TRANSCATHETER INTERVENTIONS AND COARCTATION OF THE AORTA: A SOUTH AFRICAN EXPERIENCE

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Science in Medicine in Paediatric Cardiology

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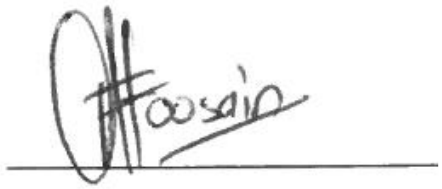
Johannesburg, 2021

DECLARATION

I Shenaaz Banoo Ghulam Hoosain declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Science in Medicine in Paediatric Cardiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



(Signature of candidate)

15th day of May 2021 in Johannesburg

DEDICATION

I dedicate this report to my family.

ABSTRACT

Background: Transcatheter interventions are alternatives to surgery when treating Coarctation of the aorta (CoA).

Objectives: To report a 19-year experience of transcatheter interventions in the management of CoA, at Chris Hani Baragwanath Academic Hospital.

Methods: Retrospective record review.

Results: From 2001 to 2020, 31 patients with native (52%) or postoperative (48%) CoA were treated via a transcatheter approach. Intravascular stent implantation (ISI) was done in 22 (71%) and Balloon angioplasty (BA) in 9 patients (29%). Covered stents (68%) were used more often for tighter CoA than bare stents (32%). Success rate was 84%. ISI had greater success in decreasing the peak gradient to < 20mmHg compared to BA (95% vs. 56%; p = 0.004). Acute complications occurred in 42%. There were no aortic wall injuries or deaths. Hypertensive arteriopathy remained as a chronic complication for both BA and ISI groups. Transcatheter re-intervention was required in 6 patients.

Conclusion: Transcatheter approaches in the management of CoA are relatively safe and effective in a resource limited centre. The spectrum of patients treated at our institution has broadened with low rates of complications. This is attributed to better patient selection, increased case experience, adoption of appropriate techniques, employment of ISI where possible and the use of covered intravascular stents.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

NOMENCLATURE

CoA - Coarctation of the Aorta

BA - Balloon angioplasty

ISI - Intravascular stent implantation

LMICs - Low- and middle-income countries

CHBAH - Chris Hani Baragwanath Academic Hospital

PIG – Peak instantaneous pressure gradient derived from echocardiogram doppler

PTP – Peak to peak, pressure gradient derived from invasive cardiac catheterization

TS – Tuberous sclerosis

Transcatheter interventions and Coarctation of the Aorta:

A South African experience

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INTRODUCTION

Coarctation of the aorta (CoA) is the congenital narrowing of the thoracic aorta usually distal to the left subclavian artery.[1-5] It accounts for 4 - 7% of congenital heart defects.[2-8] The narrowing results in a pressure gradient within the aorta. This may be an isolated lesion or be associated with other congenital heart defects.[2] Coarctation may be classified according to the presence of previous intervention into: native and non-native coarctation (recurrent).[2, 4]

Native coarctation of the aorta is defined as a congenital narrowing of the aorta prior to performing any corrective intervention.[2, 4] The non-native (recurrent coarctation) entity compromises post-surgical residual stenosis/hypoplasia and residual, recurrent or intimal ingrowth induced stenosis after a catheter intervention.[4]

Normally, coarctation of the aorta is identified during the childhood years and repaired surgically, however these cases continue to be at risk for a recurrence of the coarctation.[1, 5, 7] Coarctation may infrequently be diagnosed in adolescence or adulthood.[1, 5, 9] If left untreated, it has a poor prognosis with a high morbidity and mortality rate.[3]

Percutaneous and surgical interventions can be employed to reduce the pressure gradient across the coarctation thus limiting morbidity and mortality.[2, 3, 8, 9] Until the 1970's, when percutaneous balloon angioplasty (BA) was first described, surgery was the only option for treating coarctation of the aorta.[4, 8] Now, transcatheter interventions have become an alternative to surgery in the management of native and recurrent non-neonatal coarctation of the aorta.[2, 3, 7, 9]

The American Heart Association has published guidelines for transcatheter interventions in the management of coarctation of the aorta.[4, 10] Transcatheter approaches include primary balloon angioplasty, primary intravascular stent implantation (ISI), or balloon angioplasty followed by stenting.[4]

Balloon angioplasty has been recommended as the treatment of choice for most patients with recurrent coarctation of the aorta. It can be employed in those patients older than a month of age with native CoA if there is no associated arch hypoplasia. The CoA may recur more often in those patients less than 6 months of age who have undergone BA. Those who have had BA for a native CoA are at greater risk of aneurysm formation.[4, 10]

The use of bare stents for the treatment of coarctation of the aorta was first described in 1991.[2, 9] They can be used for both native and recurrent coarctation of the aorta. The patient must be of sufficient size to receive a stent which can be expanded to adult size in the future. This is usually recommended in the older child, adolescent, and adult population.[4, 10]

The introduction of covered stents in 1999 has seen a reduction in the incidence of complications seen with bare stents, such as aortic rupture and the development of intra-stent aneurysms to <1%.[2, 4] The additional benefits to using a covered stent include occluding an undesired patent ductus arteriosus or pre-existing aneurysm, and creating a new segment in aortic atresia.[4]

Transcatheter interventions are technically challenging, however they are relatively safe and effective when used in appropriately selected patients.[1, 4] Currently, there is limited research into transcatheter interventions in the management of coarctation of the aorta from low- and middle-income countries (LMICs).

The aim of our study was to review 19 years of transcatheter interventions of coarctation of the aorta at Chris Hani Baragwanath Academic Hospital (CHBAH), a tertiary institution in Johannesburg, South Africa.

METHODS AND SUBJECTS

Design

A retrospective record review was done.

Setting

The paediatric cardiology service at CHBAH receives both paediatric and adult congenital heart disease referrals from the surrounding primary health care clinics, hospitals, and other provinces such as the North West Province. Patients with coarctation of the aorta are usually diagnosed clinically and with an echocardiogram. All transcatheter procedures are done in the cardiac catheterization laboratory at the same hospital.

