% (27 patients). The population was heterogeneous with complex cardiac anomalies. The mortality was statistically significant in neonates as compared to other age groups. Increased risk of re-coarctation was observed also in neonates. There were no difference between SF and EEA technique in both mortality and the incidence of re-coarctation. Patch aortoplasty was significantly associated with re-coarctation. Finally authors insinuated an individualised approach to CoA repair while there is no randomised trial yet available. They advocated EEA for long coarctation while SF would be suitable for short and simpler coarctations. It is interesting that in day-to-day practice many surgeons believe the opposite; meaning that a challenging long CoA with small diameter would be better to be addressed by SF rather than EEA technique. This disparity demonstrates that even after three decades how subjective is the surgical approach and the technique of choice for the correction of CoA.

Patient group	Outcomes	Key results	Comments
-Infants	- Mortality - Re-coarctation	- No difference SF vs. EEA - SF more reproducible	- Cox proportional hazard multivariate analysis with Kaplan-Meier curve for statistical analysis

Table 5. Summary of Hopkins et al study

2.2.2.3 Trinquet et al

Paediatric heart surgeons from the Department of Thoracic and Cardiovascular Surgery of Laennec hospital in France reported their experience with surgical management of CoA. Their aim similar to many of their contemporary studies was to find out which operation is the best to repair the CoA (Trinquet 1988). This study is one the first cohorts which have reported a relatively large number of patients underwent EEEA technique. Casenotes of 178 patients who underwent CoA during 70s and 80s were retrospectively reviewed. The majority of operations were EEEA with 99 patients (55%). Other main surgeries were EEA with 45 (25%) patients and SF with 26 (15%) patients. Complex

coexisting congenital heart disease was also included in this population and isolated CoA was only 35% (63 patients). The age of patients were 29 ± 22 day-old which did not differ between isolated CoA and complex patients. Total in-hospital mortality was as high as 19.7% and similar to many studies in 80s this was more prevalent among neonates. The rate of early mortality has been analysed as per type of complex surgery as well as the repair technique and presented on a table; however there was no test of significance performed. Ironically authors have concluded from the table which included only numeric variables that the type of repair did not affect the early mortality. Post-operative chylothorax was observed in 1 (0.5%) patient and phrenic nerve injury also in 1 (0.5%) patients. There was no neurological complications. The post-operative complications were not reported separately for isolated CoA therefore it is not possible to ignore the impact of complex concomitant surgery on post-operative outcome which may not be attributed to CoA alone. Seventeen (9.6%) more patients died during the follow-up period which majority occurred within the first year after discharge. Although the influence of arch tubular hypoplasia has been considered and measured statistically, there was not anatomical description or definition of arch hypoplasia. Re-coarctation definition was described as existence of a persistent peak pressure gradient of more than 20 mmHg across the repaired site. The rate of re-coarctation for each surgical technique was not mentioned while a total of 15 (10.8%) of patients developed re-stenosis of the repaired aorta. The comparison between the techniques have been performed by Kaplan-Meier curve which did not show any significant difference. Interestingly the rate of re-coarctation was significantly associated with the concomitant VSD.

Patient group	Outcomes	Key results	Comments
- infants	- Mortality - Re-coarctation -post-op complication	- No difference SF vs. EEA	- Actuarial probability for statistical analysis - Heterogeneous population

Table 6. Summary of Trinquet et al study

2.2.2.4 Beekman et al

Beekman et al published their results in surgical management of CoA for more than 35 years with a focus on SF technique (Beekman 1986). Medical record of 125 patients with mean age of 2.5 ± 0.5 day-old was retrospectively reviewed. The mean follow-up was recorded as 7.9 ± 3.6 years which does not match with 35 years report and it may reflect a higher number of patients operated towards recent years of study. Patients were halved into two groups as per surgical technique: 63 (50%) patients for EEA and 62 (50%)

patients for SF technique. This is one of the rare studies where authors have excluded patients with concomitant complex congenital heart disease such as interrupted arch, HLHS, etc. the SF technique was introduced into the institution's practice from the second half of study period. Seven (11.3%) and 19 (30.1%) patients died in the hospital from SF and EEA groups respectively. This was statistically significant in favour of SF technique. Since the complex concomitant anomalies were excluded, the early mortality rate in this population as per today's practice is considered high. Twelve (19%) patients from EEA and 5 (8%) patients from SF group developed re-coarctation. The threshold in this study for the definition of re-coarctation was the highest among the similar studies where a systolic BP gradient of more than 40mmHg between the upper and lower limbs was considered as re-coarctation. Patients who developed re-coarctation in SF group were significantly younger than EEA group. This is an individualised approach for neonates while at the beginning of the life due to small size vessels it is deemed SF technique is safer than EEA with end-to-end anastomosis of two small vessels. This issue has been insinuated by authors at the discussion section. Interestingly among the patients who developed re-coarctation, patients who underwent SF technique had a higher gradient across the repaired site as compared to EEA patients. HTN was more prevalent in EEA group which did not match with the latter finding on peak pressure gradient. The Kaplan-Meier curve comparing EEA with SF with regard to freedom from re-coarctation did not show any significant difference.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation - Post-op HTN	- SF superiority	- Student t and Chi-Square test for univariate and Breslow's proportional hazard for multivariate analysis - Surgically Heterogeneous

Table 7. Summary of Beekman et al study

2.2.2.5 Kopf et al

In a small study 25 patients with the age of less than 3-month-old who underwent CoA repair towards the end of 70s, were reviewed retrospectively (Kopf 1986). In this small sample size concomitant complex congenital heart disease has also been included with isolated CoA therefore the high degree of heterogeneity has made this study an institutional case report. One (4%) patient died in the hospital. During the follow-up

authors noted a peak gradient of more than 30mmHg significantly in complex patients. Out of 23 patients who underwent SF technique 3 (13.6%) patients developed re-coarctation requiring re-intervention. As mentioned above the study does not add to the current practice in surgical management of CoA.

Patient group	Outcomes	Key results	Comments
- Infants	- Re-coarctation - Mortality	- Increase of peak gradient across the repaired site in complex surgeries	- No multivariate analysis -Actuarial probability for statistical analysis - Heterogeneous population

Table 8. Summary of Kopf et al study

2.2.2.6 Levinsky et al

Paediatric cardiac surgeons from the Department of Thoracic and Cardiovascular Surgery of Beilinson Medical Centre in Israel reported their 5-year experience in repairing CoA (Levinsky 1986). Twenty-eight patients with an age of ranging from 2 day-old to 60-day-old were retrospectively studied. The majority of operation were performed using SF technique with 21 (75%) patients. Similar to the previous study (Kopf 1986) they also included complex cardiac anomalies concomitant with isolated CoA. With a small sample size and high degree of heterogeneity this study was destined to remain a case report which may not elicit reliable outcomes on exclusively CoA surgery. Total early mortality was 10.7% (3 patients) which has not been dissected as per surgical techniques. In this study there was no statistical analysis of the results or comprehensive report of post-operative complications. Re-coarctation occurred in one (4.7%) patients from SF group. Only one patient underwent EEA who also developed re-coarctation. In conclusion section authors have mentioned that the operative mortality of CoA is desirable as compared to medical management only. Undoubtedly this statement is compatible with late 70s soar in surgical management of CoA; however by today's standard this is considered as a high mortality.

Patient group	Outcomes	Key results	Comments
- Infants	- Re-coarctation - Mortality	- No difference SF vs. EEA	- Poor statistical analysis with no multivariate analysis - No specific follow-up

Table 9. Summary of Levinsky et al study

2.2.2.7 Sanchez et al

Sanchez et al retrospectively studies the outcome of CoA repair in 26 patients who underwent surgery between 1979 and 1983 (Sanchez 1986). The aim was to investigate the re-stenosis rate and to examine the factors which may have an impact on re-coarctation. Therefore authors were interested to explore if re-stenosis can be predicted at any stage of the care. All of patients in this population underwent SF technique. Complex cardiac anomaly was identified in 23% of patients which has created a small sample size with heterogeneity. Early mortality occurred in 3 (11.5%) patients. The outcome was gauged by a classification proposed by authors which entailed the systolic BP gradient between the upper and lower limbs. The classification of outcome included good, fair and poor for an increasing systolic BP gradient. Clearly relying only on BP gradient and then labelling an outcome as good or poor is not sufficient; while patients with a high gradient and no re-coarctation may still be considered as an acceptable outcome. It is important to take persistent HTN into account in the context of all CoA operations regardless of successful repair. Re-coarctation incidence was 26% (6 patients) requiring re-intervention. Similar to previous studies discussed in this Chapter (Kopf 1986, Levinsky 1986) the authors demonstrated that the rate of re-coarctation is significantly higher in complex group of patients with other congenital heart disease. This study is not well powered to support the statistical findings.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	-High re-coarctation rate	- No multivariate analysis - Heterogeneous population

Table 10. Summary of Sanchez et al study

2.2.2.8 Ziemer et al

Ziemer et al retrospectively studied the outcome of surgical repair of CoA in 100 patients between 1972 and 1984 (Ziemer 1986). The period of study coincided with the emergence of PGE_1 as well as introduction of SF technique in the authors' institution. The majority of operations were performed by SF technique which soon became favourable in this institution. Seventy patients (70%) underwent SF and 24 patients (24%) had EEA for CoA repair. Only less than a third of population were diagnosed with isolated CoA (29%). Early mortality was 33.3% (9 patients) in EEA group versus 7 patients (11.4%) in SF group. This comprised all patients including complex cardiac defects while mortality in isolated CoA was 3.4%. Patients had a main follow-up of 3.4 years. Actuarial survival

for isolated CoA was calculated 85.5% ± 6.7% at 8 years. Re-coarctation occurred in 4 (25%) patient of EEA group and 9 (15%) of SF group. The Kaplan-Meier curve of freedom from re-coarctation was presented for comparing EEA vs. SF. The actuarial freedom from re-coarctation for EEA after 5 years was 92.9% ± 6.9 vs. SF which was reported at 75.2% ± 9.1. This shows EEA technique superiority; however there was no log rank presented to test the significance on this Kaplan-Meier curve. This is important while the re-coarctation rate in EEA was higher than SF. In conclusion section authors emphasised that there was no superiority between SF and EEA. Although they also hoped absorbable sutures would make a decisive difference in the outcome of CoA surgery. We now know that non-absorbable sutures are the standard material in many institutions around the world.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	- No difference SF vs. EEA	- Actuarial probability for statistical analysis - Heterogeneous population - Short follow-up

Table 11. Summary of Ziemer et al study

2.2.2.9 Palatianos et al

Paediatric cardiac surgeons and cardiologists from University of Miami School of Medicine, retrospectively studied the change of surgical trend in the management of CoA (Palatianos 1985). In this study 107 patients were included which was biased by both age (adults included) and complex concomitant congenital heart disease. The surgical trend may not be assessed accurately while the surgery for complex lesions as well as surgery of CoA in adults is entirely different from those of neonates or infants. The main surgical techniques were EEA in 48 (45%) and SF in 36 (33%) patients. Early mortality was observed in EEA group with 5 (10.4%) patients who died in the hospital. It was mentioned that two patients with distal aortic arch hypoplasia underwent SF technique; however there is no description of arch hypoplasia in this group of patients. Paraplegia post-operatively was observed in one (0.9%) patient with aberrant right SA. The definition of re-coarctation was not clear in this study; however 7 (6.5%) patinets from EEA group and 2 (1.8%) from SF group required re-intervention for re-stenosis of the repaired site. This finding was comparable with the difference of systolic BP gradient between upper and lower limbs in patients younger than 1-year-old with EEA (32 ± 27) vs. SF (6.7 ± 9.4).

This was statistically significant in favour of SF technique. The only finding which was not demonstrated previously was the occurrence of re-coarctation more commonly 12 months or more after surgery. In similar studies almost invariably the majority of re-coarctations occurred in the first 12 months after surgery. The authors' studied population was severely heterogeneous therefore it may not be possible to draw a conclusion from this rather surprising outcome. In summary authors mentioned that SF was the favourable technique with regard to freedom from re-coarctation.

Patient group	Outcomes	Key results	Comments
- Children and Adults	- Mortality - Re-coarctation	- SF superiority	- Heterogeneous population (Age and Surgical intervention) - Only univariate analysis

Table 12. Summary of Palatianos et al study

2.2.2.10 Waldman et al

Waldman et al in a small retrospective study reviewed the casenotes of 31 patients who underwent CoA repair by EEA (45%) or SF (20%) techniques (Waldman 1982). Patch aortoplasty was performed in the rest of population. Patients' age ranged from 1-day-old to 30-day-old. In this small population complex anomalies such as interrupted arch and TGA were included therefore many patients underwent a concomitant PA banding for staged operation. This has made the population heterogeneous despite an appropriate age selection. One (3.2%) patient died in the hospital. Serial echocardiography revealed that the residual peak pressure gradient across the repaired site subsides through the time. Authors have utilised both systolic BP gradient and peak pressure gradient across the repaired site as an indicator for the diagnosis of re-coarctation. A peak pressure gradient of 30 mmHg and above was used for defining re-coarctation. Two (14.2%) patients in EEA group and one (16.6%) in SF group were identified with a diagnosis of re-coarctation who required re-intervention. Authors in conclusion emphasised that the choice of operation should be on the basis of anatomy and not individual preferences. For example for discreet CoA repair EEA technique was mentioned as the operation of choice; however for a long segment of CoA or distal arch hypoplasia they advocated SF technique. This is of course prior to emerging EEEA technique in 90s.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	- No difference SF vs. EEA - Choice of operation should be based on the CoA anatomy	- Actuarial probability for statistical analysis - Short follow-up - Heterogeneous population

Table 13. Summary of Waldman et al study

Author	Year	Location	Age (days)	Follow-up (years)	Total	Operation N (%)			Re-coarctation N (%)			In-hospital mortality N (%)			Superior technique
						EEA	EEEA	SF	EEA	EEEA	SF	EEA	EEEA	SF	
Van Son	1989	Netherlands	80 +/- 77	4.7 +/- 3.5	70	51 (72%)	0	19 (28%)	4 (9%)	0	5 (16%)	12 (23.2%)	0	2 (10.5%)	No Difference
Hopkins	1988	UK	(31 - 360)	5.4 +/- 3.2	179	32 (18%)	0	124 (70%)	5 (15.6%)	0	15 (12%)	Total = 27 (15%)			No Difference
Trinquet	1988	France	29 +/- 22	0.5 (0 - 1.8)	178	45 (25%)	99 (55%)	26 (15%)	Total = 15 (10.8%)			Total = 8% (isolated CoA)			No Difference
Beekman	1986	USA	2.5 +/- 0.5	7.9 +/- 3.6	125	63 (50%)	0	62 (50%)	12 (19%)	0	5 (8%)	19 (30.1%)	0	7 (11.3%)	SF
Kopf	1986	USA	21 (1 - 86)	6	25	0	0	23 (92%)	0	0	3 (13%)	0	0	1 (4.3%)	N/A
Levinsky	1986	Israel	(2 - 60)	Not Specified	28	1 (3.5%)	0	21 (75%)	1 (100%)	0	1 (4.7%)	Total = 3 (10.7%)			N/A
Sanchez	1986	USA	16 (2 - 65)	1 (0 - 5.5)	26	0	0	26 (100%)	0	0	6 (26%)	Total = 3 (11.5%)			N/A
Ziemer	1986	USA	12+/-8	3.4 +/- 3	100	24 (24%)	0	70 (70%)	4 (25%)	0	9 (15%)	8 (33.3%)	0	7 (11.4%)	No Difference
Palatianos	1985	USA	6.4 yrs (4 - 27 yrs)	(0.5 - 9.2)	107	48 (45%)	0	36 (33%)	7 (6.5%)	0	2 (1.8%)	5 (10.4%)	0	0	SF
Waldman	1982	USA	(1 - 30)	2.4	31	14 (45%)	0	6 (20%)	2 (14.2%)	0	1 (16.6%)	Total = 1 (3.2%)			No Difference

Table 14. Summary of published literatures 1980 – 1989: EEA: resection of coarctation and End-to-End Anastomosis; EEEA: resection of coarctation and Extended End-to-End Anastomosis; SF: no resection and Subclavian Flap; N/A: Not applicable (Study examines only one technique and there is no comparison of other techniques); Age: Median (range) or Mean ± Standard deviation or median alone (yrs: years, m: months, if not specified it is days); Follow-up: Median (range) or Mean ± Standard deviation or median alone, Number (%) for surgical techniques.

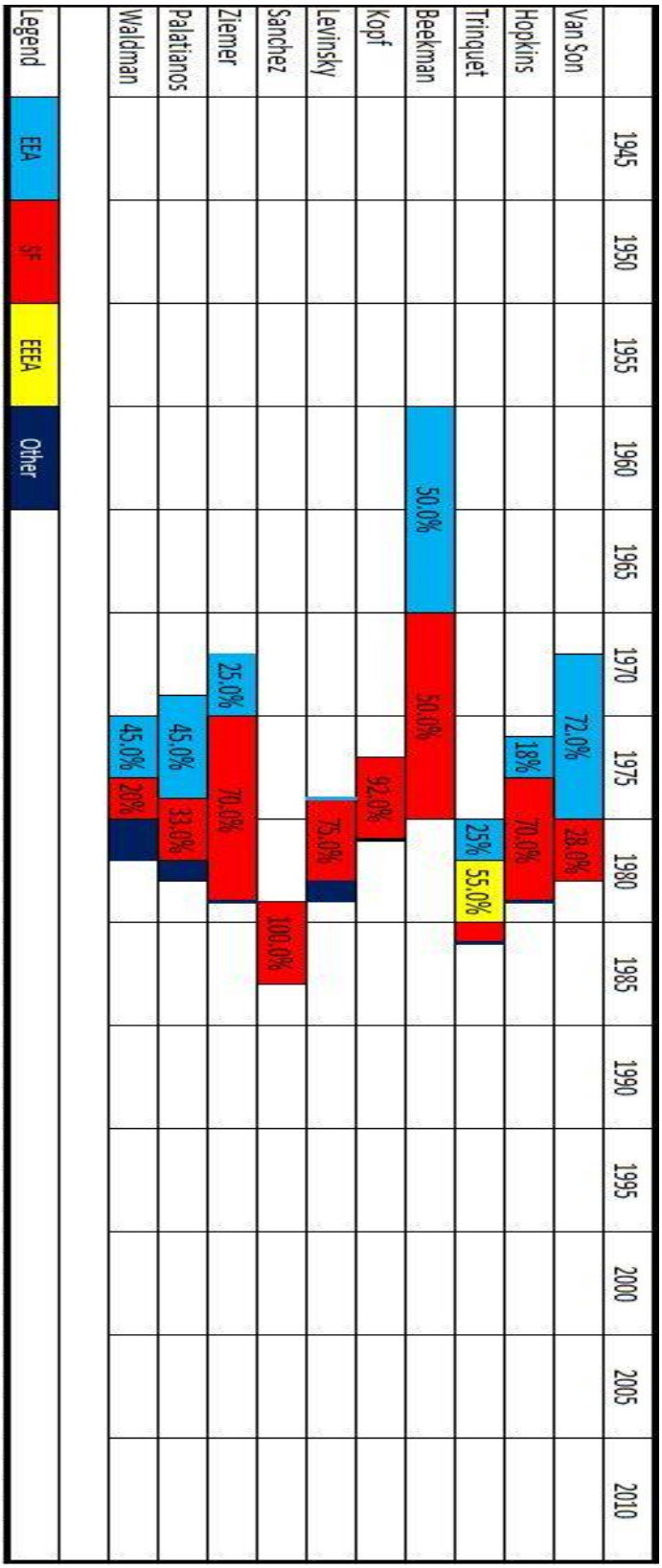

Figure 13. Published literatures 1980 – 1989. Horizontal bar shows the study period. The surgical techniques are demonstrated in different colours (legend) with the percentage of the used technique in the specified study period.

2.2.3 Year 1990 – 1999

2.2.3.1 Jelly et al

Paediatric cardiac surgeons from Saudi Arabia studied the outcome of CoA repair over a period of 12 years (Jelly 1999). They reviewed 83 patients who underwent CoA repair with three major techniques: SF 54 (63%), EEEA 7 (8%) and combination of EEA and SF in 22 (26%). Population age was focused on neonates with a mean of 21 $\pm$ 7 day-old and range of 1 day-old to 28 day-old; however only 23 (28%) patients had an isolated CoA. Despite dividing the patients into three groups as per concomitant congenital heart disease still the population is a heterogeneous sample for studying outcomes while statistical analysis has not been performed separately for these groups with regard to different surgical approaches. Authors have applied three different criteria for defining the occurrence of re-coarctation: 1- systolic and diastolic BP above the 90^{th} percentile for age 2- a disparity of 20 mmHg or higher in systolic BP between the upper and lower limbs 3- peak pressure gradient of more than 25 mmHg across the repaired site. PA banding performed in more than half of patients which from a haemodynamic point of view is significant. This may have flow and haemodynamic implications on antegrade flow which in return may affect the outcomes such as persistent HTN. Analyse of these patients in a same group as isolated CoA will not elicit a reliable results. This can be applied to post-operative complication while complex patients may develop more complications or longer PICU stay as compared to isolated CoA. Early mortality in isolated CoA group was 9% (2 patients) and overall early mortality has been reported 14% (12 patients) which is higher than similar populations reported in this Chapter. Evidently early mortality was significantly higher in complex group. The mean follow-up was 25 months ranging from 6 months to 11 years. Eight more patients died during the follow-up reducing the sample size to 74 patients. Re-coarctation was observed in 5 patients (7%) and a significant difference was also noted between SF vs. EEEA while EEEA patients developed less re-coarctation. Interestingly patients with SF + EEEA did not develop re-coarctation at all which was statistically significant. Authors have compared the main three groups with regard to occurrence of re-coarctation which statistically did not seem correct. Group 3 comprised a very heterogeneous group of patients with a variety of congenital heart diseases including TGA, Taussig-Bing anomaly and double outlet right ventricle. Comparing this group with group 2 which includes CoA + VSDs is not a reliable

comparison. The number of re-intervention was less than total number of patients who were diagnosed by a strict criteria for re-coarctation. Authors have not clarified why at least four patients who were diagnosed with re-coarctation did not require any intervention. One of the major drawback in this study was the absence of arch pathology analysis while arch hypoplasia plays a major role in both the management and outcome of CoA.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	-EEEA+SF superiority	-Heterogeneous population (Surgical intervention) -Chi-Square and Fisher's exact tests for statistical analysis

Table 15. Summary of Jelly et al study

2.2.3.2 Backer et al

Backer et al exclusively studied the outcome of CoA surgery with EEEA in their institution over a period of 7 years (Backer 1998). Fifty-five patients were identified and their medical records were retrospectively reviewed. This group of patients comprised isolated CoA and other congenital heart diseases; therefore as a result more complex patients required median sternotomy and CPB for surgery (38%). The median age was 21-day-old. Authors have presented a schematic figure of their deployed technique for repairing CoA by which the distal arch is excised inferiorly up to the origin or LCCA and then it is anastomosed with a speculated descending aorta. This is a technique which in some studies has been referred to as side-to-side anastomosis rather than end-to-side and was discussed earlier in this Chapter (Wood 2004). Re-coarctation was defined as an upper and lower limbs difference in systolic blood pressure at 20 mmHg and greater. One (1.8%) patient died in the hospital and two (3.6%) other patients did not survive during the follow-up period. Chylothorax occurred in 2 (3.6%) patients. Rate of re-coarctation in the whole population was low and reported at 3.6% (2 patients). The study sample size is low therefore as a wide spectrum of patients with different cardiac anomalies were included in this study, the manuscript seemed as an institutional case report. Once again there was no mention of arch hypoplasia and the reason that authors embarked on a more

complex operation for even an isolated CoA. Pathology of the arch in this population was dissected with no statistical analysis.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	- Only EEEA assessed with 3.6% re-coarctation	- No multivariate analysis - Heterogeneous population

Table 16. Summary of Backer et al study

2.2.3.3 Cobanoglu et al

Cobanoglu et al from Division of Cardiopulmonary Surgery of Oregon Health Sciences University conducted a retrospective study with direct focus on comparison between the EEA vs. SF techniques with regard to CoA repair outcomes (Cobanoglu 1998). In 12 years 86 infants with a mean age of 24 day-old and mean weight of 3.5 Kg were identified. SF and EEA techniques were used in 47 (55%) and 39 (45%) of patients. There were also concomitant complex congenital heart diseases in the population. Definition of re-coarctation requiring re-intervention was defined as "Blood-pressure gradient greater than 30 mm Hg with arterial hypertension was considered an indication for re-intervention." Distribution of procedures performed in authors' institution as per procedure has shown a tendency to perform CoA repair with SF technique in younger patients who are at the first or second week of life. This reflects a general consensus that small lumen of major vessels may inflict post-surgery contracture on the suture line while SF acts as a patch covering the anterior aspect of the artery without any circular suture line. The mean cross clamp time was 18 minutes $\pm$ 4 minutes with no significant difference between the two groups. Six (7%) of patients died in the hospital. Although no difference was detected between the two groups with regard to early mortality, given the distribution of complex anomalies in both groups comparison of SF vs. EEA technique was not accurate from a statistical point of view. Understandably coexisting significant VSDs and univentricular hearts were an independent risk factor for a reduced survival. This is the reason that CoA needs to be examined and evaluated as a sole pathology and not with concomitant anomalies which may even be the primary culprit leaving the CoA as a less significant lesion. Nine patients developed re-coarctation while it was not calcified how many of patients were available at follow-up. The rate of re-coarctation considering a total of 86 patients was 10.4%. The data on this section were all presented in numbers without

percentage. There were no significant difference between SF and EEA in relation to the rate of re-coarctation. Interestingly there was a group of nine patients with presumably peak pressure gradient of higher than 20 mmHg who were still under surveillance. Although the definition of re-coarctation has been set as per systolic pressure gradient between the upper and lower limbs it was not clear why at follow-up different monitoring modalities have been used for borderline patients. If by "gradients" authors meant the disparity between arm and leg then the question would be: why authors did not use echocardiography or MRI for borderline cases.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation - Post-op complication	- No difference EEA vs. SF	- Comparison of actuarial survival with Wilcoxon test - Fisher's exact test for statistical analysis

Table 17. Summary of Cobanoglu et al study

2.2.3.4 Seirafi et al

Paediatric cardiac surgeons from New England Medical Centre and Tufts University School of Medicine retrospectively reviewed 176 consecutive patients who presented with CoA and underwent repair with predominantly EEA (88, 50%), EEEA (21, 12%) and SF (43, 25%) (Seirafi 1998). The median age was 11-month-old however the age range included a wide spectrum of patients including adults (1-day-old – 33-year-old). Moreover 63 (35%) patients or more than a third of population underwent another cardiac surgical intervention for a more complex congenital heart disease. Re-coarctation was defined as a systolic BP gradient between the right arm and one of the lower limbs of more than 20 mmHg. This also was further confirmed by echocardiography. Early mortality in this population was 3.4% (6 patients). Another 7 patients did not survive within 3 months which was relatively high; however these patients were majority from the complex cardiac anomaly group. Ten-year survival was 100% for isolated CoA patients. Persistent coarctation was observed in 27 (15.3%) patients who required re-intervention. Authors noticed that persistent late HTN regardless of re-coarctation is inversely proportional to the age of operation; meaning if patients were operated at a younger age the rate of persistent HTN would be lower. There were no statistical significant differences between the surgical techniques with regard to the rate of re-

coarctation. It has been mentioned in the manuscript that arch hypoplasia is an important factor which may have an impact on the outcome of repair; however there was no analysis on the arch in this population. Authors have also highlighted that without an RCT it is unlikely to identify the superior surgical technique by observational studies. While previously there was a trend to wait and operate on the CoA patients with a delay as long as 1-2 years, the authors message in late 90s advocated and early operation while evolving surgical techniques and materials allowed early intervention in small sized patients.

