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Article

Electrocardiographic features and Characteristics of Pericardial Disease in Children

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Disclosures

No financial disclosures or conflicts of interest

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3 October 2022

To whom it may concern and
Research Office, Health Sciences
University of the Witwatersrand

Dear Madam/Sir,

Re: **Dr Kevanya Coopoo, MMed Student number 0601581F**
Author Contribution to the manuscript entitled " Electrographic features and Characteristics of Pericardial Disease in Children"

This letter serves to confirm the author percentage contribution to abovementioned manuscript as follows:
Dr Kevanya Coopoo: 60%

Dr Vijay Mammen: 20%

Prof Antoinette Cilliers: 20%

Yours sincerely,

Prof Antoinette Cilliers, MBBCH, FCP (SA)
Head of Paediatric Cardiology, Chris Hani Baragwanath Academic Hospital
University of the Witwatersrand
Johannesburg, South Africa

For Sarushka, my motivator and guiding light

ACKNOWLEDGEMENTS

Many thanks to the CHBAH paediatric cardiology department for the use of their electronic database and clinical files for patient identification and data collection.

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ABSTRACT

Electrocardiographic features and Characteristics of Pericardial Disease in Children

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Introduction
There is little information regarding the aetiology, diagnosis and outcomes of pericardial disease in children on the African continent. The diagnosis is made easy using echocardiography, but it is not always available in a resource-limited setting. The electrocardiogram (ECG) is an inexpensive and easily available tool that can be used to detect pericardial disease, but little data is available regarding its use in children. This study reports the characteristics of pericardial disease in children and their ECG features in a South African peri-urban setting.

Methods
This retrospective descriptive study was conducted at a tertiary level hospital in Johannesburg, South Africa. The paediatric cardiology database was searched to identify all children with pericardial effusions from 1st January 1993 to 30th April 2019. Only patients that needed procedures or surgical intervention were selected for the study cohort, as it was expected that they would have ECGs available as part of their pre-procedure assessments. Available ECGs were collected and analysed for abnormalities. Other data such as age at presentation, sex, Human Immunodeficiency Virus (HIV) status, tuberculosis (TB) status, medications, pericardial fluid characteristics, details of pericardial surgical intervention and clinical outcome was also sourced from patient records and analysed. Basic descriptive statistics, such as percentages and frequencies was used for data interpretation.

Results
Over the 26-year period, 724 cases of echo-proven PEs were identified. There were 79 patients who underwent interventions, which comprised the study cohort. Seventy-eight percent were over 5 years of age and the majority had large pericardial effusions. Infectious causes predominated, of which TB was the most common (60%). Forty-five percent were documented as HIV positive. The most common procedure performed was the insertion of a pericardial drain. Fifty-four percent of patients had resolution on follow-up, 4% had disease recurrence, 14% of the cohort died and 24% had unknown outcomes. The predominant ECG features in the 25 ECGs that were legible were those of sub-acute or chronic pericarditis, showing abnormal T-waves in 96% and sinus tachycardia in 80%. Other abnormalities were: decreased chest lead QRS voltages (52%), PR segment depression (48%) and decreased limb lead QRS voltage (40%), Less common findings were

electrical alternans (28%), ST segment elevation (12%) and ‘Spodick’s sign’ (8%).

Conclusions
The study showed that infectious causes, in particular TB, are the predominant causes of paediatric pericardial disease in South Africa. The majority of children, however, had complete resolution of their pericardial disease despite the need for invasive interventions. Although few ECGs were located and legible, all showed abnormalities with the majority displaying features of sub-acute or chronic pericarditis, suggesting that most children undergoing invasive treatment have later stages of pericardial disease. The few ECGs that were available for interpretation constitute a notable study limitation, but provide a basis for future studies on ECG changes in children with pericardial disease.

GLOSSARY

ADA – Adenosine deaminase
ART – Anti-retroviral therapy
CHBAH- Chris Hani Baragwanath Academic Hospital
ECG – Electrocardiogram
Echo – Echocardiography
HIC – High-income countries
LAD – Left axis deviation
LMIC – Lower-and-middle income countries
MIC – Middle-income countries
RAD – Right axis deviation
TB – Tuberculosis

INTRODUCTION

Pericardial disease is rare and poorly studied in children[1–5] and can manifest as acute pericarditis, pericardial effusions, cardiac tamponade or constrictive pericarditis.[1,4] The natural course of pericarditis in children is mostly benign, with a similar recurrence rate (15-30%) as adults.[6] Mortality can result from undiagnosed and untreated cardiac tamponade and constrictive pericarditis.[7]

Causes can be infectious (bacterial, viral and rarely fungal or parasitic), non-infectious (neoplastic, autoimmune, inflammatory or connective tissue disorders, post-myocardial infarction, metabolic disease, post-radiation therapy or post-traumatic/iatrogenic) or idiopathic (no identifiable cause).[6,8,9] Acute infectious causes of pericarditis are common in the paediatric population worldwide,[2] but the etiology varies between lower-and-middle income countries (LMICs) and high income countries (HICs). Bacterial infectious causes, particularly tuberculosis (TB), predominates in LMICs.[6,10]

Acute pericarditis is acute inflammation of the pericardium of less than 4 weeks duration, whereas sub-acute pericarditis presents with symptoms over several days or weeks without a clear-cut acute onset (usually 4-6 weeks duration).[6] Pericarditis is recurrent if it occurs in a patient who previously had pericarditis and has been asymptomatic for at least 4-6 weeks.[11] Pericarditis may or not be associated with a pericardial effusion, which is a pathological collection of fluid between the visceral and parietal pericardial layers that exceeds the normal volume of the pericardial cavity (usually 10-50ml). In “dry” pericarditis, there is no associated pericardial effusion, whereas in serous, fibrinous or purulent pericarditis, the pericarditis is associated with a pericardial effusion.[4,6,8,12] Slow accumulation of pericardial fluid can often be well tolerated, but with rapid accumulation the intra-pericardial pressure surpasses intra-cardiac pressure, the heart is compressed and cardiac tamponade develops. If the fluid accumulation is rapid, even small volumes can cause tamponade. The parietal pericardium is not distensible and the increased intra-pericardial pressures in cardiac tamponade are transmitted to the heart, causing decreased end-diastolic ventricular filling and subsequent decreased cardiac output with ensuing hypotension, shock and death.[4]

Pericarditis of more than 3 months duration is considered chronic.[6] In chronic pericarditis, the persistent inflammation can lead to constrictive pericarditis, which is a thickening and fusion of the visceral and parietal pericardial layers, causing a restriction in the filling of the ventricles during diastole. This decrease in cardiac preload, in turn, leads to an inability to increase cardiac stroke volume, leading to decreased cardiac output and heart failure. In constrictive pericarditis, the pericardial cavity is usually devoid of fluid as the two pericardial layers are adhered together. [12] Some patients with constrictive pericarditis may, however, have pockets of fluid between the pericardial layers, and they are then classified as having effusive-constrictive pericarditis. This pathology presents with features of both pericardial effusion and pericardial constriction. The pericardial fluid exerts a pressure due to the constricted visceral pericardium, but the pressure remains elevated even after

the fluid has been removed via pericardiocentesis. Treatment is thus via visceral pericardiectomy. In LMICs, the predominant cause of effusive-constrictive pericarditis is TB and is thus a common manifestation of pericardial disease in South Africa due to the country's TB endemicity.[12–14]

Pericardial disease can be medically or surgically managed and is guided by the severity and underlying cause. Infections are an important cause of paediatric pericardial disease and thus antibiotics are often empirically started until the cause is known.[9] Treatment for idiopathic/viral causes is usually an anti-inflammatory agent: non-steroidal anti-inflammatories, colchicine, corticosteroids or a combination thereof.[6,8] There are a few different surgical management options. Pericardiocentesis is the least invasive, and is the drainage of pericardial fluid under echocardiography (echo) or fluoroscopic visualization. Pericardiocentesis is indicated for drainage of large or haemodynamically significant effusions, for evacuation of purulent effusions and for diagnostic purposes (especially when malignant or infectious causes are suspected).[6,9,14] If there is re-accumulation of effusions post pericardiocentesis, a more invasive surgical procedure such as a pericardiectomy or a pericardial window may be indicated.[6] Pericardiectomy is the definitive management of constrictive pericarditis and entails removal of parts or all of the pericardium to relieve the constriction.[6] Pericardiectomy may also be indicated for loculated effusions, effusions with thick adhesions, for biopsy purposes, for chronic recurrent effusions, purulent pericarditis with persistent infection or in cases unresponsive to medical treatment.[6,15] A pericardial window (pericardiotomy) involves creation of a communication between the pericardial space and pleural cavity, which allows drainage of fluid into pleural space to relieve the effects of large effusions and tamponade that recur.[6] Pericardial biopsy can be performed to aid diagnosis, but it only improves diagnosis rates by 5-6%; it is found more valuable in cardiac tamponade where it aids diagnosis in over 50% of patients.[12]

Clinical diagnosis of acute pericarditis requires at least two of the following features: characteristic chest pain, a pericardial friction rub on auscultation, ECG features of pericarditis or a new or enlarging pericardial effusion on echo.[8] Detection of pericardial effusions is very accurate using echo, which is a sensitive, non-invasive and bedside test, but requires training and expertise.[16,17] The ECG is an inexpensive and easily available adjunct in the diagnosis of pericardial disease, especially where access to paediatric cardiologists and echo may not be available.

Several ECG features are associated with pericardial disease. These include diffuse PR segment depression with associated ST segment elevation, decreased QRS and T-wave voltages, abnormal T-wave polarity, electrical alternans and sinus tachycardia.[18–27] The value of utilising the ECG in diagnosing pericardial disease has been studied mainly in adult populations.[18–23,25–32] These studies emphasize the low sensitivity of ECG signs in detecting pericardial disease in adult patients. However, little evidence is available for paediatric populations.

The ECG changes found in pericardial disease are due to the inflammation

and injury to the sub-epicardium and myocardium in pericarditis, which leads to an alteration in electrical conduction through the heart.[18] The resultant abnormal atrial and ventricular repolarization causes PR segment and ST segment changes (in relation to the TP segment) respectively, which correlates with stage 1 of Spodick's four-stage sequence of acute pericarditis.[24,25,33] The acute phase (stage 1) is characterized by concave ST-segment elevation and PR segment depression in most leads. PR segment depression, more so than ST segment elevation, is a better indicator of pericardial inflammation.[29] The atria sit mainly posteriorly on the right, thus the average atrial polarity is negative for most of the electrodes, thus PR depression occurs rather than elevation (except for the aVR lead).[25] "Spodick's sign" is a down-sloping TP segment best identified in lead II and in the lateral precordial leads (V4-V6). It is a feature of stage 1 pericarditis and helps distinguish these ECGs from acute coronary syndrome (ACS) which also presents with ST elevation (ST elevation of pericarditis is usually concave, whereas ACS ST elevation is usually convex).[27,34] ST segment elevation can be found in most of the ECG leads (except in aVR and V1 where there is ST segment depression), but more so in the inferior leads and aVL.[24] PR segment depression usually precedes ST elevation and in early stage 2, the ST-segment elevation resolves but PR-segment changes often remain. In late stage 2, T waves may flatten. T-wave inversion occurs in stage 3 with eventual resolution of ECG changes in stage 4.[25,35] An updated review by Spodick in 2003, however, indicates that stage 1 of the original 4-stage sequence is often the only ECG feature observed because the disease is not allowed to progress due to prompt and early treatment.[27] Another ECG feature of pericarditis is sinus tachycardia, which occurs as a compensatory mechanism to increase cardiac output.[20]

Other ECG features of pericardial effusions are low voltage QRS complexes and electrical alternans. QRS micro-voltage is due to any cause of increased distance of the myocardium from the ECG electrodes, alteration in the electrical conduction of the cardiac muscle and decreased cardiac size (and thus contractility) due to compression of the heart by the excess pericardial fluid.[18,21,24,26] Micro-voltage is usually found in the ECGs of patients with moderate to large effusions and the absence of low QRS voltage makes the diagnosis of pericardiac tamponade improbable.[19,36] Electrical alternans is a beat-to-beat variance in QRS amplitude on the ECG and is due to the pendular motion of the heart within the fluid-filled pericardium. It is very specific to pericardial tamponade, but can be seen in the ECGs of large effusions as well.[20,24,30]

In constrictive pericarditis, there is a conflict of data on the typical p-wave changes found in the ECGs of these patients. A small study of 18 adult patients with chronic constrictive pericarditis demonstrated abnormal p-waves in 94% of their patients, namely in the form of bifid p-waves – "pseudomitrale".[31] Usually, a bifid p wave is not suggestive of left atrial enlargement unless it is greater than 0,08 seconds long in infants or greater than 0,1 seconds in children.[37] LAD (left-axis deviation) and p-mitrale occur due to the preferential pericardial constriction in the atrio-ventricular groove, which is represented on the ECG as left atrial enlargement.[38] There is also a

predilection for marked fibrosis at the heart's base, which is anatomically represented by the presence of p-mitrale in the inferio-lateral leads.[32] Conflicting literature, however, states that in lieu of there being minimal fluid over the left atrium (owing to the way in which the pericardial sac reflects), p-wave changes are not often seen. In the patients where the atria are affected by pericarditis, atrial fibrillation may occur.[23] In a study of 116 adult patients with constrictive pericarditis, 31% showed left atrial enlargement. However, the same study also found that 5% of their patients with constrictive pericarditis who had basal fibrosis (usually with annular constriction) had right axis deviation and right ventricular hypertrophy. Due to the irregular distribution of fibrosis, a change in cardiac shape and rotation occurs with subsequent changes in the ECG axis with manifestation of RAD and right ventricular hypertrophy on ECG.[32]

This study thus aims to provide a report on paediatric pericardial disease and the associated ECG features in a South African peri-urban setting.

MATERIALS AND METHODS

This retrospective descriptive study was conducted at Chris Hani Baragwanath Academic hospital (CHBAH), a tertiary level hospital in Soweto, Johannesburg. The CHBAH paediatric cardiology patient database (Microsoft Access 2010) was searched to identify the study sample of children with pericardial effusions over a period of 26 years (January 1993 – April 2019). Most effusions were very small and clinically insignificant (diagnosed on echo as an incidental finding). Therefore, cases selected for analysis in the study cohort were those needing interventions such as a pericardiocentesis, pericardial drain insertion, pericardiotomy or pericardiectomy. It was expected that these patients would have ECGs as part of their pre-procedure assessments and probable confirmation of the aetiology based on laboratory analysis of the pericardial fluid or tissue histology. A total of 79 patients with Echo-proven pericardial effusions that required procedures were identified. This included patients with pericardial tamponade, constrictive pericarditis and effusive-constrictive pericarditis.

Data was collected on patients' age, sex, HIV and TB status, medications, pericardial pathology type and characteristics, pericardial fluid characteristics, details of pericardial surgical intervention and clinical outcome. The sizes of the effusions were determined using echocardiography according to the width of the echo-free pericardial space (in mm) seen in both systole and diastole: these were designated as small (<10mm), medium (10-20mm) or large (>20mm).[6,11,18,29,35] These variables were entered into onto a Microsoft Excel spreadsheet (Microsoft® Excel® for Mac 2011, version 14.5.8) for analysis. Both the Paediatric Cardiology electronic database and paper-based patient hospital records were sourced for information. ECGs were retrieved and analysed by the primary investigator.

A subset of 25 patients that had legible 12-lead ECGs done prior to their interventions were analysed.

In the absence of previously documented ECG measurements in paediatric pericardial disease, the deviations and cut-off values reported in adult pericardial disease were applied. The investigated deviations are as follows:[8,19–22,26,28–31,33,34,37,39]

- Stage 1 pericarditis:
    - PR segment depression of ≥0,5mm from baseline in any lead except in aVR and V1.
    - Concave ST-segment elevation >2mm in the left precordial leads and more than 1mm in all the other precordial leads and limb leads.
    - "Spodick's sign" (demonstrated by blue arrows in figure below): a down-sloping TP segment best identified in lead II and in the lateral precordial leads (V4-V6).

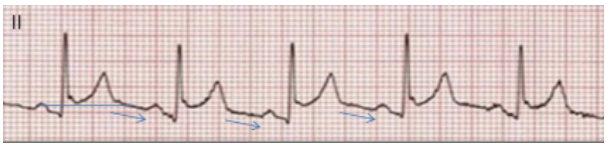


FIGURE 1.*Spodick's sign demonstrated in lead II of this ECG of acute pericarditis.* [34]

- Stage 2:
    - In early stage 2, the ST-segment elevation resolves but PR-segment changes often remain
    - Late stage 2: Flattened T waves
- Stage 3: Positive T-waves in the right precordial leads from 7 days to 7 years of age, or inversion of T-waves in the left precordial leads (V5 and V6), regardless of age.
- Stage 4: normal ECG due to eventual resolution of ECG changes.

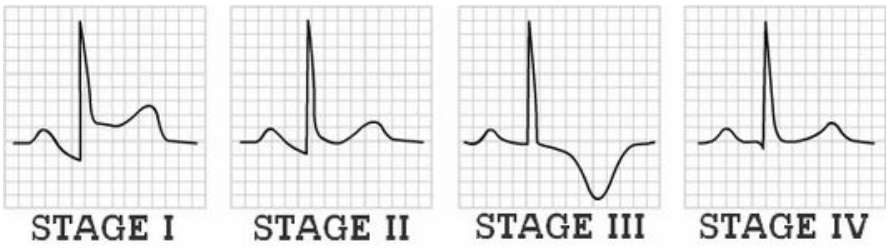


FIGURE 2.*The four-stage ECG sequence of acute pericarditis as described by Spodick in 1973* [25]

Other expected ECG deviations:

- QRS axis deviation: any deviation from the normal age- and sex-related ranges as per ADDENDUM 1. As mentioned above, both LAD and RAD have been associated with constrictive pericarditis.
- Low QRS voltage: QRS complex size of ≤5mm in the limb leads and/or ≤10mm in the praecordial leads.
- Electrical Alternans: A peak-to-peak change in QRS amplitude of ≥1mm in successive beats in ≥1 sequential leads
- Sinus tachycardia: Heart rates higher than the normal age- and sex-related values as per ADDENDUM 2.
- P-mitrale = P wave duration of ≥0,1 seconds in children or ≥0,08 seconds in infants.

- There are usually no expected changes in the PR interval of adults with pericarditis[31]

Distribution of leads:
- Limb leads: leads I, II, III, aVR, aVL and aVF
- Precordial leads: leads V1–6
- Left precordial leads: V4–6
- Right precordial leads: V1 and V3R

Basic descriptive statistics, such as percentages and frequencies, were used for data interpretation. Statistical analysis was done with the aid of a biomedical statistician using MATLAB R2020b statistical program.

This study was approved by the WITS Human Research Ethics Committee (medical) (ref. no M180488).

RESULTS

Of the 27581 patients seen over a 26-year period, there were 724 cases of Echo-proven pericardial effusions, providing a prevalence of 2.6%. There were 79 patients (11% of the total number of pericardial effusions) that underwent interventions for pericardial effusion, pericardial tamponade, constrictive pericarditis and effusive-constrictive pericarditis.

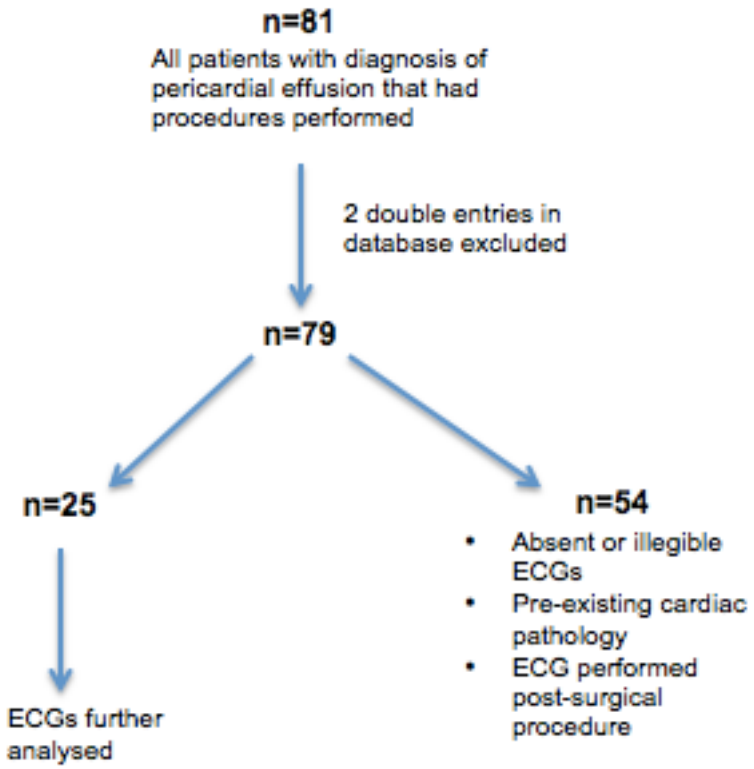


FIGURE 3. Study sample selection

The study sample and population characteristics are shown in figure 1 and

table I. The majority of patients (78%) were over 5 years of age, with a median age of 8.2 years. Forty-five per cent were documented to be HIV positive. Uncomplicated pericardial effusions (i.e. effusions without constriction or tamponade) were the most common pericardial disease presentation (63%). Eleven percent had effusive-constrictive pericarditis and 8% had constrictive pericarditis. Pericardial tamponade was seen in 18%. Half of the effusions were classified as large. The most common medical treatments prescribed were anti-TB treatment (59%) and oral corticosteroids (52%).

Infective causes were the most common aetiology, with 47 cases (60%) ascribed to TB. Only 13% (n=6) of these 47 TB patients had a definitive TB diagnosis: 2 patients demonstrated TB on sputum and 4 demonstrated TB in pericardial tissue histology. Thirteen patients were diagnosed based on raised ADA levels of >30U/L, 6 patients had a positive Mantoux test and 6 had a positive TB contact. For the other infectious causes, bacteria were cultured in 4 children: two children (aged 9,5 and 10,3 years) with *Staphylococcus aureus* (one cultured from blood and the other from pericardial fluid), one aged 5 months with *Haemophilus influenzae* (cultured from blood) and one aged 2 months with *Streptococcus pneumonia* with Austrian syndrome (Pneumococcal meningitis, pneumococcal pericarditis and pneumococcal septicaemia) which was cultured from pericardial fluid.

TABLE I: Population Characteristics

Characteristics	Total (n=79)	Percentage
Age		
0-28 days	3	4
>28 days – 12months	10	13
>1 year – 5 years	12	15
>5 years – 12 years	31	39
>12 years	19	24
Unknown	4	5
SEX		
Male	39	49
Female	40	51
HIV STATUS		
Negative	29	37
Positive	24	30
Unknown	26	33
Type of Pericardial disease		
Pericardial effusion	50	63
Pericardial effusion with tamponade	14	18
Constrictive pericarditis	6	8
Effusive-Constrictive pericarditis	9	11
Size of Effusion (n=74*)		
Small	3	4
Medium	20	27
Large	37	50
Unknown	14	19
Cause of Pericardial Disease		
Infective		
TB	47	60
• TB demonstrated in sputum	2	
• TB demonstrated in pericardial tissue histology	4	
• Raised pericardial fluid ADA >30U/L	13	
• Positive Mantoux test	6	
• Positive TB contact	6	
Staphylococcus aureus	2	3
Haemophilus influenza	1	1
Streptococcus pneumoniae	1	1
Unspecified	2	3
Non-infective		
Systemic Inflammatory	4	5
Malignancy	9	11
Trauma	1	1
Hydrops fetalis	1	1
Unknown	11	14
Medications used**		
TB treatment	47	59
Corticosteroids	41	52
Antibiotics	20	25
Diuretics	14	18
Chemotherapy	3	4
ART	9	11

** This value excludes the 6 patients with constrictive pericarditis*

***Most patients were given more than one medication*

A total of 95 procedures were performed, with 17 children having more than one intervention (Table II). Pericardial drain insertion was the most common procedure, which was done in 53 patients. Fifty-five patients had pericardial fluid drained following insertion of a drain, pericardiocentesis or surgical drainage, of which only 41 had documented fluid volumes. The median fluid volume drained was 300ml (mean, 377 +/- 285ml).

Eleven patients had a pericardial biopsy, the majority of which (n=7) showed non-specific inflammation. The other 4 patient biopsies showed TB (n=2), purulent pericarditis (n=1) and lymphoma (n=1).

Eight patients underwent pericardiectomies for constrictive pericarditis while one patient had a pericardiectomy for recurrent pericardial effusions that did not resolve with medical treatment and closed drainage.

There were 26 patients less than 5 years old including 3 neonates. All 3 neonates had pericardial drains inserted for large pericardial effusions causing haemodynamic instability. Two neonates were premature, one with a gestational age (GA) of 34 weeks and respiratory distress syndrome and the other with a GA of 35 weeks and hydrops fetalis secondary to rhesus incompatibility. There were no details available on the third neonate.

TABLE II: Procedures including surgical Intervention

	Total	Percentage
Procedure (n=95)		
Pericardiocentesis	19	20
Pericardial drain	53	56
Pericardiotomy/pericardial window/open drainage	14	15
Pericardiectomy	9	9
Fluid characteristics		
No. of patients with fluid drained	55	
Fluid type		
Serous	16	29
Sero-sanguinous	19 (TB=10, Malignancy=5)	35
Sanguinous	6 (TB=4, Malignancy=1)	11
Purulent	11 (TB=6, bacterial=3)	20
Not specified/Unknown	3	5
Fibrin strands present on echo	21 (all were found in TB patients except for 4 with unknown aetiologies)	27
Pericardial Biopsy (n=11)		
Results		
TB	2	18
Fibrinous pericarditis/ Non-Specific inflammation 3 with TB pericarditis 2 with other infectious aetiology (no organism cultured) 2 with unknown cause	7	64
Suppurative pericarditis (no organism cultured)	1	9
Malignancy (lymphoma)	1	9

The average duration of follow-up was 290 days (median of 86 days). Fifty-four per cent (n=43) of cases had complete resolution of their pericardial disease. Recurrence of pericardial effusion occurred in 4% (n=3) and 5% (n=4) developed pericardial constriction following drainage of pericardial fluid. There were 11 deaths, with an overall mortality rate of 14%. Pericardial disease was thought to be the cause of death in one patient with constrictive pericarditis in whom the family refused surgical intervention. Four deaths were possibly intervention related: two patients died post pericardial drain-insertion, one patient died post drain-removal and one died intra-operatively during a pericardiectomy. The details pertaining to these deaths were not available in the medical records. Two deaths were unrelated to the pericardial pathology: one child died of nosocomial pneumonia and the other had Non-Hodgkins Lymphoma with superior vena cava syndrome caused by thoracic outlet obstruction. The cause of death was not recorded in 4 patients. The outcomes were unknown in 19 patients (24%).

Legible ECGs were available in 25 patients (Table III). All 25 ECGs were abnormal and were recorded, on average, 14 days prior to the surgical procedures. All ECGs were in sinus rhythm. The main abnormalities found were: T-wave flattening with or without inversion in 24 patients (96%), sinus tachycardia in 20 patients (80%), decreased chest lead QRS voltage in 13 patients (52%), PR segment depression in 12 patients (48%), decreased limb lead QRS voltage in 10 patients (40%), and electrical alternans in 7 patients (28%). Seven (28%) of the 24 patients with T-wave flattening had abnormal T-wave polarity as well. The other ECG deviations present in a minority of the patients were: ST segment elevation in 3 patients (12%), Spodick's sign in 2 (8%), P-mitrale in 1 (4%), left axis deviation in 2 patients (8%) and RAD in 1 patient (4%).

TABLE III: Proportion of ECG Features in each pericardial pathology

ECG Feature	Pericardial Effusion; n=13	Cardiac Tamponade; n=4	Constrictive pericarditis; n=1	Effusive-constrictive Pericarditis; n=7
Rate				
Normal	4	0	0	1
Tachycardia	9	4	1	6
Bradycardia	0	0	0	0
P wave changes				
Nil	12	4	1	7
p-mitrale	1	0	0	0
p-pulmonale	0	0	0	0
QRS axis deviation?				
Normal	10	4	1	7
RAD	1	0	0	0
LAD	2	0	0	0
Mean QRS voltage				
Limb Leads				
Normal	7	3	0	5
Decreased	6	1	1	2
Increased	0	0	0	0
Chest Leads				
Normal	8	1	0	3
Decreased	5	3	1	4
Increased	0	0	0	0
PR segment				
Present	8	0	1	3
Absent	5	4	0	4
ST segment elevation				
Present	3	0	0	0
Absent	10	4	1	7
Spodick's sign				
Present	1	0	0	1
Absent	12	4	1	6
T-Wave abnormality				
Nil	1	0	0	0
Present	12	4	1	7
- Only flattening present	9	3	1	4
- Flattening with inverted T-waves	3	1	0	3
Electrical Alternans				
Present	4	0	0	3
Absent	9	4	1	4

DISCUSSION

This study demonstrated that infectious causes, in particular TB, were the predominant aetiology in the study cohort, confirming that TB is still an important cause of pericardial disease in South Africa. The majority of patients had complete resolution of their pericardial disease, despite needing invasive procedures as part of their management. The majority of ECGs in our study showed deviations from the norm, which mostly demonstrated features of sub-acute or chronic pericarditis. This suggests that most patients needing interventions have later stage disease. The small number of ECGs available for interpretation constitutes a limitation in the overall analysis of ECG changes in children. However, this does provide a platform for further studies around the interpretation of ECGs in the other phases of pericarditis in children.

The overall prevalence of pericardial disease in children at CHBAH was 2.6% of the total number of patients seen over a 26-year period. The low prevalence is a feature seen worldwide. An American study done over an 11-year period had a cohort of 32 children,[9] whereas two studies looking at children with significant effusions, from India and Turkey, had sample sizes of 25 patients over a 38 month period and 10 patients over a 33 month period respectively.[4,16] The small study samples in all of these studies corroborate the rarity of pericardial disease in children.[1–5]

The predominant cause of pericardial disease was found to be probable TB in 60% of the study patients, in contrast to an American paediatric study of 32 patients, which had no patients with TB, despite infections being the leading cause of pericardial effuions in their study.[9] Three other paediatric studies, Indian (LMIC), Turkish (MIC) and Portuguese (HIC), had 52%, 30% and 4% of their cohorts having TB pericardial disease, respectively.[2,4,16] This correlates with the higher TB endemicity that is associated with LMICs.[13,40] Despite the majority of our sample having large or significant effusions, cardiac tamponade was a rare presentation with only 19% showing echocardiographic features consistent with tamponade. This may have been due to TB pericarditis, which was the dominant probable cause in the study cohort, having a typical slow and subtle progression. A study undertaken in South Africa demonstrated a relatively long symptom duration with a median duration of 24 days in patients with TB pericardial effusions.[40] Due to the high virulence of TB, most patients present in the sub-acute or later stages of their pericardial disease.[32] In addition, another study from Africa showed that TB pericarditis rarely presents with cardiac tamponade.[13]

The current study cohort consisted of a younger median age of 8.2 years, compared to other studies, where median ages of 10-14 years were documented.[2,4,9,16] Patients with TB pericarditis tend to present at a younger age than other causes of pericarditis,[40,41] which may account for the younger age of our study patients compared to other studies.

Infectious causes of pericardial disease, including TB, predominate in LMICs,[4,16,42] which is reflected in our cohort where 53 patients (67%) had

infectious aetiologies. This is also supported by an Indian paediatric study, where 67-76% of children had infectious aetiologies. This is in contrast to studies from HIC where only 34-48% patients had infectious pericardial disease.[2,4,9,16] Organisms predominating in patients with purulent pericarditis include *S. aureus*, *H. influenzae* and *S. pneumoniae.*[16] All three organisms were identified in our study: two patients had *S. aureus* (one of which was a 10-year-old child with concurrent osteomyelitis), one had *H. influenza* and another had *S. pneumoniae*. The initiation of the pneumococcal conjugate and *Haemophilus influenza* vaccines into the South African expanded programme on immunization (EPI) in 2000 and 1999 respectively, have contributed to the reduction in the levels of purulent pericarditis caused by these organisms.[9] The children in this study who had *Streptococcus pneumoniae and Haemophilus influenzae* pericarditis were diagnosed in 2006 and 2000 respectively, after the initiation of the corresponding vaccines into the EPI. However, both patients were young infants (2 and 5 months of age respectively) at the time of infection and thus would have not yet have been fully immunized against these organisms.[9]

Pericardiocentesis and insertion of pericardial drains were the predominant interventions performed in this study and only a minority of cases required surgical interventions in the form of pericardiectomy in 9 patients (11%) and pericardiotomy/pericardial window in 14 patients (18%). Similarly, surgical drainage was undertaken in 12% of the children in a study from India which looked at children with significant pericardial effusions (defined as effusions with an echo-free space of >10mm in front of either ventricle) with or without tamponade.[16] In comparison, the number of surgical procedures was much lower in a large multicenter paediatric US study investigating idiopathic pericarditis. Pericardiectomy was performed in 2% and pericardiotomy in 2,4% of their cohort.[15] Pericardiectomy is a rare procedure usually done for refractory pericardial effusion not responding to medical treatment, or in cases of constrictive pericarditis.[3,7,13] Pericardiectomy was the second most common procedure performed in our study sample, however, which is most likely due to the high proportion of probable TB pericarditis in our sample (60%) as compared to the HIC studies that were reviewed (0-4%).[2,9]

There were 11 deaths in this study with a mortality rate of 14%, which is close to the mortality rate found in a paediatric study in India (20%), also classified as a LMIC. Both our cohort and the Indian cohort mortality rate is higher than the paediatric studies from Turkey which is a MIC (0% mortality) and the United States of America (4% mortality).[4,7,43] Only one patient in our study cohort was suspected to have died from pericardial disease while 4 patients died during or shortly after their interventions. Of the remaining 6 patients, 2 died from other causes and 4 patients had no documentation of cause of death. In the American study, both mortalities recorded were unrelated to pericardial pathology – one child died due to meconium aspiration syndrome, and one was a premature infant who died from a cardiomyopathy. This study cohort included all patients and not those undergoing procedures, as was the case in our study cohort.

Outcomes were known in 76% of the cohort. Complete resolution of pericardial disease occurred in 54% of patients with an average follow-up duration of 290 days. Recurrence of pericardial effusion occurred in 3%. Other paediatric studies have showed similar recurrence rates ranging from 3 to 16%.[2,7,9,15,16,40,41] The outcome of pericardial disease in children is therefore good if prompt and appropriate treatment is instituted.[7]

The majority (92%) of ECGs showed features of sub-acute or chronic (i.e. late stage 2 and stage 3) pericarditis, in the form of T-wave flattening with or without inversion. The study sample, in the way it was selected, introduced a selection bias because all the patients underwent surgical procedures mostly because they did not respond to medical therapy over time and may account for the predominance of the latter stages of ECG pericarditis features.

PR segment depression is a non-specific sign of acute pericarditis, but when used in conjunction with Spodick's sign, it makes the diagnosis of pericarditis more likely. The presence of both of these signs helps to differentiate early repolaristation from pericarditis because both may present with PR segment depression.[34] Spodicks' sign is present in approximately 80% of adult patients with acute pericarditis.[34] In comparison, Spodick's sign was found in only 2 study patients: one with pericardial effusion (who had PR segment depression as well) and one with effusive-constrictive pericarditis without PR segment depression. The low frequency of this sign may be attributed to the predominance of the latter stages of ECG pericarditis features in our study patients.

Small or micro-voltage QRS complexes are usually associated with moderate-large pericardial effusions.[19] In our study, micro-voltage QRS complexes were present in the limb leads of 40% and in the chest leads of 52% and was spread across all the categories of pericardial pathologies in the study cohort, not just in patients with pericardial effusion. An American study with an adult cohort found that QRS micro-voltage was very specific (98%) but not sensitive (10%) for differentiation of large effusions from small.[19] Of the 14 patients with low voltage QRS complexes, 57% (n=8) had large effusions, 14% (n=2) had small effusions and 29% (n=4) had effusions of unknown size. A South African paediatric TB pericarditis study showed micro-voltage QRS complexes in 25% of their patients across the chest leads (pericardial effusion sizes were not specified).[40] Conversely, 100% of the children in a study from India, all with large effusions, exhibited QRS micro-voltages (the affected leads were not specified).[16]

The ECG changes in this study cohort did not always follow the expected patterns for the various stages or types of pericardial pathology. For example, electrical alternans, which is usually a sign of cardiac tamponade and large effusions, was not evident in the study's 4 cases with pericardial tamponade. It was instead present in 3 patients with large pericardial effusions and in 1 patient with recurrent idiopathic pericardial effusion of unknown size. Both LAD and p-mitrale as well as RAD and RVH may be present in patients with constrictive pericarditis.[23,31,32,38] However, QRS axis deviations were instead found in 3 patients who had non-constrictive pericardial effusions. LAD was

found in 2 patients: 1 with a purulent pericardial effusion (size not specified) with stage 1-2 acute pericarditis features on ECG and another with a large autoimmune pericardial effusion, with P-mitrale and late stage 2 acute pericarditis ECG features. The third patient had RAD and had a large pericardial effusion ascribed to TB.

LIMITATIONS

The major limitation in this study is its retrospective design with inevitable missing data, particularly legible ECGs. Also, the study sample included only those patients undergoing therapeutic interventions thereby excluding a large subset of patients with pericardial disease that may have had relevant data for analysis. Nevertheless, at the time of evaluation, this study group constituted the largest single-centre paediatric cohort with pericardial disease being analysed.

CONCLUSION

The high prevalence of infectious causes in this study, specifically tuberculosis, emphasizes the need for preventive measures, early diagnosis and treatment. The majority of children in the study cohort had complete resolution of their pericardial disease suggesting a good outcome with appropriate management. In addition, the presence of ECG changes suggestive of pericardial disease in the majority of available cases can be used to support a clinical diagnosis of pericardial disease. However, further studies are needed to include a wider range of pericardial disease in children for ECG analysis to assess for typical changes.

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ADDENDUM 1: Normal Paediatric QRS axis for age

Age	QRS axis range (2nd – 98th centiles)	
	Boys	Girls
0-1month	75-140°	63-155°
1-3 months	37-138°	39-121°
3-6 months	(-6)-107°	17-108°
6-12 months	14-122°	1-102°
1-3 years	(-4)-118°	2-121°
3-5 years	7-112°	3-106°
5-8 years	(-10)-112°	27-117°
8-12 years	(-21)-114°	5-117°
12-16 years	(-9)-112°	5-101°

From: Rijnbeek PR, Witsenburg M, Schrama E, Hess J and Kors JA. New Normal Limits for the Paediatric Electrocardiogram. European Heart Journal. 2001;22(8):702-711 [44]

ADDENDUM 2: Normal paediatric ECG heart rate for age

Age	Heart rate range (2nd to 98th centiles)	
	Boys	Girls
0-1month	129 – 192 bpm	136 – 216 bpm
1-3 months	126 – 187 bpm	126 – 200 bpm
3-6 months	112 – 165 bpm	122 – 191 bpm
6-12 months	106 – 194 bpm	106 – 187 bpm
1-3 years	97 – 155 bpm	95 – 178 bpm
3-5 years	73 – 123 bpm	78 – 124 bpm
5-8 years	62 – 113 bpm	68 – 115 bpm
8-12 years	55 – 101 bpm	58 – 110 bpm
12-16 years	48 – 99 bpm	54 – 107 bpm

From: Rijnbeek PR, Witsenburg M, Schrama E, Hess J and Kors JA. New Normal Limits for the Paediatric Electrocardiogram. European Heart Journal. 2001;22(8):702-711 [44]

RESEARCH PROTOCOL

Title

Electrocardiographic features and Characteristics of Pericardial Disease in Children

Introduction

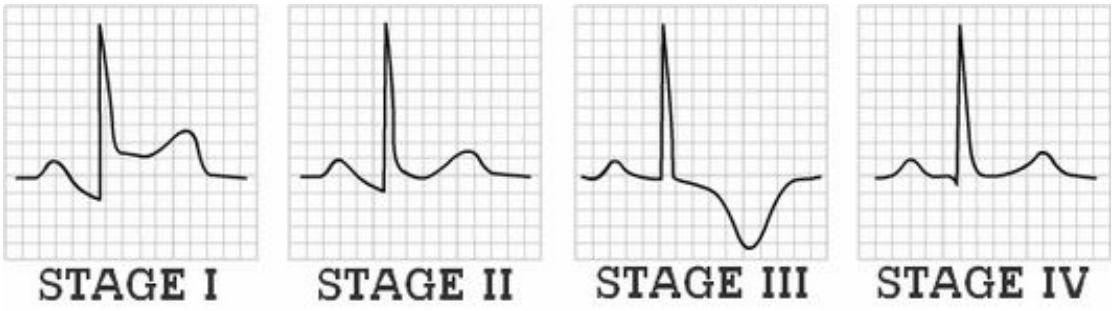
Pericardial disease in children is a poorly studied pathology, the majority of the studies that were reviewed for this paper deal with adult cohorts (8,10,19–22,25–32,42,45–51). Several pericardial diseases affect children, including pericarditis, pericardial effusion, cardiac tamponade and constrictive pericarditis, but are rare occurrences (1,4). The researcher acknowledges that the electrocardiogram (ECG) is an inexpensive and easily available adjunct in pericardial disease diagnosis, especially in peripheral centers where access to paediatric cardiologists and echocardiography (ECHO) may not be available. The value of utilising the ECG in diagnosing pericardial disease has been studied mainly in adult populations (19–22,25–32,45,48), with the majority of studies being done more than 10 years ago - many of the studies originating as far back as the 1970s and '80s (19,21,22,25–32,48). Despite the lack of literature on specific paediatric ECG changes in pericardial disease, the researcher has included paediatric norms related to each of the adult ECG features described. This study therefore aims to provide a recent report on paediatric pericardial disease and the associated ECG features in the South African setting.

Pericarditis

Pericarditis is rare in childhood (1) and is characterized by inflammation of the visceral and parietal layers of the pericardium. Acute infectious causes of pericarditis predominate in the paediatric population (2). The etiology of paediatric pericarditis varies between the low-to-middle income (previously referred to as "developing") and high-income (previously referred to as "developed") countries. Bacterial infectious causes – in particular, tuberculosis pericarditis – predominate in low-to-middle income countries, whilst viral pericarditis, post-pericardiotomy syndrome and radiation therapy are more prevalent in high-income countries (10). The natural course of pericarditis in children is mostly benign, but devastating mortality can occur as a result of secondary cardiac tamponade or constrictive pericarditis (7).

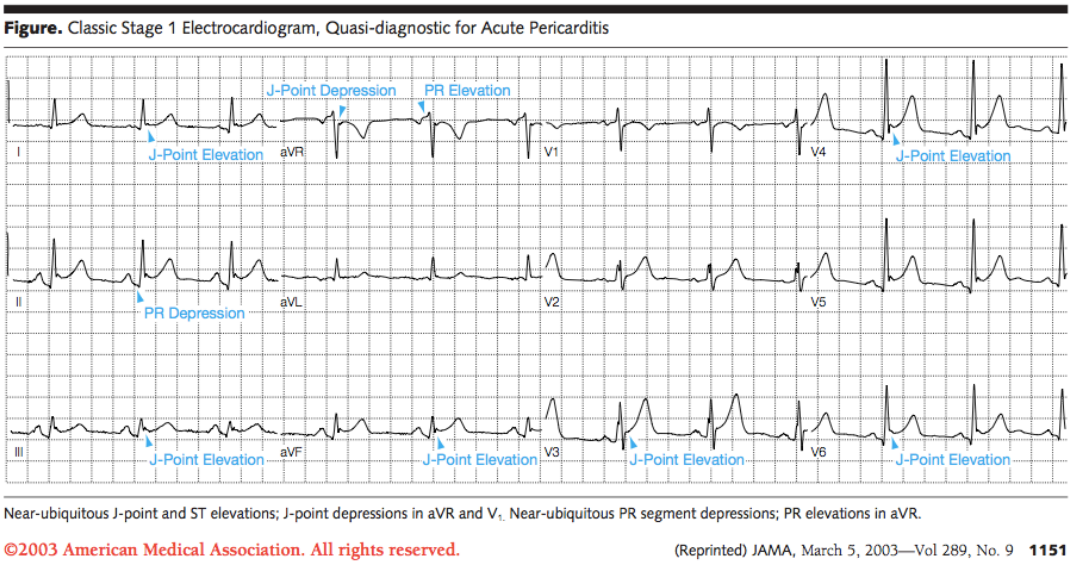
ECG features: Spodick first described the four-stage ECG sequence of acute pericarditis in 1973 (8,25). The acute phase (stage 1) is characterized by concave ST-segment elevation and PR segment depression in most leads. In stage 2, the ST junctions return to baseline – ST-segment elevation has resolved and T waves may be normal or flattened, but PR-segment changes often remain. Stage 3 denotes a change in T-wave polarity where there is T-wave reversal/inversion. Lastly, stage 4 consists of resolution of ECG

changes where the T-waves return to the upright position.



The four-stage ECG sequence of acute pericarditis as described by Spodick in 1973 (45)

An updated review by Spodick in 2003 (27) explains that the early ECG features of acute pericarditis are standard for several aetiologies, namely diffuse ST-segment elevation (i.e. J-point elevations) with associated PR-segment depression (the presentation of which often precedes the ST-segment elevation if the ECG is done within the early disease process or with timely medical treatment). It is now recognised that often due to prompt medical treatment, Stage 1 of Spodick's original 4 stage sequence is the only ECG feature observed - See diagram below (27):



Classic stage 1 Electrocardiogram (27)

It is important to note that PR segment depression can often be mistaken for ST-segment elevations, or early repolarization (27).

In children (33): Abnormal ST-segment changes in the left ventricular leads (I, aVL, V_5 and V_6), flat or low T waves and an abnormal T-wave axis are associated with pericarditis. Depression or elevation of the ST-segment is considered normal up to 2mm in children in the left praecordial leads (V_4, V_5 and V_6). In children, normal T-wave polarity differs to adults. In lead V1, T-wave inversion is normal from approximately 7 days to 7 years of life (the wave is normally upright out of this age bracket). Also, any inversion of T-waves found in the left praecordial leads is considered abnormal at any age.

Pericardial Effusion

A pericardial effusion is another manifestation of pericarditis, also rare in the paediatric population (4), the detection of which is very accurate using echocardiography (which is both sensitive and non-invasive) (16). It is a pathological collection of fluid between the parietal and visceral surfaces of the pericardium exceeding the normal volume of the pericardial cavity. The normal volume is between 15-50ml in healthy adult individuals (8) – there is insufficient data available on the normal pericardial volume in children. Slow accumulation of pericardial fluid can often be well tolerated. When intra-pericardial pressure exceeds intra-cardiac pressure cardiac tamponade develops. The parietal pericardium is not distensible and the increased intra-pericardial pressures are transmitted to the heart, causing decreased end-diastolic ventricular filling and subsequent decreased cardiac output. The compensatory mechanisms (increase in venomotor tone, increased peripheral vascular resistance and increased heart rate) eventually become exhausted, with ensuing hypotension, shock and even death (4). If the fluid accumulation is rapid, small volumes can cause tamponade.

There are numerous causes of a pericardial effusion, namely infectious (viral, bacterial, immune complex-mediated, fungal and parasitic) and non-infectious causes (systemic inflammatory diseases, metabolic, malignant and traumatic pathologies) (4,16,42). In low-to-middle income countries, infectious causes predominate – especially that of tuberculosis (TB) (46). In the South-African context, a study based in a Western Cape adult cohort identified TB pericarditis as the most common cause of pericardial effusions in the South African setting, with half of the affected study population being co-infected with Human Immunodeficiency Virus (HIV) (46). This is in contrast to the infrequent incidence of TB pericarditis in high income countries which is estimated at <4% (27,46). This data extends to the paediatric population as well, as a study in Northern India showed the majority of pericardial effusions being caused by TB, albeit in a small study sample of 25 children (16). This demonstrates the importance of the diagnosis and management of pericardial effusions against the backdrop of high TB disease burden, partially attributable to high HIV infection prevalence (46,47). Although numerous studies have documented the predominance of infectious causes amongst low-to-middle income countries, a recent study with a North American paediatric cohort, however, demonstrated that infection is overall an important cause of pericardial effusions in children (9).

***ECG features**:* Low QRS complex voltage on the ECG has been associated with pericardial effusion since 1923 when studied by Oppenheimer and Mann (48). Several adult studies investigating its value in diagnosis have been performed, most of which document the lack of sensitivity but high specificity in detecting pericardial effusion and cardiac tamponade (19,20,22,28). A paediatric study found that sinus tachycardia and low ECG voltage were ECG features of pericardial effusion (4), but did not specify the numerical norms or cut-off values used – such values being provided by adult studies as QRS complex sizes of less than 5mm in limb leads and less than 10mm in praecordial leads (8,19–22,26,28–31). Low QRS voltage has been found to be highly specific (also with a high positive predictive value) in detecting

moderate to large effusions and cardiac tamponade, but is a test with poor sensitivity and low negative predictive value (19,20). One study, however, reported a diagnostic value in low QRS voltage when serial ECGs are performed – when available for comparison, a decrease in QRS voltage in later ECGs may allude to the development of pericardial effusion in that patient (26). It is important to note that low QRS voltage in the ECG can also be caused by several other factors – any cause of decreased voltage produced by the myocardium (eg. thin-walled ventricles, myocardial ischaemia, infiltrative heart conditions and myocardial oedema), increased distance between the heart and the ECG electrodes (seen in morbid obesity and emphysema), decreased cardiac size and volume and increased resistivity of the interposed tissues (21,26,30).

Electrical alternans, another ECG sign, is a beat-to-beat variance in QRS amplitude and is postulated to be due to the pendular motion of the heart within the fluid-filled pericardium (20,30). Its value in pericardial effusion diagnosis has mainly been explored in case studies. It has been found to be a specific sign in distinguishing patients with effusion from patients without, but is not sensitive in differentiating small from moderate/large effusions and in detecting cardiac tamponade (19). The value of electrical alternans in cardiac tamponade diagnosis is conflicted by an American study in 2015, which demonstrated its high sensitivity and positive predictive value in detecting cardiac tamponade, with an odds ratio of 12.3 (20). The low sensitivity of electrical alternans, however, can be attributed to its presence in other conditions, namely supraventricular and ventricular tachycardia, hypothermia, electrolyte abnormalities, prolonged QT syndrome and bradycardia (19).

Sinus tachycardia is another ECG sign of cardiac tamponade, and when combined with low QRS voltage and electrical alternans, it has a 100% specificity and positive predictive value in diagnosing cardiac tamponade (20).

In children(33): Low QRS voltage is defined as limb lead (I, II, III, aVR, aVL, aVF) complexes with sizes of less than 5mm. The upper limit of normal heart rates (i.e. tachycardia) is age-dependent (see appendix 1 (33)).

Constrictive Pericarditis

Constrictive pericarditis is also a rare phenomenon in children – most pericardial diseases in children are acute processes, whereas constrictive pericarditis occurs as a result of chronic pericardial inflammation (3). This chronic inflammation leads to the thickening and fusion of the visceral and parietal pericardial layers, causing a restriction in the filling of the ventricles during diastole. This decrease in cardiac preload, in turn, leads to an inability to increase cardiac stroke volume, leading to decreased cardiac output and heart failure. In low-to-middle income countries, constrictive pericarditis has become more common due to the high disease burden of TB. Tuberculosis is the most common cause of constrictive pericarditis in low-to-middle income countries, which can be extrapolated to most of the South African population due to our high TB prevalence (10,46).

ECG features: The ECG features of constrictive pericarditis have mainly been explored in adult studies. Low QRS voltage, non-specific ST and T wave abnormalities, p-mitrale and right axis deviation are all features that have been described (31,32,49,50).

In children (33): Normal QRS voltages, ST-segment changes and T-wave abnormalities have been described as above. P-mitrale in paediatric ECGs is defined as P wave duration of more than 0.1 seconds in children and more than 0.08 seconds in infants. Right axis deviation is considered normal in the newborn period due to in-utero high pulmonary vascular pressures and a relatively thick right ventricle. As children age, their QRS axis changes to eventually reach the adult mean value of +50 degrees by age 3 (normal QRS axis for age is described in appendix 1 (33)).

Imaging

Chest X-ray (CXR), ECG, ECHO, computed tomography (CT) and magnetic resonance imaging (MRI) are all diagnostic modalities used in the detection of pericardial effusion and tamponade(51). The current first line diagnostic tool is ECHO (51). The advantages are numerous, including its non-invasive nature, speed of acquisition, cost-effectiveness and ease of access (relatively widely available and can be done at the bedside). The researcher believes it also avoids the deleterious effects of radiation exposure and intravenous contrast administration employed in CT and MRI. In haemodynamically unstable patients, echocardiography also provides data showing cardiac function and fluid dynamics (51). The disadvantage of echo diagnosis of pericardial disease lay in that its accuracy is operator-dependent, requiring a trained cardiologist or sonographer – which is not available in primary health care, level one and level two health care facilities. Added to this, technical factors for unsatisfactory echo diagnosis would be poor echo windows in patients with emphysema or small vertical hearts (28).

Not much is known on pericardial disease in children, especially of the electrocardiographic features thereof. All of the previous studies emphasize the low sensitivity of ECG signs in adult populations. This study will aim to show the value of these signs in a paediatric population and in the setting of low-to-middle income countries. Despite previous studies demonstrating the low sensitivity of ECG diagnosis, perhaps emphasis should be placed on the specificity of these signs. A test with high specificity may allow a clinician to initiate timeous medical treatment of pericardial disease in peripheral centers without confirmatory echocardiography before referral.

Objectives

Primary Objectives:

To assess the ECG changes found in paediatric pericardial disease and their diagnostic value.

Secondary Objectives:
To look at other descriptive variables of the sample population, viz. patient demographics, HIV status, presence of TB, etiology of pericardial disease, pericardiocentesis details, medical and surgical treatments of patients and outcomes

Methods

Study Design
Retrospective Descriptive Study.

Study Site and Population
The study population will be derived from the Chris Hani Baragwanath Academic Hospital (CHBAH) paediatric cardiology patient database from January 1993 – April 2019.
A preliminary review of the Paediatric Cardiology database has revealed a total of 724 cases of pericardial effusion of which 81 underwent pericardiocentesis either for relief of pericardial tamponade or diagnostic purposes, and 46 have been diagnosed with constrictive pericarditis. The majority of the 724 cases are small and insignificant effusions diagnosed on echocardiography as an incidental finding. Our study population will be derived from the 81 patients with pericardial effusions who underwent pericardiocentesis for diagnostic purposes or treatment of tamponade as these patients are more likely to have had electrocardiograms stored in their files. This has guided the development of the inclusion and exclusion criteria, as listed below:
Inclusion Criteria:
- children aged 0-14 years
- with ECHO-proven pericardial disease (pericardial effusions or constrictive pericarditis)
- with adequate 12-lead ECGs done within one week of their ECHO diagnosis (prior to any medical/surgical intervention)
- who underwent pericardiocentesis for treatment or diagnostic purposes

Exclusion Criteria:
- Patients with primary congenital or non-pericardial acquired cardiac disease
- Patients without adequate ECGs in their files

Data Collection
The electronic database of the CHBAH paediatric cardiology department will be scanned using the aforementioned inclusion criteria. Where data is not available on the database, patients' files will be retrieved and reviewed. The relevant patient clinical data and ECG records will be duplicated and kept on file for later measurement and analysis as specified below (See appendix 2 for the data sheet upon which anonymous patient details and variables will be recorded).

Study Variables

Demographic data including age, sex and HIV status of affected patients, aetiology and characteristics of effusion fluid drained, measurement of the size of the effusion measured at echocardiography, medical treatment employed (including dose and duration of corticosteroid use), surgical procedures performed, their indications and outcomes of management.
The data will also consist of various ECG features, namely: rate, rhythm, p-wave changes, PR- interval, QRS axis and voltage, PR segment depression, ST-segment changes, T-wave abnormalities and electrical alternans. The ECGs will be analysed by the primary investigator and measurements/changes documented on the data sheet (see appendix 2).

The ECG deviations being investigated are defined as follows (8,19–22,26,28–31,33):

- QRS axis deviation: any deviation from the norms as per appendix 1
- Low QRS voltage: QRS complex size of less than 5mm in the limb leads (I, II, III, aVR, aVL and aVF)
- PR segment depression: In adults, any depression in ≥1 lead (except aVR) with associated ST segment elevation (defined as elevation of ≥0,5mm from baseline) is considered abnormal. In children, there are no specific values on the degree of PR-segment depression which is abnormal, thus any PR-segment depression found in the study patients, will be documented as abnormal.
- ST-segment changes/abnormalities: ST-segment depression or elevation more than 2mm in children in the left praecordial leads (V_4, V_5 and V_6) as well as any ST-segment changes in the other leads will be considered abnormal.
- T-wave changes/abnormalities: T-wave polarity opposing the norm (of being inverted in lead V_1 from approximately 7 days to 7 years of life, and being upright in the first week of life and after 7 years of age) and any inversion of T-waves in the left praecordial leads, regardless of age, will be considered abnormal.
- Electrical Alternans: A peak-to-peak change in QRS amplitude of ≥1mm in successive beats in ≥1 lead
- Sinus tachycardia: Tachycardia will be defined as being higher than the normal age-related heart rate values as per appendix 1.

Data analysis

Using ECHO as the gold standard for pericardial effusion diagnosis, the sensitivity, specificity, positive and negative predictive values for the specified abnormal ECG parameters would be calculated. Tables and graphs will be used to describe data where possible. The Chi-square test will be used to analyze categorical variables. Where variables are continuous an unpaired Student's t-test or Mann–Whitney U test will be used for data with a normal and non-normal distribution respectively. The significance will be set at p-value <0,05. The relationships between the data sets (namely, any ECG changes found) will be calculated using the Pearson correlation coefficient. The data will be analysed with the aid of a statistician. A statistical computer program will be used in the analysis of the data (SPSS or STATA depending on statistician's preference).

Ethics

The Chris Hani Baragwanath paediatric cardiology database receives a five-yearly WITS ethics clearance for its use. The researcher will also apply for ethics clearance via the WITS Human Research Ethics Committee for use of this database and its application in her research. All patient data will be kept anonymous.

Timing

	2019	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sept	Oct	Nov
Literature review		■	■									
Preparing protocol				■	■							
Protocol assessment						■	■					
Collecting data								■	■			
Data analysis										■		
Writing up											■	■

Funding

Costs for this study would be minimal and would include photocopying costs needed to duplicate the ECG and clinical data on record for each patient for subsequent analysis. Transport costs would also be a factor, as data collection would involve travelling (CHBAH). The primary researcher would cover these costs.

Study Limitations

Possible limitations that may be encountered are:

- Insufficient patient numbers, leading to type II error with data analysis
- Lack of serial ECGs to detect development/resolution of ECG changes before and after medical/surgical management
- The possibility of disease processes other than pericardial disease causing ECG changes (e.g. right ventricular hypertrophy)

The researcher will attempt to minimize these factors as far as possible, and take cognisance of these challenges when the data is reported.

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Protocol Appendix 1 (33):

(A) Normal paediatric ECG heart rate:

Age	Heart rate range (beats per minute)
Newborn	90 – 180
6 months	105 – 185
1 year	105 – 170
2 years	90 – 150
4 years	72 – 135
6 years	65 – 135
10 years	65 – 130
14 years	60 – 120

(B) Normal Paediatric QRS axis:

Age	Normal axis range (degrees)
Newborn	+30 to +180
1 – 3 months	+10 to +125
3 months – 3 years	+5 to +110
Children older than 3 years	+20 to +120

Protocol Appendix 2: DATA SHEET

Subject Code number:						
Patient details						
Age	Years			Months		
Sex	Male			Female		
HIV status	Negative		Positive		Unknown	
TB?	Yes			No		
If TB:	pre-Rx		On Rx		Prev. TB off Rx	
Pericardial Disease features						
Diagnosis	Pericarditis					
	Pericarial Effusion					
	Pericardial Tamponade					
	Constrictive Pericarditis					
Cause	**Infectious**					
	Bacterial	TB	Viral	Fungal	Parasitic	
	Non-infectious					
	Systemic inflammatory	Metabolic	Malignant	Trauma (including post-pericardotomy syndrome)		Other:
Medical Treatment given, if any:						
	if steroids used:	Dose (mg)				
		Duration (days)				
Surgical Procedure/s						
Surgical procedure performed:						
Date						
Indication	Diagnostic			Treatment		
	Volume (ml)					
	Protein level					
	Transudate/ Exudate					
	ADA level					
	Cytology					
	Microbiology					
	Suggested/suspected final diagnosis					
If Biopsy done, Result:						
ECG features						
Date						
Normal/Abnormal ECG	Normal			Abnormal		
IF ABNORMAL, document abnormalities:						
Rate	Normal		Bradycardia		Tachycardia	
Rhythm	Sinus			Non-sinus		
p-wave changes:	Nil		P-pulmonale		P-mitrale	
QRS axis	Normal		RAD		LAD	
Mean QRS voltage (mV)	Chest leads:		Limb Leads:		Average:	
PR interval	Normal		shortened		prolonged	
If PR-segment depression:	Lead/s involved:			Measurement (mm)		
If ST-segment changes:	Lead/s involved:			Measurement (mm)		
If T-wave abnormality:	Flattened/low	Lead/s involved:		Abnormal polarity	Lead/s involved:	
If Electrical alternans	Lead/s involved:					
Outcome						
Resolution:	**Yes**			**No**		
	with medical Rx			With surgical Rx		
Recurrence? (yes/no)				volume of fluid reaccumulated (ml):		
Other Information						

APPENDIX: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Prof Antoinette Cilliers

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180488

NAME: (Principal Investigator)	Prof Antoinette Cilliers
DEPARTMENT:	Paediatrics Division of Paediatric Cardiologist Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Request to use the Paediatric Cardiology Patients in 1993 for purpose of restropective analysis for publication (Ref 070470,M020806 and M130384)
DATE CONSIDERED:	Ad hoc
DECISION:	Approved unconditionally
CONDITIONS:	Renewal of M130384
SUPERVISOR:	
APPROVED BY:	Prof C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	14/05/2018

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 Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Philip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in April and will therefore be due in the month of April each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

14 MAY 2018

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX: Turnitin Report

00100697:Coopoo_FINAL_draft_for_submission_20sept2022.docx

by Kebashni Thandrayen

Submission date: 22-Sep-2022 03:45PM (UTC+0200)
Submission ID: 1906192864
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