Study population

Participants were obtained from a population of patients consulted at CHBAH paediatric cardiology department, over a 19-year period (March 2001 to March 2020). All patients who

underwent a transcatheter intervention at CHBAH for the management of coarctation of the aorta were included into the study if they met the inclusion criteria. These included patients older than 1 month of age with the presence of a native or recurrent congenital CoA diagnosed using the following criteria: systemic hypertension with an upper limb to lower limb systolic blood pressure gradient of ≥20 mmHg, and/or, a descending aorta echocardiogram doppler gradient - peak instantaneous gradient (PIG) of ≥20 mmHg, and a narrowing of the thoracic aorta confirmed on echocardiogram, computed tomography or aortogram. Neonates were excluded as it is recommended that these patients have a surgical repair due to the long-term side effects of BA, re intervention rates associated with ISI and the technical challenges imposed by small arteries accommodating large sheaths required for interventions. [2]

Data source and Collection

Patients meeting the inclusion criteria were identified using the paediatric cardiology electronic database. Medical records were accessed through the paediatric cardiology filing system. These resources were used in completing the data collection sheet which was entered into an excel spread sheet.

Outcome/Measurements

The primary end point was a successful outcome, defined as an invasive aortic systolic peak to peak (PTP) pressure gradient <20 mmHg post procedure, without major complications and if ISI was done, that the stent was implanted in a suitable position.[1, 3] Secondary end points included complications (including death), chronic hypertensive arteriopathy, the need for antihypertensive medications and evidence of recoarctation. Recoarctation was defined clinically (upper limb to lower limb systolic blood pressure gradient of ≥20 mmHg at rest) and/or with echocardiography (descending aorta PIG of ≥20 mmHg), and/or cardiac catheterization (systolic PTP ≥ 20 mmHg), and/or angiography showing intimal proliferation and lumen narrowing.

Statistical Analysis

Data were analysed using Statistica® and Minitab® software systems. Descriptive statistical methods were employed. A comparison of variables was made between BA and ISI groups. Quantitative data was presented as means and ranges. Qualitative data was presented as

frequency (percentages). Student's t-test was used where appropriate for continuous variables. P-levels ≤0.05 were accepted as significant.

Ethics

The study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Clearance Certificate No. M200643) and the University of Witwatersrand Post-Graduate Research Committee.

RESULTS

Study Population

The total number of patients potentially fulfilling the inclusion criteria, identified via the paediatric cardiology database was thirty-four. After screening the records, 3 patients were excluded, since their procedures were done at another health care facility. A total of 31 patients underwent a transcatheter intervention in the management of coarctation of the aorta between March 2001 to March 2020.

Baseline Characteristics of the total study population

Table I summarizes the main baseline characteristics of the total study population. The population comprised of more males than females (17 vs. 14: n = 31). Seventy one percent (22/31) of the patients had associated cardiac defects of which 10 patients had more than one associated defect. The presence of a bicuspid aortic valve and left to right shunts were the most common. Five (5/31; 16%) patients had clinical features in keeping with syndromes such as CATCH 22, Cornelia de Lange, Turners, Marfans and Tuberous sclerosis (TS). However, only the patient with TS was confirmed.

CHBAH is a central referral centre for children and adults, thus there is a wide range in age at diagnosis, age, and weight of patients at initial transcatheter intervention. There is a similar number of patients with native and recurrent CoA who underwent a transcatheter intervention. Intravascular stent implantation was more often employed (22/31; 71%). Fifteen of the 22 patients (68%) were implanted with covered stents and 7 with bare stents (7/22; 32%).

(Table III)

Type of surgery in patients with recurrent coarctation of the aorta

All patients with recurrent coarctation of the aorta had a previous surgical intervention (15/15; 100%). Sixty percent of patients with recurrence of aortic coarctation had previous surgical patch aortoplasty. (Figure 1)

Balloon angioplasty (BA) vs Intravascular stent implantation (ISI)

Age and Weight of patients at intervention

Balloon angioplasty was done mostly in children less than 10 years of age. The exception was an adolescent 18 years of age, with recurrence of coarctation after patch aortoplasty. BA achieved a 63% reduction in PTP pressure gradient. On follow up, she remained with hypertensive arteriopathy and a high PIG on echocardiogram. It was planned to implant an intravascular stent, but the patient was lost to follow up. (Table II)

In contrast, ISI was often performed in the adolescent and the adult population. There was a significant difference in the mean age of patient's (in years) between ISI and BA (17 ± 7 vs. 4.5 ± 5.6; $p = 0.0001$). Two children < 10 years had ISI. The first was a 9 year 6-month-old who weighed 15 kg with a native CoA thus meeting the criteria for ISI. The gradient across the CoA was abolished, however he did complicate acutely with excessive bleeding and haematoma formation at the site of sheath insertion. The other was a 6-year-old with complex cardiac anatomy, possible CATCH 22 syndrome and recurrent coarctation after patch aortoplasty. Surgical intervention was thought to be more risky than percutaneous intervention at the time. There was concern regarding vascular injury and proximity of the CoA to the left main bronchus. With the assistance of computerized software, it was shown that a stent dilated to 10mm will be safe. A 28mm covered stent, dilated to 10mm, was successfully inserted with the gradient abolished. The patient remains well on follow up, with no need for reintervention to date. (Table II)

In keeping with the age at intervention, patients who underwent ISI, weighed significantly more than those who had BA (47 ± 16.7 vs 18.5 ± 14.6; $p = 0.0002$). (Table II)

Type of coarctation at intervention

Balloon angioplasty is the preferred treatment for recurrent coarctation in children.[2, 7] Three patients (33%), who were all less than 6 years of age, with native coarctation underwent BA. (Table II) All procedures were successful, with one patient requiring re intervention with ISI 6

years after BA. Thirteen patients (59%) with native CoA and 9 (41%) with recurrent CoA had ISI. (Table II)

Treatment Success

Patients who underwent BA had higher starting PTP (mmHg) gradient (45 ± 17.5 vs 30 ± 12.4; p = 0.015). After BA, the mean PTP gradient decreased significantly to 18 ± 6 (p = 0.0012). After ISI, the mean PTP gradient decreased significantly from 30 ± 12.4 to 5 ± 6.7 (p = 0). Although BA did have a significant reduction in mean PTP gradient, ISI had an overall greater reduction in mean PTP gradient, pre- and post-procedure, compared to BA (84% vs 60%; p = 0). (Table II)

The minimum mean lumen diameter of the CoA increased significantly in both groups. (Table III) Although not significant, ISI had a greater average percentage increase of the CoA diameter.

Hospital Stay

The short hospital stays and lower need for intensive care in patients that underwent BA and ISI is demonstrated in Table II. There was no significant difference regarding time to discharge (days) between groups (3 ± 0.6 vs 2.7 ± 0.5; p = 0.345). Only one patient in the study population required intensive care post procedure. This was a 21-year-old female with recurrent coarctation after surgical patch and subclavian flap aortoplasty. She had Graves' disease and complicated acutely with Takatsubo cardiomyopathy. However, a 34cm bare stent dilated to 18mm was successfully implanted at the time. She made a quick recovery and was discharged home after a total of 5 days in hospital. On follow up, she developed a median nerve palsy which resolved, and the LV apical dilatation improved with normal left ventricular function after treatment using B-blockers.