Patient group	Outcomes	Key results	Comments
- Children and Adults	- Re-coarctation - Mortality -Post-op complication	- No difference SF vs. EEA vs. EEEA	- Heterogeneous population (age, surgical intervention and pathology)

Table 18. Summary of Seirafi et al study

2.2.3.5 Van Son et al

Van Son et al from Leipzig studied a small group of patients (N=25) retrospectively (Van Son 1997). In this group all patients underwent resection of coarctation and extension of incision into the arch. End-to-side anastomosis was performed in all of the patients. Half of patient underwent anastomosis of descending aorta to proximal arch and the other half underwent anastomosis of descending aorta to the distal ascending aorta. Authors have not defined the anatomical difference between distal ascending aorta vs. proximal arch, while this operation in a patient with isolated CoA and normal arch seems aggressive. The study period is also short and only covers 18 months. Eleven (44%) patients were diagnosed with arch hypoplasia. VSD requiring surgical closure was also reposted among the population. Authors criteria for operating via left thoracotomy was: the size of arch immediately distal to the origin of BCA equal to patients weight plus one and no intra-cardiac defects which require correction or closure. This criteria was compatible with the definition of proximal arch hypoplasia which requires a better and wider access through median sternotomy. What authors have depicted on the schematic figures describing their surgical technique was called end-to-side where the insertion of descending aorta into arch is more proximal than a classic EEEA. In the former a cul-de-sac (Figure 9.) is created which may create turbulence and flow disturbances which has been discussed in this Chapter. There was no reported early or late mortality. The only observed complication was the occurrence of RLN injury in one (4%) patient. Re-coarctation

occurred in one (4%) patient who required re-intervention. Although authors advocated the above technique for the repair of CoA, the sample size is small and heterogeneous to support the claims in discussion section. Undoubtedly this technique can be reserved for severe arch hypoplasia involving the proximal arch as well as bovine arch group from which few patients with this anatomical variation were included in the studied population. The follow-up was extremely short for the assessment of re-coarctation as well as other post-operative parameters including HTN. This paper remains as an institutional care report, albeit with a successful immediate results.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	- Low re-coarctation rate for EEEA	- Heterogeneous population - Poor statistical analysis - Short follow-up

Table 19. Summary of Van Son et al study

2.2.3.6 Pfammatter et al

In 1996 paediatric cardiac surgeons and cardiologists from Berne Children's hospital in Switzerland published their experience in surgical management of CoA (Pfammatter 1996). In 6 years they retrospectively retrieved the clinical data of 46 patients with mean age of 12 $\pm$ 8. In the title it is mentioned that the study is focused on EEA however in operative technique section there were a variety of surgical interventions performed; which makes the surgical categorisation difficult and vague. For example when ductal tissue was seen at the time of operation the SA was transected and re-implanted after trimming the proximal arch. Although authors have not specified how many of patients underwent this particular operation, this may not be categorised as classic simple EEA. On the other hand a relatively large proportion of patients (32%) underwent excision of coarctation and extended endo-to-side anastomosis which again may not be categorised as EEA. Only 27 (59%) patients underwent EEA. Authors defined re-coarctation as a systolic blood pressure disparity of more than 20mmHg between the upper and lower limbs. Although echocardiography has been used to monitor the patients during the follow-up period; there was no criteria for echocardiographic characteristics of re-coarctation and more importantly only BP monitoring has been chosen for re-intervention: systolic BP disparity between the upper and lower limbs of more than 30 mmHg. It is important to consider that non-invasive monitoring of BP in particularly neonates is not reliable (Devnick 2013). Arch hypoplasia was not studied and it was not

clarified what criteria was applied to those of patients who underwent extended excision. Moreover if arch hypoplasia necessitated extended excision why all of these operations were performed via left thoracotomy and not median sternotomy where the exposure is more desirable. There were no early mortality on this study. Rate of re-coarctation was 13%. It would have been more accurate to consider echocardiography at follow-up as the first line of diagnosing re-coarctation; while technological advances during the 90s could have also allowed this. None of patients required anti-HTN medication at follow-up; however 11 (24%) patients demonstrated a higher right arm systolic BP above the 95 percentile. A total rate of 13% for re-coarctation has been reported with no difference between the surgical groups.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation -Post-op complication	-No difference EEA vs. EEEA	- No multivariate analysis - Short follow-up

Table 20. Summary of Pfammatter et al study

2.2.3.7 Conte et al

One of the largest and first retrospective studies which exclusively studied the outcome of CoA repair with EEEA technique, was performed by the Department of Paediatric Cardiac Surgery, Marie-Lannelongue Hospital and Paris Sud University (Conte 1995). Apparently from 1983 EEEA was the operation of choice in this institution to treat all CoA surgically. In this study 307 consecutive neonates were included with a mean age of 13 $\pm$ 8 day-old. Ninety-five (31%) patients were diagnosed with isolated CoA while the rest had concomitant congenital heart disease for which they were categorised into separate groups. Definition of arch pathology and hypoplasia was according to Moularet classification (Moularet 1976). Therefore there were three categories for hypoplasia: 1- distal arch 2- complete transverse arch 3- complex arch (for example short arch). Overall mortality was 7.5%; however this was 2% (2 patients) in isolated CoA group. Ten-year survival in isolated CoA group was reported at 98% $\pm$ 3%. The rate of post-operative chylothorax (0.9%), left phrenic palsy (0.6%) was relatively low considering extensive dissection and mobilisation of major structures in EEEA operation. No neurological deficits were reported. Although authors need to be commended for a satisfactory outcome with low post-operative complications, morbidities were not discussed in separate groups of congenital heart disease. Re-coarctation was not clearly defined but a

total of 30 (9.8%) patients presented with re-stenosis of repaired site. Patients with arch hypoplasia significantly developed more re-coarctation as compared to patients with no arch hypoplasia. Interestingly authors demonstrated that re-coarctation was associated with the degree of arch hypoplasia. As per Moularet classification the more hypoplasia extends to proximal arch the more the degree of hypoplasia. Therefore 50% of patients with proximal complex arch hypoplasia developed re-coarctation which was statistically significant as compared to other arch hypoplasia categories. While there were no difference between sternotomy vs. thoracotomy with regard to re-coarctation rate it would have been interesting to know if surgical exposure played a role in a high re-coarctation rate in this complex group of patients. It is important to consider that the proposed operation for all CoAs including isolated ones is a complex surgery which requires a learning curve to be completed by the surgeons. This was in contrast with EEA and SF techniques which are reproducible with shorter learning curves.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	-Re-coarctation more in patients with proximal arch hypoplasia	- Actuarial probability with no multivariate analysis

Table 21. Summary of Conte et al study

2.2.3.8 Han et al

Han et al from the department of Cardiovascular Surgery and Children's Hospital and Medical Centre in Seattle retrospectively studies the outcome of CoA repair in ten years (Han 1995). The age of population had a mean of 10.5-day-old. Review of medical records identified 146 patients from which 126 (86%) and 14 (10%) underwent SF and EEA techniques for the repair of CoA respectively. PA banding was a common concomitant procedure and was carried out in 62 (42%) patients at the same time with CoA repair. Early mortality was 11% (16 patients). All mortalities occurred in patients who underwent a concomitant operation for another major congenital heart disease. Mean ischaemic cross clamp was reported 24 minutes which was not difference between SF vs. EEA groups. Authors have not analysed the arch status and also there was no criteria for the definition of re-coarctation which occurred in 16 (11%) patients. Twelve (9.5 %) patients with SF and two (14.5 %) patients with EEA developed re-coarctation. All of the patients with re-coarctation underwent re-intervention. Similar to other studies discussed

in this Chapter the occurrence of re-coarctation in infants after CoA repair was mainly in the first 12 months after surgery. Authors emphasised that their data did not support the superiority of SF over EEA despite superior freedom from re-coarctation as compared to EEA technique. Authors claimed that the comparison of SF vs. EEA was not statistically significant. The preferred technique which has been performed in authors' institution was SF technique. Generally data have been poorly presented with no statistical test. Therefore it is not clear what analysis has been used to reject the null hypothesis.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	- No difference SF vs. EEA	- No criteria for arch hypoplasia - High in-hospital mortality - Heterogeneous population - No multivariate analysis - No specific follow-up

Table 22. Summary of Han et al study

2.2.3.9 Wu et al

Paediatric surgeons and cardiologists from Grantham and Queen Mary Hospital reported their study on 85 patients who underwent CoA repair in Hong Kong (Wu 1995). Isolated CoA only comprised 20% of the population and other congenital heart diseases which required correction at the same time was prevalent at 80% among the population. Predominant technique for CoA repair was SF technique with 56 (66%) patients and then EEA technique with 18 (22%) patients. Early mortality was 16.5% which was relatively high and reflects a mixed and heterogeneous population. The mean follow-up was 38.2 months covering 71 patients who survived the hospital discharge. Definition of re-coarctation was set based on two findings: 1- arm-leg systolic BP gradient of more than 20 mmHg 2- Echocardiography of repaired site where the diameter is less than 50% of descending aorta diameter. The latter criteria has been rarely used by similar studies discussed in this Chapter as it is operator dependant and subjective. The surgical techniques did not show any significant impact on the occurrence of re-coarctation; however interestingly the size of distal transverse arch, named region 4 by authors, was significantly associated with re-coarctation. This finding should have prompted the authors for further investigation of the population with regard to arch pathology. The arch has been analysed as per zones from 1 to 6 however information on transverse arch length is not available. Re-coarctation occurred in 12 (17%) patients which includes patients

with complex operations including PA banding. Assessment of re-coarctation in a mixed population with other defects with significant haemodynamic implications may not reliably examine the independent risk factors. The rate of re-coarctation was not significantly different between the surgical techniques mainly EEA vs. SF.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	- No difference SF vs. EEA	- Heterogeneous population -Arch analysis by zone definition - No multivariate analysis

Table 23. Summary of Wu et al study

2.2.3.10 Zehr et al

Zehr et al who has consistently worked on CoA and the outcomes of surgery reported a thirty year experience of their institution in managing CoA (Zehr 1995). The retrospective review of casenotes identified 179 patients with the age of less than 12-month-old. The main surgical interventions were EEA and SF in 65 (36%) and 85 (47%) patients respectively. In this study complex cardiac defects and anomalies were also included in the population. In review of institutional practice it became evident that SF technique was not initially used by the surgeons and it was first introduced in 1972; while EEA technique has been performed for repairing CoA as early as 1962. Seven (3.9%) patients died intra-operatively and 16 (8.9%) patients did not survive while still hospitalised. The relatively high early mortality reflects the heterogeneous population with complex cardiac diseases. The patients fundamentally have been categorised as per decade of operation into three decades and isolated CoA hardly comprised a quarter of patients in each group. This means that authors did not attempt to reduce the heterogeneity of their population by categorising them into at least isolated and non-isolated CoA. This has led to unreliable results which may not be applied to isolated CoA management. This study bias also applies to post-operative complications. Rate of total left phrenic nerve injury, paraplegia and RLN injury were reported at 3.3% (6 patients), 0.5% (1 patient) and 0.5% (1 patient) respectively. Re-coarctation occurred in 23 (16.4%) patients. There is no defined criteria for re-coarctation and it seems an arm-leg gradient of more than 30 mmHg was evident in patients with re-coarctation. Authors have presented a long and elaborated table of univariate and multivariate analysis of confounding factors which may not elicit a meaningful results while there were patients included in this analysis that CoA is not the

primary pathology in them. The rate of re-coarctation in EEA was 23% vs. SF which was reported at 11%. In this analysis patch aortoplasty was significantly associated with re-coarctation but there was no statistical difference between SF and EEA in re-coarctation occurrence. Interestingly absorbable sutures which were monofilament, caused more re-coarctation compared to non-absorbable sutures. PA banding and complexity of concomitant operation was significantly associated with a high risk of re-coarctation. The era of operation which was categorised into three separate decades was not an independent risk factor for the occurrence of re-coarctation.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	- No difference SF vs. EEA	- Univariate, multivariate and actuarial probability performed - Heterogeneous population - Long follow-up

Table 24. Summary of Zehr et al study

2.2.3.11 Merrill et al

Merrill et al from the department of Cardiac and Thoracic Surgery and Division of Paediatric cardiology and Vanderbilt University school of Medicine in the United States retrospectively studied the outcome of CoA repair in a relatively long period of time in 139 neonates. The mean age was 10-day-old. The majority of operations were performed using two main techniques: EEA in 38 (27%) patients and SF in 92 (67%) patients. Complex cardiac defects and anomalies were also included into the population as a coexisting pathology. PA banding and other concomitant procedures were also performed in this population. A large number of patients (92%) presented with congestive heart failure (CHF) which may reflect a delay in performing the operation from the time that these patients were diagnosed with CoA. It is important to consider that in years prior to 80s the pre-operative management of CoA was without PGE_1. Only 26% of patients with isolated CoA were identified in the population. Early total mortality was 7.2%; however all mortalities occurred in the complex groups and patients with isolated CoA were discharged from the hospital with no mortality. During the follow-up period 20 patients died from which none of them belonged to the isolated CoA group. For follow-up at 5 years 15 patients from EEA and 24 patients from SF group were available. A systolic BP gradient between upper and lower limbs along with 50% luminal narrowing of the repair site, were set as the definition of re-coarctation. For luminal narrowing there was no

reference for comparison. In previous discussed studies descending aorta usually at the level of diaphragm has been mentioned as the reference location. Authors did not find the hypoplastic arch as an independent risk factor for re-coarctation; however there is no mention of a definition for arch hypoplasia in this study. Interestingly at 5 years follow-up patients who underwent CoA repair with SF technique had a significant superior freedom from re-coarctation as compared to EEA technique.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	- SF superior technique	- High re-coarctation rate - Heterogeneous population - Kaplan-Meier curves and Cox proportional hazard for statistical analysis

Table 25. Summary of Merrill et al study

2.2.3.12 Quaegebeur et al

In a multi-centre large scale retrospective study medical records of 322 patients who underwent surgical repair of CoA were analysed (Quaegebeur 1994). The follow-up in these patients was relatively short with a mean of 13 months ranging from 3 days to 32 months. Complex coexisting congenital heart disease including the interrupted arch was included in the study population. The main techniques used to repair the CoA were EEA in 27 patients (8%), EEEA in 92 patients (29%) and SF in 112 patients (38%). The non-risk adjusted survival in the population which indeed included complex cases, for one and two years were 93% and 84% respectively. Similar to counterpart studies PA banding was prevalent in the population for staged operations. In the multivariate analysis the concomitant congenital heart disease including VSD and PA banding were significantly associated with a high risk of mortality which was not surprising. In a specific group of arch hypoplasia which was not clarified or defined by authors at least in the methodology section, extension of end-to-end repair proximal to LCCA was significantly associated with mortality. This is a complex procedure which is usually performed via median sternotomy for better access. Moreover the pathology falls into the category of a congenital heart disease coexisting with CoA, rather than a subcategory of CoA alone. Re-coarctation occurred in 6 (4%) patients who underwent EEA. The re-coarctation rate for EEEA and SF techniques were 4% (one patient) and 5% (6 patients) respectively.

There was no statistically significant difference between the operative techniques with regard to re-coarctation

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	- No difference SF vs. EEA vs. EEEA	- Univariate and multivariate analysis performed - Heterogeneous population

Table 26. Summary of Quaegebeur et al study

2.2.3.13 Van Heurn et al

Van Heurn et al published their outcomes in the surgical treatment of CoA with a focus on EEEA (Van Heurn 1994). Within a time frame of 5 years at the end of 80s, medical records of 151 patients who underwent CoA repair were retrospectively analysed. Nearly half of patients (48%) were diagnosed with isolated CoA; however the other half had complex concomitant congenital heart disease which required surgical intervention at the same time. Predominant surgical technique was EEEA with 77 patients (50%) and then EEA with 43 (28%) and SF with 15 (10%) patients. The EEEA group comprised a rather heterogeneous operations and not all of them necessarily included extended excision with end-to-end anastomosis. In this group 31% underwent classic EEEA while 2.6% had the extension of incision into the SA flap and 4% had a combinations of both. The two latter techniques which were called radical extension by authors are rarely used and they are preserved for special circumstances or as a bail-out procedure. Therefore the EEEA population was mixed with different approaches and has been analysed as one technique or group. Arch hypoplasia diagnosis in this study was rather subjective. There was no definition as per measurements while echo report and surgeon judgment only were the criteria used to diagnose a patient with arch hypoplasia. Authors have defined re-coarctation as a peak pressure gradient of 20 mmHg or more across the repaired site. Overall early mortality occurred in 13 (8.6%) which is a relatively high early mortality however this represents all group of patients including the complex cases. Early mortality in EEA, EEEA and SF group of patients were 2.6%, 3.3% and 0.6% respectively (calculated as per total population). Post-operative complications and comorbidities have been analysed in the whole population while due to a high degree of heterogeneity the analysis may not elicit reliable results for the assessment of peri-operative complications in CoA. Neurological deficit and necrotising enterocolitis (NEC) were observed in two (1.3%) patients for each complication. Early mortality was associated with the complexity

of the procedure and concomitant cardiac anomalies; however there were no differences between the surgical techniques with regard to early mortality. Not surprisingly more death occurred in the complex group during the follow-up period. A Kaplan-Meier curve demonstrated that the EEEA was significantly associated with a reduction in the rate of re-coarctation and patients with EEEA technique had a higher rate of freedom from re-stenosis. Although authors demonstrated the superiority of EEEA it seemed too radical to apply this technique to a simple isolated CoA which can be dealt with by a much simpler procedure. One major drawback in this study was not considering the role of hypoplastic arch in re-coarctation which was stemmed from a subjective definition for arch hypoplasia.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation -Post-op complications	- EEEA superiority	- Univariate and multivariate analysis performed - Heterogeneous population

Table 27. Summary of Van Heurn et al study

2.2.3.14 Amato et al

The paediatric cardiac surgeons who first describe the operative technique for EEEA (Amato 1977), retrospectively studies the surgical treatment of CoA by various techniques in their institution between 1979 and 1990 (Amato 1991). Review of medical records retrospectively identified 139 patients with a wide spectrum of age ranging from 1-day-old to 21-year-old. The majority of population had associated complex congenital heart disease (63.6%). The EEA technique was used in 27 (18%) of patients and the SF technique in 79 (52%) patients. There were also a very wide range of other procedures performed from PTFE or Dacron patch aortoplasty to SA flap augmentation which are currently obsolete procedures and will not be discussed in this thesis. Early mortality occurred in 2 (1.3%) patients and by considering the complex cases it was indeed a very low mortality by 80s standards. Re-coarctation was defined as the systolic BP disparity between the upper and lower limbs of more than 20 mmHg. There was no clarification on follow-up mean or median. One (3.7%) patient in EEA group and 5 (6.3%) in SF group developed re-coarctation requiring re-intervention. There were no occurrence of re-coarctation in patients who received patch aortoplasty or interpositional graft. This is highly likely due to the fact that these patients are usually older and by considering the wide spectrum of age in this study these procedures have probably performed in adult

patients. The worst outcome belonged to SA flap re-implantation where the SA button is re-implanted on the coarctation site. This operation is rarely performed today. Surprisingly there was no statistical analysis of the results and therefore no test of significance or examining the null hypothesis has been performed. For this reason the quality of the study remains at the level of an institutional case report which may not influence the CoA practice. The weakness of the study was particularly augmented while the authors and their institution are pioneers in the field of CoA surgical treatment. By simple comparison of techniques it could be perceived from the discussion section that authors wanted to move away from SF and preferred EEA as an alternative in their institution. While the title emphasised on the "extension" there were no data or analysis presented to suggest any benefit in extending the anastomosis. Therefore it seems the title is misleading and not appropriate for the text. Finally the authors proposed a classification system which includes concomitant complex operation and also the extent of coarctation tissue into the arch. The classification is not used currently after more than 20 years from publication of this study. The main reasons are: 1- CoA is a separate congenital disease and when coupled with more complex cases it may not even become a secondary lesion, so it should be analysed as an isolated disease. 2- Extension of coarctation tissue or extension of tubular hypoplasia into the arch is separate from arch hypoplasia which is on the basis of accurate pre-operative measurements by echocardiography images or other imaging modalities such as MRI. Arch hypoplasia other than isthmus involvement is a separate pathology and also should be considered as a separate congenital disease which commonly co-exist with CoA. Similarly this is commonly seen with VSD.

Patient group	Outcomes	Key results	Comments
- Children and Adults	- Mortality - Re-coarctation	- EEA superiority	- Heterogeneous population - Poor statistical analysis

Table 28. Summary of Amato et al study

2.2.3.15 Messmer et al

Paediatric surgeons from the Department of Thoracic and Cardiovascular Surgery and Paediatric Cardiology of Aachen in Germany retrospectively studied 53 infants (age < 1-year-old) who underwent CoA repair (Messmer 1991). The main surgical intervention included EEA in 11 (20%) and SF in 20 (37%) patients. The CoA population was mixed with patients who presented with a concomitant complex intra-cardiac defect requiring surgical intervention at the same time. This included concomitant operations as complex as surgery for HLHS. Re-coarctation was defined as a difference between systolic BP of upper and lower limbs of more than 20 mmHg while echocardiography was not available for all patients. Early mortality in total was 7.5% however 2 (3.7%) patients from SF group did not survive while hospitalised. There were no early mortalities in EEA group. There was no mention of post-operative complications and comparison between the groups of surgical technique. Re-coarctation occurred in one patient (9%) from EEA group. The rest of re-coarctation (8 patients) during the follow-up period occurred in the group of surgical techniques other than SF and EEA i.e. patch aortoplasty or SA displacement. In methodology the operative techniques have been elaborately described while there was no mention of statistical analysis. There was no test of significance. Interestingly the authors have used absorbable sutures for EEA and SF cases with polydioxanone or PDS (Ethicon, Cincinnati, Ohio).

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	- No difference SF vs. EEA	- Heterogeneous population - Poor statistical analysis

Table 29. Summary of Messmer et al study

2.2.3.16 Sciolaro et al

Sciolaro et al retrospectively studied the patients who underwent CoA repair in their institution with a focus on comparing SF technique with EEA (Sciolaro 1991). They have modified the conventional EEA technique where instead of a circular end-to-end they made the incision obliquely to create an oval end-to-end. They hypothesised that this may reduce the risk of contracture which may occur at a circular suture line leading to re-stenosis. A total of 56 patients underwent CoA repair with two techniques only: EEA (40%, 22 patients) and SF (60%, 34 patients). The population included concomitant congenital heart disease for which a simultaneous procedure has been performed. Total

early mortality occurred in 2 patients (3.5%). In authors' institution SF technique was introduced in 1979. The 7-year actuarial survival in patients who were younger than 3-month-old (86% ± 9%) was lower than those of older than 3-month-old (94% ± 3%). Clearly complex cardiac anomalies played an important role in this outcome and the survival results may not be applied to isolated CoA. Re-coarctation was not defined and post-operative complications were not analysed or compared between the groups. Freedom from re-coarctation was 93% ± 6% and 53% ± 20% in SF and EEA groups respectively; which was statistically significant. It is notable that this significant difference was observed in patients who were younger than 3-month-old. The difference in freedom from re-coarctation in patients who were older than 3-month-old was not significant between the groups. Similarly there was no difference between the two groups with their overall population. This study is one of the rarest studies in the literature which examined the impact of training in theatre on the outcome of CoA. In authors' institution trainees performed 10 (18%) operations as the primary operator while 46 (82%) operations were performed by the responsible consultant. Re-coarctation occurred in 3 (30%) patients whose operation was performed by a trainee vs. 4 (8.6%) patients in consultant group. Although there is a difference but this was not statistically significant ($p < 0.1$). In summary authors have advocated SF for patients younger than 3-month-old and an "individualised" decision on the approach of choice to operate on patients who are older than 3-month-old.

Patient group	Outcomes	Key results	Comments
Children < 4 yrs	- Mortality - Re-coarctation	- SF superiority	- Actuarial probability with no multivariate analysis

Table 30. Summary of Sciolaro et al study

2.2.3.17 Shrivastava et al

Shrivastava et al from Southampton General Hospital retrospectively reviewed the case notes of 110 patients who underwent the repair of CoA between 1974 and 1988 (Shrivastava 1991). Patients' age ranged from 1-day-old to 1-year-old. The major surgical techniques which were compared later were EEA in 23 (20%) and SF (83 (75%). Similar to majority of studies discussed in this Chapter other coexisting congenital heart diseases were included in this population. Thirty-nine (35.5%) patients with isolated CoA were identified. Early mortality occurred in 9 patients (8.2%) in total; however in isolated CoA group was 5.1%. Chylothorax occurred in 3 (2.7%) patients. There was no specified

definition of re-coarctation; however 23 (22.7%) patients were identified with a peak pressure gradient of more than 20 mmHg across the repair site out of which 12 patients underwent redo surgery. Interestingly in majority of these patients synthetic patch has been used to redo the CoA repair. There was no report of outcome and in particular the incidence of aortic aneurysm in this group of patients with redo surgery. Type of surgery and the technique by which CoA has been repaired was not an independent risk factor for the occurrence of re-coarctation. Inclusion of complex cases in this population has made the results on CoA unreliable.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	- No difference SF vs. EEA	- Heterogeneous population - Only univariate analysis

Table 31. Summary of Shrivastava et al study

2.2.3.18 Kron et al

At the beginning of 90s paediatric surgeons from University of Virginia Health Sciences Centre published their results on the management of CoA in the past decades (Kron 1990). This study covers a large period of time from 1967 to 1989 identifying 197 patients who underwent surgery for CoA repair. The casenotes were studied retrospectively which revealed that 76 (39%) patients underwent EEA and 58 (30%) underwent SF techniques. The mean follow-up is not clarified; however authors have used echocardiography for the diagnosis of re-coarctation at out-patient clinics after discharge. A peak gradient of 30 mmHg and greater was set as the definition of re-coarctation requiring re-intervention. Early mortality in EEA and SF groups were 3 (1.5%) each. There was no analysis of early post-operative complications and the comparison between the groups. Rate of post-operative aneurysm was significantly high in patients who underwent repair of CoA using Dacron path while this occurred in 9 patients out of 56 patients (16%). There were no aortic aneurysm associated with SF or EEA technique. Younger patients were significantly more at risk of re-intervention as compared to older population. This finding has also been observed on multiple studies appraised in this Chapter. Statistical analysis has confirmed that SF technique is significantly associated with higher freedom from re-coarctation as compared to EEA technique.

Patient group	Outcomes	Key results	Comments
- Children	- Mortality - Re-coarctation	- SF superiority	- Heterogeneous population - Poor statistical analysis

Table 32. Summary of Kron et al study

Author	Year	Location	Age (days)	Follow-up (years)	Total	Operation N (%)			Re-coarctation N (%)			In-hospital mortality N (%)			Superior technique
						EEA	EEEA	SF	EEA	EEEA	SF	EEA	EEEA	SF	
Jelly	1999	Saudi Arabia	21+/-7	25 (6 - 11)	86	0	7 (8%)	54 (63%)	0	5 (20%)	4 (8%)	Total= 14%			EEEA + SF
Backer	1998	USA	21	1.7 +/- 1.5	55	0	55 (100%)	0	0	2 (3.6%)	0	0	1 (1.8%)	0	N/A
Cobanoglu	1998	USA	24.2+/-22.1	7.8 +/- 4.1	86	39 (45%)	0	47 (55%)	5 (5.8%)	0	4 (4.6%)	5.10%	0	8.50%	No difference
Seirafi	1998	USA	132 (1 - 33 yrs)	7.5 (0 - 24)	176	88 (50%)	21 (12%)	43 (25%)	Total=15% (no difference)			Total= 7.5%			No difference
Van Son	1997	Germany	22 (5 - 39)	1.5	25		25 (100%)	0	0	1 (4%)	0	0	0	0	N/A
Pfammatter	1996	Switzerland	12+/-8	2 (1 - 7.5)	46	27 (59%)	15 (32%)	0	Total=13% (no difference)			0	0	0	No difference
Conte	1995	France	13+/-8	5+/-3	307	0	307 (100%)	0	0	30 (9.8%)	0	0	1 (2%)	0	N/A
Han	1995	USA	10.5 (1 - 30)	Not Specified	146	14 (10%)	0	126 (86%)	2 (14.2%)	0	12 (9.5%)	Total= 15%			No difference
Wu	1995	Hong Kong	15.6 +/- 8.5	3.2 +/- 3.1	85	18 (22%)	0	56 (66%)	2 (11.1%)	0	9 (16%)	Total= 16.5%			No difference
Zehr	1995	USA	25 +/- 53	13.8+/-10.4	179	65 (36%)	0	85 (47%)	23.0%	0	11.0%	Total= 3.9%			No difference
Merrill	1994	USA	10.8 (1 - 28)	3.6 (0 - 26.6)	139	38 (27%)	0	92 (67%)	Total= 13.9%: 5-year (SF superior)			Total=7.2%			SF
Quaegebeur	1994	USA	6 (0 - 23)	1.1 (0 - 2.7)	322	27 (8%)	92 (29%)	112 (38%)	6 (4%)	1 (4%)	6 (5%)	Total=15%			No difference
Van Heurn	1994	UK	12 (2 - 90)	Not Specified	151	43 (28%)	77 (50%) *	15 (10%)	11 (26%)	8 (10%) *	6 (40%)	4 (2.6%)	5 (3.3%)	1(0.6%)	EEEA
Amato	1991	USA	(1 - 21 yrs)	Not Specified	139	27 (18%)	0	79 (52%)	1 (3.7%)	0	5 (6.3%)	Total=2 (1.3%)			EEA~
Messmer	1991	Germany	0.9	3 (0 - 9.6)	53	11 (20%)	0	20 (37%)	1 (9%)	0	0	0	0	2 (3.7%)	No difference
Sciolaro	1991	USA	Not Specified	3.3 +/- 2	56	22 (40%)	0	34 (60%)	10 (18%)	0	5 (9%)	Total=2 (3.5%)			SF^
Shrivastava	1991	UK	40.3 (1 - 364)	5.3 (1 - 15)	110	23 (20%)	0	83 (75%)	6 (5.4%)	0	7 (6.3%)	2 (1.8%)	0	7 (6.3%)	No difference
Kron	1990	USA	Not Specified	Not Specified	197	76 (39%)	0	58 (30%)	15 (21%)	0	5 (9.1%)	3 (1.5%)	0	3 (1.5%)	SF

Table 33. Summary of published literatures 1990 – 1999: EEA: resection of coarctation and End-to-End Anastomosis; EEEA: resection of coarctation and Extended End-to-End Anastomosis; SF: no resection and Subclavian Flap; N/A: Not applicable (Study examines only one technique and there is no comparison of other techniques); Age: Median (range) or Mean ± Standard deviation or median alone (yrs: years, m: months, if not specified it is days); Follow-up: Median (range) or Mean ± Standard deviation or median alone, Number (%) for surgical techniques.

* EEEA group included other techniques; ~ No test of significance, ^ Older than 3-month-old patients

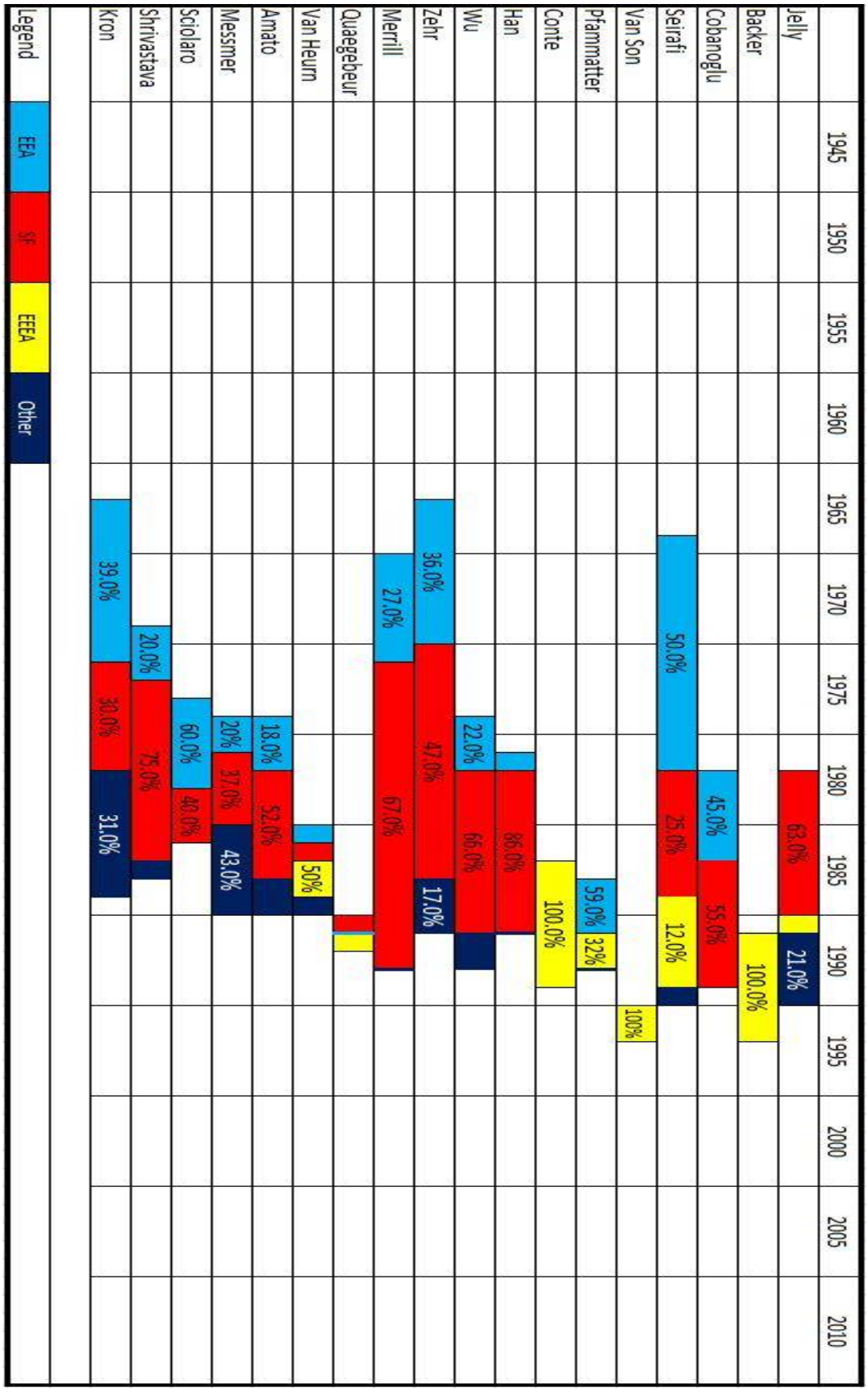

Figure 14. Published literatures 1990 – 1999. Horizontal bar shows the study period. The surgical techniques are demonstrated in different colours (legend) with the percentage of the used technique in the specified study period.

