Description of the children with aortic stenosis at the Chris Hani Baragwanath Academic Hospital over 20 years

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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 Medicine (Med) in the branch of Paediatrics

DECLARATION

I, Jacqueline Faria Mendes, declare that this research report is my own work. It is submitted for the degree of Master of Medicine in the field of Paediatrics, in the University of the Witwatersrand, Johannesburg. It has not been submitted for any other degree or examination at this or any other University.

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Jacqueline Faria Mendes

12th day of October 2017

DEDICATION

S. D. G.

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My sincerest and deepest gratitude I extend to my supervisors Professor Antoinette Cilliers and Dr Hopewell Ntsinjana.

Professor Cilliers, an exemplary clinician, allowed me unreserved access to her wealth of experience and data gathered over decades of service to the children of Chris Hani Baragwanath Hospital and beyond. Professor Cilliers' support, guidance and patience were invaluable.

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I was blessed to have had the privilege of working with these two phenomenal leaders in the field of paediatric cardiology.

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PUBLICATIONS AND PRESENTATIONS

None by submission date.

ABSTRACT

Introduction

Data about congenital heart disease, in particular aortic stenosis, remains scarce from the African continent. Aortic stenosis can be supravalvular, valvular or subvalvular. Anecdotal evidence in our setting suggested that the aortic stenosis subtype profile differed to that of western literature. A retrospective record review of all children presenting to Chris Hani Baragwanath Academic Hospital with aortic stenosis from 1984 to June 2015 was undertaken.

Results

The majority of the patients 76% (n=205), presented with subvalvular aortic stenosis. Boy and girl children were almost equally effected. The echocardiographical peak instantaneous gradient measured across the stenotic left ventricular outlet obstruction varied depending on the level of stenosis. The majority of subvalvular aortic stenoses 123 (62%) presented with mild peak instantaneous gradients ($p<0.005$) at presentation, most likely due to its copresence with ventricular septal defects. Furthermore, the majority of children with subvalvular aortic stenosis presented with co-existing cardiac lesions. Consequently, the majority of patients with discrete subaortic stenosis (n=116, 61%) required surgical intervention.

Conclusion

DSAS was highlighted as the predominant aortic stenosis subtype in this population. This is different to western literature where valvular aortic stenosis is most common. Boys were not found to be significantly more affected than girls, as reported in other countries. The majority of patients had associated cardiac lesions, and most of which required invasive surgical treatment.

Key words

Congenital cardiac lesions, aortic stenosis, valvular, subvalvular, peak instantaneous gradient, isolated discrete subvalvular stenosis.

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ABBREVIATIONS

aDSAS	Associated cardiac defects with Discrete Subvalvular Aortic Stenosis
ANOVA	Analysis of Variance
AR	Aortic regurgitation
AS	Aortic stenosis
BAV	Balloon Aortic Valvuloplasty
CHBAH	Chris Hani Baragwanath Academic Hospital
CVJA	Cardiovascular Journal of Africa
DoPC	Department of Paediatric Cardiology
DSAS	Discrete Subvalvular Aortic Stenosis
iDSAS	Isolated Discrete Subvalvular Aortic Stenosis
IQR	Inter-quartile range
LVOT	Left Ventricular Outflow Tract
LVOTO	Left Ventricular Outflow Tract Obstruction
mmHg	Millimetres of Mercury
n	Sample size from the study population
N	Population size relevant to the study group
PDA	Patent Ductus Arteriosus
PdA	Paediatric cardiology Database for South Africa
PIG	Peak Instantaneous Gradient
SAS	Subvalvular Aortic Stenosis
SD	Standard deviation
TOF	Tetralogy of Fallot
TSAS	Tunnel-type Aortic Stenosis
VSD	Ventricular Septal Defect

RESEARCH PROTOCOL

1. INTRODUCTION

This report focuses on the incidence, characteristics and outcomes of patients with aortic stenosis at Chris Hani Baragwanath Academic Hospital (CHBAH) over the past two decades. Aortic stenosis can be congenital or acquired and may be associated with known genetic disorders.

Left ventricular outflow tract obstruction (LVOTO) including aortic stenosis occurs in approximately six per cent of children with heart disease.[1,2] Aortic stenosis is a complex anomaly with various levels of possible obstruction of the left ventricular outflow tract, which may occur at the valve (valvular), below the valve (subvalvular) and above the valve (supravalvular). The most common type reported worldwide is valvular aortic stenosis.[1] The most frequent type that has been recorded on the paediatric cardiology database at CHBAH is the subvalvular type which has a different aetiology and genetic substrate to the valvular type. These differences could be related to ethnicity of the population of children treated at our institution, who may have less of a predisposition to the valvular type but have a greater susceptibility to the subvalvular type. Subvalvular AS has been described to be the least common AS subtype in the Chinese population, possibly showing the influence of population type.[3] The paucity of data from the rest of Africa regarding prevalence of the various types of aortic stenosis allows for a unique opportunity to provide the first such profile from the continent.

2. BACKGROUND

The burden of congenital heart disease falls most heavily on countries with the lowest incomes and the highest fertility rates.[4]

The crude incidence rate of congenital heart anomalies is approximately 8.8 per 1000 live births.[5] The reported —Data from the European Surveillance of Congenital Anomalies central database for 29 population-based congenital anomaly registries in 16 European countries covering 3.3 million births during the period 2000 to 2005 also reported the total prevalence of CHD in Europe was 8.0 per 1000 births (95% CI 7.9 to 8.1).[6]

Globally, it is estimated that six percent of all congenital heart defects in children are left ventricular outflow tract obstruction.[5] This includes constriction somewhere at the level of the aortic valve. The most prevalent stenosis is encountered at the level of the valve (71%), then subvalvular stenosis (23%) and supravalvular stenosis (6%).[7] Though literature from China reported that amongst their paediatric population group, subvalvular AS and not supravalvular AS was the least common type.[3]

2.1. Aortic Stenosis – Theory

There are various anatomical constrictions which make up the gamut of AS:

2.1.1. Valvular aortic stenosis

Eighty-five per cent of stenotic aortic valves are bicuspid, and fourteen per cent have no separation of the leaflets.[8] Aortic stenosis that is congenital may be progressive. Children usually present soon after birth with an ejection systolic murmur. Newborn infants with critical stenosis of the aortic valve may develop signs of hypoperfusion or respiratory distress related to pulmonary edema within days to weeks after birth.[7]

However, older children with mild to moderate AS may present later in life with syncopal attacks or chest pain. These symptoms are indications for treatment as is pressure gradients greater than 70 mmHg on echocardiogram.[8] The treatment of choice includes surgical or balloon valvuloplasty.