Follow-up

The mean follow-up duration was 5 ± 6.6 years for the BA group vs 3.6 ± 3.7 years for ISI group. The rate of loss to follow up was high. (Table II) This could be attributed to patients being followed up at their referral hospitals, patients originating from neighbouring countries with incorrect local addresses, or patients passing away. However, there was an adequate average follow up time to draw conclusions on rates of reinterventions, symptoms, and chronic complications. Hypertensive arteriopathy remained a chronic complication of CoA in both the

groups, but patients who underwent ISI had a greater chance of hypertension improvement. Three patients had successful pregnancies following their interventions.

Complications

There were no acute minor or major aortic wall injuries and there were no deaths. The BA group had no significant acute or chronic complications recorded. The minor acute complication recorded was in a 2-and-a-half-month infant with possible CATCH 22 syndrome and recurrent coarctation after surgery. He developed signs of sepsis after the procedure.

Although the ISI group presented with more complications all were minor complications except for the patient described previously who developed Takatsubo cardiomyopathy and another patient who had a cardiac arrest due to a large, long sheath across a tight CoA. The patient responded to cardiopulmonary resuscitation followed by successful stent placement. (Table II) Five patients developed acute minor peripheral vascular complications (excessive bleeding, haematoma formation, reduced lower limb perfusion and arterial thrombus). Technical procedural complications (stent migration, pinhole defect in balloon, stent trapped in the valve of the long sheath) occurred in 5 patients. Chronic complications included a patient developing a median nerve palsy and another with numbness of the leg from which arterial access was obtained.

Reintervention

Majority of the study population (20/31; 65%) did not require any reintervention procedure. Six patients (n = 31; 19%) underwent a reintervention using a transcatheter approach. The re-intervention rate was higher in the ISI group (3% vs 11%). These patients (5/6; 83%) had balloon dilatation of their existing stent for restenosis related to growth of the patient. A patient who had BA, required an ISI on reintervention (1/6;17%). The mean interval between initial and repeat intervention was 4.7 ± 2.5 years (range 1 – 8 years).

DISCUSSION

In correlation with existing literature[2], our study clearly demonstrated that CoA may be an isolated lesion or be associated with other congenital heart defects. In our study a similar number of patients with native and recurrent coarctation underwent a transcatheter intervention (16/31; 52% vs. 15/31; 48%).

Patch aortoplasty involves an incision across the CoA with suturing of a prosthetic patch to enlarge the stenotic area.[2] The re coarctation rate is lower (5-12%) as it avoids the use of a circumferential suture line which contributes to the higher re coarctation rate (> 50%) in cases where resection of the coarctation with end-to-end anastomosis is done.[2] However, in this cohort of patients, recurrence of CoA was seen more often in patients in whom surgical patch aortoplasty was done.

Balloon angioplasty was mostly done in children less than 10 years of age. In contrast, ISI was often performed in the adolescent and adult population. Intravascular stent implantation was more often employed (22/31; 71%) with most patients having covered stents implanted. (15/22; 68%). The covered stents were used for tighter CoA anatomy. Fourteen of the 15 patients (93%) had a coarctation diameter ≤ 50% the diameter of the ascending aorta and aorta at the level of the diaphragm.

In order to limit complications from BA, the Paediatric Cardiology Unit at the CHBAH in recent times has used the following published international guidelines which include : primary interrogation and dilatation with a compliant balloon, staged dilatations with a non- compliant balloon and not oversizing the balloon diameter.[4] The balloon diameter used is determined by the diameter of the isthmus and aorta at the level of the diaphragm. Care is taken not to exceed 3 times the minimum lumen diameter of the CoA.[4]

The benefits of the transcatheter approach include absence of a surgical scar, shorter hospital stay, reduced need for intensive care services and quicker time to recovery.[11] This advantage was evident in both groups in our study. The average hospital stay was 3 days and only one patient needed intensive care post procedure.

These procedures were done by various operators with varying experience over the 19-year study period, including fellows in training under supervision and qualified Paediatric Cardiologists. There were no acute minor or major aortic wall injuries and there were no deaths. Hypertension after the intervention may worsen acutely, improve or remain as a chronic arteriopathy.[4, 5, 12] Of those who remained with chronic hypertensive arteriopathy, 10 (n = 17; 59%) had their first intervention to treat the coarctation beyond the neonatal period (mean age at intervention 12 years ± 7.6; range 3 – 29 years).

Ultimately, the aim of transcatheter interventions is to reduce the pressure gradient thus improving arterial hypertension and long-term outcome in patients with coarctation of the

aorta.[4] Overall success rate, determined by a PTP < 20mmHg, was 84% (26/31). Treatment success prior to discharge was more often achieved with ISI. The choice between BA and ISI usually depended on the patient's age, weight, and morphology of the CoA. The minimum mean lumen diameter of the CoA increased significantly in both groups. This relief in pressure provided clinical improvement. These findings were consistent with data from another centre.[13]

BA may be ineffective if it only stretches the narrow area of the CoA, as early and late recoil of the coarctation may occur.[4, 9] Thus, a high reintervention rate would be expected in this group due to restenosis.[9] The recoil and resultant insignificant relief of the pressure gradient was evident in our study. However, only one patient required reintervention for restenosis in the BA group. BA is also associated with aortic wall complications including dissection, rupture, and aneurysm formation.[4, 9] These complications were not observed in this study.
Patients who had ISI, were more likely to have a reintervention. This was expected, as there is a need for future stent expansion dictated by the patient's growth and for in stent neointimal proliferation.[14] In addition, the higher rate of reintervention in the ISI group could be affected by the higher loss to follow up in the BA group.

Sohrabi et al demonstrated excellent results of ISI with significant haemodynamic effects and low complication rates, which were also seen in our study.[1] However, their patients with implanted covered stents had a lower re-coarctation rate.[1] This is in contrast to our study where all patients requiring re intervention in the ISI population had previous covered stents implanted. The reason may be that the initial balloon diameter used was slightly undersized to avoid initial overexpansion of tighter CoA with the intention of re-intervening at a later stage. Sasikumar et al, on the other hand, demonstrated similar findings to our study, where patients in the covered stent group had higher incidence of re intervention and neointimal in stent proliferation.[15]

Our study concludes that BA and ISI are effective therapies for native and recurrent CoA in patients > 1 month old. Stenting is preferred in adolescents and adults when the size of vessels permits, as it achieves better gradient reductions with minimal risk. For those who are not candidates for stenting, balloon angioplasty versus surgery is best decided by patient anatomy, age, and weight at the time of intervention.