2.2.4 Year 2000 – 2016

2.2.4.1 Tulzer et al

One of the most recent retrospective studies was conducted by Tulzer et al in Austria (Tulzer 2016). The focus of this study was on the outcomes of excision of coarctation tissue in patients with arch hypoplasia which may or may not be coupled with VSD. The two techniques of EEA and end-to-side were analysed. The data for 183 patients younger than 12-month-old who were operated in the past 17 years from 1996 was collected. The study included a heterogeneous population while hypoplastic arch with haemodynamic significance as well as sternotomy approach were all included. Median sternotomy was performed for patients with more complex anomaly i.e. hypoplasia of proximal arch. All of patients who has their operation via median sternotomy were placed on cardiopulmonary bypass (CPB). In few of these operations deep hypothermic circulatory arrest (DHCA) and antegrade cerebral perfusion was used. The operative approach via median sternotomy was more utilised through the time, however this was correlated to the complexity of the case rather than the surgeon's choice. This complexity is reflected in the univariate analysis of pre-operative characteristics. There is a significant difference between patients who underwent EEA versus end-to-side while the severity of aortic hypoplasia, critical pre-operative status (duct dependant) and pre-operative PICU stay are all higher in end-to-side group. The reported in-hospital mortality was 0%. Paraplegia occurred in one patient with aberrant right SA. The study did not find any other immediate postoperative complications including recurrent laryngeal nerve (RLN) palsy or bronchial compression. The definition of re-coarctation was "presence of a typical coarctation Doppler flow pattern with increased systolic and end-diastolic velocities and/or difference of more than 15 mmHg in systolic BP at rest between upper and lower limbs". Eleven patients were detected with re-coarctation (7.9% in 139 patients available at follow-up) while 3 of them underwent re-operation and the rest had percutaneous intervention. Freedom from re-intervention in 10 years was 90.12 %. Interestingly the patients who had their coarctation repaired via median sternotomy developed less re-coarctation as compared to the patients who underwent left thoracotomy. It is apparent from authors' comment that repair of complex arch hypoplasia which may require CPB via median sternotomy were performed via thoracotomy in early years. In fact this conclusion may not be applied to all coarctation repairs performed via thoracotomy. It is not clear if there

was a criteria for definition of arch hypoplasia (distal vs. proximal) or institutional strategy for surgical approach sternotomy vs. thoracotomy. Low birth weight (LBW) was not associated with the rate of re-coarctation.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation -Post-op complications	- Low re-coarctation rate for EEEA	-Univariate and multivariate analysis - Heterogeneous population

Table 34. Summary of Tulzer et al study

2.2.4.2 Mery et al

Mery et al from Texas Children Hospital studied 343 patients from 1-day-old to 18-year-old who all had their coarctation repaired via left thoracotomy (Mery 2015). The majority of this population underwent excision of coarctation completed by either EEEA or EEA. Only 2% underwent the repair of coarctation with SF technique. Intra-operative mortality was 1% and all patients were neonates. Two patients from older children age category underwent coarctectomy with an interpositional graft due to a large coarctation. Four (1.1%) patients died intra-operatively however there was no mortality on follow-up. Post-operative complications are reported as per age group categories: neonate (0 – 30 day-old), infant (1 – 12 month-old), children (age greater than 1 year-old). Surprisingly the most common complication was pneumothorax requiring chest tube insertion. This is a recognised and rather rare complication which occurs due to micro-injuries to the left lung while retracted by a swab or instruments. The length of hospital stay was longer in neonates where they comprised the sicker group of patients with higher rate of pre-operative intubation, ICU stay and PGE_1 infusion. A high peak velocity of more than 2.5 m/s was observed in a quarter of patients. Although there is no difference between the age group with regard to immediate post-operative high gradient across the repaired site, it is not clear this complication is related to which surgical approach. Moreover the authors did not clarify what strategy was taken into account to address the immediate detected high gradient, where in many institutions it is considered as repair failure promoting a redo repair operation. The high gradient post-operatively was significantly associated with the rate of re-coarctation. The criteria for re-intervention was peak velocity of 2.5 m/s across the repaired site. During the follow-up period 14 (4%) patients, all from EEA group (not statistically significant) and mainly neonates at the time of

surgery (not statistically significant) underwent re-intervention for re-coarctation. Re-intervention in the form of a redo surgery was performed in four patients and the rest received balloon angioplasty percutaneously. The anatomy of aorta with regard to arch hypoplasia: proximal vs. distal, was not a risk factor to re-coarctation. The freedom from re-intervention in a 10-year time frame was 95%. It is of note that a third of patients who had successful repair of coarctation were still hypertensive at follow-up. There was a significant link between the peri-operative HTN and long term refractory high BP.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	- No difference SF vs. EEEA vs. EEA	- Heterogeneous population - Univariate and multivariate analysis

Table 35. Summary of Mery et al study

2.2.4.3 Adams et al

Penn State Hershey Medical Cent ran a study to examine the long-term results of SF in neonates who underwent surgery between 1966 and 1991 (Adams 2013). A total of 55 patients were studied who comprised a heterogeneous population from which 71% of patients had complex concomitant congenital heart disease with significant haemodynamic implications. Therefore the in-hospital mortality rate was as high as 12.7%. Ironically the lower long term survival in complex group versus simple (isolated) coarctation was not statistically significant on Kaplan-Meier curve (log rank=0.07). Post-operative complications are reported in the context of early mortality rather than reporting all spectrum of complications. This makes it impossible to assess the complications in isolated coarctation group. The reported complications are as follows: neurological deficit (not clear what the nature of deficit is), endocarditis (possibly with more complex congenital heart valve disease background), HTN crisis, pneumonia and arrhythmia. None of the mentioned complications are commonly associated with CoA surgery or reported by other cohorts. The authors have not assessed the immediate post-operative gradient across the repaired site which is important in the assessment of post-operative re-coarctation. Left arm size was not examined by measurement at follow-up however patients were asked about noticing any discrepancies on telephone interviews; where no positive answers obtained. Re-coarctation occurred in three patients from a total of 16 patients who presented with an isolated coarctation and underwent SF repair. All three

patients underwent re-operation from which two patients did not survive. This study similar to previous studies (Mery 2015) reported a high rate of HTN at 33% in treated patients during the follow-up period. As authors covered a relatively long time frame where CoA operation was not as developed as today, they emphasise that mortalities particularly in isolated CoA repair can be attributed to the era of practice. Although this is not examined statistically, in a previous study (Mery 2015) the year of operation was not an independent risk factor for mortality or re-coarctation.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation - Post-op complications	- Low mortality and re-coarctation in SF patients	- Heterogeneous population -Univariate and multivariate analysis

Table 36. Summary of Adams et al study

2.2.4.4 Troung et al

The outcome of isolated CoA repair via left thoracotomy which was performed between 2005 and 2011 was investigated retrospectively at Utah Primary Children's Medical Centre (Truong 2014). Pre-operative and post-operative two-dimension echocardiography images were examined. The studied population with regard to age and pathology is homogeneous with a focus on neonates and infants < 90-day-old who presented with an isolated CoA. The rate of re-coarctation was inversely proportional to patient's weight, meaning LBW was an independent risk factor for future repair failure. This also has been hypothesised by many surgeons while they believe that suturing small size structures to each other may not necessarily address the lumen integrity which may lead to stenosis or impingement. The aortic dimensions including transverse arch, distal arch and arch diameter did not influence the occurrence of re-coarctation. The patients with small transverse arch as low as z = - 2.8 had successful repair with no re-coarctation. Interestingly this was also applied to the proximal arch where repair is more challenging via left thoracotomy however there is no mention of conversion to sternotomy in this study. High sino-tubular junction (STJ) measurements were associated with a high risk of re-coarctation and this was the only parameter from the entire aortic measurements which was identified as an independent risk factor. The authors' explanation about this rather unusual finding was that STJ is a surrogate for proximal size of the aorta and when

STJ is increased this means there is a considerable discrepancy between the proximal and distal of aorta where CoA is located. Therefore distal of aorta and coarctation area may require more aggressive management during the repair to minimise the discrepancies. This hypothesis needs haemodynamic studies to examine the role of shear stress and energy loss on the aortic wall particularly the repaired area. Post-operative increased velocity across the repaired site at 2.5 m/s was significantly associated with re-coarctation in future. Accepting high velocity or pressure gradient across the repaired site by the surgeon is rather prevalent and has been observed frequently. There has been an argument on whether to define a high gradient as residual coarctation or re-coarctation; which seems a grey area with no consensus. Diastolic flow continuation in abdominal aorta immediately after surgery was not an independent risk factor for re-coarctation. There were no mortalities caused by cardiac events in-hospital or during the follow-up period. Authors also studied the impact of suture material, Prolene vs. Polydioxanone on re-coarctation which did not show any difference. This is an important finding while historically non-absorbable sutures are deemed to restrict the growth of repaired location therefore causing re-coarctation. An increased post-operative gradient across the repaired aorta was associated with a high risk of re-coarctation. The rate of re-coarctation was 8% with no difference between the surgical techniques. Generally the aim of this study was to create a model based on aortic measurements to predict the incidence of re-coarctation after repair. Finally authors emphasised that their study is limited to a short period of follow-up, and low incidence of re-coarctation.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	- No difference EEA vs. EEEA	- Heterogeneous population -Univariate and multivariate analysis - Short follow-up

Table 37. Summary of Troung et al study

2.2.4.5 Kumar et al

The Children's National Medical Centre in Washington DC studied their CoA repair in 8 years (Kumar 2011). The incentive for running the study was the lack of evidence and a paucity in the literature regarding the impact of surgical technique on re-coarctation rate as the most common post-operative complication. The agreed definition of re-coarctation

on which the study was based, was different from the similar studies where majority agreed that the peak velocity of 2.5 m/s across the repaired site is defined as re-coarctation. The authors defined re-coarctation as "a resting BP gradient of greater than 20 mmHg with a corresponding decrease in the diameter of the aorta by 50%". With this definition the rate of coarctation was reported 14.3% (11 patients). Similar to Truong study (Truong 2013) the size of transverse arch was not associated with re-coarctation. The size of left ventricular out-flow tract (LVOT) also did not affect the repair failure. However the growth of ascending aorta at 3 months follow-up was significantly more in patients who did not suffer from re-coarctation vs. patients who developed re-coarctation requiring intervention. The size of proximal ascending aorta was also studied and in contrast with what Truong et al (Truong 2013) demonstrated, it was inversely proportional to re-coarctation incidence; meaning the smaller the proximal ascending aorta the more the risk of re-coarctation. Authors reported an institutional policy to manage the immediate post-repair intra-operative high pressure gradient. They advocated that surgeon needs to wait up to 30 minutes for the post-repair pressure gradient to settle and if not the repair needs to be revised. The increase of post-operative BP and persistent HTN was significantly associated with an increased pressure gradient across the repaired site. Interestingly the authors demonstrated that in patients with re-coarctation the pressure gradient starts to increase almost immediately after surgery. The increase of gradient was associated with the risk of re-coarctation. This was more evident when the patients who later developed re-coarctation, at the time of discharge had a recorded BP of almost double of patients' BP with no future re-stenosis. This finding was further examined on a receiver operating characteristic curve (ROC) which showed that an increased BP gradient between upper and lower limbs prior to discharge is an independent risk factor as well as a predictor of re-coarctation during the follow-up. A systolic BP gradient cut-off of 13 mmHg at the time of discharge with sensitivity and specificity of 91% and 76% respectively, was identified as the re-coarctation predictor. The systolic BP gradient between the upper and lower limbs was deemed by authors more reliable than the intra-operative pressure gradient across the repaired site. They argued that several factors may influence the accuracy of immediate gradient particularly shortly after cross clamp release. They referred to a study in which the pathophysiology of aortic cross clamp and its influence on haemodynamic after releasing the clamp has been examined (Gelman 1995). In this study the release of the clamp has been associated with reactive hyperaemia and an increase in post-coarctation venous system compliance which both can lead to

vasodilatation and a drop in BP. Although in majority of CoA repairs via left thoracotomy the heart is beating and perfused by the coronary arteries, there is some degree of myocardial depression after releasing the clamp due to accumulation of vasoactive and myocardial depressant metabolites. Hypothermia is also another cofounding factor which may influence the accuracy of the pressure gradient. This is due to the discrepancies between the upper and lower body temperature during the operation by cooling blanket. Therefore the upper and lower body vasculature may behave differently while re-warming and at the conclusion of surgery. Authors also insinuated that anaesthetic medications may augment the vasodilatory state which in return decreases the specificity of the pressure gradient. Moreover the LV function as the main contributor to the flow across the aorta including the repaired site can reduce the pressure gradient when the function is subnormal or abnormal. The main surgical technique by which the surgical repair of CoA was performed were EEA and EEEA. There was no difference between the two techniques with regard to the incidence of re-coarctation. All re-coarctations but one occurred in the first year of follow-up.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation - Post-op complication	- No difference EEA vs. EEEA	- Heterogeneous population -Univariate and multivariate analysis

Table 38. Summary of Kumar et al study

2.2.4.6 Bentham et al

Department of Paediatric Cardiology and Cardiothoracic Surgery, John Radcliffe Hospital in Oxford studied the catheter-based management of re-coarctation of patients who had previously undergone CoA repair (Bentham 2010). In 6 years 89 patient presented with CoA requiring surgical repair. This population represent a rather heterogeneous population where other complex congenital heart disease including interrupted arch anomaly coexisted with CoA. The study is focused on the 11 patients who developed re-coarctation during the follow-up; therefore a thorough demographic data presentation for the whole population who underwent surgery is not available. This includes no mention of age as well as follow-up characteristics. Majority of patients underwent SF repair of CoA; however patch aortoplasty and interpositional graft have also been performed without being specified in which group of patient. Although 11

patients were identified with re-coarctation, only 6 of them presented with isolated CoA. The rest of patients had other major cardiac defects which does not allow the assessment of re-coarctation while the primary pathology is not CoA. Authors have not reported the list of concomitant complex congenital heart disease coexisted with CoA and listed them as "complex" only which makes the analysis of this high risk group where the majority of mortality has occurred, more difficult. The location of re-coarctation was identified in one patient proximal to the brachiocephalic artery (BCA) without clarification of initial surgical intervention as the location of stenosis is extremely rare in the context of isolated CoA. The rest of 10 patients had repair failure due to the stenosis or re-coarctation distal to the origin of the left common carotid artery (LCCA). Although the surgical technique in this group was also not investigated, one can speculate that all of these patients underwent SF technique were subclavian artery is absent at follow-up imaging. All patients with re-stenosis underwent catheterisation and placement of at least one stent. The mean age of this group is reported as young as 46-day-old. A median of 51 days after surgery has been reported for the stent placement but it is not clear why these infants with less than 2 months after surgery were not operated for redo repair of re-coarctation. It is not surprising that at an average follow-up of 2.9 years with a range of 0.3 to 5.5 years re-catheterisation performed in 13 occasions. This included balloon dilatation of a previously stented aorta. Authors at discussion section agreed that stent deployment in early life is controversial however due to poor data presentation from the initial surgical intervention and native aorta anatomy they failed to establish a sensible reason for re-coarctation and rationalising the deployment of stent in this group of patients. There is no statistical analysis of the impact of different surgical approach on re-coarctation.

Patient group	Outcomes	Key results	Comments
- Not specified	- Re-coarctation	-Successful endovascular intervention for the management of re-coarctation	- Univariate analysis only - The initial population of CoA repair is not presented

Table 39. Summary of Bentham et al study

2.2.4.7 Dehaki et al

A 10-year experience in the management of 188 patients with CoA has been reported by Iranian congenital heart surgeons (Dehaki 2010). This study included patients under 14-

year-old. In this population other congenital heart diseases such as Shone's complex, severe arch hypoplasia and mitral stenosis are included therefore the study heterogeneity makes it difficult to assess the CoA and the treatment outcome as an isolated disease. It is reported that PDA is highly prevalent but it is not clear how many of these patients were duct dependant or on PGE_1 pre-operatively. The morphology of CoA is categorised as discrete with 78% of patients in this group and long segment with 21% of population. Patch repair of the coarctation was the dominant surgical technique which may represent the institutional preference between 1994 and 2004. The re-stenosis was defined as the pressure gradient of 25 mmHg or more across the repaired site which at follow-up identified a relatively large number of patients: 54 (29%); who later underwent catheterisation. Re-coarctation was confirmed in 19 (10.1%) patient who required either stenting or balloon dilatation. The highest recurrence rate of stenosis was observed in the patch aortoplasty group and the lowest was in patients who underwent SF repair of CoA. There is no statistical analysis on this finding and it is not clear how significant the finding is. Univariate analysis revealed that patients with discrete morphology of CoA are less at the risk of re-coarctation as compared to the long segment group. The significant variables were not entered a multivariate model. Authors performed the same statistical analysis on the presence or absence of PDA which showed re-coarctation is significantly associated with the absence of PDA meaning less patients developed re-stenosis of repaired site when at presentation had a PDA. This is not elaborated at the discussion section and it is not clear why authors focused on this aspect of the disease. Generally data has been poorly presented with minimal statistical support.

Patient group	Outcomes	Key results	Comments
Not specified children	- Mortality - Re-coarctation	- SF superiority	- Poor statistical analysis

Table 40. Summary of Dehaki et al study

2.2.4.8 Brown et al

One of the largest group of patients who underwent surgical repair of CoA with a relatively long follow-up, was studied by Indiana University School of Medicine in the United States (Brown 2009). They retrospectively studied 1,012 patients with a median follow-up of 14.2 years ranged from 2 weeks to 44 years. Half of patient presented with an isolated CoA, 215 with VSD and the rest with other complex congenital heart diseases

where CoA may not be labelled as the primary pathology. The study heterogeneity is more complicated by the fact that adult patients are also included in the studied population. The dominant operations were EEA and then SF in children however in older patients and adults patch aortoplasty and interpositional graft was prevalent. Re-coarctation has been well described and categorise as per primary surgical procedure however the age group and concomitant heart disease have not been taken into account. This has made the interpretation and further analysis of re-coarctation difficult. Arch hypoplasia has been defined as the narrowing of the lumen diameter less than 50% that of descending aorta. Authors have included proximal and distal arch hypoplasia in one group as arch hypoplasia by which the impact of arch anomaly on re-coarctation may not be accurately examined. The management and pathophysiology of proximal vs. distal arch needs to be evaluated in two separate groups. Total mortality has been reported at 3% (32 patients). Although the mortality has been presented on a separate table as per surgical approach there is no mention of concomitant cardiac anomalies on these patients while the mortality of CoA with concomitant congenital heart disease is much higher than of isolated CoA. In this population more patients in EEA group succumbed into early mortality and also later presented with re-coarctation during the follow-up period. Re-coarctation occurred in 117 patients (11.5%) from which 65 patients were re-operated. Surgical site aneurysm occurred in 9% of patients requiring re-intervention which necessitated re-operation. The majority of these patients had previously undergone patch aortoplasty. As the population is not homogenous age wise it is difficult to understand the time of presentation. Patients with re-coarctation underwent re-intervention with a median of 4.8 years after initial surgery however the range of re-intervention time is as wide as one week to 33 years. It is not clear if neonates or infants presented in the first year of post-operative period as reported by other studies. The follow-up was complete for 95% for which taking the large sample size into account, this is a satisfactory follow-up. Re-coarctation in this cohort was predicted by a gradient of more than 20 mmHg in systolic BP between the upper and lower limbs. Authors expressed concerns on the outcome of catheterisation and balloon aortoplasty vs. redo surgery; however the population is densely heterogeneous with regard to primary intervention which does not allow to draw a conclusion that can be applied to the current practice. For example is not clear if a complication after balloon aortoplasty is due to the fact that the patient had undergone more complex surgery with multiple cardiac defects as compared to a patient with isolated CoA undergoing redo surgery.

Patient group	Outcomes	Key results	Comments
- Children and Adults	- Mortality - Re-coarctation	- No difference SF vs. EEA	- Heterogeneous population (surgical intervention) - Univariate and multivariate analysis - Large sample size

Table 41. Summary of Brown et al study

2.2.4.9 Karamlou et al

Cardiologists at the Hospital for Sick Children in Toronto conducted a retrospective study to examine the outcome of CoA repair in a high risk group of neonates with LBW (Weight < 2.5 Kg) (Karamlou 2009). In this population 36 neonates were studied who had an overall survival of 76% which is lower than neonates with normal weight. Patients had other congenital heart diseases with haemodynamic significance such as: VSD, atrioventricular septal defect (AVSD) and mitral as well as aortic valve stenosis. Considering the high risk nature of this group it would have been ideal if isolated CoA could have been studied separately in this group of patients; although only two patients underwent a concomitant operation for heart defects. Interestingly despite small size of patient the predominant surgical intervention to repair the coarctation was EEA. Six operations were performed via median sternotomy as the arch anatomy was complex with hypoplasia. Re-coarctation occurred in 5 patients (13.8%) which is slightly higher than previously discussed studies where re-coarctation rate was around 10%. It was demonstrated that aortic valve growth improved in EEA group as compared to other surgical techniques. Interestingly patients with smaller transverse arch after CoA repair with EEA technique showed more rapid trajectories of growth compared with patients who underwent CoA repair with other techniques. There was a similar observation on isthmus size between different techniques. The isthmus size and growth after repair was similar between the different surgical techniques and showed rapid growth to catch up with normal growth rate. Authors have hypothesised that patients with coexisting VSD require a prompt surgical intervention; however in their population it is not specified if the concomitant VSDs were of haemodynamic significance. Finally it was concluded that in the management of CoA the attention should be focused on the entire aorta and not

only the coarctation area. Therefore it is prudent to remove any obstruction, hypoplasia or flow-limiting lesion from the antegarde flow pathway from LVOT to descending aorta.

Patient group	Outcomes	Key results	Comments
- Infants	- Re-coarctation - Post-op complication	- EEEA superiority	- Univariate, multivariate and actuarial probability analysis is performed - Heterogeneous population - Expanded arch hypoplasia definition (from distal to proximal arch hypoplasia included)

Table 42. Summary of Karamlou et al study

2.2.4.10 Kaushal et al

In a large group of patients with CoA (N=201) the outcome of surgery has been studied for EEEA technique (Kaushal 2009). Patients with patch augmentation were excluded. Neonates (53%) and infants are the main population with a median age of 23 days. The definition of hypoplastic arch was a transverse arch length in millimetre which is less than the weight of the patients in kilograms plus one. All operations were performed via the left thoracotomy except for 44 (21.8%) patients. In the latter group of patient the operation has been performed via median sternotomy on CPB with DHCA. Twenty eight patients from sternotomy group also had concomitant complex congenital heart disease which was operated at the same time. In 16 patients the aortic arch was deemed too hypoplastic to be amenable to repair via a left thoracotomy therefore for a better access sternotomy was chosen as the approach of choice. These patients underwent a complex operation with CPB and DHCA via sternotomy for an isolated CoA and hypoplastic arch; while in many previous studies the operation had been done safely via left thoracotomy. This is the result of a different definition for arch hypoplasia in this study which has led to a shift of complex group of patients into the studied sample. In summary the sternotomy population has made the sample a heterogeneous one. Other reasons for sternotomy were common BCA artery trunk and aberrant right SA. The patients in thoracotomy group who were diagnosed intra-operatively with residual coarctation (N=3) following EEEA repair, underwent re-performing the repair with SF technique. In-hospital mortality has been reported at 2% (4 patients). These patients were complex cases with concomitant

congenital heart disease and pre-operative comorbidities. One of these patient was placed on extracorporeal membrane oxygenation (ECMO) pre-operatively. Patients were followed up for a mean of 5 years and 93% of patients did not show any re-coarctation. Late mortality occurred in 2% of population (4 patients). The time interval from the first operation to re-intervention was 3 to 132 months with a mean of 41 months. This is comparable with other studies discussed in this Chapter. On a multivariable Cox model with hazard ratios, intra-operative VDS repair, sternotomy approach, pre-operative inotrope and hypoplastic transverse arch were all significantly associated with an increased arte of mortality. This is not surprising while as mentioned above there are patients with complex anomalies and severe hypoplastic arch included in this population of whom few were in critical condition pre-operatively. Certainly by including these patients in the same group with isolated CoA patients, one may not elicit a meaningful statistical analysis. Sternotomy has been identified as a risk factor; however CPB and DHCA are possibly the culprit while all sternotomy patients underwent CPB and DHCA showing the complex nature of these operations.

Patient group	Outcomes	Key results	Comments
- Infants and Children	- Mortality - Re-coarctation	- Low re-coarctation for EEEA patients	- Heterogeneous population - Univariate and multivariate analysis

Table 43. Summary of Kaushal et al study

2.2.4.11 Thomson et al

Thomson et al have studied the outcome of CoA repair in a rather heterogeneous group of patients where concomitant congenital heart disease was prevalent with more complex arch hypoplasia (Thomson 2006). It is apparent that in many patients the CoA is not the primary pathology and the extent of arch hypoplasia is that in few patients after resection of coarctation end-to-side anastomosis was performed. The focus of the study was also on arch reconstruction; however this is in the context of CoA as a coexisting pathology. Patients underwent EEEA (73%) or end-to-side anastomosis. The operations have been divided between three groups of isolated CoA, CoA with VSD and CoA with complex congenital heart disease. The degree of arch hypoplasia was considered for this pre-operative stratification. The survival over 10.6 years was demonstrated on a Kaplan-Meier curve where isolated CoA repair had the best survival as compared to CoA + VSD

and Complex groups. Early mortality occurred in 9 patients (4.7%). The incidence or re-coarctation during follow-up was 4.2 % (7 out of 165 available patients at follow-up). The authors did not identify the type of arch intervention in these patients presented with re-coarctation as side-to-side anastomosis technique is usually preserved for an aortic arch with more complexity or hypoplasia. In this study it was also demonstrated that patients who were born prematurely had higher incidence of re-coarctation after repair however it is not clear how many of these premature patients underwent complex cardiac surgery which can be expected in this specific group of patients.

Patient group	Outcomes	Key results	Comments
- Infants and Children	- Mortality - Re-coarctation	- Low re-coarctation for EEEA patients	- Heterogeneous population - Univariate and multivariate analysis

Table 44. Summary of Thomson et al study

2.2.4.12 Pandey et al

One of the largest studies which exclusively studied the outcome of CoA repair with SF technique has been conducted by Royal Liverpool Children's NHS Trust (Pandey 2006). In this study 399 patients were investigated retrospectively with a median follow-up of 14 years. The population constitutes 58% of the institution practice in repairing CoA. Patients were divided into two main groups: isolated group (134 patients) and CoA with concomitant congenital heart disease namely complex group (265 patients). Similar to other CoA studies male population was nearly twice the size of female patients. The main population were infants presented with CoA or CoA and coexisting anomaly with a median age of 22 days ranging from 3 to 49 days therefore comprising a homogenous population from an age point of view. The authors as per institutional protocol defined the arch hypoplasia as when the arch is 1 mm in diameter smaller than the patient's weight. SF technique had been used frequently in this institution particularly when the arch hypoplasia exists or labelled as borderline. In patients who underwent only SF repair of CoA a mortality of 36 patients (10.6%) has been reported while in complex group is more than double. During the follow-up out of 124 patients who remained alive and had undergone isolated CoA repair, 20 patients developed re-coarctation requiring re-intervention. One of these patients did not survive the re-intervention and another patient develop re-re-coarctation at a later date during the follow-up. This gave a rate of 14.9 %

re-coarctation for isolated CoA repair. The median age for intervention in the isolated CoA group was 33 months. Neonates showed a significantly higher arte of re-coarctation as compared to infants. A third of population were still hypertensive at follow-up which is comparable with similar studies in this Chapter. Regarding the left arm development authors have sent out questionnaires with a relatively high response at 84%. Two major developmental aspects of left arm were asked about: 1- the disparity between the left and right arm 2- the disparity between the muscular density between the left and right arm. Nearly a third of patients (28.8%) reported that they have noticed a disparity between the two arms from a muscular development point of view while 24.6% of patients reported a discrepancy in the length of two arms. Interestingly authors could demonstrate that the later the CoA repair with SF the higher the risk of left arm underdevelopment; meaning infants whose LSA has been ligated for CoA repair were less exposed to the risks of left arm muscular development or growth problems. Of note that during the follow-up period these patients demonstrated a significant discrepancy between the systolic BP of the left arm vs. right arm; while the left arm readings were lower.

