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Incidence of Arterial Hypertension & Re-coarctation long-term after Stent Therapy of the Aortic Coarctation

Mohamed Hosny Mohamed Fayed

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1. Prof. Dr. Peter Ewert
2. Priv.-Doz. Dr. Bernhard Voss

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Mohamed Hosny Mohamed Fayed

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Chairman: Prof. Dr. Jürgen Schlegel

Supervisors: Prof. Dr. Andreas Eicken

Prof. Dr. Amal Abdellatef

Examiners of the Dissertation:

1. Prof. Dr. Peter Ewert
2. Priv.-Doz. Dr. Bernhard Voss

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List of Abbreviation:

B

BES · Ballon expandable stents
BIB · Balloon-in-Balloon
BRS · Baroreceptor reflex sensitivity

C

CHD · congenital heart diseases
CoA · Coarctation of aorta
CP · Cheatham Platinum

H

HLH · Hypoplastic left heart syndrome

I

IAA · Interrupted aortic arch

L

LVH
Left ventricular hypertrophy ·

M

MRI · Magnstic resonance imaging

P

PTFE · polytetrafluoroethylene

R

Re-CoA · Recoarctation of aorta

T

TA · Tricusped atresia

V

VSD · Ventricular septum defect

Abstract

Aims: Stent implantation has become the treatment of choice for native aortic coarctation (CoA) and recurrent aortic recoarctation (Re-CoA) in children, adolescents and adults. In our study, we sought to analyse the intermediate and long term results after interventional CoA stenting.

Methods and Results: The data of all 218 patients who underwent stent implantation in our hospital between February 1999 and October 2017 were retrospectively analysed. Native CoA was diagnosed in 101 patients and Re-CoA in 117 patients. Median age at intervention was 17.6 years. The median peak invasive systolic pressure gradient declined from 26.2 mmHg to 2.7 mmHg ($p< 0.005$). The most common procedure-related complications included femoral artery complications in 9 patients, stent fracture in 9 patients and stent dislocation in 7 patients. There was one procedure related death due to an aortic rupture after stent implantation. At a median follow-up time of 31 months, 4 patients died. In 85 patients a re-dilatation and in 25 patients a second stent-implantation was necessary at the first re-intervention. The systolic blood pressure declined significantly from 144 mmHg before stenting to 131 mmHg at the last visit ($p< 0.005$), the need of antihypertensive medication increased from 51% to 63%. At the time of the follow-up, 78.5% of the patients were classified to be normotensive vs. 18% before stenting.

Conclusion: CoA stenting is an effective means for treatment of native – and Re-CoA with manageable procedural complications and low mortality. Up to 50% of these patients need at least one further catheterization with re-intervention. CoA stenting with proper antihypertensive medications results in better control of blood pressure.

1. Introduction

1.1 Coarctation of Aorta

Aortic coarctation (CoA) is a congenital narrowing of the upper descending thoracic aorta, resulting in obstruction to blood flow through the aorta (Deanfi et al., 2009). CoA accounts for 5 - 8 % of children born with congenital heart diseases (CHD) (Keith et al., 1958). The majority of coarctation is newly diagnosed in childhood; less than 25% are recognized beyond 10 years of age (Allen et al., 2013). Most of these patients are relatively healthy, presenting only chronic hypertension as co-morbidity, requiring lifelong treatment for this chronic condition (Musto et al., 2008). An increased rate of intracranial aneurysms suggests that wall abnormalities are not confined to the aorta (Connolly et al., 2003). Coarctation of the aorta therefore should be considered a complex cardiovascular syndrome rather than an isolated narrowing at the aortic isthmus.

1.2 CoA Pathology & anatomic consideration

CoA consists of a constricted aortic segment comprising localized medial thickening with some infoldings of the media and superimposed neointimal tissue. The localized constriction may form a shelf-like structure with an eccentric opening or it may be a membranous curtain-like structure with a central or eccentric opening (Rao, 2005).

CoA is usually located in the juxta-ductal position immediately distal to the left-subclavian artery in a left-sided arch. Infrequently, it can also exist in the

transverse aortic arch and abdominal aorta or be a part of a long-segment arch hypoplasia as seen in various left-sided obstructive lesions such as hypoplastic left heart syndrome (Vergales et al., 2013). Collateral vessels that connect arteries from the upper part of the body to the vessels below the level of coarctation may be seen; these may be present as early as a few weeks of life (Rao, 2005).

1.3 Associated Defects

Bicuspid aortic valve may be seen in nearly two thirds of infants with CoA. Mitral valve anomalies, although less frequent than those of the aortic valve, are also seen with CoA. Some patients with CoA may have cerebral aneurysms, predisposing them to development of cerebrovascular accidents with severe hypertension later in life. CoA is the most common cardiac defect seen in Turner's syndrome (Rao, 2005).

1.4 Pathogenesis & Pathophysiology

The exact mechanism by which CoA is developed is not clearly understood. Two hypotheses are most involved: hemodynamic and ectopic ductal tissue. In the first hypothesis, an abnormal pre-ductal flow or abnormal angle between the ductus and coarctation are invoked. Spontaneous postnatal closure of the ductus arteriosus completes the development of aortic obstruction. A high incidence of CoA in congenital heart defect patients with decreased antegrade aortic flow in utero and virtual absence of CoA in patients with right heart obstructions increases tendency to the hemodynamic hypothesis. Abnormal extension of ductal tissue into the aorta "ectopic ductal tissue" has been

postulated to create coarctation shelf, and with ductal closure, development of aortic coarctation. This theory, however, does not explain the variable degrees of isthmic and aortic arch hypoplasia seen with CoA (Rao, 2005).

1.5 Diagnosis of CoA

The hallmark clinical finding in coarctation of the aorta is hypertension proximal to the lesion, with diminished blood pressure distal to the obstruction. Consequently, clinical diagnosis can be made by the presence of diminished lower extremity pulses, differences in timing between upper extremity central pulses (often brachial) and lower extremity central pulses (often femoral), or the presence of a supine arm-leg blood pressure gradient. In patients with an aberrant right subclavian artery, all four extremities may be supplied by vessels distal to the obstruction, thus making diagnosis difficult. In neonates, a patent ductus arteriosus may help by limiting the degree of physiologic obstruction around a juxta-ductal coarctation, but at the expense of possibly obscuring the diagnosis. Therefore, a neonatal coarctation may not manifest itself until the ductal tissue fully constricts (Russell et al., 1991).

Transthoracic echocardiographic techniques have become the standard in confirming clinical suspicion of coarctation. This can best be demonstrated in the suprasternal view by demonstrating a narrowed aortic lumen in addition to measuring of the Doppler derived gradient across the coarcted segment. In older patients where acoustic windows may be suboptimal, it can be difficult to visualize the descending aortic segment of concern. In these patients, magnetic resonance imaging and less often computed tomography scanning has become the modality of choice in the evaluation and management of both native and

recurrent coarctations. This includes being able to make accurate predictions about severity of the coarctation gradient as seen at the time of cardiac catheterization (Nielsen et al., 2005).

1.6 Mechanism of systemic hypertension

Previous studies showed the potential roles of different factors in this hypertensive state, including mechanical, functional, and structural abnormalities in the systemic arterial bed (Sehested et al., 1982) (de Divitiis et al., 2001). Early elastic fiber fragmentation, fibrosis, and cystic medial necrosis can be found in the walls of the ascending and descending aorta, and lead to an increased stiffness of the aorta (Niwa et al., 2001). A number of recent studies in both humans and animals indicate that reduced baroreceptor reflex sensitivity (BRS) may play a role in the development of hypertension (Lohmeier et al., 2005). some of these factors appear to exist within the fetal or neonatal period before repair (Paton et al., 2006). Another factor that has been shown to lead to the subsequent risk of hypertension is the age at the time of the original repair (O'Sullivan et al., 2002) ; aortic stiffness and increased pulse wave velocity are more common in patients with late repair and long-standing pre-stenotic hypertension and in the vessels proximal to the coarctation (Hager et al., 2007). As a result, signs of preterm atheromatosis appear early in life as an increased carotid intimal–medial thickness in young adults and children, as well as a diminished endothelium-dependent and endothelium-independent vasodilatation in the right brachial artery (JJ et al., 2004) (Meyer et al., 2005). All these pathologic conditions, including restenosis, lead to an increased cardiovascular morbidity and mortality, such as coronary artery disease,

stroke, heart failure, ruptured aortic and cerebral aneurysms, and sudden cardiac death (Toro-Salazar et al., 2002). Therefore, coarctation is treated at presentation, which is usually in early childhood. The actual recommendation, residual systolic blood pressure gradient at the coarctation site of greater than 20 mmHg (Rosenthal, 2001). Identifying hypertension is an important component of the long-term follow-up of these patients.

1.7 Surgical treatment of CoA

The past 5 decades have seen many improvements in the therapeutic options for treatment of native coarctation of the aorta in children and adults. Surgery and catheter interventional techniques are available alternatives for management of CoA. Native coarctation has historically been treated by surgery. The first surgery was performed in 1944 (CRAFOORD & C, 1945). Since that time, several surgical procedures have been developed, each associated with a different risk of restenosis or aneurysm formation.