The spectrum of patients treated at CHBAH has broadened with low rates of acute and chronic complications. This can be attributed to better patient selection for each intervention, increased case experience, adoption of appropriate techniques, employment of ISI where possible and the use of covered intravascular stents.

LIMITATIONS

This was a retrospective record review with incomplete data in some cases. The sample size was dependent on the number of cases treated at CHBAH which is a tertiary referral centre receiving referrals from several centres, which may also account partly for poor follow-up data. The evaluation of success and complication rates throughout the study period could be affected by the fact that the procedures were done by various operators and different techniques could have been utilized.

CONCLUSIONS AND RECOMMENDATIONS

Transcatheter interventions in the management of coarctation of the aorta, outside the neonatal period, are an effective treatment option, especially in resource challenged health care facilities. Definitive management ultimately depends on the morphology of the coarctation and the patient's age and weight at presentation. Chronic hypertension requiring medical therapy may persist if the patient's initial treatment, whether surgical or percutaneous, occurs beyond the neonatal period.

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Conflict of Interest: None

Author Contributions:

Dr S G Hoosain was responsible for the protocol, study design, conceptualization, data collection and analysis, article, and study documents.

Prof A Cilliers was responsible for the supervision of all aspects of this study.

Funding sources: Self-funded by principal author.

Table I: Baseline patient characteristics

	Total Study Population (n = 31)
Gender	
• Male, n (%)	17 (55%)
• Female, n (%)	14 (45%)
Age at diagnosis of CoA	
• Mean (SD) (years)	8 (± 9.5)
• Range (years)	0.02 – 36
Type of CoA at initial transcatheter intervention	
• Native, n (%)	16 (52%)
• Recurrent, n (%)	15 (48%)
Type of initial transcatheter intervention	
• Balloon angioplasty, n (%)	9 (29%)
• Intravascular stent implantation, n (%)	22 (71%)
Age at initial transcatheter intervention	
• Mean (SD) (years)	14 (± 9)
• Range (years)	0.2 – 36
Weight at initial transcatheter intervention	
• Mean (SD) (kg)	39.6 (± 20.5)
• Range (kg)	7 – 77
Isolated CoA, n (%)	9 (29)
Concomitant heart defects	
• Bicuspid aortic valve, n (%)	9 (29)
• Ventricular septal defect, n (%)	8 (26)
• Patent ductus arteriosus, n (%)	8 (26)
• Atrial septal defects, n (%)	3 (10)
• Mitral stenosis, n (%)	2 (7)
• Discrete subaortic stenosis, n (%)	2 (7)
Confirmed genetic syndromes, n (%)	1 (3)

Table II: Balloon angioplasty (BA) vs Intravascular stent implantation (ISI)

	BA (n = 9)	**ISI (n = 22)**	***P***
Age at intervention			
• Mean (SD) (years)	4.5 (± 5.6)	17 (± 7)	0.0001
• Range (years)	0.2 – 18	5.8 – 36	
Number of patients per age category			
• Child (< 10 years), n (%)	8 (89)	2 (9)	
• Adolescent (10 – 19 years), n (%)	1(11)	12 (55)	
• Adult (≥ 19 years), n (%)	0	8 (36)	
Weight at transcatheter intervention			
• Mean (SD) (kg)	18.5 (± 14.6)	47 (± 16.7)	0.0002
• Range (kg)	7 – 52	15 – 77	
Native CoA, n (%)	3 (33)	13 (59)	
Recurrent CoA, n (%)	6 (67)	9 (41)	
Pre intervention PTP			
• Mean (SD) (mmHg)	45 (± 17.5)	30 (± 12.4)	0.015
• Range (mmHg)	19 - 69	10 – 52	
Post intervention PTP			
• Mean (SD) (mmHg)	18 (± 6)	5 (± 6.7)	0.00004
• Range (mmHg)	12 - 32	0 – 19	
Post intervention PTP < 20mmHg, n (%)	5 (56)	21 (95)	0.004
ICU admission post procedure, n (%)	0	1 (5)	
Time to discharge			
• Mean (SD) (days)	2.7 (± 0.5)	3 (± 0.6)	0.345
• Range (days)	2 – 3	2 – 5	
Hypertension requiring medical treatment			
• Prior to procedure, n (%)	5 (56)	16 (73)	
• Post procedure, n (%)	5(56)	12 (55)	
Follow up duration			
• Mean (SD) (years)	5 (± 6.6)	3.6 (± 3.7)	0.402
• Range (years)	0.08 - 17	0 – 13	
Lost to follow up, n (%)	7 (78)	12 (55)	
Complications			
• Acute, n (%)	1 (11)	12 (55)	
• Chronic, n (%)	0	3 (14)	
Patients requiring reintervention, n (%)	1 (11)	5 (23)	
Interval between initial and repeat intervention			
• Mean (SD) (years)	6 (± 0)	4.4 (± 2.7)	0.617
• Range (years)	6 - 6	1 – 8	

Table III: Intervention

	BA	ISI	*P*
Diameter of CoA			
• Pre procedure Mean (SD; Range) (mm)	3 (± 1.1; 2 - 5)	7 (± 3; 2.7 – 12)	0.0081
• Post procedure Mean (SD; Range) (mm)	5 (± 1.7; 3 – 6)	13 (± 3; 9 – 18)	0.000001
Average increase of CoA diameter Mean (SD; Range) (%)	57 (± 37.6; 11 – 122)	121 (± 75; 33 – 344)	0.0567
Diameter of Balloon Mean (SD; Range) (mm)	8 (± 3; 5 – 14)	13 (± 3; 9 – 18)	0.0002
Type of Stent (n = 22)			
• Bare, n (%)		7 (32)	
• Covered, n (%)		15 (68)	