Patient group	Outcomes	Key results	Comments
- Infants and Children	- Mortality - Re-coarctation	- Arm discrepancy and arm underdevelopment after SF: 28.8% and 24.65 respectively	- Heterogeneous population - Univariate and multivariate analysis

Table 45. Summary of Pandey et al study

2.2.4.13 Sudarshan et al

Melbourne Royal Children's Hospital has reported the outcome of CoA repair in a high risk group of patients with LBW (weight < 2Kg) over a period of 15 years (Sudarshan 2006). The studied patients were fundamentally premature neonates with median gestational age of 33 weeks. LBW in this group was defined as < 2 Kg with a median of 1.6 Kg ranging from 1 to 2 Kg. Twenty-four patients were identified who underwent CoA repair with predominantly the EEEA (13 patients) and then SF (9 patients) techniques. The mean transverse arch in this group was 3.1 mm (2.5 mm – 4.0 mm) with a median Peak velocity of 3.6 m/s across the coarctation. The patients in this sample also suffered from a wide spectrum of congenital heart diseases with VSD in majority (62.5%), hypoplastic left heart syndrome (HLHS), double outlet right ventricle and TGA. Few patients also had severe non-cardiac anomalies such as hyaline membrane disease and

bronchopulmonary dysplasia. This wide spectrum of anomalies without any doubt has influenced the outcome of CoA repair regardless of the repair strategy. Patients were followed up with a mean of 4.5 years. In-hospital mortality occurred in three patients who also had a very complex coexisting cardiac defects and anomalies. Therefore it is not unrealistic to mention that there were no mortalities in the isolated CoA group while authors have not created this group of patients. A high rate of phrenic nerve injury (16.6%, 4 patients) after surgery was reported which can be related to the small size of the patients. Two patients (8.3%) suffered from chylothorax requiring a prolong drainage and conservative management. No RLN injury was reported. Late mortality during the follow-up occurred in one patient (5%) who had an isolated coarctation repair. One patient (5%) with a complex cardiac anomaly also did not survive during the follow-up. Re-coarctation was defined as a symptomatic patient with peak pressure gradient of 25 mmHg and more across the repaired site. Nearly a third of patients (29.2%) developed re-coarctation however 4 patients (16.7%) underwent re-intervention. Further studies confirmed a mild re-stenosis in those three patients who did not have re-intervention. All re-coarctations occurred less than a year after surgery. No difference was observed between EEEA and SF groups regarding the mortality rate as well as the incidence of re-coarctation. This finding may not have enough rigor to be applicable in practice while firstly the sample size is small secondly the population is not homogeneous. Following a multivariate analysis it became evident that heart failure, descending aorta cross clamp time, non-cardiac anomalies and post-operative ICU stay were an independent risk factor for mortality. It is of paramount to emphasise that this findings also may not be meaningful while the complex patients are among the studied sample who are sicker and may require longer cross clamp time, longer ICU stay or operations for non-cardiac anomalies. Although the study was conducted in one of the renowned paediatric cardiac surgery units, the biased study design does not allow application of authors experience with the management of CoA in this high risk group in day-to-day practice.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	- No difference EEEA vs. SF	- Heterogeneous population - Univariate and multivariate analysis - Small sample size - Medium follow-up

Table 46. Summary of Sudarshan et al study

2.2.4.14 Wright et al

Wright et al from University of Michigan Medical School retrospectively studied the outcome of CoA repair in a decade which has been performed exclusively with EEEA technique (Wright 2005). Eighty-three patients with a median of 21 days (2 – 365 days) were identified from whom 72 (78%) patients underwent the operation via left thoracotomy. The remainder had the same operation via median sternotomy where the transverse arch hypoplasia was deemed too severe to be repaired via thoracotomy. The latter group were placed on CPB and underwent the surgery with DHCA. Patients with coexisting congenital heart disease with haemodynamic significance were excluded from the study. The median weight was 3.7 Kg ranging from 1.7 Kg to 9.3 kg showing that LBW patients were indeed included. Two patients whose operation was performed via left thoracotomy without conversion to sternotomy had their repair re-performed by SF technique. Seizure was prevalent among patients who underwent DHCA with the incidence of 19%. Chylothorax and RLN injury occurred in two (2.4%) and one (1.2%) patients respectively who underwent thoracotomy. Early mortality was recorded 1%. Eleven percent of patients, not clear from which group (sternotomy vs. thoracotomy), were discharged with a residual peak pressure gradient of more than 15 mmHg. The patients were followed up with a mean of 4.5 years. Re-coarctation was defined as the presence of peak gradient pressure across the repaired site of 15 mmHg and more which demonstrated a lower threshold as compared to similar studies (Kaushal 2009). Re-coarctation occurred in 5% of patients who were available at follow-up. All re-coarctations occurred within the first year of follow-up period. It would have been interesting to investigate those patients with residual pressure gradient and to examine the impact of residual gradient on re-coarctation occurrence; however this has not been reported by authors. Once again all patients were combined together for re-coarctation assessment while sternotomy group comprised a high risk group with more complex arch anatomy which naturally may not be appropriate to compare them with an isolated CoA repair and examine the rate of re-coarctation. This is a common bias in majority of CoA studies. Authors in comment section has emphasised that they have made the population homogenous by excluding other coexisting congenital heart disease while severe arch hypoplasia still comprised a considerable fraction of sample size. In other words severe arch hypoplasia is a separate pathological entity which commonly coexists with CoA. In

fact distal/isthmus arch hypoplasia can be studied in combination with CoA while a repair with EEEA technique can offer a satisfactory outcome. However the pathology of proximal arch in the form of hypoplasia is a more complex entity and requires further detailed investigations into other aortic parameters such as LVOT, aortic valve, as well as STJ.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation - Post-op complication	- The importance of arch hypoplasia in CoA repair	- Heterogeneous population - Univariate and multivariate analysis

Table 47. Summary of Wright et al study

2.2.4.15 Adeeb et al

Adeeb et al from one of the largest paediatric cardiac surgery institutions in Malaysia reported their experience in surgical management of CoA. In 11 years they retrospectively studied 114 patients who underwent surgery for CoA. Nearly half of patients had concomitant congenital heart disease (TGA, double outlet right ventricle and tetralogy of Fallot). The follow-up period ranged from 72 to 150 months. Majority of operations were EEA and then SF; however 20 patients underwent Dacron path augmentation and interpositional graft. Four adults and 9 patients older than 9-year-old were also included in the study group. Re-coarctation occurred in patients with the age of younger than 48-month-old. The rate of re-coarctation in EEA, SF and interpositional graft was 1.7% (2 patients), 2.6% (3 patients) and, 0.8% (one patient) respectively. Although the type of surgery was not an independent risk factor for re-coarctation rate, neonates (age < 30 days) developed more re-coarctation as compared to other age groups. Authors claimed that significantly more comorbidities occurred in EEA group vs. SF and other surgical techniques; however data presentation is poor and there is no presentation of statistical test to support this statement. Chylothorax, RLN injury and neurological deficit (not specified) all occurred post-operatively with EEA technique. Early mortality was reported at 5.2% which is higher than in-hospital mortality of similar studies in years after 2000. Authors have implied to an early "learning curve" as the possible reason for unsatisfactory results with EEA. It seems after this study they decided to move on to EEEA but no results have been presented to rationalise the change in institutional practice.

Patient group	Outcomes	Key results	Comments
- Children and Adults	- Mortality - Re-coarctation	- No difference EEA vs. SF	- Poor statistical analysis - Heterogeneous population

Table 48. Summary of Adeeb et al study

2.2.4.16 Maia et al

Paediatric cardiologist from Heart Institute (InCor), University of Sao Paulo Medical School, retrospectively reviewed the outcome of CoA repair in 113 patients who underwent surgery over a period of 26 years (Maia 2004). The age limit was set at 14-year-old; however there was no explanation for the age threshold. Cyanotic heart defect were excluded which was an uncommon exclusion criteria as non-cyanotic complex congenital heart diseases may still make the sample heterogeneous. For this reason 79% of the population had an associated intra-cardiac anomaly leaving only 21% for isolated CoA. The patients were divided into three groups for age (0 -1, 1 – 10 and 10< year-old). The predominant surgical intervention was EEA with 79 patients (69.9%) and then SF with 13 (11.5%). Patch augmentation was used frequently in this group of patients (12.3%). The mean weight of the patients at the time of operation was 3.95 Kg. For post-operative BP monitoring a patient was identified hypertensive when the mean of 2 measured systolic/diastolic BP on the right arm was equal or higher than 95th percentile for age. Authors also elaborated their protocol for definition of post-operative HTN in patients older than 18-year-old which was mean of systolic/diastolic BP higher than 140/80 mmHg. For re-coarctation authors relied on BP disparity of 20 mmHg and greater between upper and lower limbs. Echocardiography was also performed on all patients but one at follow-up. The instantaneous continuous peak pressure gradient across the repaired site when was plotted against the systolic BP disparity between the upper and lower limbs, a significant correlation was demonstrated. Magnetic resonance imaging (MRI) was performed during the follow-up period in 66 patients (58%), however it was not clarified what the criteria was for MRI. Re-coarctation occurred in 14 patients (14%). Interestingly the occurrence of re-coarctation was significantly higher in older patients (age > 10 year-old), which is in contrast with majority of studies appraised earlier on this Chapter. Re-coarctation occurred mostly in patients who underwent EEA (10 patients 71% of re-coarctation group) but there was no statistical analysis to compare different techniques. Probably the comparison of different surgical techniques could not have led to a

meaningful result while population is severely heterogeneous with other complex congenital heart diseases. Echocardiography was compared vs. systolic BP gradient between the upper and lower limbs which showed more sensitivity and less specificity for echocardiography. One of the major advantages of this study was using MRI to accurately measure the aorta at different levels which were: ascending aorta diameter, transverse arch length, distal arch length and isthmus diameter. The growth of proximal arch was significantly different in age groups; while this was not observed at distal arch which interestingly remained hypoplastic in nearly half of population. Although in patents with other intra-cardiac defects flow implications would not be similar to those of isolated CoA, this finding may help to explain that despite a satisfactory repair of CoA, patients still remained hypertensive for several years.

Patient group	Outcomes	Key results	Comments
- Children and Adults	- Re-coarctation	- No difference EEA vs. SF	- Heterogeneous population - Univariate and multivariate analysis - Follow-up with combination of MRI and Echocardiography

Table 49. Summary of Maia et al study

2.2.4.17 Wood et al

Wood et al from Our Lady's Hospital for Sick Children from Republic of Ireland presented one of the largest studies with a focus on the outcome of CoA repair in patients with hypoplastic arch (Wood 2004). In this population the difference in the used surgical technique with previously explained EEEA was a side-to-side anastomosis rather than an end-to-end in the latter. All patients underwent excision of the coarctation followed by an incision on the inferior arch extending beyond the origin of LSA up to the origin of LCCA. Then the transected descending aorta was spatulated to accommodate the extended arch incision with a side-side anastomosis. There was no report of sternotomy or conversion to sternotomy while all operations performed vie left thoracotomy. Regional aortic cross clamp was used but none of the patients were placed on CPB or underwent DHCA. This technique has been described as end-to-side as well. Although in this thesis patients with side-to-side were not exclusively examined, this unique population which entailed a large number of patients with arch hypoplasia made it

interesting to be appraised and discussed in this Chapter. The retrospective review of medical records identified 181 patients who were later categorised into three groups as per pathology: 1- isolated CoA 2- CoA + VSD 3- Complex congenital heart disease coexisting with CoA. The age median was 13.5 days ranging from 1 to 300 day-old. Authors defined an arch as hypoplastic when the transverse arch diameter was less than 1mm per Kg plus one. By applying this definition 107 (59%) patients were identified with hypoplastic arch. Patients were followed up regularly in 3-month intervals and then yearly. Early total mortality was observed in one patient (0.5%) from the complex group. None of patients in isolated CoA group died in the hospital. Despite extensive mobilisation of major structures to avoid tension on the suture lines, the total incidence of chylothorax (injury to the thoracic duct), phrenic nerve palsy and RLN injury (proximity to the arch) were as low as 3 (1.6%), 2 (1.1%) and 0 respectively. No neurological complications observed post-operatively. Greater number of patients did not survive during the follow-up in the complex group (25%). Re-coarctation was defined as a resting peak pressure gradient across the repaired site of greater than 20 mmHg. Four patients (2.2%) were identified with this definition having re-coarctation. Three of these patients were infants with LBW as low as 0.85 Kg. More than a quarter of population (27%) underwent concomitant PA banding for another congenital heart disease. Flow haemodynamics and the antegrade flow is significantly different in this particular group of patients as compared to isolated CoA group. Including patients with PA banding in the analysis of re-coarctation along with isolated CoA is a bias which may not consider all confounding factors. In four patients who developed re-coarctation it is not clear if they also underwent PA banding as a supplement to CoA repair. Authors hypothesised that while tubular hypoplasia of the arch is an independent risk factor for re-coarctation (McElhinney 2001), more aggressive surgical approach needs to be taken into account to address the pathologic arch. For this reason they denounced EEA or SF techniques in this group of patients and advocated excision of coarctation followed by an extended side-to-side anastomosis. Although arch hypoplasia has been defined, it is perceived that the authors have considered transverse arch as an anatomical location of hypoplasia which includes both proximal and distal arch. As mentioned previously this is a separate pathology not always co-existing with CoA. Authors need to be commended for the excellent outcome of the operations which are rather challenging via left thoracotomy; however they did not explain why patients with isolated CoA and no hypoplastic arch should undergo a more complex repair than EEA or SF techniques. This implies that

probably historically the side-to-side approach is a well-established approach of choice in authors' institution. In a constructive reflection in discussion section authors expressed concerns about the patients who later developed re-coarctation while authors deemed they probably should have been operated via median sternotomy with CPB as well as DHCA to improve the access in small neonates. In this study it was also postulated that generally an elliptical suture line behaves better in the context of growing aorta as compared to a circular suture line.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality	- Low mortality and re-coarctation for EEEA patients	- Poor statistical analysis - Heterogeneous population

Table 50. Summary of Wood et al study

2.2.4.18 Omeje et al

Omeje et al reported their experience in the management of CoA in children's University Hospital of Bratislava in Slovakia (Omeje 2003). In a decade 201 patients' medical records who presented with symptomatic CoA and underwent surgical correction were retrospectively reviewed. They also similar to Wood et al (2004) categorised patients into three groups as per concomitant cardiac anomaly. Isolated CoA was identified in 139 (69.2%). This population also comprised complex concomitant congenital heart disease such as TGA. The mean age has been reported as 3.5 years with a range of 2-day-old to 18-year-old which was a rather old group of patients as compared to the similar studies. This can reflect a malfunctioning referral system or late presentation of patients. As patients were older in this group there was a rise in the mean of patients' weight at 13.8 Kg. the majority of operations comprised EEA (51%) and then patch aortoplasty or augmentation (22%). The latter technique has possibly been used for older patient while generally this technique has a high association with the development of aortic aneurysm in neonates. Authors have reflected on their practice with regard to patch augmentation and interestingly they observed a constant reduction in using this technique from 1992 towards 2001. They also treated the CoA with SF (12%) and EEEA (12%) techniques. PA banding and staged operations were also performed in the patients who underwent CoA repair. PA banding rate was as high as 20%. Of note three patients (1.5%) who underwent total arch reconstruction were also included in the studied population which

has made the study sample more heterogeneous. The authors had a rather low threshold for diagnosis of re-coarctation which was defined as a peak pressure gradient of 20 mmHg and above across the repaired site. Re-coarctation occurred in 19 (10%) of patients. Majority of re-coarctations occurred in neonates and EEA group. Interestingly patients with patch augmentation did not develop any re-coarctation and this is can be explained by the fact that older children underwent this surgical technique. By using Kaplan-Meier curve authors have demonstrated that the younger the patient the higher the incident of re-coarctation. This means that the majority of re-coarctations occurred in the first few months after surgery and also it was more prevalent in neonates rather than older children. The follow-up in this population was not long enough to study the rate of aortic aneurysm. This is important while as mentioned previously a relatively high number of patients had undergone arch patch augmentation. Another interesting finding presented on Kaplan-Meier curve was the rate of re-coarctation as per years of experience in authors' institution. This is important from governance point of view and it was lacked in many studies presented in this Chapter. This reflective report helped to improve the current practice and it supported young surgeons who were at the beginning of their learning curve. Yearly outcome is also important for institutions which are particularly interested in training where case selection and supervised training in theatre can fulfil the educational needs of the institution as well as maintaining good results. Statistical analysis showed re-coarctation is more associated with EEA however this group of patients were predominantly neonates with a possible concomitant intra-cardiac anomaly. While the surgical groups were severely biased by age and concomitant defects the conclusion may not be applied to the day-to-day practice.

Patient group	Outcomes	Key results	Comments
- Children and Adults	- Mortality - Re-coarctation	- EEEA superiority	- Actuarial probability and multivariate analysis is performed

Table 51. Summary of Omeje et al study

2.2.4.19 Uchytil et al

Uchytil et al from Brno Centre of Cardiovascular Surgery and Transplantation in Czech Republic retrospectively studied 342 patients who underwent surgery for CoA repair.

They have included all age groups therefore the mean age is as old as 7.2-year-old with a wide range from 2-day-old to 44-year-old. Infants only comprised 10% of the study population which shared a similar ratio with adult patients. Age heterogeneity may influence the accuracy of data analysis on the outcome of CoA particularly regarding the different surgical techniques. For example 50% of the population underwent EEA however it was not clear how many of these patients were adults while development of collaterals and complex plexus of arteries make this operation an entirely different from those of performed on infants. In-hospital mortality for patients younger than 3-month-old was 0.08% (N=3) indicating a desirable immediate outcome. Authors have analysed their institutional trend in surgical techniques which have been used through the time for repairing CoA. Apparently patch aortoplasty has been popular at the beginning of 80s, however towards the end of the decade EEA has been opted as the favourable technique. Patch aortoplasty has been used widely for the repair of CoA via left thoracotomy while it is easy to perform the operation and extensive mobilisation or dissecting the major structures is not necessary in this technique. Towards late 80s studies have started to emerge warning surgeons on the prevalence of aortic aneurysm and the associated with patch aortoplasty (Bromberg 1989). As a result in many intuitions the patch aortoplasty became obsolete as the first line of surgical management of CoA in children particularly in neonates. During the follow-up patients were monitored by BP and the systolic BP gradient between the upper and lower limbs. A systolic BP gradient of 20 mmHg and greater between the upper and lower limbs was set to detect the patients with potential re-coarctation. Echocardiography was not used for follow-up which in many centres now is the standard diagnostic tool to monitor the patients after CoA repair. Moreover in adult patients computed tomography scan (CT-scan) is mandatory in many institutions after surgery. This may cause missing patients with re-coarctation who may have near normal BP or low gradient with recurring stenosis. This group of patients may require echocardiography as soon as possible. In the population three patients developed aneurysm in whom the age of surgery as well as the age of presentation was not specified. These three patients received a stent percutaneously. Ten patients developed re-coarctation requiring re-intervention. The age of these patients and particularly the age of operation was not clarified. The re-coarctation data was presented on a table where neonates have significantly developed more re-coarctation as compared to other age groups including adult patients. The number of re-coarctation on this table did not match with the discussed total number of re-coarctation in the result section. Generally the data

has been poorly presented and as they have covered a large population it is expected to dissect the population characteristics before and after surgery in more details.

Patient group	Outcomes	Key results	Comments
- Children and Adults	- Mortality - Re-coarctation	- No difference SF vs. EEA	- Only univariate analysis - Heterogeneous population - Large sample size - Long follow-up

Table 52. Summary of Uchytil et al study

2.2.4.20 Walhourt et al

Following an increased incidence of aortic aneurysm after patch aortoplasty with Dacron graft for CoA repair, paediatric surgeons from Netherlands reported their experience with Polytetrafluoroethylene (PTFE) in a more focused age group of patients with a long-term follow-up (Walhout 2003). Although their population comprised concomitant complex surgeries for other congenital heart diseases, the age of patients was exclusively limited to the children younger than 3-year-old. The sample size was large including 262 patients who underwent either patch aortoplasty or EEA. The population was divided between three groups with regard to complexity of operation: isolated CoA, CoA + VSD, CoA with complex concomitant operation. Nearly half of the patients (N=118) received PTFE patch for the repair of CoA. Echocardiography was the backbone of this study during the follow-up period in detecting re-coarctation. In the patch group re-coarctation, late HTN and aortic aneurysm occurred in 30 (25%), 8 (6.7%) and 8 (6.7%) of patients respectively. In EEA group re-coarctation occurred in 19 (14%) with a rate of late HTN at 2.2% (N=3). No aortic aneurysm was observed in EEA group. The Kaplan-Meier curve and subsequent log-rank testing did not demonstrate any difference between the two groups regarding the rate of re-coarctation, although more patients developed re-coarctation in patch group. Rate of re-coarctation was higher in neonates as compared to other age group and this was a common finding in similar studies discussed in this Chapter. The authors have reported that the actuarial 15-year probability of freedom from aortic aneurysm after patch aortoplasty was 93% + 3.1%. A false aneurysm occurred four days after surgery while all other aortic aneurysms developed on the medial side of aorta opposite the patch. It has been postulated that Dacron graft when it was used as a patch to repair the CoA area may induce an increased wall tension and high energy shear stress on the adjacent

aortic wall. Different tensile strengths impose an altered haemodynamics with an increased pressure and shear stress transferred to the aortic wall opposite the patch; that is the posterior wall. Therefore the development of aortic aneurysm in this patients was commonly at the postero-medial aspect of the aortic wall and not on the suture lines. Authors hypothesised that the same pathophysiology can be applied to PTFE patch while it does not have the same tensile strength and may become more rigid with time. Authors also noted that re-coarctation may be more associated with arch hypoplasia; however the definition of arch hypoplasia in this population was not clear and more importantly none of the patients underwent EEEA to address at least distal arch hypoplastic status. In summary this paper is one of the major retrospective studies by which the day-to-day practice was influenced and more surgeons started to refrain from using patch materials as the first line of surgical treatment.

Patient group	Outcomes	Key results	Comments
- Children	- Mortality - Re-coarctation	- EEA superiority	- EEA was compared vs. patch aortoplasty which is now obsolete - Heterogeneous population

Table 53. Summary of Walhourt et al study

2.2.4.21 Younoszari

Younoszai et al from Paediatric Cardiology and Paediatric Cardiothoracic Surgery, University of California retrospectively studied the outcome of coarctation excision and end-to-side in 88 patients who underwent CoA repair (Younoszai 2002). The technique is similar to those of EEEA; however in end-to-side technique the descending aorta is anastomosed to the inferior aspect of the arch almost in front of LCCA. This operation has been reported by surgeons from the same institution during the 90s as a successful approach to address the arch anomaly (Rajasinghe 1996). Arch hypoplasia particularly when the pathology involves the proximal arch is a risk factor for the development of re-coarctation after EEA operation. End-to-side anastomosis allows the surgeons to create a larger arch in diameter, although the length might be affected and became shorted in size. Younoszai et al did not define arch hypoplasia and more importantly the rationale that why a more complex surgery needs to be done on patients who did not have any arch pathology i.e. isolated CoA. In addition this operation requires a wider access to the entire

arch; therefore performing the operation routinely via left thoracotomy may not be advisable (Wood 2004). The patients were categorised as neonates (age < 1-month-old) or paediatric (age > 1-month-old). There were associated cardiac defects for which patients underwent additional operations such as PA banding and VSD repair. Complex anomalies were corrected via median sternotomy and CPB. The complex CoA patients were not analysed separately particularly with regard to the rate of re-coarctation. No early mortality was reported. One (1.1%) patient developed left phrenic nerve palsy requiring diaphragm placation and another patient (1.1%) developed post-operative chylothorax requiring prolonged conservative management with a chest tube thoracostomy. Similar to those of EEEA in which extensive dissection and mobilisation of major vessels is crucial the rate of chylothorax, left phrenic nerve injury as well as RLN injury was not higher than other techniques of CoA repair. Re-coarctation was defined as when "either the blood pressure gradient between the right arm and a leg was equal or more than 20 mmHg or the flow velocity in the proximal descending aorta was equal or more than 2.5 m/s". By this definition 3 infant (5.5%) were diagnosed with re-coarctation. Authors believed that incorporating the descending aorta into the mid-arch and tying off the distal arch zone is the main reason that the rate of re-coarctation remains low. Although authors need to be commended for the satisfactory short-term outcome, the length of follow-up is not long enough to detect all re-coarctations. The median follow-up is only 1.5 year while more complex techniques have been deployed in this group requiring longer follow-up. Authors have described their end-to-side technique on a schematic figure which has been demonstrated in Figure 15. As shown in this Figure, the tied-off distal arch where inadvertently a cul-de-sac is created induces flow turbulence. Laminar flow arrays the endothelial cells in the flow direction while the flow disturbance and non-laminar flow has an impact on endothelial cell proliferation and disarray (Davies 1986). This phenomenon may affect the endothelial hyperplasia and re-stenosis in long-term.

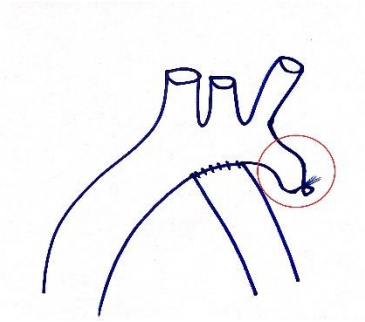

Figure 15. The conclusion of end-to-side anastomosis explained by Younoszai et al (2003). The red circle demonstrates the area of cul-de-sac with flow disturbance. (Younoszai AK, Reddy VM, Hanley FL, Brook MM. Intermediate term follow-up of the end-to-side aortic anastomosis for coarctation of the aorta. Ann Thorac Surg. 2002; 74 (5): Page 1632)

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	- Low rate of re-coarctation in EEA patients	- Heterogeneous population -Actuarial probability performed with no multivariate analysis

Table 54. Summary of Younoszari et al study

2.2.4.22 Narasinga et al

Narasinga et al from United Arab Emirates Al-Mafraq hospital reported their experience in repairing CoA with EEEA technique (Narasinga 2002). They retrospectively investigated their repair operations in three years 1997 – 2000 and reported the outcomes in 21 patients. Although the follow-up is relatively short compared to other large volume studies, the sample size represents the country population which is not more than 6 million. Twenty (95%) patients underwent EEEA and only one patient had his CoA repaired by patch augmentation using PTFE patch. Arch hypoplasia was reported in 8 patients therefore EEEA was not solely used in this group of patients. Hypoplastic arch constituted a very wide spectrum of pathology and anomalies affecting the surgical approach as well as outcomes. Authors have defined an arch as hypoplastic when a 5 mm segment of the distal arch is less than 50% diameter of the descending aorta just before diaphragm. A re-coarctation is also defined as an increases peek gradient pressure across the repaired site at 20 mmHg or greater. The studied population was homogeneous age wise, however there were concomitant heart defects which as per authors' definition was also categorised as complex cases. In the complex group three patients underwent repair

of CoA with EEEA; however they also received PA banding for a coexisting large VSD. It is clear that these patients may not be compared with isolated CoA with regard to re-coarctation or other complications not only immediately after operation but also during the follow-up after discharge. For example two of these complex patients did not survive after discharge; however they are included in the total mortality rate for CoA repair. This bias was not exclusively observed in this study and the majority of examined and critically appraised studies suffered from the lack of focus on isolated CoA which needs to be genuinely isolated with no concomitant congenital heart diseases requiring any kind of intervention. Although no in-hospital mortality was reported, a relatively high rate of re-coarctation within the first 15 months after surgery has been observed. Five patients (23.8%) developed re-coarctation with recurring high gradient across the repaired site up to 60 mmHg. All of these patients underwent balloon aortoplasty with successful results. In discussion section authors have analysed the patients with re-coarctation. The re-analysis of the arch revealed that these patients had more severe arch hypoplasia which involved transverse arch. This represents arch hypoplasia in both proximal and distal segments. Many surgeons advocate sternotomy for repairing CoA in these patients where the access is better and the operation can be performed safely on CPB and even with DHCA (Kaushal 2009, Thomson 2006). This is a common bias in the study of CoA where the complexity of arch hypoplasia is not well appreciated. For example in this population the intention to treat of those patients with re-coarctation was CoA repair however arch analysis after recurrence it was discovered that these patients probably should have not been categorised as CoA repair and could have been investigated as a failed arch repair under arch repair population and not CoA population.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation	- Low rate of re-coarctation in EEEA patients	- Heterogeneous population - Small sample size - Poor statistical analysis

Table 55. Summary of Narasinga et al study

2.2.4.23 Corno et al

Corno et al conducted a retrospective study to evaluate the outcome of surgery for treating CoA with a long follow-up exceeding 30 years (Corno 2001). The authors retrieved the data of 104 paediatric patients who underwent CoA repair operation in their institution.

The adult patients were also studied. The surgical technique included a wide spectrum of operations over a thirty years practice including: SF, EEA, EEEA, patch aortoplasty, end-to-end conduit interposition and LSA to descending thoracic aorta which the two latter are now obsolete in today's practice. EEA and SF techniques comprised 53.9% (N=56) and 14.4% (N=16) of population in paediatric patients respectively. Re-coarctation has not been defined in this study; while the peak pressure gradient across the repaired site of more than 20 mmHg was reported in 7 patients out of 91 paediatric patients at follow-up (7.7%). These seven patients were labelled as re-coarctation. On a table it has been demonstrated that with regard to the surgical technique 10 patients (10%) developed re-coarctation for which they underwent re-operation. Because there was a lack of re-coarctation definition, there was a disparity between the text and the table and it seems authors have applied different criteria for detecting re-coarctation. Statistical analysis confirmed that EEA technique is superior to other techniques including SF approach. Although authors emphasised that their study was limited by a small sample size, the conclusion by which the superior surgical technique was confirmed has been elaborated cautiously.

Patient group	Outcomes	Key results	Comments
- Not specified (all groups included)	- Mortality - Re-coarctation	- EEA superiority	- Heterogeneous population - Small sample size - Poor statistical analysis - All age groups included - Heterogeneous population

Table 56. Summary of Corno et al study

2.2.4.24 McElhinney et al

In one the largely cited studies ran by The Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, the impact of patients weight on the outcome of CoA repair has been examined (McElhinney 2001). During 90s 103 patients with a median weight of 3.3 Kg ranging from 1 Kg to 6.4 Kg underwent repair of CoA via left thoracotomy. This study was one of the rarest studies appraised in this Chapter which has excluded patients with complex congenital heart diseases and concomitant surgeries. A quarter of population were born prematurely. Nearly 405 of patient were on PGE_1 infusion pre-operatively. Not only the patients in this population were homogeneous with regard to the surgical management but also they were from a similar

age group where the median age was 18 day-old ranging from 1-day-old to 90-day-old. Major operations were either EEA (62%) or SF (32%). Aortic diameter were measures at 4 main locations: 1- diameter of ascending aorta proximal to BCA 2- diameter of transverse arch between LCCA and LSA 3- aortic isthmus diameter 4- descending aorta diameter. Age and weight as continuous variables were significantly correlated to the diameter of ascending aorta and transverse arch. Follow-up exceeded 9 years. One patient (0.9%) died peri-operatively in the hospital and another patient did not survive during the follow-up. On echocardiography data there was no mention of re-coarctation definition or criteria, however it was reported that re-intervention was performed in 15 (15%) patients in which the median peak pressure gradient across the repair site was as high as 55 mmHg (range: 25 mmHg – 100 mmHg). Freedom from re-intervention for re-coarctation was 90% at 6 months and 82% at 2 years. All re-interventions took place within the first year of follow-up and this was similar to many similar studies which were discussed in this Chapter. Authors hypothesised that as the growth is at its climax in the first year, unprecedented adverse outcomes after surgical repair and reconstruction is more common during this period of time. Following Cox regression analysis it was interesting to observe that weight or being premature is not an independent risk factor for re-coarctation; however age of younger than 2-week-old was significantly correlated to the incidence of re-coarctation. Transverse arch and transverse arch / ascending aorta ratio was significantly associated with an increased risk of re-coarctation. The reason for this finding is underestimating arch hypoplasia by majority of coarctation studies. In this study arch hypoplasia was not defined therefore the impact of transverse arch in re-coarctation has become significant due to the fact that these patients probably should have been operated by extending the incision into the proximal arch to address the hypoplastic condition i.e. EEEA technique. In this study comparing two major surgical techniques SF vs. EEA did not show any difference in causing re-coarctation during the follow-up period.