1.7.1 Patch aortoplasty

Concerns about recoarctation rates following end-to-end anastomosis led to attempts to augment the coarcted segment with a prosthetic material (Patch aortoplasty). Initially, the prosthetic material used was made of Dacron (Maxey et al., 2003). While this technique originally demonstrated a lower rate of recoarctation, it fell out of favor when significant aneurysms were seen developing on the wall opposite the prosthetic graft in 20-40% of cases (Vergales et al., 2013). Polytetrafluoroethylene (PTFE) was thought to reduce the mechanical factors believed to lead to aneurysm formation by being more

distensible than Dacron, but still demonstrated a recoarctation rate of 25% along with a 7% aneurysm rate (Walhout et al., 2003). Patch aortoplasty is still being used, however, in the setting of more complex aortic arch reconstructions. This is especially evident in severe arch hypoplasia, as seen in infants with hypoplastic left heart syndrome.

1.7.2 Subclavian Flap aortoplasty

This technique, which utilizes one's own tissue, was first described by Waldhausen in 1966 (Vergales et al., 2013), but did not move into mainstream practice until many years later to reduce long-term complication rates.

Initial proponents of this technique touted lower recoarctation rates in infants because of the use of one's native tissue to perform the repair (Sousa et al., 1983)**.** Recent long-term studies have demonstrated upwards of a 23% recurrence rate from neonatal repair, but also have shown much lower recurrence rates when the operation was performed on older children (0-3%) (Vergales et al., 2013).

1.7.3 Coarctation Resection with Interposition Graft

This technique has been reserved for patients in whom outgrowth of the graft is not a concern, or in patients with long segment coarctation. The main disadvantage of this technique is that the tube graft will not grow with the patient. Yet, for adult-sized patients presenting with long-segment coarctation, this technique may be preferable at many centers. However, in our unit the surgical group always tried to avoid a tube graft interposition in children with coarctation of the aorta and usually in pediatric patients' treatment was possible without a tube graft.

1.7.4 Coarctation resection with extended end-to-end anastomosis

This is the preferred method in most surgical centers and is currently thought to better deal with residual ductal tissue in addition to the frequently encountered problem of transverse arch hypoplasia. The most recent data suggests low mortality, shorter cross-clamp times, and lower recoarctation rates at 4-13% looking at patients 5-10 years post-surgery (Brown et al., 2009). The procedure has low mortality even on patients under two kilograms (Sudarshan et al., 2006).

while the requirement for tube graft interposition or patch augmentation of the coarctation segment increased significantly the risk for aneurysm formation as the child reached teenage years, end-to-end resection of the native coarctation segment was not possible to be performed in the majority of surgical patients over the age of 8 (T. J. Forbes et al., 2011).

1.7.5 Long term consideration

Even if the results are excellent and repair can be performed with freedom from major complications in 93.5% of patients (Mavroudis et al., 2014), survival remains limited due to comorbidities and reinterventions / reoperations needed in long term follow-up (Bambul Heck et al., 2018). The ultimate aim for any coarctation repair is the resolution of the a systolic brachial–ankle gradient, as persistent hypertension can be observed in as many as 50% of patients even with a “perfect” repair, particularly if initial repair is performed after 1 year of age (Instebø et al., 2004). For those patients without obvious restenosis, the most important risk factor was the use of

prosthetic material at surgical intervention “tube graft or patch”. This may be due to that non-compliant prosthetic material might cause early pulse wave reflection already at the coarctation site and increase pulse wave velocity to the natural reflection area at the bifurcation of the abdominal aorta, this leads to an increase of the systolic blood pressure and enhance the effects of the inborn and acquired aortic stiffness seen in patients with coarctation (Hager et al., 2007).

1.8 Balloon angioplasty for CoA treatment

During the last 25 years, many centers have shifted from surgical to endovascular treatment of CoA in patients older than 5 years of age. A perceived higher risk associated with an open surgery in particular with repeated surgery for CoA, and a convenience argument for the patient; shorter hospital stay, lower risk of infection & avoidance of general anesthesia, has facilitated this shift (SINGER et al., 1982). In 1982 balloon dilation was introduced as a treatment of aortic re-coarctation (Re-CoA) after surgical repair, with post-operative restenosis and persistent hypertension (SINGER et al., 1982). Fawzy et al. showed excellent long-term results of balloon angioplasty in adolescents and adults with discrete native coarctation of the aorta and proposed that it should be used as a first option for the treatment of aortic coarctation (Fawzy et al., 2004).

Aneurysm formation at the dilation site has remained a long-term concern. Many reports showed increased risk for aortic wall trauma with endovascular angioplasty describing high aneurysm rates “7% to 20%” (Fawzy et al., 2004) (Brandt et al., 1987). It has been suggested that aneurysm development may

be caused using an oversized balloon; media tear and cystic medial necrosis may be potential causes of aneurysm formation (Paddon et al., 2000) (Parikh et al., 1991).

1.9 Stent implantation for CoA treatment

Since the early 1990s, balloon expandable stents have been used in the management of CoA in children (Shah et al., 2005). Although satisfactory and similar clinical outcomes were observed with both techniques (Stenting & balloon dilatation), stenting was a better means to relieve the stenosis and minimize the risk of developing immediate aortic wall abnormalities (Pedra et al., 2005). Furthermore, restenosis was common in balloon angioplasty; being reported in up to 20—30% of patients, because of the elastic recoil properties of the aorta (Mann et al., 2001). The main advantages of stenting compared with balloon angioplasty are the ability to expand a tubular long-segment narrowing or an hypoplastic isthmus, to increase the diameter of the stenosed segment without intimal tear, to decrease the possibility of restenosis and to prevent aneurysm formation because of support to the weakened aortic wall segment by the stent (Peters et al., 2009). Furthermore, the radial support to the vessel wall and the opposition of the torn vessel intima to the media with the possibility to perform redilatation “especially in young patients” with no need for over sizing to avoid major transmural tears. Stent implantation prevents acute re-modeling of the aortic wall (Tzifa et al., 2006) (Golden & Hellenbrand, 2007).

Stent implantation is now the treatment of choice for native CoA and postsurgical aortic re-coarctation “Re-CoA” in children, adolescents, and adults in many cardiac centers, with excellent short-term results (Eicken et al.,

2006). In a recent study that compared coarctation stenting, surgery, and balloon angioplasty; surgical treatment utilizing resection and end-to-end anastomoses significantly decreased in children older than 8 years of age, (T. J. Forbes et al., 2011), as the patient reaches young adulthood, the aorta becomes less compliant and mobile, and stent therapy becomes the treatment of choice (T. J. Forbes et al., 2013).

1.10 Comparison of surgical and interventional treatment of CoA

The safety and efficacy of stent implantation for CoA treatment cannot be fully evaluated without considering the other two treatment modalities, surgery and balloon angioplasty. Although stenting of CoA has been performed over the past 3 decades, few studies directly compare the three treatment modalities of surgery, stenting, and balloon angioplasty. Forbes et al. compared the safety and efficacy of surgical, stent, and balloon angioplasty treatment of native CoA acutely and at follow-up in a large study between 2002 and 2009 (T. J. Forbes et al., 2011); 217 patients underwent stent placement, 61 underwent balloon angioplasty, and 72 underwent surgery. Although all three groups showed significant improvement acutely and at short-term and intermediate follow-up in upper to lower-extremity blood pressure gradient, stent treatment had the lowest acute complication rates between the three treatment modalities “2.3% for stenting, 8.1% for surgery, and 9.8% balloon angioplasty; $P < .001$”. Furthermore, stent and surgical therapy achieved better hemodynamic and integrated aortic arch imaging outcomes than balloon angioplasty at short-term and intermediate follow-up. The stent group

required planned re-interventions “20%”, with no differences among the three groups regarding the need for unplanned re-interventions. In the most recent follow up of the 478 patients, the aneurysm rate remained at 2.8% and 4.4% at short and intermediate term follow up, respectively. This is like surgical colleagues and significantly less than the balloon angioplasty (T. Forbes et al., 2013).

1.11 Stents in congenital heart diseases

There are different classifications of stents used in interventional cardiology according to various features; the material of which they are made, the target region, their configuration, size, coverage, coatings, and drug-eluting properties. But, the most common classification is based on delivery mechanism: Balloon-expandable versus self-expandable stents (Peters et al., 2009). For CoA treatment, balloon-expandable stents are the commonly used. Balloon-expandable stents “BES” are mounted on balloons, positioned across the site of obstruction and are implanted by inflating the balloon. The size of the inflated balloon determines the expanded diameter of the stent. BES were firstly uesd for the treatment of congenital heart lesions in 1987 (Mullins et al., 1988). The benefits of BES are high radial support with accurate stent placement and possibility of redilatation. Several stents can be dilated to a diameter > 20mm.

1.11.1 Characteristics of ideal stents in pediatric cardiology

1- Low stent profile combined with high trackability and flexibility to negotiate steep curves.

2- Radio-opacity and visibility for accurate placement.

3- Compatible with magnetic resonance imaging (MRI) without artifacts.

4- Possible expansion with minimal foreshortening.

5- High radial strength.

6- Low rigidity with no material fatigue over time.

7- Resistance to thrombus formation and corrosion.

8 - Avoidance of neointimal proliferation.

9 - Round and soft edges to avoid the intimal damage.

10- Possibility of redilatation with patients' growth.