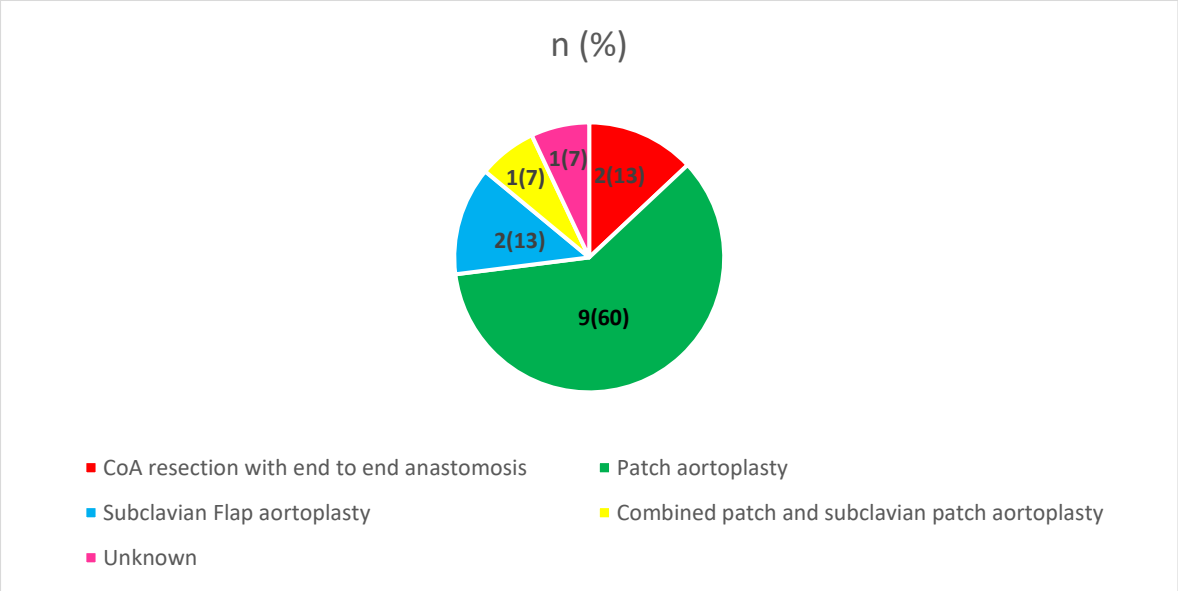

Figure 1: Type of surgery in patients with recurrent coarctation of the aorta (n = 15)

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APPENDIX 1 – APPROVED PROTOCOL

1. TITLE

Transcatheter interventions and Coarctation of the Aorta: A South African experience

Applicant: Shenaaz Banoo Ghulam Hoosain (0209222N)

Master of Science in Medicine in Paediatric Cardiology

Supervisor: Prof A M Cilliers, MBBCH, DCH, FCP (SA)

2. INTRODUCTION

Coarctation of the aorta is the congenital narrowing of the thoracic aorta usually distal to the left subclavian artery.(1-5) It accounts for 4 - 7% of congenital heart defects.(2-8) The narrowing results in a pressure gradient within the aorta. This may be an isolated lesion or be associated with other congenital heart defects such as a ventricular septal defect, bicuspid aortic valve, patent ductus arteriosus, hypoplastic left heart syndrome and other complex defects.(2)

Coarctation may be classified broadly into two groups, which are linked to the timing of occurrence of the coarctation: native and non-native coarctation. Native coarctation of the aorta is defined as a congenital narrowing of the aorta prior to performing any corrective intervention. Mechanisms of this type of narrowing consist of a discrete narrowing, tubular hypoplasia, angulation and tortuosity of the aortic arch.(2, 4) The non-native (recurrent coarctation) entity compromises post-surgical residual stenosis/hypoplasia and residual, recurrent or intimal ingrowth induced stenosis after a catheter intervention.(4)

Normally, coarctation of the aorta is identified during the childhood years and repaired surgically, however these cases continue to be at risk for a recurrence of the coarctation.(1, 5, 9) Coarctation

may infrequently be diagnosed in adolescence or adulthood.(1, 5, 9) If left untreated, it has a poor prognosis with a high morbidity and mortality rate.(3) Morbidities include arterial hypertension, congestive cardiac failure, early atherosclerosis, coronary artery disease, myocardial infarction, cerebrovascular accidents, intracranial haemorrhage, aortic aneurysm formation, aortic dissection, and sudden death.(1-4)

Percutaneous and surgical interventions can be employed to reduce the pressure gradient across the coarctation thus limiting morbidity and mortality.(2, 3, 7, 9) Indication for intervention includes an upper limb to lower limb systolic blood pressure gradient of ≥20 mmHg at rest.(2, 4) However, interventions may be considered in patients with a lower gradient if it is associated with hypertension at rest, left ventricular hypertrophy or dysfunction, exercise induced hypertension and severe narrowing on imaging studies.(2, 4)

The first successful surgical repair of coarctation of the aorta was done in 1944.(2, 4, 8). Surgical techniques include resection of the coarctation with end to-end anastomosis, patch aortoplasty, subclavian flap aortoplasty and interposition graft placement.(2, 3, 5) However, each has its own complications from high recoarctation rate, aneurysm formation and decrease growth of the left upper limb and claudication of the arm with the subclavian flap surgery.(2, 3, 5) Patients who undergo surgery are also exposed to aortic clamping, long anaesthetic times, longer hospital stays and other surgical complications such as thoracic duct injury, haemorrhage and wound dehiscence. Surgical therapy in the neonatal period remains the gold standard due to the lower mortality rate.(3, 5, 7)

Until the 1970's, when percutaneous balloon angioplasty was first described, surgery was the only option for treating coarctation of the aorta.(4, 8) Now, transcatheter interventions have become an alternative to surgery in the management of native and recurrent non neonatal coarctation of the aorta.(2, 3, 8, 9) The benefit of the transcatheter approach include absence of a surgical scar, shorter hospital stay, reduced need for intensive care services and quicker time to recovery.(11) Definitive management ultimately depends on morphology of the coarctation, the patient's age and weight at

presentation.(2) The transcatheter approach is rapidly becoming the treatment of choice in selected patients.(4, 8, 11)

The American heart association has published guidelines for transcatheter interventions in the management of coarctation of the aorta.(4) Transcatheter approaches include primary balloon angioplasty, primary intravascular stent implantation, or balloon angioplasty followed by stenting. (4).