Patient group	Outcomes	Key results	Comments
- Infants	- Mortality - Re-coarctation - Post-op complication	- No differcne SF vs. EEA	- Short follow-up - Univariate and multivariate analysis is performed

Table 57. Summary of McElhinney et al study

2.2.4.25 Jahangiri et al

Paediatric surgeons and cardiologists from Royal Brompton hospital retrospectively examined the outcome of SF technique for CoA repair in 185 patients (Jahangiri 2000). Other significant congenital heart diseases were also included in the population. Neonates comprised 68% and infants constituted 28% of population with median age of 18-day-old at the time of operation. This is one the rare studies in this Chapter where the arch hypoplasia has been defined and evaluated thoroughly. The arch assessment has been carried out at three different level of patent's care: 1- pre-operative echocardiogram 2- by surgeon at the time of surgery 3- in the follow-up period by various diagnostic tools including echocardiography and MRI. If the diameter of aorta between LCCA and LSA was less than 50% of the diameter of ascending aorta the arch was labelled as hypoplastic. After applying this definition, 41 patients (22%) were identified with arch hypoplasia. During the follow-up re-coarctation was defined as disparity of more than 20 mmHg in systolic BP between upper and lower limbs, or a peak pressure gradient of more than 25 mmHg across the repaired site. Early mortality was 3% (6 patients) and survival at 5 years was as high as 98% $\pm$ 2%. Early mortality was significantly associated with arch hypoplasia. Although the definition of arch hypoplasia was clearly elaborated, it is important to note that as per authors' definition the hypoplasia may be applied to the transverse arch up to the origin of LCCA. These operations are challenging via thoracotomy and SA patch over the coarctation area may not necessarily be able to address the arch pathology up to the origin of LCCA. Although SF technique is the authors' approach of choice, there is no report of post-operative complications such as arm ischaemia as well as arm growth problems. During the follow-up period (median 6.2 years) the rate of re-coarctation has been reported at 65 (11 patients). Similar to other studies appraised in this Chapter the authors demonstrated that neonates have a significantly higher rate of re-coarctation as compared to infants. It is interesting that half of patients diagnosed with arch hypoplasia still remained hypoplastic. This finding confirmed further that this particular group of patients requires more advanced surgical treatment managing the arch hypoplasia other than simple EEA or SF techniques. The authors have applied Moulaert et al (1976) definition of distal arch hypoplasia which deals with an area between the LCCA and LSA. It is notable that SF technique no matter how perfectly performed may not correct the anomaly of this region. This issue has been discussed by the authors in the discussion section. Jahangiri et al have emphasised that

the controversies in the field of CoA treatment remained unanswered and the best way forward to address these controversies and concerns is to perform a RCT.

Patient group	Outcomes	Key results	Comments
- Infants and Children	- Mortality - Re-coarctation	- Suggestion of RCT for CoA studies - Low re-coarctation rate for SF patients	- Univariate and multivariate analysis is performed - Heterogeneous population - Long follow-up

Table 58. Summary of Jahangiri et al study

2.2.4.26 Dodge-Khatami et al

In one of the largest studies with long follow-up, congenital heart surgeons from Children's Memorial Hospital in Chicago examined the rate of re-coarctation after surgical repair of CoA in 271 patients. In 40 years 69 (25%), 61 (22%) and 18 (6.6%) patients underwent EEEA, SF and EEA operations respectively. More than a third of population underwent patch aortoplasty (43%, N=11). The institution had ceased usage of Dacron graft technique in 1978; however was still using PTFE patch for repairing CoA. The EEEA technique was adopted in early 90s. The median age has been reported 156-day-old and 35% of population had concomitant congenital heart disease. Long-term follow-up was available for 52% of population. Despite including complex surgeries into the studied sample early mortality remained as low as 1% (3 patients). Paraplegia occurred in one patient (0.4%) whose operation was complicated after performing EEA. Multiple aortic clamping and increased ischaemic time played a role in paraplegia. RLN injury was reported in 6 (2%) patients and chylothorax in four patients (1.5%). Three aortic aneurysms occurred in association with Dacron and PTFE aortoplasty and in one patient occurred after repairing CoA with SF technique. The authors have divided the aortic arch into three parts: 1- proximal transverse arch 2- distal transverse arch 3- isthmus and defined each part's hypoplasia against the ascending aorta diameter. This model of investigating the arch for hypoplasia had been described by Moulaert et al (1976) where the morphology of the arch and hypoplasia has been thoroughly studied. Although the arch hypoplasia model and anatomical categories has been re-described by the authors, they did not clarify that their patients who were labelled as hypoplastic arch (37 patients, 14%) belongs to which category. This remains a major bias in this study which inevitably affects the outcome measurement. Therefore it is not surprising to observe that half of

patients who later developed re-coarctation were also diagnosed to have a hypoplastic arch. Majority of these patients were also operated with EEEA technique which may seem that the surgical technique was not adequate to address the pathology; however the problem is in the definition of arch hypoplasia which may allocate a wrong patient to a wrong operation. Re-coarctation was detected by using BP monitoring only and was defined as a systolic BP disparity of more than 20 mmHg between upper and lower limbs. More patients who initially underwent EEA developed re-coarctation (33%) as compared to SF (20%) and EEEA (7%). Interestingly the rate re-coarctation in the patch group which is now obsolete was only 5% and this was statistically significant as compared to EEA. In neonates SF vs. EEEA techniques which were the majority of performed surgical techniques in this age group, were compared. Statistical analysis confirmed that the difference between the two techniques in causing re-coarctation was significant while there was 6.3 times higher risk of re-operation in SF group.

Patient group	Outcomes	Key results	Comments
- Children and Adults	- Mortality - Re-coarctation	- EEEA superiority vs. SF	- Superior results with patch aortoplasty which is now obsolete - Univariate and multivariate analysis is performed - Heterogeneous population

Table 59. Summary of Dodge-Khatami et al study

Author	Year	Location	Age (days)	Follow-up (years)	Total	Operation N (%)			Re-coarctation N (%)			In-hospital mortality N (%)			Superior technique
						EEA	EEEA	SF	EEA	EEEA	SF	EEA	EEEA	SF	
Tulzer	2016	Austria	35 (1 - 345)	6.3 (0.2 - 18.2)	183	0	111 (61%)	0	0	10 (5.4%)	0	0	0	0	N/A
Mery	2015	USA	53 (12 - 108)	6 (0 - 19)	341	44 (13%)	291 (85%)	6 (2%)	0	14 (4.1%)	0	0	4 (1.1%)	0	No difference
Adams	2013	USA	35 (1 - 250)	22 (2.4 - 34.9)	55	0	0	16 (29%)	0	0	2 (3.6%)	0	0	1 (1.8%)	N/A
Troung	2013	USA	12.5 (1 - 85)	1 (0.5 - 6)	84	4 (5%)	73 (87%)	0	0	5 (5.9%)	0	0	0	0	No difference
Kumar	2011	USA	10 (2 - 290)	1.8 (1 - 5.1)	77	36 (47%)	41 (53%)	0	5 (6.4%)	6 (7.7%)	0	Total= 1.2%			No difference
Betham	2010	UK	Not specified	Not specified	88	0	0	75 (85.2%)	0	0	6 (6.8%)	Not specified			N/A
Dehaki	2010	Iran	5.4	6.7 (1 - 2.8)	188	39 (21%)	0	31 (17%)	19 (10.3%)	0	6 (3.2%)	Total= 2.1%			SF
Brown	2009	USA	90 (2 - 44yrs)	Not specified	1012	473 (47%)	0	264 (26%)	50 (11.0%)	0	20(8%)	17 (4.0%)	0	9 (3.0%)	No difference
Karamlou	2009	Canada	11 (2 - 69)	Not specified	36	3 (8%)	16 (45%)	15 (44%)	0	1 (2.7%)	2 (5.5%)	Not specified			EEEA
Kaushal	2009	USA	23 (1 - 4053)	5	201	0	201 (100%)	0	0	8 (3.9%)	0	0	4 (2%)	0	N/A
Thomson	2006	UK	1 (1 - 15.2y)	4.2 (1 - 10.6)	191	0	141 (73%)	0	0	7 (4.2%)	0	Total= 4.7%			N/A
Pandey	2006	UK	22 (3 - 600)	14 (9.2 - 17.3)	134	0	0	134 (100%)	0	0	20 (14.9%)	0	0	10 (7.4%)	N/A
Sudarshan	2006	Australia	17 (6 - 58)	4.5 (0 - 13)	24	0	13 (54%)	9 (38%)	0	2 (8.3%)	1 (4.1%)	Total= 13.6%			No difference
Wright	2005	USA	21 (2 - 365)	4.5	83	0	83 (100%)	0	0	4 (6.0%)	0	0	2 (2.4%)	0	N/A
Adeeb	2004	Malaysia	(0 - 40yrs)	8 (6 - 12.5)	114	54 (47%)	0	38 (33%)	2 (1.7%)	0	3 (2.6%)	Total= 5.2%			No difference
Maia	2004	Brazil	48m (11 - 14yrs)	4.6 (0 - 26)	113	79 (70.0%)	0	13 (11.5%)	10 (14%)	0	1 (9%)	Not specified			No difference
Wood	2004	Ireland	13.5 (1 - 300)	7.5 (0.5 - 16)	181	0	181 (100%)	0	0	4 (2.2%)	0	0	1 (0.5%)	0	N/A
Omeje	2003	Slovakia	42m (2 - 18 yrs)	Not specified	201	101 (51%)	24 (12%)	24 (12%)	10 (4.9%)	1 (0.5%)	0	Not specified			EEEA
Uchytil	2003	Czech R.	85m (2 - 44 yrs)	8.1 +/- 6.1	342	189 (55%)	0	24 (7%)	8 (2.3%)	0	2 (0.5%)	Total= 2.9%			No difference
Walhout	2003	Netherlands	34m	11.9 (0 - 29.3)	262	133 (51%)	0	0	19	0	0	Total= 2.6%			EEA*
Younoszai	2002	USA	2.2 (0.4 - 6.3)	1.5	88	88 (100%)	0	0	3 (3.4%)	0	0	0	0	0	N/A
Narasinga	2002	UAE	41+/_42	2.7+/-1.2	21	0	20 (95%)	0	0	5 (23.8%)	0	0	0	0	N/A
Corno	2001	Switzerland	Not specified	Not specified	104	56 (54%)	0	16 (14%)	1 (0.9%)	0	3 (2.8%)	0	0	0	EEA
McElhinney	2000	USA	18 (1 - 90)	1 (0.5 - 9.3)	103	64 (62%)	0	34 (32%)	Not specified			0	0	0	No difference
Jahangiri	2000	UK	Not specified	6.2+/- 4.6	185	0	0	185(100%)	0	0	11 (6%)	0	0	5 (3%)	N/A
Dodge-Khatami	2000	USA	158 (1 - 17 yrs)	5.2	271	18 (7%)	69 (25%)	61 (22%)	6 (2.2%)	5 (1.8%)	12 (4.4%)	Total= 2%			EEEA~

Table 60. Summary of published literatures 2000 – 2016: EEA: resection of coarctation and End-to-End Anastomosis; EEEA: resection of coarctation and Extended End-to-End Anastomosis; SF: no resection and Subclavian Flap; N/A: Not applicable (Study examines only one technique and there is no comparison of other techniques); Age: Median (range) or Mean ± Standard deviation or median alone (yrs: years, m: months, if not specified it is days); Follow-up: Median (range) or Mean ± Standard deviation or median alone, Number (%) for surgical techniques.

* EEA compared vs. Patch aortoplasty; ~ Patch aortoplasty was the superior technique which is not studied in this thesis

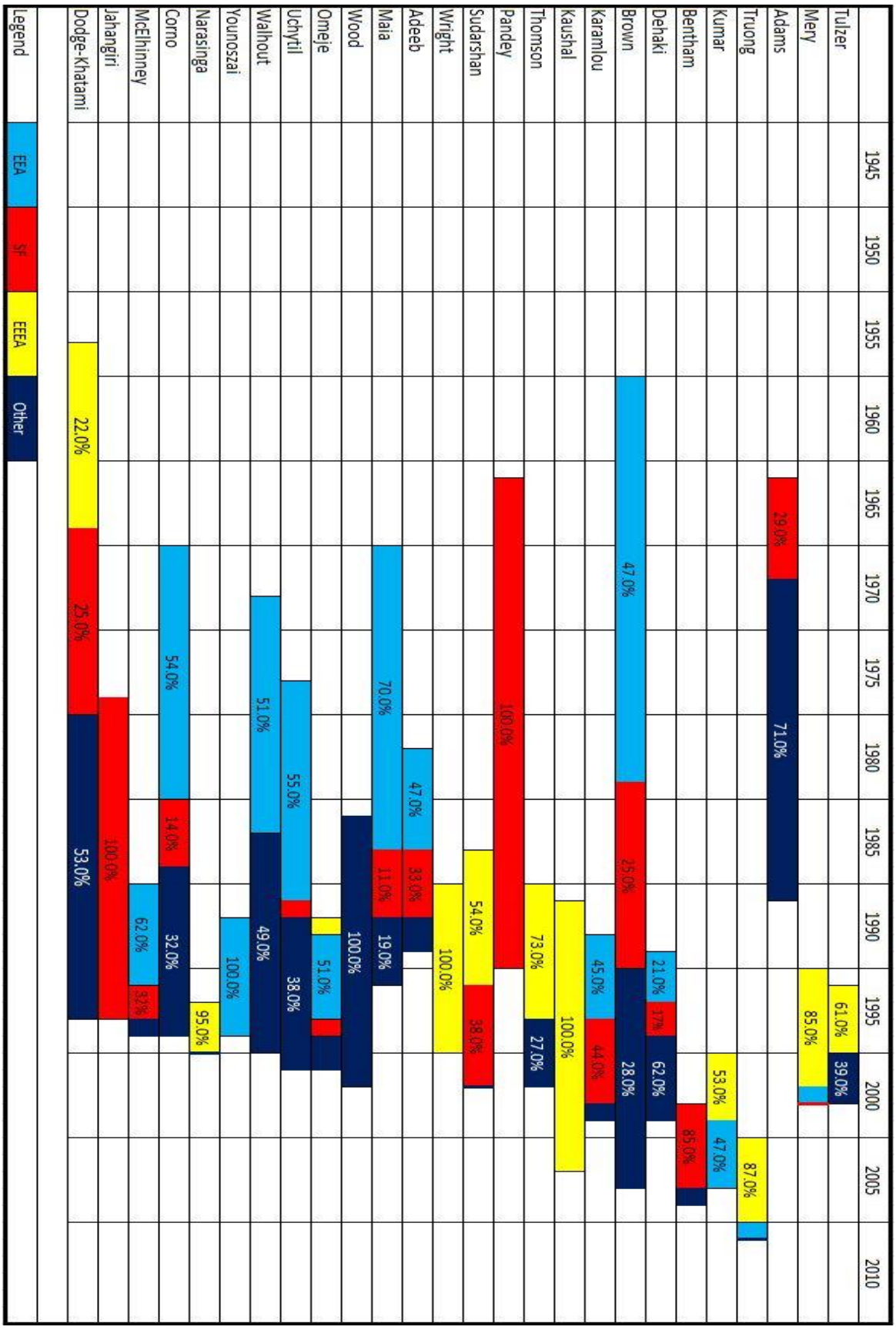

Figure 16. Published literatures 2000 – 2016. Horizontal bar shows the study period. The surgical techniques are demonstrated in different colours (legend) with the percentage of the used technique in the specified study period.

2.3 Discussion

The literature search and systematic review covered a wide spectrum of studies across the world which represent the surgical practice in the field of CoA during the past decades. The initial attempt in this thesis was to perform a meta-analysis or quantitative analysis on the retrieved data extracted from the literature. Meta-analysis is a part of systematic review which may not exist without it; however a systematic review can stand alone without a quantitative analysis. One of the important requirement for meta-analysis is the mathematical analysis of combined outcomes. The data retrieved from different studies need to be homogenous to allow an unbiased output of results. Heterogeneity particularly when it is clinical such as patients with different surgical intervention, hinders mathematical analysis of combined data. This may lead to out-put of invalid results. The meta-analysis of observational studies is common in medicine; while it is rare with no quantitative analysis in the field of CoA surgical repair. There is no guidelines for meta-analysis of observational cohorts and the majority of these quantitative studies are performed by applying the available guidelines on RCTs (Meuller 2018). Lack of guidelines for observational studies is a more pronounced problem when a high degree of heterogeneity exists in the combined data. In this situation applying RCT's guideline may jeopardise the validity and reliability of the study. There is no consensus on a statistical tool which can accurately gauge the heterogeneity. There are particular statistical measurements suggested to neutralise the heterogeneity in favour of performing a meta-analysis on observational studies (Rothstein 2008). On the other hand the ability of these statistical models to deal with a high degree of heterogeneity is limited. One of the major reasons for not being able to run a quantitative analysis on combined observational studies is a high level of statistical heterogeneity. In this Chapter there were appraised studies where no test of significance or event statistical analysis had been performed. This was also evident about different metric of same outcomes. For example there were no unified definition of re-coarctation among the appraised literature. Few studies adopted the principles of echocardiography and discussed a cut off for peak pressure gradient across the repaired site; however this was also different between these studies from 20 to 40 mmHg. Few other studies relied on the disparity of systolic BP between the upper and lower arm with inconsistency in a cut off figure similar to those of echocardiography. Of note the systolic BP gradient has been denounced by other studies as a mean to gauge the recurrence of coarctation (Thomson 2006). It is important to consider low quality of imaging technology before 70s which might have influenced the definition of re-

coarctation in those studies. Majority of final papers for systematic review in this Chapter suffered from a high degree of heterogeneity due to a wide spectrum of surgical intervention performed on patients which were concomitant with CoA repair. In many of these individuals even the CoA may not be considered as the primary pathology. For example patients with HLHS and proximal hypoplastic arch and coexisting CoA who underwent a complex surgery via median sternotomy, CPB and DHCA may not be comparable with a patient from the same population who had EEA via left thoracotomy and ischaemic clamp time of 18 minutes. This is largely due to different study design among different studies. For instance a large sample size which does include CoA also comprised concomitant congenital heart disease which need to be operated at the same time with CoA repair. Initially these patients were divided into three groups which is traditionally: 1- isolated CoA 2- CoA + VSD 3- CoA + Complex cardiac anomalies. Unfortunately this categorisation have not guaranteed a separate analysis; while it was very common for these studies to combine the groups together and measure the outcomes. This has been observed particularly with regard to post-operative complications while mortality and re-coarctation in some studies have been analysed separately. In many appraised studies patients underwent CoA and PA banding at the same time to allow a staged operation in future. PA banding although might be considered a simple operation, it has significant haemodynamic implications which may affect the pattern of antegrade flow in the aorta. These patients may not be comparable with isolated CoA with regard to the risk of re-coarctation. While in majority of appraised studies VSD has been reported as one of the most common intra-cardiac defects coexisting with CoA; in few papers re-coarctation rate has been studied in a mixed group of patients including isolated CoA and VSD + CoA. It is of note that in early studies it has been demonstrated that a large or unrestrictive VSD had an impact on the rate of re-coarctation (Trinquet 1988); however even in studies published after year 2000 this finding was not appreciated which inevitably has led to heterogeneity of the population and unreliable results.

One of the major factors saturating the combined data with heterogeneity was patient's age. This was prevalent in large cohorts from regional institutions reporting a large number of patients. Similar to those of surgical intervention an age categorisation was initially performed; however soon during the study and statistical analysis the patients were mixed age wise. This was more problematic when in few large and recognised studies adult patients were also included along with neonates. In the systematic review performed in this thesis many papers on CoA with reasonable data were excluded from

appraisal due to different outcome measurements. One of the main reasons of losing literatures in the systematic review during the primary filtration was lack of data presentation on surgical intervention of CoA. This was commonly observed in the studies reported by interventional cardiologists with a focus on re-coarctation; while the initial surgical journey of patients was not included. Clinical heterogeneity was commonly observed in studies by which the arch hypoplasia has been investigated. There were not identical definition and surgical intervention for the management of arch hypoplasia which coexisted with CoA. The definition of arch hypoplasia comprised a wide spectrum from an anatomical point of view based on echocardiography to observational information based on surgeon's intra-operative report. This has led to create a rather highly heterogeneous sample in each study where patients with hypoplastic proximal arch that should be analysed separately are included in statistical analysis with patients who underwent isolated CoA. It is surprising to observe that even in studies after year 2000, a hypoplastic arch as a separate pathology which commonly co-exists with CoA was not appreciated. Of note in many studies performed before 80s arch hypoplasia was not even reported in CoA population even when the sample was highly heterogeneous. For the abovementioned reasons a decision was made not to embark on quantitative analysis in this theses and only carry on with qualitative systematic review.

There is a considerable decrease in the rate of in-hospital mortality among the appraised studies through the time. This is largely owed to the usage of PGE_1 in the management of CoA which started in 80s; meaning less neonates in the cohorts after 90s were presented with CHF and critical condition. This was also evident about the surgical technique while the 70s' and even 80s' studies represent the surgeons' learning curve in the surgical management of CoA with different techniques. Majority of debates on suture materials belonged to 80s studies while today this issue has completely resolved with the usage of non-absorbable suture materials in majority of institutions. In early studies which go back to 60s and 70s the main focus was on the mortality rate rather than the incidence of re-coarctation which also has led to exclude a large number of studies from the critical appraisal. In addition in 80s and 90s an epidemiological shift from adults to neonates was observed; meaning more cohorts started to emerge on surgical management of CoA in children. As demonstrated on Figures 9, 10, 11 and 12 although the surgical techniques have evolved through the time and EEEA started to be used more frequently in years after 2000; there is no particular pattern of practice across the world. Out of 56 appraised papers 23 (41%) studies could not demonstrate any difference between the surgical

techniques in re-coarctation rate. This was also observed in comparing SF vs. EEA techniques. Nineteen (34%) studies reported one preferred surgical technique with no comparison to identify the best repair. In 14 (25%) studies where the different surgical techniques were compared with regard to re-coarctation and early mortality rate, 6 (43%), 3 (22%) 4 (28%) and one (7%) studies concluded in favour of SF, EEA, EEEA and SF+EEEA techniques respectively.

Generally after introducing PGE_1, more neonates could be stabilised and undergo surgery. This was also associated with an increase in the rate of re-coarctation in the past four decades. It has been demonstrated that the rate of re-coarctation is inversely proportional to the patient's age and it is more prevalent in neonates (Sudarshan 2006). This finding is also discussed in Chapter 3. Based on appraised studies in this Chapter Figure 17 demonstrates an increase in the rate of re-coarctation during 80s.

Figure 17. Rate of re-coarctation in four decades, the Y axis demonstrates the rate in percentage

The CoA repair technique has been evolved through the time. While patch aortoplasty became obsolete in late 80s, EEEA emerged to address the hypoplasia of the arch. Although SF has remained the preferred technique in many institutions, in the past 10 years there is an increase of EEA and EEEA techniques in the reported cohorts (Figure 18).

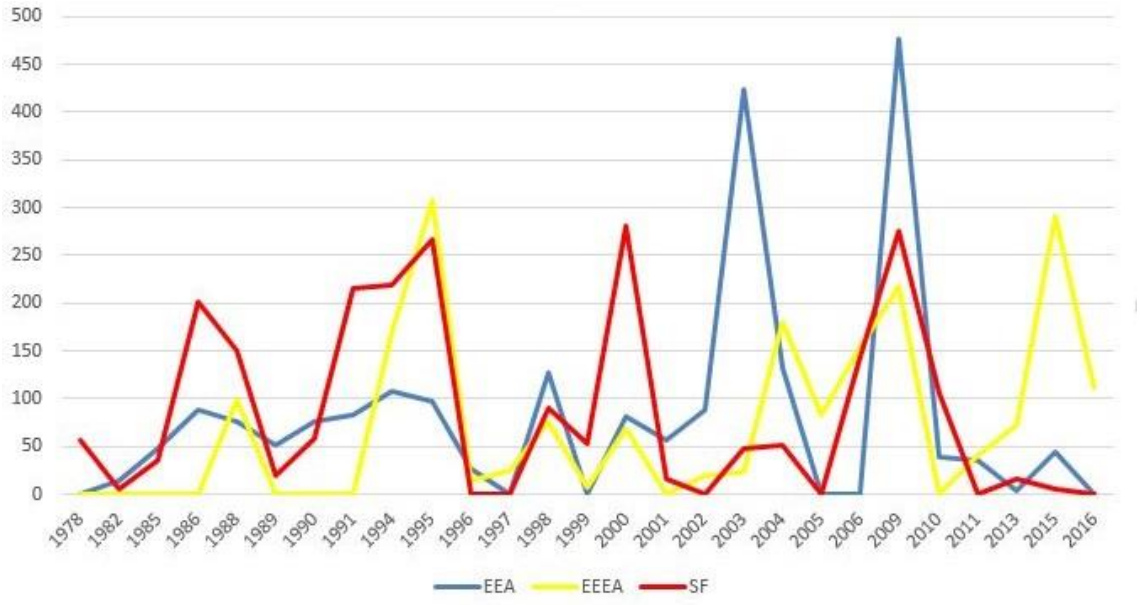

Figure 18. EEA, EEEA and SF techniques, X axis demonstrates the year of study publication and Y axis shows the total number of reported procedures

The role of training in the management of CoA and outcomes has been entirely ignored in the majority of appraised literatures. Sciolaro et al were the only investigators who examined the impact of training on outcomes which did not reveal any significant difference between the trainee and the consultant surgeon as the primary operator (Sciolaro 1991).

Ziemer et al in 1986 were the first to highlight the need for RCTs to examine the outcomes in CoA repair with different surgical repair strategies. Although several other authors also emphasised on the importance of RCTs in surgical management of CoA (Jahangiri 2000, Seirafi 1998), more than 30 years after the first RCT proposal there is no randomised studies performed on CoA to date.

In all appraised studies, prenatal diagnosis as the mainstay of CoA diagnosis have not been reported. This was also experienced by the author of this thesis as explained in the next Chapter only 2 (1.7%) patients were diagnosed prenatally.

In summary although there is no definite superiority identified among the appraised studies, the EEEA as an emerging repair technique has been appreciated which successfully addresses the arch hypoplasia.

3. Resect or not to resect: Is that the question?

3.1 Background

Since the first repair of CoA in children, the surgical technique and approach has been debated for decades. Today re-stenosis after repair is the main worry of surgeons which may become a persistent problem throughout the patient's life. EEA has been opted by many surgeons as the technique of choice while many other surgeons believe that SF technique provides a more reliable repair by avoiding circumferential anastomosis. On the other hand not resecting the coarctation tissue and jeopardising the left arm development have been emphasised by EEA supporters as the potential factors for failure. Several years after a rivalry between the two abovementioned techniques surgeons started to adopt a more aggressive approach to address the arch hypoplasia at the same time and that's how EEEA came to life. This was not the end of disputes as many surgeons criticised the latter technique for its complexity, long learning curve and less reproducibility. While surgeons entirely moved on from patch aortoplasty for undesirable outcomes; there were no direction towards the best surgical repair. There are numerous institutional cohorts within the past half a century with no RCTs to address a simple question: should coarctation be resected? Although initially this was considered as a common sense; the failing EEA technique in conjunction with glorious reports on SF approach from the institutions of excellence, made the situation even more complicated.

Royal Hospital for Children of Glasgow which was formerly called Royal Hospital for Sick Children or Yorkhill is a centralised institution where cardiac surgery across Scotland since 2000 is performed in this hospital. Cardiac surgery department covers nearly one million children in Scotland and on average performs 350 - 400 operations per year. Literature search revealed that the outcome of CoA repair has not been reported in Scotland previously. In the past decade on average 25 CoA operations per year have been performed in Scotland. This operations included both isolated and complex CoA repairs concomitant with other cardiac surgeries. The advantage of reporting from a centralised regional institution for retrospective studies is lower rate of missing patients in follow-up. Despite a satisfactory outcome in repairing CoA, the surgical practice and the technique of choice in Scotland is individualised which is similar to several other

counterpart institutions across the world. Therefore exploring the Scottish experience in repairing CoA with the view to examining the major surgical techniques: EEA, SF and EEEA and their impact on re-coarctation was the main drive behind the study in this Chapter. It was also aimed to have a rather focused aim on isolated CoA in children as an independent pathology to eliminate any risk of bias inflicted by complex operations as well as adult patients.

The findings of systematic review in Chapter 2 directed the study design in this Chapter. This includes avoiding heterogeneity, designing primary and secondary outcomes as well as the impact of repair technique on re-coarctation rate.

3.2 Patients and Methods

From January 2002 to December 2012, 117 consecutive patient with the age of less than 16-year-old underwent surgery for the repair of CoA. Patients' data was retrieved retrospectively from casenotes, hospital electronic database and out-patient clinic correspondence. Further supplemental data was also obtained from Scotland picture archiving and communication system (PACS) this included pre-operative and post-operative CT-scan or MRI where available. Echocardiography images were also retrieved electronically.

All echocardiography images were retrieved in entirety with cine images to allow more accurate measurement of the aortic parameters. Echocardiography parameters which were measured and calculated for this study are as follows:

- Left Ventricular Function (LVF)
- LVOT largest diameter (mm) in parasternal view
- Mitral valve annulus (mm) in parasternal view
- Aortic valve hinge points distance (mm) in parasternal and long axis view
- Ascending aorta dimeter (mm)
- Transverse arch length from the proximal BCA to distal LSA (mm)
- Arch diameter between BCA and LCCA (mm)
- Arch diameter between LCCA and LSA (mm)
- Isthmus dimeter (mm)
- Descending aorta diameter distal to coarctation (mm)
- Descending aorta diameter distal to the repaired site (mm)

- VSD
- ASD
- PDA

The following parameters were investigated pre-operatively only: ASD, VSD, PDA, Mitral valve annulus, Aortic valve hinge points distance and LVOT.

The aortic parameters which were measured by echocardiography are summarised in Figure 19.

