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A Study of Pediatric Heart Transplant Patients in Relationship to Post Transplant Coronary Artery Disease

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A Study of Pediatric Heart Transplant Patients in Relationship to Post Transplant Coronary Artery Disease

by

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in Preventive Care

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Each person whose signature appears below certifies that this dissertation in his/her opinion, is adequate in scope and quality as a dissertation for the degree of Doctor of Public Health.

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ABSTRACT OF THE DISSERTATION

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Doctor of Public Health in Preventive Care

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Post transplant coronary artery disease influences short and long-term survival of pediatric heart transplant recipients. Associated cardiovascular disease risk factors among non-heart transplant adult and pediatric heart populations for development of coronary artery disease have been documented. Little is known about these typical cardiovascular disease risk factors as well as other possible risk factors in the development of post transplant coronary artery disease. **Objective**: The purpose of this research was to examine children/adolescents (n=194), 5-18 years old, at least one-year post heart transplant. This study also investigated if there were physiological and psychological/behavioral differences between recipients with (n = 28) and without post transplant coronary artery disease (n = 166). **Method**: Archival (physiological) data were collected from the Loma Linda Heart Institute computer database, and behavioral prospective data were obtained from a mailed survey of parents (n = 173) (Child Behavior

Checklist and Demographic Information Form). **Results**: Total number of rejection episodes (4.88 vs 2.88) and mean triglyceride levels (115.50 vs 85.90) were higher for recipients with post transplant coronary artery disease. Parents reported psychological variables of anxiety/depression (50.67 vs 54.58), aggression (51.33 vs 54.26), and thought problems (50.00 vs 55.32) were higher for recipients without post transplant coronary artery disease. Recipients whose parents smoked in the past or currently smoke had a greater total number of rejection episodes (4.82 vs 2.58) than recipients with parents who did not smoke in the past or currently.

Conclusions: The results indicate that rejection episodes, triglyceride levels, and parental smoking behavior generate a greater risk for developing post transplant coronary artery disease. Addressing the implications of these results for pediatric heart transplant recipients, parents, and transplant programs should be accomplished by professionals who hold the skill and experience in the fields of preventive care and mental health. Focal point to lifestyle wellness dynamics such as nutrition, smoking cessation, and successful long-term behavior change in conjunction with transplant medical care will offer recipients the best chance for a long and improved quality of life.

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CHAPTER 1

INTRODUCTION

Pediatric heart transplantation is now a widely accepted medical therapy for children with end-stage heart disease (Luikart, 2001; Suddaby, 1999; Baum, Berstein, Starnes, Oyer, Pitlick, Stinson, & Shumway, 1991). Transplantation has been used in the treatment of children with acquired and congenital heart disease and performed successfully as early as the neonatal period (Webber, 1997; Baum et al., 1991). Heart transplantation in children at Loma Linda University began in the laboratory in 1978. This beginning research involved the use of animal models in context to cross species' transplant of the heart. Loma Linda University Medical Center entered the medical world arena in 1984 when an infant known as "Baby Fae" received the heart of a baboon due to the unavailability of a human donor heart. Since that point, Loma Linda has become a world leader in human to human infant heart transplantation accounting for approximately 50 percent of heart transplants in infants less than six months of age (Loma Linda University Medical Center, 2004). The five year actuarial survival rate of the cardiac transplanted children at Loma Linda University Children's Hospital (LLUCH) was 75% as of June, 2002. The national survival rates as of 1997 are 65% for pediatric heart transplant recipients (Loma Linda University Medical Center, 2004).