Balloon angioplasty (BA) mainly causes stretching of the narrow area of the aorta,(4) and may create a therapeutic tear of the intimal and medial layers.(4) This technique may be ineffective if it only stretches the narrow area, as early and late recoil of the coarctation may occur.(4, 9) If the therapeutic tear extends beyond the narrow area it can lead to aortic wall complications, such as, aortic dissection, rupture and the formation of false aneurysms.(4, 9) These complications can be limited by using primary interrogation and dilatation with a compliant balloon, staged dilatations with a non-compliant balloon and not oversizing the balloon diameter. (4). Balloon angioplasty is the preferred treatment for recurrent coarctation in children.(2, 7)

The use of stents for treatment of coarctation of the aorta was first described in 1991.(2, 9) Intravascular stent implantation (ISI) overcomes many of the complications of balloon angioplasty, namely aortic wall injury and restenosis.(1, 2, 4, 6, 9) An adequate result may be achieved with just stretching of the aortic wall without creating a therapeutic tear.(4) Thus, ISI has fewer aortic wall complications, with an incidence of 1-5%.(4, 9) ISI is preferred when intervening in a patient who has had previous surgery to treat congenital coarctation of the aorta, since these patients have a higher risk of aortic dissection.(4) In addition, ISI is the intervention of choice in patients with long segment narrowing, tortuous coarctation, hypoplastic isthmus or hypoplastic transverse arch, and in adults or adolescents.(4, 6)

However, ISI is not without its limitations. The procedure requires skill, larger intravascular sheaths, implantation of a foreign body and anti-coagulation medication.(4, 5) In children less than 10 years of age, ISI is best avoided due to possible access site vascular injury and the need for repeated re-dilations of the stent as the patient grows.(4, 5, 7) However, patients who have had ISI demonstrate fewer complications compared to patients who underwent BA or surgery.(2, 8). ISI exhibits superior results to BA and surgery; thus, it is recommended for both native and recurrent coarctation in older children, adolescents, and adults.(7, 11)

The introduction of covered stents in 1999 has seen a reduction in the incidence of complications such as aortic rupture and the development of intra-stent aneurysms to <1%.(2, 4) The additional benefits to using a covered stent includes occluding an undesired patent ductus arteriosus or pre-existing aneurysm, and creating a new segment in aortic atresia.(4) A randomised control trial done by Sohrabi et al,(1) demonstrated a lower rate of coarctation recurrence when using a covered stent, however these patients experienced a higher rate of pseudoaneurysm formation. In contrast, the development of aneurysms were not evident in another multicentre study.(9) Limitations to covered stent use include the need for larger intravascular sheaths, occlusion of important smaller vessels, and more severe consequences if it embolizes.(4)

In general, complications from transcatheter interventions can be classified into aortic wall complications, peripheral vascular complications, procedure related and hypertension.(4) Strokes, emboli, and vascular injury at access sites constitute peripheral vascular complications which present acutely.(4) Procedural factors include stent migration, stent fracture, stent embolization and balloon rupture. Stent migration can be prevented by using a balloon in a balloon (BIB) angioplasty catheter. It is recommended to use a BIB catheter if using balloon diameters > 15mm, as the inner balloon provides stability of the stent once inflated.(4) Hypertension after the intervention may worsen acutely, improve or remain as a chronic arteriopathy.(4, 5, 12) Some patients develop an acute rise in blood pressure post procedure and will require control of blood pressure with intravenous anti-

hypertensives for at least 24 hours.(4) Aortic wall complications can occur acutely or present later. Therefore, patients need long term follow up to detect complications timeously.(4, 5)

Transcatheter interventions are technically challenging, however they are relatively safe and effective when used in appropriately selected patients.(1, 4) Chris Hani Baragwanath Academic Hospital (CHBAH), the facility at which data on which this study will be based, is a tertiary level hospital and receives referrals from various other hospitals. The paediatric cardiology department at CHBAH provides care to the paediatric population, as well as to adults with grown up congenital heart disease. Cardiothoracic surgery is available at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), which is situated 17km away.

Currently, there is limited research into transcatheter interventions in the management of coarctation of the aorta from low- and middle-income countries (LMICs). Research into the use of transcatheter approaches, selected population demographics, incidence of complications and the identification of risk factors is necessary. This will assist to improve skills, knowledge, and facility-based protocols for safe and effective practices.

3. AIM AND OBJECTIVES

The aim of this study is to review 19 years of transcatheter interventions of coarctation of the aorta at CHBAH, Soweto, South Africa. Peri-procedural results will be described, and long-term outcomes will be evaluated where possible.

Study objectives will include:

1. To describe the demographic characteristics of patients undergoing transcatheter interventions of coarctation of the aorta at the facility.
2. To describe the type of coarctation (native vs recurrent), the number or procedures done, and the types of intervention (BA vs ISI).

3. To compare the characteristics of the BA and ISI groups.

4. To compare overall success and complication rates, as well as the types of complications (including the need for re-intervention).

5. To compare the findings of the study to reports from other centers.

4. METHODS

4.1 Study design

This will be a retrospective record review of patients who underwent a transcatheter intervention of coarctation of the aorta.

4.2 *Study population*

4.2.1 Inclusion Criteria

All patients who underwent a transcatheter intervention for the management of coarctation of the aorta between March 2001 and March 2020 will be included into the study if they meet the following criteria:

- Presence of native or recurrent congenital coarctation diagnosed using the following criteria:
    - Systemic hypertension with an upper limb to lower limb systolic blood pressure gradient of ≥20 mmHg, and/or,
    - Descending aorta echocardiogram doppler gradient of ≥20 mmHg, and,
    - Thoracic aorta narrowing confirmed on echocardiogram, computed tomography or aortogram.
- Age >1 month old

4.2.2 Exclusion Criteria

- Neonates or age ≤1 month old, since the gold standard for management of coarctation in this age group is surgery.
- Coarctation of the aorta secondary to other causes e.g., Takayasu arteritis

A preliminary review of the database shows that, during the chosen study period, a total of 153 patients were diagnosed with congenital coarctation of the aorta. Of these patients, 68 underwent surgical repair. Thirty-three patients have undergone percutaneous treatment.

4.3 Procedure

The paediatric cardiology service at CHBAH accepts referrals from the paediatric outpatient department, surrounding primary health care clinics, primary and district hospitals, and the adult cardiology department (for adults with congenital cardiac disease). Patients with coarctation of the aorta are usually diagnosed clinically, combined with an echocardiogram. All transcatheter procedures are done in the cardiac catheterization laboratory at the same hospital.

All patients consulted at the paediatric cardiology department are entered into an electronic database from which patients meeting the inclusion criteria will be identified. Medical records will then be accessed through the paediatric cardiology filing system.

4.4 Data collection

The investigator will review the records and database information, completing the data collection sheet. All selected data for analysing will be entered into a data collection sheet designed for this purpose. Resources utilized will include patient records, database notes, data collection sheets and the investigators time Data collected will include patient demographics, description of the coarctation, procedure related variables, type of balloons and stents used,

focused clinical data, complications, information on follow up and subsequent interventions (Appendix A).

4.5 Outcome /Measurements

The variables on the data collection sheet have been included, based on data recorded in previous publications reporting on percutaneous interventions. These variables are necessary to analyse the study objectives, and to compare them to reports from other centres.