2.1.2. Bicuspid aortic valve

It occurs in approximately 1 to 2% of the population. It is important as the patient may go onto develop a stenotic valve later on in life, but this complication is only seen in patients that are over 40 years of age.[8]

2.1.3. Discrete Subvalvular Aortic Stenosis

Discrete Subvalvular Aortic Stenosis (DSAS) is a thin membranous diaphragm or a thick fibromuscular obstruction. It may be encountered in isolation or associated with other congenital cardiac abnormalities. DSAS occurs in 5% of children with heart disease, and constitutes 20% of LVOTO in children in the western literature.[2] DSAS may not be present at birth but develop over time and therefore continuously progress in severity, and despite

management it may recur with time. One hypothesis is that an underlying abnormality in left ventricular outflow tract (LVOT) architecture creates turbulence, which then contributes to progressive LVOT thickening, fibrosis, and scarring, with scarring.[9]

2.1.4. Diffuse Subaortic Stenosis

This is associated with any diffuse hypertrophy of the left ventricle. The most common cause is idiopathic.[8]

2.1.5. Supravalvular Aortic Stenosis

It may be a localized or diffuse narrowing just superior to the level of the coronary arteries. Therefore with this anatomical aberration coronary perfusion may be affected.[8] Supravalvular Aortic Stenosis may occur in isolation but it is associated with Williams syndrome.[8]

Aortic stenosis almost always coexists with a second cardiac malformation or anomaly.[10] The most common defect is the patent ductus arteriosus (34%), ventricular septal defect (20%), aortic coarctation (23%), pulmonic stenosis (9%), and other lesions (14%).[10]

2.2. Aortic Stenosis – Epidemiology

The most common type of aortic stenosis reported worldwide is valvular aortic stenosis.[1] However, at CHBAH the most frequent type appears to be the subvalvular type, which has a different aetiology and genetic substrate to the valvular type. These differences could be related to ethnicity of the population of children treated at the CHBAH. A study by Chandra et al

demonstrated inter-racial differences of aortic dimension and frequency in adult patients with bicuspid aortic valves.[11] Aortic stenosis both valvular and subvalvular is seen more commonly in males (75%),[12] contrary to other cardiac congenital abnormalities in which females are the majority of patients.[4] In 2000, females accounted for 52% and 57% of the CHD population in children and adults, respectively.[13]

The reasons for the greater susceptibility to the subvalvular type in the CHBAH are not clearly understood. Therefore confirming this variance may translate into managing AS patients in South Africa differently than is described globally. The paucity of data from Africa describing the prevalence of the various types of aortic stenosis allows for a unique opportunity to provide the first such profile from the continent.

3. AIM AND OBJECTIVES

3.1. Main Aim

The description of the paediatric population with AS presenting to the Department of Paediatric Cardiology at Chris Hani Baragwanath Academic Hospital from the 1984 to 2015.

3.2. Specific Objectives

3.2.1. Describe the types and proportions of all cardiac lesions in the Paediatric Cardiology database (PdA),

3.2.2. Describe the paediatric patients with AS on the PdA, including the subset of patients with isolated DSAS,

3.2.3. Describe the echocardiography and cardiac catherisation findings of the AS lesions.

4. METHODOLOGY

Various demographic and surgically related parameters of patients with AS were extracted from a computerized database and clinic files.

4.1. Study Design

A retrospective record review will be undertaken and descriptive analysis will be completed. No intervention will be undertaken during this study.

4.2. Study Setting

Chris Hani Baragwanath Academic Hospital (CHBAH) is located in Soweto, in the south of Johannesburg, Gauteng. It is one of forty hospitals in the province. CHBAH was reported to be the third largest hospital in the world, with approximately 3 200 beds. It is a teaching hospital for the University of the Witwatersrand Medical School. It offers medical care for children in a large catchment area, and is the referral centre for neighbouring provinces.[14]

4.3. Study Population

The population will include all paediatric patients that have sought medical management at the Chris Hani Baragwanath paediatric cardiology unit during the study period.

4.4. Study Period

The study period will extend from January 1984 to the 30 June 2015.

4.5. Data Management

4.5.1. Data Collection and Capture

The principal researcher will be responsible for the collection, capture and collation of data. Nominal data may be categorised and coded for analysis. Where appropriate numerical data will be categorised and coded.

Patient information will be extracted from two sources:

1. The **P**aediatric Cardiology **D**atabase for South **A**frica

The **P**aediatric Cardiology **D**atabase for South **A**frica ("PdA") was initiated by Professor Antoinette Cilliers in 1984. In which every patient attended by a physician in the Department of Paediatric Cardiology at CHBAH, both in-patient and outpatient, is entered. This has led to a database that is rich in patient information (demographic details, echocardiographic recordings, diagnoses, complementary investigations and follow up). This database has been entered into a Microsoft Office Access software package. The gatekeeper of the paediatric cardiology database is Professor Antoinette Cilliers, co-researcher on this study.

2. Patient Cardiology Files

In the event data are missing from the PdA, or more information is required, patients' cardiology files will be accessed. The patient forename, surname and hospital number will be used to identify the patient from the patient in the PdA.

Study Tools

The study tool was developed in Microsoft Office Excel 2003 (Tool I). Please see appendix.