The development and implementation of heart transplantation procedures has been successful in offering an extended life for both adults and children suffering from

end stage cardiac disease. Although this surgical procedure is life saving, it is not without complications relative to the short and long-term outcomes of the patient. Complications associated with the survival of the pediatric heart transplant patient include infection, hypertension, tumors, chronic rejection, non-compliance, hyperlipidemia, and more recently post transplant coronary artery disease (Suddaby, 1999; Pahl, Fricker, Armitage, Griffith, Taylor, Uretsky, Beerman, & Zuberbuhler, 1990; Pahl, Zales, Fricker, & Addonizio, 1994; Waldo, Behrman, Kliegman, & Arvin, 1997; Addonizio, Hsu, Smith, Gersony, & Rose, 1990; & Uretsky, Murali, Reddy, Rabin, Lee, Griffith, Hardesty, Trento, & Bahnson,1987).

The leading causes of death in the pediatric heart transplant population have been identified as infection, rejection (acute and chronic), graft coronary artery disease, pulmonary hypertension, non-specific graft failure, and malignancy mortality (Waldo et al., 1995). More specifically, infection accounts for 32%, rejection 23%, graft coronary artery disease 20%, pulmonary hypertension 9%, non-specific graft failure 5%, and other unknown causes 7%, in the pediatric heart transplant patient (Waldo et al., 1995). There have been efforts to understand particular risk factors such as rejection episodes and the association with post transplant coronary artery disease. Given that the first three factors account for 75% of deaths among pediatric heart transplant patients, a better understanding of these causes is critical.

Very little research has addressed the possible association between risk factors and post transplant coronary artery disease. Research designed to understand post transplant coronary artery disease among pediatric heart transplant recipients has

identified demographic and physiological variables likely related to post transplant coronary artery disease. Pahl et al. (1994) attempted to understand the mechanisms and possible risk factors for post transplant coronary artery disease in the pediatric heart transplant population. These efforts provided support that specific risk factors, such as rejection episodes, are associated with post transplant coronary artery disease among this population. In addition, Pahl et al.'s research suggests that exploration of other risk factors for post transplant coronary artery disease is needed. Further investigation of rejection episodes and other possible risk factors for post transplant coronary artery disease is imperative to increase understanding, treatment, and prevention of post transplant coronary artery disease. Classical risk factors for coronary artery disease have been established for adult and pediatric healthy populations. Exploration of physiological and psychosocial risk factors will provide insight for interventions in a preventive and rehabilitative context in this special medical population.

A. Research Questions

Based on a retrospective/prospective cross-sectional study design, by examining the archival and surveyed data of pediatric heart transplant recipients and their parent(s), the following research questions were posed:

1) Is there a significant difference between heart transplant recipients with and without post transplant coronary artery disease for physiological, psychological, and demographic factors who were/are at least five to 18 years of age, one year post transplant, from the Loma Linda Medical Center?

2) What physiological, demographic, and psychosocial risk factors are associated with an increased risk in the development and promotion of post transplant coronary artery disease among heart transplant recipients who were/are at least five to 18 years of age, one year post transplant, from the Loma Linda Medical Center?

B. Theoretical Model

The theoretical model discussed in understanding the multi-etiological development and progression of post transplant coronary artery disease in a pediatric heart transplant population is the biopsychosocial model. The biopsychosocial model stems from the hierarchical constructs of general systems theory (Smith & Nicassio, 1995). Heart disease is best understood and studied from the general systems theory and biopsychosocial model due to its multi-factorial development, progression, and implications in mortality (Smith & Nicassio, 1995).

Post transplant coronary artery disease is a limiting factor to survival among pediatric heart transplant patients (Pahl et al, 1994; Waldo et al, 1995). The biopsychosocial model is important in understanding chronic non-infectious diseases by indicating that the development of coronary artery disease is etiologically multifactorial. The biopsychosocial model allows for the incorporation of biological, psychological, and social aspects of human life in order to understand the development and treatment of non-infectious disease. The biopsychosocial model describes the interactive process of genetics, environment, and lifestyle.