11- Wide struts to maintain blood flow to jailed vessel branches.

12- Retrievability and possibility of repositioning if needed.

Till now there is no available stent that includes all of these features, so the selecting the right stent is one of the most challenges encountered by pediatric interventional cardiologist (Peters et al., 2009).

The most commonly used stent in pediatric cardiology is the Cheatham platinum “CP” stent, which is made from 90% platinum and 10% iridium. These stents have excellent visibility on fluoroscopy and maintain excellent radial strength even at larger diameters. They have rounded edges, are more malleable and are MRI compatible. The rounded edges cause fewer traumas to the vessels and the balloons. This stent was the first to be developed for exclusive use in pediatric cardiology CP stents are available in a covered version, with an outer polytetrafluoroethylene “PTFE” membrane. The

covering is initially approximately 7 mm in diameter and will stretch over the range of diameters of expansion “usually from 12 to 24 mm diameter” and will cover the stent when expanded (Peters et al., 2009).

1.11.2 Balloons used in stent implantation

One of the most important developments in equipment for the delivery of large-diameter stents has been the Balloon-in-Balloon “BIB™; NuMed Inc.” catheter, the first balloon specifically designed for stent delivery in the CHD population. These catheters have an inner balloon and a longer outer balloon that is double the diameter of the inner balloon. The BIB catheters are available in outer balloon sizes of 12 - 30 mm. The BIB catheters offer the important advantage of opening the stent more uniformly along its length but require a larger arterial sheath for introduction. With a stent hand crimped onto the balloon, it is necessary to upsize the long sheath by 1F, greater than is necessary for the BIB catheter alone. BIB catheters require an 8F – 16F sheath for introduction depending on the balloon diameter, if a covered stent is mounted on the balloons in smaller balloons a sheath with three additional French sizes needs to be taken. BIB catheters prevent stent flare and offer more precise control over stent placement (Peters et al., 2009). Single-balloon catheters are still sometimes preferable in smaller patients to reduce risk of injury to the femoral artery at the access site.

Stent implantation for CoA treatment is an evolving procedure, with significant improvements being observed over the past 2 decades regarding acute complications. In a recent study, the acute complication rate, such as stent

fracture & stent displacement, was 5% (15/302) (Holzer et al., 2010). In contrast, the acute complication rate in the previous era (1989–2005) was much higher at 14.3% (81/565) (T. J. Forbes, Garekar, et al., 2007). The main improvement was observed in stent positioning and decreased balloon ruptures. However, there is still limited information available on the long-term follow-up of CoA stenting in children. This retrospective, single-Centre study reported the acute and long-term results in children, adolescents, and adult patients who underwent endovascular stent placement for both native COA and Re-COA.

2. Patients and Methods

2.1 Study subjects

We retrospectively analysed the data of all consecutive patients older than 6 years, who underwent cardiac catheterisation for native and recurrent aortic coarctation at German Heart Centre Munich between February 1999 and October 2017. Only patients above 6 years old were included in our study for evaluation of stents expandable to adult size with or without the need of implantation of a second larger stent. The diagnosis of CoA and Re-CoA was established by clinical means (absence of femoral pulses, blood pressure gradient >20 mm Hg between right arm and legs, elevated blood pressure at the right arm), standard echocardiography provided images of the aortic arch. Flow acceleration was detected using Doppler flow calculations and typically the presence of a diastolic “run-off” signal.

Indications of cardiac catheterisation were clinical and echocardiographic evidence of CoA (flow acceleration in Doppler flow and the presence of a diastolic “run-off” signal). In the case of a significant CoA, defined as an aortic narrowing >50 % on angiography and additional arterial hypertension in at least at the upper body part, stent implantation was performed even if the invasive peak systolic pressure gradient between the ascending and the descending aorta was less than 20 mmHg. Technical success was defined by successful stent placement with no evidence of severe acute complications “rupture, cardiac arrest, or death” and a pullback gradient of less than 20 mmHg.

Arterial hypertension was defined as systolic blood pressure greater than the 95th percentile for blood pressure for age, height, and gender normal values for children (Neuhauser et al., 2011) and as systolic blood pressure greater than 139 mmHg or diastolic blood pressure greater than 89 mmHg for adult patients (Mancia et al., 2013).

Informed consent to analyse and publish data anonymously was present from all patients or the legal guardian, as appropriate. The study was in accordance to good clinical practice and the Declaration of Helsinki (version 2013), the local ethical board approved the study protocol (project number 310 /17 S). Data collection included patient's demographics, cardiac catheterisation and operation reports, radiologic and echocardiographic studies. Baseline clinical information, other comorbidities, medications were also recorded

2.2 Procedure

A written Informed consent was obtained from all patients or the parents of the children. The procedure was performed under deep sedation with midazolam and propofol. Femoral arterial access was gained percutaneously. When the CoA lesion was near-atretic, additional brachial arterial access was obtained for aortic arch angiograms and for crossing the CoA with a wire. After measurement of the initial gradients and angiography, the diameters of the transverse arch, CoA, and descending aorta above the diaphragm were measured using catheter magnification or the calibration markers on the catheters. The length of the chosen stent was based on the individual anatomy. The stent should cover the stenotic segment, leave free flow to the carotid arteries. If the subclavian artery needed to be covered, usually a bare

metal stent was chosen initially. If a covered stent was needed to cover the subclavian artery, the cover was reopened to guarantee free flow to the brachial artery and to avoid a subclavian steal. The maximum balloon diameter was chosen based on either the transverse or the distal arch diameter, whichever was greater, and on occasions 1 to 2 mm greater. A long sheath (usually Mullins, Cook, Bloomington, Indiana) placed over an ultra-stiff, 0.035-inch guide wire (Amplatz ultra-stiff; Cook Medical Inc., Bloomington, Indiana, United States of America) was used in all patients for stent delivery. The wire was positioned in the ascending aorta in the majority of cases. The sheath size ranged between 10- and 16-F and was chosen to be 2- to 3-F larger than that required for the introduction of the balloon catheters. The stent was crimped onto a BIB balloon (NuMED Inc.). This balloon allows for readjustment of position after inflation of the inner balloon. Rapid right ventricular pacing was used during stent deployment in 34 cases. Hemostasis was achieved by manual compression. Heparin at a dose of 50 to 100 IU/kg with maximum 5000 U was given to maintain the activated clotting time _200 to 220 s during the procedure. Antibiotics were given at the beginning of the procedure and continued for 24 h. Aspirin was administered to all patients the evening before the procedure at a dose of 3 to 5 mg/kg and continued for 6 weeks to 6 months (Tzifa et al., 2006) (Magee et al., 1999).

2.3 Follow-up

All of our patients after stent implantation were invited to a regular follow up examination. Patients underwent clinical follow-up 1, 3 and 6 months after stent implantation. Thereafter, yearly follow-up was performed. If the patient was not in regular follow-up at our institution, external clinical documentation files at our institution were reviewed or primary cardiologist was requested to provide last medical records.

Apart from cardiological examination, special attention was paid to the blood pressure values of both arms and legs. The systolic blood pressure was taken under resting conditions using auscultation and the Doppler-technique at the arm arteries, dorsal foot arteries, or posterior tibial arteries. A significant residual gradient was defined as a systolic BP gradient between the right arm and either leg > 20 mmHg at rest. Twenty-four hours ambulatory blood pressure monitoring (ABP), was performed for patients with resting arterial hypertension. Measurements were taken every 20 min between 6 a.m. and 6 p.m. and every 60 min during the night. The day and- night profiles of BP and day–night rhythms were evaluated.

All patients had a standardized echocardiographic examination. The cw-Doppler flow pattern was analysed for the presence of diastolic run-off, and flow acceleration. A significant Doppler gradient was defined as a systolic pressure gradient across the coarctation > 20 mmHg. Left ventricular hypertrophy was defined when the left ventricular posterior wall end-diastolic diameter exceeded the 95th percentile (Roge et al., 1978).

To evaluate the long-term results of CoA stenting, the last follow-up data were involved in our study. The median follow up time was 31 months (range 1 –

216 months). Patients with systemic arterial hypertension, or arm to leg pressure difference > 20 mmHg by cuff spygmometry underwent re-catheterization to evaluate stent and re-coarctation.

2.4 Statistical Analysis

Data analysis was performed with SPSS 25.0 software (SPSS; Inc., Chicago, Ill). Continuous variables were summarized as mean ± standard deviation (SD) or median and range, as appropriate. Comparisons between categorical variables in two groups were performed with Chi-Quadrat test and comparisons between continuous variables were tested with the independent t-test. Univariate and multivariable logistic regression analyses were performed to analyse the potential risk factors influencing complications and re-interventions. Tested risk factors included data for patient characteristics (gender, age at catheterisation, age at follow-up) and clinical status (body weight, height, presence of prosthetic material at the previous coarctation site, brachial-ankle blood pressure difference, arterial hypertension, antihypertensive medication, type of the aortic arch, type of the circulation, type of the coarctation). Time dependent survival was analysed using Kaplan-Meier survival estimate. A p value < 0.05 was considered to be statistically significant.