4.5.2. Study Variables

The variables available for analyses from the PDA-database included (Table 4.1):

- The number of paediatric patients with AS
- The demographic details of the paediatric patients with AS
- The cardiac defects associated with AS
- The description of a subset of patients with isolated DSAS.
- The description of peak and mean pressure gradients across the LVOT (recorded from echocardiography and cardiac catheterisation)

Table 4.1: List of variables by objective:

Objective 1:	Congenital cardiac lesions: VSD, ASD, PDA, coarctation of the aorta
Objective 2:	Province, age, sex, type of AS, associated cardiac lesions, co-morbidities if any, syndromes.
Objective 3:	Echocardiography: anatomical presentation of AS (supravalvular, valvular, subvalvular), doppler findings (PIG (mmHg) across LVOT), aortic regurgitation (AR), Cardiac catheterisation: PIGs (mmHg) across LVOT

4.5.3. Statistical Analyses

Stata release 10.0 (StataCorp LP), for Microsoft Windows, was the preferred software for analyses. The descriptive analyses reported proportions and percentages. Central tendency and data dispersion will be described in normally distributed data using mean and standard deviation (±SD), and in non-normally distributed data, median and inter-quartile range (IQR) respectively.

Table 4.2: Univariate analyses of data and relevant variables

Descriptive analyses	**Variable**	**Distribution**	**Description**	**Variables**
Univariate	Categorical		Percentages	Type of cardiac lesions, AS subtype, sex, province, cardiac lesions, syndromes,AR
	Continuous	Non-normal	Median (IQR)	Age, PIG

Bivariate analyses will be undertaken to determine correlations and associations - One-way ANOVA, Pearson Chi-Square tests, Fisher Exact test will be utilised depending on the type and number of data analysed.

Table 4.3: Bivariate analyses of data and relevant variables

Analytical analyses	**Dependent variable**	**Distribution**	**Statistical test**	**Variables**
Bivariate	Categorical	Chi-distribution	Pearson Chi-square Test	Type of AS, AR sex, province, cardiac defects
			Fisher's Exact Test	Type of AS, AR sex, syndromes cardiac defects
	Continuous	Non-normal	Mann-Whitney Test, Wilcox Rank-sum Test	Age, PIG
		Normal	One-way ANOVA	Age, PIG

4.5.4. Study Instrument

The study tool will encompass an excel spreadsheet developed on Microsoft Office. The patient's name will remain confidential with the development of a study number as an identifier. There will be a reference chart, which will have the patient's name and the patient's hospital number. The principle researcher will only have access to this reference chart.

5. ETHICS APPRAISAL

The study was approved by the University of the Witwatersrand Human Research Ethics Committee, M150848.

6. TIMEFRAMES OF THE STUDY

The overall timeframe of the study will be span from August 2015 to June 2017 (Table 6.1).

Table 6.1: Study Timeframes

Deliverable	Date
Ethics Appraisal	August 2015
PDA data collection	September 2015
Record review	November 2016
Analysis & draft report	December 2016
Final report	January 2017
Submit manuscript for publication	June 2017

7. LIMITATIONS

The findings are strongly reliant on the completeness and availability of patients' cardiology files and the PdA.

8. BUDGET REQUIREMENTS

The budgetary requirements will be the responsibility of the researcher. No expenses are anticipated.

9. REFERENCE LIST

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AUTHOR GUIDELINES FOR JOURNAL SUBMISSION

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SUBMISSIBLE REPORT

INTRODUCTION

The burden of congenital heart disease weighs most heavily on countries with the lowest incomes and the highest fertility rates.[1]

The crude incidence rate of congenital heart anomalies reported in the USA is approximately 8.8 per 1000 live births,[2] with a similar prevalence reported in European countries at approximately 8.0 per 1000 live births.[3] In South Africa the estimated prevalence is approximately 0.6 – 0.8 per 1000 live births, which translates into an estimated 11000 children annually, of which 4500 may require surgical intervention.[4]

Left ventricular outflow tract obstruction (LVOTO) refers to congenital heart disease, presenting as a stenotic area in the anatomical left ventricular outflow tract (LVOT) or in the descending part of the aortic arch, including the aortic valve. In the paediatric population, hypoplastic left heart syndrome and coarctation of the aorta are also considered in the gamut of LVOTO.[5,6] Congenital LVOTO commonly occurs with other cardiac defects and is rarely identified alone.[6]

Aortic stenosis (AS), a LVOTO, is clinically relevant in our setting, as children can present at any age depending on the type and severity of the AS. Newborn infants with critical aortic stenosis may develop signs of hypoperfusion or respiratory distress, secondary to pulmonary oedema within days to weeks after birth.[7] Other patients may present later in life with syncope, and effort intolerance with or without features of left ventricular hypertrophy and cardiac failure.[5]

AS contributes to approximately 3 percent of all congenital cardiac defects.[8] A male to female preponderance of 4:1 is documented in the literature.[7,8]

There are three levels of stenosis viz. above the aortic valve or supravalvular AS, at the level of the valve or valvular stenosis and below the aortic valve or subvalvular stenosis. Subvalvular stenosis (SAS) may be a fixed membranous type of narrowing, described as a discrete subvalvular stenosis (DSAS), or it may be a variable muscular tunnel-type form (TSAS).[6]

The most common subtype of AS reported in the international literature is valvular stenosis (71%), followed by subvalvular stenosis (23%) and supravalvular stenosis (6%).[7,9] Contrary to mainstream literature, a study from China reported that subvalvular AS and not supravalvular AS was the least common subtype identified in their paediatric population.[10] It appeared that AS subtype prevalence could differ amongst population groups.

1. Supravalvular Aortic Stenosis

Supravalvular AS is the least common type of AS.[8] It is an annular stenosis above the aortic valve[7] and is commonly found in patients with Williams syndrome (elfin features, mental retardation and peripheral pulmonary stenosis).[8,11] The main histological feature in supravalvular AS is the reduction and disorganization of elastin fibres within the aortic media.[12]

Surgical intervention is recommended once the patient is symptomatic or has a mean pressure gradient greater than 50 mm Hg.