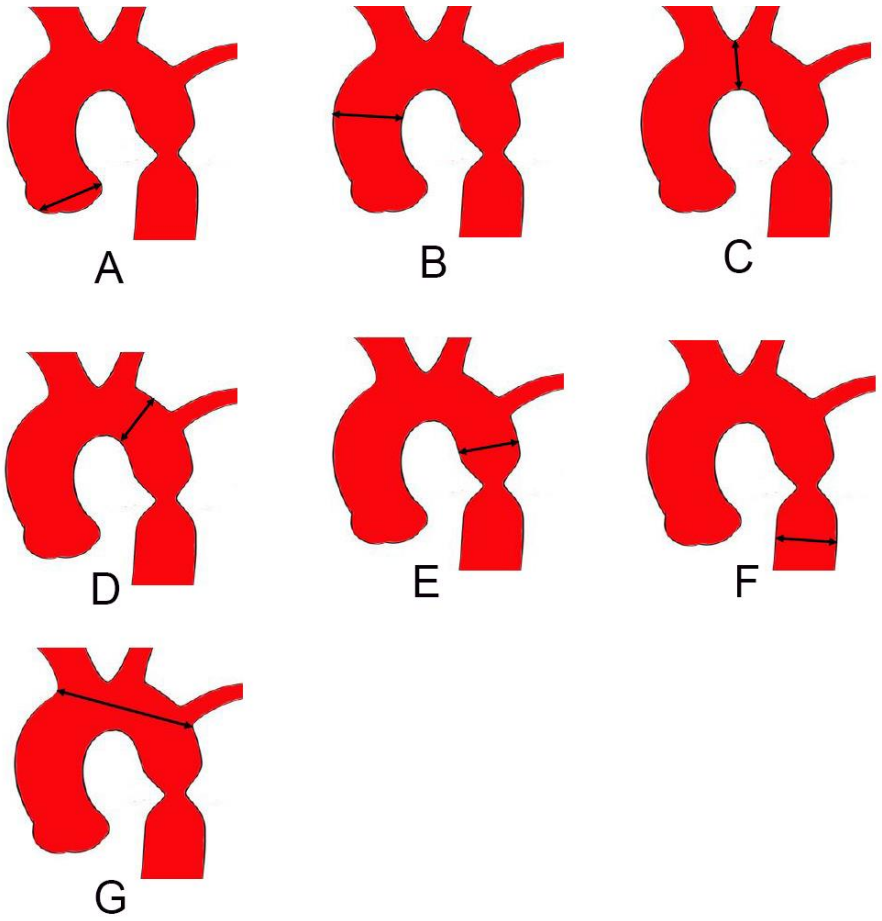

Figure 19. Aortic parameters measures by echocardiography. A: Aortic valve hinge points distance (mm), B: Ascending aorta dimeter (mm), C: Arch diameter between BCA and LCCA (mm), D: Arch diameter between LCCA and LSA (mm), E: Isthmus dimeter (mm), F: Descending aorta diameter distal to coarctation (mm), G: Transverse arch length from the proximal BCA to distal LSA (mm).

In order to increase the accuracy and reliability of echocardiography measurements, all retrieved data were re-checked by two separate operators. One of the operators was a senior specialist registrar in paediatric cardiology subspecialising in paediatric cardiac imaging and the second operator was one of the consultant paediatric cardiologists. Both operators have been acknowledged on the acknowledgement page. A sample of echocardiographic view which has been used for measurements and assessment is demonstrated on Figure 20. Follow-up was performed at central or peripheral cardiology departments on yearly basis.

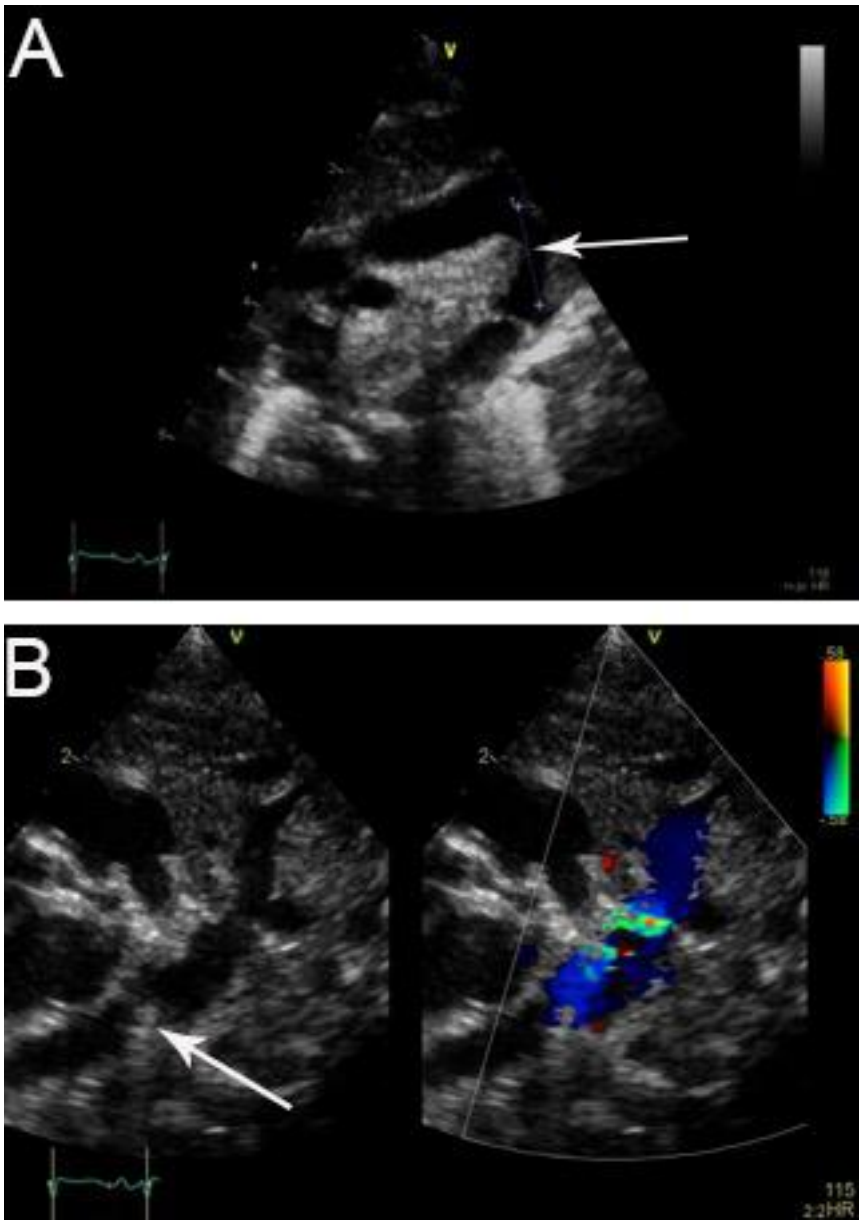

Figure 20. Echocardiographic parasternal window for arch assessment. A: The transverse arch length is measured by built-in tools (white arrow) B: CoA (white arrow).

3.2.1 Definitions

Patients were retrospectively enrolled into the study by applying the following definitions which were exclusively defined and used for this study:

Isolated CoA: A discrete stenosis of descending aorta which is not associated with other congenital heart disease with haemodynamic significance. Therefore by applying this definition all patients with stenosis proximal to the origin of LSA and interrupted arch were excluded from the study.

Restrictive VSD: A defect in interventricular septum which is small enough to restrict the flow through it and does not require any intervention to close it. The decision of not intervening was made by a multi-disciplinary team (MDT) comprising paediatric cardiac surgeons as well as paediatric cardiologists. On available follow-up echocardiography images all restrictive VSDs were either spontaneously closed or reduced to a smaller size. By applying this definition all patients with non-restrictive VSDs or requiring intervention were excluded from the study.

Small ASD or patent foramen ovale (PFO): A defect in interatrial septum which is small enough not imposing any haemodynamic disturbances. It also does not require any intervention. The decision of not intervening was made by a multi-disciplinary team (MDT) comprising paediatric cardiac surgeons as well as paediatric cardiologists.

Arch/aorta hypoplasia: The definition described by Moulaert et al in 1976 was used for this study. According to their definition: “The proximal arch segment is defined as hypoplastic when the external diameter of that segment amounts to 60% or less of that of the ascending aorta. The corresponding limit for hypoplasia in the distal arch is 50%, and for the isthmus 40%.” According to this definition distal arch is a segment between LCCA and LSA. Therefore all patients with proximal and distal arch hypoplasia were excluded from the study. This is in accordance with the definition of CoA and exclusion of patient with any stenosis proximal to the origin of LSA. To verify pre-operative echocardiographic evaluation of the arch, surgeon’s observation on the operation note was also used to confirm the diagnosis of arch hypoplasia.

BAV: A true BAV with no haemodynamic significance (no stenosis and no regurgitation) which does not require any intervention. The decision of not intervening was made by a multi-disciplinary team (MDT) comprising paediatric cardiac surgeons as well as

paediatric cardiologists. By applying this definition all BAVs requiring intervention at the same time were excluded from the study.

LBW: the WHO definition was considered for patients born with a low weight. For this purpose weights less than 2.5 Kg were considered as LBW.

Re-coarctation: Re-stenosis of the repaired site which was identified at follow-up by echocardiography. A peak velocity of 2.5 m/s in the descending aorta detected by a continuous Doppler while the transducer is positioned at suprasternal notch and a peak pressure gradient of greater than 25 mmHg across the repaired site in combination with clinical presentation and symptoms which mandates a re-intervention was considered as re-coarctation. The peak pressure gradient was obtained using the modified Bernoulli equation:

Peak pressure gradient = $4 \times (V_1 - V_2)^2$

(V_1: Flow velocity in the ascending aorta V_2: Flow velocity in the descending aorta)

This definition is also in accordance with American Heart Association (AHA) guidelines where a peak pressure gradient of greater than 20 mmHg across the repaired site is an indication for re-intervention (transcatheter balloon angioplasty) regardless of patient's age (Feltes 2011).

Deprivation: This has been defined as per Scottish Index of Multiple Deprivation released in 2016 (SIMD 2016) a criteria which has been launched by the Scottish government (www.isdscotland.org 2019) for the past decade. By SIMD multiple aspect of deprivation such as nutrition, crime rate and education have been combined together and presented as an index. In this model Scotland has been given geographical ranks by an index from 1 which is the most deprived to 6505 which is the least deprived. In this study SIMD deciles which have been introduced by the similar authorities have been used for analysis. In SIMD model of deprivation deciles are ranked from 1 to 10 which is from the most deprived to the least deprived.

3.2.2 Surgical intervention:

All surgical approaches (as treated) in this study were via left thoracotomy with incision in the 4^{th} or 5^{th} intercostal space. None of operations (intention-to-treat) were performed on complete CPB or DHCA. Two patients underwent left heart bypass for the repair of CoA. There were no induced hyperthermia during the procedures. Ischaemic cross clamp

has been utilised and the cumulative ischaemic time has been recorded. Anastomosis was performed with non-absorbable sutures in a contentious fashion. The surgical techniques by which in this study the CoA was treated are listed below:

EEA technique: The duct was tied off and coarctation segment resected. After limited mobilisation of the two ends, the two ends of the aorta were anastomosed to each other in an end-to-end fashion.

SF technique: The duct was tied off. The SA was ligated and transected as distal as possible. A longitudinal continuous incision was made on the anterior surface of the SA, isthmus and coarctation site. The SA flap was turn down and anastomosed to the aorta to cover the incision on the isthmus and coarctation site. No resection of coarctation was performed in SF technique.

EEEA technique: Similar to those of EEA with a difference in spatulating the inferior arch of the proximal end. Also spatulating of the distal end might have been performed; however there were no patients with side-to-side or end-to-side in the study population.

EEA + SF technique: Is a combination of the two procedures. The key feature is the use of SA flap with excision of the coarctation tissue.

Interposition graft: the coarctation segment is resected and instead of end-to-end anastomosis a synthetic tube graft has been used to connect the two ends of the aorta.

3.2.3 Statistical analysis

Categorical data were displayed as frequencies and percentages, and comparisons were made with the Chi-square test. Normality criteria were checked with D'Agostino-Pearson test and met for each continuous variable. Paired- or independent-sample t-test was used for normally distributed data, as appropriate, and data were presented as mean and standard deviations. Box and whisker charts for age and weight are presented. Considering time-dependent outcomes, Kaplan–Meier analyses was used to assess the probability of re-coarctation, and groups were compared using Log Rank test. For this purpose, data was compared according to the following variables: surgical techniques, age (less or more than 30-day-old), and weight (less or more than 2.5 kg). Kaplan-Meier graphs are presented with number at risk. The 95% confidence interval of the function is also demonstrated. Censored cases are shown as single hash marks for each point of time. Risk factors for re-coarctation were analysed using a Cox regression model. Univariable

analysis was performed for preoperative variables (e.g. age, weight,) and echocardiographic data (e.g. impaired LVF, diameters, etc.). Variables are included in the multivariate logistic regression model using a stepwise approach in case of univariate *p* value of less than 0.10. Two different multivariable Cox regression models are created: for baseline characteristics and for the pre-operative echocardiography data. As for Cox regression, proportional hazard assumption is tested with Schoenfeld residuals and is not violated in the described outcome for any variable. "Delta" variables are created as paired differences between the pre-discharge and the follow-up echocardiographic values. Interaction between "Delta gradients" or "Delta velocities" and surgical techniques was evaluated with one-way analysis of variance (ANOVA) with multiple pairwise comparisons using Bonferroni's test, in which a *p* value of less than 0.01 was considered statistically significant. In all other cases, a *p* value of less than 0.05 was considered statistically significant to reject the null hypothesis. Statistical analysis was performed using Stata Statistics (version 13.0, 2013; StataCorp, College Station, Texas).

3.2.4 Ethical approval

This study has been reviewed twice in 2014 and 2016 by the institutional review board (Royal Hospital for Sick Children and Royal Hospital for Children) and the ethical approval has been waived. The review of follow-up was competed in 2016 while the author of this theses was given an honorary employment in Royal Hospital for Sick Children only for this purpose. Mrs Emma-Jane Gault the Research Governance Officer in University of Glasgow has been informed regarding the current format of this thesis. She was also informed that all retrieved data will remain in Royal Hospital for Sick Children and will not be transferred to any other entities outside the Royal Hospital for Sick Children jurisdiction.

3.3 Results

The results have been analysed in four different timeline: Pre-operative, Operative, early post-operative and late post-operative. Isolated CoA in Scotland has also been discussed in this section.

3.3.1 Pre-operative characteristics

Patients' mean age was 296-day-old ranging from 3-day-old to 13.3-year-old (Figure 21). Male patients comprised 69.2% (81 patients) of the population. Neonates (age < 30-day-old) were 53.8% (63 patients). Patients at the time of surgery had a mean weight of 6.4 Kg ranging from 1.6 Kg to 43.7 Kg (Figure 22). Antenatal diagnosis of isolated CoA carried out in only 2 (1.7%) patients.

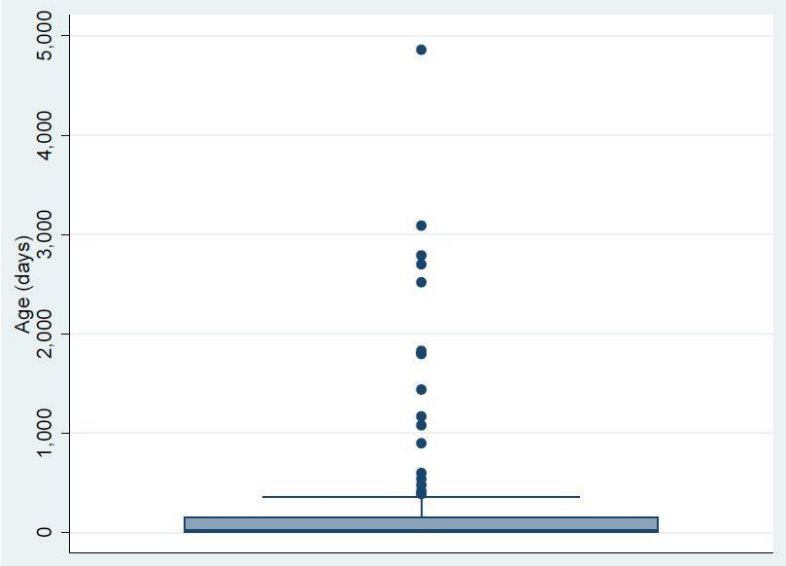

Figure 21. Box and whisker plot for age

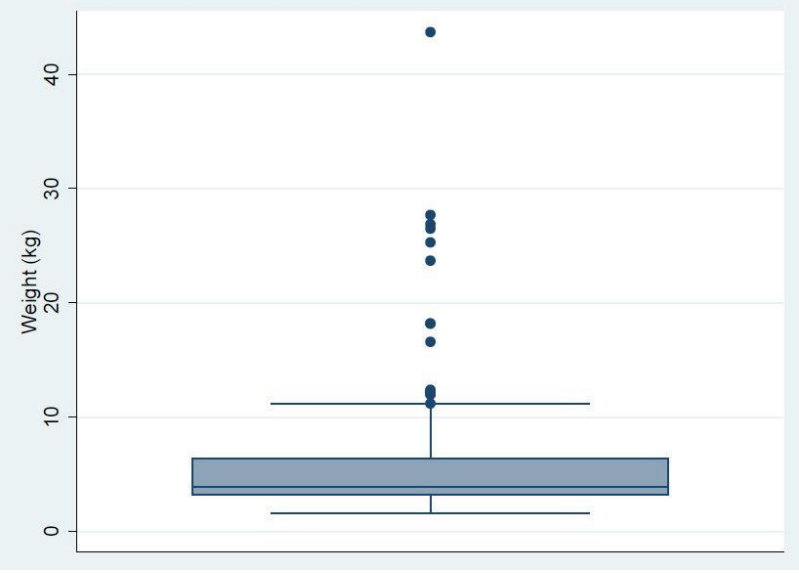

Figure 22. Box and whisker plot for weight

Failure-to-thrive was the cardinal clinical manifestation of symptomatic patients with 55 (47%) patients. Similarly 54 (46.1%) of patients were transferred from a PICU of the referring hospital; however not all of them remained intubated and ventilated. Patients who remained ventilated for at least 72 hours after transfer were 36 patients (30.8%). In one (0.8%) patient ventilation was due to an ear nose and throat (ENT) intervention and not for respiratory failure or critical condition. One (0.8%) other patient underwent hemicolectomy for NEC pre-operatively and remained ventilated until surgery for CoA repair. None of the transferred patients for surgery of isolated CoA died prior to surgery. Fifty-six patients (47.9%) were duct dependant in whom PGE_1 infusion was required prior to surgery. In one (0.8%) patient PGE_1 could not maintain the DA patency; therefore the patient was operated as an emergency before 24 hours after admission. Patients who presented with CHF requiring inotropes prior to surgery were 11.1% (13 patients) of the population. The incidence of Turner syndrome in this population was 6% (7 patients). Other associated congenital syndromes with isolated CoA involving one (0.8%) patient each, were as follows:

- Agenesis of corpus callosum
- Acrocephalosyndactyly
- Apert syndrome
- Pierre Robin syndrome
- Short stature syndrome

Incidental finding of CoA was identified in 45 (38.5%) patients. Forty-two (93.3%) of these patients were identified by detecting a murmur at routine examination. Thirty-eight (32.5%) patients underwent an elective operation for the treatment of CoA, while 3 (6.7%) patients were diagnosed by ENT specialist when they presented with stridor. The preoperative characteristics are summarised on Table 61. The most prevalent associated congenital heart disease was BAV (24.7%) and then VSD (14.5%). This is demonstrated on Table 62. Three (5.1%) patients pre-operatively underwent balloon aortoplasty and dilatation of coarctation by catheter intervention. One of these patients was diagnosed incidentally and all of them later underwent surgical repair of CoA electively. Echocardiography was available for two of them during the follow-up period which demonstrated a peak velocity of 2.4 m/s and 1.6 m/s across the repaired site. None of these patients developed re-coarctation.

	Number (Total = 117)	Percentage %
Age (day-old)	296.6 ± 731.4 (range 3 ds – 13.3 yrs)	
Age < 30-day-old	63	53.8
Male	81	69.2
Weight (Kg)	6.4 ± 6.4 (range 1.6 - 43.7)	
Weight < 2.5 Kg	8	6.8
Failure to thrive	55	47.0
DiGeorge syndrome	0	0
Trisomy	0	0
Turner syndrome	7	6.0
Prostin infusion	56	47.9
Ventilation	36	30.8
Inotropes infusion	13	11.1
Admission from ICU	54	46.1
Elective	38	32.5
Incidental finding	45	38.5
Arch hypoplasia	10	8.5

Table 61. Summary of pre-operative characteristics (ds: day-old, yrs: year-old)

	Number (Total = 117)	Percentage %
VSD	17	14.5%
BAV	29	24.7%

Table 62. Concomitant congenital heart disease with no haemodynamic significance (VSD: Ventricular septal defect; BAV: Bicuspid aortic valve)

3.3.2 Operative results

The summary of surgical techniques and operative data is presented on Table 63. One (0.8%) patient with LBW (weight = 2.3Kg) and arch hypoplasia initially underwent EEEA operation. However after releasing the clamp it was noted that the high peak pressure gradient was not acceptable. As the exposure was difficult a decision was made to convert to median sternotomy to assess the entire arch at the same time. The patient was placed on CPB with a total time of 222 minutes and cross clamp time of 111 minutes. The repair was taken off and once again re-anastomosed with EEEA technique; however a bovine vein patch was used to augment the anastomosis site. Patient stayed in PICU for 7 days and discharged home on post-operative day 30 with peak velocity across the

repaired site at 2 m/s; however did not survive during the follow-up period for a non-cardiac reason which will be discussed later in this Chapter.

	Number (Total = 117)	Percentage %
Type of operation (Intention-to-treat)		
EEA	38	32.5
EEEA	24	20.5
EEA+SF	6	5.1
IG	1	0.9
SF	48	41.0
Type of operation (As treated)		
EEA	33	28.2
EEEA	24	20.5
EEA+SF	6	5.1
IG	1	0.9
SF	53	45.3
Conversion to sternotomy	1	0.8
Patch augmentation	2	1.7
Coarctation resection	64	54.7
Complete CPB	1	0.8
Left heart CPB	2	1.7
Ischemic X-clamp (min)	20.5 ± 9.5 (range 10 – 72)	

Table 63. Summary of surgical techniques and operative characteristics

Two (1.7%) patients who were 5- and 7.5-year-old with incidental finding of CoA and concomitant BAV underwent CoA repair with EEA technique via left thoracotomy using left heart bypass. The CPB in these two patients were 24 and 40 minutes and the ischaemic cross clamp 16 and 36 minutes. Both patients were discharged home and did well during the follow-up period. In one of the patients who underwent SF technique PTFE patch was also used in combination with SA flap to augment the anastomosis site. This patient was discharged home with a peak velocity of 1.6 m/s across the repaired site which became 2.4 m/s with no continuation of diastolic flow in the arch during the follow-up period; although patient remained asymptomatic with no re-intervention. Post-operative CT-scan of this patient also did not reveal any re-stenosis. Five (4.2%) patients with an intention-to-treat were supposed to undergo CoA repair by EEA technique however as per surgeon decision mainly due to isthmus hypoplasia these patients underwent SF technique.

3.3.3 Early post-operative results

A summary of early post-operative complications are presented on Table 64. Early mortality occurred in one (0.8%) patient. This patient presented in 2004 with severe CoA which was duct dependant. Prior to cardiac surgery patients developed NEC requiring hemicolectomy. The patient remained on PGE_1 infusion and ventilated in PICU until the operation. The patient had a normal arch anatomy and underwent EEA with ischaemic clamp time of 12 minutes. Although patient was initially discharged from PICU post-operatively; due to persistent large bowel disease did not survived in the hospital and died 3 months after operation. Immediate post-operative echocardiography in PICU revealed a peak velocity of 1.9 m/s across the repaired site. Post-operative cardiopulmonary arrest occurred in 1 (0.8%) patient, a 2-month-old patient who presented with duct dependant CoA admitted to PICU on ventilation, inotropes and PGE_1 pre-operatively. The patient's aortic arch was anatomically normal; however he was in CHF with impaired LVF. The patient underwent an uneventful surgery with SF technique and 20 minutes ischaemic cross clamp time. On his day of surgery he developed cardiopulmonary arrest requiring 25 minutes cardiopulmonary resuscitation (CPR). The CPR was successful although a brain CT-scan which was ordered after an episode of seizure revealed a right parietal focal infarct. This patient at the time of discharge and during the follow-up did not show any neurological deficit. Neurological event occurred in 4 (3.4%) patients. As stated previously one of them was the patient who developed cardiopulmonary arrest with a prolonged CPR who was discharged with no neurological deficit. Two other patients developed minor intracranial haemorrhage in caudothalamic region with no neurological dysfunction from whom one of them developed seizure post-operatively which prompted the brain CT-scan. At follow-up these two patients did not have any neurological deficit. One (0.8%) remaining patient developed a permanent paraplegia. This patient had an aberrant right SA who initially underwent EEA. The operation became complicated by persistent high gradient across the repaired site which eventually the SF was performed as a bail-out procedure. The surgeon had to reconstruct the anastomosis three times with a cumulative 72 minutes ischaemic cross clamp time which is the highest recorded ischaemic cross clamp time in the study population. The patient was discharged home; however during the follow-up period up to age of 11-year-old used walking aids due to permanent paraplegia. Statistical analysis revealed that the incidence of neurological event is significantly associated with an increased ischaemic cross clamp time ($p = 0.001$).

Superficial wound infection on the site of left thoracotomy happened in 9 (7.7%) patients. All wounds entirely healed at the first post-operative clinic review and did not require invasive intervention. One of the most common early complications was an injury to the RLN causing vocal cord palsy. Six (5.1%) patients were diagnosed with RLN injury out of which 4 patients' symptoms subsided significantly prior to discharge. None of these patients had swallowing difficulties and they were discharged home. Respiratory failure occurred in 4 (3.4%) patients who were all neonates and were discharged home. One of them was managed by non-invasive ventilation support and continues positive airway pressure (CPAP). The other three patients were previously admitted from PICU for surgery needed to be re-intubated and stayed in PICU post-operatively 25, 12 and 10 days. Horner's syndrome was observed in 2 (1.7%) patients and chylothorax in 3 (2.6%) patients. All patients with chylothorax were initially put on conservative management. One (0.8%) of the patients did not respond to conservative management and therefore underwent left sided pleurodesis for prolonged chylothorax. All of these patients did well during the follow-up period. Low cardiac output was observed in one (0.8%) patient who presented with duct dependant CoA and pre-operative PICU admission. The patient's LVF was impaired pre-operatively which required inotropic support after surgery. This patient was discharged home and was doing well during the follow-up period. The only patient who developed renal failure with deranged urea and creatinine was the patient who required CPR after cardiopulmonary arrest. The renal failure regressed by conservative management. The patient had a normal renal function at follow-up. Four patients developed NEC post-operatively; however in one of the patients persistent NEC pre-existed as described above. The other three patients were managed conservatively with satisfactory outcomes. There were no sepsis or use of ECMO in the study group. No immediate left upper limb ischaemic event was recorded for the patients who underwent SF technique.

	Number (Total = 117)	Percentage %
ICU stay (days)	2.1 ± 3.6 (range 1-25)	
Respiratory failure	4	3.4
NEC	4	3.4
Horner's syndrome	2	1.7
Vocal cord palsy	6	5.1
Cardiac arrest	1	0.8
Renal failure	1	0.8
Neurologic events	4	3.4
Seizure	2	1.7
ECMO	0	0
Chylothorax	3	2.6
Low cardiac output	1	0.8
Pacemaker implantation	0	0
Wound infection	9	7.7
Re-exploration for bleeding	1	0.8
Sepsis	0	0
In-hospital death	1	0.8

Table 64. Summary of early post-operative complications

3.3.4 Late post-operative results

Patients were followed up for 51.6 ± 50.8 months with a maximum range of 188.2 months. All the patients who survived in the hospital and discharged were reviewed in out-patient clinic. After the first year 5 patients were lost during the follow-up leaving the study with a complete follow-up at 95.6%. One (0.8%) patient who underwent EEEA and required conversion to sternotomy and was discussed above in this Chapter, died during the follow-up period. This is the only late mortality which occurred 4.5 months after operation. The cause of death was salmonellosis and severe diarrhoea. This patient's last echocardiography before death revealed satisfactory repair with a peak velocity of 1.8 m/s across the repaired site.

Re-coarctation as the primary endpoint occurred in 11 (9.5%) survivors. Five (8%) patients whose coarctation was resected during the operation developed re-coarctation versus 6 (11.3%) re-coarctation in patients with no resection. Statistically there were no difference between resection and no resection with regard to re-coarctation rate.

	Resection	No resection	P value
Re-coarctation	5 (7.8%)	6 (11.3%)	0.371

	Re-coarctation	P value
Type of operation (as treated)		0.630
EEA	2 (6.2%)	
EEEA	1 (4.3%)	
EEA+SF	1 (16.6%)	
IG	0 (0.0%)	
SF	7 (13.2%)	

Table 65. Re-coarctation as per surgical techniques

The comparison between resection vs. no resection with regard to the incidence of re-coarctation was also examined by a Kaplan-Meier curve (Figure 21) which did not show any statistical differences (Log rank = 0.404).

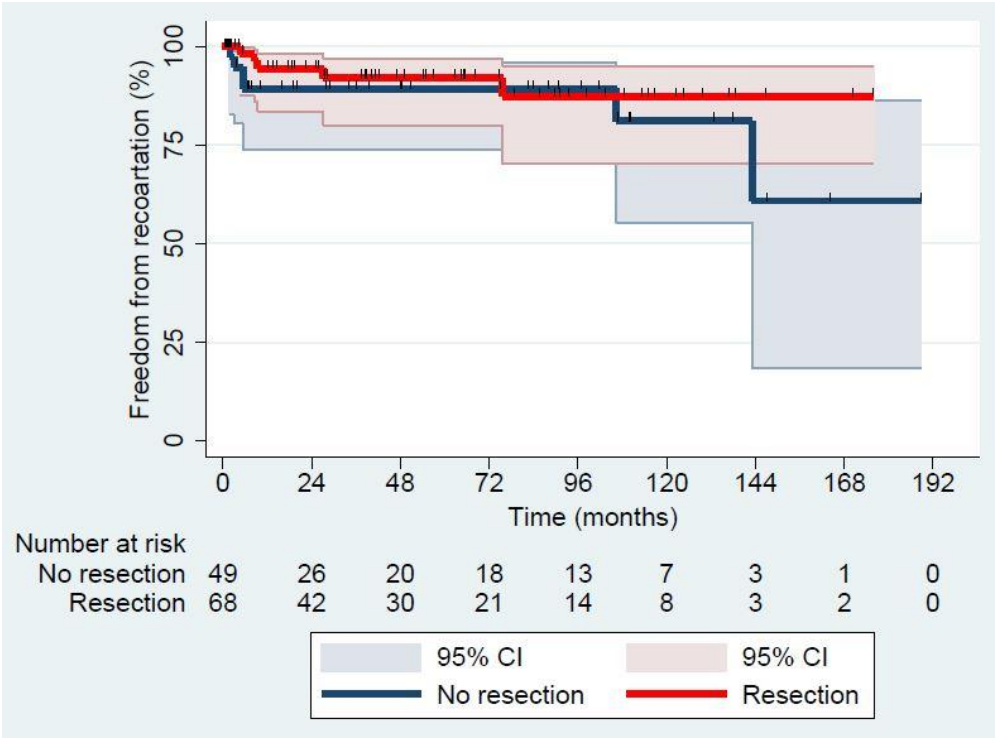

Figure 23. Kaplan-Meier curve: Resection vs. no resection

The surgical technique did not have an impact on re-coarctation rate (Table 10). Nine (81.8%) of patients with re-coarctation were neonates. Seven (63.6%) patients developed re-coarctation in the first year after surgery. All of patients with re-coarctation underwent

catheterisation and then balloon dilatation with immediate satisfactory outcome and peak pressure gradient of less than 15 mmHg across the repaired site. One (9%) patient developed re-re-coarctation 4.5 months after re-intervention for which underwent second balloon aortoplasty with satisfactory results. A summary of patients with re-coarctation and their management is demonstrated on Table 66.