The primary end point will be a successful outcome, defined as an invasive aortic systolic peak to peak pressure gradient <20 mmHg post procedure, without major complications and if ISI was done that the stent was implanted in a suitable position.(1, 3)

Secondary end points will include complications including death, chronic hypertensive arteriopathy, the need for antihypertensive medications and evidence of recoarctation. Recoarctation will be defined clinically (upper limb to lower limb systolic blood pressure gradient of ≥20 mmHg at rest) and/or with echocardiography (descending aorta doppler gradient of ≥20 mmHg), and/or cardiac catheterization (systolic peak to peak pressure gradient >20 mmHg), and/or angiography showing intimal proliferation and lumen narrowing.

Table 4.5.1 Measurement of Variables

Scale of measurement of Variable	
Categorical	**Continuous**
Gender	Age
Type of comorbidities	Weight
Presence of dysmorphic features	Measurement of parameters involving the coarctation, stents and balloons used
Year in which the intervention was performed	Non-invasive and invasive pressure gradients
Type of anaesthesia	
Anatomy and description of the coarctation	
Description of equipment utilized	
Complications and follow up parameters	

5. DATA ANALYSIS

As per the variables recorded on the data collection sheet, descriptive statistical methods will be employed. A comparison will be made of all variables recorded on the data collection sheet between BA and ISI groups. Quantitative data will be presented as mean or medians and ranges. Qualitative data will be presented as frequency (percentages) and ranges. Categorical variables will be compared using the Chi square test or Fisher's exact test, as appropriate. Student's t-test or Kruskal Wallis tests will be used where appropriate for continuous variables. P-levels ≤0.05 will be accepted as significant.

6. ETHICS

Permission to use the paediatric cardiology electronic database has been granted (Appendix B).

The use of the database for research purposes has been approved by Human Research Ethics Committee (Medical) of the University of Witwatersrand (clearance number: M 180488) (Appendix

C). Permission from the paediatric department (Appendix D) and CEO (Appendix E) of CHBAH has been obtained. Anonymity of patients will be maintained through use of unique study numbers. This protocol has also been submitted to the University of Witwatersrand Post-Graduate Research Committee and University of Witwatersrand Ethics Committee for evaluation and approval.

7. FUNDING

All expenses of the research will be funded by the investigator.

8. STUDY WEAKNESSES

This is a retrospective record review with a high possibility of missing data. The rationale behind the choice of transcatheter intervention may not always be explained in the records, which will make the analysis of the method of patient selection for the different procedures difficult. The sample size is dependent on the number of cases done at CHBAH and CHBAH is the only facility performing these procedures in the public sector in Johannesburg presently. CHBAH receives referrals from many centres especially for transcatheter interventions, consequently there is potential for poor follow-up data, as these patients may have continued care at their referral centre.

9. TIMING

YEAR 2020	*Literature review*	*Preparing protocol*	*Protocol assessment and corrections*	*Ethics application and corrections*	*Collecting data*	*Data analysis*	*Writing up – thesis*	*Supervisor review*
March								
April								
May								
June								
July								
August								
September								
October								
November								
December								

10. REFERENCES

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9. Taggart, N.W., et al., *Immediate Outcomes of Covered Stent Placement for Treatment or Prevention of Aortic Wall Injury Associated With Coarctation of the Aorta (COAST II).* JACC: Cardiovascular Interventions, 2016. **9**(5): p. 484-493.
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11. Yang, L., et al., *A systematic review and meta-analysis of outcomes of transcatheter stent implantation for the primary treatment of native coarctation.* International Journal of Cardiology, 2016. **223**: p. 1025-1034.
12. Baykan, A., et al., *Is hypertension the fate of aortic coarctation patients treated with Cheatham Platinum (CP) stent?* Journal of Interventional Cardiology, 2018. **31**(2): p. 244-250.
13. Salcher, M., et al., *Balloon Dilatation and Stenting for Aortic Coarctation.* Circulation: Cardiovascular Interventions, 2016. **9**(6): p. e003153.
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15. Sasikumar, D., et al., *Early and late outcome of covered and non-covered stents in the treatment of coarctation of aorta- A single centre experience.* Indian heart journal, 2020. **72**(4): p. 278-282.

11. APPENDIX A -DATA COLLECTION SHEET

STUDY NUMBER:	
Gender	Male □ Female □
Age at diagnosis of coarctation of the aorta	_____Months
Age (months) at initial transcatheter intervention	_____ Months
Weight (kg) at initial transcatheter intervention	_____ Kg
Comorbidities	
a) Cardiac	
b) Non cardiac	
Syndromic/Dysmorphic	Yes □ No □ Features _____ Confirmed chromosomal abnormality Yes □ No □
Date (year) of initial transcatheter intervention	20□□
Type of Coarctation	Native □ Recurrent □
Mode of diagnosis	Clinical □ Echocardiogram □ CT □
Recurrent coarctation	Type of previous intervention: Surgery □ BA □ ISI □
	If surgery, type? Patch □ Graft □ End to end anastomosis □ Subclavian flap □
Coarctation anatomy	Ascending aorta diameter_____mm Coarctation diameter Pre intervention _____mm Post intervention _____mm Aorta diameter at level of diaphragm_____ mm

	Length of coarctation _____mm
Anaesthesia	General □ Conscious sedation □
Type of initial transcatheter intervention	BA □ ISI □
Balloon angioplasty (BA)	Type of Balloon: Compliant □ Non-compliant □ Diameter of Balloon _____mm
Intravascular stent implantation (ISI)	Type of stent: Bare □ Covered □ Length of stent _____ cm Pre- mounted □ Not pre mounted □ Number of stents used _____ Type of Balloon: Non- Compliant □ BIB □ Diameter of Balloon _____ mm
Upper limb to lower limb systolic blood pressure gradient	Pre intervention _____ mmHg Post intervention _____mmHg
Peak instantaneous gradient (PIG) on echocardiogram	Pre intervention _____ mmHg Post intervention _____mmHg
Peak to peak gradient (PTP), invasive on cardiac catheterization	Pre intervention _____ mmHg Post intervention _____mmHg
Reduction (%) in PTP after initial transcatheter intervention	_____ %
Complications	
a) Acute	
b) Chronic	
Hypertension requiring treatment	Pre intervention Yes □ No □
	Post intervention Yes □ No □
Intensive or high care facility needed	Yes □ No □

Time to discharge (days)	_____ Days
Follow up	Duration _____ months Lost to follow up Yes □ No □ If yes, Reason? Symptomatic Yes □ No □ If yes, type of; symptoms? If Hypertension present pre procedure, has it: Resolved □ Worsened □ Unchanged □
Subsequent interventions	Reintervention needed Yes □ No □ Total number of reinterventions _____ Reason for intervention _____ Type of reintervention: Surgery □ BA □ ISI □ Interval between initial transcatheter intervention _____ years Age at subsequent intervention _____months Weight at subsequent intervention _____kg
Comments	Add notes on other information e.g., hypoplastic transverse arch, coarctation proximity to left subclavian artery, vascular access other than femoral artery !!!!

