THE PREVALENCE OF ECG ABNORMALITIES AND ABNORMAL TROPONIN T LEVELS IN PATIENTS WITH NON-TRAUMATIC SUB-ARACHNOID HAEMORRHAGE

Samantha Anne Nash

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the Degree of Master of Medicine in the branch of Neurosurgery

Johannesburg
13/08/2020

DECLARATION

I, Samantha Nash declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Neurosurgery, in the University of the Witwatersrand, Johannesburg.

It has not been submitted before for any degree or examination at this or any other University.

Dr Samantha Nash

13th Day of August 2020

PUBLICATIONS AND PRESENTATIONS

Nash S. The prevalence of ECG Abnormalities and Abnormal Troponin T levels in patients with Non-traumatic Subarachnoid Haemorrhage- Oral presentation of preliminary findings. The Society of Neurosurgeons of South Africa 28th Biennial Congress, August 2019. CTICC, Cape Town.

ABSTRACT

In this prospective study, electrocardiogram (ECG) and high sensitivity Troponin-T (hs-cTnT) levels were evaluated in patients presenting to Chris Hani Baragwanath Academic Hospital (CHBAH) Neurosurgical department with non-traumatic sub-arachnoid haemorrhage (SAH). ECG changes are well recognised in world literature, in patients with non-traumatic SAH. To the authors knowledge, this has never been investigated in South African patients. Thirty-two patients met the inclusion criteria out of a total of 40 patients. ECG and serum hs-cTnT levels were done within 7 days of onset of initial symptoms. hs-cTnT levels were stratified as normal (<15 ng/L), positive (15-100 ng/L) and high positive (>100 ng/L).

59.38% of patients in this study were female and 40.63% male, and 65.63% of patients fell between the ages of 41-60 years of age. 46.88% of patients had a World Federation of Neurological Societies(WFNS) grade of 1 or 2 as per the WFNS grading of SAH while 9.38% and 31.25% of patients were a WFNS grade 3 and grade 4 respectively. The most common Computed Tomography of Brain (CTB) finding was Intraventricular haemorrhage (IVH). The cause of SAH was secondary to ruptured aneurysm in 81.25% of patients. 56.25% of all participants had an elevated serum hs-cTnT (total of positive and high positive categories) level whereas 87.5% of all participants had ECG changes. With regards to specific ECG abnormalities, the most common changes found were ST, T wave and QTc interval changes.

This research project shows that the prevalence of ECG abnormalities in a patient population attending CHBAH are in keeping with international literature. In this study we had a higher prevalence of raised hs-cTnT levels which may be due to increased

underlying cardiac co-morbidity in the study population, late sample collection times, or result cut points being too low amongst others . A further study could be performed to evaluate whether ECG changes or raised hs-cTnT levels denote a poorer prognosis in patients with SAH.

ACKNOWLEDGEMENTS

I would like to thank Professor John Ouma and Dr Christos Profyris for the endless advice and guidance.

Thank you to Dr Matthew Procter and Dr Jonathan Hooijer for their priceless input.

All the registrars in the CHBAH Neurosurgery department that helped with identifying participants.

LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
AVM	Arteriovenous Malformation
CHBAH	Chris Hani Baragwanath Academic Hospital
CTA	Computed Tomography Angiogram
CTB	Computed Tomography of Brain
DSA	Digital Subtraction Angiogram
ECG	Electrocardiogram
GCS	Glasgow Outcome Scale
HCP	Hydrocephalus
hs-cTnT	High Sensitivity Troponin-T
IVH	Intraventricular Haemorrhage
PNS	Parasympathetic Nervous System
SAH	Sub-Arachnoid Haemorrhage
SNS	Sympathetic Nervous System
WFNS	World Federation of Neurological Societies

LIST OF FIGURES

LIST OF TABLES

TABLE OF CONTENTS

1.0 INTRODUCTION

ECG abnormalities are recognised in the literature following a Sub-Arachnoid Haemorrhage (SAH). ECG abnormalities resulting from a neurological cause can be misdiagnosed as myocardial ischaemia or infarction in a patient presenting with a history of collapse. This might result in misdiagnosis, delay in treatment or commencement of treatment that may be harmful to the patient.

SAH is defined as blood found in the sub-arachnoid space, which is between the arachnoid membrane and the pia mater[4.] The aetiology of SAH is classified as trauma-related or spontaneous. Trauma-related SAH is the more common of the two. In the spontaneous group, those due to ruptured intracranial aneurysms make up 75-80%[4]. Also falling into this group are those secondary to Intracranial Arteriovenous Malformations (AVMs), making up 4-5% of cases[4], while in 14-22% of cases, no cause is found[4].

The estimated annual incidence of aneurysmal SAH is 9.7-14.5 per 100 000 population in the US[4], while no data exist for the South African population. The peak age of aneurysmal SAH is 55-60 years[4]. In people suffering from spontaneous SAH, 10-15% die before reaching the hospital[4] while the mortality in patients that get to a medical facility is 10% in the first few days, with the 30-day mortality being as high as 46% in some studies[4]. Two major factors causing an increased mortality and morbidity after the initial bleed are vasospasm and rebleeding. The risk of rebleeding is 15-20% in the first 2 weeks post SAH[4]. Vasospasm causes mortality in a further 7% of patients and severe disability in another 7%[4]. Up to 66% of patients who have had successful treatment of

their aneurysm do not return to the same quality of life as before the bleed[4]. These statistics highlight the multiple factors associated with non-traumatic SAH and the high morbidity and mortality associated with this condition.

1.1 ELECTROCARDIOGRAM ABNORMALITIES AND NON-TRAUMATIC SUB-ARACHNOID HAEMORRHAGE

Sommargren et al described two main categories of ECG (12 lead) abnormalities seen in patients with SAH: Morphological waveform changes and Arrhythmias (Sinus bradycardia or tachycardia, supraventricular or ventricular arrhythmias)[10]. The ECG changes associated with SAH primarily reflected repolarisation abnormalities involving the ST segment, T wave, U wave and the QTc interval. Abnormally prolonged QTc intervals with large T waves have been found commonly in SAH patients. Burch et al described broad, slurred, or inverted T waves associated with long QTc intervals as "Cerebral"," Neurogenic" or "Giant" T waves[2]. The prevalence of ECG abnormalities in patients with SAH was reported as 27-100%[2,19]. AD Harries et al reported that up to 50% of patients with SAH will have ECG abnormalities, most of which had no evidence of heart disease[5]. Brouwers et al showed that the most pronounced ECG changes occurred during first 72 hours after the SAH and most of these changes resolved within 12 days[2] while AD Harries noted that ECG abnormalities could persist up to 6 weeks after insult[5]. Di Pasquale[17] et al reported that 90% of patients had some ECG abnormalities in first 48 hours following SAH[2]. Benninger et al reported that most commonly found ECG abnormalities seen in SAH patients were those involving the QT interval, T wave and ST segments[2]. As described in this literature, there is a high

prevalence of ECG abnormalities in patients with non-traumatic SAH, which suggests that these findings would occur in patients seen at CABAH, but has not been studied up till now.

Studies have described the concept of the Brain-Heart axis (Figure 1)[7]; the anterior cingulate cortex, amygdala, parabrachial nucleus, hypothalamus, periaqueductal grey matter, anterior insula and some areas of the medulla are thought to play a very important role in modulating cardiac function. Through the sympathetic and parasympathetic nervous system, in response to stressful and emotional situations and in homeostatic reflexes, these structures are involved in cardiac activity (specifically with regards to the force of contraction and heart rate regulation). The insular cortex plays a critical role in the management of the heart's chronotropic activity. The etiological theories surrounding what causes these ECG abnormalities in SAH are controversial. Some suggest a neurogenic aetiology where there is unilateral alteration of sympathetic tone to the heart. Benninger et al postulated that there is an increase in central sympathetic activity in these patients[2]; this is thought to be due to activation of the hypothalamus[2]. Calcium influx associated with sympathetic activity after Central Nervous system injury releases degrading enzymes that can damage subendocardial conductive networks and alter cardiac automaticity, refractoriness and repolarization[16.] This resulted in a hyperdynamic cardiovascular state, leading to the ECG abnormalities that were seen in their patients. This was associated with a higher mortality and was suggested that it was a predictor of those patients that would develop vasospasm. In the

setting of vasospasm, it is thought that it also affects the small hypothalamic blood vessels[5]. This could result in lesions in hypothalamus. This damage could lead to an