3. Results

3.1 Patients

There were 218 patients treated with an interventional stent implantation. A total of 101 patients [46.3%] were diagnosed with native CoA and 117 patients [53.7%] developed Re-CoA after surgical correction (86 patients with end to end anastomosis,13 patients with graft interposition, 6 patients with aortic arch reconstruction, 3 patients with subclavian flap). From Re-CoA patients, 22 patients had more than one surgical operation for recurrent CoA. The detailed patient characteristics are given in table 3.1. The different morphologies of the aortic arch after coarctation repair were defined according to Ou et al. (Ou et al., 2007).

All the types of balloons and stents, which have been used, are listed in Table 3.3. Covered stents were used in 69 patients [31.7%], bare metal stents in 149 patients [68.3%].

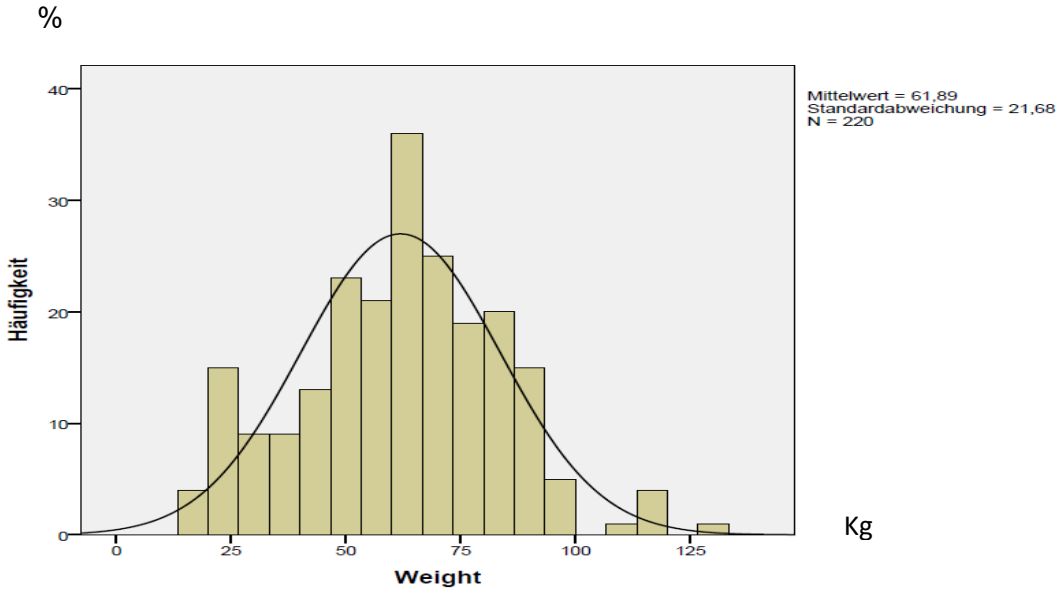

Figure 3. 1: Patients weight at time of stent implantation

Total number of patients	218
Sex (females/ males)	75 / 143
Age at cardiac catheterisation (years)	17.6 (6.0-62.9)
Weight (kg)	63.2 (16-130)
Height (cm)	165 (74 -193)
CoA Type	
Isolated CoA	177 (81.2%)
CoA with VSD	22 (10.1%)
CoA associated with a complex CHD	19 (8,7%)
HLH/ TA	3 (1,4%)
IAA	13 (5.9%)
Mid-aortic syndrome	1 (0.5%)
Aortic isthmus atresia	2 (0.9%)
Turner Syndrome	4 (1.8%)
Biventricular / Univentricular circulation	215 / 3
Type of the aortic arch	
Normal	169 (77.5%)
Gothic	25 (11.5%)
Crenel	24 (11%)

Table 3.1: Patient characteristics

VSD: ventricular septal defect, HLH: Hypoplastic left heart syndrome, TA: Tricuspid atresia, IAA: Interrupted aortic arch.

Re-CoA art	Frequency	Percentage (%)
End to end anastomosis	86	72
Dacron interponat	13	11
Patch augmentation	10	8
Subclavian flab	3	2,5
Aortic arch reconstruction	6	5
Ballon dilatation	1	0,5

Table 3.2: Characteristics of Re-CoA patients

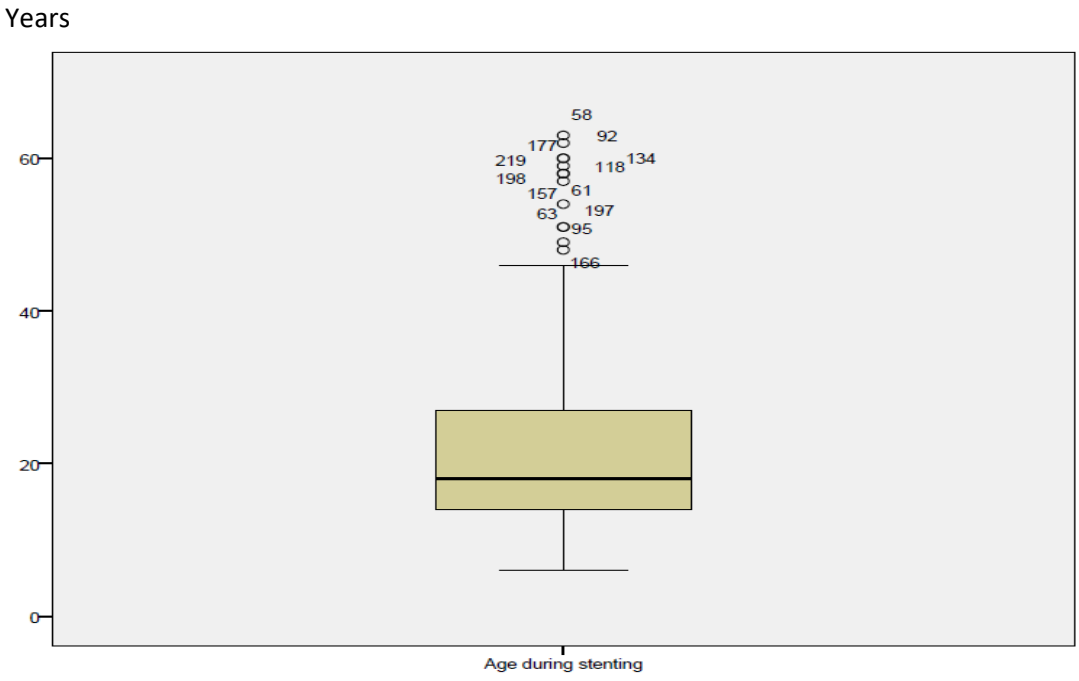

Figure 3. 2: Age distribution at time of stent implantation

Stent type	Total number of patients	Number of patients with a native CoA	Number of patients after CoA-surgery
Palmaz Genesis	14 (6.4%)	0	14 (6.4%)
Intra Stent Mega LD	26 (11.9%)	9 (4.1%)	17 (7.8%)
Intra Stent Max LD	37 (17%)	12 (5.5%)	25 (11.5%)
Andra Stent XL	9 (4.1%)	3 (1.4%)	6 (2.7%)
Bare Cheatham Platinum Stent	53 (24.3%)	11 (5%)	42 (19.3%)
Covered Cheatham Platinum Stent	69 (31.7%)	57 (26.1%)	12 (5.6%)
Advanta Stent	7 (3.2%)	7 (3.2%)	0
Cook Formula Stent	3 (1.4%)	2 (0.9%)	1 (0.5%)
Total	**218**	**101**	**117**

Table 3.3: All types of used stents for aortic coarctation.

3.2 Acute Procedural results

A successful endovascular treatment, defined as a pullback gradient < 20 mmHg after stent implantation, was achieved in 209 of all 218 patients. In 7 of the 9 patients with a pullback gradient >= 20 mmHg, a further re-intervention (in 3 patients re-stent implantation, in 6 patients a balloon angioplasty) was undertaken, with a final pullback gradient <20 mmHg. Two other patients were lost to follow-up.

The narrowed segment of the aorta was widened in all patients from a median diameter of 7.6 mm (range 1-19 mm) to a median diameter of 14.5 mm (range 6.2-24 mm) ($p< 0.005$). The median systolic peak-to-peak gradient between the ascending aorta and the descending aorta was lowered from 26.2 mmHg (range 5-109 mmHg) to a median of 2.7 mmHg (range 0- 50 mmHg) ($p< 0.005$).

Comparing the patients with a native CoA vs. patients with a Re-CoA, patients with a native CoA had significantly higher gradients before stenting (30.9 ± 16.2 mmHg in patients with native CoA vs. 22.3±9.5 mmHg in patients with Re-CoA, p<0.005). Accordingly, the gradient relief was significantly higher in patients with a native CoA (28.4 ± 15.7 mmHg in patients with native CoA vs. 19.4 ± 9.6 mmHg in patients with Re-CoA, p<0.005).

Patients with higher peak-to-peak systolic gradients, with multiple aortic coarctation surgeries before stenting, with a crenel type of the aortic arch and with a higher weight, had significantly higher residual gradient after stent implantation (p< 0.005, p=0.007, p=0.016 and p=0.023, respectively).