Age at surgery	Surgical technique	Time to 1st re-intervention (month)	Time to 2nd re-intervention (month)	Intervention	Current status
23-day-old	EEA+SF	27	-	Balloon dilatation	Alive
3-day-old	SF	3	-	Balloon dilatation	Alive
3-day-old	EEA	9	-	Balloon dilatation	Alive
120-month-old	SF	5.5	-	Balloon dilatation	Alive
12-day-old	SF	1.5	4.5	Balloon dilatation	Alive
5-day-old	SF	1.5	-	Balloon dilatation	Alive
4-day-old	SF	8.5	-	Balloon dilatation	Alive
19-day-old	SF	34	-	Balloon dilatation	Alive
20-day-old	EEEA	75	-	Balloon dilatation	Alive
45-day-old	EEA	4.5	-	Balloon dilatation	Alive
27-day-old	SF	146	-	Balloon dilatation	Alive

Table 66. Patients with re-coarctation

The impact of LBW and age as a neonate on the rate of re-coarctation was also examined. The LBW did not have any influence on the occurrence of re-coarctation which is demonstrate on Figure 24 (Log rank=0.057). Interestingly more re-coarctation occurred in patients with a weight of greater than 2.5 Kg. As mentioned above the majority of patients with re-coarctation were neonates and a subsequent Kaplan-Meier curve (Figure 25) revealed that the occurrence of re-coarctation is significantly associated with neonate's age group (Log rank = 0.029).

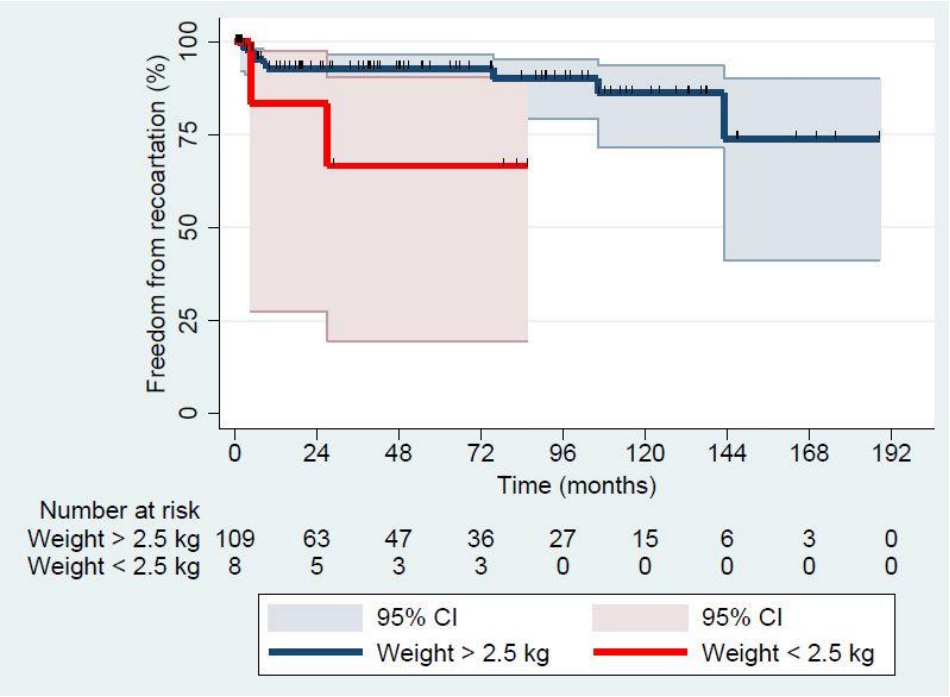

Figure 24. Kaplan-Meier curve: Weight > 2.5 Kg vs. weight < 2.5 Kg

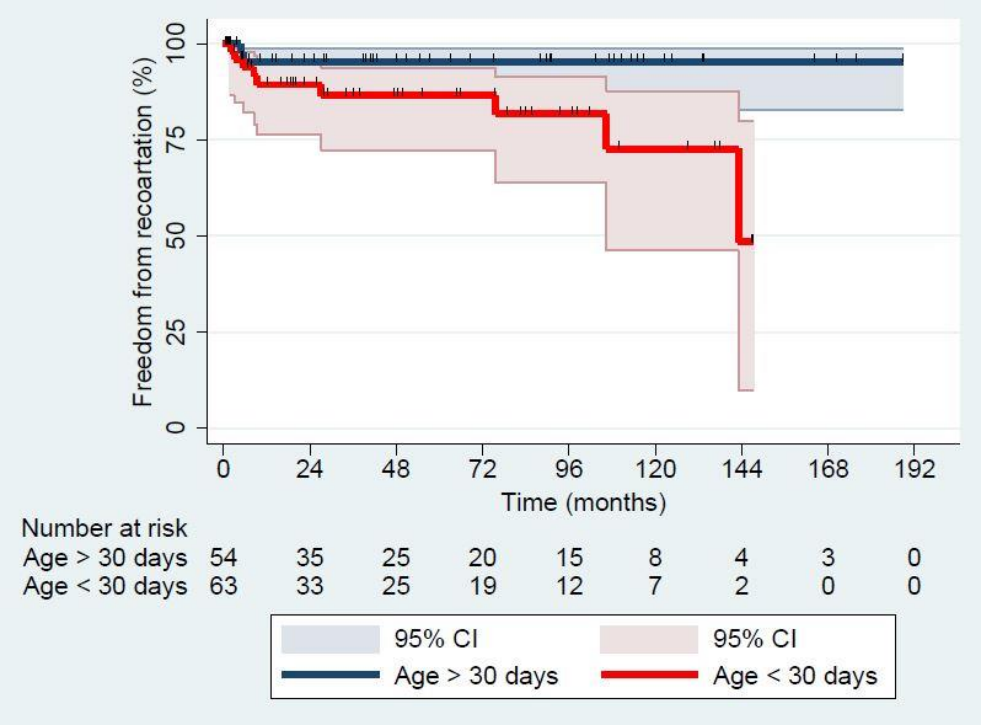

Figure 25. Kaplan-Meier curve: Neonates vs. age > 30 day-old

Total freedom from re-coarctation in the population is demonstrated on a Kaplan-Meier curve which is shown on Figure 26. Freedom from re-coarctation at 5 and 8 years was 92% $\pm$ 0.3% and 89% $\pm$ 0.4% respectively.

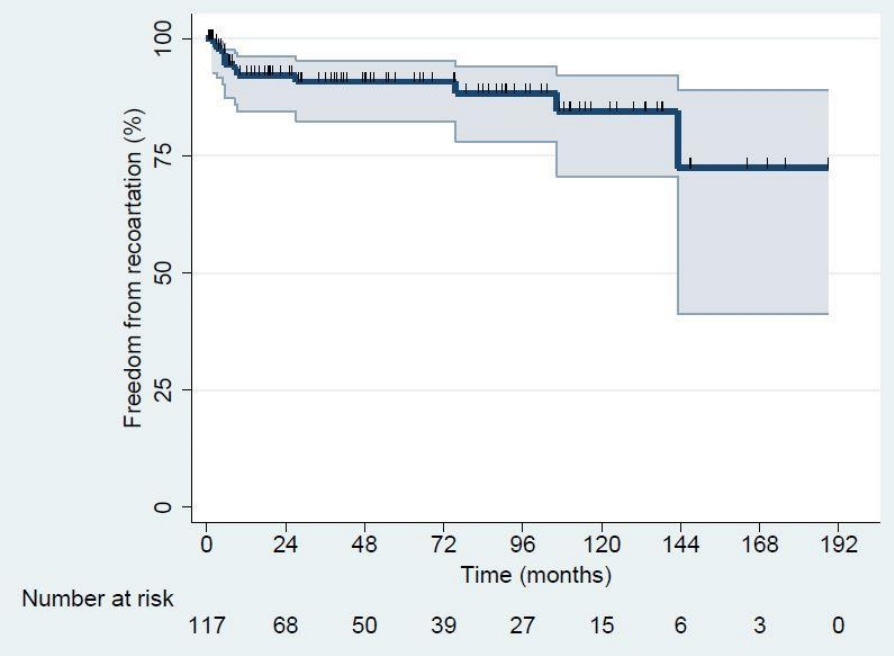

Figure 26. Kaplan-Meier curve showing freedom from re-coarctation for all patients

Echocardiography performed on all 117 patients pre-operatively; however the moving images for the purpose of measurement analysis were available for 100 (85%) patients. Similarly on all patients after surgery and prior to discharge echocardiography has been performed. The images belonged to earlier studies were missing in 15 patients meaning that cine images prior to discharge was available for 87%. During the follow-up period all 115 survivors underwent echocardiography across Scotland in central or peripheral centres. Many of these images are only focused on isthmus peak velocity or gradient with inadequate views to analyse the arch or the aorta entirely. The echocardiography images at follow-up which had a sufficient quality to allow a full analysis as per methodology protocol were available in 50 (43%) of patients. Echocardiographic reports were used for data collection in all of those patients whose cine images were not retrievable.

The echocardiographic characteristics as per methodology protocol for aortic measurements at three points of care: pre-operative, pre-discharge and during follow-up, are summarised in Tables 12, 13 and 14 respectively.

Variable	Mean	Std. Dev.	Min	Max
MV annulus	11.97	4.8	6	26
LVOT	7.58	2.58	4	18
AV hinge point	7.53	2.90	4	18
Asc. aorta	9.55	3.51	5	23
Transv.arch	12.91	4.46	4	34
Arch BCA-LCCA	6.04	2.82	2	18
Arch LCCA-LSA	4.69	1.97	1	12
Isthmus V_{max}	2.93	1.14	1	6
Descend aorta	7.31	1.95	4	14
Impaired LVF	N=34 (32.7%)			
PDA	N=53 (51.9%)			
VSD	N=24 (23.8%)			
ASD	N=63 (63%)			

Table 67. Pre-operative echocardiographic parameters and measurements in millimetres (parameters discussed in methodology section)

Variable	Mean	Std. Dev.	Min	Max
Asc. aorta	9.74	3.28	5	21
Transv. arch	11.47	3.42	4	20
Arch BCA-LCCA	6.37	2.60	3	18
Arch LCCA-LSA	5.33	1.95	3	12
Descend aorta	7.73	1.96	5	16
Isthmus V_{max}	1.825	0.467	0.94	3.1
Isthmus G	13.93	7.47	2.8	38
Impaired LVF	N=12 (12%)			

Table 68. Pre-discharge echocardiographic parameters and measurements in millimetres (parameters discussed in methodology section)

Variable	Mean	Std. Dev.	Min	Max
Asc. aorta	15.62	5.33	9	32
Transv. arch	14.21	5.4	5	28
Arch BCA-LCCA	10.84	4.26	5	25
Arch LCCA-LSA	8.90	3.17	3	17
Descend aorta	11.4	4.60	1.2	33
Isthmus V_{max}	1.94	0.46	0.80	3
Isthmus G	16.09	7.68	1.5	37
LV wall thickness	6.60	1.93	3	14
Impaired LVF	N=1 (2%)			

Table 69. Follow-up echocardiographic parameters and measurements in millimetres (parameters discussed in methodology section)

As demonstrated on Tables 67, 68 and 69. The LV impairment was reduced to 2% of patients at follow-up from 32.7% of patients at presentation. Although there are minor changes in the size of aortic parameters between pre-operative and pre-discharge echocardiography; the difference remained insignificant.

Comparing the pre-operative aortic measurements between the patients who later developed re-coarctation and the one who remained free from re-coarctation, did not show any significant differences (Table 70.)

	Re-coarctation	N	Mean	Standard deviation	Standard error	*p* value
AV hinge points	0	92	7,67	2,939	,306	0.056
	1	6	5,33	,816	,333	
Asc aorta diameter	0	93	9,71	3,559	,369	0.086
	1	6	7,17	1,169	,477	
Transverse arch length	0	90	13,00	4,559	,481	0.482
	1	6	11,67	2,658	1,085	
Arch diameter between BCA-LCCA	0	91	6,16	2,865	,300	0.093
	1	6	4,17	,983	,401	
Arch diameter between LCCA-LSA	0	88	4,77	2,010	,214	0.128
	1	6	3,50	,837	,342	
Isthmus diameter	0	91	2,96	1,144	,120	0.551
	1	6	2,67	1,211	,494	
Descending aorta diameter (post coarct)	0	91	7,38	1,975	,207	0.207
	1	6	6,33	1,506	,615	

Table 70. Pre-operative echocardiography parameters: re-coarctation vs. no re-coarctation (Asc aorta: Ascending aorta)

Statistical analysis for comparing between the patients with re-coarctation and the ones free from re-coarctation with regard to pre-discharge echocardiography, did not demonstrate any significant difference (Table 71).

	Re-coarctation	N	Mean	Standard deviation	Standard error	*p* value
Asc aorta diameter	0	95	9,85	3,342	,343	0.224
	1	7	8,29	1,890	,714	
Transverse arch	0	62	11,48	3,434	,436	0.941
length	1	3	11,33	4,041	2,333	
Arch diameter	0	91	6,49	2,639	,277	0.690
between BCA-LCCA	1	6	4,50	,837	,342	
Arch diameter	0	83	5,39	2,011	,221	0.368
between LCCA-LSA	1	7	4,71	,951	,360	
Descending aorta	0	94	7,83	1,993	,206	0.068
diameter (post coarct)	1	7	6,43	,787	,297	
Isthmus Vmax	0	95	1,83	,474	,049	0.755
	1	7	1,77	,407	,154	
Isthmus Gradient	0	95	13,99	7,599	,780	
	1	7	13,10	5,842	2,208	0.762
Diastolic flow	0	95	,11	,309	,032	0.156
continuation in arch	1	7	,29	,488	,184	

Table 71. Pre-discharge echocardiography parameters: re-coarctation vs. no re-coarctation (Asc aorta: Ascending aorta)

The peak velocity (V_{max}) across the repaired site between the pre-discharge echocardiography and the last echocardiography available at follow-up was not also significantly different ($p = 0.793$). To confirm the results obtained for V_{max} the difference was also examined for the peak pressure gradient at pre-discharge echocardiography vs. follow-up echocardiography which was similarly insignificant ($p = 0.421$). This comparison was also performed between the different surgical techniques. Therefor the V_{max} from pre-discharge echocardiography and its change at the follow-up echocardiography was compared between EEA, EEEA, EEA+SF, SF and interpositional graft groups. Peak velocity significantly decreased in EEEA technique as compared to SF technique ($p = 0.0001$) (Table 72). To confirm the results obtained for V_{max} the difference was also examined for the peak pressure gradient. The analysis revealed that the difference between EEEA and SF is significant ($p = 0.008$) while the peak pressure gradient was reduced by EEEA technique significantly more than SF technique (Table 73). There were no differences between other techniques.

		Pre-discharge Vmax		Follow-up Vmax		Delta Vmax	
		Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Procedures (as treated)	EEA	1,7927	,4742	2,0291	,3947	,0413	,4514
	EEEA	1,8475	,4708	1,9278	,3997	-,2283	,5159
	ESF	2,0600	,4578	1,6000	,4637	,1000	1,1358
	IG	2,2000	.	.	.	,5000	.
	SF	1,7969	,4717	1,9538	,5229	,8124	1,0846

Row Mean-Col Mean	EEA	EEEA	ESF	IG
EEEA	-.269638 1.000			
ESF	.058696 1.000	.328333 1.000		
IG	.458696 1.000	.728333 1.000	.4 1.000	
SF	.771049 0.009	1.04069 0.000	.712353 1.000	.312353 1.000

Table 72. Bonferroni statistical analysis of comparing different surgical techniques with regard to changes of pre-discharge vs. follow-up V_{max}

Procedures (as treated)		Pre-discharge gradient		Follow-up gradient		Delta gradient	
		Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
	EEA	13,7450	7,3216	16,5013	6,8684	,2764	7,4160
	EEEA	14,0235	7,5892	15,8450	6,7223	-1,6428	8,2597
	ESF	16,9883	7,9815	11,0320	4,7950	1,6000	19,4800
	IG	20,0000	.	.	.	8,0000	.
	SF	13,4736	7,6377	16,7000	8,9758	8,5306	11,5166

Row Mean-Col Mean	EEA	EEEA	ESF	IG
EEEA	-1.91918 1.000			
ESF	1.3236 1.000	3.24278 1.000		
IG	7.7236 1.000	9.64278 1.000	6.4 1.000	
SF	8.25416 0.023	10.1733 0.008	6.93056 1.000	.530556 1.000

Table 73. Bonferroni statistical analysis of comparing different surgical techniques with regard to changes of pre-discharge vs. follow-up Peak gradient

Although the aortic growth and increase of pre-discharge vs. follow-up echocardiography parameters in size were significant there were no significant changes between the peak velocity and gradient in the whole population (Table 74.)

	Pre-discharge echocardiography	Follow-up echocardiography	*p* value
Ascending aorta (mm)	9.74±3.28	15.62±5.33	<0.001
Transv.Arch (mm)	11.47±3.42	14.21±5.4	<0.001
Arch BCA-LCCA (mm)	6.37±2.60	10.84±4.26	<0.001
Arch LCCA-LSA (mm)	5.33±1.95	8.90±3.17	<0.001
Descending aorta (mm)	7.73±1.96	11.4±4.60	<0.001
Isthmus Vmax (m/s)	1.825±0.467	1.94±0.46	0.793
Isthmus Gradient (mmHg)	13.93±7.47	16.09±7.68	0.422

Table 74. Aortic growth

The patients were also divided into two major surgical groups: complete resection of re-coarctation vs. no resection of re-coarctation. All stand-alone SF techniques fell into the latter category. Pre-operative and post-operative characteristics were compared between these two groups; which did not show any significant differences (Table 75). Comparison of follow-up echocardiography parameters and aortic measurements between the two groups also did not show any significant differences; however transverse arch growth was better in the group of patients which the coarctation was resected vs. patients whose coarctation was not excised. This was not statistically significant while *p* value was just 0.050 (Table 76.)

	Resection N=64	No resection N=53	*p* value
Age (days)	273.7 ± 626.7	328.3 ± 861.8	0.692
Age < 30 days	38 (55.9%)	25 (51.0%)	0.603
Male	48 (70.6%)	33 (67.3%)	0.708
Weight (kg)	6.3±5.5	6.5±7.5	0.846
Weight < 2.5 kg	5 (7.3%)	3 (6.1%)	0.795
Failure to thrive	28 (41.2%)	27 (55.1%)	0.136
Turner syndrome	5 (7.3%)	2 (4.1%)	0.462
Prostin infusion	31 (45.6%)	25 (51.0%)	0.562
Preoperative ventilation	19 (27.9%)	17 (34.7%)	0.435
Preoperative inotropes	4 (5.9%)	9 (18.4%)	0.034
Admission from ICU	30 (44.1%)	24 (49.0%)	0.603
Elective	24 (35.3%)	14 (28.6%)	0.444
Incidental finding	27 (39.7%)	18 (36.7%)	0.744
Arch hypoplasia	6 (8.8%)	4 (8.2%)	0.900
ICU stay (days)	2.3±4.1	2.0±2.8	0.640
Respiratory failure	3 (4.4%)	1 (2.0%)	0.486
NEC	3 (4.4%)	1 (2.0%)	0.486
Horner's syndrome	0 (0.0%)	2 (4.1%)	0.093
Vocal cord palsy	4 (5.9%)	2 (4.1%)	0.663
Cardiac arrest	0 (0.0%)	1 (2.0%)	0.237
Renal failure	0 (0.0%)	1 (2.0%)	0.237
Neurologic events	2 (2.9%)	2 (4.1%)	0.738
Seizure	1 (1.5%)	1 (2.0%)	0.814
Chylothorax	3 (4.4%)	0 (0.0%)	0.136
Low cardiac output	0 (0.0%)	1 (2.0%)	0.237
Wound infection	4 (5.9%)	5 (10.2%)	0.387
In-hospital death	1 (1.5%)	0. (0.0%)	0.394

Table 75. Pre-operative and post-operative characteristics: complete resection of coarctation vs. no resection of coarctation.

	Coarctation resection	N	Mean	Standard deviation	Standard error	*p* value
Asc aorta diameter	0	27	15,70	5,777	1,112	0.924
	1	40	15,58	5,068	,801	
Transverse arch length	0	12	11,67	4,499	1,299	0.050
	1	26	15,38	5,565	1,091	
Arch diameter between BCA-LCCA	0	26	11,38	4,446	,872	0.405
	1	38	10,47	4,151	,673	
Arch diameter between LCCA-LSA	0	21	8,38	2,747	,600	0.337
	1	34	9,24	3,412	,585	
Descending aorta diameter (post coarct)	0	25	11,69	5,955	1,191	0.690
	1	38	11,21	3,520	,571	
Isthmus Vmax	0	33	1,940	,5250	,0914	0.921
	1	46	1,951	,4166	,0614	
Isthmus Gradient	0	33	16,36	8,887	1,547	0.802
	1	50	15,92	6,865	,971	

Table 76. Comparison of follow-up echocardiography: complete resection of coarctation vs. no resection of coarctation.

To identify the independent risk factors for the occurrence of re-coarctation all pre-operative, operative and post-operative variables were examined in a univariate model. The analysis revealed that weight (p = 0.012), pre-operative PICU (0.006), arch hypoplasia (p = 0.022), pre-operative mitral valve annulus size (p = 0.023), pre-operative LVOT size (p = 0.010) and pre-operative aortic valve hinge points (p = 0.023) were significantly associated with the risk of re-coarctation (Table 77). However all the above mentioned variables failed to remain significant when tested by Cox multivariate model (Table 78). Therefore statistically no variable was identified which can be used as a re-coarctation predicator.

Variable	HR	95% CI	P value
Age	0.98	0.97-1.00	0.147
Weight	0.44	0.22-0.83	0.012
Failure to thrive	13.17	1.68-103.11	0.014
Turner syndrome	1.55	0.19-12.31	0.675
Prostin infusion	8.76e+15	-	1.000
Admission from ICU	18.6	2.36-146.89	0.006
Incidental finding	3.15e-17	-	1.000
Arch hypoplasia	4.82	1.26-18.45	0.022
Preop impaired LVF	4.14	0.76-22.67	0.101
Preop MV annulus size	0.62	0.41-0.94	0.023
Preop LVOT size	0.36	0.17-0.78	0.010
Preop AV hinge points	0.47	0.24-0.90	0.023
Preop isthmus size	0.82	0.37-1.79	0.615
Preop Asc. aorta size	0.57	0.32-1.03	0.063
Preop trans. Arch length	0.91	0.73-1.13	0.403
Preop arch size BCA-LCCA	0.49	0.22-1.08	0.076
Preop arch size LCCA-LSA	0.59	0.30-1.14	0.117
Preop descending aorta size	0.67	0.38-1.18	0.167
Preop VSD	2.46	0.55-10.98	0.239
Preop ASD	4.17	0.50-34.75	0.186
Postop gradient	0.97	0.88-1.08	0.654
Postop isthmus V_{max}	0.68	0.13-3.49	0.650

Table 77. Univariable model for the risk of re-coarctation (HR: Hazard Ratio; CI: Confidence Interval)

Multivariable analysis (Pre-operative characteristics)

Variable	HR	95% CI	P value
Weight	0.55	0.26-1.17	0.123
Failure to thrive	3.16	0.36-27.96	0.300
Preop ICU	3.59	0.39-33.23	0.261
Arch hypoplasia	2.27	0.54-9.45	0.261

Multivariable analysis (Pre-operative echocardiography data)

Variable	HR	95% CI	P value
Pre MV annulus size	0.65	0.38-1.12	0.128
Pre LVOT	0.42	0.12-1.41	0.161
Preop AV hinge point	0.97	0.35-2.69	0.956

Table 78. Multivariable model for the risk of re-coarctation (HR: Hazard Ratio; CI: Confidence Interval)

3.3.5 Isolated CoA in Scotland

Congenital heart disease is the most common birth defect which encompasses a broad spectrum of anomalies of heart and major vessels affecting both structure and function. In the United Kingdom 9 per 1000 live-born infants suffer from a type of heart or major vessels anomaly (Knowles 2005). CoA accounts for up to 5% of patients born with a congenital heart anomaly (Cohen 1989).

The surgical practice for the repair of isolated CoA in Scotland between 2002 and 2012 was analysed to discover any particular trend in performing CoA repair through the time. As Figure 27 shows the operative techniques did not show any trend; although with a narrow margin SF technique was a more favourable technique. It was also evident that EEA technique is re-gaining more popularity in recent years.

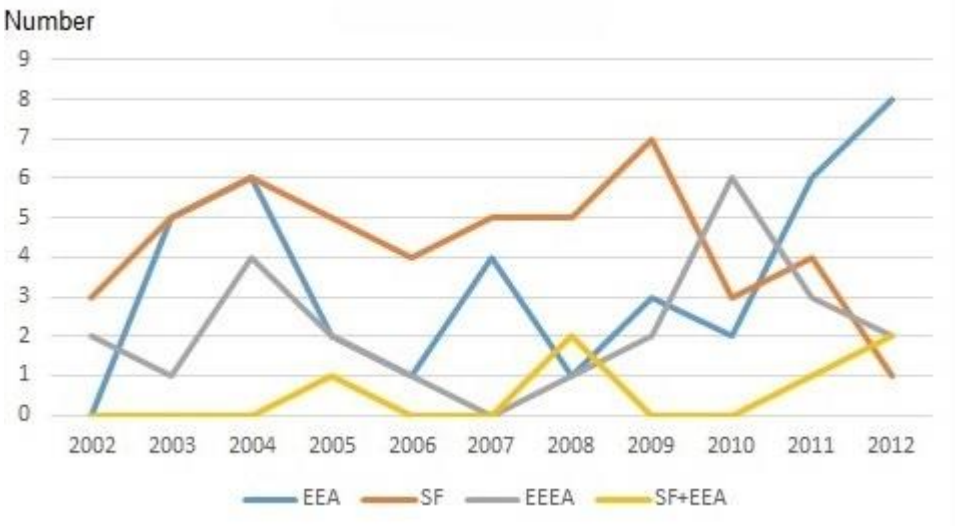

Figure 27. Surgical trend for treatment of isolated CoA in Scotland (2002 – 2012)

Scotland with 5.4 million population and an area of 80.077 km^2 is a relatively large country in Europe considering its population density (65 person per 1 km^2). The referral system among Scottish health boards is a robust system to refer the patients diagnosed with congenital heart defect to the centre for surgical intention which is Royal Hospital for Children in Glasgow. The regional distribution of patients with isolated CoA who were referred for medical management and eventually surgical intervention, from 2002 to 2012, is demonstrated in Figure 28.

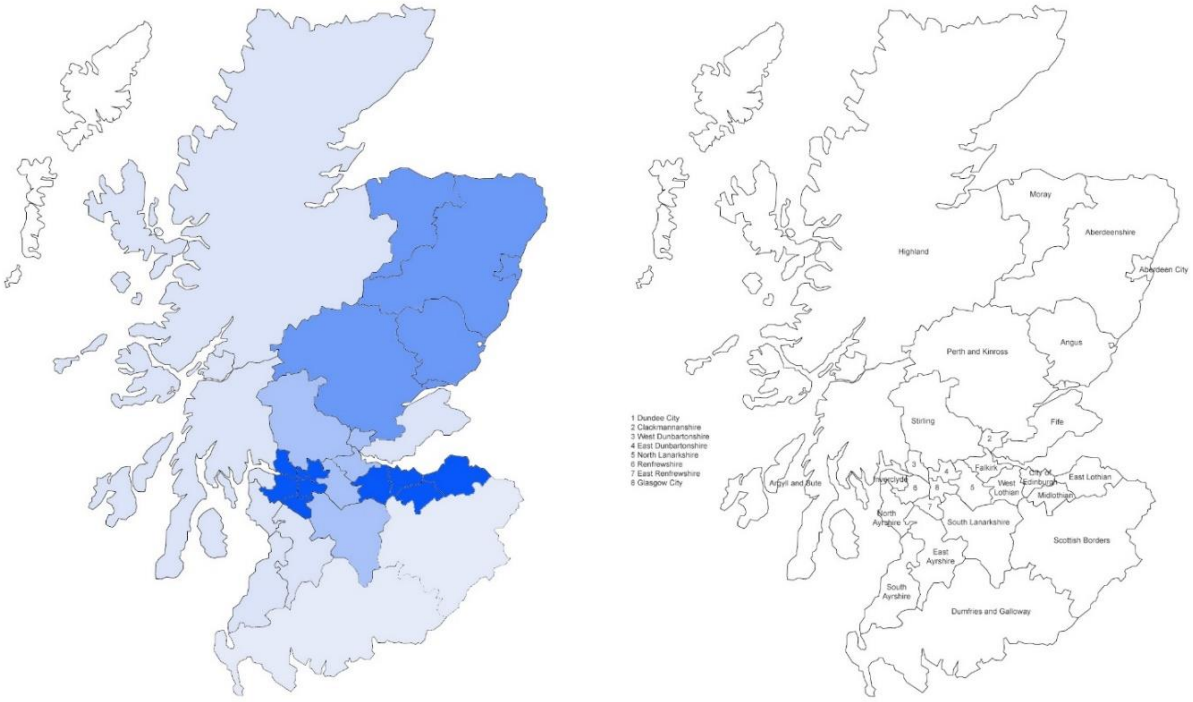

Figure 28. Regional distribution of referring centres between 2002 and 2012, from which patients with isolated CoA were referred. The frequency of referrals is from dark blue (high frequency) to light blue (low frequency) and white (no referrals).

The geographical distribution of patients who were born with isolated CoA is analysed on the map of Scotland (Figure 29). This distribution correlates to the frequency of referrals from the health boards which is demonstrated on Figure 28.

The impact of deprivation on the outcome of surgery with regard to re-coarctation was examined using SIMD model which has been described in the methodology section of this Chapter. The population was divided into SIMD deciles and then the re-coarctation

rate was examined against the one to ten deciles (Figure 30). Deprivation did not have an impact on the rate of re-coarctation (p = 0.769).