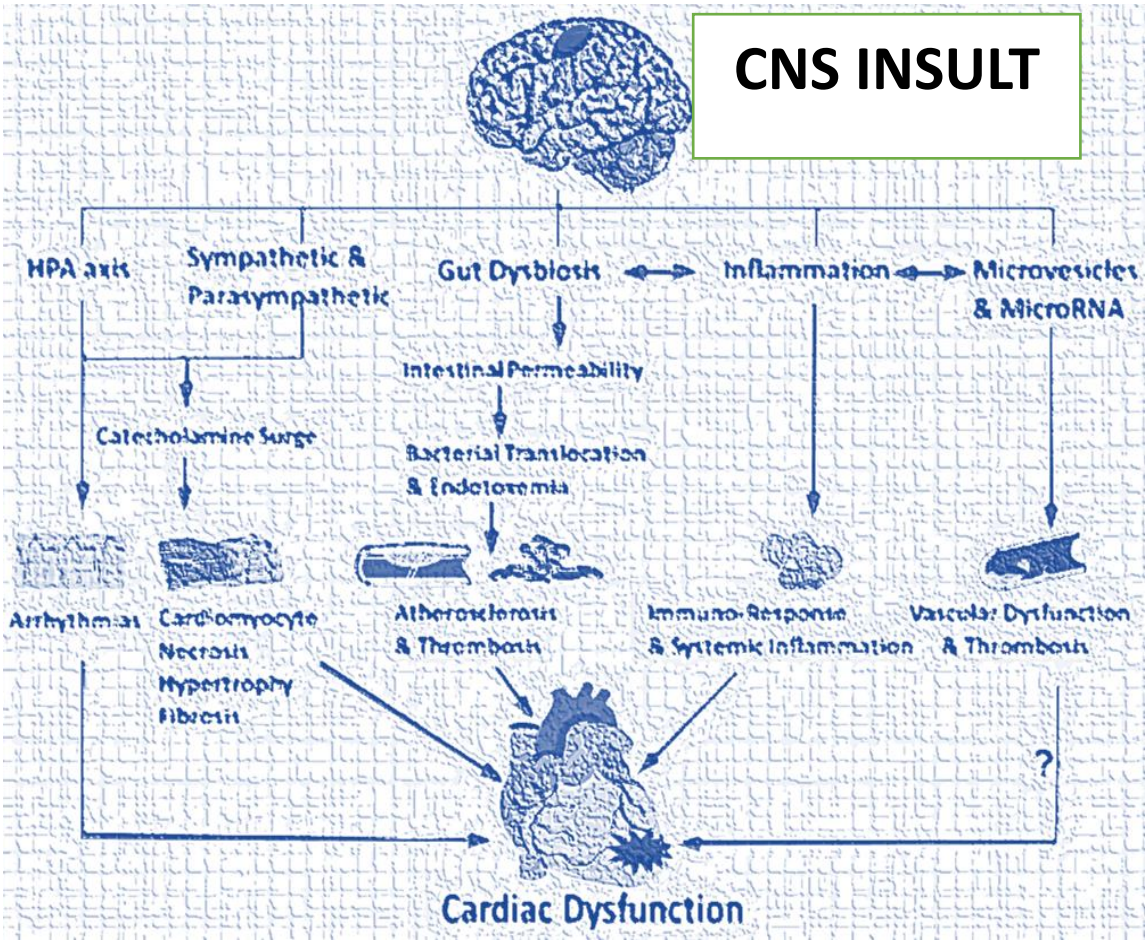

Figure 1: Heart-Brain Axis[3]

abnormal hypothalamic response and there-fore result in an increased catecholamine production via sympathetic system and an increase in circulating steroid levels via the Pituitary-Adrenal axis.

The Heart Brain Axis can be approached from two points of view[16]:

1. Effects of Cardiovascular disease on nervous system, or
2. Effects of neurological disorders on the Cardiovascular system

There is a complex network of cortical and subcortical regions involved in processing and control of Cardiovascular function (figure 2)[16]. This involves interconnected cortices (orbitofrontal cortex, dorsal cingulate cortex) which process afferent information ascending from the periphery and other brain areas and modulate efferent autonomic outflow; Subcortical forebrain structures (including amygdala and hippocampus); and brain stem areas (including hypothalamus, the red nucleus of the stria terminalis, periaqueductal grey, parabrachial region and ventrolateral medulla).

The Insular cortex (as mentioned earlier) plays a central role in regulation of Heart Brain Axis[16]. The posterior area of the insula is said to receive cardiac afferent input via thalamus and its rostroventral area integrates above information with that received from higher cortical centres.

The Amygdala receives inhibitory projections from the prefrontal and orbitofrontal areas and connects to the hypothalamus and brainstem nuclei involved in the control of cardiac function. It seems to modulate the effects of emotional stimuli on heart.

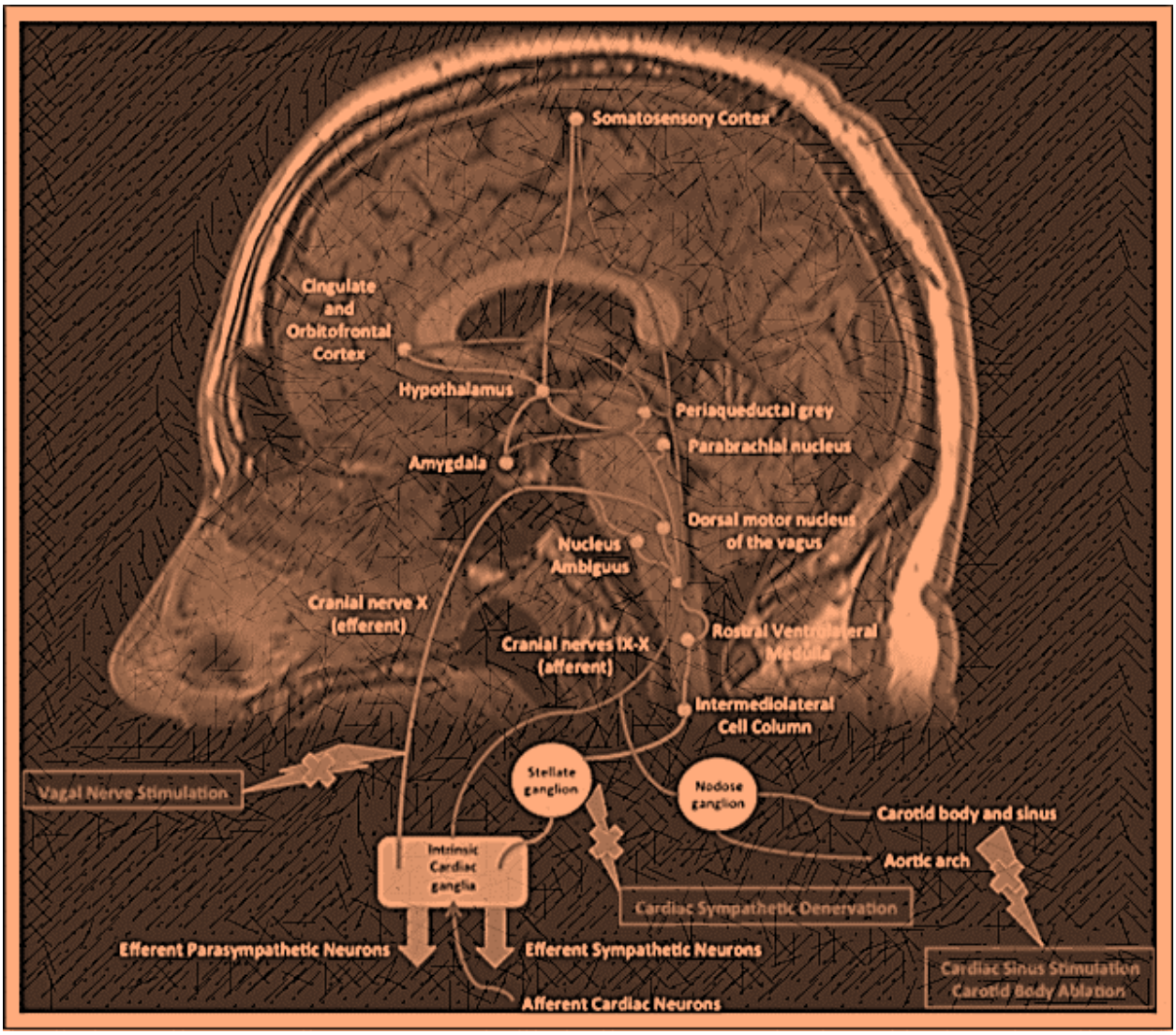

Figure 2: Neural control of Cardiovascular system; Afferent and efferent pathways are shown in green and red lines, respectively. Some potential sites for therapeutic interventions are shown in blue text boxes. The figure illustrates the major Cortical, subcortical and brain stem areas involved in control of the CV function. Most of shown areas are interconnected[16].

The Central Nervous System regulates the Cardiovascular function through cardiomotor sympathetic and parasympathetic outflow to cardiac conduction and myocardium. Sympathetic activation results in an increased heart rate and conduction velocity, enhances cardiac contractility and performance especially in physiological stress. Parasympathetic activation generally decreases heart rate and contractility. There are also multiple neuromodulators that affect the balance between SNS and PNS: Brain-derived and C-type natriuretic peptides, Angiotensin II, Neuropeptide Y, Vasoactive intestinal Peptide, Nitric Oxide.

Deregulation in function and structure of either central or peripheral components of the Autonomic Nervous System (SNS and PNS) is associated with prominent Cardiovascular manifestations. These might include:

- Autonomic failure: this has not been shown to be associated with SAH.
- Paroxysmal sympathetic hyperactivity (PSH): This has been shown to be associated with SAH.
- Stress-induced Cardiomyopathy (SIC): This is a form of acquired acute heart failure. Also known as Takotsubo cardiomyopathy and has been described in SAH. It has been proposed to be caused by catecholamine surge that may result in coronary artery spasm or cardiac microvascular dysfunction.
- Sudden cardiac death (SCD): Definition: unexpected deaths because of cardiac arrest in temporal proximity (usually within 1 hour) to the triggering event without another known pathogenesis[16]. This occurs most frequently in patients with a preexisting

coronary artery disease, but neurological injury can cause SCD by inducing fatal arrhythmias or massive myocytolysis and cardiac infarction.

There has also been a lot of research into the release of catecholamine's either systemically or within the actual myocardium itself. It has been shown that catecholamine's can produce ECG abnormalities in patients with no clinical apparent heart disease and can produce cardiac lesions identical with those found in SAH patients[5]. Corticosteroids are also thought to play role in potentiating cardiotoxic effects of catecholamines. They cause a decrease in the total body exchangeable potassium, which depletes the myocardial intracellular potassium, causing the cell to be prone to injury. Autopsy studies of patients with SAH revealed areas of subendocardial and myocardial lesions. Cropp and Manning et al found that post-mortem studies revealed a macroscopically normal heart but there were histological lesions present in form of myocytolysis in 80% of patients with SAH, and in those that had these lesions 70% had ECG abnormalities[5]. There has been no proven significant relationship between plasma levels of norepinephrine and the presence of ECG abnormalities in patients with SAH[10]. With regards to Cardiac enzymes (Troponin T), elevated serum levels are found in some patients with SAH and ECG abnormalities, but this is not a consistent finding[10].

Yasser L Sakr et al looked at the relationship between ECG abnormalities and neurological outcome in patients with aneurysmal SAH[9]. He found that 66.7% of patients had abnormal ECGs within 24 hours of the initial insult, and they had no prior

history of ischaemic heart disease. Of these 83 % were repolarisation abnormalities. It was found that ST segment abnormalities (especially depression) related to poorer prognosis and this was reflected in higher APACHE II (Acute physiology and chronic evaluation) scores and higher World Federation of neurological societies (WFNS)[11] and Hunt and Hess grades – see figure 3[13,14] and 4[15]. This might mean that the presence of ST segment depression in patients presenting with aneurysmal SAH may denote a poorer prognosis.

GRADE	ORIGINAL WFNS	MODIFIED WFNS
1	GCS 15	GCS 15
2	GCS 13-14 Without focal neurological deficits	GCS 14
3	GCS 13-14 With focal neurological deficits	GCS 13
4	GCS 7-12	GCS 7-12
5	GCS 3-6	GCS 3-6

Figure 3: WFNS Grade in SAH[13,14]

Grade	Description
I	Asymptomatic or minimal headache and slight nuchal rigidity
II	Moderate to severe headache, nuchal rigidity, no neurological deficit (except cranial nerve palsy)
III	Drowsiness, confusion, or mild focal deficit
IV	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances
V	Deep coma, decerebrate rigidity, moribund
*Serious systemic disease such as hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease, and vasospasm on angiography result in next less favourable category.	

Figure 4: Hunt and Hess Grade: Used to Classify Severity of Sub-Arachnoid Haemorrhage[15].

1.2 SERUM TROPONIN T LEVELS AND NON-TRAUMATIC SUB-ARACHNOID HAEMORRHAGE

The Troponin complex regulates the contraction of striated (skeletal and cardiac) muscles and it is made up of 3 subunits[12]. These are Troponin C, T and I. Troponin C binds to calcium ions. Troponin T binds to tropomyosin and attaches the complex to the muscle filament. Troponin I bind to actin and decreases Troponin C affinity for calcium and inhibits actin-myosin interactions. Cardiac and skeletal Troponin T is encoded by different genes and therefore the proteins produced are distinct from each other. This allows tests to differentiate between Cardiac Troponin T/I and skeletal Troponin T/I. With regards to Troponin C, skeletal and cardiac forms are indistinct, so no assays have been developed to distinguish between the two. Most of cardiac Troponin is bound to myofilaments and 3-8% of the total is free in the cytosol. When the sarcolemmal membrane of the cardiomyocyte is disrupted, initially the Troponin from the cytoplasmic pool is released. This is the followed by a more protracted release from quantities bound to deteriorating myofilaments. The cardiac Troponin begins to rise in 3-4 hours after the myocardial injury and will remain increased for 10-14 days. Cardiac Troponin T is a biomarker of myocardial injury. It is more specific for myocardial damage than creatinine kinase but is not always indicative of an ischaemic injury[12]. In a retrospective study by Ahmed N. Mahmoud et al, it was found that 37% of patients admitted with spontaneous SAH had elevated Troponin T levels[6]. They also showed by univariate analysis that elevated Troponin T level increased the risk of patient death in hospital. But this risk was lost in multivariable regression analysis. Cardiac Troponin T is a specific marker for cardiac lesions, but its downfall is that it is too sensitive. It does not

differentiate cardiac necrosis from just a cardiac lesion. Increased levels can also be found in other conditions (stroke, acute myocarditis, acute pericarditis, sepsis, pulmonary embolism, heart failure, renal insufficiency)[12]. In this study we will look at serum high-sensitivity Troponin T (hs-cTnT), as this is the test offered at Chris Hani Baragwanath Hospital. Most conventional assays detect hs-cTnT in very few normal patients, but some hs assays detect Troponin-T in nearly 100 percent depending on population. Therefor detectable values with a high sensitivity assay should not automatically be considered abnormal.

1.3 PROGNOSTICATION

In a study by Ibrahim et al, it looked at whether ECG abnormalities could predict which patients would develop angiographic vasospasm after aneurysmal SAH[8]. The pathophysiology of vasospasm is not clearly understood but one of the proposed mechanisms, as discussed earlier, is a pathological hyperactivity of the Sympathetic nervous system (SNS). This is also one of the mechanisms that are thought to account for the ECG abnormalities found in SAH. It was found that female sex, high subarachnoid clot burden, WFNS grade 4-5, clipping and prolonged QT interval were associated with higher incidence of angiographic vasospasm. It was found that a tachycardia was the strongest independent predictor of angiographic vasospasm. When tachycardia and ST changes were present during the risk period for vasospasm, this predicted poor patient outcome[8]. This will not be assessed in my study.

At CHBAH, where limited resources are available, it is important to have evidence to use to advocate resources to specific investigations. In the patient population of this hospital, is the prevalence of ECG abnormalities like what has been reported around the world? And if so, should it be routinely monitored and investigated in these patients from a cardiac perspective. Normally patients with SAH are delayed in getting into CHBAH neurosurgical unit due to various factors. These factors include late presentation, delayed referral, lengthy time awaiting CT scans and bed shortages.

1.4 STUDY AIMS AND OBJECTIVES

The aim of this study is to assess the prevalence of ECG abnormalities or increased serum hs-cTnT level in patients presenting with non-traumatic SAH at CHBAH, a predominantly black African population... To the author's knowledge, there has not been a study in South Africa looking at the prevalence of these two parameters. In the South African public health sector, where resources are limited and there are delays transferring and in diagnosis, factors that will help to further prognosticate patients are very important. Although this was not an aim of this study, it could be looked at in further expansion of this study.

This current research projects objectives are as follows:

i. To assess the prevalence of ECG abnormalities in patients presenting with non-traumatic SAH

ii. To assess the prevalence of raised hs-cTnT levels in patients presenting with non-traumatic SAH

iii. To identify if there is an association between raised hs-cTnT levels and ECG abnormalities in patients presenting with non-traumatic SAH

iv. To compare the WFNS grade in patients found to have ECG abnormalities or raised serum hs-cTnT levels vs. Those with normal ECG and normal hs-cTnT levels

2. MATERIALS AND METHODS

2.1 STUDY DESIGN

This research project is a cross-sectional study. It was prospectively carried out at CHBAH from the 15th January 2019 to the 11 October 2019.

2.2 STUDY LOCATION AND POPULATION

Patients were referred to the Neurosurgical unit at this hospital and were all inpatients. This department serves not only the population of Soweto but is the main referral hospital for Sebokeng, Leratong, Natalspruit, Kopanong and Tshepong hospitals

All patients were either directly admitted to CHBAH or were referred from one of the previous mentioned referral hospitals. They were triaged in casualty and then referred on to the Neurosurgical registrar on call for assessment. All patients 18 years and older, all sex and races presenting with non-traumatic SAH (diagnosed on non-contrast CTB) were included in this study.

2.3 DATA COLLECTION

The patient's hospital files were used to collect the necessary data needed for this study. A non-contrast CT Brain for each patient was reviewed (done on the hospital PACS system) and reported on by consultant radiologist. CT angiograms were done for all

participants, the nature of the reported pathology was collected for data analysis. A 12 lead ECG was done for each patient and analysed along with the serum hs-cTnT results.

A data collection sheet (Annexure A) was used to record data from participant's files by the author. The inclusion criteria were all patients older than 18 years diagnosed with non-traumatic SAH. All non-traumatic SAH were diagnosed via non-contrast CTB and reported on by a Radiology consultant. Additional investigations such as a CT angiogram of the brain was included in the data sheet. No patients were excluded based on not having a CTA. All patients had at least one 12-lead ECG done within the first 7 days of their hospital presentation. The post resuscitation WFNS score within the first 24 hours of presentation at CHBAH was documented. This was calculated using the recorded GCS and clinical findings of the patient noted in their hospital files.

No patients were excluded from the study because a known cardiovascular history of previous myocardial infarction or previously diagnosed cardiac arrhythmia. This was set up to exclude patients with possible pre-existing ECG abnormalities that would not be related to the current SAH presentation.

ECG's for each participant were reviewed by the author and a consultant physician (Dr Jonathan Hooijer) looking at the rate, rhythm and morphological waveform changes (Annexure A table 2). If there had been a dispute between these findings, then a second consultant physician will have been asked to review the participants ECG. This was not necessary. Each participant had a hs-cTnT peripheral blood test done as part of routine blood set. These results were correlated with the presence of ECG abnormalities. Data collection was planned over 12-month period.

The hs-cTnT levels were arranged in categories (normal, between 15-100 and >100 ng/L) and ECG abnormalities were in a binary format (yes/no). The following variables were also categorical:

- Age: 18-30 years, 31-40 years, 41-50 years, 51-60 years, greater than 60 years
- Race: Caucasian, African, Indian
- Sex: Male or female
- WFNS grade: 1, 2, 3, 4, 5
- CTB additional findings: None, Intraventricular haemorrhage, Intracerebral haemorrhage, Ventriculomegaly
- CTA findings: Arteriovenous malformation, Aneurysm, Normal, Not done

2.4 DATA ANALYSIS

Statistical analysis was undertaken using the Stata/MP 13.0 program with help from The Philip Tobias Statistics centre.

Absolute numbers expressed as proportions were calculated for gender, sex, age category, race, CTB additional findings, CTA findings, abnormal or normal ECG and type of ECG change. hs-cTnT will be a continuous variable.

ECG's were all performed within 7-days of symptom onset. QT intervals on ECG's are commonly calculated using the Bazet formula - which usually over or under corrects for bradycardias and tachycardias. The Frederica formula was used to assess QT intervals in

this study as it is more reliable. Sokolow Lyon voltage criteria was used to determine left ventricular hypertrophy.

Expanding on the hs-cTnT, the result will be divided into normal (<15 ng/L), positive (15-100 ng/L) and high positive (>100 ng/L). These have been expressed in the form of frequency tables. A Fisher's exact test will be used to evaluate the association between abnormal/ normal ECG and normal/ positive hs-cTnT levels (>15 ng/L), and the association between normal/ abnormal ECG and WFNS grade. Statistical significance was considered significant when a p-value was less than 0.05.

2.5 ETHICS

This study was approved by the Human Research Committee (Medical) at the University of the Witwatersrand with Clearance Certificate Number M180963 – see appendix B. Informed consent was obtained from each participant or from their immediate family if the participant was incapable of giving consent– see appendix F. Participants or their families were given study information sheets which explained surrounding the study and the information required from each participant – see appendix E. All identifying information were removed from the data sheet and only a study number was used. All the information required will be obtained from the patient's hospital files, the hospital PACS (Picture Archiving and Communicating System) and the National Health Laboratory System results portal.

3.0 RESULTS

3.1 RECORDS REVIEWED

A total of 40 patients with non-traumatic SAH presented to CHBAH or were referred from peripheral hospitals during the period of 15th January 2019 to 11th October 2019. Of these 40 patients, 5 demised before either an ECG or a hs-cTnT level could be done and 3 presented outside the 7-day period post onset of symptoms. Only 32 patients met the criteria for this research project. Their medical records, radiology reports and laboratory results were obtained and reviewed.

3.2 DEMOGRAPHIC DETAILS

The demographic data collected for this research project included age (arranged categorically), sex and race. They were organised into frequency tables.

In this study 59.38% (n=19) of patients were female and 40.63% (n=13) of patients were male as seen in Table 3.1.

Table 3.1: Gender frequency

GENDER	FREQ.	PERCENT (%)
FEMALE	19	59.38
MALE	13	40.63
TOTAL	**32**	**100.00**

The age of the participants was arranged in 5 categories. The frequency of each age category was as follows (table 3.2):

- 18-30 years: 15.63% (n=5)
- 31-40 years: 9.38% (n=3)
- 41-50 years: 31.25% (n=10)
- 51-60 years: 34.38% (n=11)
- >60 years: 9.38% (n=3)

Table 3.2: Age Frequency

AGE (YEARS)	FREQ.	PERCENT (%)
18-30	5	15.63
31-40	3	9.38
41-50	10	31.25
51-60	11	34.38
>60	3	9.38
TOTAL	**32**	**100.00**

In this study 78.13% (n=25) of patients were African, 12.5% (n=4) where white, 3.13% (n=1) were Indian and 6.25% (n=2) were mixed race (table 3.3).

Table 3.3: Race Frequency

RACE	FREQ.	PERCENT (%)
AFRICAN	25	78.13
INDIAN	1	3.13
MIXED RACE	2	6.25
WHITE	4	12.50
TOTAL	**32**	**100.00**

3.3 WFNS GRADE

The distribution of WFNS grade was as follows: 25% (n=1) had a grade of 1, 21.88% (n=7) had a grade of 2, 9.38% (n=3) had a grade of 3, 31.25% (n=10) had a grade of 4 and 12.5% (n=4) had a grade of 5 (table 3.4). 46.88% of participants in this study were either a grade 1 or 2.

Table 3.4: Frequency of WFNS Grade

WFNS GRADE	FREQ.	PERCENT (%)
1	8	25.00
2	7	21.88
3	3	9.38
4	10	31.25
5	4	12.50
TOTAL	**32**	**100.00**

3.4 CTB (NON-CONTRAST) FINDINGS

Every CTB had a SAH (inclusion criteria), but the author wanted to evaluate what was the most frequent associated pathology in addition to the SAH. The presence of an Intracranial haemorrhage, Intraventricular haemorrhage and/or Ventriculomegaly was evaluated. Many patients had more than one additional finding. 18.75% (n=6) of patients had an SAH only (table 3.5.1), 65.63% (n=21) had also an Intraventricular haemorrhage (table 3.5.1), 50% (n=16) had also an Intracranial haemorrhage (table 3.5.2), and 25 % (n=8) had ventriculomegaly (table 3.5.3).

Table 3.5.1: Frequency of additional CTB findings: IVH

CTB_IVH	FREQ	PERCENT (%)
NO	11	34.38
YES	21	65.63
TOTAL	**32**	**100.00**

Table 3.5.2: Frequency of additional CTB Findings: ICH

CTB_ICH	FREQ.	PERCENT (%)
NO	16	50.00
YES	16	50.00
TOTAL	**32**	**100.00**

Table 3.5.3: Frequency of additional CTB Findings: HCP

CTB_HCP	FREQ.	PERCENT (%)
NO	24	75.00
YES	8	25.00
TOTAL	**32**	**100.00**

Table 3.5.4: Frequency of additional CTB Findings: SAH only

CTB_SAH ONLY	FREQ.	PERCENT (%)
NO	**26**	**81.25**
YES	**6**	**18.75**
TOTAL	**32**	**100.00**

3.5 CTA FINDINGS

All patients had a CTA done after the non-contrast CTB. 81.25% (n=26) were found to have an aneurysm (table 3.6.1) on CTA. 6.25% (n=2) were found to have an AVM (table 3.6.2) and 12.5% (n=4) the CTA was found to be normal (table 3.6.3).

Table 3.6.1: Frequency of CTA Findings: Aneurysm

CTA_ANEURYSM	FREQ	PERCENT (%)
NO	6	18.75
YES	26	81.25
TOTAL	**32**	**100.00**

Table 3.6.2: Frequency of CTA Findings: AVM

CTA_AVM	FREQ	PERCENT (%)
NO	30	93.75
YES	2	6.25
TOTAL	**32**	**100.00**

Table 3.6.3: Frequency of CTA Findings: Normal

CTA_NORMAL	FREQ.	PERCENT (%)
NO	28	87.50
YES	4	12.50
TOTAL	**32**	**100.00**

3.6 ECG FINDINGS

ECG's were assessed as being normal or not. There was no exclusion of specific ECG changes and they were all performed within 7-days of symptom onset. 87.5% (n=28) of patients were found to have an abnormal ECG. Only 12.5% (n=4) were found to have a normal ECG (table 3.7).

Table 3.7: Frequency of Normal and Abnormal ECG

ECG_ABNORMAL	FREQ.	PERCENT (%)
NO	4	12.50
YES	28	87.50
TOTAL	**32**	**100.00**

3.7 HIGH SENSITIVITY TROPONIN-T RESULTS

hs-cTnT levels were taken within 7-days of initial symptoms. According to the NHLS reference ranges for hs-cTnT interpretation in suspected Acute Coronary Syndrome (ACS), a value greater than 100 ng/L (WHO rule-in level) would rule-in ACS. A value of less than 15 ng/L would rule out ACS. A value between 15-100 ng/L would mean that the patient is at possible risk of ACS. hs-cTnT results were tabulated as negative (<15 ng/L), positive (15-100 ng/L) and high positive (>100 ng/L). In table 3.8, 43.75% (n=14) of patients had a negative hs-cTnT level. 43.75% (n=14) of the patients had a positive hs-cTnT result. Only 12.5% (n=4) were shown to have a hs-cTnT level greater than 100 ng/L (High positive). It is noted that the NHLS at CHBAH uses a Roche instrument to determine hs-cTnT levels.

Table 3.8: Frequency Normal, Positive and High positive hs-cTnT levels

TROP_NORMAL (<15 ng/L)	FREQ.	PERCENT (%)
NO	18	56.25
YES	14	43.75
TOTAL	**32**	**100.00**

TROP_POSITIVE (15-100 ng/L)	FREQ.	PERCENT (%)
NO	18	56.25
YES	14	43.75
TOTAL	**32**	**100.00**

TROP_HIGH POS (>100 ng/L)	FREQ	PERCENT (%)
NO	28	87.50
YES	4	12.50
TOTAL	**32**	**100.00**

The hs-cTnT results ranged from 0 ng/L to 336 ng/L, with the mean being 46.09 ng/L.

VARIABLE	RESULT (ng/L)
hs-cTnT (ng/L)	**46.09 +/- 79.35 (n=32)**

3.8 TYPE OF ECG CHANGES OBSERVED

ECG's were evaluated with regards to morphological waveform abnormalities and rate and rhythm changes. 40.63% (n=13) were found to have ST segment changes, 28.13% (n=9) had a prolonged QT interval, 65.63% (n=21) had t-wave changes, 12.5% (n=4) had a sinus tachycardia, 15.63% (n=5) had a sinus bradycardia and 53.13% (n=17) were found to have other ECG changes above those defined on the collection data sheet (table 3.9). Only 3.13% (n=1) was found to have U-wave changes. No patients were found to have Q-wave changes. Changes found that were grouped as 'other' included left ventricular hypertrophy, heart blocks, peaked p-waves, poor R-wave progression, prolonged PR interval and atrial flutter.

Table 3.9: Frequency of type of ECG changes

ECG_ST CHANGES	FREQ.	PERCENT (%)
NO	19	59.38
YES	13	40.63
TOTAL	**32**	**100.00**

ECG_LONG QT	FREQ.	PERCENT (%)
NO	23	71.88
YES	9	28.13
TOTAL	**32**	**100.00**

ECG_T-WAVE	FREQ.	PERCENT (%)
NO	11	34.38
YES	21	65.63
TOTAL	**32**	**100.00**

ECG_OTHER	FREQ.	PERCENT (%)
NO	15	46.88
YES	17	53.13
TOTAL	**32**	**100.00**

ECG_SINUS TACHY	FREQ.	PERCENT (%)
NO	28	87.50
YES	4	12.50
TOTAL	**32**	**100.00**

ECG_SINUS BRADY	FREQ.	PERCENT (%)
NO	27	84.38
YES	5	15.63
TOTAL	**32**	**100.00**

3.9 HYPERTENSION

Each participant/participants family member in this research project were asked whether they were known to be hypertensive on treatment or not. 59.38% (n=19) were not known to be hypertensive prior to this presentation. 40.63% (n=13) of patients were known hypertensives on treatment (table 3.10).

Table 3.10: Frequency of Hypertension

HPT	FREQ.	PERCENT (%)
NO	19	59.38
YES	13	40.63
TOTAL	**32**	**100.00**

3.10 ASSOCIATION BETWEEN ABNORMAL ECG'S AND RAISED hs-cTnT LEVELS

The presence of normal/abnormal ECG's was compared to normal/raised (total of both positive and high positive categories) hs-cTnT results in Table 3.11. There was no statistically significant difference with a p Value of 0.295.

Table 3.11: Fisher's exact test comparing ECG findings and Raised hs-cTnT results

ECG_ABNORMAL	TROP_POSITIVE		TOTAL
	NO	YES	
NO	3 75.00	1 25.00	4 100.00
YES	11 39.29	17 60.71	28.00 100.00
TOTAL	14 43.75	18 56.25	32 100.00

Fisher's exact = 0.295

3.11 ASSOCIATION BETWEEN WFNS GRADE AND ABNORMAL ECG's OR RAISED TROPONIN-T LEVELS

Comparing whether any specific WFNS grade was associated with abnormal ECG's showed no statistical significance with a p Value of 0.868 (table 3.12 and 3.14).

Comparing whether any specific WFNS grade was associated with a raised hs-cTnT (total of positive and high positive category) level no statistical significance was found (table 3.13); p Value was 0.461. The Fisher's exact test comparing only high positive hs-cTnT levels and WFNS grades also showed no clinical significance; p Value of 0.442.

Table 3.12: Fisher's exact test comparing WFNS grade to abnormal ECGs

ECG_Abnormal	WFNS_Grade					
	1	**2**	**3**	**4**	**5**	**Total**
No	2	1	0	1	0	**4**
	50.00	25.00	0.00	25.00	0.00	**100.00**
Yes	6	6	3	9	4	**28**
	21.43	21.43	10.71	32.14	14.29	**100.00**
Total	**8**	**7**	**3**	**10**	**4**	**32**
	25.00	**21.88**	**9.38**	**31.25**	**12.50**	**100.00**

Fisher's exact = 0.868

Table 3.13: Fisher's exact test comparing WFNS grade to raised Troponin-T level

Trop-T Positive	WFNS_Grade					
	1	**2**	**3**	**4**	**5**	**Total**
No	4 28.57	2 14.29	0 0.00	6 42.86	2 14.29	**14** **100.00**
Yes	4 22.22	5 27.78	3 16.67	4 22.22	2 11.11	**18** **100.00**
Total	**8** **25.00**	**7** **21.88**	**3** **9.38**	**10** **31.25**	**4** **12.50**	**32** **100.00**

Fisher's exact = 0.461

Table 3.14: Distribution of Abnormal ECG's to WFNS Grade

ECG ABNORMAL	WFNS GRADE					TOTAL
	1	**2**	**3**	**4**	**5**	
NO	2	1	0	1	0	**4**
YES	6	6	3	9	4	**28**
TOTAL	**8**	**7**	**3**	**10**	**4**	**32**

4. DISCUSSION

4.1 STUDY SAMPLE

A total of 40 patients were referred to the Neurosurgery department at CHBAH during the period of 15th January 2019 to the 11 October 2019 with non-traumatic SAH. This was less than the proposed sample size of 50 patients (more than calculated 30 required). The data collection was stopped early as the objectives could be assessed with the current sample size, based on an initial analysis that a sample size of 30 would be adequate for assessment, thus an extension of the data collection period was not warranted.. Out of the total 40 patients with non-traumatic SAH, 32 patients met the inclusion criteria laid down for this research project. The actual number of 32 is less than total number because of several reasons. Firstly, available beds are always a problem at CHBAH. So, patients must wait in peripheral hospitals until beds become available for transfer. This compromised the study by either patient arriving after the 7-day period for data collection or possibly having demised before transfer could take place (this occurred in 3 patients). CHBAH casualty/trauma departments have a high patient load and this is also transferred to the radiology department. Sometimes the time it takes for patients to be assessed, imaging to be done and then ultimately referral to the Neurosurgical unit could amount to 1-2 days. In patients that have a high mortality, unfortunately 5 patients demised before both an ECG and/or a serum hs-cTnT could be done. This equated to a 15% mortality, which is comparable to other literature for early mortality in patients with SAH that get to a medical facility[4]. Unfortunately, during the period of data collection, the Angiogram suite at CHBAH where Digital Subtraction Angiograms are done was not functional due to equipment problems. This could have

also further decreased sample numbers as some patients might have been directly transferred to Charlotte Maxeke Johannesburg Academic Hospital for a DSA instead of CHBAH.

This is a relatively small study compared to international standards[17].

4.2 DEMOGRAPHIC DETAILS

Demographic analysis of the research project reveals that gender distribution was skewed toward females at 59.38% compared to 40.63% being males. The reported ratio of female to male who present with an aneurysmal SAH is approximately 3:1[4]. In this study the ratio was found to be 1.4:1 marginally in favour of females. Keeping in mind this is a small sample size, there was an almost equal number of male and females.

This study showed a large proportion of patients fell into a younger age category compared to other well recognised studies (average ages), peak age for aneurysmal SAH being 55-60 years[4]. Around only 20% of cases occur between the ages of 15-45 years[4]. In this study, it was found that of the 26 patients that had an aneurysmal SAH on CTA, 34.61% (n=9) were between the ages of 41-50 years and 34.61% (n=9) were between the ages of 51-60 years. In this study 53.81% (n=14) of aneurysmal SAH were between the ages of 18-51 years and 46.15% (n=12) were 51 years or older.

Most referring areas to CHBAH predominantly comprise of patients of African descent. This is seen in this study with 78% of patients in this study being African.

4.3 WFNS GRADE

The higher the WFNS grade the poorer the prognosis. 46.88% of patients were found to either be a grade 1 or grade 2 indicating a better clinical grade. 31.25% of patients were found to be a grade 4. This is possibly indicative of the fact that higher clinical grades are less likely to reach a medical facility compared to the lower clinical grades.

4.4 CTB FINDINGS

SAH is complicated by ICH in 20-40%, by IVH in 13-28% and acute HCP in 15-20% of patients[4]. 3% of patients who did not have acute HCP on initial CTB will develop it within 1 week of SAH[4]. From the data collected in this study, the frequency of SAH complicated by ICH and HCP was comparable with above figures. The frequency of IVH was found to be two times higher than reported figures. This might be related to the aetiology of vascular lesions or the specific anatomical location of the ruptured aneurysm. Three specific aneurysms are associated with a higher incidence of IVH, these are basilar tip, anterior communicating and distal posterior inferior cerebellar artery aneurysms[4.] The actual anatomical location of the aneurysm or vascular malformation was not looked at in this study.

4.5 CTA FINDINGS

As discussed in the literature review, SAH secondary to ruptured aneurysm makes up 75-80% of patients[4]. 4-5 % of SAH is due to AVM and no cause can be determined in

14-22%[4]. Although the sample size in this study was small, the frequency of CTA findings was comparable.

It has been shown in some centres that CTA can demonstrate up to 97% of aneurysms[18] (this is centre dependent). The gold standard for evaluation of cerebral aneurysms is a DSA. It detects source of SAH in 80-85% of SAH, and the remainder are termed "angiographic negative SAH"[4]. In this study the category 'Normal CTA', patients went on to have a DSA to ensure that no aneurysm was missed.

4.6 ECG FINDINGS

Prevalence of ECG changes in literature ranges from 27%-100%[2,19]. This is a very wide range. Reasons suggested for this could be related to different study design, methods used for evaluation and definitions of ECG changes. With regards to this study figures of 87.5% were found. This is a high prevalence. Whether this has any prognostic implications was out of the scope of this study, but from literature there is a strong suggestion that it is prognostic. When looking at ECGs, all waveform and morphological abnormalities were noted. Some of these changes might not be directly related to SAH but because there is no statistical association between a specific ECG change and SAH in literature, the author felt all changes would be documented. From this analysis one could perhaps ascertain which changes were more prevalent. Also, of note, is that hypertension (previously diagnosed) was present in 40% of patients in whom ECG changes (e.g. LVH, t-wave changes) were found. Many of patients seen presenting to casualty for unrelated conditions are diagnosed with hypertension for the first time.

These patients might also have ECG changes, such as LVH, ST and T wave changes, due to uncontrolled hypertension. This might have added to the high frequency found in this study.

This high prevalence might have implications to the acute management of patients with SAH. The standard protocol is to maintain blood pressure at high normal ranges to ensure cerebral perfusion especially when vasospasm is present. This is done with intravenous fluids and vasopressors. In the setting of ECG changes with possible myocardial injury, this would have deleterious effects on patient outcomes.

4.7 hs-TROPONIN-T RESULTS

Multiple factors play a role in interpreting these results. hs-cTnT values were not taken at the same time period after onset of symptoms. This is due to the variability of presentation and referral. They were taken anywhere from the day of presentation to 7-days post symptom onset. In some participants the hs-cTnT levels were marginally elevated therefor it would be necessary to do a repeat level after 6 hours to ascertain a trend to interpret the result more accurately. This was not done. The prevalence found in this study was higher than in other studies. This could also be related to different tests done by different laboratories to measure levels (not a standardized test), different reference ranges used and whether hs-cTnT or conventional cTnT was evaluated. In patients with hs-cTnT levels >100 ng/L, further investigations would be required to rule out Myocardial infarction. From this study the author can state that there was a higher

prevalence of positive Troponin-T results compared to other literature, whether this relates to cardiac morbidity is uncertain.

4.8 TYPE OF ECG CHANGES OBSERVED

In literature reviewed, the most common morphological changes seen are related to T-Wave (large, broad, inverted), ST segment (elevation/depression) and QT interval (prolonged) abnormalities[2,4,5,10,17,19]. Rhythm abnormalities most frequently seen were sinus bradycardias and sinus tachycardias[2,4,5,10,17,18]. This research project reflects similar findings with the exception of U-wave changes. Big U-waves were seen in as much as 47% of patients in some series[19].

Most changes observed were like those seen in myocardial infarction. 'Other' ECG changes were found to be the most frequent in this study, within this category Left ventricular hypertrophy was most common, followed by T-wave changes, ST segment changes and then prolonged QT interval.

None of the patients in this study had had baseline ECGs prior to this presentation. Therefor it is not possible to say which changes were pre-existing and which changes occurred de novo at the time of the SAH.

4.9 HYPERTENSION

This was one variable that did not appear in any of the other studies the author came across. In South Africa the prevalence of hypertension in the 1998 Demographic and Health Survey was estimated at 21%, showing a slightly higher frequency in women

(14%) than in men (11%)[20]. This has increased to 77.3% in the 2008 Demographic and Health Survey[20]. This could be attributed to rapid urbanisation, an ageing population, increase in psychosocial stress, diet and lifestyle changes. It was found that 59.38% of patients were known hypertensives in this study. This is likely an under-estimation as some participants had features on ECG of chronic Hypertension but were not known to be. Hypertension is considered a risk factor for SAH[4].

7/17 patients that were found to have 'Other' ECG changes had features of left ventricular hypertrophy (41.18%). Of these, only 2/7 were known to be hypertensive. It is thus possible that there is a large proportion of patients with undiagnosed hypertension, only identified when they present for an unrelated illness.

As aforementioned, due to the high prevalence of diagnosed/undiagnosed hypertension in this patient population, this could have resulted in an over estimation of prevalence of ECG changes in this specific study group. However, because hypertension is a risk factor for SAH which could cause the same ECG changes, this would require further study. There could also be selection bias.

4.10 ASSOCIATION BETWEEN ABNORMAL ECG'S AND RAISED hs-TROPONIN-T LEVELS

When looking at this association, the idea was to see whether patients with ECG changes post SAH were more likely to have elevated hs-cTnT results. The p-Value using Fisher exact test was not significant (p-Value 0.295). This supports the theory surrounding the pathogenesis of ECG changes in patients with SAH as its related to a central increase in

sympathetic output and not to an intrinsic primary cardiac lesion. This is not to say that it cannot cause a secondary cardiac lesion or that central nervous system pathology and primary cardiac lesions cannot co-exist, but a larger sample size would be needed to explore this hypothesis.

When further analysis was done to evaluate if certain ECG changes were associated with a higher prevalence of a raised (total of positive and high positive categories) hs-cTnT levels, it was found that there was no statistical significance (Table 4.10).

The topic of cardiac transplantation comes to the forfront[5]. In SAH patients that are assessed for transplantation, when there are significant ECG changes in a patient with SAH, even though it is possible that there is no intrinsic cardiac lesion, this creates doubt as to whether the heart should be used for transplantation. Beta-blockage is known to be cardioprotective, and perhaps further thought into giving potential organ donors beta-blockers to help prevent cardiac damage from the detrimental effects of an overactive autonomic system should be given.

Table 4.10: p Values for ECG changes vs Raised Troponin-T

ASSOCIATION	**p-Value**
ST changes vs Raised Troponin-T	0.725
T-wave changes vs Raised Troponin-T	1.000
Prolonged QTc vs Raised troponin-T	1.000

Sinus Bradycardia vs Raised Troponin-T	0.631
Sinus Tachycardia vs Raised Troponin-T	0.613

The author then wanted to evaluate whether there was a statistical association between above mentioned ECG changes in table 4.10 and high positive hs-cTnT (>100 ng/L). Although none of the associations had statistically significant p-values, it's worthwhile to note that with Sinus Tachycardia vs High positive hs-cTnT the p-value was 0.066. Although not significant it is thought by the author that with a bigger sample size the trend might be to move towards significance. This could be indicative of higher sympathetic output in these patients, leading to greater cardiac damage and higher incidence of vasospasm which could relate to a possible higher morbidity.

4.11 ASSOCIATION BETWEEN WFNS GRADE AND ABNORMAL ECG'S AND RAISED hs-TROPONIN-T LEVELS

This was decided as an objective to evaluate if ECG changes were related to a specific WFNS grade. The assumption being that the higher the WFNS grade, the higher the risk of morbidity and mortality, the more likely a person was to have ECG changes. This would suggest that abnormal ECG's in this patient population might confer a poorer outcome. This was not found to be with a p-Value of 0.868. This was not statistically significant. When running a Fisher's exact test on ST-segment changes and WFNS Grade the p-value was found to be 0.085. Although this is also not statistically

significant, there is a possibility with larger sample numbers that this will approach 0.05. This then might suggest that when ST-segment changes are present that this confers a higher WFNS Grade and therefor poorer clinical outcome.

On analysis of positive hs-cTnT results and WFNS grade, again no statistical significance was found (p-value of 0.461). Comparing High positive hs-cTnT results and WFNS grade, the p- value was 0.442. This suggests that an isolated High Positive hs-cTnT does not infer a higher clinical grade with regards to WFNS grade.

6.0 LIMITATIONS

Limitations in this study can be looked at as related to either ECG's or hs-cTnT levels. Looking at ECG's first, they were done anytime from presentation to day 7. This was decided on because many patients are only referred to neurosurgical units on day 2 or 3, possibly even later if patient coming from referral hospital. ECG's are also not routinely done on all patients. If 48 hours was taken as cut-off for ECG's to be done (based on study by Di Pasquale et al[17], most ECG changes occur within first 48 hours), many patients would have been excluded. Importantly a single ECG is just a snapshot of a larger picture. Therefore it is not always representative of all changes that have occurred or resolved at the time it is done. In the study done by Di Pasquale et al[2], it was shown that in 90% of patients cardiac arrythmias were detected. They used 24-hour Holter ECG's which were done at time of admission. With just a single ECG, the frequency of arrythmias are likely to be an underestimated. Also, because no control ECGs were

performed it is not possible to prove a definitite causal relationship between NASAH and ECG changes.

Considering serum hs-cTnT sampling, again this was taken anytime from presentation to day-7 for the same reasons mentioned above. This makes it very difficult to interpret results with regards to positive levels and cardiac significance (myocardial ischaemia). What would have been required would be to repeat hs-cTnT levels 6 hours after first sampling was done to establish a trend in levels. It is also difficult to compare exact hs-cTnT levels to other studies as different centres and laboratories use different tests to analyse samples and have different reference ranges.

Further limitation was that the ECG and hs-cTnT were not necessarily done at the same time, so the ECG is not always a reflection of the cardiac electrical activity at time of hs-cTnT result. This perhaps could have affected the statistical associations between the two variables.

Not all patients had a CTA, and of those who did, only 6, were reported as having non-aneurysmal changes which, could only be analysed separately if a larger sample size were obtained and this was a desired objective.

Lastly, bed availability is always a limitation in state hospitals and this delays patient being transferred timeously. This affected the sample size.

6.0 CONCLUSION

This study shows a high prevalence of ECG changes in patients with SAH (87.50%) which is comparable to other studies around the world. This is the first study, to the authors knowledge, looking at this in South Africa. This high frequency warrants routine ECG's in patients presenting with SAH. This as a baseline ECG will also help when patients with SAH must be evaluated for cardiac complaints such as a possible myocardial infarction. The proposed reasons for this are mentioned. The prevalence of raised hs-cTnT levels was found to be higher (56.25%) in this study compared to other reviewed literature. This also has implications on investigating patients with an SAH for possible myocardial infarction. One must consider that these patients might have ECG changes and raised hs-cTnT levels but not be suffering from myocardial infarction.

No clinical significance was found with regards to the associations between ECG abnormalities and raised hs-cTnT results nor with ECG abnormalities/ Raised Troponin-T results and WFNS Grade. There was an indication that if the sample size was larger there might have been a statistical significance between the presence of Sinus Tachycardia and High positive Troponin-T results (p value of 0.066) as well as the presence of ST-segment changes and WFNS Grade (p-value of 0.085).

From this study, other prospective projects could be carried out looking at follow up ECG's in patients that had abnormal ECG's, this will help to ascertain which ECG changes were related to the SAH. A standardised study where ECG and hs-cTnT are done at the same time and within 48 hours of presentation. This will help to better correlate ECG changes found to hs-cTnT levels. It would also be helpful to describe the outcomes in these patients, seeing if there is a correlation between any variable and a higher mortality. Having shown significant correlation between SAH and ECG

abnormalities, a further prospective study may be warranted to assess the value of ECG changes with regards to prognostication of patients.

In our resource limited setting, any additional factors that will help in prognostication of patients is very valuable.

5.0 REFERENCES

1. Bederson JB, Connolly Jr ES, Batjer HH, Dacey RG, Dion JE, Diringer MN, Duldner Jr JE, Harbaugh RE, Patel AB, Rosenwasser RH. Guidelines for the management of aneurysmal subarachnoid haemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. Stroke. 2009 Mar 1;40(3):994-1025.
2. Benninger F, Raphaeli G, Steiner I. Subarachnoid haemorrhage mimicking myocardial infarction. Journal of Clinical Neuroscience. 2015 Dec 1;22(12):1981-2.
3. Chen Z, Venkat P, Seyfried D, Chopp M, Yan T, Chen J. Brain–heart interaction: cardiac complications after stroke. Circulation research. 2017 Aug 4;121(4):451-68.
4. Greenberg MS. SAH and aneurysms. Handbook of neurosurgery. 8th ed. New York: Thieme Medical. 2006;pg1156-1200.
5. Harries AD. Subarachnoid haemorrhage and the electrocardiogram-a review. Postgraduate medical journal. 1981 May 1;57(667):294-6.
6. Mahmoud AN, Elgendy AY, Mansoor H, Elgendy IY. Cardiovascular Abnormalities and in-Hospital All-Cause Mortality in Patients with Spontaneous Sub-Arachnoid Haemorrhage: An Observational Study. Cardiology and therapy. 2017 Jun 1;6(1):33-40.
7. Manea MM, Comsa M, Minca A, Dragos D, Popa C. Brain-heart axis-Review Article. Journal of medicine and life. 2015 Jul;8(3):266.
8. Ibrahim GM, Macdonald RL. Electrocardiographic changes predict angiographic vasospasm after aneurysmal subarachnoid haemorrhage. Stroke. 2012 Aug;43(8):2102-7.

9. Sakr YL, Lim N, Amaral AC, Ghosn I, Carvalho FB, Renard M, Vincent JL. Relation of ECG changes to neurological outcome in patients with aneurysmal subarachnoid haemorrhage. International journal of cardiology. 2004 Sep 1;96(3):369-73.

10. Sommargren CE. Electrocardiographic abnormalities in patients with subarachnoid haemorrhage. American Journal of Critical Care. 2002 Jan 1;11(1):48-56.

11. Winn HR. Youmans Neurological Surgery E-Book. Elsevier Health Sciences; 2011

12. Xu RY, Zhu XF, Yang Y, Ye P. High-sensitive cardiac troponin T. Journal of geriatric cardiology: JGC. 2013 Mar;10(1):102.

13. Drake CG. Report of World Federation of Neurological Surgeons Committee on a universal subarachnoid haemorrhage scale. J Neurosurg. 1988. 68: 985-6.

14. Sano H, Satoh A, Murayama Y, Kato Y, Origasa H, Inamasu J. Modified World Federation of Neurosurgical Societies subarachnoid haemorrhage grading system. World Neurosurg. 2015. 83: 801-7.

15. Hunt W. E, Hess R.M. Surgical Risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurgery 1968. 28(1): 14-20.

16. Tahsili-Fahadan P, Geocadin RG. Heart–brain axis: effects of neurologic injury on cardiovascular function. Circulation research. 2017 Feb 3;120(3):559-72.

17. Di Pasquale G, Pinelli G, Andreoli A, Manini G, Grazi P, Tognetti F. Holter detection of cardiac arrhythmias in intracranial subarachnoid haemorrhage. The American journal of cardiology. 1987 Mar 1;59(6):596-600.

18. Hoh BL, Cheung AC, Rabinov JD, Pryor JC, Carter BS, Ogilvy CS. Results of a prospective protocol of computed tomographic angiography in place of catheter

angiography as the only diagnostic and pre-treatment planning study for cerebral aneurysms by a combined neurovascular team. Neurosurgery. 2004; 54: 1329-40; discussion 1340-2.

19. Chatterjee S. ECG changes in subarachnoid haemorrhage: a synopsis. Netherlands Heart Journal. 2011 Jan 1;19(1):31-4.

20. Ntuli ST, Maimela E, Alberts M, Choma S, Dikotope S. Prevalence and associated risk factors of hypertension amongst adults in a rural community of Limpopo Province, South Africa. African journal of primary health care & family medicine. 2015;7(1).

ANNEXURE A

Table 1: Data Collection Sheets

Variable	Category	X
AGE (Years)	**18-30**	
	31-40	
	41-50	
	51-60	
	>60	
Gender	**Male**	
	Female	
Race	**Caucasian**	
	African	
	Indian	
WFNS	**1**	
	2	
	3	
	4	
	5	
CTB	**IVH**	
	ICH	
	HCP	

CTA	**Aneurysm**	
	AVM	
	Normal	
	Not Done	

Variable	**YES**	**NO**
ECG Changes		
Raised Troponin T		
Known Hypertension		

Table 2: Data Collection sheet for ECG changes observed

Morphological Changes	**Yes/No**	**Arrhythmias**	**Yes/No**
ST Segment (Depression or Elevation)		Sinus Tachycardia	
Abnormal Q waves		Sinus Bradycardia	
QTC interval (Prolonged or shortened)		Supraventricular	
T waves (inverted, flattened, peaked)		Ventricular	
Long QRS interval		Other	
U wave			

Other			

ANNEXURE B:

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Samantha Nash

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180963

NAME: (Principal Investigator)	Dr Samantha Nash
DEPARTMENT:	Neurosurgery Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	The prevalence of ECG abnormalities and abnormal Troponin T levels in patients with non-traumatic sub-arachnoid haemorrhage
DATE CONSIDERED:	28/09/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Christos Profyris
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	07/12/2018

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 on the Third Floor, Faculty of Health Sciences, Phillip 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 **September** and will therefore be due in the month of **September** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

ANNEXURE C:

a0018860:MMED_FInal_Thesis_Turnitin.docx

ORIGINALITY REPORT

9%	5%	3%	6%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to Midlands State University Student Paper	3%
2	depot.erudit.org Internet Source	1%
3	Pouya Tahsili-Fahadan, Romergryko G. Geocadin. "Heart–Brain Axis", Circulation Research, 2017 Publication	1%
4	ajcc.aacnjournals.org Internet Source	1%
5	"ESICM 2013 - Abstracts of Oral Presentations and Poster Sessions", Intensive Care Medicine, 2013 Publication	<1%
6	Submitted to The University of Manchester Student Paper	<1%
7	Submitted to University College London Student Paper	<1%
	phcfm.org	

8	Internet Source	<1%
9	psychology.wichita.edu Internet Source	<1%
10	James E. Wiseman, Negin Agange, Jeffrey C. Milliken. "Coarctation of the Aorta Presenting as Spontaneous Subarachnoid Haemorrhage in the Absence of Cerebral Aneurysm: A Report of a Rare Clinical Entity", Heart, Lung and Circulation, 2010 Publication	<1%
11	repository.up.ac.za Internet Source	<1%
12	www.hst.org.za Internet Source	<1%
13	Submitted to Riga Stradins University Student Paper	<1%
14	Submitted to Universiti Kebangsaan Malaysia Student Paper	<1%
15	Submitted to University of Stellenbosch, South Africa Student Paper	<1%
16	philender.com Internet Source	<1%

17	Student Paper	<1%
18	Tipper, G.. "Detection and evaluation of intracranial aneurysms with 16-row multislice CT angiography", Clinical Radiology, 200505 Publication	<1%
19	Submitted to University of Pretoria Student Paper	<1%
20	journals.lww.com Internet Source	<1%
21	Submitted to Sultan Qaboos University Student Paper	<1%
22	Huang, C.C.. "The 12-lead electrocardiogram in patients with subarachnoid hemorrhage: early risk prognostication", American Journal of Emergency Medicine, 201206 Publication	<1%
23	Katharina M. Busl, Mahesh Raju, Bichun Ouyang, Rajeev K. Garg, Richard E. Temes. "Cardiac Abnormalities in Patients with Acute Subdural Hemorrhage", Neurocritical Care, 2013 Publication	<1%
24	insights.ovid.com Internet Source	<1%

25	Ntuli, Samuel T., Eric Maimela, Mariannes Alberts, Solly Choma, and Sekgothe Dikotope. "Prevalence and associated risk factors of hypertension amongst adults in a rural community of Limpopo Province, South Africa", African Journal of Primary Health Care & Family Medicine, 2015. Publication	<1%
26	&NA;. "SOCIETY OF CRITICAL CARE MEDICINE 40TH CRITICAL CARE CONGRESS SAN DIEGO, CALIFORNIA, USA JANUARY 15–19, 2011 :", Critical Care Medicine, 12/2010 Publication	<1%
27	"Abstracts Programme", European Journal of Heart Failure, 2019 Publication	<1%
28	Submitted to University of Keele Student Paper	<1%
29	mafiadoc.com Internet Source	<1%

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

ANNEXURE D: CONSENT FROM CHBAH CEO

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 23rd August 2018

TITLE OF PROJECT:

The incidence of ECG Changes and how this relates Troponin T levels in patients found to have Non-Traumatic Sub-Arachnoid Haemorhage at Chris Hani Baragwanath Academic Hospital

UNIVERSITY: Witwatersrand

Principal Investigator: Dr Samantha Nash

Department: Neurosurgery

Supervisor : Dr C Profyris

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 23/08/2018

Approved/Not Approved
Hospital Management
Date: 31 08 2018

ANNEXURE E: PATIENT INFORMATION SHEET

STUDY INFORMATION DOCUMENT

Study title: The Prevalence of ECG Abnormalities and raised Troponin T levels in patients with Non-Traumatic Sub-Arachnoid Haemorrhage.

Thank you for considering being part of this research project.

Introduction:

I am doing research on Non-traumatic sub-arachnoid haemorrhage, and their relationship with Electrocardiograms and serum Troponin T Levels. Research is a process used in seeking new knowledge. In this study we want to learn if there is a correlation between non-traumatic sub-arachnoid haemorrhage and ECG changes as well as raised Troponin T levels. We want to obtain data like age, sex, and race of patients enrolled in this study as well as presence of ECG changes and Troponin T blood levels. This information will be compared with each other in an anonymous fashion. This information will possibly help us better to prognosticate patients in the future. An ECG is a non-painful, non-invasive test that helps us assess the electrical activity of the heart. Troponin T is a specific marker in the blood that can indicate possible damage to heart cells. It is used in general medicine as an indicator of a heart attack. In this study it will be used to assess if there is any damage to heart tissue in patients presenting with a sub-arachnoid haemorrhage.

We are asking you to take part in a research study.

What is involved in the study?

1. Enrolled patient's files will be used to obtain information about age, race, sex, blood results, electrocardiogram assessment, CT brain assessment.
2. The study will run from December 2018 to November 2019
3. Electrocardiograms are often performed in patients presenting with non-traumatic sub-arachnoid haemorrhage as presenting symptoms are sometimes similar to patients with cardiac events. A Troponin-T will be added to initial assessment bloods if not taken with these bloods. Blood specimens will not be kept.
4. The electrocardiogram will take 5 minutes to administer and is a non-invasive pain free procedure. Blood draw will also take about 5 minutes to perform and will be part of routine blood required for patient (not additional).
5. Only 2-3mls of blood is needed for the Troponin-T blood test and this is a once off test.

Risks of being involved in the study: There will be a small amount of pain experienced on blood taking. This is not additional pain to be experienced as routine bloods will always have to be taken by casualty staff and this test will be added on the request form.

Benefits of being in the study: There is no direct benefit to the Participant in this study. In the long term this study might help to better prognosticate patients presenting with non-traumatic sub-arachnoid haemorrhage and ECG changes. It can also better help us to be more aware of possible cardiac risks in these patients if the incidence is found to be significant.

Alternative procedures or courses of treatment that might be advantageous to the subject will be offered.

The Participant will be given pertinent information on the study while involved in the project and after the results are available if requested by participant.

A participant might be excluded from study if they are known to have had a previous heart attack or arrhythmias.

Participation is voluntary and refusal to participate will involve no penalty or loss of benefits to which the Participant is otherwise entitled. The participant may discontinue participation at any time without penalty, or loss of benefits to which the Participant is otherwise entitled. There is no requirement to provide a reason for withdrawing and any data collected on such a person will in default be destroyed, unless the Participant specifically consents to its retention.

Confidentiality: Normally personal information will be treated in the strictest confidence and will only be available to the Principal Investigator (PI) and his/her Supervisor, in the case wherein the PI is a postgraduate student. The only exceptions - and all of them are rare - would normally be:

1. personal information may be disclosed if required by law
2. the Human Research Ethics Committees of the University may exceptionally require personal data to respond to a formal complaint, or for a compliance audit

3. the South African Health Products Regulatory Authority (SAHPRA), which is the successor body to the South African Medicines Control Council (SAMCC), might conceivably require access to personal data, if investigating a drug trial

If results are published, this may, exceptionally, lead to cohort, or more rarely, individual identification. All data collected in the course of the study will be securely retained for two (2) years, if a scientific publication arises from the study and six (6) years, if there is no publication. Thereafter it will be destroyed accordingly.

Contact details of researcher/s:
Researcher: Dr Samantha Nash 011 933 8102 coconutmansam@gmail.com
Supervisor: Dr C Profyris 011 489 1011

Contact details of HREC administrator and chair – for reporting of complaints / problems.

This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg ("Committee"). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.

If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for reading this Study Information Sheet.

ANNEXURE F: PATIENTS CONSENT FORM

PARTICIPANT CONSENT SHEET

The Prevalence of ECG Abnormalities and raised Troponin T levels in patients with Non-Traumatic Sub-Arachnoid Haemorrhage at Chris Hani Baragwanath Hospital.

1. I have been given a Participant Information Sheet which explains the nature and processes involved in this study, which is attached hereto;
2. I was given time to read it, or had it read to me, in the language I best understand;
3. I was given time to ask any questions I wanted to and found any answers given to me to be reasonable and satisfactory;
4. I believe I fully understand why the study is being conducted and what the intended outcomes will be;
5. I understand that there will be no immediate benefit to me or my family member, should consent be given to participate, nor will there be a receivement of any payment; conversely, participation will not cost anything;
6. I understand that, even if initially consent to take part in the study is given, it can be subsequently withdrawn at any time and would not be required to give any reasons; if that happened, any data collected about me or my family member for the purposes of the study would immediately be destroyed, unless consent for it to be retained is given.
7. I have been given a range of contact details, listed below. If I require further information or become concerned about any aspect of this study I am free to speak to any of these contacts.

Contact details:

Dr Samantha Nash, Principal Investigator, telephone no. 011 933 8102, or by e-mail at coconutmansam@gmail.com,

Dr C Profyris, Supervisor, on telephone no. 011 489 1011

Professor CB Penny, Chairperson of the Human Research Ethics Committee (Medical) at the University of Witwatersrand, on telephone no. 011 717 2301, or by e-mail at Clement.Penny@wits.ac.za.
Ms. Z Ndlovu or Mr Rhulani Mkansi, Committee Secretariat, telephone nos.: 011 717 2700 or 1234, or by e-mail at: Zanele.Ndlovu@wits.ac.za or Rhulani.Mkansi@wits.ac.za

Name of Participant/ Guardian/ Relative: _____
Date: _____
Place: _____
Signature or mark _____

Witnessed by:

Name of Witness: _____
Signature: _____
Date: _____