2. Valvular Aortic Stenosis

Valvular AS imposes its restriction at the level of the aortic valve.[8] The stenotic valve can be unicuspid, bicuspid or tricuspid.[8] Valvular stenosis can cause symptoms in infancy, and is associated with a high mortality rate.[13] In the newborn period critical AS can occur presenting with left ventricular insufficiency, requiring emergency intervention by means of balloon angioplasty or surgical valvotomy.[14-16] A peak pressure gradient, greater than 70 mmHg on echocardiogram without symptoms, or symptoms of syncope or chest pain in older children are indications for treatment.[17] The treatment of choice includes surgical or balloon valvuloplasty.

3. Subvalvular Aortic Stenosis

a) Discrete Subvalvular Aortic Stenosis

Discrete subvalvular aortic stenosis (DSAS) is a thin membranous diaphragm, encountered in isolation or associated with other congenital cardiac abnormalities. DSAS occurs in 5% of children with heart disease constituting 20% of LVOTO in children in the western literature.[18] DSAS is commonly found in association with other congenital cardiac defects, such as patent ductus arteriosus and ventricular septal defects. A few reports have identified tetralogy of Fallot as a rare association in children with DSAS.[19,20]

The aetiology of DSAS is speculative. One hypothesis is that a reduced left ventricular aortic angle creates turbulence, which then contributes to progressive LVOT thickening, fibrosis and scarring. The jet across the stenotic membrane can damage the previously normal aortic valve resulting in aortic regurgitation.[21,22] The supposition that fixed SAS is an acquired lesion is supported by proof of its gradual development, its progressive nature and its rarity in infants.[23]

DSAS is unpredictable; and despite excision it may recur.[23,24] Approximately 16-46% recur after initial surgical intervention, especially in patients with complex lesions.[25] Recurrence is generally associated with high peak instantaneous gradients.[20,26] A mean gradient derived echocardiographically, in excess of 50 mmHg has been linked to recurrence and poor outcomes. The turbulent jet created by the DSAS may cause damage to the aortic valve which is downstream from the discrete stenosis.[27] Early removal of fixed DSAS has been shown to be beneficial in preventing damage occurring to the aortic valve.[28]

b) Tunnel-type Subvalvular Aortic Stenosis (TSAS)

TSAS is any diffuse, long, tunnel-like narrowing of the left ventricle, frequently associated with other congenital heart lesions.[25]

Aortic stenosis and its various levels of involvement require different treatment approaches. Aortic valvular stenosis is the most frequent subtype, followed by DSAS reported in the western world, DSAS has been described least commonly in China; however anecdotally it was our population's most common AS subtype. The treatment of DSAS is more invasive, requiring open heart surgery as opposed to valvular AS which can be treated with percutaneous balloon valvuloplasty. Open heart surgery is a technically demanding and expensive therapeutic intervention which can be limiting in a resource constrained setting. Despite the asymptomatic child having a good outlook even with severe obstruction, those with symptoms may have mortality rates as high as 25% per year, making timeous management essential.[29]

Furthermore, interventions directed toward relief of AS should be considered as palliative rather than curative, the susceptibility of recurrence mandates lifelong patient follow-up, and many of our paediatric cardiology patients come from other parts of Gauteng, other provinces and neighbouring countries, which makes necessary follow-up challenging.[13]

A comprehensive review of the literature has not identified any previous publications detailing the clinical profile of children with aortic stenosis in an African setting.

METHODOLOGY

A retrospective record review of children with aortic stenosis was undertaken using a computerized electronic database *(see below for the list of variables and Appendix C)*, which documented information, concerning every patient presenting to the Paediatric Cardiology clinic at the Chris Hani Baragwanath Academic Hospital (CHBAH) over more than two decades from 1984 to June 2015. CHBAH is a tertiary/quaternary hospital, with approximately 3 200 beds, it is situated in the townships of Soweto (population of 1.1 million) in Johannesburg, South Africa.[14] The computerized electronic database known as the Paediatric Cardiology Database for South Africa ("PdA"), utilises Microsoft Office Access Software, and was commenced in 1984. It records demographic details, echocardiographic recordings, diagnoses, complementary investigations and follow up. Additional or missing data, were sourced from cardiac clinic patient records.

The mean instantaneous gradient across the valve stenosis was not consistently documented for each patient; therefore the peak instantaneous gradient (PIG) acquired using echocardiography was reported instead. The PIG measured across the AS was categorized into ordinal categories:[30]

- Mild PIG (0-20 mmHg)
- Moderate PIG (21-50 mmHg)
- Severe PIG (> 50 mmHg)

Descriptive and limited comparative analyses were completed using various demographic and clinical related parameters of the children with AS.

Statistical Analysis

Stata release 10.0 (StataCorp LP), for Microsoft Windows, was the preferred software tool for analyses. The descriptive analyses reported proportions and percentages. Central tendency and data dispersion were described in non-normally distributed data, by median and inter-quartile range (IQR). A value of $p < 0.05$ was considered statistically significant. Bivariate analyses were undertaken to determine any statistically significant patient differences or similarities between the AS subtypes and within the SAS subtype (age, sex, presence of cardiac defects, PIG, recurrence, aortic regurgitation) - Pearson Chi-square test, and Fisher's exact test was utilized for categorical data, depending on sample numbers. Mann-Whitney U-test and Kruskal-Wallis H-tests were performed for non-parametric data, depending on the number of comparative groups; in more than two groups the latter test was used. A regression model was used to determine any significant predictors in the isolated DSAS compared to the DSAS group associated with cardiac defects cardiac defects. The covariates identified during the univariate analysis at the 10% significant level were used in the model, peak instantaneous gradient and aortic regurgitation were run in the model.

Loss to Follow up

The patients lost to follow up, were defined as those patients that missed follow up appointments consecutively. The study period ranges more than two decades, this made verifying the causes for missed appointment less clear.

Ethics Approval

The study was approved by the University of the Witwatersrand Human Research Ethics Committee, M150848.

RESULTS

The "PdA" Population

The total number of patients documented on the PdA during the study period was 22 669. The majority of patients were registered with a Soweto residential address and at least one-third of patients reported residential addresses from neighbouring referral provinces.

Congenital Heart Defects

Forty-two percent (n=9408) were diagnosed with a congenital cardiac defect, of which 77% (n=7272) were acyanotic anomalies (Table 1). The two most common congenital defects identified were patent ductus arteriosus in 28% (n=2676) and ventricular septal defects in 22% (n=2102). Tetralogy of Fallot (TOF) was the most common cyanotic defect (5%).