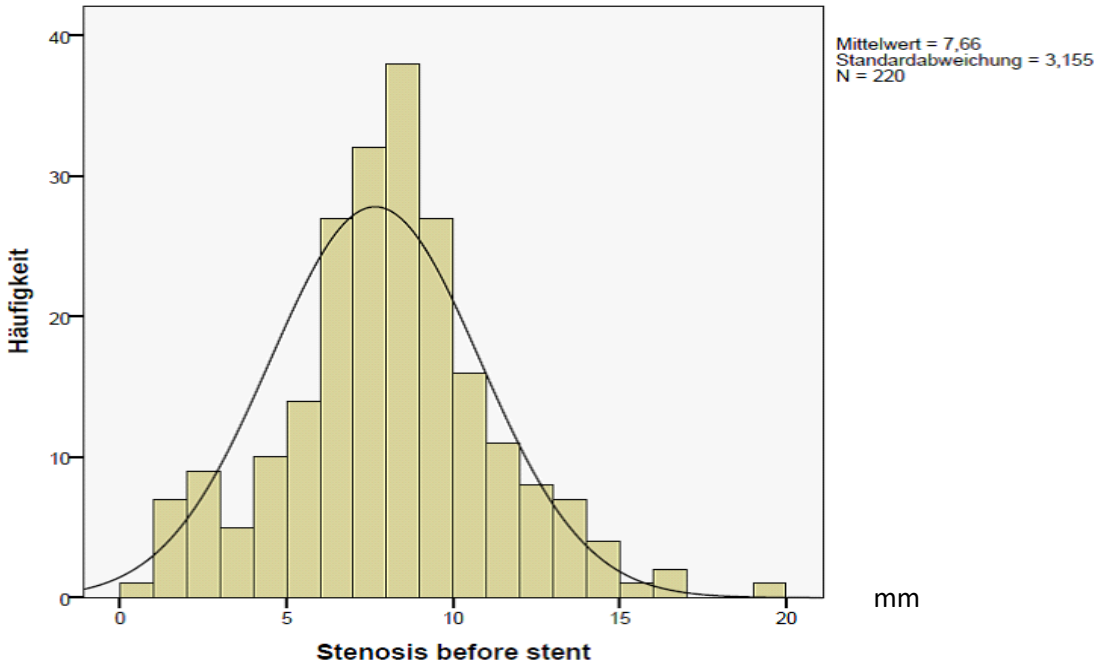

Figure 3. 3 : CoA diameter before stent implantation

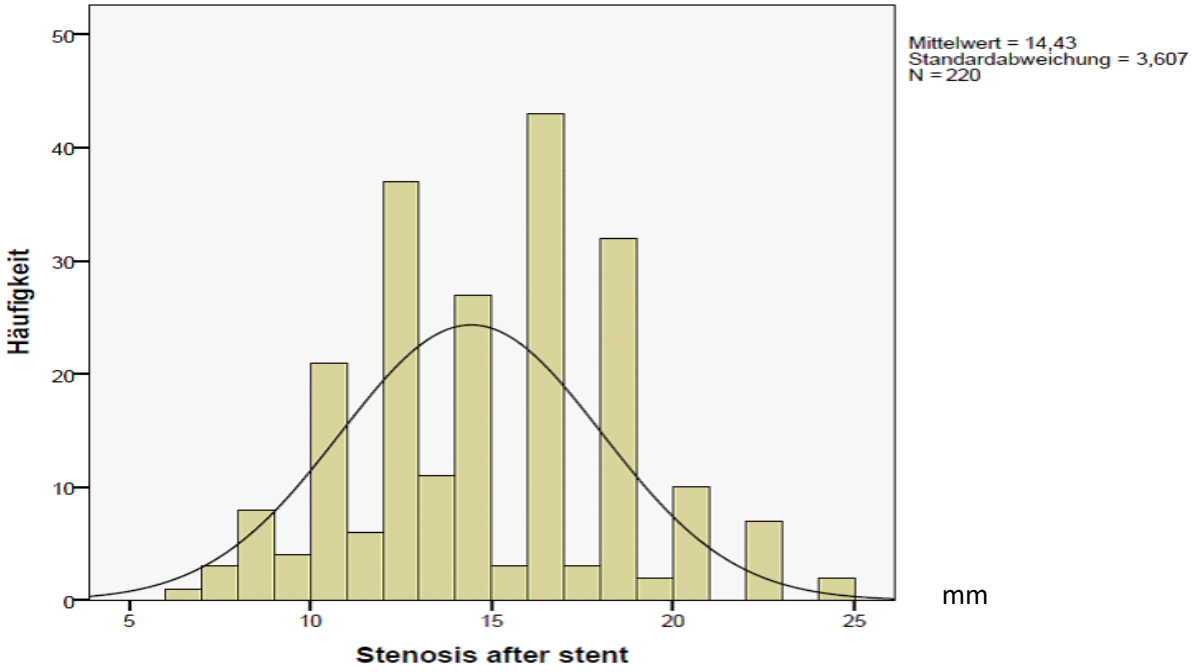

Figure 3. 4 : CoA diameter after stent implantation

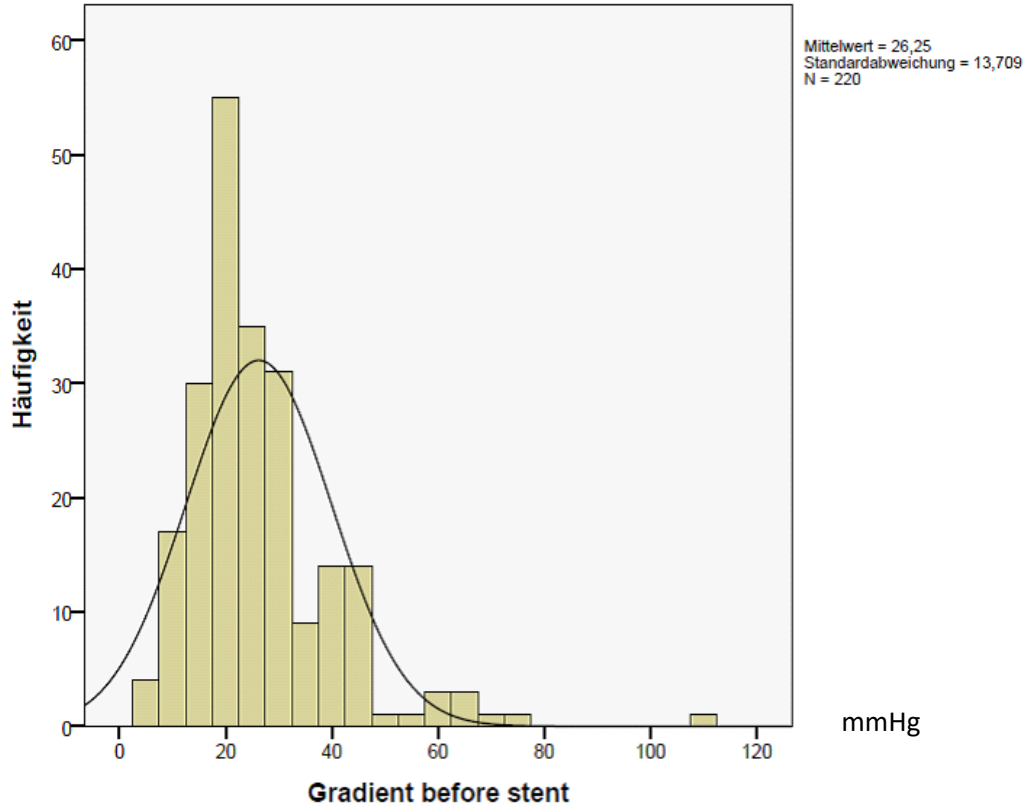

Figure 3. 5: Pressure gradient across CoA before stent implantation

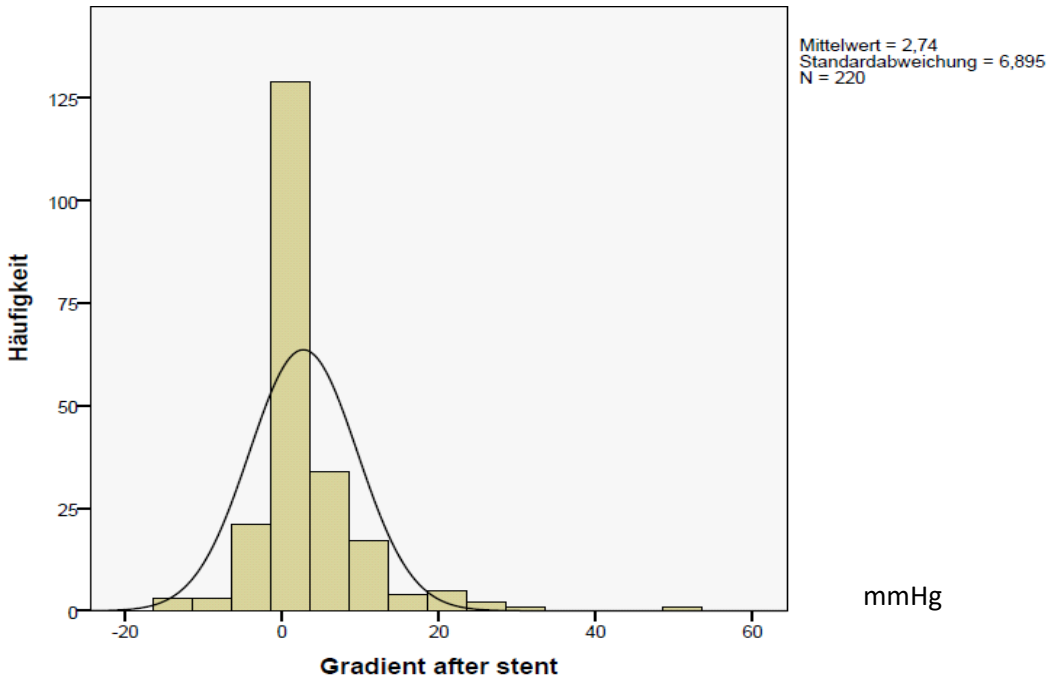

Figure 3. 6 : Pressure gradient across CoA after stent implantation

3.3 Procedural Complications

There were in total 32 [14.7%] procedure-related complications. The most frequent complications were stent fracture and femoral artery complications with 9 patients, respectively. Another 7 patients had stent dislocation. Two of the dislocated stents had to be removed surgically, three stents dislocated to abdominal aorta and were fixed there and the other two stents were successfully managed by an overlapping second stent. In the logistic regression, there was no significant correlation between stent displacement and descending aorta diameter, rapid ventricular pacing, arch type and percentage expansion. Aortic rupture occurred in 2 patients with a Re-CoA after end-to-end anastomosis. One female patient, at the time of the intervention 60 years old, died because of an aortic rupture. This patient was scheduled 11 months after the first stent implantation for re-catheterization and had an aortic