APPENDIX 2 – ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr SBG Hoosain

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200643

NAME: (Principal Investigator)	Dr SBG Hoosain
DEPARTMENT:	School of Clinical Medicine Department of Paediatrics and Child Health Medical School University
PROJECT TITLE:	Transcatheter interventions in the management of Coarctation of the Aorta: A 19-year single centre South African experience
DATE CONSIDERED:	2020/06/26
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor A Cilliers
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/07/17

This clearance certificate is valid for 5 years from the date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in June and will therefore reports and re-certification will be due early in the month of June each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

APPENDIX 3 – AUTHOR GUIDELINES

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Disclosures

Authors must declare all financial disclosures and conflicts of interest in the cover letter and on the title page of the manuscript.

Ethics

All studies must be in compliance with institutional and international regulations for human and animal studies such as the Helsinki declaration (2008) (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects) and the South African MRC ethics guidelines (https://www.samrc.ac.za/research/ethics/guideline-documents). Human studies require ethics committee approval and informed consent which must be documented in your manuscript. Animal studies require ethics committee approval and must conform to international guidelines for animal research. Compliance with these requirements must be documented in your manuscript.

Content

1. Title page: It should contain the title of the manuscript, the names of all authors in the correct sequence, their academic status and affiliations. If there are more than 4 authors, the contribution of each must be substantiated in the cover sheet. The main author should include his/her name, address, phone, fax and email address.
2. Authors are solely responsible for the factual accuracy of their work.
3. Articles should be between 3 000 and 5 000 words in length.
4. A 200-word abstract should state the main conclusions and clinical relevance of the article.
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6. Abbreviations and acronyms should be defined on first use and kept to a minimum.
7. Tables should carry Roman numeral, I, II etc., and figures Arabic numbers 1, 2 etc.
8. References should be numbered consecutively in the order that they are first mentioned in the text and listed at the end in numerical order of appearance. Identify references in the text by Arabic numerals in superscript after punctuation, e.g. …trial.[13]

The following format should be used for references:

Articles
Kaplan FS, August CS, Dalinka MK. Bone densitometry observation of osteoporosis in response to bone marrow transplantation. Clin Orthop 1993;294:73-8. (If there are more than six authors, list only the first three followed by et al.).

Chapter in a book
Young W. Neurophysiology of spinal cord injury. In: Errico TJ, Bauer RD, Waugh T (eds). Spinal Trauma. Philadelphia: JB Lippincott; 1991:377-94.

Online media
Perreault, L. (2019). Obesity in adults: Role of physical activity and exercise. UpToDate. Retrieved January 12, 2020, from https://www.uptodate.com/contents/obesity-in-adults-role-of-physical-activity-and-exercise

9. Articles are to be submitted on the online SA Heart® platform https://tinyurl.com/y9prlopt. The text should be in MS Word. Pages should be numbered consecutively in the following order wherever possible: Title page, abstract, introduction, materials and methods, results, discussion, acknowledgements, tables and illustrations, references.
10. Where possible all figures, tables and photographs must also be submitted electronically. The illustrations, tables and graphs should not be imbedded in the text file, but should be provided as separate individual graphic files, and clearly identified. The figures should be saved as a 300 dpi jpeg file. Tables should be saved in a MS Word or PowerPoint document. If photographs are submitted, two sets of unmounted high quality black and white glossy prints should accompany the paper. Figures and photographs should be of high quality with all symbols, letters or numbers clear enough and large enough to remain legible after reduction to fit in a text column. Each figure and table must have a separate self-explanatory legend.
11. Remove all markings such as patient identification from images and radiographs before photographing.
12. Include 3 challenging questions on the content of the manuscript relating to the key messages. The questions will be included in a questionnaire for CPD accreditation purposes. Please supply each question with a choice of 4 - 5 possible answers of which only one is correct (multiple correct answers not allowed) and highlight the correct answer. Please do not supply questions with a simple yes/no option.

Submission of manuscripts

The manuscript should be submitted online on the SA Heart® Journal open access platform https://tinyurl.com/y9prlopt. Follow further instructions on this website.

APPENDIX 4 – TURNITIN REPORT

0209222n:Transcatheter_interventions_and_Coarctation_of_the_Article_for_TURNITIN_02122020.docx

ORIGINALITY REPORT

9%	3%	8%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Thomas J. Forbes. "Procedural results and acute complications in stenting native and recurrent coarctation of the aorta in patients over 4 years of age: A multi-institutional study", Catheterization and Cardiovascular Interventions, 08/01/2007 Publication	1%
2	Harris, Kevin C., Wei Du, Collin G. Cowley, Thomas J. Forbes, and Dennis W. Kim. "A prospective observational multicenter study of balloon angioplasty for the treatment of native and recurrent coarctation of the aorta : Angioplasty for Coarctation", Catheterization and Cardiovascular Interventions, 2013. Publication	1%
3	issuu.com Internet Source	1%
4	"42nd Annual Meeting Association for European Paediatric Cardiology, 16–19 May, 2007; Warsaw Medical Academy Congress Center",	1%

	Cardiology in the Young, 2007 Publication	
5	" Abstracts and Posters of the 3 World Congress of Pediatric Cardiology & Cardiac Surgery: Toronto, Ontario, Canada, 27–31 May, 2001 ", Cardiology in the Young, 2009 Publication	<1%
6	Troy A. Johnston. "Endovascular stents for treatment of coarctation of the aorta: Acute results and follow-up experience", Catheterization and Cardiovascular Interventions, 08/2004 Publication	<1%
7	Submitted to Mansoura University Student Paper	<1%
8	Ziyad M. Hijazi. "Catheter intervention for adult aortic coarctation: Be very careful!", Catheterization and Cardiovascular Interventions, 08/2003 Publication	<1%
9	www.science.gov Internet Source	<1%
10	Submitted to University of Oklahoma Health Science Center Student Paper	<1%
11	Musto, C.. "Endovascular treatment of aortic	

	coarctation: Long-term effects on hypertension", International Journal of Cardiology, 20081128 Publication	<1%
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