As proposed by Engel in 1977, the biopsychosocial model was a landmark departure from the traditional biomedical model. The traditional biomedical model

assumes that all illness is reflective of a biological break down, and that disease is fixed solely in the physiological explanation of disease. This reductionistic philosophy frequently disregards the psychological and social differences among patients who share a common medical diagnosis (Smith & Nicassio, 1995). Engel's model, therefore, expands the notion that the biomedical model (specific biochemical deviation), regarded generally as specific criterion for the diagnosis of disease/illness, excludes the complex interaction of the patient, the social context in which he/she lives, and the complimentary system developed by society to address the disruptive nature of illness (Engel, 1977).

The implication of the biopsychosocial model in the clinical understanding of disease can be understood through patient care. For example, when determination of a biological abnormality occurs in an organ of a patient (e.g., the heart and integral vessels), its full meaning and impact on that particular patient's functioning must be considered in the context of the patient's coping resources (e.g., psychological domains and behaviors), and relationships with significant others (e.g. the individual's environment). For instance, research indicates that factors such as depression, anxiety, stress, and social support are related to the early development of coronary heart disease (Rozanski & Blumenhal, & Kapln, 1999). The biomedical model is not designed to address the implications of behavioral and social components that affect the process of a disease such as coronary heart disease.

The understanding of coronary artery disease is considered to be a consequence of the physiological, environmental, social, and psychological

interactions that can be altered to promote or regress the process of atherosclerosis disease (Rozanski & Blumenhal, & Kapln, 1999). The pediatric heart transplant patient is in a multi-complex situation demanding enormous amounts of energy in conditions that are invasive physically, psychologically, and socially. Medical management, pre-evaluation, and post follow-up care is essential to comprehensive care. Heart disease demands such an approach. Specific programs that include exercise prescription, lifestyle changes such as dietary modification, psychological stress, and related social and personality risk factors in the initial development of coronary heart disease require an approach that considers all elements of a patient's life (Smith & Nicassio, 1995). The implications to the study of preventive care and psychology are evident with the special population of pediatric heart transplant recipients.

CHAPTER 2

LITERATURE REVIEW

A. Cardiovascular Risk Factors and Non-Transplant Children/Adolescents

While there has been an association between certain physiological and psychosocial risk factors and coronary artery disease within adult populations (Rozanski & Blumenhal, & Kapln, 1999; Farmer & Gotto, 1977), these same risk factors for the development of coronary artery disease have also been explored in child/adolescent populations (American Heart Association web site, 2004; Kwiterovich, 1995). Certain risk factors associated with the development of early lesions of coronary artery disease in youth include elevated plasma levels of total cholesterol and its major carrier low density lipoprotein (LDL); increased levels of triglyceride, and very low density lipoprotein (VLDL); a low level of high density lipoprotein (HDL), obesity, high blood pressure, cigarette smoking, and diabetes (American Heart Association, 2004).

The landmark article supporting the idea that coronary artery disease begins to develop in childhood/adolescents was authored by Enos et al (Enos, Beyer, & Holmes, 1955). In this article, the authors described the high frequency of advanced coronary artery lesions in young US soldiers killed in the Korean War. Evidence of coronary artery disease, primarily in the aorta, was observed in 77 percent of these soldiers whose average age was 22 years.

In support of the work by Enos et al (1955), the International Atherosclerosis Project (IAP) evaluated the pathology of atherosclerosis in 23,000 sets of aortas and coronary arteries collected from individuals in 14 countries. The IAP findings indicated that after 10 years of age early onset of fatty streaks in the aorta and the rapid increase of these streaks occur in all geographic locations. The IAP strongly supported the understanding that fatty streaks develop in children, coronary fatty streaks form in adolescence, and fibrous plaques begin to develop and progress into the twenties (American Academy of Pediatrics Part 2, 1992).