aneurysm at the previously stented coarctation site. After implantation of a Covered Cheatham Platinum Stent, an aortic rupture occurred, leading to the death of the patient. Another female patient, at the time of the intervention 32 years old, could be saved by emergency NuDEL implantation “NuDEL catheter: 45-mm, covered CP stent pre-mounted on a 24 × 50 mm balloon-in- balloon” (Eicken et al., 2017). Table 3.4 shows the incidence of all procedure related complications in patients with a native CoA and in patients with a Re-CoA.

	All patients n=218	Patients with native CoA n= 101	Patients with Re-CoA n=117	
No complications	188 (86.3%)	88 (87.1%)	98 (83.8%)	
Stent displacement	7	2	5	
Stent fracture	9	3	6	
Aneurysm	3	1	2	
Aortic dissection	3	1	2	
Femoral artery complications				
Femoral artery closure	5	4	1	
Femoral artery pseudo-aneurysm	3	2	1	
Femoral artery rupture	1	0	1	
Aortic rupture	2	0	2	
Total number of complications	**32 (14.7%)**	**13 (12.8%)**	**19 (16.2%)**	**p=0.31**

Table 3.4: Acute procedural complications after stent implantation in aortic coarctation.

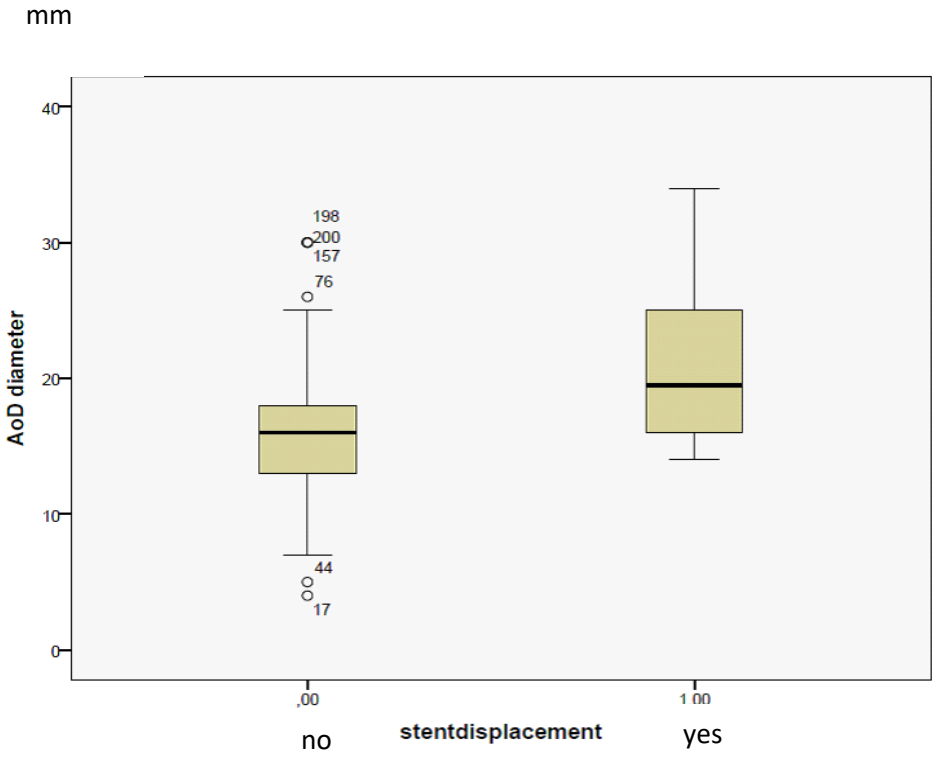

Figure 3. 7 : Correlation between stent displacement and aortic diameter

3.4 Survival and Re-interventions

Our cohort of patients was observed for a median of 31 months (range 0- 216 months). There was a total of 4 deaths during this period of time. Median age at death was 31.9 years (range 18.6- 60.3 years) and median time to the first stenting was 4.6 years (range 0.8 - 8.3 years). One patient died during stenting due to an aortic rupture, as described above. Two patients died due to heart failure, one of them had originally a complete atrioventricular septal defect and a mitral valve replacement and one patient had tricuspid atresia with a univentricular circulation. Another patient died due to myocardial infarction which was not associated to the procedure. On Kaplan- Meier survival analysis, the overall survival at 5 years was calculated to be 94% [Fig 3.8].

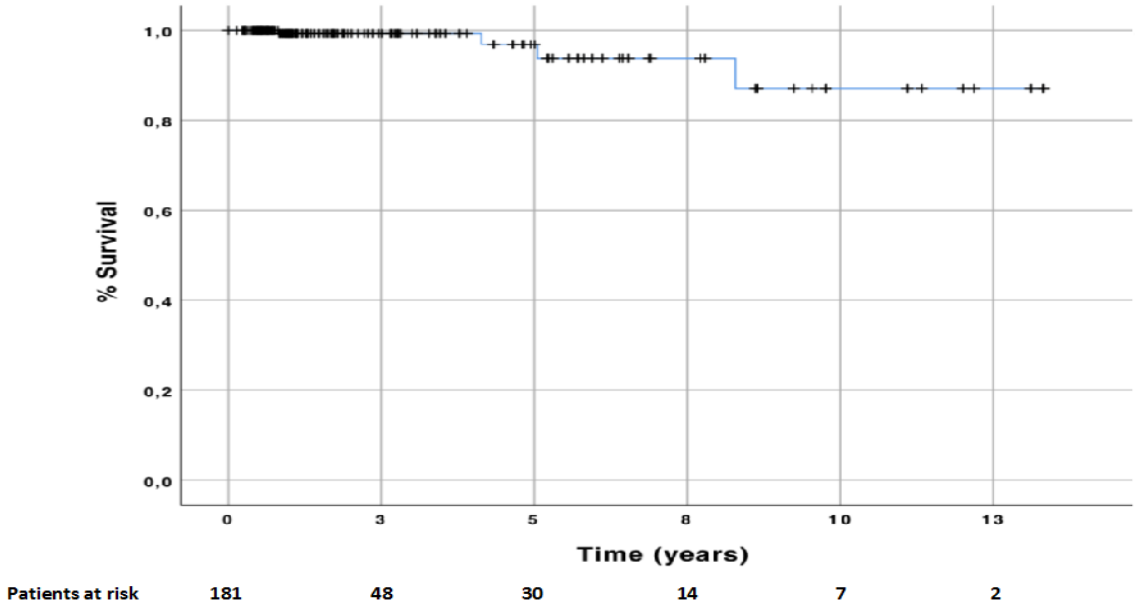

Figure 3. 8 : Kaplan- Maier estimate survival of 218 patients after CoA stenting

During this follow-up time, 135 patients were scheduled for re-catheterization; in 85 patients a re-dilatation and in 25 patients a second stent-implantation was necessary at the first re-intervention. The detailed information regarding re-interventions is given in table 3.5.

Stenting in a native CoA or Re-CoA did not have an impact on later re-intervention rate (p=0.800). By means of re-interventions, a gradual target-ratio of 1:1 for the diameter of the coarctation site and AoD could be achieved, as shown in figure 2. In the logistic regression, patients with a higher percentage of expansion of the coarctation during stenting had significantly higher rate of re-intervention in follow-up (p< 0.005).

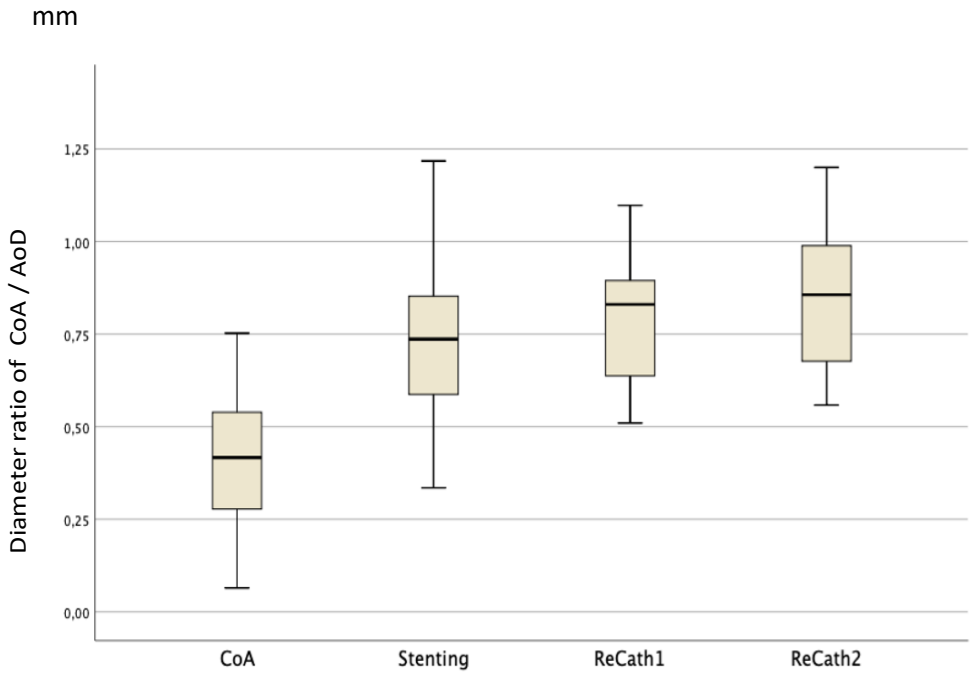

Figure 3 9 .: Reintervention after CoA stenting

	All patients n=218		Patients with native CoA n= 101		Patients with Re-CoA n=117	
	BA	Stent	BA	Stent	BA	Stent
Second intervention	85	25	38	9	47	16
Third intervention	17	18	8	7	9	11
Fourth intervention	1	5	0	1	1	4
Fifth intervention	0	1	0	0	0	1
Sixth intervention	0	1	0	0	0	1
Total number of further interventions	**103**	**50**	**46**	**17**	**57**	**33**

Table 3.5: Re-intervention rate in patients after stenting of aortic coarctation.

3.5 Arterial hypertension

From 218 eligible patients, data on blood pressure readings was complete in 181 patients with a median follow-up time of 31 months (range 0- 160 months). The right arm systolic blood pressure was lowered significantly from a median value of 144 mmHg (range 92 - 246 mmHg) before stent implantation to a median value of 131 mmHg (range 92 – 204 mmHg) at the last follow-up visit ($p< 0.0005$). At the same time, the use of antihypertensive treatment increased from 51.8% to 63% of the study population. Considering patients with a native CoA vs. patients with a Re-CoA, both of the subgroups had significantly more antihypertensive treatment after the stent implantation ($p =0.005$ and $p<0.005$, respectively). Also, the number of patients who were normotensive without antihypertensive treatment showed a significant increase from 14.2% to 31% of the study population ($p<0.005$).

Beta-adrenergic blocking agents were the mostly used antihypertensive treatment. Seventy-three patients were treated with a beta-adrenergic blocking agent (according 33.5% of the study population) before stenting vs. 77 patients after CoA-stenting [42.5% of the study population]. Forty-nine patients [22.5%] were treated with angiotensin-converting-enzyme inhibitor or angiotensin II type 1 receptor antagonists before stenting and 52 patients [28.2%] after stenting, 28 patients [12.8%] were treated with a calcium channel blocker before stenting and 28 patients [15.5%] after stenting, 14 patients [6.4%] were treated with a diuretic therapy before stenting and 19 patients [10.5%] after stenting.

The overview of hypertension status and antihypertensive treatment of the patients before and after CoA-Stenting is given in table 3.6 and table 3.7.

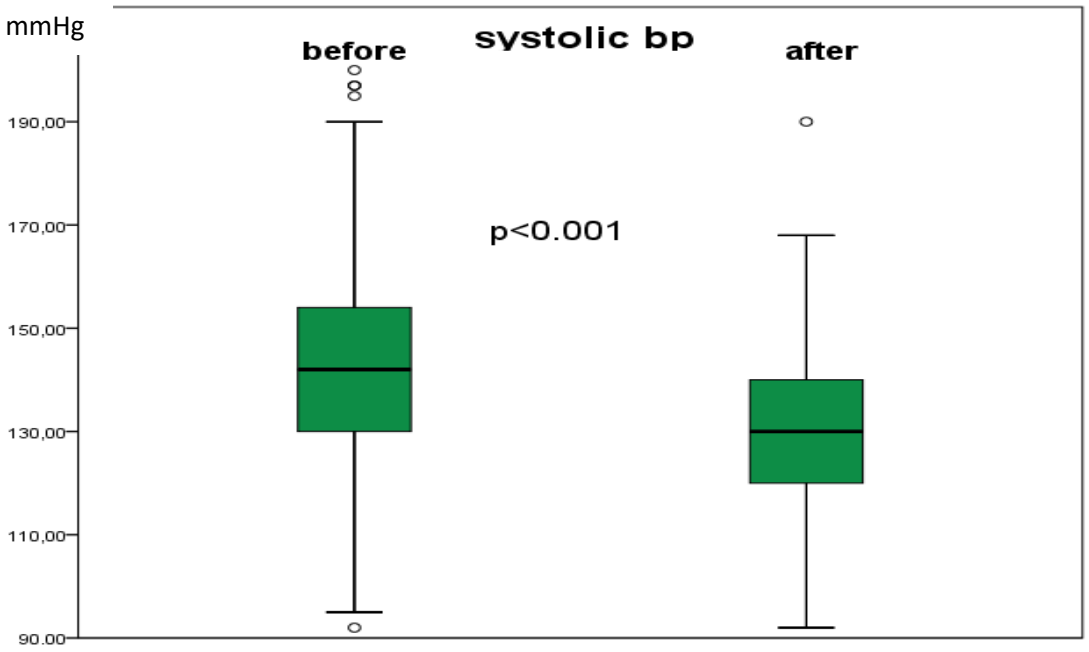

Figure 3. 10 : systemic blood pressure before and after stent implantation

	Before CoA- Stenting n=218	After CoA-Stenting n= 181	
No antihypertensive treatment	105 (48.2%)	67 (37.0%)	
Antihypertensive treatment	113 (51.8 %)	114 (63%)	
Monotherapy	73 (33.5 %)	68 (37.6 %)	
Dual therapy	30 (13.8 %)	33 (18.2%)	
Triple therapy	10 (4.5%)	11 (6.1 %)	
Quadruple therapy	0	2 (1.1 %)	
			p<0.005

Table 3. 6: The use of antihypertensive treatment before and after interventional stenting of aortic coarctation.

		Before CoA-Stenting n=218	After CoA-Stenting n= 181
Arterial hypertension	with antihypertensive medication	104 (47.7%)	28 (15.5%)
	without antihypertensive medication	74 (33.9%)	11(6%)
Normotensive	with antihypertensive medication	9 (4.2%)	86 (47.5%)
	without antihypertensive medication	31 (14.2%)	56 (31%)

Table 3. 7: The comparison of blood pressure status and use of antihypertensive medication before and after interventional stenting of aortic coarctation.

4. Discussion:

4.1 Efficacy of CoA stenting

The present study is important because, in contrast to previous reports with similar findings (Holzer et al., 2010), it provides the data of the largest number of patients 218 in a single center over 18 years, since long-term follow-up data on clinical effectiveness of stent implantation for CoA treatment are still lacking (Hartman et al., 2015). This study shows that stent implantation in patients with native and recurrent CoA was safe, effective, and yielded good hemodynamic short- and mid-term results. It has low mortality and an acceptable rate of complications. CoA stenting with proper antihypertensive medications results in better control of blood pressure. Our results are supported by other studies, with acute success rates approaching 100% (Thanopoulos et al., 2012). Our results showed that stent implantation resulted in significant widening of the stenosed area and in significant reduction of blood pressure gradients. These results are in concordance with other previously published reports (Eicken et al., 2006).

4.2 CoA stenting vs. Balloon angioplasty

In many cases, a Re-CoA could be successfully treated with a balloon angioplasty and an open surgery can be avoided. However, with a sole balloon angioplasty, only 69% of the patients show a satisfactory result in long-term follow-up (Gendera et al., 2018). With an intravascular stent implantation, the recoil phenomena at the coarctation site can be counteracted and a significant

widening of the stenotic area and significant gradient relief can be achieved in the longer time of follow-up (Eicken et al., 2006) (Yang et al., 2016) as we have confirmed in the current study. While CoA stenting was initially used for Re-CoA after surgery or balloon angioplasty, there is an increasing tendency to treat even the younger children with a native CoA with stent implantation (Mann et al., 2001).

4.3 Peri-procedural morbidity & mortality

However, stenting a native CoA is technically challenging. The diameter of the circumscriptive native coarctation may be 1-2 mm and adult patients, also those with Re-CoAs, have a higher risk to encounter aortic complications. Hence, we have 2 adult patients with aortic rupture in our study population. Even if one could be saved by emergency NuDEL implantation (Eicken et al., 2017), we have lost the other patient during the procedure. This is the reason, why we prefer, not to expand the stent to the full size at the first time of the implantation, but rather schedule the patients in 6-12 months for re-catheterisation and sequentially dilate the stent to the target size. With this strategy, we think to be able to limit the aortic complications.

4.3.1 Frequency of peri-procedural complications

Our study demonstrated a total complication rate of 14,7% in a mean follow-up time of 31 months , with rate of aortic wall injuries 3,6% in concordance with the largest multi-institutional study with complication rate 14,2% (T. J. Forbes,

Garekar, et al., 2007). Forbes et al. report in their multicentre study showed a higher complication rate of 19.3 % in a cohort of 176 patients and mean follow-up time of 1.5 years (T. J. Forbes et al., 2011) and Sadiq et al. in their cohort of 56 patients and mean follow-up time of 3.8 years a complication rate of 27% (Sadiq et al., 2013). Other studies reporting lower rates of complications are difficult to compare due to low numbers of patients and shorter follow-up time (Białkowski et al., 2011) (Erdem et al., 2011). We think that the low rate of severe complications in our study is because of avoidance of pre-stent angioplasty, which significantly increased the likelihood of encountering aortic wall complications (T. J. Forbes, Garekar, et al., 2007). Fortunately, in our cohort, most of these complications could be managed without further surgical intervention, as similar reported in the previous studies (T. J. Forbes et al., 2011). Also, the mortality of the endovascular stent implantation is low with estimated survival rate of 95%, 5 years after stenting, Studies on long-term survival after surgical intervention of a CoA also report low mortality on long-term, however higher perioperative mortality with 1.7-2.4% (Hager et al., 2007). Nevertheless, an intervention or an operation in adult patients with CoA, especially in those with Re-CoA, remains challenging with higher rate of morbidity and mortality.

4.3.2 Stent displacement

One complication encountered in our study was stent displacement 7 of 218 [3,2%], this is in concordance with a systemic review of 45 studies between 1990 & 2014, where stent migration was the most frequent peri-procedural complication [2.4%] (Hartman et al., 2015). Stent displacement has been

described in other studies, with occurrence ranging from 0 to 4.1% in smaller reports (Ebeid et al., 1997) (Moltzer et al., 2010). Because of post-stenotic dilatation, the stent might not be well adapted with its distal segments; usually, this is not critical, if anchoring has been achieved in the proximal half to two-thirds of the stent. Some degree of apposition may be achieved with flaring of the distal and proximal parts with larger balloons, but this may lead to stent migration (Peters et al., 2009). In a review of the literature, the most common causes for stent migration were either balloon rupture during stent deployment or deployment of the stent on an undersized balloon catheter (with respect to diameter of the proximal aorta). In contrast, 100 % of stent displacement in our study occurred in patients with larger aortic diameters (> 14mm). The use of cardiac output controlling measures; like right ventricular rapid pacing may decrease the likelihood of encountering stent migration. However, in our early experience in deployment of stents with right ventricular pacing in patients with large aortic diameter, there was no notable decrease in encountering stent migrations. Furthermore, a residual waist better maintains the stent in its final position, thereby reducing the risk of stent displacement (Peters et al., 2009).

4.3.3 Aortic wall injury

Acute aortic wall rupture occurred in 2/220 patients [0.9%]. In our experience, old age & aggressive post-stent angioplasty in the same setting significantly increased the likelihood of encountering this life threating complication. Our study demonstrated aortic dissection in 3 patients [1.4%] in comparison to one of the largest multi-intustional study 9 of 565 [1.5%] (T. J. Forbes, Garekar, et al., 2007). Aortic aneurysm occurred in low rate 3/218 [1.4%], nearly the same

rate of a large study 1/102 [0.98%] (Chakrabarti et al., 2010) (64). We assume that use of covered CP stents in our patients 69/218 [31.7%] played a significant role in reduction and prevention the complications of aneurysm formation. This explanation coincides with results of previous studies (Tzifa et al., 2006).

4.4 Stents used in our study

The use of covered stents for complex coarctations, especially in older patients with lower aortic wall compliance, have been associated with encouraging results (Hijazi, 2003). Other studies showed that patients with covered CP stent implantation experienced a non-significantly higher occurrence of pseudo-aneurysm formation comparing to bare CP stent implantation (Sohrabi et al., 2014).

Our first choice now is the Covered Cheatham Platinum (CP) stents [31,7%], or Bare CP stents [24,3%] as those stents are more flexible and can be easily dilated up to adult vessel diameters [20–25 mm]. The Genesis XD (Cordis) stent might also be suitable, but can only be dilated up to 18 mm. The Andra stent [4.1%] – the first peripheral cobalt chromium stent – can be dilated up to 25 mm in the XL and up to 32 mm in the XXL version (Peters et al., 2009).

4.5 Blood pressure control after CoA stenting

Another factor regarding the therapeutic success of CoA stenting is the rate of patients with arterial hypertension after the procedure. Arterial hypertension is a common finding in the long-term follow-up of aortic coarctation patients, even

after excellent surgical repair. Hence, in our centre, only 30% of the patients after surgical aortic coarctation repair were normotensive in a median follow-up time of 30 years (Heck et al., 2017). A systematic review of the reports published between January 1990 and December 2014 showed that that blood pressure after stenting was an underreported variable, being available in only 15 of the 45 studies (Hartman et al., 2015). The literature showed that freedom from residual obstruction does not mean freedom from arterial hypertension. The cause of this tendency to hypertension is still unclear, with hypotheses involving the presence of an inherent arteriopathy, arterial stiffness caused by chronic shear stress, and abnormal flow or abnormal renal homeostasis as potential contributions (Morgan et al., 2013). It is clear, that in contrast to children, a significant number of adult patients remain hypertensive after surgical or interventional treatment (Eicken et al., 2006). Hartman et al in his systemic review concluded that significant hypertension may persist in a substantial number of patients, ranging from 25-51% (Hartman et al., 2015). In our study, at a median follow-up time of 31 months after CoA stenting, 78.5% of the patients were classified to be normotensive vs. 18.4% before stenting. There are two factors, leading to this outcome. The first one is, a better adjustment of the antihypertensive medication. Before stenting, 34% of the patients were hypertensive and did not have an antihypertensive treatment. In contrast, only 6% of the patients were hypertensive without antihypertensive medication after stenting. Similar to that, the number of patients with arterial hypertension and hypertensive treatment decreased from 48% to 16% after stenting. The other factor, affecting higher rate of normotensive patients after the procedure is probably the stenting itself, since the number of patients who

were normotensive without antihypertensive treatment increased from 14% to 31% of the study population.

4.6 Reintervention after CoA stenting

In the current study 47,2 % of patients underwent stent angioplasty with repeated dilatation and in 22,9 % a second stent implantation was necessary. In comparison to previous studies, recurrence of stenosis has been reported in around 11% of all patients (Peters et al., 2009). Stent redilatation in our study was an elective approach in staged coarctation stenting, because most of our patients were children with median age 17,6 years old, with growing aorta. After complete endothelial healing “nearly after 6 months”, stent redilatation to the desired diameter “usually the diameter of the pre-stenotic aortic arch or the descending aorta at diaphragm level” can be performed.

Placing a non-distensible metal stent into a growing aorta is a possible cause for restenosis; the body size of the children may grow more than double from the time of initial stent placement to adulthood, leaving the stent area as a fixed hypoplasia, therefor the stent should be regularly monitored and electively dilated according to the patient’s growth, even with absence of a resting gradient, to avoid the development or progression to hypertension (Morgan et al., 2013).

4.6.1 Neointimal proliferation

Another cause of restenosis is hyperplasia of the endothelial intima of the vessel. Narrowing of the lumen by 1–2 mm is seen in all cases, but true intimal hyperplasia is seen in less than 25% of patients (T. J. Forbes, Moore, et al., 2007) Risk factors facilitating neointimal proliferation include younger age, lower weight and Re-CoA (Lezo et al., 1999) as well as stent over-dilation, minimal stent overlap and sharp angle between the stent and the vessel wall (Duke et al., 2003). In a previous study of stent redilatation for CoA (28 patients), success rate has been reported in 93% of patients (Zanjani et al., 2008). Four main factors may lead to the failure of CoA stent redilatation: Severe neointimal hyperplasia, a history of surgical CoA repair, the association of Williams syndrome and the rare development of aortic wall dissection (Zanjani et al., 2008). Drug-eluting stents or systemic administration of anti-proliferative drugs may theoretically overcome some of these problems (Kuehne et al., 2008), but no sufficient data have yet been published.

5. Conclusion:

The large number of patients over a median follow-up time of 31 months as a single-centre study is the strength of this study. Nevertheless, there are some limitations. The main limitation is the retrospective design of the study. Furthermore, and we had limited number of available follow-up data, especially regarding blood pressure status.

To conclude, the intermediate outcome of our study with 218 patients and a mean follow-up time of 31 months, is encouraging for endovascular stent implantation as a treatment of choice in patients with native and recurrent aortic coarctation. The mortality is low, the procedure related complications are manageable and CoA stenting with proper antihypertensive medications results in better control of blood pressure. However, patients with a CoA, those with surgical repair as well as those with endovascular stent implantation, have higher risk of comorbidities such as Re-CoA or persistent arterial hypertension in long-term follow-up. Therefore, all these patients need life-long surveillance, preferably in a centre, specialized in adults with congenital heart disease.

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