Table 1: List of congenital heart defects subdivided by acyanotic and cyanotic lesions (Total N = 9408) (PdA; 1984 - 2015)

Acyanotic Congenital Heart Defects	n	(%)	Cyanotic Congenital Heart Defects	n	(%)
Patent ductus arteriosus	2676	(28%)	Tetralogy of Fallot	493	(5%)
Ventricular septal defects	2102	(22%)	Pulmonary atresia	152	(2%)
Peripheral pulmonary stenosis	756	(8%)	Tricuspid atresia	142	(2%)
Atrio-ventricular septal defects	649	(7%)	Transposition of the great vessels	127	(1%)
Pulmonary valve stenosis	445	(5%)	Other	1222	(13%)
Other	644	(7%)			
Total	**7272**	**(77%)**	**Total**	**2136**	**(23%)**

Left ventricular outflow tract obstructive lesions comprised 8% (n/N=722/9408) of all congenital heart defects. Aortic stenosis was identified in 268 children, 37% of LVOTO and

3% of all congenital cardiac defects. The median age of presentation for children with AS was 17 months (IQR; 3-57). Fifty-five percent (n=149) were male children.

Aortic Stenosis Subtypes

Four percent (n=11) of AS were supravalvular, 17% (n=47) were valvular and 76% (n=205) were subvalvular (DSAS and TSAS). Two percent (n=5) of children presented with both subvalvular and valvular stenoses. These five children were excluded from the analyses.

Seventy-two percent and 77% of children with supravalvular and valvular AS respectively, reported residential addresses from outside the province of Gauteng compared to 32% of patients with subvalvular AS, though this was substantial it was not significant (Fisher's exact; p=0.13) (Table 2). Children with valvular AS, had a tendency to present at a younger median age 4 months (IQR; 0.3-76) compared to those children with subvalvular AS and supravalvular AS which presented at 19 months (IQR; 4-17) and 46 months (IQR; 8-92) respectively (Kruskal Wallis; p=0.07). Males constituted the larger proportion of supravalvular lesions (72%), and half of the other two subtypes, but it was not significant, possibly influenced by the small sample size (Fisher's exact; p=0.07) (Table 2).

The majority (86%) of subvalvular AS lesions co-existed with cardiac defects, and hence only 28 (14%) were found in isolation, conversely, significantly more isolated lesions (n=25; 53%) were found with valvular AS and supravalvular AS (n=4; 36%) (Fisher's exact; $p<0.05$).

The PIG differed significantly between the AS subtypes, a lower number (n=75/119; 38%) of the children with subvalvular AS presented with moderate or severe PIG, in contrast, to the higher number of those with supravalvular (n=9/10; 90%) and valvular AS subtypes (n=32/39;

82%) which had moderate or severe PIGs (Fisher's exact; $p<0.05$) (Table 2). One-half (53%) of children required surgical intervention to relieve the aortic stenosis (all types) more frequently than balloon valvuloplasties (Pearson χ^2; $p<0.05$) (Table 2).

Table 2: The demographic and clinical profile of children with aortic stenosis by subtype (PdA; 1984 - 2015)

Demographic & Clinical details		**Supravalvular (N = 11)**	**Valvular (N = 47)**	**Subvalvular (N = 205)**	**p-value**
Age (months)	median (IQR)	46 (8-92)	4 (0.3-76)	19 (4-17)	p = 0.07
Male	n (%)	8 (72%)	26 (55 %)	112 (55%)	p = 0.07
Black African Ethnicity	n (%)	11 (100%)	45 (96%)	197 (96%)	p = 0.07
Outside Gauteng	n (%)	8 (72%)	36 (77%)	64 (32%)	p = 0.13
Isolated Aortic Stenosis Lesion (i.e. no other cardiac defects)	n (%)	4 (36%)	25 (53%)	28 (14%)	p < 0.05
Peak Instantaneous Gradient (mmHg)					
Mild PIG (0-20 mmHg)	n/N (%)	1/10 (10%)	7/39 (18%)	123/198 (62%)	
Moderate PIG (21-50 mmHg)	n/N (%)	5/10 (50%)	16 /39 (41%)	37/198 (19%)	
Severe PIG (> 50 mmHg)	n/N (%)	4/10 (40%)	16 /39 (41%)	38/198 (19%)	p < 0.05
Intervention undertaken	n (%)	4 (36%)	17 (36%)	119 (58%)	
Balloon valvuloplasty	n/N (%)	1/4 (25%)	7/17 (41%)	2/119 (2%)	
Surgical resection	n/N (%)	3/4 (75%)	10/17 (59%)	117/119(98%)	p < 0.05

Supravalvular Aortic Stenosis

The following cardiac defects were the only defects found to co-exist with supravalvular AS, namely; peripheral pulmonary stenosis, right pulmonary artery stenosis and one left pulmonary artery stenosis (n=7; 64%). Nine of the 11 (82%) children with supravalvular aortic stenosis were confirmed to have Williams Syndrome on chromosomal analysis. The majority (n=7/11;

64%) of these were treated conservatively. The four children that underwent surgery had a median gradient of 42 mmHg (IQR; 38-57) and no significant PIG was noted between the children that underwent surgery and those that did not (Mann-Whitney; p=0.85). None of the children experienced a recurrence, and none were found to have infective endocarditis as a complication.

Valvular Aortic Stenosis

Seventeen children (36%) underwent surgery for the valvular lesion and the co-existing cardiac defect (coarctation repair 22%, PDA coiling 6% and ASD repair 6%). The median time from presentation to surgery was 191 days (IQR; 3-480). Balloon valvuloplasties were performed in only seven of the cases (41%), and six were performed after 2004 when balloon interventions had become the standard of care for valvular aortic stenosis. Three of the total ten (30%) aortic valve replacements were undertaken before 2000. The remainder of the aortic valve surgical repairs were carried out during the repair of the co-existing cardiac lesion. Three of the seventeen children required a second intervention in the form of an aortic valve replacement, 2 months, 10 years and 11 years, after the first procedure, which was a balloon valvuloplasty in all three cases.

The children that underwent surgery had significantly higher PIGs than those that were treated conservatively, median PIG (uncategorised) 51 mmHg (IQR; 48-78) versus median PIG 38 mmHg (IQR; 32-51) respectively, (Mann-Whitney; $p<0.05$). The children that had surgery were significantly older than those treated conservatively, median age of 72 months (IQR; 0.3-110) versus 3 months (IQR; 0.1-15) (Mann-Whitney; $p<0.05$). Approximately 20% died immediately after the operation or within the year of follow up. Almost two-thirds (n=29) of patients were lost to follow-up.

Subvalvular Aortic Stenosis

The children with SAS (n=205) in the PdA population were made up of 195 (95%) children with DSAS, and 10 (5%) with TSAS (Table 3).

None of the TSAS were identified in isolation and the overwhelming majority (n=8; 80%) were found to coexist with a ventricular septal defect (Table 3). Amongst the DSAS subgroup, 28 (15%) were isolated lesions, with more than half (n=101; 52%) co-existing with a ventricular septal defect and 39 (20%) with a patent ductus arteriosus. An interesting finding was that there were 6 patients with TOF and DSAS. "Other" associations with a DSAS (Table 3) included mitral valve disease (n=3); atrial septal defect (n=1); double chamber right ventricle (n=1); double outlet right ventricle (n=1); hypoplastic left heart syndrome (n=1); Shone's complex (n=2); single ventricle (n=1); truncus arteriosus (n=2); and total anomalous pulmonary venous drainage (n=1).

Table 3: The cardiac defects co-existing with discrete and tunnel-type subvalvular stenosis (PdA; 1984 - 2015)

Type of Subvalvular Stenosis	Co-Existing Cardiac Defect	Number (n)	(%)
Tunnel-type SAS (N = 10)	Isolated lesion	-	-
	Ventricular septal defect	8	(80)
	Patent ductus arteriosus	1	(10)
	Coarctation of the aorta	1	(10)
Discrete SAS (N = 195)	Isolated lesion	28	(15)
	Ventricular septal defect	101	(52)
	Patent ductus arteriosus	39	(20)
	Coarctation of the aorta	6	(3)
	Tetralogy of Fallot	6	(3)
	Other**	15	(7)

** Other – listed in text.

The majority of patients with SAS (73%) did not have aortic regurgitation (AR) which is a well-recognized consequence of this type of AS. Only trivial to mild AR was documented in 25% of patients with SAS, moreover, less than 2% had moderate AR and less than 1% had severe AR. There was no association noted between the severity of the PIG and severity of AR (Pearson χ^2; p=0.88).

Sixty-one percent of patients with DSAS and 86% of patients with TSAS presented with a mild PIG (Figure 1). The majority of patients with DSAS and mild PIG (n=116; 61%) underwent surgical intervention. These were usually associated with a ventricular septal defect. However, only 70% of children with severe PIG were documented to have had surgery (Figure 1). Two of the 23 (9%) children with a PDA and with a severe PIG underwent a PDA ligation, at least 6 (26%) required a PDA ligation and DSAS resection.

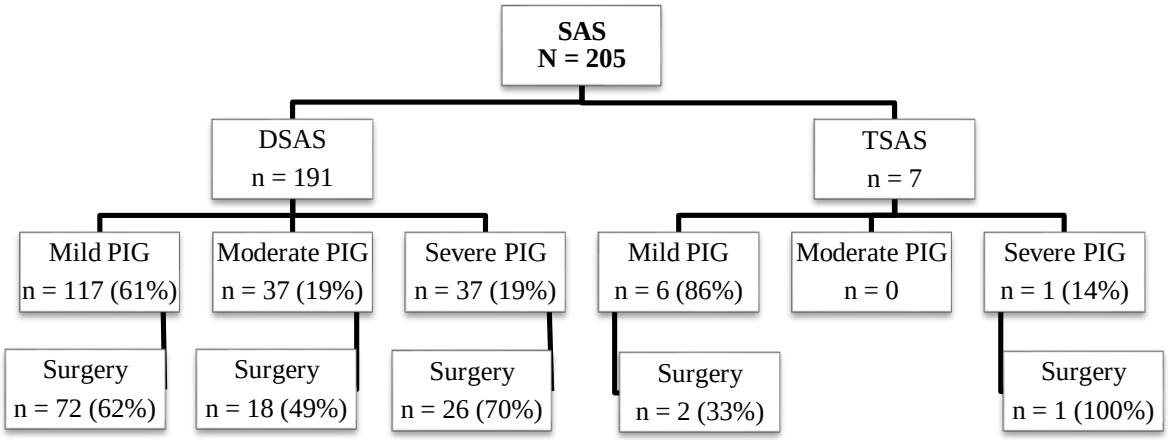

Figure 1: A comparison of peak instantaneous echocardiographic gradients between discrete and tunnel-type subvalvular stenosis (PdA 1984 - 2015)

Of the children who had surgery, only 25% (n=27) had recurrence of the DSAS requiring repeat interventions. None of the patients with TSAS that underwent surgery (n=3) had a recurrence. More than two-thirds of patients in the SAS group were lost to follow up.

There was a significant relationship shown between the severities of PIG in DSAS lesions with co-existing lesions (Table 4). The majority of children (n=87; 83%) with mild PIGs and DSAS presented with ventricular septal defects, whilst only 4% (n=4) had patent ductus arteriosus. In contrast, children with severe PIGs were mostly associated with patent ductus arteriosus (n=23; 66%) (Pearson χ^2; $p<0.05$).

Similarly, the PIG category of patients with TSAS also differed with the co-existing cardiac defect; mild gradients were demonstrated with VSDs and coarctation, while severe gradients with PDAs, though not significantly (Fisher-exact; p=0.71) *(not demonstrated in a table).*

Table 4: A comparison of the presenting peak instantaneous gradients of children with DSAS and co-existing cardiac defects (PdA; 1984 - 2015)

Cardiac defect occurring with DSAS	**Peak instantaneous gradient category**			
	Mild	**Moderate**	**Severe**	**Total**
	n (%)	**n (%)**	**n (%)**	
Ventricular septal defect	87 (83%)	7 (30%)	3 (9%)	**97**
Patent ductus arteriosus	4 (4%)	12 (52%)	23 (66%)	**39**
Coarctation of the aorta	4 (4%)	2 (9%)	0 -	**6**
Tetralogy of Fallot	6 (6%)	0 -	0 -	**6**
Other	3 (3%)	2 (9%)	9 (26%)	**14**
Total	**104 (100%)**	**23 (100%)**	**35 (100%)**	**162**

(Pearson χ^2; $p < 0.05$)

Isolated Discrete Subvalvular Stenosis (iDSAS)

Table 5 expounds on a subset of patients with DSAS that do not have any co-existing cardiac defects (n=28). The median age at presentation was slightly but not significantly older, at 36 months (IQR; 4-59), compared to 17 months (IQR; 4-46) of those with associated cardiac defects (*aDSAS)* (Mann-Whitney; p=0.21). Fifty-seven percent (n=16) of children were male (Pearson χ^2; p=0.77).

The majority of children with *iDSAS* presented with mild PIG (n=12; 43%) and moderate PIG (n= 14; 50%). Two children (7%) had a severe PIG compared to 21% (n=36) of patients in the *aDSAS* group (Fisher's exact; p<0.05) (Table 5).

Table 5: A comparison of demographic and clinical details between children with *iDSAS* and *aDSAS* (PdA; 1984 - 2015)

Demographic & Clinical details		***iDSAS*** **(N=28)**	***aDSAS*** **(N=177)**	**p – value**
Age (months)	median (IQR)	36 (4 - 59)	17 (4 - 46)	p = 0.21
Male	n (%)	16 (57%)	96 (54%)	p = 0.77
Peak Instantaneous Gradient				
Mild PIG (0-20 mmHg)	n/N (%)	12/28 (43%)	111/170 (65%)	
Moderate PIG (21-50 mmHg)	n/N (%)	14/28 (50%)	23/170 (14%)	
Severe PIG (> 50 mmHg)	n/N (%)	2/28 (7%)	36/170 (21%)	p < 0.05
Aortic Regurgitation is present	n/N (%)	15/28 (54%)	41/177 (23%)	p < 0.05
No Recurrence of DSAS	n/N (%)	15/19 (79%)	83/106 (78%)	p = 0.60

Fifty-four percent (n=15) of *iDSAS* presented with AR, a significantly higher number than the *aDSAS* group (n=41; 23%) (Pearson χ^2; p<0.05). Fourteen children had trivial or mild AR, one child had moderate AR and one child had severe AR. A similar percentage of children with

iDSAS or *aDSAS*, experienced a recurrent DSAS lesion, during their follow-up period (Fisher's exact; p=0.60) (Table 5).

Table 6: The types of surgical treatment performed in *iDSAS* patients according to the peak instantaneous gradient category (PdA; 1984 - 2015)

Peak instantaneous gradient category	**Treatment**	
	Conservative n (%)	**DSAS Resection n (%)**
Mild PIG (0-20 mmHg)	6 (50%)	6 (50%)
Moderate PIG (21-50 mmHg)	8 (57%)	6 (43%)
Severe PIG (> 50 mmHg)	2 (100%)	0
Total	16	12

(Pearson χ^2; p = 0.66)

Twelve of the *iDSAS* (43%) children underwent a DSAS resection (Table 6). Half of the patients that underwent surgery required a second operation due to recurrence, detected during the follow-up period. There was no noteworthy relationship with PIG category and recurrence (Pearson χ^2; p=0.26). A large proportion 89% (n=25) were lost to follow-up.

AR remained a significant confounding factor using multivariate analysis (data not shown in table) when comparing the *iDSAS* to the *aDSAS* group ($p < 0.05$) and PIG did not remain as a significant factor in the model (p=0.38).

DISCUSSION

PdA Population

Over the study period almost 23 000 children were seen in the Department of Paediatric Cardiology, CHBAH and were entered into the database. The most common congenital defects identified, were patent ductus arteriosus and ventricular septal defects, in keeping with international literature.[17] Left ventricular outflow tract obstructive lesions constituted 8% of all the congenital cardiac lesions on the database which closely approximates data published from other parts of the world.[31,32]

AS population

Aortic Stenosis Subtypes

The most common AS subtype documented in our study population was SAS which is different to publications emanating from America, Europe and China, in which, valvular AS was reported as the most common subtype.[7,8] Supravalvular stenosis was noted as the least common subtype in our study, which is congruent with the majority of literature, except those from China.

Sex of Aortic Stenosis

The sex distribution of children with AS is largely male in the literature, however in our population boy and girl children were almost equally affected, 1.3:1 compared to 4:1 in the international literature.[10,32]

Age of AS diagnosis

Children in this study cohort presented with AS at a younger age, within their first 2 years of life, compared to 6 years in quoted literature.[33,34] A possible reason for the younger presentation may be the result of its co-existence with serious cardiac defects. The late age of presentation has remained a strong postulate for the theory of DSAS development, being an acquired lesion rather than congenital. However this was not found to be the case in our population. This could possibly highlight the importance of a genetic cause as a disease initiate, or that our population group experiences a more rapid progression of disease.

Ethnicity

The majority of patients seen at the study institution are of black African ethnicity. This may support the suggestion of a possible genetic substrate for the younger age at presentation as well as the predominance of DSAS as opposed to valvular stenosis as in the western literature. This would require further research, as black African children were by far, the most common ethnic group seen at CHBAH during the study period and therefore a more varied ethnic study group within South African context would be informative.

PIG at presentation

There existed a statistical significant difference between the PIGs at presentation between the different AS subtypes. Children with supravalvular and valvular AS mostly presented with a PIG in the moderate to severe categories, while the group with subvalvular AS were mostly recorded as having mild PIGs. This again may be attributed to the type of co-existing congenital cardiac defect identified in the various subtypes.

Subvalvular Stenosis population

Associated cardiac defects

Subvalvular stenosis (DSAS and TSAS) in eighty percent of the cases, was associated with other cardiac defects compared to only 20-50% reported in the literature.[35] The most common cardiac lesions in order of frequency were VSDs, PDAs, and coarctation of the aorta. In contrast, the most common associated defect reported in the literature is PDAs. Six children with TOF were found to have a DSAS, thought to be a rare association first described in 1976.[19,20,36] Changela et al (2010) described that only 1% of patients with TOF were found to have a subaortic membrane.[20] This emphases the importance of excluding the presence of a DSAS in all patients with TOF.

Peak instantaneous gradients

The majority of children with DSAS and TSAS presented with PIGs in the mild category, which is most likely due to a falsely reduced gradient, caused as a result of the decompression of pressures proximal to the DSAS in the presence of the VSDs. More patients with a PDA and a DSAS were found to have severe gradients, related to increased flow from the left to right shunt across the LVOT.[37,38]

Surgery & Recurrence

A large proportion of children in the study cohort had surgery to resect their DSAS despite mild PIGs, primarily because of the association with co-existing cardiac defects that made surgical intervention necessary. This is in contrast with other centres where valvular aortic

stenosis is more prevalent and where the majority of interventions are balloon valvuloplasties. Surgical treatment is expensive and requires highly trained medical staff which can be a prohibitive factor in resource limited settings such as ours**.**

Furthermore, a lower DSAS recurrence rate of 20% was found in our study population compared to a recurrence rate of 30-40% documented in the literature.[28,39,40] One postulation for the lower recurrence rate is the high numbers lost to follow up.

The analyses of the recurrence group did not show any association with PIG category at surgery. However, PIG severity has been shown to predict recurrence in other studies. Perhaps the study number may have been too small to show a significant relationship.[40,41]

Isolated Discrete Subvalvular Stenosis

Isolated DSAS is a rare subgroup that is not associated with any cardiac defects but may be related to subtle anatomical variations of the heart, such as a reduced ventricular aortic angle, which is speculated to cause turbulence in the LVOT that results in the formation of a DSAS.[22] The ventricular-aortic angles were not a standard measurement in this cohort.

Peak instantaneous gradients

The *iDSAS* group was not significantly different from the larger *aDSAS* group, neither by age or sex distribution, but the PIGs were higher, falling within the "Moderate PIG" category. In

addition, this group was significantly more likely to have aortic regurgitation compared to *aDSAS.*

Surgery & Recurrence

No relationship was found to exist between recurrence and the PIG category. The lack of an association between the PIG and recurrence, may further strengthen the suggestion, which the substrate for the development of a DSAS is more likely to be genetic in aetiology, or related to the geometry of the LVOTO and that is not correctable surgically.

Follow Up

A significantly large number of children were lost to follow up. These were patients that consecutively missed follow up appointments. Possible explanations may be medical migration back to other provinces or surrounding countries or loss to follow up as a result of death.[42]

LIMITATIONS

Although most of the patients with AS were captured on the database, the retrospective nature of the study and the inevitable problem of missing data from case files reduced the quality of the study. It was difficult to verify inaccurate and incomplete information as the study had extended over more than two decades. This study methodology does lend itself to these innate limitations. The limited parameters collected over the years restricted the uni-, bi- and multivariate analyses possible in this study. The large number of children lost to follow up was

significant, which made calculating recurrence and evaluating management success less accurate.

CONCLUSION

The study population was comprised of mainly black African children from Soweto, neighbouring provinces and adjacent African countries. The profile of AS within the designated study group has been shown to be different to that of international literature. DSAS was highlighted as the predominant AS subtype at presentation, a small percentage of patients with DSAS were identified without cardiac defects. A similar proportion of patients with or without cardiac defects experienced DSAS recurrence. Some of these findings may suggest the possibility of a genetic or anatomical cause for the development of DSAS. Most of these patients required invasive surgical treatment. This study has successfully demonstrated the benefit of conducting research to better understand disease profiles in one's local setting.

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APPENDICES

APPENDIX A: ETHICS CLEARANCE CERTIFICATE FROM MAY 2013

R14/49 Professor Antoinette Cilliers

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130388

NAME: (Principal Investigator)	Professor Antoinette Cilliers
DEPARTMENT:	Division of Paediatric Oncology CH Baragwanath Academic Hospital
PROJECT TITLE:	Request to us the Paediatric Cardiology Patients Strted in 1993 for Purpose of Retro-spective Analyses for Publication (Previously M020806 and M070470)
DATE CONSIDERED:	Ad hoc
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 15/04/2013

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

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 resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature

Date 11 May 2013

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX B: ETHICS CLEARANCE CERTIFICATE FROM SEPTEMBER 2015

R14/49 Dr Jacqueline Faria Mendes and Dr Hopewell Ntsinjana

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150848

NAME: (Principal Investigator)	Dr Jacqueline Faria Mendes and Dr Hopewell Ntsinjana
DEPARTMENT:	Paediatrics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Description of the Children with Aortic Stenosis at the Chris Hani Baragwanath Academic Hospital over 20 Years
DATE CONSIDERED:	28/08/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Aintonnette Cilliers

APPROVED BY: _____

Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 02/09/2015

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

DECLARATION OF INVESTIGATORS

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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 resubmit the application to the Committee. **I agree to submit a yearly progress report**.

_____ _____

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX C: DATA COLLECTION SHEET

Please note: Tool here in portrait but was printed in landscape for easier use.

Tool 1: Example of data collection sheet

Abbreviations:

no - number
dob - date of birth
wt - weight (kg)
lt - length/height (cm)
prov - province
diag - diagnosis
como - comorbidities
echo - echocardiography
cath - cardiac catheterisation
proc - procedure
peak - peak gradient pressure (mmHg)
mean - mean gradient pressure (mmHg)

study no.	sex	dob	first seen	Wt (kg)	Lt/ht (cm)	age (mnth)	prov	AS type	diag 1	diag 2	como	assoc	echo		cath		proc	co mp lic
													peak	mean	peak	mean		

APPENDIX D: TURNITIN REPORT