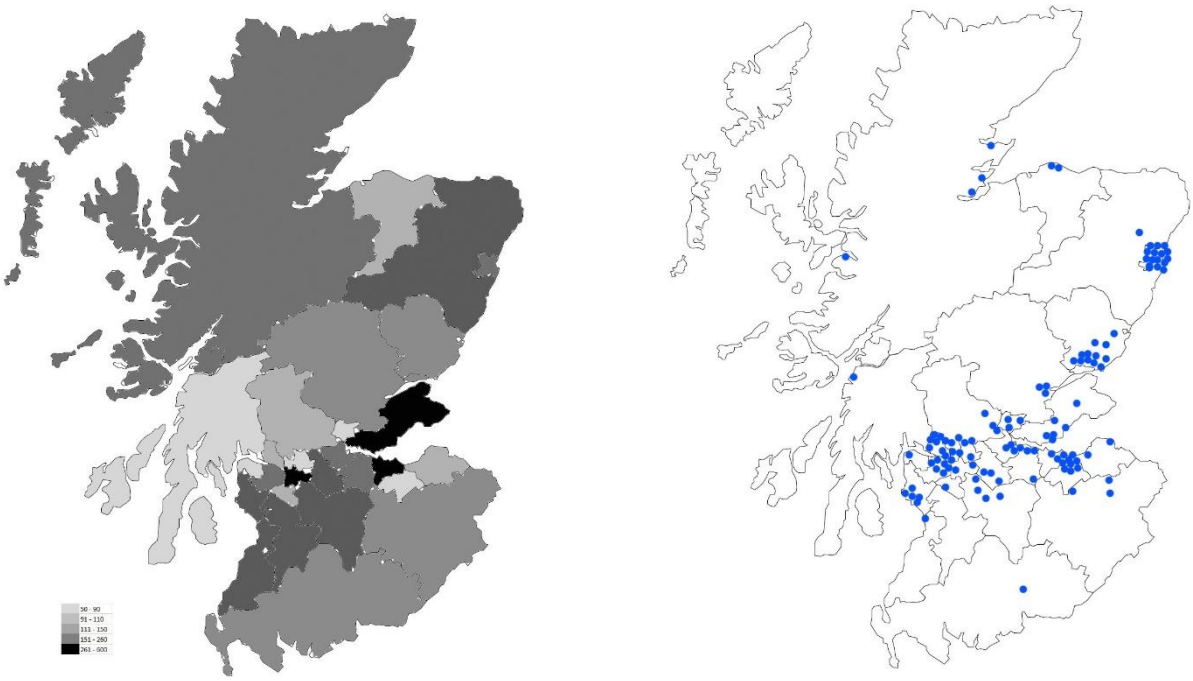

Figure 29. Scotland population density (left) and geographical distribution of patients born with isolated CoA across Scotland (right) between 2002 and 2012.

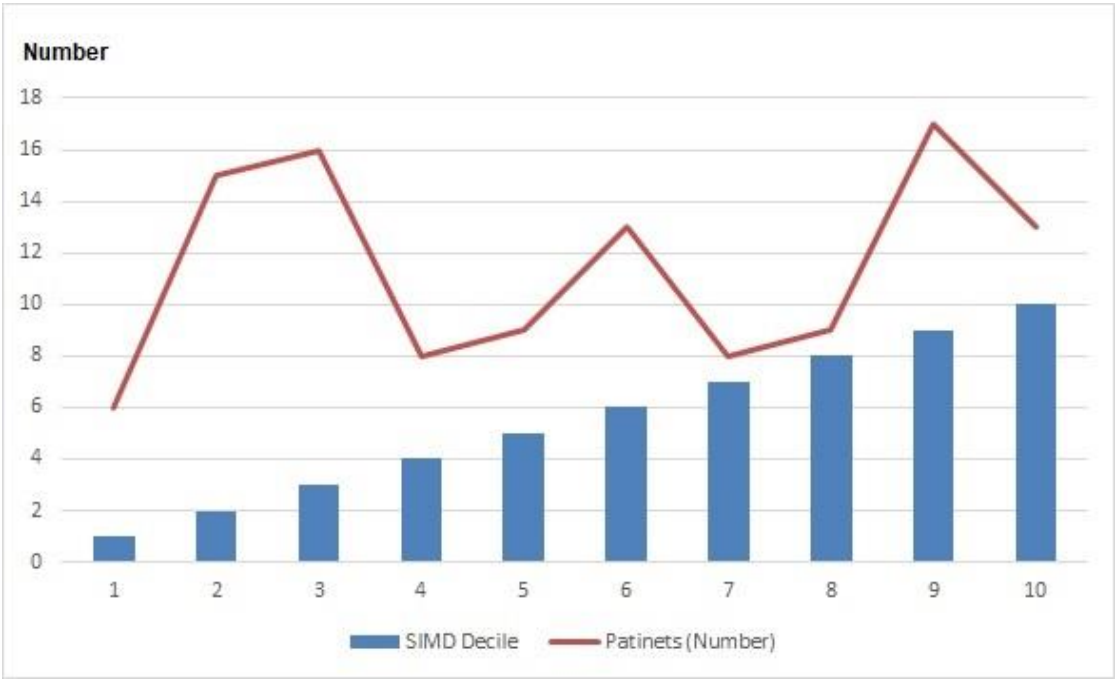

Figure 30. Distribution of patients with isolated CoA between 2002 and 2012 as per deprivation deciles from 1 (the most deprived) to 10 (the least deprived).

3.4 Study limitations

This study inherits inevitable bias caused by a retrospective design. Casenote BP records were difficult to interpret and even unreliable particularly for neonates where multiple BPs were recorded with a wide range for a patient. Several patients during the follow-up did not have a recorded systole and diastole BP; however it was mentioned that BP is satisfactory. It has been demonstrated that non-invasive BP in neonates may not be reliable as compared to older children (Devinck 2013, Konig 2012). On the other hand in the context of CoA studying HTN is important while unsatisfactory outcomes are linked to persistent HTN. The sample size was also small as the exclusion criteria was strict to prevent selection bias. This caused all variables which were recognised as an independent risk factor for re-coarctation by univariable model, to fail to be significant in a multivariable model. Although aortic measurements and echocardiography images were re-checked by two separate operators still there is a chance of subjective measurements. In fact one of the best ways to measure the aortic parameters is MRI which was not performed pre-operatively for majority of patients. Almost 57% of patients at follow-up did not have a recorded echocardiography which would be retrievable with all available moving images. Although all patients underwent echocardiography at follow-up; not all the images were exclusively recorded for aortic measurements. Basically the majority of follow-up echocardiography emphasis is on either peak velocity or peak pressure gradient across the repaired site. The echocardiographic reports were useful to complete the follow-up; however the aortic measurements for 57% of patient remained incomplete. Left arm development has not been investigated in the out-patient clinic reviews. Although no immediate in-hospital left arm ischaemic event was associated with the SF technique; longer follow-up of the left arm is required to monitor the limb development. The finding of this study may be applied to the current clinical practice whereas the most accurate evaluation of different techniques for repairing CoA and their impact on outcomes is to perform a multi-centre RCT. Undoubtedly this population requires a longer follow-up for at least 20 and 30 years to have a better understanding of the relationship between CoA repair and patient's quality of life as well as the longevity.

3.5 Discussion

After more than half a century of surgical practice in repairing isolated CoA still it is not clear what the best surgical technique is. There are numerous retrospective studies reported their institutional results on surgical technique and outcomes in the past few decades. Patch aortoplasty in neonates was one of the first alternative techniques which was denounced by paediatric surgeons. This was not due to superiority of other techniques but an increasing association with aortopathy and aortic aneurysm was the main reason (Parikh 1991). Since then the focus of practice was mainly on EEA and SF; although EEEA successfully stemmed from EEA for particular group of patients. Resecting or leaving the ductal tissue has been the centre of an ongoing debate. The pattern of ductal tissue in the coarctation segment is in the form of a circumferential band around the lumen; however there are distal extension of ductal tissue from this aortic band. The ductal tissue may behave as a closing duct where multiple sequences of histological events are triggered such as medial thickening with ischaemic degeneration and intimal proliferation (Russell 1991). This can be accompanied by extreme events such as formation of thrombosis as well as fibrosis process. Surgeons who advocate SF technique believe that this technique by providing the opportunity to cut through the coarctation band disrupts the circumferential contraction effect. Histological examination demonstrated that the extension of ductal tissue may not end necessarily before the incision on the coarctation area; therefore the risk of re-coarctation might be increased. In other words it is important not to be conservative while performing an incision on the coarctation area. The surgeons who have advocated EEA technique as a preferable operation for CoA repair, have expressed worry about leaving the ductal tissue behind in SF technique (Jones 1991). Arterial distensibility has been examined in CoA patients with both SF and EEA techniques (Bassareo 2009) and it has been demonstrated that arterial stiffness post CoA repair is more prevalent in SF technique. This cam make the situation more complicated in the event of re-coarctation when the patient needs transcatheter balloon aortoplasty. In contrast Barreiro et al demonstrated the opposite while balloon angioplasty in their patients who underwent SF technique had satisfactory results (Barreiro 2007). Although it is postulated that re-coarctation with SF technique occurs early in younger neonates; this also has been reported for EEA technique (Merrill 1994). It can be similarly hypothesised that in EEA the excision is limited to the narrowed area of isthmus which can be seen easily by naked eyes. Wide excision by many surgeons is considered as unforgiving while the suture lines might be under tension an also there is a

risk of isthmus and descending aorta tethering. In fact limited excision in EEA technique may not address the removal of the ductal tissue while the coarctation band which may not be visible is left behind. Comparing the suture lines between the two techniques, has caused speculations that a circumferential anastomosis with two flushed ends of the aorta in EEA may inherit an iatrogenic stricture (Schuster 1962). This may act as a coarctation band in future. That's why few surgeons have advocated an elliptical anastomosis rather than circular in EEA technique which needs to be fashioned during the coarctation resection (Wood 2004). Beekman et al have reported almost a 50% reduction in mortality when they decided to change the practice from EEA to SF technique in their institution (Beekman 1986). It is important to consider the less advanced surgical instruments and the suture materials which were used in late 70s and early 80s.

Both SF and EEA techniques have been criticised for inability to address a hypoplastic arch particularly at distal arch and isthmus region (Jones 1991, Van Heurn 1994, Vouhe 1988). In our study arch hypoplasia was not a risk factor for re-coarctation. Interestingly it has been observed that following CoA repair in the context of distal and isthmus arch hypoplasia, the hypoplastic state remains for several months (Maia 2004).

In our study SF was used for the primary repair of CoA and also was used as a bail-out operation in five patients who were initially intended to be operated by EEA technique. Using SF as a bail-out technique was reported previously (Kaushal 2009, Wright 2005) showing that SF technique is easy to performed with a high degree of reproducibility.

The rate of re-coarctation in our population was 9.5% which is comparable with other similar studies (Conte 1995, Maia 2004, Kumar 2011).

In-hospital mortality rate of CoA repair in modern era of paediatric cardiac surgery has significantly reduced from 15% in 80s (Hopkins 1988) to 0.8% in our study. The only in-hospital mortality in our study was due to a non-cardiac reason. Generally CoA repair is considered as a safe operation with low post-operative complications.

Neurological deficit in the form of paraplegia is a grim outcome of CoA. In our study among four patients with neurological event three of them recovered with no deficit prior to discharge however one patient developed permanent paraplegia. This patient had an aberrant right SA which has been previously recognised in the literature as a risk factor for spinal cord injury during the CoA repair (Hjortdal 2003). Paraplegia has already been reported in other studies with similar rate (Thomson 2006).

Prediction of re-coarctation by pre-operative and operative characteristics is a desirable ability for every surgeon. With excluding the age we could not demonstrate any association between pre-operative and operative characteristics and re-coarctation. It has been shown that a systolic gradient of 13 mmHg at the time of discharge is significantly associated with the risk of re-coarctation (Kumar 2011). This cut-off had a sensitivity and specificity of 91% and 76% respectively. The peak gradient across the repaired site may not only be associated with re-stenosis therefore a decrease in the peak gradient after discharge and during the follow-up period is not uncommon (Siewers 1991) and was also observed in our study. The only pre-operative predictor of re-coarctation in our study was age of younger than 30-day-old. This finding which has been observed previously (Kumar 2011) is due to an accelerated growth in neonates.

In our study there were no difference between the surgical techniques with regard to the rate of re-coarctation and this was similar to several studies which have been published previously (Mery 2015, Troung 2013, Kumar 2011, Brown 2009, Adeeb 2004, McElhinney 2000).

Interestingly the reduction in peak velocity or pressure gradient across the repaired site was significantly better in EEEA patients as compared to SF group. Although this did not happened in the context of arch hypoplasia and with no clinical manifestation; this may imply advantages of EEEA technique in providing a larger lumen and a better antegrade flow (Van Heurn 1994). EEEA demonstrated a better growth in transverse arch which with a narrow margin was not statistically significant (p = 0.05). Both of the above findings in relation with EEEA technique have been observed and reported previously (Karamlou 2009). EEEA technique can be advocated in the following situations with satisfactory results: 1- LBW 2- isthmus or distal arch hypoplasia 3- CoA with a long segment. In decision making to choose a repair technique for patients the physiology of re-coarctation should be considered. Generally re-coarctation is the conclusion of two opposite forces: 1- antegrade flow which by expanding the lumen encourages the growth 2- scar healing which may contracts and hamper the growth (Kumar 2011). Therefore in principle the surgical technique should improve the antegrade flow while reducing the risk of suture line contraction.

It has previously shown that LBW patients are at higher risk of re-coarctation (Truong 2013); however in our study there were no difference between the neonates who were born with a weight of less than 2.5 Kg with other patients. Surgical advances have

changed the CoA practice enabling performing small anastomosis regardless of patient's weight. If the aortic arch is normal small anastomosis in a LBW patient in day-to-day surgery even by using EEA technique can be performed safely without imposing risk of re-coarctation. If arch hypoplasia is located at the isthmus region then EEEA probably would be the technique of choice to avoid post repair high peak velocity. In many studies were weight was identified as a culprit for the incidence of re-coarctation the sample was heterogeneous by including complex aortic arch hypoplasia in the population. It has been demonstrated in large studies with LBW neonates that catch up growth after surgery occurs and the patients with LBW exhibits a satisfactory aortic growth particularly in the transverse arch after few months post-operatively (Karamlou 2009). There are published studies with a focus on LBW patients who underwent CoA repair with no association between LBW and the re-coarctation rate (McElhinney 2001, Sudarshan 2006).

In Royal Hospital for Children all CoA anastomosis are performed by non-absorbable sutures. In a recent study the suture material has been investigated for the incidence of re-coarctation which did not show any difference between absorbable and non-absorbable sutures (Troung 2013). Older studies have reported a contradicting results from satisfactory outcome with absorbable (Messmer 1991) and unsatisfactory results with absorbable sutures (Zehr 1995). Barreiro et al demonstrated that the incidence of re-coarctation in absorbable group was 15.5 % vs. non-absorbable which was 5%; however this was not statistically significant (Barreiro 2007).

One of the criticism of SF technique is the sacrifice of the SA to reconstruct an autologous flap for anastomosis. It seems a risky and aggressive sacrifice; however the classic Blalock-Taussig shunt in which the SA is similarly tied off and turned down for anastomosis has been performed in numerous neonates for several years with ignorable left arm comorbidities (William 2007). On the other hand limb gangrene which is indeed a significant event following SA sacrifice has been reported (Hussain 1997, Geiss 1980). The association of SF technique and insufficient development of the left upper arm is another worry of surgeons who refrain from SF technique. It has been demonstrated that the cessation of main blood supply to the left upper arm in long-term may affect the arm development with both length and muscular (circumferential) growth (Zehr 1995, Pandey 2006). The underdeveloped left arm may cause a discrepancy with the right arm of up to 2.5 cm in 5% of patients receiving SF technique (Van Son 1989). Left upper limb claudication is another aspect of SA sacrifice which may affect the patient's quality of

life during the adolescence (Marcheix 2007). In a retrospective study with patients who underwent SF technique 28.8% of patients reported that they have noticed a disparity between the two arms from a muscular development point of view while 24.6% mentioned that the left arm is shorter. Generally the risk of arm developmental issues in infants was significantly higher than neonates (Pandy 2006). Therefore it is safer to utilise the SF technique in younger neonates.

Turner syndrome is the most common congenital disease which is associated with CoA. This was also observed in our study while 7 (6%) of patients were born with both Turner syndrome and isolated CoA. It has been hypothesised that patients with Turner syndrome usually suffer from abnormal aorta with reduced distensibility as well as tissue oedema which may not only make the repair and anastomosis challenging but also may inflict re-stenosis. This was not observed in our study while there were no association between the Turner syndrome as an independent risk factor and re-coarctation.

Mortality of neonates in pre-operative period have significantly reduced through the time. This is largely owed to the arrival of PGE_1 into practice at late70s and early 80s as well as advanced medical management in well-equipped PICUs. Although the management of isolated CoA in critically ill patients prior to surgery has significantly improved, it has been shown that delay in diagnosis may have an adverse effect on outcomes (Brown 2013). Incidental finding of CoA is common and observed in 38.5% of our population. This coveys an important message on training of medical team who delivers the primary care including the GPs. Majority of our patients with incidental finding were diagnosed by listening to the chest and detecting a murmur. This should encourage a general awareness on CoA and its management which crucially depends on an early diagnosis.

All of the patients in our study who developed re-coarctation were manged safely by transcatheter balloon aortoplasty and only one patient came back for the second re-intervention. Although surgical re-intervention in the past has been the predominant management for re-coarctation, recent studies have demonstrated that surgical re-intervention is associated with higher mortality and morbidities (Brown 2013). This finding sends out an important message that a strong paediatric cardiac surgery service requires a strong cardiology service with experienced interventional cardiologists who can manage re-coarctation which is unfortunately an inevitable outcome of CoA repair with satisfactory results.

One of the key finding of the retrospective study was the superiority of EEEA technique in lower gradient across the repaired site. Although this did not reveal any clinical advantages, it confirms the findings of systematic review in Chapter 2, where EEEA was more adopted in recent years to treat the concomitant arch hypoplasia with less re-coarctation rate. This also confirms that the surgical strategy should be based on clinical, anatomical and physiological presentations.

Currently there is no unified guidelines on surgical repair of CoA with no consensus on the superior technique. The surgical intervention of choice needs to provide the surgeons with the ability to address the CoA with anatomical variations and concomitant pathologies such as arch hypoplasia. Low gradient in EEEA patients during the follow-up period indicates more attention to this approach in patients with isolated CoA and isthmus hypoplasia.

3.6 Conclusion

Finally it seems it is not possible to champion one technique over another and we should appreciate that CoA repair techniques are fundamentally individualised and will be decided as per patients. This also conveys the message that isolated CoA needs to be recognised as a complex pathology which does not limit to the coarctation area. This is also reflected in the post-operative management while a quick safe and successful operation with early discharge is not the whole story. In fact while major studies have demonstrated that these patients' longevity in long-term is significantly lower than the normal population (Brown 2013, Cohen 1989); we then may embrace the fact that we are dealing with a tortuous, multi-factorial and of course resilient pathology.

4. The Future

4.1 Computational simulation for haemodynamic studies

Congenital heart disease encompasses an array of structural cardiovascular lesions which results in abnormalities of blood flow and circulatory physiology. Addressing these lesions by surgery or interventional technologies can potentially improve the circulation with the caveat being any intervention has limitations.

Clinical-based studies are still the mainstay of research in the field of congenital heart disease; however the burden of research logistics has made clinical studies and particularly RCTs challenging. Ethical process has been identified as one of the main challenges to rectify. The difficulty remains with researchers, institutions and institutional review boards (Block 2006). Sample size is another obstacle to run rigor RCTs while large population is required to identify a certain outcome and have a meaningful statistical analysis (Giannakoulas 2009). In fact there is a high volume of research on measuring surgical outcomes which merely relies on cohorts as well as case reports such as the appraised papers in Chapter 2. The complex nature of congenital heart disease imposes difficulties on surgical risk stratification which inevitably affects the outcome measurement (Kang 2004).

For decades mammalian and non-mammalian models have been the base of research on genetics of heart anomalies and understanding the genes leading to cardiac diseases. Recently scientists have made progress in understanding the genes mutation responsible for ASD and ventricular septal defect VSD (Misra 2012). Although they succeeded in producing mice born with ASD or VSD who were carrying the deleted gene, this breakthrough is in its infancy to study various aspects of defects and surgical options. In fact technology is now far away from creating desirable defects in animal models for research. On the other hand loss to follow-up is a major drawback of research projects including large cohorts particularly in the field of CoA. The nature of heart anomalies mandates a well-programmed and prolonged follow-up which not only has an impact on clinical evaluation but also it is of paramount to measure the outcome. Loss to follow-up which is not uncommon and has been reported up to 20 years inevitably impinges on clinical studies (Wray 2013). This was also experienced by the author of this theses in retrieving echocardiography data during the follow-up period.

The emergence of patient-specific and hypothetical computational modelling has enhanced research on cardiovascular defects as a potent and effective backup for clinical studies or animal models. Computational based analysis of the circulation allows the creation of patient-specific models of the region of interest and to represent the entire circulation in complete. Advances in scan technology and computer applications have enabling the opportunity to integrate anatomy and circulation physiology.

In 90s the advancement in computer science and technology of clinical imaging boosted innovative ideas to meticulously understand the anatomy and physiology of diseases in planning surgical intervention and improving outcomes (Taylor 1996). Now computational modelling has significantly evolved with high-end softwares as well as imaging modalities. The foundation of computational modelling is simulating the anatomy and physiology to get as close as possible to reality. The simulation of blood flow and vessels dynamics has opened a new Chapter in the field of cardiovascular science. The computational models have been utilised to calculate different aspects of blood flow and its interaction with blood vessels. In early 90s one-dimensional flow equations was used to successfully create one of the first computational model of systemic circulation. The model provided a reliable platform to study aortic stenosis and its haemodynamic implications (Stergiopulos 1996). The progress in computing technology and mathematical models has increased the importance of simulation and its role in planning interventions and prevention of diseases.

Modelling process starts with extraction of patient-specific data from imaging modalities such as CT-scan or MRI. The information is transformed into a multi-task computer software to construct the three-dimensional models which will be the base of computational modelling process. The natural complexity of cardiovascular system imposes some difficulties on designing a realistic computational model to simulate the physic phenomena. In vascular models with inlet-outlet and multi-branch pattern, boundary conditions need to be defined and quantified to elicit a model as accurate as possible. The boundary conditions which can be determined mathematically specify several factors such as wall sheer stress, lumen truncation effect and flow-pressure in branches. It has been demonstrated that coupling the models with a zero-dimensional (lumped) and 1-dimentional models allows the boundary conditions to be explicitly defined reducing the model error (Vignon-Clementel 2010, Taylor 2009). A zero-dimensional model applies electrical analogues (resistance, compliance, etc.) of

Windkessel circuit to obtain an overview of haemodynamic interaction (Yubing 2011); while a one-dimensional model deals with the flow and the interaction between the blood flow and the lumen compliance (Fromaggia 2003). Although they have been significant breakthroughs in creating accurate models to study the blood flow dynamics still the model validation remains a concern while accurate benchmarking is costly as well as challenging (Tiago 2014).

Recently the magnetic resonance angiography images of patients with CoA and without CoA were used to create a computational representative of the aorta and the arch branches (LaDisa 2011). In this study the imaging data was converted into geometrically representative computer models. Inflow and outflow boundary conditions as well as wall deformation parameters were calculated by a computer software. For CFD simulations a stabilised finite element was used and then flow simulations were run for 4 to 6 cardiac cycles. On this model blood flow velocity, BP and wall displacement (distensibility) were visualised. TAWWS and OSI were also calculated where a low TAWWS and high OSI may indicate atherogenesis. Volume-rendered velocity during peak systole, mid-to-late systole and end diastole at both rest and exercise was mapped. In patients with CoA blood velocity magnitude was significantly higher than patients without CoA. This increased velocity significantly subsided after CoA repair. Interestingly the reduction of blood velocity magnitude and not the peak velocity, was more in EEEA as compared to EEA. Systolic displacement from 0 to 1 mm was also mapped which showed an increase in systolic displacement of ascending aorta in CoA patients while after surgical repair with EEA the systolic displacement significantly reduced. In EEEA at anastomosis site a mild increase in systolic displacement was observed as compared to EEA technique. It was concluded that EEEA could restore the arch anatomy which was very similar to patients with normal anatomy. This also means that TAWSS will be lower in this group of patients therefore exposing larger fractions of the aorta to harmful WSS. This may also explained the persistent HTN after CoA repair with malfunctioning baroreceptors due to erratic signals produced by WSS. Authors have concluded that although their study is a case report requiring further validation; the future of CoA repair and battling the long-term comorbidities might be tackled by CFD studies in larger cohorts.

As discussed in previous Chapters there is no consensus on gauging coarctation and re-coarctation despite of published guidelines. It is now recommended that the gradient can be computed non-invasively by softwares in which the MRI images are used (Itu 2013).

In a recent study with the help of CFD the out-come of CoA repair with EEA technique was investigated (Yang 2018). In this study there is a significant energy loss prior to repair with an increased the afterload.

4.2 Virtual surgery

Models can be used to simulate blood flow, determine circulatory inefficiencies and consequences to the ventricular workload. Specific in silico modifications of the model can reproduce the effects of surgery and predict haemodynamic consequences. Ultimately models can be used as a tool to predict the effect and benefit of intervention on a given lesion and to inform specific operational details of the intervention.

Examples of this technology approach include optimising the extra-cardiac systemic vein to pulmonary artery flow configuration in Fontan circulations (Zelicourt 2010) and determining ideal shunt type and size in Norwood palliation of HLHS (Migliavacca 2001). Rapid prototype through 3D printing technology can create physical models of the anatomical region of interest. These have been used to aid surgical planning (Costello 2014) and used as a template to design anatomical-specific vascular stents and trans-catheter prosthetic valve implants (Moore 2018). The model can also be used to explain the operation to parents and relatives as well as to train junior surgeons (Figure 31).

Physical models created in vascular-like compliant materials have been incorporated within bench-mock circulations can allow direct analysis of flow disturbances with specific lesions. These have been used to study the effects of aneurismal development in bicuspid aortic valve disease (Ferrara 2018). Potentially mock circulations will allow prediction and planning of surgical or catheter-based intervention.

Figure 31. 3D model of CoA in one of the studied neonates in the Chapter 3 of this theses. The 3D image was constructed by the author of this thesis and the model was printed by the Royal Hospital for Children's 3D printer.

In summary modern scanning and computer technologies allows the creation of detailed patient-specific models that can be used to analyse the circulation and predict the effects of intervention in congenital heart lesions. Two approaches are available: 1- Computational-based analysis where theoretical models are developed in silico, 2- Rapid prototype physical models incorporated within mock circulations. Each approach will have a specific remit and application, but can also be complementary in the analysis of a given lesion.

The future would be the development of softwares by which the CoA can be simulated pre-operatively. The computer may guide the surgeon on the best repair technique; which may provide the best haemodynamics as per anatomy as well as the clinical presentation.

4.2 Discussion

Currently there is no unified guidelines on surgical repair of CoA with no consensus on the superior technique. The surgical intervention of choice needs to provide the surgeons with the ability to address anatomical variations and concomitant pathologies such as arch hypoplasia. Low gradient across the repaired site in EEEA patients during the follow-up period indicates more attention to this approach in patients with isolated CoA and isthmus hypoplasia. One of the key findings of the retrospective study was the superiority of EEEA technique in lower gradient across the repaired site. Although this did not reveal any clinical advantages, it confirms the findings of systematic review in Chapter 2, where EEEA was more adopted in recent years to treat the concomitant arch hypoplasia with less re-coarctation rate. This finding may contribute to future softwares by which the best repair strategy can be identified following anatomical, physiological and clinical data entry.

It is well described that the repair of CoA requires a long-term follow-up while the successfully operated patients may have a shorter life span as compared to the normal population (Cohen 1989, Brown 2013). This emphasise the importance of a robust and structured follow-up for at least three decades post-operatively. The follow-up needs to be facilitated by a standardised imaging which fundamentally includes echocardiography and MRI. While the latter may impose costs on healthcare, echocardiography remains the gold standard of imaging in follow-up of these patients. Echocardiography needs to be performed according to a protocol which includes standard windows (parasternal and

suprasternal) in short and long axis. The standard measurements of the entire aorta as per Chapter 3 protocol will allow clinicians to monitor the aortic growth and the change of gradient across the repaired site. Other clinical observations such as BP in upper and lower limbs, left arm measurements in SF cases and the exercise tolerance would be extremely informative. While the follow-up process is distributed across the health boards led by the local cardiology service, the need for a pan-UK registry is inevitable. The suggested registry by the author of this thesis, is an online secure database where patients' identifiable information are excluded and patients are coded by registry numbers which include date of birth. The database encompasses the data discussed in Chapter 3 as per three stages of care: pre-operative, peri-operative and post-operative. In long-term follow-up patients' movements can also be monitored to reduce the risk of losing patients in follow-up. The registry may be utilised to run large volume cohort studies which are well powered by prospective data entry and sample size in the absence of RCTs in this field.

There are plans in place to follow-up the current population for at least another decade. During This time the follow-up procedure can be audited to optimise the long-term post-operative care as well as collecting information.

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Appendix-I

Abstract presented at the Society for Cardiothoracic Surgery in Great Britain and Ireland (Including primary data without the aortic measurements)

Do surgical strategies for the repair of aortic coarctation have an impact on the rate of recoarctation?

Shaikhrezai K[1], Prabhu N[2], Ilina M[2], Danton M[1]

[1] Department of paediatric cardiac surgery, Royal hospital for sick children (Yorkhill), Glasgow, UK

[2] Department of paediatric cardiology, Royal hospital for sick children (Yorkhill), Glasgow, UK

Acceptance notification:

SCTS Notification of Acceptance Inbox ×

SCTS <scts@webges.com>
to me

Dear Kasra Shaikhrezai,

SCTS ANNUAL MEETING – EDINBURGH – 10TH – 12TH MARCH 2014

Further to your recent abstract submission I am pleased to inform you that your abstract entitled

Do surgical strategies for the repair of aortic coarctation have an impact on the rate of recoarctation?

has been accepted for **oral presentation** during the above Annual Meeting.

Please find details about your presentation below:

Lecture: #287 - Do surgical strategies for the repair of aortic coarctation have an impact on the rate of recoarctation?
Session: Congenital 4
Session Type: Congenital
Date: 03-11-2014
Time: 4:00 PM-5:15 PM

Appendix-II

University of Glasgow | College of Medical, Veterinary & Life Sciences

WORD COUNT FOR SUBMISSION OF THESES FOR EXAMINATION

NAME OF STUDENT: KASRA SHAAIKHREZAI

STUDENT ID: 2154148

DATE OF SUBMISSION OF SOFTBOUND THESIS: 01.04.2019

DEGREE: MD

NUMBER OF WORDS: 36,787

SIGNATURE OF STUDENT: