UNIVERSITY OF CALGARY

Prevalence and Determinants of Myocardial Dysfunction associated with Severe Traumatic Brain Injury in Pediatrics

by

Audrey Lim

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCE

DEPARTMENT OF COMMUNITY HEALTH SCIENCES

CALGARY, ALBERTA

July, 2005

UNIVERSITY OF CALGARY

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Prevalence and Determinants of Myocardial Dysfunction associated with Severe Traumatic Brain Injury in Pediatrics" submitted by Audrey Lim in partial fulfillment of the requirements for the degree of Master of Science.

_____

Supervisor, Dr. Reginald Sauve, Department of Community Health Sciences

_____

Dr. Christopher Doig, Department of Community Health Sciences

_____

Dr. Mark Hamilton, Department of Clinical Neurosciences

_____

Dr. Alf Conradi, Department of Pediatrics, University of Alberta

_____

Dr. Bruce Culleton, Department of Medicine

July 6, 2005

Date

ABSTRACT

Objective: Myocardial dysfunction is a recognized phenomenon associated with severe brain injury in adults. However the incidence is unknown in pediatrics. The primary objective of this study was to determine the prevalence and clinical predictors of myocardial dysfunction in children with severe brain injury.

Design: A retrospective cohort study.

Setting: Pediatric intensive care units in academic tertiary care hospitals.

Subjects: All patients aged 1 month to 16 years with severe traumatic brain injury, Glasgow Coma Scale ≤ 8, admitted to the pediatric intensive care units.

Results: The prevalence of myocardial dysfunction in this study population was 31% (95% CI 23.0%, 40.6%). Amongst the children that succumbed to brain death (n=18), the prevalence of myocardial dysfunction was 77.8% (95% CI 52.3%, 93.6%). From multivariate analysis, PRISM III-12 score was a statistically significant predictor of myocardial dysfunction.

Conclusions: The prevalence of myocardial dysfunction in children with severe brain injury that succumbed to brain death is higher than in children without brain death.

ACKNOWLEDGEMENT

I would like to express my heartfelt thank you to God and the many people who have assisted and supported me through this endeavor. Firstly, I would like to thank my supervisory committee Drs Sauve, Conradi, Doig and Hamilton for their patience and guidance. A special thank you to Dr Sauve, my supervisor, for his advice, support and encouragement during this time.

I wish to express my gratitude to Vicki Stagg for her invaluable statistical assistance and Linda Lim for her editorial help.

Most of all, I would like to thank my husband and daughter and my mom for their love, support and understanding during the thesis.

Thank you!

DEDICATION

This thesis is dedicated to the children who have sustained severe brain injury and death.

TABLE OF CONTENTS

Approval page		ii
Abstract		iii
Acknowledgements		iv
Dedication		v
Table of Contents		vi
List of Tables		x
List of Figures		xii
CHAPTER ONE: INTRODUCTION		**1**
1.1	Introduction to the research problem	1
1.2	Significance of the problem	1
1.3	Literature review	2
	1.3.1 Sympathetic storm	4
	1.3.2 Neurogenic catecholamine cardiotoxicity	5
	1.3.3 Hormonal depletion	7
1.4	Purpose of the study	9
1.5	Research questions	10
	1.5.1 Primary questions	10
	1.5.2 Secondary questions	10
1.6	General objectives	11

1.6.1 Primary objectives 11

1.6.2 Secondary objectives 11

CHAPTER TWO: METHODOLOGY 12

2.1 General study design 12

2.2 Study population 12

2.2.1 Inclusion criteria 12

2.2.2 Exclusion criteria 13

2.3 Setting 13

2.4 Study period and sample size justification 14

2.5 Data collection procedure 15

2.5.1 Pediatric Risk of Mortality III scores 17

2.5.2 Questionnaire 18

2.6 Study variables 19

2.6.1 Outcome variable 19

2.6.2 Predictor variables 20

2.7 Statistical analysis 20

2.7.1 Descriptive statistics 20

2.7.2 Univariate and bivariate analysis 21

2.7.3 Multivariate analysis 21

2.8 Ethical considerations 21

CHAPTER THREE: RESULTS **22**

3.1 Descriptive statistics 22

3.1.1 Patient characteristics 22

3.1.2 Indicator of severity of injury 25

3.1.2.1 GCS score 25

3.1.2.2 PRISM III score 25

3.1.3 Mortality data 25

3.2 Outcome variable: Myocardial dysfunction 28

3.2.1 Bivariate analysis 31

3.3 Multivariate analysis 34

3.3.1 Model building: Backward stepwise method 34

3.3.1.2 Collinearity 37

3.3.1.3 Interaction 42

3.3.1.4 Final parsimonious model 43

3.4 Procurement data 46

3.5 Pattern of inotrope use 56

CHAPTER FOUR: DISCUSSION **60**

4.1 Study overview 60

4.2 Overview of study findings 60

4.2.1 Primary research objectives 61

4.2.1.1 Prevalence of myocardial dysfunction 61

4.2.1.2 Clinical determinants of myocardial dysfunction 63

4.2.1.3 Multivariate analysis 65

4.2.2 Secondary research objective 66

4.5 Strength 68

4.5.1 Impact on clinical care 68

4.6 Limitations 69

4.7 Recommendation for future studies 70

REFERENCES **72**

APPENDIX 2.1: Head injury codes found in ICU patients 83

APPENDIX 2.2: Brain injury data form 87

APPENDIX 2.3: The Pediatric Risk of Mortality III score 95

APPENDIX 2.4: Questionnaire 96

APPENDIX 2.5: Questionnaire cover letter 97

LIST OF TABLES

Table 3.1	General patient characteristics, indicator of severity of injury and cranial CT findings	24
Table 3.2	Clinical characteristics of patients by survival status	27
Table 3.3	Summary of the questionnaire in the assessment of myocardial dysfunction and donor cardiac function	29
Table 3.4	Population characteristics and bivariate analysis of patients with and without myocardial dysfunction	33
Table 3.5	Categories of PRISM III-12 score and proportion of myocardial dysfunction	35
Table 3.6	Exploring six variables in a full model of myocardial dysfunction	36
Table 3.7	Exploring variable “brain death” in the model of myocardial dysfunction	37
Table 3.8	Exploring variable “GCS score” in the model of myocardial dysfunction	38
Table 3.9	Exploring the two variables of “brain death” and “GCS score” in the model of myocardial dysfunction	38
Table 3.10	Stepwise model building of predictive model of myocardial dysfunction with variable “revised PRISM III-12 score”	40
Table 3.11	Summary of the likelihood ratio tests of dropping variables “GCS	42

score", "brain death" and "PRISM III-12 score"

Table 3.12 Testing for interactions between variables in the model building 42

Table 3.13 The final parsimonious model of predictors of myocardial dysfunction 43

Table 3.14 Summary of the diagnostic model testing with Goodness-of-fit test and the Receiver Operator Characteristic Curve 44

Table 3.15 Cardiac donors with myocardial dysfunction 47

Table 3.16 Cardiac donors without myocardial dysfunction 52

LIST OF FIGURES

Figure 3.1	The Receiver Operator Characteristic Curve of the parsimonious model of the predictors of myocardial dysfunction	45
Figure 3.2a	Graph of the pattern of dopamine use in four cardiac donors with myocardial dysfunction	49
Figure 3.2b	Graph of the pattern of epinephrine use in three out of four cardiac donors with myocardial dysfunction	50
Figure 3.2c	Graph of the pattern of norepinephrine use in two out of four cardiac donors with myocardial dysfunction	51
Figure 3.3a	Graph of the use of dopamine in 1 donor without myocardial dysfunction	53
Figure 3.3b	Graph of the use of norepinephrine in 1 donor without myocardial dysfunction	54
Figure 3.3c	Graph of the use of neosynephrine in 1 donor without myocardial dysfunction	55
Figure 3.4	Pattern of inotrope use in patients with myocardial dysfunction and brain death	57
Figure 3.5	Pattern of inotrope use in patients with myocardial dysfunction where care was withdrawn	58

CHAPTER ONE: INTRODUCTION

1.1 Introduction to the research problem

Acute intracranial hypertension secondary to severe traumatic brain injury (1, 2), subarachnoid hemorrhage (SAH) (3, 4), status epilepticus (5-7) and in brain injuries culminating in brain death (8-10) can lead to significant neurogenic cardiopulmonary complications. This is well documented in the adult literature. In the pediatric population, profound myocardial dysfunction associated with severe brain injury is a clinically important phenomenon, however it has not been well recognized. It is imperative to have a better understanding of neurogenic cardiovascular dysfunction in pediatrics as it has significant implications in the management of children with severe brain injury, as well as organ management in children who unfortunately have succumbed to brain death.

1.2 Significance of the problem

The incidence of brain death among patients admitted to the pediatric intensive care unit is 0.9% (11), with trauma being the most common admitting diagnosis. One of the important sequelae of severe brain injury is myocardial dysfunction. While myocardial dysfunction associated with severe cerebral injury leading to brain death has been a reported phenomenon in 10% to 42% of adults (10, 12, 13), the incidence of myocardial dysfunction associated with acute brain death is currently unknown in the pediatric population as it has not been studied systematically.

Presently there is only one study in pediatrics reporting echocardiographic evidence of systolic left ventricular dysfunction in 57% of pediatric patients who met brain death criteria (14). It is important to gain a better understanding of the associated myocardial dysfunction, as data from the International Heart Transplant Registry has shown that 25% of recipient deaths after transplantation were due to "cardiac failure" that was unrelated to acute rejection or infection. Many of the families are approached regarding organ donation after their child has been diagnosed with brain death. Awareness of these issues needs to be raised in order to identify successful donors and prevent the unnecessary loss of donor hearts. Therefore it is important to know the incidence and identify clinical determinants of myocardial dysfunction associated with acute brain death and the impact this has on potential cardiac donors in the pediatric population. Having a better knowledge of myocardial dysfunction associated with severe brain injury will also improve the management and help in the prognostication of these critically ill children.

1.3 Literature review

Since the 1940's, severe brain injury and brain death, have been recognized to produce myocardial dysfunction characterized by hemodynamic instability (10), electrocardiographic and echocardiographic alteration, myocardial isoenzyme release and histopathological changes (12, 15-18). The histological changes most commonly described are contraction band necrosis (15), focal coagulative necrosis, subendocardial

petechial hemorrhage, edema formation, interstitial mononuclear cell infiltration and myocyte eosinophilia (12). Gulinanes et al (19) have also shown through animal studies that there was profound alteration in cardiac contractility underlying the hemodynamic derangement associated with brain death.

A large number of cases of electrocardiographic changes associated with acute neurological injury have been reported in adults (20-22). The abnormalities seen include ST segment elevation and depression, T wave inversion, J wave or the Osborn wave, prolonged QT interval and pathological Q waves (23). Mayer et al (24) reported that the presence of either inverted T waves or severe QTc prolongation on a 12-lead ECG had a sensitivity of 100% and a specificity of 81% for predicting left ventricular dysfunction in adult patients with brain injury. The combination of electrocardiographic change and myocardial injury in SAH is a common example of neurogenic cardiovascular dysfunction seen in adult critical care (3).

Brain death also causes significant biventricular systolic dysfunction that may contribute to early postoperative cardiac failure in heart transplant recipients (25) and complicate the histological interpretation of rejection.

Several animal studies (26-29) have been done to delineate the cause of myocardial dysfunction associated with severe cerebral injury. Yeh et al. has demonstrated with a balloon expansion rabbit model that acute increased intracranial pressure (ICP) causes select changes in myocardial gene expression and this is implicated in ventricular remodeling in myocardial dysfunction associated with acute brain death (30). Other proposed mechanisms of myocardial injury include excessive catecholamine

release known as sympathetic storm, catecholamine toxicity, and hormonal depletion associated with rapid disintegration of the hypothalamic-hypophyseal axis.

1.3.1 Sympathetic storm

It has been well known that brain death causes massive neuronal depolarization and excessive catecholamine release. During intracranial hypertension when the ischemic threshold of the brain was overcome, a decrease in heart rate, mean arterial pressure, and cardiac output were observed. With further increase in the ICP there is progressive cerebrospinal ischemia beginning in the cerebrum and progressing to the pons, medulla oblongata and the spinal cord in an orderly rostrocaudal fashion. With further progression of the ischemia as it approaches the brain stem, there is mixed vagal and sympathetic stimulation which gives rise to the Cushing response, which is a triad of bradycardia, hypertension and irregular breathing pattern (31-33). There is also clinical and experimental evidence to support an association between intracranial hypertension and hypothalamic lesions (34). Experimental evidence suggests that the insula has a cardiac chronotropic organization, and may be involved in the genesis of arrhythmias seen in epilepsy or after cerebral hemorrhage or stroke. Insular cortex involvement may predispose the patient to sudden cardiac death.

Shivalkar et al (33) demonstrated that irreversible myocardial damage could be caused by a sudden increase in ICP created by inflation of Foley catheter balloon in the cerebral ventricles in dogs. Novitzky et al (35) also showed that baboons undergoing bilateral sympathectomy prior to an increase in ICP did not have any evidence of

myocyte injury on histological examination, while baboons with incomplete or no cardiac denervation developed evidence of myocyte injury. Cardiac lesions can occur very quickly after brain death when the ICP is acutely raised, however, when the ICP is built up slowly, the hemodynamic changes and cardiac structural damage are less intense. These typical lesions are believed to be caused by sympathetic storm and catecholamine excess that occurs during the process of brain death (36-41).

Clinical evidence shows that patients dying of acute intracranial lesions large enough to produce acute intracranial hypertension show scattered foci of transmural myocardial injury. These myocardial lesions were not seen in patients dying of noncerebral causes (37). Also, patients dying within a few hours after the sudden increase in ICP did not reveal such damage. From autopsy studies of patients dying at various periods after sudden increases in ICP, it appears that focal myocardial damage requires at least six hours for development, and up to 12% of the patients dying from acute cerebral lesions show such cardiac damage (33, 37, 42, 43).

1.3.2 Neurogenic catecholamine cardiotoxicity

The sympathetic mediated catecholamine storm may play a major role in the pathophysiology of both neurogenic cardiovascular dysfunction and neurogenic pulmonary edema via the resultant acute ventricular dysfunction and catecholamine cardiotoxicity. Catecholamines affect the cardiac potential by contributing to early and late afterdepolarizations, which predispose patients to cardiac arrhythmias (23). The final common pathway to late afterdepolarization involves increase in the intracellular

calcium, which in turn causes activation of an ionic channel that conducts a transient inward current that may reach a threshold amplitude and thereby produce a sustained arrhythmia.

The myofibrillar necrosis noted in more recent studies is histologically similar to the cardiac lesions seen with catecholamine infusions (44), physiologic stress with or without exogenous corticosteroids (45, 46), nervous system stimulation in animals (47, 48), and reperfusion of transiently ischemic cardiac muscle (49, 50). Furthermore, it is also similar to the so-called "catecholamine cardiomyopathy" described in human pheochromocytoma (51). Norepinephrine is known to stimulate synthesis of adenosine 3', 5' cyclic phosphate, which causes opening of calcium channels with influx of calcium and efflux of potassium. Persistently high levels of norepinephrine may result in failure of the calcium channels to close, leading to cell death and causing the classical contraction band necrosis seen histologically (23). Free radicals released as a result of reperfusion or by metabolism of catecholamines to the toxic metabolites adrenochrome may contribute to cell membrane damage and cell death. Free radicals inactivate enzymes and cause lipid peroxidation. The enzymes targeted by free radicals include calcium stimulated ATPase and Na^+, K^+-ATPase in the sarcoplasmic reticulum which causes an increased efflux and decreased reuptake of calcium by the sarcoplasmic reticulum, leading to calcium overload (45).

The pathogenesis of catecholamine cardiotoxicity is attributed to relative hypoxia that occurs because of the direct stimulation of the myocardium, the coronary microcirculatory effect, membrane permeability alteration, catecholamine oxidation

products, and other contributory pathogenic factors (39). Excessive catecholamine administration or release exceeding physiological levels may deplete the energy reserves of cardiac muscle cells. This leads to the complex biochemical and subsequent structural changes.

1.3.3 Hormonal depletion

Significant reductions in plasma levels of hormones in adult patients with brain death, particularly the thyroid hormones, have been documented by several authors (52-61). In animal studies, following the induction of brain death, a rapid reduction of free triiodothyronine (FT3) and thyroxine (T4) have been observed (62). Plasma TSH (thyroid stimulating hormone) remained unchanged, however reverse triiodothyronine (rT3) rose markedly (54, 60). This pattern of thyroid hormone profile corresponds to the "euthyroid sick syndrome" state (8). Thyroid hormones are needed in the regulation of cellular metabolism of proteins, lipids and carbohydrates through complex effects on DNA and messenger RNA (63). Triiodothyronine (T3) is also an important regulator of Na^+, K^+-ATPase in the heart. The lack of active thyroid hormones can lead to cellular metabolic disturbance and a shift to anaerobic metabolism affecting various organ functions. There is also a reduction in antidiuretic hormone, cortisol, and insulin levels which may play an important role in the kinetic circulatory changes. These endocrine changes and the diffuse cellular mitochondrial injury are associated with reduction in myocardial energy phosphates, ATP and glycogen, as well as significant tissue lactate accumulation

suggesting impairment of aerobic metabolism (62). Myocardial high energy stores are depleted and subsequently cardiac function deteriorates (64).

In order to investigate the hypothesis that hormonal depletion leads to myocardial injury, Galinanes et al used a rat model after hypophysectomy (19). Hypophysectomy induced a deterioration of cardiac contractile function that was identical to the cardiac dysfunction induced by brain death, however it is irreversible. In the absence of disruption of the hypothalamic-pituitary axis, the cardiac dysfunction associated with brain death may be reversible. These observations have important potential implications for post-transplant cardiac function.

There is considerable evidence from both experimental and clinical studies that brain death is associated with neuroendocrine changes however, the link between brain death and disruption of the hypothalamic-pituitary axis remains controversial. Other research has demonstrated increased levels of thyroid hormones, cortisol and normal levels of insulin in humans and animals after brain death (65). Galinanes (19) proposed that these differing results might be explained, in part, on the basis of differences in species and experimental conditions, as well as the wide variety of causes of brain injury in the clinical situation, which may influence the timing and severity of any hypothalamic-pituitary insufficiency.

Advocates of supplemental T3 therapy such as Novitzky et al (66) reported that supplemental T3 therapy in brain dead potential organ donors led to improvement of metabolic and hemodynamic derangements, and reversal from anaerobic to aerobic metabolism. T3 leads to reactivation of the mitochondria, stimulating aerobic metabolism

(67). The adverse metabolic changes seemed to be reversed leading to maintenance of myocardial high energy stores, and resulting in an improvement in donor cardiac function (68-73). The mechanism by which T3 improves hemodynamics and cardiac function appears to be two-fold; the immediate extranuclear effects include increased mitochondrial respiration, increased amino acid and glucose transport across cell membranes resulting in increased contractility, and the later effects of nuclear binding with induction of mRNA and modulation of protein synthesis.

1.4 Purpose of the study

Neurogenic cardiovascular dysfunction is a known phenomenon in adults. It is a complex problem of neuro-cardiac axis interaction that has significant implications with regards to managing both pediatric and adult brain-injured patients who may be potential organ donors.

There is currently a paucity of pediatric studies on this subject. It is important to investigate the association of myocardial dysfunction associated with severe cerebral injury in children as the clinical presentation and determinants may be different compared to the adult population. It is also important to grasp the magnitude of this problem in pediatrics and to review the group of children with myocardial dysfunction associated with brain death in comparison to the group without brain death to understand the differences if any as this will impact on the acute management as well as successful organ donation.

To optimize the management of children with severe cerebral injury and myocardial dysfunction, the diagnosis of myocardial dysfunction must be made with accuracy. There are currently no universal criteria used in the evaluation of donor cardiac function. This information will be helpful in identifying successful donors and prevent the unnecessary rejection of donor hearts.

1.5 Research questions

1.5.1 Primary questions

1) What is the prevalence of myocardial dysfunction associated with severe traumatic brain injury (GCS ≤ 8) leading to brain death in children aged 1 month to 16 years?
2) What is the prevalence of myocardial dysfunction associated with severe traumatic brain injury (GCS ≤ 8) in children aged 1 month to 16 years who do not succumb to brain death?
3) What are the clinical determinants or predictors of myocardial dysfunction associated with severe traumatic brain injury (GCS ≤ 8) in children aged 1 month to 16 years?

1.5.2 Secondary questions

1) What are the criteria used across North America in the diagnosis of myocardial dysfunction in children with severe traumatic brain injury?

2) What is the impact of myocardial dysfunction associated with brain death on organ (heart) donation?

1.6 General objectives

1.6.1 Primary objectives:

1) To determine the prevalence of myocardial dysfunction associated with severe traumatic brain injury leading to brain death in the pediatric population (ages 1 month to 16 years old) using a retrospective cohort study design.
2) To compare the prevalence of myocardial dysfunction in children with severe traumatic brain injury in children who survives versus those who succumbed to brain death.
3) To determine the clinical determinants of myocardial dysfunction in children with severe traumatic brain injury.

1.6.2 Secondary objectives

1) To review the criteria used by the pediatric cardiac transplant centers in North America and Canada in the diagnosis of myocardial dysfunction in children aged 1 month to 16 years with severe traumatic brain injury.
2) To determine the impact of myocardial dysfunction associated with brain death on organ (heart) donation and procurement.

CHAPTER TWO: METHODOLOGY

2.1 General study design

The study was conducted by a retrospective chart review of all pediatric patients aged 1 month to 16 years admitted to the intensive care unit at the following three hospitals in Alberta: the Alberta Children's Hospital (Calgary), the Stollery Children's Hospital (Edmonton) and the Foothills Medical Centre (Calgary). The coordinators of the department of health records of each hospital were contacted and an exhaustive and comprehensive list of International Classification of Diseases-9 (ICD-9) and 10 (ICD-10) codes relating to head or brain injury and trauma was generated (Appendix 2.1). This was done in an attempt to capture all patients that were eligible to be included in this study.

A retrospective cohort study design was chosen for this study. There are currently no pediatric studies on this subject; therefore this serves as an exploratory study, the results of which can be used as a pilot for further research in this area.

2.2 Study population

Both the inclusion and exclusion criteria for this study were determined prior to commencing the chart review.

2.2.1 Inclusion criteria

All patients aged 1 month to 16 years admitted with the diagnosis of severe traumatic brain injury defined as having a Glasgow Coma Scale (GCS) score of less than

or equal to eight, with or without leading to brain death, were eligible for inclusion into this retrospective study.

2.2.2 Exclusion criteria

The exclusion criteria included any patients with the following:

1. Hypoxic ischemic encephalopathy
2. Non-traumatic brain injury
3. Congenital Heart Disease
4. Metabolic disorders
5. Cardiac contusion

Patients with the above diagnosis were excluded to eliminate any possibility of pre-existing primary heart disease or secondary heart disease from diseases such as metabolic disorders or hypoxic ischemic encephalopathy. Patients with pre-existing heart disease may potentially confound the determination of myocardial dysfunction associated with severe traumatic head injury, which is the outcome variable in this study. Patients with non-traumatic brain injury are excluded as the focus of this study is on brain injury sustained after trauma in otherwise healthy patients.

2.3 Setting

Calgary is a city set in Southern Alberta, a province with year 2002 population of 2.54 million. There are two pediatric intensive care units in the province of Alberta. These are located at the Stollery Children's Hospital in Edmonton and the Alberta

Children's Hospital in Calgary. The Foothills Medical Centre in Calgary is a tertiary hospital and the adult intensive care unit serves as an overflow unit for patients 14 to 16 years of age with severe trauma at times when the pediatric intensive care unit at the Alberta Children's Hospital is over the bed census and unable to accommodate the patient

2.4 Study period and sample size justification

The sample size is determined using the following calculation:

Sample size: $n = (196/10)^2 \pi (1- \pi)$

$= (384.16) (0.15) (1-0.15)$

$= 48.98$

The maximum discrepancy between the study sample and population is set at ± 10%, with 95% certainty that the discrepancy is within these limits ($Z = \pm 1.96$). π is the unknown population proportion that one is trying to estimate.

From the adult studies it is estimated that the incidence of myocardial dysfunction associated with brain death is 10% to 42% (10, 12, 13).For the purpose of this study, the incidence in the pediatric population, which is unknown at this time, is estimated to be 15%.

From the above calculation, a sample size of 50 patients is required to detect an estimated incidence of myocardial dysfunction of 15%.

The number of children who are admitted to the pediatric intensive care unit, with severe traumatic brain injury is approximated from previous census to be eight per year at the

Alberta Children's Hospital and 10 per year at the Stollery Children's Hospital. The number of patients aged 14 to 16 admitted to the Foothills Medical Centre with severe traumatic brain injury is estimated to be one to two patients per year. Therefore a six-year (January 1996 to December 2002 inclusive) retrospective chart review will yield a sample size of 114 patients. A larger sample size would be desirable but is not feasible, as children with severe traumatic injury with severe brain injury or brain death are small in numbers.

2.5 Data collection procedure

Medical record of all the patients generated from the appropriate ICD-9 or ICD-10 codes were retrieved and reviewed for inclusion or exclusion into the study.
All the medical records of patients that satisfied the inclusion criteria was systematically analyzed for demographic data (age, gender), relevant past medical history such as previous head injury, the cause of trauma, the GCS score recorded at the scene. The patient's course in the intensive care unit was summarized through hemodynamic and respiratory parameters as well as doses and types of inotropes used. The progression of neurological damage of patients who succumbed to brain death was carefully recorded and correlated with hemodynamic parameters during eight time periods – i) the emergency department, ii) admission into the intensive care unit,
iii) at maximal intracranial pressure recording, iv) an hour pre-declaration of brain death, v) at the time of brain death declaration vi) first period of donor maintenance, vii) second period of donor maintenance, and viii) at the time of organ procurement where data was

collected before the patient is transferred into the operating room. The doses of inotrope usage during the above time periods were recorded in a table format in an attempt to produce a continuum of the progression of the patient's cardiovascular and neurological status. The above information was also recorded for patients with severe brain injury who did not succumb to brain death.

The results of radiographic investigations such as cranial CT scans, electrocardiographic and echocardiographic findings were recorded together with any formal neurological testing and nuclear scans done for the declaration of brain death. Biochemical markers and investigations specifically Troponin levels and CKMB fractions results were collected. Information on neurological and cardiovascular management, resuscitation and neurosurgical procedures such as the insertion of ICP monitoring device and craniotomy were recorded. Data on organ procurement was collected and any missing information was then obtained from the Human Organ Procurement and Exchange (HOPE) program.

All the above data was uniformly collected using a data entry form (Appendix 2.2) specifically designed and entered into an ACCESS (Microsoft) database created for this study. The charts were reviewed by one investigator.

2.5.1 The Pediatric Risk of Mortality III (PRISM III) scores

The PRISM score is a validated scoring system that predicts mortality in critically ill children and provides a relative scale of severity of illness (74). The PRISM score is a second-generation physiology-based predictor initially derived from the Physiology Stability Index (75). The PRISM III is a validated third-generation pediatric physiology-based score for mortality risk (76) that was developed from a database consisting of 32 diverse pediatric intensive care units in the United States of America. In comparison to the PRISM scoring system, the PRISM III scoring system utilized more appropriate age-adjusted physiologic variable ranges, and a formal method for assessing mental status was established to account for the frequent use of sedation and paralysis in the critically ill children.

The PRISM III (Appendix 2.3) score has 17 physiologic variables subdivided into 26 ranges. In the validation of the PRISM III score, data was collected in the first 12 hours of stay (PRISM III-12) as well as the first 24 hours of stay (PRISM III-24) in the pediatric intensive care unit. Overall the PRISM III-24 model is more accurate for individual patient assessment of mortality risk as it incorporates the most information over the longest period of time, whereas the PRISM III-12 model is better for quality assessment since by shortening data acquisition time, it separates the observation from the treatment period (76).

The PRISM III scoring system is appropriate for use in this study of patients with severe trauma and head injury as the score was validated using 32 diverse pediatric intensive care units with critically ill patients including trauma and head injuries which

are similar to this study population. In this retrospective study, the PRISM III-12 and the PRISM III-24 scores served as a marker of severity of illness. It will be tested for its utility as a predictive variable for myocardial dysfunction.

For each patient in this retrospective study, a PRISM III-12 and a PRISM III-24 score was calculated retrospectively based on the data obtained on admission into the pediatric intensive care unit and the data obtained 24 hours into the admission into the pediatric intensive care unit respectively. The PRISM III-24 score was not able to be calculated for patients who were either transferred or deceased within 24 hours of their stay in the intensive care unit.

2.5.2 Questionnaire

There is currently no uniform standard method of assessing the cardiac function of potential donors for heart transplantation. To explore and review the current practices in North America, a questionnaire (Appendix 2.4) was mailed to 9 major cardiac centers at the following hospitals:

1. Alberta Children's Hospital, Calgary, Alberta, Canada
2. Stollery Children's Hospital, Edmonton, Alberta, Canada
3. Hospital for Sick Children, Toronto, Ontario, Canada
4. Montreal's Children's Hospital, Montreal, Quebec, Canada
5. B.C. Children's Hospital, Vancouver, British Columbia, Canada
6. Boston's Children's Hospital, Boston, Massachusetts, USA
7. Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

8. Loma Linda Children's Hospital, Loma Linda, California, USA
9. Arkansas Children's Hospital, Little Rock, Arkansas, USA

To ensure good response, a letter (Appendix 2.5) explaining the objectives of the study as well as the purpose of the questionnaire was electronically sent to the heads of the cardiology departments at each center. The responses received from the questionnaire were then summarized and described.

2.6 Study variables

2.6.1 Outcome variable

The outcome variable in this study is the presence or absence of myocardial dysfunction associated with patients with severe brain injury or brain death. Currently there is no clear operational definition available in the literature. The operational definition for myocardial dysfunction for this study is derived from the summary of the responses from the questionnaire sampling the current practices of assessing for myocardial dysfunction, as well as the patient's hemodynamic status, electroechocardiographic findings coupled with the need for inotropic support.

2.6.2 Predictor variables

The predictor variables are:

1. Age
2. Gender
3. Cause of injury
4. GCS score recorded at the scene
5. PRISM III-12 score
6. PRISM III-24 score
7. Presence or absence of brain death

2.7 Statistical analyses

All data analyses were performed using Stata Version 8.0 software (Stata Corporation, College Station, Texas, USA).

2.7.1 Descriptive statistics

Descriptive statistics were used to describe each variable separately using summary measures including means, medians and standard deviations. Descriptive statistics will be used to describe the study population. The prevalence of myocardial dysfunction associated with brain death in this population of children with severe traumatic brain injury was then calculated. The number of hearts procured from donors with or without myocardial dysfunction will be determined.

2.7.2 Univariate and bivariate analysis

Univariate analysis was first carried out to assess each variable's measure of central tendency and dispersion. Bivariate analyses using Pearson's chi square statistic was performed to explore the association between the outcome variable, myocardial dysfunction, and the seven predictor variables as listed above.
A level of statistical significance is set at p value of 0.05.

2.7.3 Mutivariate analysis

Mutivariate analysis was performed using logistic regression to explore a predictive model for myocardial dysfunction. Backward stepwise model building approach was used.

2.8 Ethical considerations

All patients' identifications were removed from the database to ensure patient confidentiality. Each individual hospital's procedure for review of medical records was adhered to. Ethics approval for reviewing of the medical records was not obtained, as it is not feasible to obtain written consent from each family.

CHAPTER THREE: RESULTS

3.1 Descriptive statistics

During the period of January 1996 to December 2002, a total of 406 patients were identified using predetermined ICD-9 and 10 codes (Appendix 2.1) and screened for inclusion criteria. Of the 406 patients, 366 charts were available for review. Forty charts at the Stollery Children's Hospital, between the periods of January 1996 to December 1998, were not available at the time of this study as they were archived on microfiche. Of the 366 charts reviewed, 69 out of 225 charts from the Alberta Children's Hospital, 36 out of 125 charts from the Stollery Children's Hospital and 10 out of 16 charts from the Foothills Medical Centre met the predetermined inclusion criteria making a total sample of 115 patients. This sample size satisfied the preset calculated sample size for the study of 114 patients.

3.1.1 Patient characteristics

General characteristics of the sample population are detailed as follows and shown in Table 3.1. There were a total of 66 (57%) boys and 49 (43%) girls making a male/female ratio of 1.3 : 1. The mean age was 9 years for both the boys and girls.

Majority of the injury was due to motor vehicle collision (60%), followed by fall (13%) and bicycle related injury (3.5%). Other injuries included skateboarding, skiing, riding in all terrain vehicle and toboggan accidents. There were 4 children (3%) that had suffered non-accidental injury.

All patients had at least one cranial CT scan done during admission. The most common cranial CT finding was skull fracture (53.0%), followed by cerebral edema (47.0%), effaced cisterns (25.0%), subdural hemorrhage (25.0%), contusion (22.6%) and DAI (diffuse axonal injury) (20.8%). The results of the above univariate analysis are presented in Table 3.1.

Table 3.1: General patient characteristics, indicator of severity of injury and cranial CT findings

Characteristics	n=115
Age, mean (SD), y	9 (5.1)
Gender (males:females)	66 : 49 (1.3 : 1)
Mechanism of injury	
Motor vehicle collision	69 (60%)
Passenger	49
Pedestrian	18
Driver	2
Fall	15 (13%)
Bicycle	4 (3.5%)
NAI	4 (3.5%)
Others	23 (20%)
PRISM 12, mean (SD)	11.4 (8.2)
PRISM 24, mean (SD)	10.0 (6.6)
GCS score, mean (SD)	5 (1.8)
CT head results	
Skull fracture	61 (53%)
Cerebral edema	54 (47%)
Cistern effaced	29 (25%)
Subdural hemorrhage	29 (25%)
Contusion	26 (22.6%)
DAI	24 (20.8%)
Subarachnoid hemorrhage	23 (20%)
Intraventricular hemorrhage	17 (14.8%)
Epidural hemorrhage	12 (10%)
Normal	9 (7.8%)
Uncal herniation	7 (6%)
Brainstem injury	7 (6%)
Infarction	3 (2.6%)

NAI: non-accidental injury

DAI: Diffuse axonal injury

3.1.2 Indicator of severity of injury

GCS score was used to assess the severity of the brain injury, and the Pediatric Risk of Mortality (PRISM III) score was used to assess the overall severity of illness.

3.1.2.1 GCS score

The mean GCS score of the patients recorded at the scene of injury was 5 (SD 1.8, n=115). The GCS score of each patient at presentation to the respective hospitals however was inconsistently recorded therefore meaningful analysis cannot be carried out.

3.1.2.2 PRISM III score

The mean Pediatric Risk of Mortality Score III-12 (PRISM III-12) score and the mean PRISM III-24 score for this study sample was 11.4 (SD 8.2, n=113) and 10 (SD 6.6, n=90) respectively. The PRISM III-24 score could not be calculated for patients who expired or who were transferred within the first 24 hours of their stay in the intensive care unit. As such only 90 patients had sufficient data for the PRISM-III 24 score to be successfully calculated.

3.1.3 Mortality data

Out of 115 patients, 87 survived (75.6%) and 28 were deceased (24.3%). The causes of death were as follows: 18 (64%) of the patients succumbed to brain death, 4 (14%) to cardiac arrest and 6 (21%) patients expired after care was withdrawn

following discussion with their families of the critical nature of the brain injury, severe hemodynamic compromise and extremely poor prognosis.

The mean age of the children who succumbed to brain death was 8.4 (SD 5.6) years old. The mean age of children who survived was 9.3 (SD 5.1) years old however there was no statistical significant difference.

The median GCS score at the scene was 3 for the group of patients who died of brain death compared to 6 for the patients who survived. The mean PRISM III-12 score for the patients who succumbed to brain death was 20 (SD 7.4) compared to 8.6 (SD 5.7) for the patients who survived and this difference was statistically significant.

The mean PRISM III-24 score was 19 (SD 6.2) for those patients who succumbed to brain death after 24 hours of stay. The PRISM III-24 score cannot be calculated for patients who expired within the first 24 hours. The median length to declaration of brain death for patients who succumbed was 2 days and the median length of stay in the intensive care unit for patients who survived was 5 days. The above results are presented in detail in Table 3.2.

Table 3.2: Clinical characteristics of patients by survival status.

	Brain death	**Other death**	**Survived**
	n=18 (15.7%)	n=10 (8.7%)	n=87 (75.6%)
Age, mean (SD), y	8.4 (5.6)	10.2 (4.9)	9.3 (5.1)
Females	6 (33.3%)	4 (40.0%)	39 (44.8%)
Males	12 (66.7%)	6 (60.0%)	48 (55.2%)
Mechanism of injury:			
Motor vehicle collision	14 (77.8%)	5 (50.0%)	50 (57.5%)
Fall	2 (11.1%)	1 (10.0%)	13 (14.9%)
NAI	2 (11.1%)	0	2 (2.3%)
Bicycle	0 (0.0%)	0	4 (4.6%)
Others	0	4 (40.0%)	18 (20.7%)
PRISM 12, mean (SD)	20.0 (7.4)*	21.1 (11.0)	8.6 (5.7)
PRISM 24, mean (SD)	19.0 (6.2)*	16.2 (8.3)	8.1 (4.85)
GCS score at the scene	3	5	6
(n=111) (median)			
Length of stay, days (median)			5
Time to death, days (median)	2	1.5	.

* p value <0.01

NAI: non-accidental injury

3.2 Outcome variable: Myocardial dysfunction

The primary outcome of this study was the prevalence of myocardial dysfunction of children with severe brain injury. To assess the current standard of practice in the determination of myocardial dysfunction and its effect on donor assessment, a questionnaire was sent to nine selected pediatric cardiac centers in Canada and the United States to explore and review the current practices in donor assessment and the determination of myocardial dysfunction. The response rate from the questionnaire was 56%. A summary of the responses from the questionnaire is summarized in Table 3.3. As can be seen from the summary of the responses, the general consensus used to determinethe presence of myocardial dysfunction were the patient's systolic and diastolic function, results of echocardiogram and the need for inotropic support. The criteria used in the acceptance or rejection of donor hearts were similar amongst the centers.

As such for the purpose of this study, the clinical criterion used in the case definition of myocardial dysfunction was developed with guidance from the results of the questionnaire as follows:

1) poor ventricular function defined as a shortening fraction of less than 23% on the echocardiogram and/or

2) the need for more than two inotropic support at any one time period, or

3) the need for more than one inotropic support for more than one time period.

There are 8 pre-determined time periods as previously described in the methodology.

Table 3.3: Summary of the questionnaire in the assessment of myocardial dysfunction and donor cardiac function

Pediatric cardiac center	**Investigations in assessment of potential cardiac donor**	**Criteria used in determination of myocardial dysfunction**	**Criteria used in acceptance of donor hearts**	**Criteria used in rejection of donor hearts**	**No. of potential cardiac donor per year**	**Cardiac transplants performed per year**
Loma Linda Children's Hospital	ECG ECHO	SF < 23%	SF >23% Absence of segmental hypokinesis Normal structure	SF <23% Important segmental wall motion abnormality	± 20	20 - 30
Hospital for Sick Children	ECG ECHO Troponin CKMB	-Function & use of inotropes	Stable on minimum inotropes Normal ECHO or mildly reduced function	Abnormal ECHO & ECG Multiple inotrope use		15 - 20

Pediatric cardiac center	**Investigations in assessment of potential cardiac donor**	**Criteria used in determination of myocardial dysfunction**	**Criteria used in acceptance of donor hearts**	**Criteria used in rejection of donor hearts**	**No. of potential cardiac donor per year**	**Cardiac transplants performed per year**
Stollery Children's Hospital	ECHO	Systolic & diastolic function	Normal function	Poor function	6	5
B.C. Children's Hospital	ECG ECHO Troponin	Systolic & diastolic function	Normal ECHO	Abnormal ECHO Ischemia on ECG Elevated troponin	1- 2	One performed in an emergency situation
Alberta Children's Hospital	ECG ECHO Troponin	Decreased systolic function by ECHO Elevated troponin	Normal systolic function No ischemia on ECG	Abnormal systolic function Abnormal structure	4-6	0

The objective of the above clinical criterion was to capture as many patients as possible with myocardial dysfunction especially patients who may not have had echocardiograms. Out of 25 (22%) patients who had echocardiograms done, 7 (28%) had shortening fraction less than 23%. Using the predetermined case definition of myocardial dysfunction, the prevalence of myocardial dysfunction in this study population was 31% (95% CI 23.0%, 40.6%) (Table 3.4).

3.2.1 Bivariate analysis

Bivariate analysis using Pearson's chi square statistic was performed to explore the association between the outcome variable - myocardial dysfunction and the seven predictor variables namely "age", "gender", "mechanism of injury", "PRISM III-12 score", "PRISM III-24 score", "GCS score", "brain death".

The results of the bivariate analysis showed that the association between myocardial dysfunction and the variables "brain death", "PRISM III-12 score" and "GCS score" were statistically significant. The prevalence of brain death (38.9%) was higher in those who had myocardial dysfunction than those who did not (5.0%) (p value < 0.01). The mean PRISM III-12 score was higher in patients with myocardial dysfunction in comparison to the patients who did not have myocardial dysfunction of 18 versus 9 (p value <0.01) respectively. For the patients with myocardial dysfunction, the mean GCS score at the scene was 4 (SD 1.8) compared to 6 (SD 1.7) for the group without myocardial dysfunction (p < 0.01). The differences in age, gender and mechanism of injury were not found to be statistically different between the two groups of patients. The

above results and the differences in the use of inotropes, the results of electrocardiograms and echocardiograms are presented in Table 3.4.

Table 3.4: Population characteristics and bivariate analysis of patients with and without myocardial dysfunction

	Myocardial dysfunction n=36 (31%)	**No myocardial dysfunction** n=79 (69%)
Age, mean (SD), y	8.5 (5.3)	9.6 (5.1)
Gender (males:females)	21:15	45:34
Mechanism of injury:		
Motor vehicle collision	24 (66.7%)	49 (62.0%)
Fall	4 (11.1%)	12 (15.2%)
NAI	3 (8.3%)	1 (1.3%)
Bicycle	0	4 (5.1%)
Others	2 (5.6%)	3 (3.8%)
PRISM 12, mean (SD) (n=112)	18.0 (9.5)* (n=35)	9.0 (5.6) (n=77)
PRISM 24, mean (SD) (n=90)	14.6* (7.4)(n=27)	8.2 (5.3) (n=63)
GCS (at scene), mean (SD) (n=111)	4.0 (1.8)	6.0 (1.7)
Brain death	14 (38.9%)*	4 (5.1%)
Max ICP, mean (SD)	53.5 (30.9)	46.6 (20.9)
Inotropes:		
Dopamine	33 (91.7%)* 95% CI (77.5%, 98.0%)	19 (24.1%) 95% CI (15.1%, 35.0%)
Epinephrine	25 (69.4%)* 95% CI (51.2%, 83.7%)	2 (7.4%) 95% CI (0.3%, 8.9%)
Norepinephrine	19 (52.8%)* 95% CI (35.5%, 69.6%)	0
ECG (n=52):		
Normal	4 (7.7%)	13 (25.0%)
ST segment changes	9 (17.3%)	8 (15.4%)
T wave abnormality	3 (5.8%)	6 (11.5%)
Arrhythmia	4 (7.7%)	2 (3.8%)
QTc > 0.49	4 (7.7%)	4 (7.7%)
ECHO (n=25):		
Normal	9 (36.0%)	7 (28.0%)
SF <23%	7 (28.0%) *	0
SF > 23%	9 (36.0%) *	8 (32.0%)
Decreased function	9 (36.0%) *	0

* p value < 0.01

NAI: non-accidental injury

3.3 Multivariate analysis

3.3.1 Model building: Backward stepwise method

Logistic regression was performed to explore a predictive model for the primary outcome of myocardial dysfunction. Backward stepwise model building approach was used using the seven clinical variables as listed in the bivariate analysis to develop the final multivariate regression model. First a full model consisting of the patient's clinically significant variables consisting of "brain death", "PRISM III-12 score", "GCS score", "gender", "mechanism of injury" and "age" was built and analyzed.

Clinically, the variable PRISM III-12 score should be fitted in the model rather than the PRISM III-24 score as PRISM III-24 score may have more interdependence with myocardial dysfunction and the score may be affected by the interventions that have been carried out in the intensive care unit during the 24 hours. In addition, there may be the possibility of interdependence and collinearity when PRISM III-24 score was used together with PRISM III-12 score. This meant that neither variable would remain a significant predictor if the other were present in the model. As such, PRISM III-24 score was not used for model building.

As the PRISM III-12 score was a continuous variable, the PRISM score was divided into clinically meaningful categories for the analysis. The PRISM III-12 score was divided into three categories and tested for its predictive utility of myocardial dysfunction as shown in Table 3.5.

Table 3.5: Categories of PRISM III-12 score and proportion of myocardial dysfunction

PRISM III-12 score categories	**Number with myocardial dysfunction** n=36	**Number of patients** n=113	**Proportion with myocardial dysfunction**
0 – 10	11	76	0.14
11 - 25	18	28	0.64
26 - 50	7	9	0.78

As can be seen in Table 3.5, the proportion of patients with myocardial dysfunction was increased as the PRISM III-12 score increases. In the PRISM III-12 score category of 26-50, the proportion of patients with myocardial dysfunction was 78%. The number of patients in each cell, especially in the PRISM III-12 category of 26 to 50, was small but combining the cells together would not be clinically justified.

A full clinical model using the variables brain death, PRISM III-12 score, GCS score, age, gender and mechanism of injury was developed and presented in Table 3.6. A cut off point of $p<0.05$ was used to determine which factors contributed to the model.

Table 3.6: Exploring six variables in a full model of myocardial dysfunction

Variable	**Odds ratio**	**P value**	**95% CI**
Brain death (yes vs no)	3.8	0.09	0.83, 17.86
PRISM III-12 ϕ			
11-25	7.7	**0.001**	2.23, 26.38
26-50	14.4	**0.018**	1.57, 131.5
GCS score*			
3	2.7	0.3	0.5, 14.6
4	1.0	0.9	0.14, 7.63
5	0.3	0.3	0.04, 2.51
6	0.3	0.3	0.03, 2.24
7	0.5	0.5	0.07, 3.9
Age (y)	1.0	0.76	0.9, 1.1
Gender (males vs female)	0.7	0.51	0.2, 2.1
Motor vehicle collision (MVC vs non-MVC)	0.5	0.28	0.15, 1.7

*GCS score 8 as the reference

ϕ PRISM III-12 score < 10 as the reference group

As can be seen from the full model, the variables that contributed significantly were PRISM III-12 score in the category of 11-25 and 26-50. The variables "age", "gender" and "MVC" did not contribute significantly to the model.

The variables "brain death" and "GCS score" may contribute more to the model when they are included into the model separately and this was examined in the following section.

3.3.1.2 Collinearity

The variable "brain death" was a statistically significant predictor of myocardial dysfunction when added to the model by itself with an odds ratio of 11.9 (p value 0.001) as shown in Table 3.7. This can be interpreted as the odds of having myocardial dysfunction in patients with brain death is 11.9 times compared to patients without brain death.

Table 3.7: Exploring variable "brain death" in the model of myocardial dysfunction

Variable	Odds ratio	P value	95% CI
Brain death	11.9	**0.001**	3.56, 39.95

Next, the variable "GCS score" was explored. In Table 3.8, a GCS score of 3 was a statistically significant predictor of myocardial dysfunction with an odds ratio of 5.6 (p value of 0.012). This is interpreted as the odds of having myocardial dysfunction in children with a GCS score of 3 is 5.6 times that of children with GCS score of 8.

Table 3.8: Exploring variable "GCS score" in the model of myocardial dysfunction

Variable	Odds ratio	P value	95% CI
GCS score*			
3	5.6	**0.012**	1.46, 21.53
4	1.8	0.47	0.35, 9.79
5	0.5	0.42	0.07, 2.98
6	1.0	1.0	0.20, 4.88
7	0.4	0.28	0.06, 2.28

*GCS score 8 as the reference

As can be seen from Tables 3.7 and 3.8, the variables "brain death" and "GCS score" were statistically significant predictors of myocardial dysfunction when added individually into the model. However, when the two variables were added together in the model, the variable "GCS score" became statistically insignificant (Table 3.9).

Table 3.9: Exploring the two variables of "brain death" and "GCS score" in the model of myocardial dysfunction

Variable	Odds ratio	P value	95% CI
Brain death (yes vs no)	7.7	**0.003**	1.99, 29.97
GCS score*			
3	3.12	0.11	0.76, 12.72
4	1.00	0.998	0.16, 6.14
5	0.46	0.42	0.07, 2.98
6	0.61	0.57	0.11, 3.35
7	0.29	0.21	0.04, 1.95

*GCS 8 as the reference

A possible explanation is the presence of collinearity amongst the variables “brain death”, “PRISM III-12 score” and “GCS score”. The components of the PRISM III-12 scoring system include the GCS score as well as the pupillary reflexes, therefore the variables “brain death”, “PRISM III-12 score”, “GCS score” may be predicting similar events and providing similar information of the severity of the underlying brain injury. For example, one of the criteria for the declaration of brain death is fixed, dilated pupil and one of the components in the PRISM III-12 score is pupillary reflexes classified into two categories of “one fixed pupil” and “both fixed pupils” respectively. Therefore in the patients who satisfied the clinical criteria for brain death, this will be reflected and included in the PRISM III-12 score.

The GCS score usually help in indicating the severity of the brain injury therefore both variables of “brain death” and “GCS score” may not be completely independent.

To investigate the possibility of collinearity between “PRISM III-12 score” and the “GCS score”, the PRISM III-12 score was recalculated removing the GCS score. This revised variable, “revised PRISM III-12 score” was then divided into three categories and added into the model as shown in Table 3.10.

Table 3.10: Stepwise model building of predictive model of myocardial dysfunction with variable "revised PRISM III -12 score"

Variable	Odds ratio	P value	95%CI
Brain death (yes vs no)	3.5	0.105	0.77, 16.05
Revised PRISM III-12 score$^{\phi}$			
11 - 20	7.02	**0.001**	2.13, 23.14
21 - 35	12.98	**0.017**	1.57, 107.33
GCS score*			
3	2.14	0.347	0.44, 10.43
4	0.90	0.918	0.13, 6.35
5	0.34	0.291	0.045, 2.52
6	0.32	0.257	0.043, 2.32
7	0.46	0.430	0.065, 3.21

*GCS score 8 as the reference

ϕRevised PRISM III-12 score <10 as the reference

As can be seen from Table 3.10, using the revised PRISM III-12 score did not make a difference in the model building, the variables "brain death" and "GCS score" remain statistically insignificant. The GCS score is just one of the components of the PRISM III-12 score, there may be other components of the PRISM III scoring system such as pupillary reflexes that may contribute to multi-collinearity. Further model building was done using the PRISM III-12 score.

The variables “age”, “gender”, and “MVC” did not appear to contribute significantly to the model. The likelihood-ratio test was used to test these findings. When the variables “age”, “gender” and “MVC” were dropped from the model, the p value from the likelihood-ratio test was 1.51, p value 0.68 (degrees of freedom=9), indicating that the variables dropped will not affect the model. Hence “age”, “gender” and “MVC” were not significant factors.

The next variable with p value more than 0.05 was the variable “GCS score”. The results of the likelihood-ratio test of dropping the variable “GCS score” was 13.16, p value 0.02 (degrees of freedom=9). This indicated that the variable “GCS score” should not be dropped from the model. Although the variable “GCS score” may not have statistical significance in the model, it does have clinical contribution to the prediction of myocardial dysfunction.

The variable “brain death” was dropped and the likelihood-ratio test yielded a result of 2.74 with p value of 0.098 (degrees of freedom=9). The results of the likelihood-ratio test indicated that dropping the variable “brain death” from the model may not have an influence on the final model as the p value was marginally insignificant.

The variable “PRISM III-12” was a significant predictor, in both categories, in the model as shown in Table 3.6. Therefore it should be kept in the final model. This is confirmed by the likelihood-ratio test yielding a result of 15.23 with a p value of 0.0005 (degrees of freedom=9). The results of the above likelihood-ratio test are summarized in Table 3.11.

Table 3.11: Summary of the likelihood ratio tests of dropping variables "GCS score", "brain death" and "PRISM III-12 score"

Variable dropped	Likelihood ratio chi square	P value	Degrees of freedom
GCS score	13.6	0.02	9
Brain death	2.74	0.098	9
PRISM III-12	15.23	0.0005	9

Thus, from the results of the likelihood ratio test the variables "PRISM III-12 score", "GCS score" should be included in the final model. The variable "brain death" may contribute to the final model of myocardial dysfunction.

3.3.1.3 Interaction

Next, interactions between the variables were assessed before building of the final model and the results are presented in Table 3.12.

Table 3.12: Testing for interactions between variables in the model building

Variable*	Coefficient	P value	95% CI
PRISM III-12 x brain death	0.163	0.93	-3.13, 3.46
Brain death x GCS score 3	0.118	0.95	-0.366, 3.90
Brain death x GCS score 4	-0.156	0.93	-4.48, 4.17
PRISM III-12 x GCS score	No observations		

*Brain death x GCS score 5 & 6 dropped due to collinearity

There were no interactions between the variables “PRISM III-12 score”, “brain death” and “GCS score” as shown in Table 3.12. Thus the above identified that the variables “PRISM III -12 score”, “brain death” and “GCS score” were independent variables influencing the risk of myocardial dysfunction.

3.3.1.4 Final parsimonious model

For the final model, the variable “PRISM III-12 score”, “GCS score” and “brain death” were fitted as presented in Table 3.13.

Table 3.13: The final parsimonious model of predictors of myocardial dysfunction

Variable	Odds ratio	Standard Error	P value	95% CI
Brain death (yes vs no)	3.5	2.72	0.105	0.77, 16.05
PRISM III-12*				
11-25	**7.02**	4.27	**0.001**	2.13, 23.14
26-50	**12.98**	13.99	**0.017**	1.57, 107.34
GCS score†				
3	2.14	1.73	0.35	0.44, 10.44
4	0.90	0.89	0.92	0.13, 6.36
5	0.34	0.35	0.29	0.05, 2.52
6	0.32	0.32	0.26	0.06, 3.20
7	0.46	0.45	0.43	0.07, 3.21

*PRISM III-12 scores < 10 as the reference group

†GCS 8 as the reference group

As can be seen from the Table 3.13, the only statistically significant contributor to the model was “PRISM III-12 score” in both categories. The p values of the other two variables “brain death” and “GCS score” were not significant and the 95% confidence interval crosses over 1.

To further assess the utility of the above model and models without the variables “brain death” and “GCS score” Goodness-of-fit test and Receiver Operator Characteristic Curve (ROC) were performed and the results are shown in Table 3.14.

Table 3.14: Summary of the diagnostic model testing with Goodness-of-fit test and the Receiver Operator Characteristic Curve

No.	Model with the following variables	No. of covariates	Goodness-of-fit test Pearson’s chi square	P value	l-ROC
1	Brain death, GCS scores, PRISM III-12 scores	22	15.2	0.295	**0.8585**
2	GCS scores, PRISM III-12 scores	14	6.63	0.357	0.8531
3	PRISM III-12 scores	3	0.00	.	0.7754

From the above diagnostic testing, the models 1 and 2 cannot be rejected with a p value of 0.295 and 0.357 respectively from the Goodness-of-fit test. Model 1 has the

largest area under the curve of 0.8585 from the l-ROC test signifying that the model has relatively good predictive power of myocardial dysfunction. The ROC curve is plotted in Figure 3.1. The standard errors of each variable were relatively small in the model as shown in Table 3.13.

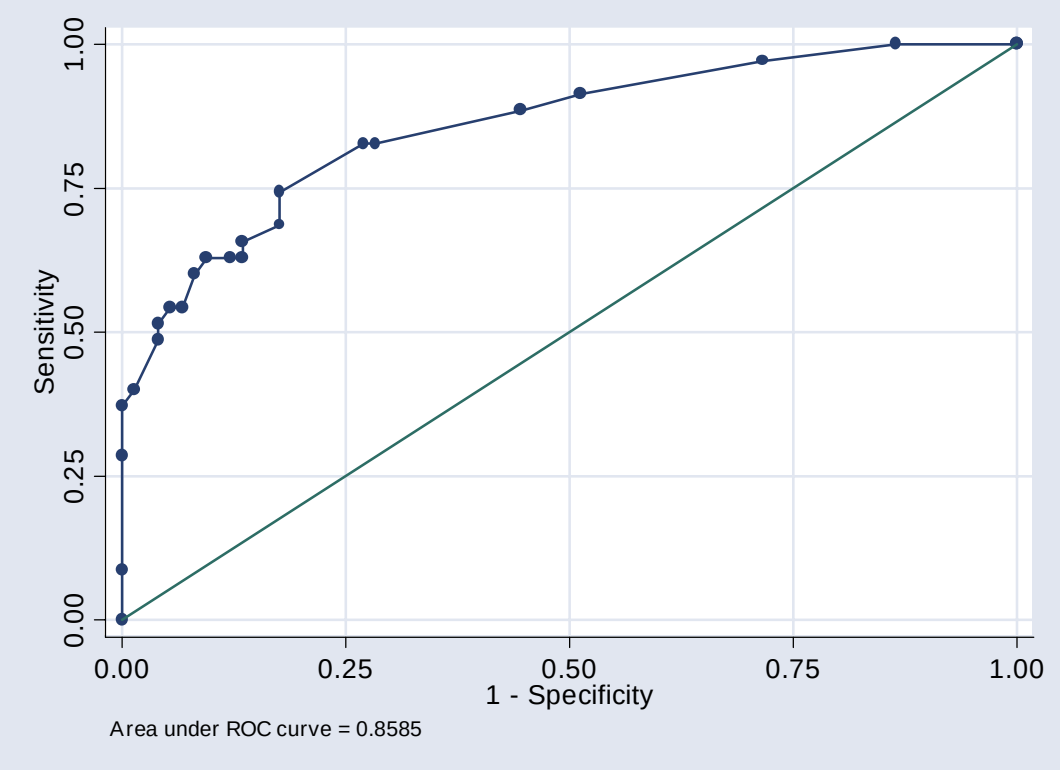


Figure 3.1: The Receiver Operator Characteristic Curve of the parsimonious model of the predictors of myocardial dysfunction

The Receiver Operator Characteristic (ROC) curve is a plot of sensitivity against 1-specificity and calculates the area under the curve. Sensitivity is the fraction of observed positive-outcome cases that are correctly classified; specificity is the fraction of

observed negative-outcome cases that are correctly classified. High values of sensitivity are desirable, the area under the ROC curve has been suggested as the most natural measure of the predictive strength of the logistic relationship.

A model with no predictive power would be a 45 degree line. The greater the predictive power, the more bowed the curve, and hence the area beneath the curve is often used as a measure of the predictive power. A model with no predictive power has an area of 0.5; a perfect model has an area of 1. The area under the ROC curve for this study was 0.8585.

In summary, the final clinical model of myocardial dysfunction consists of the variables "PRISM III-12 score", "GCS score" and "brain death" as shown in Table 3.13. However, the only predictor variable is "PRISM III-12 score". The odds of having myocardial dysfunction in children with a PRISM III-12 score of 11 to 25 is **7 times** that of children with PRISM III-12 scores of less than or equal to 10, controlling for brain death and GCS score. The odds of having myocardial dysfunction in children with a PRISM III-12 score of 26 to 50 is **13.5 times** that of children with PRISM III-12 scores of less than or equal to 10, controlling for brain death and GCS score.

3.4 Procurement data

The data on organ procurement, specifically the heart, was retrospectively reviewed in this study population. The mortality rate of this study population was 24%.

There were 18 patients who were clinically declared brain dead and consent for organ donation was given by 16 (89%) of these families. There were a total of 6 hearts, 14 sets of kidneys, 14 livers, 5 pancreas and 5 spleens procured.

To assess the impact of myocardial dysfunction on procurement of heart, the group of patients with hearts procured was analyzed. Four out of the six cardiac donors were classified as having myocardial dysfunction and the details are presented in Table 3.15.

Table 3.15: Cardiac donors with myocardial dysfunction

Study no.	Inotropes	Maximum dose required, mcg/kg/min	Shortening fraction, %	Cardiac arrest
22E	Dopamine	25	30- 50	No
	Epinephrine	0.3		
	Norepinephrine	0.4		
46A	Dopamine	20	32	In ER
	Epinephrine	0.5		
	Norepinephrine	0.25		
56A	Dopamine	20	36	No
	Epinephrine	0.1		
	Norepinephrine	1.5		
65A	Dopamine	20	17 -23	No
	Epinephrine	2		

As can be seen from the above Table 3.15, the shortening fraction measured by echocardiogram was normal for patients 22E, 46A and 56A while on inotropic support, except for patient 65A who had poor shortening fraction results. The use of inotropic support for this group of donors is presented graphically in Figure 3.2a, b, c.

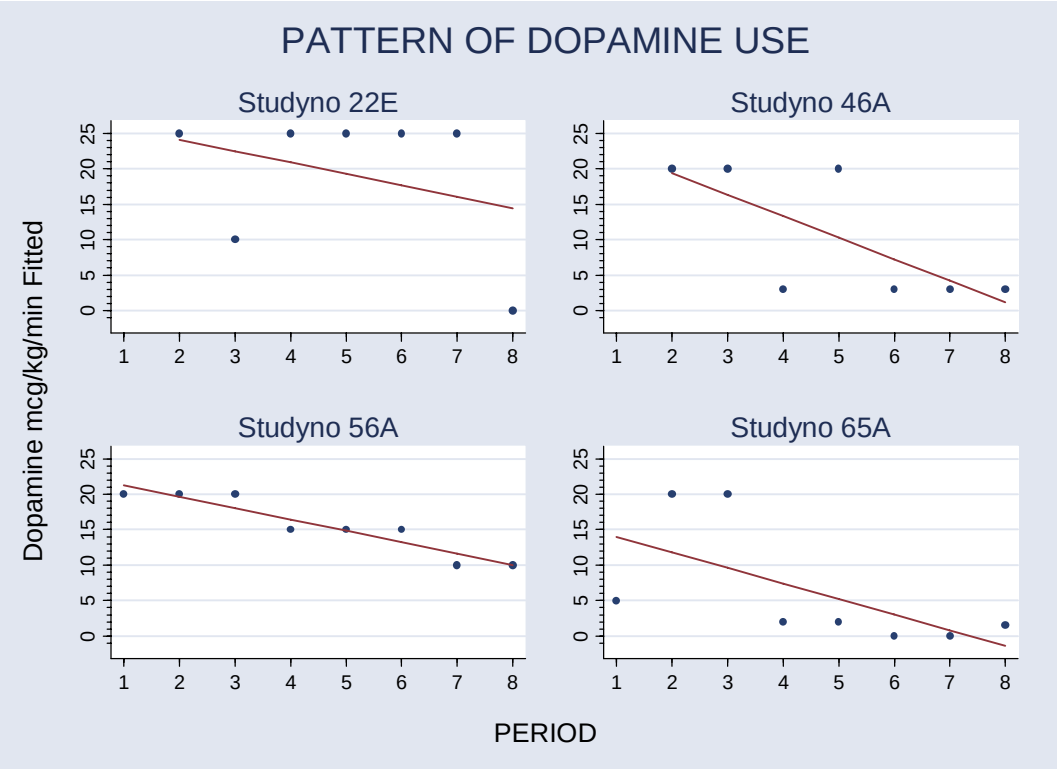


Figure 3.2a: Graph of the pattern of dopamine use in four cardiac donors <u>with</u> myocardial dysfunction

Period:

1: Emergency; 2: Following admission into ICU; 3: Time of maximum ICP; 4: Hour pre-declaration of brain death; 5: Declaration of brain death; 6: Donor maintenance time 1; 7: Donor maintenance time 2; 8: Time of procurement

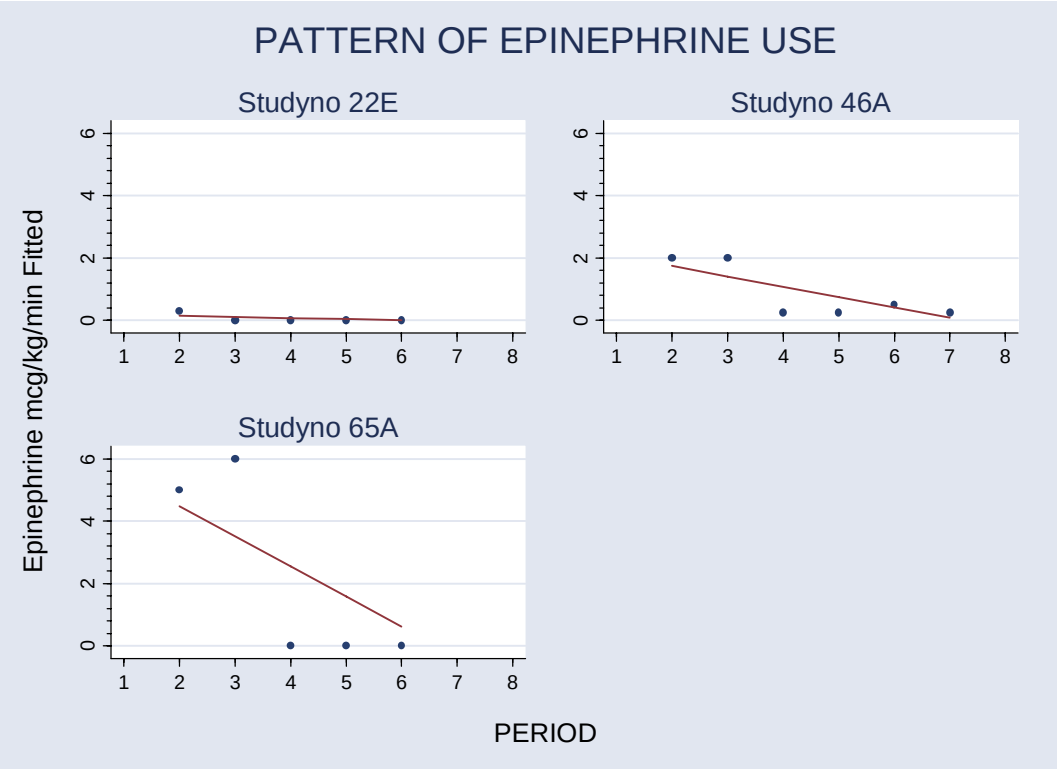


Figure 3.2b: Graph of the pattern of epinephrine use in three out of four cardiac donors <u>with</u> myocardial dysfunction

Period:

1: Emergency; 2: Following admission into ICU; 3: Time of maximum ICP; 4: Hour pre-declaration of brain death; 5: Declaration of brain death; 6: Donor maintenance time 1; 7: Donor maintenance time 2; 8: Time of procurement

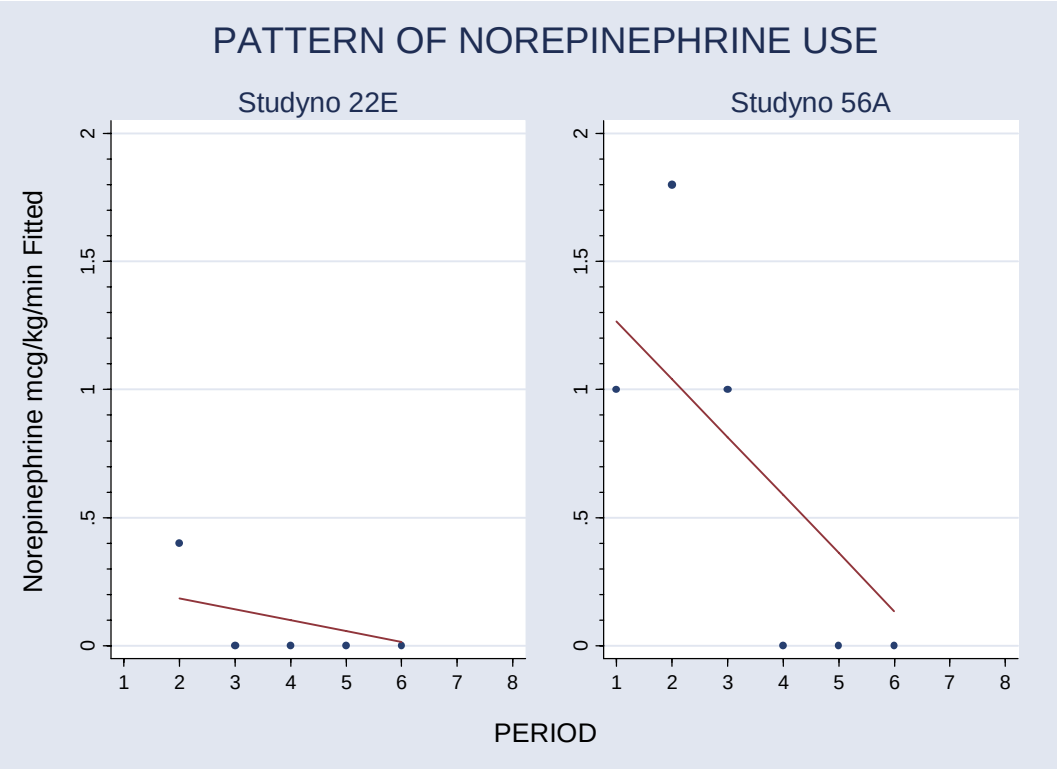


Figure 3.2c: Graph of the pattern of norepinephrine use in two out of four cardiac donors <u>with</u> myocardial dysfunction

Period:

1: Emergency; 2: Following admission into ICU; 3: Time of maximum ICP; 4: Hour pre-declaration of brain death; 5: Declaration of brain death; 6: Donor maintenance time 1; 7: Donor maintenance time 2; 8: Time of procurement

Two out of the six cardiac donors had normal cardiac function on echocardiogram but required inotropic support as detailed in Table 3.16. Attempts made to inquire regarding the status of the six recipients were unsuccessful.

Table 3.16: Cardiac donors without myocardial dysfunction

Study no.	**Inotrope**	**Maximum dose required mcg/kg/min**	**Shortening fraction**	**Cardiac arrest**
1F	Dopamine Norepinephrine	11 2	Normal	No
4F	Neosynephrine (Levophed)	2.7	Normal	No

The pattern of inotropic use of the two donors without myocardial dysfunction are presented graphically in Figures 3.3a, b, c. Attempts made to inquire regarding the status of the six recipients were unsuccessful.

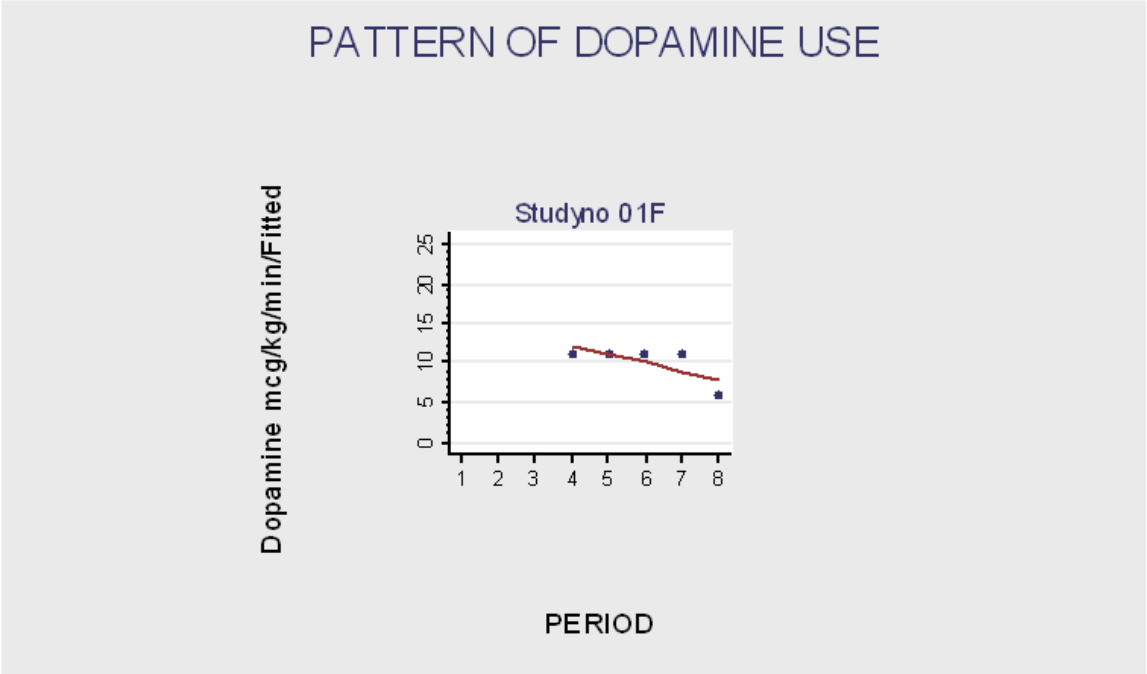


Figure 3.3a: Graph of the use of dopamine in 1 donor <u>without</u> myocardial dysfunction

Period:

1: Emergency; 2: Following admission into ICU; 3: Time of maximum ICP; 4: Hour pre-declaration of brain death; 5: Declaration of brain death; 6: Donor maintenance time 1; 7: Donor maintenance time 2; 8: Time of procurement

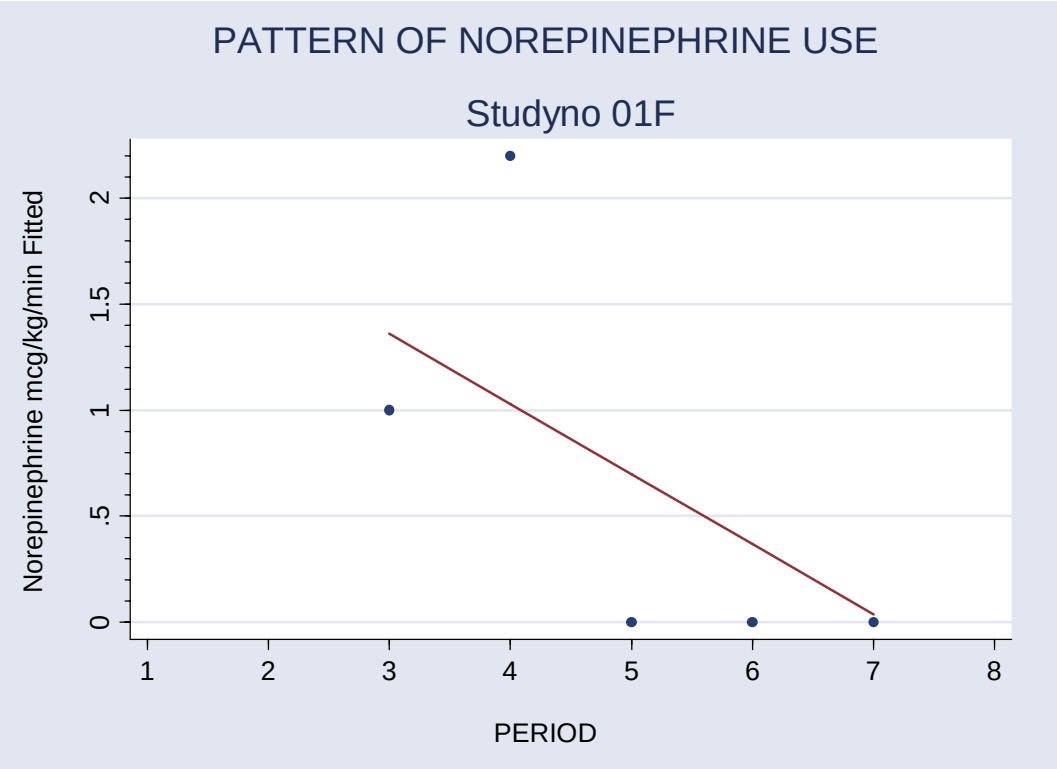


Figure 3.3b: Graph of the use of norepinephrine in 1 donor <u>without</u> myocardial dysfunction

Period:

1: Emergency; 2: Following admission into ICU; 3: Time of maximum ICP; 4: Hour pre-declaration of brain death; 5: Declaration of brain death; 6: Donor maintenance time 1; 7: Donor maintenance time 2; 8: Time of procurement

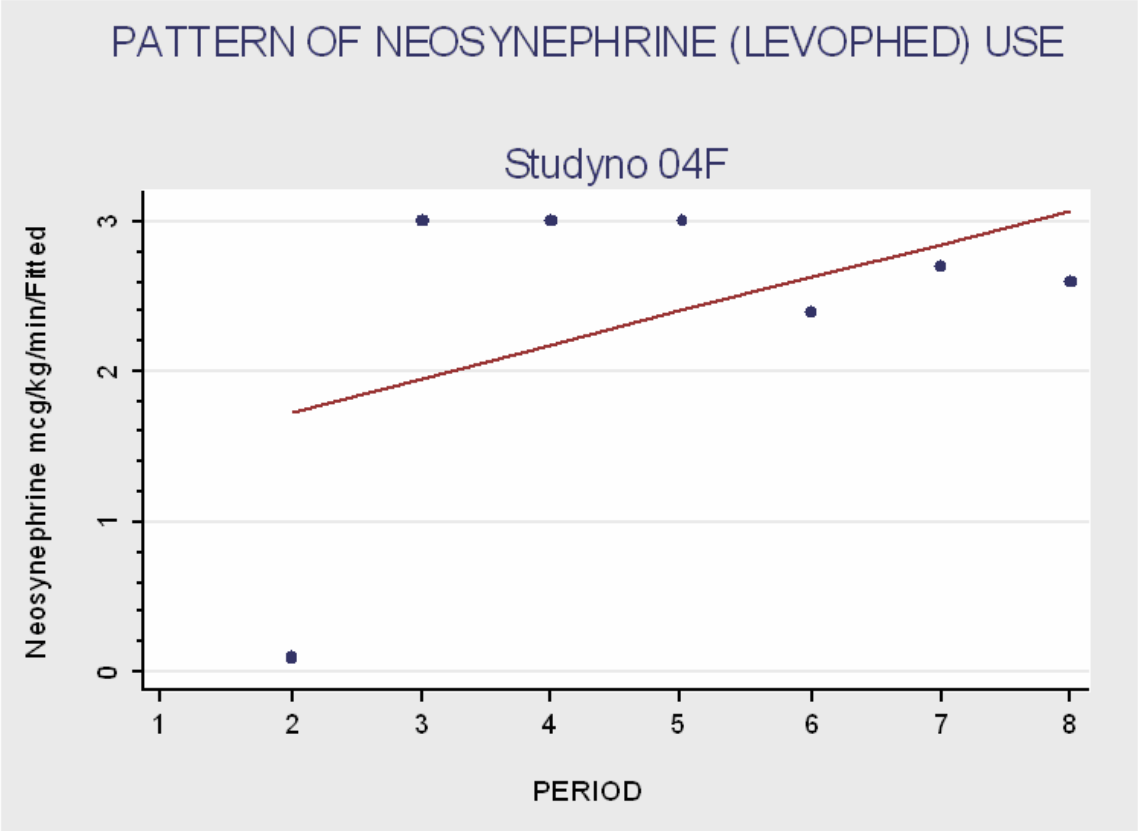


Figure 3.3c: Graph of the use of neosynephrine in 1 donor <u>without</u> myocardial dysfunction

Period:

1: Emergency; 2: Following admission into ICU; 3: Time of maximum ICP; 4: Hour pre-declaration of brain death; 5: Declaration of brain death; 6: Donor maintenance time 1; 7: Donor maintenance time 2; 8: Time of procurement

3.5 Pattern of inotrope use

There were differences in the need for inotropic support between the group of patients with myocardial dysfunction in comparison to the group of patients with relatively normal cardiac function as shown in Table 3.4. However, in the group of patients without myocardial dysfunction, 24% required dopamine and 7% required epinephrine support respectively.

The use of inotropic support was also increased in the group of patients with brain death associated with myocardial dysfunction (Figure 3.4) compared to the group of patients with myocardial dysfunction who expired after care was withdrawn (Figure 3.5).

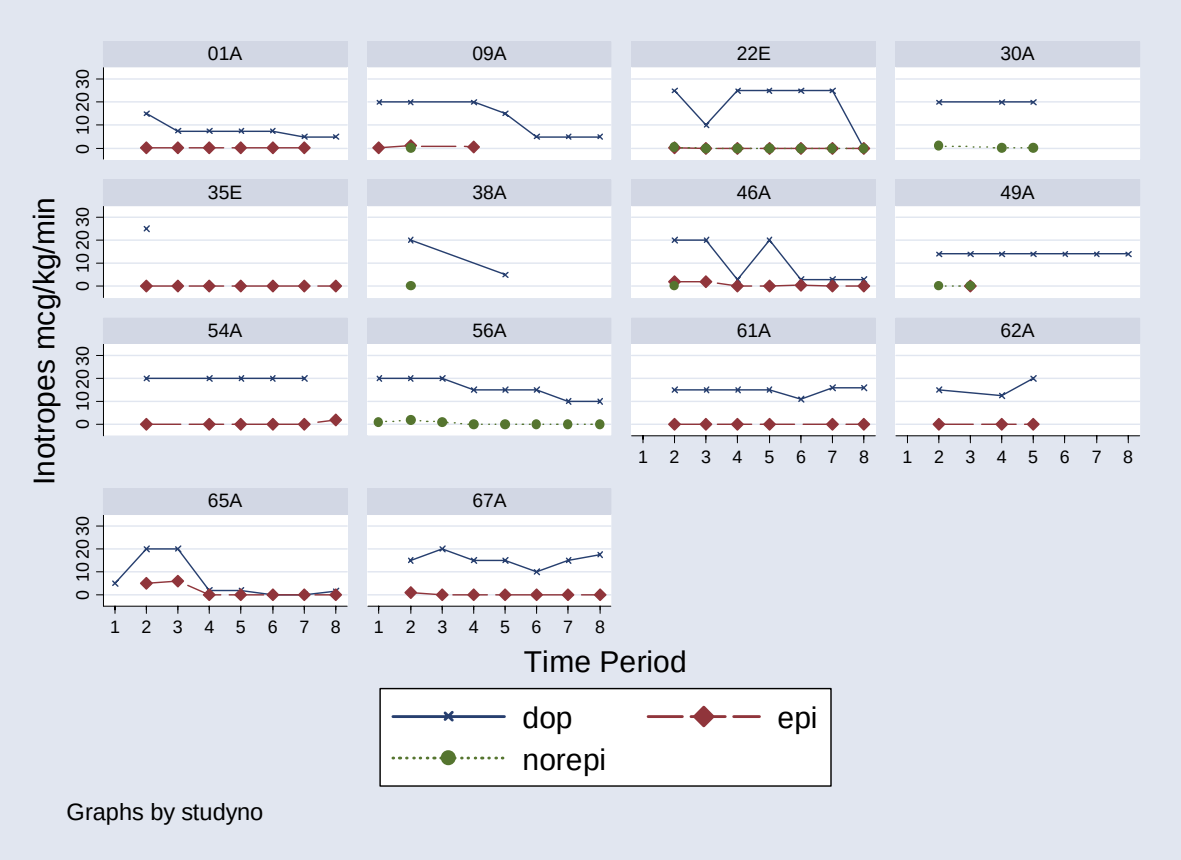


Figure 3.4: Pattern of inotrope use in patients with myocardial dysfunction and brain death (non-fitted graph)

Time period:

1: Emergency; 2: Following admission into ICU; 3: Time of maximum ICP; 4: Hour pre-declaration of brain death; 5: Declaration of brain death; 6: Donor maintenance time 1; 7: Donor maintenance time 2; 8: Time of procurement

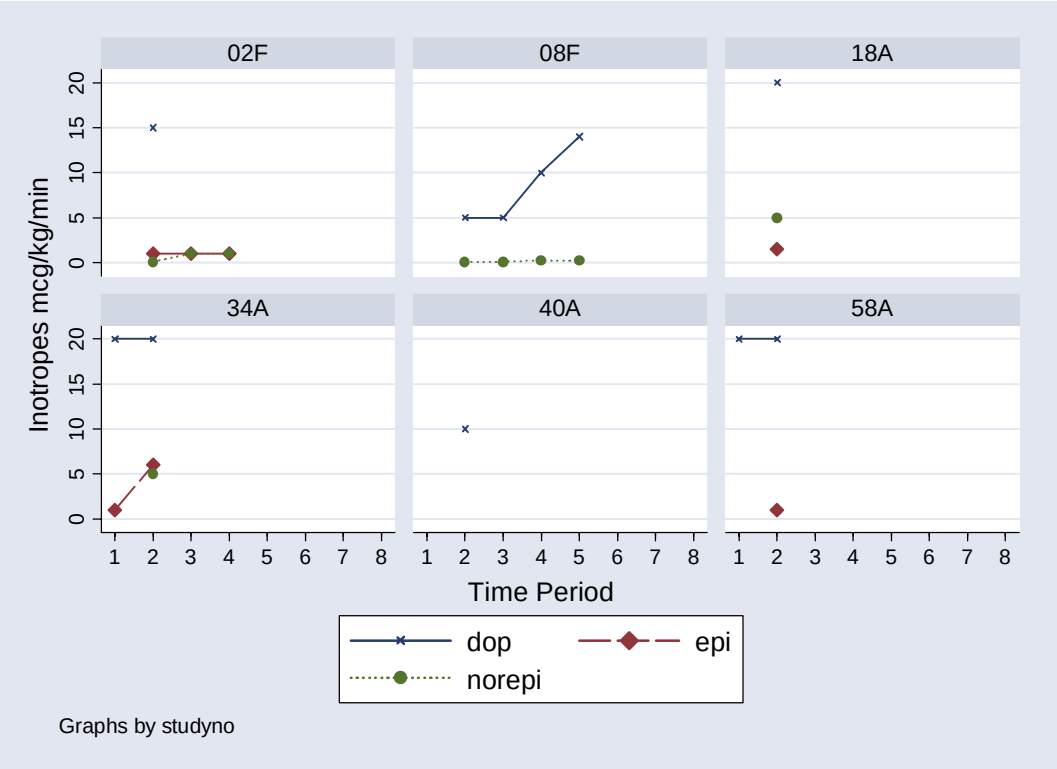


Figure 3.5: Pattern of inotrope use in patients with myocardial dysfunction where care was withdrawn. (non-fitted graph)

(Time period 5-8 not relevant as brain death was not declared)

Time period:

1: Emergency; 2: Following admission into ICU; 3: Time of maximum ICP; 4: Hour pre-declaration of brain death; 5: Declaration of brain death; 6: Donor maintenance time 1; 7: Donor maintenance time 2; 8: Time of procurement

As can be seen, there are 14 patients with brain death associated with myocardial dysfunction and 6 with myocardial dysfunction who expired after care was withdrawn. Some of these patients may have met criteria for brain death but formal declaration of brain death was not done. Visually, it can be appreciated that the trend for the need for inotropic support was higher in the group of patients with brain death over the eight described time periods. The group of patients with myocardial dysfunction that survived were not plotted as the focus was on the patients that were deceased. Further statistical anaylsis cannot be carried out as the recording of the use of inotropes were not standardized and the infusion dosages of these inotropes were over a continuum with frequent titration as necessitated by the patient's hemodynamic status. Comparison of the use of inotropes between patients with and without myocardial dysfunction will not be statistically correct as the extent of inotropic support was used in the case definition of myocardial dysfunction in this study.

CHAPTER FOUR: DISCUSSION

4.1 Study overview

The overall objective of this retrospective cohort study was to examine the prevalence of myocardial dysfunction in children with severe brain injury and the predictive factors determining myocardial dysfunction in this group of patients. The criteria for acceptance, rejection of donor hearts and the impact of myocardial dysfunction on organ donation were briefly explored. An in-depth study of these issues are important but beyond the scope of this study.

4.2 Overview of study findings

In this retrospective cohort study of 115 patients with severe traumatic brain injury, the most common mechanism of injury was motor vehicle collision (60%). This finding is similar to the findings reported by Humphreys et al (77) and Thakker (78). The overall mortality rate of this study was 24.3% which was higher than the mortality reported by Thakker (18.1%) and Tepas et al (6%) (79). The mortality may have been higher in this study because the patient population only included those with severe brain injury classified as GCS score of ≤ 8. The mean GCS score in this study was 5 compared to 6 reported in the study by Thakker (78).

4.2.1 Primary research objectives

4.2.1.1 Prevalence of myocardial dysfunction

The prevalence of myocardial dysfunction in this study of children admitted with severe brain injury classified as having a GCS score of ≤ 8 was **31.3%** (95% CI 23.0%, 41.6%).

Amongst the children that succumbed to brain death (n=18), the prevalence of myocardial dysfunction was **77.8%** (95% CI 52.3%, 93.6%). Amongst the children that survived (n=87), the prevalence of myocardial dysfunction was **18.4%** (95% CI 10.9%, 28.1%). Amongst the children that died after withdrawal of care (n=6), the prevalence of myocardial dysfunction was **60%** (95% CI 26.2%, 87.8%). In this group of patients, 4 out of 6 may have met clinical criteria for brain death but were not formally declared, and therefore were not included in the group of children with brain death in the analysis. This may explain the high prevalence of myocardial dysfunction in this group of children which approximated that of the group of children with brain death.

In this study, the prevalence of myocardial dysfunction in patients with brain death of **77.8%** (95% CI 52.3%, 93.6%) is higher than the reported prevalence of **10% to 42%** in adults with brain death as reported by Gilbert and Dujardin (12, 13). Myocardial dysfunction was determined by echocardiography results in both these studies.

However, in a retrospective study by Paul et al of pediatric patients that met brain death criteria, **57%** of the donors had echocardiographic evidence of systolic left ventricular dysfunction (14). One of the possible reasons for the differences in the

reported prevalence is the fundamental difference in the case definition or the method of diagnosis of myocardial dysfunction between the studies.

As there is currently no operational definition of myocardial dysfunction and echocardioagram was not performed on all patients in this study, the case definition for this study was developed with the combination of responses from questionnaires sent to major pediatric cardiac centers, assessing the current standard of practice in the determination of myocardial dysfunction and from clinical experience. The questionnaire response rate of 56% was marginal but the criteria for the determination of myocardial dysfunction and the assessment of donor hearts were consistent amongst the 5 centers, therefore any improvement in the response rate likely will not influence the case definition of myocardial dysfunction in this study. The case definition of myocardial dysfunction for this study was then developed incorporating the results of echocardiographic findings and/or the amount of inotropic support needed.

The criteria for myocardial dysfunction may be broader in this study with the goal of capturing all patients that may have myocardial dysfunction. Therefore the prevalence of myocardial dysfunction from this study may be higher than the reported prevalence by Paul et al (14).

The higher prevalence of myocardial dysfunction observed in this study and the pediatric study by Paul et al as compared to the adult studies may be related to the sensitivity of the young myocardium to the catecholamine surge secondarily to severe neurologic injury. This is supported by a study by White (10) who found that younger

hearts have a greater density of β-adrenergic receptors within the myocardium and, thus may be more vulnerable to sudden increases in sympathetic activity. The increase in the prevalence of myocardial dysfunction in children with brain death certainly supports the theory of neurogenic catecholamine cardiotoxicity and neural axis interaction causing myocardial dysfunction in this group of patients.

Although the primary objective of this study was to determine the prevalence of myocardial dysfunction in children with severe brain injury, the prevalence will approximate the incidence as incidence is "new" cases over a specified period of time. Majority of the children would have normal cardiac function as cardiac disorders are infrequent in children. Those children with congenital heart disease and other secondary cardiac problems were excluded from the study. Therefore it can be assumed that the children included in the study do not have any previous cardiac disorders therefore any case of myocardial dysfunction will be a new case thus approximating the measure of incidence.

4.2.1.2 Clinical determinants of myocardial dysfunction

Variables associated with myocardial dysfunction by bivariate analysis included "brain death", "PRISM III-12", "PRISM III-24" scores and "GCS score" (Table 3.4). Each association was statistically significant (p value < 0.01) and therefore likely not chance associations. The statistically significant association between patients with brain death and myocardial dysfunction affirms the high prevalence of myocardial dysfunction

in this group of patients. The statistical and clinical association help lend support to the theory of neurogenic catecholamine cardiotoxicity and neural axis interaction causing myocardial dysfunction in this group of patients.

The mean PRISM III-12 score for the group of patients with myocardial dysfunction was 18 (SD 9.5) in comparison to PRISM III-12 score of 9 (SD 5.6) in the group of patients without myocardial dysfunction (p value 0.001). The PRISM III score was developed to assess the risk of mortality in critically ill children and provide an objective data as an illness severity index. Brain injury is usually associated with multiple trauma, therefore physiologic instability is not unexpected in this population. Currently there are no similar studies assessing PRISM III score and myocardial dysfunction. However in a study of survival and functional outcome of children requiring endotracheal intubation for severe brain injury, the relative risk of a bad outcome for patients with a GCS score of ≤ 5 and a PRISM score of ≥ 20 was 10 times higher than the group of patients with a GCS score of ≤ 5 but a PRISM score of ≤ 20. In a study by Zygun (80) of adults with severe traumatic brain injury, 89% developed dysfunction of at least one non-neurologic organ system. The etiology of this dysfunction may be due to the body's dysregulated inflammatory response to the injury and therapy directed at supporting cerebral circulation.

The mean GCS score for the patients with myocardial dysfunction was 4 (SD 1.8) as compared to a GCS score of 6 (SD 1.7) in patients without myocardial dysfunction. The GCS score was used as an index of severity of brain injury, therefore it is not surprising that patients with high severity of brain injury indicated by lower GCS scores

would have higher risk of brain death and higher association with myocardial dysfunction. In this study population, 61% of children with brain death had a GCS score of 3 as compared to only 18% in the group of children that survived (p value <0.01).

4.2.1.3 Multivariate analysis

Multivariate logistic regression analysis showed that the PRISM III-12 score (categories 11-25, 26-50) was statistically significantly associated with the outcome of myocardial dysfunction. Stepwise backward selection techniques starting with the variables of "brain death", "PRISM III-12 score (in categories 11-25, 26-50)", "GCS score", "gender", "mechanism of injury" and "age" kept only "PRISM III-12 score (categories 11-25, 26-50)" in the model.

A full clinical model of myocardial dysfunction takes into account the variables relating to the patient that are important clinically. These variables would include the patient's brain death status, PRISM III-12 score, GCS score, gender, mechanism of injury. However in a predictive model, a parsimonious model with the least variables would optimize prediction.

The variables "brain death" and "GCS score" contributed significantly to the model when they were included into the model separately (Table 3.7, 3.8). The likely explanation was the presence of collinearity as the variable "brain death" and "GCS score" provided similar information which was the severity of the underlying brain injury. There was also presence of multi-collinearity amongst the variables "brain death", "GCS score" and the "PRISM III-12 score" as they indicate the severity of the injury and

illness. The model with the largest area under the receiver operating curve (l-ROC 0.8585) was the model that included variables “brain death”, “GCS score” and the “PRISM III-12 score (categories 11-25, 26-50)” (Table 3.14). However, the only variable with statistical significance was “PRISM III-12 score (with categories 11-25, 26-50)”. This model is interpreted as follows: the odds of having myocardial dysfunction in children with a PRISM III-12 score of 10 to 25 is **7 times** that of children with PRISM III-12 scores of less than or equal to10, controlling for brain death and GCS score. The odds of having myocardial dysfunction in children with a PRISM III-12 score of 26 to 50 is **13.5 times** that of children with PRISM III-12 score of less than or equal to 10, controlling for brain death and GCS score. It is not surprising that PRISM III-12 score is a significant predictor of myocardial dysfunction as the PRISM III-12 score is a used as an indicator for severity of illness and majority of patients with severe brain injury will have physiologic instability.

4.2.2 Secondary research objective

The secondary research objective was to determine the impact of myocardial dysfunction on organ donation and procurement. The most important current limitation to organ transplantation is donor availability therefore this is one of the important areas of study with the objective of increasing the donor pool.

The definition of a suitable donor is based on left ventricular systolic ejection phase indices and remains controversial due to the inability to predict how the poorly functioning donor heart will perform after it is transplanted (14). The current criteria for

acceptable donor hearts from the adult literature include echocardiogram showing no important segmental abnormalities or global hypokinesis, normal valves, shortening fraction greater than 23%; normal electrocardiogram or minor ST-T wave abnormalities with no conduction disorder; inotropes less than 15 mcg/kg/min of dopamine (81). These criteria may be restrictive thus limiting donor pool. In a study by Jeevanandam (81) of transplanting 33 donor hearts with myocardial dysfunction, the 30-day mortality of 6% and the 12 months survival were similar between the recipients of normal hearts that conform to the standard criteria and hearts with myocardial dysfunction. Boucek et al (82) reported myocardial dysfunction in 14% of 186 pediatric hearts that were harvested for transplantation and indicated that hearts with myocardial dysfunction can be harvested and transplanted successfully.

In our study, 4 donor hearts with myocardial dysfunction were transplanted (Table 3.15). The data on the reasons for the acceptance of the donor hearts or the status of the recipients were not available. The pattern of inotrope use of these donors as well as other patients with brain death show that inotropic requirement decreases after brain death (Figure 3.2a, b, c; 3.3a, b, c; 3.4). This finding generates the hypothesis that the sympathetic storm caused by excessive catecholamine release in patients with severe increase in intracranial pressure may have ceased after brain death, thus the myocardial function may start to show signs of improvement. This is an encouraging finding as the physiologic consequences of brain death on the myocardium may be reversible and therefore may increase the donor pool by reducing unnecessary rejection of donor hearts.

One of the possible explanations for the observation that the use of inotropic support were decreased after the declaration of brain death may be because of a change in the clinical objective as directed by the clinician. If the reason for the use of inotropic support was to achieve a certain arterial blood pressure for cerebral perfusion purposes then this may not be necessary after brain death had occurred.

4.5 Strength

The major strength of this study is the determination of myocardial dysfunction associated with severe brain injury in pediatrics. This is the first study of its kind exploring this important issue and filling the gap in knowledge in this area.

4.5.1 Impact on clinical care

Having an awareness of the possible association of myocardial dysfunction with severe brain injury in children may improve the management and in turn improve the survival and neurological outcome of these critically ill children. It can also help in prognostication and discussion with family members with regards to the course in the intensive care management.

For potential organ donors, the knowledge of the associated myocardial dysfunction will help in improving management thus optimizing perfusion to vital organs. Successful organ transplantation for the recipient depends on hemodynamic stability of the beating heart donor (83).

The finding of the pattern of inotropic use in this study where the need for inotropic support decreased after brain death, in turn signify that cardiac function may be improving after the catecholamic storm may encourage transplant team to reassess the cardiac function of potential donors who may be on large inotropic support early in the course of injury.

Echocardiographic screening is a useful method of evaluating potential cardiac transplant donors and it can help identify potential donors that would otherwise have been excluded (13). Only 22% of the patients in this retrospective cohort study had echocardiograms. This study has pointed out the lack of echocardiograms performed.in this population. It is recommended that echocardiogram should be performed on all potential cardiac donors as this will help provide information on donor cardiac function.

4.6 Limitations

One of the weaknesses of this study is the study design. There is deficit in the data as data entry in the chart was done in an ad hoc manner by clinicians and health professionals caring for the patients. This is an inherent problem with the retrospective chart review study. The PRISM III-12 and PRISM III-24 scores were calculated retrospectively from parameters gathered from the chart review and therefore may not be as accurate as real time calculation.

One of the other weaknesses of this study is that only one individual, the principal investigator, reviewed the medical records which may lead to observer bias. Steps taken

to reduce this potential problem were the use of a standardized data entry form for all the chart review and data entry and therefore may make consistency a strength in this study.

It is important in any study to have a clear, objective definition of the outcome variable, in this case myocardial dysfunction. In this study, attempts were made to obtain an objective definition therefore identifying patients with myocardial dysfunction with a level of accuracy. These attempts included a questionnaire survey of the determination of myocardial dysfunction amongst the pediatric cardiac centers and a thorough review of the individual patient's requirements for inotropic support. As echocardiograms or electrocardiograms were not done on every patient, patients who may have had mild myocardial dysfunction and who were not on any inotropic support may have been missed. These particular patients would not have been captured in the case definition. This will lead to misclassification bias of patients with myocardial dysfunction and will influence the prevalence. Most patients who had sustained severe brain injury will likely have other organ involvements as extrapolated from a study of severe brain injury in audlts (81), and may have mild myocardial dysfunction that are transient and improve without much support. Some of these patients are likely to be in hypovolemic or hemorrhagic shock from massive blood loss leading to acidosis and therefore may have myocardial dysfunction in the early resuscitation period until their fluid status is improved.

One of the limitations of this study is that degree of myocardial dysfunction was not graded. The prevalence may be influenced by the grading of myocardial dysfunction into mild, moderate and severe. This may also aid in donor assessment for organ

procurement such that hearts with mild myocardial dysfunction are not unnecessarily rejected thus improving the pool of organs.

4.7 Recommendation for future studies

The impact of myocardial dysfunction associated with severe brain injury and the consequences on organ donation is an important area in pediatrics and adults that warrants further research.

The results from this retrospective cohort study will serve as a pilot data for a future study. A better study design would be a prospective cohort study design of consecutive children admitted with severe brain injury. PRISM III score, GCS score and data on clinical course, use of inotropic support and laboratory investigations including Thyroid function test (free T3, TSH), troponin and lactate are uniformly collected. The data collected on the thyroid function test will be useful in assessing the degree of hormonal depletion associated with severe brain injury as observed in the adult studies of severe brain injury. A study protocol will be designed such that every patient will have echocardiogram and electrocardiograms done and abnormalities will be compared to pathological findings on autopsy as appropriate. Procurement data and post-transplant status of the recipients will be collected with appropriate ethics approval. Improving the hemodynamic status of the donor with drugs such as Triiodothyronine should be studied in the pediatric donors with a multi-center randomized controlled trial. The data that will be obtained from the above studies will advance the knowledge in this area of pediatrics.

REFERENCES

1. McLeod AA, Neil-Dwyer G, Meyer CH, Richardson PL, Cruickshank J, Bartlett J. Cardiac sequelae of acute head injury. Br Heart J 1982;47(3):221-6.

2. Millen JE, Glauser FL, Zimmerman M. Physiological effects of controlled concussive brain trauma. J Appl Physiol 1980;49(5):856-62.

3. Macmillan CS, Grant IS, Andrews PJ. Pulmonary and cardiac sequelae of subarachnoid haemorrhage: time for active management? Intensive Care Med 2002;28(8):1012-23.

4. Mayer SA, Fink ME, Homma S, Sherman D, LiMandri G, Lennihan L, et al. Cardiac injury associated with neurogenic pulmonary edema following subarachnoid hemorrhage. Neurology 1994;44(5):815-20.

5. Boggs JG, Marmarou A, Agnew JP, Morton LD, Towne AR, Waterhouse EJ, et al. Hemodynamic monitoring prior to and at the time of death in status epilepticus. Epilepsy Res 1998;31(3):199-209.

6. Simon RP, Bayne LL, Tranbaugh RF, Lewis FR. Elevated pulmonary lymph flow and protein content during status epilepticus in sheep. J Appl Physiol 1982;52(1):91-5.

7. Young RS, Fripp RR, Yagel SK, Werner JC, McGrath G, Schuler HG. Cardiac dysfunction during status epilepticus in the neonatal pig. Ann Neurol 1985;18(3):291-7.

8. Lutz-Dettinger N, de Jaeger A, Kerremans I. Care of the potential pediatric organ donor. Pediatr Clin North Am 2001;48(3):715-49.

9. Samuels MA. Cardiopulmonary aspects of acute neurologic diseases. In: Ropper AH, editor. Neurological and Neurosurgical Intensive Care. New York: Raven Press; 1993. p. 103-119.

10. White M, Wiechmann RJ, Roden RL, Hagan MB, Wollmering MM, Port JD, et al. Cardiac beta-adrenergic neuroeffector systems in acute myocardial dysfunction related to brain injury. Evidence for catecholamine-mediated myocardial damage. Circulation 1995;92(8):2183-9.

11. Staworn D, Lewison L, Marks J, Turner G, Levin D. Brain death in pediatric intensive care unit patients: incidence, primary diagnosis, and the clinical occurrence of Turner's triad. Crit Care Med 1994;22(8):1301-5.

12. Dujardin KS, McCully RB, Wijdicks EF, Tazelaar HD, Seward JB, McGregor CG, et al. Myocardial dysfunction associated with brain death: clinical, echocardiographic, and pathologic features. J Heart Lung Transplant 2001;20(3):350-7.

13. Gilbert EM, Krueger SK, Murray JL, Renlund DG, O'Connell JB, Gay WA, et al. Echocardiographic evaluation of potential cardiac transplant donors. J Thorac Cardiovasc Surg 1988;95(6):1003-7.

14. Paul JJ, Tani LY, Shaddy RE, Minich LL. Spectrum of left ventricular dysfunction in potential pediatric heart transplant donors. J Heart Lung Transplant 2003;22(5):548-52.

15. Baroldi G, Di Pasquale G, Silver MD, Pinelli G, Lusa AM, Fineschi V. Type and extent of myocardial injury related to brain damage and its significance in heart transplantation: a morphometric study. J Heart Lung Transplant 1997;16(10):994-1000.

16. Depasquale NP, Burch GE. How normal is the donor heart? Am Heart J 1969;77:719-720.

17. Greenhoot JH, Reichenbach DD. Cardiac injury and subarachnoid hemorrhage. A clinical, pathological, and physiological correlation. J Neurosurg 1969;30(5):521-31.

18. Talman WT. Cardiovascular regulation and lesions of the central nervous system. Ann Neurol 1985;18(1):1-13.

19. Galinanes M, Smolenski RT, Hearse DJ. Brain death-induced cardiac contractile dysfunction and long-term cardiac preservation. Rat heart studies of the effects of hypophysectomy. Circulation 1993;88(5 Pt 2):II270-80.

20. Bayer E, Ashman R, Toth LA. Electrocardiogram with large upright T wave and long Q-T intervals. Am Heart J 1947;33:796-801.

21. Cropp GJ, Manning GW. Electrocardiographic changes simulating myocardial ischemia and infarction associated with spontaneous intracranial hemorrhage. Circulation 1960;22:25-38.

22. Hugenholtz PG. Electrocardiographic abnormalities in cerebral disorders. Report of six cases and review of the literature. Am Heart J 1962;63:451-61.

23. Arab D, Yahia AM, Qureshi AI. Cardiovascular manifestations of acute intracranial lesions: pathophysiology, manifestations, and treatment. J Intensive Care Med 2003;18(3):119-29.

24. Mayer SA, LiMandri G, Sherman D, Lennihan L, Fink ME, Solomon RA, et al. Electrocardiographic markers of abnormal left ventricular wall motion in acute subarachnoid hemorrhage. J Neurosurg 1995;83(5):889-96.

25. Bittner HB, Chen EP, Milano CA, Kendall SW, Jennings RB, Sabiston DC, Jr., et al. Myocardial beta-adrenergic receptor function and high-energy phosphates in brain death--related cardiac dysfunction. Circulation 1995;92(9 Suppl):II472-8.

26. Bruinsma GJ, Nederhoff MG, Geertman HJ, van Huffelen AC, Slootweg PJ, Ferrari R, et al. Acute increase of myocardial workload, hemodynamic instability, and myocardial histological changes induced by brain death in the cat. J Surg Res 1997;68(1):7-15.

27. Farhat F, Loisance D, Garnier JP, Kirsch M. Norepinephrine release after acute brain death abolishes the cardioprotective effects of ischemic preconditioning in rabbit. Eur J Cardiothorac Surg 2001;19(3):313-20.

28. Montagna P, Sante P, Ferrera R, Ossette J, Hadour G, Chatel C, et al. [Brain death: myocardial consequences, an experimental study on pigs]. G Ital Cardiol 1997;27(4):337-41.

29. Szabo G, Sebening C, Hagl C, Tochtermann U, Vahl CF, Hagl S. Right ventricular function after brain death: response to an increased afterload. Eur J Cardiothorac Surg 1998;13(4):449-58; discussion 458-9.

30. Yeh T, Jr., Wechsler AS, Graham LJ, Loesser KE, Sica DA, Wolfe L, et al. Acute brain death alters left ventricular myocardial gene expression. J Thorac Cardiovasc Surg 1999;117(2):365-74.

31. Satur CM, Martin W, Darracott-Cankovic S, Morrison J, Wheatley DJ. An experimental method to induce variable patterns of brain death and myocardial injury. Transplant Proc 1998;30(1):211-3.

32. Schrader H, Hall C, Zwetnow NN. Effects of prolonged supratentorial mass expansion on regional blood flow and cardiovascular parameters during the Cushing response. Acta Neurol Scand 1985;72(3):283-94.

33. Shivalkar B, Van Loon J, Wieland W, Tjandra-Maga TB, Borgers M, Plets C, et al. Variable effects of explosive or gradual increase of intracranial pressure on myocardial structure and function. Circulation 1993;87(1):230-9.

34. Elrifai AM, Bailes JE, Shih SR, Dianzumba S, Brillman J. Characterization of the cardiac effects of acute subarachnoid hemorrhage in dogs. Stroke 1996;27(4):737-41; discussion 741-2.

35. Novitzky D, Wicomb WN, Cooper DK, Rose AG, Reichart B. Prevention of myocardial injury during brain death by total cardiac sympathectomy in the Chacma baboon. Ann Thorac Surg 1986;41(5):520-4.

36. Beckman DL, Iams SG. Circulating catecholamines in cats before and after lethal head injury. Proc Soc Exp Biol Med 1979;160(2):200-2.

37. Kolin A, Norris JW. Myocardial damage from acute cerebral lesions. Stroke 1984;15(6):990-3.

38. Mallov S. Role of calcium and free fatty acids in epinephrine-induced myocardial necrosis. Toxicol Appl Pharmacol 1983;71(2):280-7.

39. Rona G. Catecholamine cardiotoxicity. J Mol Cell Cardiol 1985;17(4):291-306.

40. Rosner MJ, Newsome HH, Becker DP. Mechanical brain injury: the sympathoadrenal response. J Neurosurg 1984;61(1):76-86.

41. Todd GL, Baroldi G, Pieper GM, Clayton FC, Eliot RS. Experimental catecholamine-induced myocardial necrosis. I. Morphology, quantification and regional distribution of acute contraction band lesions. J Mol Cell Cardiol 1985;17(4):317-38.

42. Hamill RW, Woolf PD, McDonald JV, Lee LA, Kelly M. Catecholamines predict outcome in traumatic brain injury. Ann Neurol 1987;21(5):438-43.

43. Norris JW. Cardiovascular manifestations of acute neurological lesions. In: Aminoff MJ, editor. Neurology and General Medicine. New York: Churchill Livingston; 1981. p. 159-167.

44. Josue O. Hypertrophie cardiaque causee par l'adrenaline et la toxinetyphique. C R Soc Biol (Paris) 1907:285-287.

45. Meerson FZ. Pathogenesis and prophylaxis of cardiac lesions in stress. Adv Myocardiol 1983;4:3-21.

46. Selye H. In: The Chemical Prevention of Cardiac Necrosis. New York: Ronald Press; 1958.

47. Melville KI, Blum B, Shister HE, Silver MD. Cardiac Ischemic Changes And Arrhythmias Induced By Hypothalamic Stimulation. Am J Cardiol 1963;12:781-91.

48. Oppenheimer SM, Wilson JX, Guiraudon C, Cechetto DF. Insular cortex stimulation produces lethal cardiac arrhythmias: a mechanism of sudden death? Brain Res 1991;550(1):115-21.

49. Braunwald E, Kloner RA. Myocardial reperfusion: a double-edged sword? J Clin Invest 1985;76(5):1713-9.

50. Hearse DJ, Humphrey SM, Chain EB. Abrupt reoxygenation of the anoxic potassium-arrested perfused rat heart: a study of myocardial enzyme release. J Mol Cell Cardiol 1973;5(4):395-407.

51. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 15-1988. A 26-year-old woman with cardiomyopathy, multiple strokes, and an adrenal mass. N Engl J Med 1988;318(15):970-81.

52. Bittner HB, Kendall SW, Chen EP, Van Trigt P. Endocrine changes and metabolic responses in a validated canine brain death model. J Crit Care 1995;10(2):56-63.

53. Gramm HJ, Meinhold H, Bickel U, Zimmermann J, von Hammerstein B, Keller F, et al. Acute endocrine failure after brain death? Transplantation 1992;54(5):851-7.

54. Harms J, Isemer FE, Kolenda H. Hormonal alteration and pituitary function during course of brain-stem death in potential organ donors. Transplant Proc 1991;23(5):2614-6.

55. Howlett TA, Keogh AM, Perry L, Touzel R, Rees LH. Anterior and posterior pituitary function in brain-stem-dead donors. A possible role for hormonal replacement therapy. Transplantation 1989;47(5):828-34.

56. Huber TS, Nachreiner R, D'Alecy LG. Hormonal profiles in a canine model of the brain-dead organ donor. J Crit Care 1994;9(1):7-17.

57. Imai K, Sato K, Ito Y, Nakayama Y, Takahashi T, Kakita A. Hormonokinetics and histopathological evaluation of rabbit brain death model. Transplant Proc 1996;28(3):1273-4.

58. Mariot J, Sadoune LO, Jacob F, Dousset B, Perrier JF, Jacob C, et al. Hormone levels, hemodynamics, and metabolism in brain dead organ donors. Transplant Proc 1995;27(1):793-4.

59. Masson F, Thicoipe M, Latapie MJ, Maurette P. Thyroid function in brain-dead donors. Transpl Int 1990;3(4):226-33.

60. Montero JA, Mallol J, Alvarez F, Benito P, Concha M, Blanco A. Biochemical hypothyroidism and myocardial damage in organ donors: are they related? Transplant Proc 1988;20(5):746-8.

61. Powner DJ, Hendrich A, Lagler RG, Ng RH, Madden RL. Hormonal changes in brain dead patients. Crit Care Med 1990;18(7):702-8.

62. Novitzky D. Donor management: state of the art. Transplant Proc 1997;29(8):3773-5.

63. Jeevanandam V. Triiodothyronine: spectrum of use in heart transplantation. Thyroid 1997;7(1):139-45.

64. Sztark F, Thicoipe M, Lassie P, Dabadie P. Modification of mitochondrial energy metabolism in brain dead organ donor. Transplant Proc 1996;28(1):52-3.

65. Hall GM, Mashiter K, Lumley J, Robson JG. Hypothalamic-pituitary function in the "brain-dead" patient. Lancet 1980;2(8206):1259.

66. Novitzky D, Cooper DK, Reichart B. The value of hormonal therapy in improving organ viability in the transplant donor. Transplant Proc 1987;19(1 Pt 3):2037-8.

67. Cooper DK, Novitzky D, Wicomb WN. Hormonal therapy in the brain-dead experimental animal. Transplant Proc 1988;20(5 Suppl 7):51-4.

68. Cooper DK, Basker M. Physiologic changes following brain death. Transplant Proc 1999;31(1-2):1001-2.

69. Novitzky D, Cooper DK. Results of hormonal therapy in human brain-dead potential organ donors. Transplant Proc 1988;20(5 Suppl 7):59-62.

70. Novitzky D, Cooper DK, Morrell D, Isaacs S. Brain death, triiodothyronine depletion, and inhibition of oxidative phosphorylation: relevance to management of organ donors. Transplant Proc 1987;19(5):4110-1.

71. Novitzky D, Cooper DK, Morrell D, Isaacs S. Change from aerobic to anaerobic metabolism after brain death, and reversal following triiodothyronine therapy. Transplantation 1988;45(1):32-6.

72. Novitzky D, Cooper DK, Reichart B. Hemodynamic and metabolic responses to hormonal therapy in brain-dead potential organ donors. Transplantation 1987;43(6):852-4.

73. Wicomb WN, Novitzky D, Cooper DK. Effects of hormonal therapy on subsequent organ (kidney) storage in the experimental animal. Transplant Proc 1988;20(5 Suppl 7):55-8.

74. Pollack MM, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. Crit Care Med 1988;16(11):1110-6.

75. Yeh TS, Pollack MM, Ruttimann UE, Holbrook PR, Fields AI. Validation of a physiologic stability index for use in critically ill infants and children. Pediatr Res 1984;18(5):445-51.

76. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. Crit Care Med 1996;24(5):743-52.

77. Humphreys PR, Jaimovich R, Hendrick EB, etal. Severe head injury in children. In: Concepts of Pediatric Neurosurgery Vol 4. Basel, Switzerland: S Karger; 1984. p. 230-242.

78. Thakker JC, Splaingard M, Zhu J, Babel K, Bresnahan J, Havens PL. Survival and functional outcome of children requiring endotracheal intubation during therapy for severe traumatic brain injury. Crit Care Med 1997;25(8):1396-401.

79. Tepas JJ, 3rd, DiScala C, Ramenofsky ML, Barlow B. Mortality and head injury: the pediatric perspective. J Pediatr Surg 1990;25(1):92-5; discussion 96.

80. Zygun DA, Kortbeek JB, Fick GH, Laupland KB, Doig CJ. Non-neurologic organ dysfunction in severe traumatic brain injury. Crit Care Med 2005;33(3):654-60.

81. Jeevanandam V, Furukawa S, Prendergast TW, Todd BA, Eisen HJ, McClurken JB. Standard criteria for an acceptable donor heart are restricting heart transplantation. Ann Thorac Surg 1996;62(5):1268-75.

82. Boucek MM, Mathis CM, Kanakriyeh MS, McCormack J, Razzouk A, Gundry SR, et al. Donor shortage: use of the dysfunctional donor heart. J Heart Lung Transplant 1993;12(6 Pt 2):S186-90.

83. Sadler AM, Jr., Sadler BL, Stason EB. The uniform anatomical gift act. A model for reform. JAMA 1968;206(11):2505-6.

Appendix 2.1

Head Injury Codes Found on ICU Patients
Severe Head Injury Study
Jan 1996 - Dec 2002

83

HI Code	Head Injury Diagnoses	Total
8020	FRACTURE NASAL BONES CLOSED	17
8021	FRACTURE NASAL BONES OPEN	4
8024	FRACTURE MALAR/MAXILLARY CLOSE	26
8025	FRACTURE MALAR/MAXILLARY OPEN	3
8026	FRACTURE ORBITAL FLOOR CLOSED	10
8027	FRACTURE ORBITAL FLOOR OPEN	1
8028	FRACTURE OTH FACIAL BONES CLOS	21
8029	FRACTURE OTH FACIAL BONES OPEN	1
8500	CONCUSSION NO LOSS CONSCIOUS	9
8501	CONCUSSION BRIEF LOSS CONSCIOU	9
8502	CONCUSSION MOD LOSS CONSCIOUS	1
8505	CONCUSSION LOSS CONSCIOUS NOS	1
8509	CONCUSSION UNSPECIFIED	2
80000	CL # VAULT SKULL NO INTRACR NO	2
80001	CL# VAULT SKULL NO INTRACR/COM	3
80002	CL# VLT SKL NO INTRACR BRF COM	3
80004	CL# VLT SKL NO INTRCR PROL COM	1
80006	CL# VLT SKL NO INTRACR COMA NO	2
80010	CL # VAULT SKULL CEREB LACN NO	1
80011	CL # VLT SKL CEREB LACN/NO COM	3
80012	CL# VLT SKL CEREB LACN BRF COM	1
80013	CL# VLT SKL CEREB LACN MOD COM	1
80014	CL # VLT SKL CER LACN PROL COM	1
80016	CL# VLT SKL CEREB LACN COMA NO	2
80021	CL# VLT SKULL DURAL HEM/NO COM	5
80022	CL # VLT SKL DURAL HEM BRF COM	2
80024	CL# VLT SKL DURAL HEM PROL COM	2
80025	CL# VLT SKL DURAL HEM DEEP COM	3
80026	CL # VLT SKL DURAL HEM COMA NO	5
80031	CL# VLT SKULL W HEM NOS/NO COM	2
80034	CL# VLT SKL W HEM NOS PROL COM	2
80043	CL # VLT SKL W INTRACR MOD COM	1
80045	CL# VLT SKL W INTRACR DEEP COM	1
80046	CL # VLT SKL W INTRACR COMA NO	1
80051	OP# VAULT SKULL NO INTRACR/COM	1
80052	OP# VLT SKL NO INTRACR BRF COM	1
80056	OP# VLT SKL NO INTRACR COMA NO	1
80061	OP # VLT SKL CEREB LACN/NO COM	1
80065	OP # VLT SKL CER LACN DEEP COM	1
80066	OP# VLT SKL CEREB LACN COMA NO	1
80069	OP# VLT SKL CEREB LACN W CONCU	2
80071	OP# VLT SKULL DURAL HEM/NO COM	1
80072	OP # VLT SKL DURAL HEM BRF COM	3
80100	CL # BASE SKULL NO INTRACR NOS	2
80101	CL # BASE SKULL NO INTRACR/COM	22
80102	CL# BAS SKL NO INTRACR BRF COM	7
80104	CL# BAS SKL NO INTRCR PROL COM	1
80109	CL# BAS SKL NO INTRACR W CONCU	1
80111	CL # BAS SKL CEREB LACN/NO COM	5
80112	CL# BAS SKL CEREB LACN BRF COM	2
80114	CL # BAS SKL CER LACN PROL COM	2
80115	CL # BAS SKL CER LACN DEEP COM	1
80120	CL # BASE SKULL DURAL HEM NOS	2

HI_Codes.xls
06/17/2003

Appendix 2.1

Head Injury Codes Found on ICU Patients
Severe Head Injury Study
Jan 1996 - Dec 2002

84

HI Code	Head Injury Diagnoses	Total
80121	CL# BAS SKULL DURAL HEM/NO COM	8
80122	CL # BAS SKL DURAL HEM BRF COM	7
80123	CL # BAS SKL DURAL HEM MOD COM	1
80124	CL# BAS SKL DURAL HEM PROL COM	3
80125	CL# BAS SKL DURAL HEM DEEP COM	4
80126	CL # BAS SKL DURAL HEM COMA NO	6
80131	CL# BAS SKULL W HEM NOS/NO COM	4
80132	CL # BAS SKL W HEM NOS BRF COM	1
80134	CL# BAS SKL W HEM NOS PROL COM	3
80135	CL# BAS SKL W HEM NOS DEEP COM	1
80140	CL # BASE SKULL W INTRACR NOS	2
80141	CL# BAS SKULL W INTRACR NO COM	4
80142	CL # BAS SKL W INTRACR BRF COM	1
80143	CL # BAS SKL W INTRACR MOD COM	2
80144	CL# BAS SKL W INTRACR PROL COM	2
80145	CL# BAS SKL W INTRACR DEEP COM	2
80151	OP # BASE SKULL NO INTRACR/COM	1
80152	OP# BAS SKL NO INTRACR BRF COM	2
80175	OP# BAS SKL DURAL HEM DEEP COM	1
80181	OP# BAS SKULL W HEM NOS/NO COM	1
80191	OP # BASE SKL W INTRACR NO COM	1
80220	CL FRACTURE MANDIBLE SITE NOS	4
80221	CL # CONDYLAR PROCESS MANDIBLE	6
80224	CL # RAMUS UNSPECIFIED MANDIBL	2
80225	CLOSED # ANGLE OF JAW MANDIBLE	2
80226	CL # SYMPHYSIS OF BODY MANDIBL	2
80228	CL # BODY MANDIBLE OTHER/UNSPE	6
80229	CL # MANDIBLE MULTIPLE SITES	3
80231	OP # CONDYLAR PROCESS MANDIBLE	1
80234	OP # RAMUS UNSPECIFIED MANDIBL	1
80235	OPEN # ANGLE OF JAW MANDIBLE	2
80236	OP # SYMPHYSIS OF BODY MANDIBL	2
80315	OTH CL # SKL CER LACN DEEP COM	1
80321	OTH CL# SKULL DURAL HEM/NO COM	2
80324	OTH CL# SKL DURAL HEM PROL COM	2
80325	OTH CL# SKL DURAL HEM DEEP COM	4
80334	OTH CL# SKL W HEM NOS PROL COM	1
80335	OTH CL# SKL W HEM NOS DEEP COM	1
80345	OTH CL# SKL W INTRACR DEEP COM	1
80382	OTH OP # SKL W HEM NOS BRF COM	1
85103	CORTEX CONTUSION NO OP/MOD COM	1
85106	CORTEX CONTUS NO OP WND/COMA N	1
85125	CORTEX LACN NO OP WND/DEEP COM	1
85140	BR STEM CONTUSION NO OP WND NO	1
85141	BR STEM CONTUS NO OPEN/NO COMA	2
85146	BR STEM CONTUS NO OPEN/COMA NO	1
85181	OTH BR LACN/CONTUS NO OPEN/COM	4
85182	OTH BR LACN/CONT NO OP/BRF COM	5
85184	OTH BR LACN/CONT NO OP/PROL CO	1
85185	OTH BR LACN/CONT NO OP/DEEP CO	6
85186	OTH BR LACN/CONT NO OP/COMA NO	3
85189	OTH BR LACN/CONT NO OP W CONCU	1
85195	OTH BR LACN/CONT W OP/DEEP COM	1

HI_Codes.xls
06/17/2003

Appendix 2.1

Head Injury Codes Found on ICU Patients
Severe Head Injury Study
Jan 1996 - Dec 2002

85

HI Code	Head Injury Diagnoses	Total
95901	HEAD INJURY NOS	16
S02000	FRACTURE OF VAULT OF SKULL, CLOSED	3
S02100	FRACTURE OF BASE OF SKULL, CLOSED	6
S02101	FRACTURE OF BASE OF SKULL, OPEN	1
S02200	FRACTURE OF NASAL BONES, CLOSED	1
S02300	FRACTURE OF ORBITAL FLOOR, CLOSED	1
S02400	FRACTURE OF MALAR AND MAXILLARY BONES, LEFORT 1, CLOSED	1
S02420	FRACTURE OF MALAR AND MAXILLARY BONES, COMBINED MIDFACE, CLOSED	1
S02430	FRACTURE OF MALAR AND MAXILLARY BONES, LEFORT 3, UNILATERAL, CLOSED	1
S02490	UNSPECIFIED FRACTURE OF MALAR AND MAXILLARY BONES, CLOSED	2
S02610	FRACTURE OF RAMUS, CLOSED	1
S02700	MULTIPLE FRACTURES INVOLVING SKULL AND FACIAL BONES, CLOSED	1
S02890	FRACTURE OF OTHER AND UNSPECIFIED SKULL AND FACIAL BONES NEC, CLOSED	1
S06000	CONCUSSION WITHOUT LOSS OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	1
S06010	CONCUSSION WITH BRIEF LOSS OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	1
S06100	TRAUMATIC CEREBRAL OEDEMA WITHOUT LOSS OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	1
S06110	TRAUMATIC CEREBRAL OEDEMA WITH BRIEF LOSS OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	1
S06140	TRAUMATIC CEREBRAL OEDEMA WITH PROLONGED LOSS OF CONSCIOUSNESS WITHOUT RETURN TO PRE-EXISTING LEVEL OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	5
S06190	TRAUMATIC CEREBRAL OEDEMA WITH LOSS OF CONSCIOUSNESS OF UNSPECIFIED DURATION WITHOUT OPEN INTRACRANIAL WOUND	1
S06200	DIFFUSE BRAIN INJURY WITHOUT LOSS OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	2
S06230	DIFFUSE BRAIN INJURY WITH PROLONGED LOSS OF CONSCIOUSNESS WITH RETURN TO PRE-EXISTING LEVEL OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	1
S06240	DIFFUSE BRAIN INJURY WITH PROLONGED LOSS OF CONSCIOUSNESS WITHOUT RETURN TO PRE-EXISTING LEVEL OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	2
S06241	DIFFUSE BRAIN INJURY WITH PROLONGED LOSS OF CONSCIOUSNESS WITHOUT RETURN TO PRE-EXISTING LEVEL OF CONSCIOUSNESS WITH OPEN INTRACRANIAL WOUND	1
S06290	DIFFUSE BRAIN INJURY WITH LOSS OF CONSCIOUSNESS OF UNSPECIFIED DURATION WITHOUT OPEN INTRACRANIAL WOUND	1
S06300	FOCAL BRAIN INJURY WITHOUT LOSS OF CONSCIOUSNESS, WITHOUT OPEN INTRACRANIAL WOUND	1
S06310	FOCAL BRAIN INJURY WITH BRIEF LOSS OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	1
S06400	EPIDURAL HAEMORRHAGE WITHOUT LOSS OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	2
S06410	EPIDURAL HAEMORRHAGE WITH BRIEF LOSS OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	1
S06490	EPIDURAL HAEMORRHAGE WITH LOSS OF CONSCIOUSNESS OF UNSPECIFIED DURATION WITHOUT OPEN INTRACRANIAL WOUND	1
S06500	TRAUMATIC SUBDURAL HAEMORRHAGE WITHOUT LOSS OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	2
S06510	TRAUMATIC SUBDURAL HAEMORRHAGE WITH BRIEF LOSS OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	1

HI_Codes.xls
06/17/2003

Appendix 2.1

Head Injury Codes Found on ICU Patients
Severe Head Injury Study
Jan 1996 - Dec 2002

86

HI Code	Head Injury Diagnoses	Total
S06530	TRAUMATIC SUBDURAL HAEMORRHAGE WITH PROLONGED LOSS OF CONSCIOUSNESS WITH RETURN TO PRE-EXISTING LEVEL OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	2
S06590	TRAUMATIC SUBDURAL HAEMORRHAGE WITH LOSS OF CONSCIOUSNESS OF UNSPECIFIED DURATION WITHOUT OPEN INTRACRANIAL WOUND	1
S06600	TRAUMATIC SUBARACHNOID HAEMORRHAGE WITHOUT LOSS OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	2
S06610	TRAUMATIC SUBARACHNOID HAEMORRHAGE WITH BRIEF LOSS OF CONSCIOUSNESS WITHOUT INTRACRANIAL WOUND	1
S06630	TRAUMATIC SUBARACHNOID HAEMORRHAGE WITH PROLONGED LOSS OF CONSCIOUSNESS WITH RETURN TO PRE-EXISTING LEVEL OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	1
S06640	TRAUMATIC SUBARACHNOID HAEMORRHAGE WITH PROLONGED LOSS OF CONSCIOUSNESS WITHOUT RETURN TO PRE-EXISTING LEVEL OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	3
S06800	OTHER INTRACRANIAL INJURIES WITHOUT LOSS OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	1
S06810	OTHER INTRACRANIAL INJURIES WITH BRIEF LOSS OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	4
S06840	OTHER INTRACRANIAL INJURIES WITH PROLONGED LOSS OF CONSCIOUSNESS WITHOUT RETURN TO PRE-EXISTING LEVEL OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	3
S06890	OTHER INTRACRANIAL INJURIES WITH LOSS OF CONSCIOUSNESS OF UNSPECIFIED DURATION WITHOUT OPEN INTRACRANIAL WOUND	3
S06910	INTRACRANIAL INJURY, UNSPECIFIED WITH BRIEF LOSS OF CONSCIOUSNESS WITHOUT OPEN INTRACRANIAL WOUND	2
S099	UNSPECIFIED INJURY OF HEAD	3
	Total Head Injury Codes	420

HI_Codes.xls
06/17/2003

APPENDICES

Appendix 2.2. **Brain Injury Data Form** **Page 1 of 8**

Study no:

DOB: (mm/dd/yyyy) Date of Admission: (mm/dd/yyyy)

Date of Death: (mm/dd/yyyy) Date of d/c from ICU: (mm/dd/yyyy)

Sex: Significant PMHx:

GCS at **scene**: E____ V____ M____ GCS in **hospital**: E____ V____ M____

Mechanism of head injury: MVC ___ Passenger___ Pedestrian ___ Bicycle___
Fall ___ Height:
NAI ___
Other ___

Management at scene:

PRISM III 12 Score: PRISM III 24 Score:

Appendix 2.2. Brain Injury Data Form **Page 2 of 8**

Vital signs	**At presentation**	**In ER**	**In ICU**	**At max ICP**	**Hour pre-brain death**	**At brain death**	**Procurement**
Pupils HR BP Temperature Mode of ventilation RR PIP MAP PEEP pH P_aO_2 PCO_2 Bic O_2 saturation ICP CPP							

Appendix 2.2. Brain Injury Data Form **Page 3 of 8**

Management	**At presentation**	**In ER**	**In ICU**	**At max ICP**	**Hour pre-brain death**	**At brain death**	**Procurement**
Fluids: NS 5% Albumin PRBC Other **Inotropes:** (max dose) Dopamine Epinephrine Norepinephrine Vasopressin Mannitol 3% Saline Lasix Thiopental Coma Hyperventilation **Sedation:** Midazolam Morphine Muscle relaxant							

Appendix 2.2. Brain Injury Data Form **Page 4 of 8**

No of episodes of hypotension:

Lowest Systolic BP: Day of admission:

Lowest Diastolic BP: Day of admission:

No of episodes of bradycardia:

Lowest HR: Day of admission:

DI: yes/no Day of admission:

SIADH: yes/no Day of admission:

Cardiac arrest: yes/no Day of admission:

Clinical brain death exam: yes/no No. of exams:

Cerebral perfusion scan: yes/no Results:

Date: (mm/dd/yyyy) Day:

Auditory Brainstem Responses: yes/no Result:

Date: (mm/dd/yyyy) Day:

Somatosensory Evoked Potential: yes/no Result:

Date: (mm/dd/yyyy) Day:

Time at declaration of brain death:

Time from brain injury to declaration of brain death:

Appendix 2.2. Brain Injury Data Form **Page 5 of 8**

Biochemistry	**In ER**	**In ICU (?time)**	**At max ICP**	**At brain death**	**Assessment for organ donation**
Arterial pH PCO_2 PO_2 Bicarbonate Lactate CKMB Troponin Na K Glucose Serum osmolarity Ionized calcium Bun Creatinine ALT AST GGT Bilirubin Hb Plt WBC INR PTT Fibrinogen D-dimer					

Appendix 2.2. Brain Injury Data Form **Page 6 of 8**

Radiological evaluation:

Cranial CT result: Day:

DAI

Cerebral edema

Cisterns effaced

Intraparenchymal contusion

Intraparenchymal hemorrhage

Uncal herniation

Transtentorial herniation

Herniation

Brainstem injury

Subdural

Epidural

SAH

Repeat CT: Day: Reason:

DAI

Cerebral edema

Cisterns effaced

Intraparenchymal contusion

Intraparenchymal hemorrhage

Uncal herniation

Transtentorial herniation

Herniation

Brainstem injury

Subdural

Epidural

SAH

Appendix 2.2. Brain Injury Data Form **Page 7 of 8**

Repeat CT: Day: Reason:

DAI

Cerebral edema

Cisterns effaced

Intraparenchymal contusion

Intraparenchymal hemorrhage

Uncal herniation

Transtentorial herniation

Herniation

Brainstem injury

Subdural

Epidural

SAH

Repeat CT: Day: Reason:

DAI

Cerebral edema

Cisterns effaced

Intraparenchymal contusion

Intraparenchymal hemorrhage

Uncal herniation

Transtentorial herniation

Herniation

Brainstem injury

Subdural

Epidural

SAH

Appendix 2.2. Brain Injury Data Form **Page 8 of 8**

MRI: Day of admission:

Other organ system injury:

Cardiology Evaluation:

ECG: Day of admission:

ECHO: Day of admission:

Doses of inotropes used during evaluation:

Cardiac catheterization: yes/no Results:

Suitability for organ (heart) donation: yes/no Reasons:

Organ donation:

Request for organ donation:

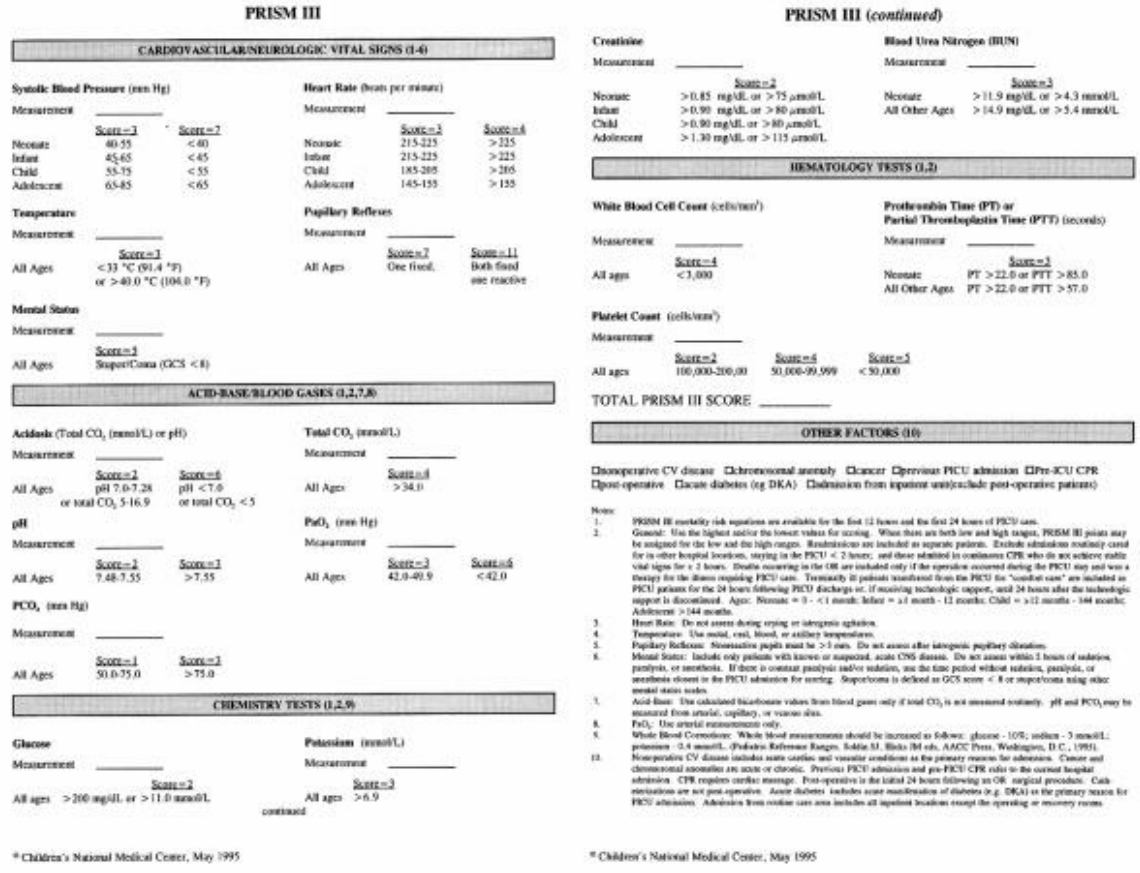
Consent given for organ donation:

Time from consent to organ procurement:

Rejection: Reasons:

Acceptance:

Appendix 2.3. The Pediatric Risk of Mortality III (PRISM III) score



PRISM III

CARDIOVASCULAR/NEUROLOGIC VITAL SIGNS (1-6)

Systolic Blood Pressure (mm Hg)

Measurement _____

	Score = 3	Score = 7
Neonate	40-55	< 40
Infant	45-65	< 45
Child	55-75	< 55
Adolescent	65-85	< 65

Heart Rate (beats per minute)

Measurement _____

	Score = 1	Score = 4
Neonate	215-225	> 225
Infant	215-225	> 225
Child	185-205	> 205
Adolescent	145-155	> 155

Temperature

Measurement _____

	Score = 1	
All Ages	< 33 °C (91.4 °F) or > 40.0 °C (104.0 °F)	

Pupillary Reflexes

Measurement _____

	Score = 7	Score = 11
All Ages	One fixed.	Both fixed one reactive

Mental Status

Measurement _____

	Score = 5
All Ages	Stupor/Coma (GCS < 8)

ACID-BASE/BLOOD GASES (1,2,7,8)

Acidosis (Total CO_2 (mmol/L) or pH)

Measurement _____

	Score = 2	Score = 6
All Ages	pH 7.0-7.28 or total CO_2 5-16.9	pH < 7.0 or total CO_2 < 5

Total CO_2 (mmol/L)

Measurement _____

	Score = 6
All Ages	> 34.0

pH

Measurement _____

	Score = 2	Score = 1
All Ages	7.48-7.55	> 7.55

PaO_2 (mm Hg)

Measurement _____

	Score = 3	Score = 6
All Ages	42.0-49.9	< 42.0

PCO_2 (mm Hg)

Measurement _____

	Score = 1	Score = 3
All Ages	50.0-75.0	> 75.0

CHEMISTRY TESTS (1,2,9)

Glucose

Measurement _____

	Score = 2
All ages	> 200 mg/dL or > 11.0 mmol/L

Potassium (mmol/L)

Measurement _____

	Score = 3
All ages	> 6.9

continued

* Children's National Medical Center, May 1995

PRISM III (*continued*)

Creatinine

Measurement _____

	Score = 2
Neonate	> 0.85 mg/dL or > 75 µmol/L
Infant	> 0.90 mg/dL or > 80 µmol/L
Child	> 0.90 mg/dL or > 80 µmol/L
Adolescent	> 1.30 mg/dL or > 115 µmol/L

Blood Urea Nitrogen (BUN)

Measurement _____

	Score = 3
Neonate	> 11.9 mg/dL or > 4.3 mmol/L
All Other Ages	> 14.9 mg/dL or > 5.4 mmol/L

HEMATOLOGY TESTS (1,2)

White Blood Cell Count (cells/mm³)

Measurement _____

	Score = 4
All ages	< 3,000

Prothrombin Time (PT) or Partial Thromboplastin Time (PTT) (seconds)

Measurement _____

	Score = 3
Neonate	PT > 22.0 or PTT > 85.0
All Other Ages	PT > 22.0 or PTT > 57.0

Platelet Count (cells/mm³)

Measurement _____

	Score = 2	Score = 4	Score = 5
All ages	100,000-200,00	50,000-99,999	< 50,000

TOTAL PRISM III SCORE _____

OTHER FACTORS (10)

☐noncperative CV disease ☐chromosomal anomaly ☐cancer ☐previous PICU admission ☐Pre-ICU CPR
☐post-operative ☐acute diabetes (eg DKA) ☐admission from inpatient unit(exclude post-operative patients)

Notes:

1. PRISM III mortality risk equations are available for the first 12 hours and the first 24 hours of PICU care.
2. General: Use the highest and/or the lowest values for scoring. When there are both low and high ranges, PRISM III points may be assigned for the low and the high ranges. Readmissions are included as separate patients. Exclude admissions routinely cared for in other hospital locations, staying in the PICU < 2 hours, and those admitted in continuous CPR who do not achieve stable vital signs for ≥ 2 hours. Deaths occurring in the OR are included only if the operation occurred during the PICU stay and was a therapy for the illness requiring PICU care. Terminally ill patients transferred from the PICU for "comfort care" are included as PICU patients for the 24 hours following PICU discharge or, if receiving technologic support, until 24 hours after the technologic support is discontinued. Ages: Neonate = 0 - < 1 month; Infant = ≥ 1 month - 12 months; Child = ≥ 12 months - 144 months; Adolescent > 144 months.
3. Heart Rate: Do not assess during crying or iatrogenic agitation.
4. Temperature: Use rectal, oral, blood, or axillary temperatures.
5. Papillary Reflexes: Nonreactive pupils must be > 3 mm. Do not assess after iatrogenic pupillary dilatation.
6. Mental Status: Include only patients with known or suspected, acute CNS disease. Do not assess within 2 hours of sedation, paralysis, or anesthesia. If there is constant paralysis and/or sedation, use the time period without sedation, paralysis, or anesthesia closest to the PICU admission for scoring. Stupor/coma is defined as GCS score < 8 or stupor/coma using other mental status scales.
7. Acid-Base: Use calculated bicarbonate values from blood gases only if total CO_2 is not measured routinely. pH and PCO_2 may be measured from arterial, capillary, or venous sites.
8. PaO_2: Use arterial measurements only.
9. Whole Blood Corrections: Whole blood measurements should be increased as follows: glucose - 10%; sodium - 3 mmol/L; potassium - 0.4 mmol/L. (Pediatric Reference Ranges, Soldin SJ, Hicks JM eds, AACC Press, Washington, D.C., 1995).
10. Noncperative CV disease includes acute cardiac and vascular conditions as the primary reasons for admission. Cancer and chromosomal anomalies are acute or chronic. Previous PICU admission and pre-PICU CPR refer to the current hospital admission. CPR requires cardiac massage. Post-operative is the initial 24 hours following an OR surgical procedure. Cath examinations are not post-operative. Acute diabetes includes acute manifestation of diabetes (e.g. DKA) as the primary reason for PICU admission. Admission from routine care area includes all inpatient locations except the operating or recovery rooms.

* Children's National Medical Center, May 1995

Questionnaire: Appendix 2.4 96

1. What are the investigations used in the assessment of cardiac function of potential organ (heart) donor?

2. What are the criteria used in the determination of myocardial dysfunction in children with severe brain injury?

3. What are the cardiac criteria used in the of acceptance donor hearts for transplants?

4. What are the cardiac criteria used in the rejection of donor hearts for transplants?

5. Are the following used prior to organ harvest to improve cardiac function?

   Insulin

   Triiodothyronine

6. What is the number of potential cardiac donor in a year at your centre?

7. What is the number of cardiac transplant performed in a year at your centre?

8. What is the number of post cardiac transplant patients that survived to hospital discharge?

End of Questionnaire

THANK YOU!

UNIVERSITY OF CALGARY

FACULTY OF MEDICINE
Department of Paediatrics, Alberta Children's Hospital

Questionnaire Cover Letter

Date:

Dear Dr

My name is Dr Audrey Lim, and I am a Graduate student in the Department of Community Health Sciences at the University of Calgary. I am conducting a retrospective study to determine the incidence and predictive factors of myocardial dysfunction in children with severe brain injury and also to study the impact of myocardial dysfunction on organ (heart) donation in children who succumbed to brain death.
This study will be conducted under the supervision of Dr Reg Sauve, Professor, Graduate Studies Program Chair, and has been approved by the Conjoint Health Research Ethics Board, University of Calgary.

A search of the literature failed to reveal an operational definition of myocardial dysfunction, as well, there was a lack of universal criteria for assessment of donor cardiac function. Enclosed is a survey to review the definition of myocardial dysfunction and the evaluation of cardiac donor function used by the cardiac transplant centers in Canada and North America, such as your center.

Your participation in this questionnaire is invaluable, as it will contribute to our knowledge of the criteria used in diagnosing myocardial dysfunction as well as the methods used in the evaluation of donor cardiac function in the various centers. This information may some day help in establishing universal criteria for assessment of donor cardiac function.

The questionnaire should take less than 20 minutes to complete. Upon completion, please return it by mail or email. A self-addressed envelope has been included for local mail.
I look forward to receiving the completed questionnaire.
A summary of the findings will be sent to you upon completion of the study.

If you have any questions regarding this research project, please contact Dr Audrey Lim [(403)943-7211 pager 3148, email: audrey.lim@calgaryhealthregion.ca]

Thank you for your time and your participation in this study.

Sincerely,

Audrey Lim, M.D., FRCPC