Systematic microscopic studies of arterial lesions among a young population have supported the early beginnings of the atherosclerosis process. Stary (1989) studied by light and electron microscope, unopened, pressure perfusion-fixed, left coronary arteries of 691 male and female individuals that had died between full-term birth and 39 years of age. More than half of these subjects were between the ages of 10-14 years and had lesions characterized by accumulation of macrophage foam cells, lipid-containing smooth muscle cells, and thinly scattered extracellular lipid, which represent the microscopic counterpart of fatty streaks. This particular microscopic study indicated that approximately eight percent of the subjects between the ages of 10-14 years had more advanced lesions which represent either lesions that were in transition to the formation of fibrous plaques or actual fibrous plaques. These data support the early beginnings of the atherosclerotic process. Though not specific to coronary artery disease in a pediatric transplant population, the strong microscopic based evidence supports the notion that development of coronary artery disease is

possible in context to development and progression among children and adolescents.

Research supports the idea that coronary artery disease begins early in life and is possibly associated with lipid levels. A post-mortem study of the aorta and coronary arteries of 150 male persons between the ages of 6-30 by Berenson et al. (1992) found a relationship between certain antecedent risk factors and the development of coronary artery disease (Berenson, Wattigney, Tracy, Newman, Srinivasam, Weber, & Dalferes, 1992). The authors of this study this study specifically concluded that the physiological condition of these aortas was associated to antemortem levels of total and LDL cholesterol and to ponderal index (weight/height). Also, fatty streaks in the coronary arteries were related to levels of VLDL cholesterol and triglyceride, systolic and diastolic blood pressure, and fatty streaks (Berenson et al., 1992). The authors suggested that lipid levels as well as other classical risk factors might be implicated in the development and progression of coronary artery disease at an early age.

Research as to the influence of lipids as well as other risk factors associated with coronary artery disease has been addressed. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study was overviewed in context to the influence of several risk factors on the progression of atherosclerosis in young people in the United States (Wissler, 1995). The assessment of the risk factors of hyperlipidemia, diabetes, smoking, and hyperglycemia were considered in context to the development of atherosclerosis among a young population. The major materials for this study were core samples of the thoracic and abdominal aorta as well as the proximal left circumflex and left anterior descending coronary arteries (Wissler, 1995). Specific

conclusions of the study were that coronary artery disease develops in young people, but at a much slower rate than aortic disease. In relationship to risk factors for the development and progression of coronary artery disease, smoking can damage the arteries of young individuals, hypertension is associated with an increased risk of áccelerated atherosclerosis in all parts of the arterial system, and obesity could increase the risk for coronary disease (Wissler, 1995).

Other research has considered the interaction of various cardiovascular risk factors such as passive smoke exposure, lipid levels, and socioeconomic status among pediatric populations. In a study conducted by Feldman et al (1991) passive tobacco smoke exposure among a healthy adolescent population from a suburban New York high school concluded that continine levels were elevated in subjects whose parents smoked. The study specifically showed that 44% of the adolescents reported that one or both parents currently smoked. Eleven percent of the subjects had elevated plasma cotinine levels that are considered indicative of exposure. The subjects in the study who had two parents that smoked had significantly higher plasma cotinine levels when compared to subjects whose parents did not smoke (Feldman, Shenker, Etzel, Spierto, Lilienfield, Nussbaum, & Jacobsen, 1991). Also as part of this study, passive smoke exposure was associated with an 8.9% greater ratio of total cholesterol to high density lipoprotein cholesterol and 6.8% lower high-density lipoprotein cholesterol. The study concluded that passive smoke exposure leads to alterations in lipid profiles predictive of an increased risk for atherosclerosis.

A study conducted by Moskowitz et al. (1990) utilizing 216 families of preadolescents children from the Medical College of Virginia twin study found that children in the 105 families of smoking parents had significantly lower HDL-C and higher whole blood 2,3-d phosphoglycerate levels than children in the 111 nonsmoking families. The study concluded that children exposed to passive tobacco smoke over a long period of time might be at elevated risk for early development of coronary artery disease (Moskowitz, Mosteller, Schieken, Bossano, Hewitt, & Segrest, 1990).

Consistent changes have also been found in children exposed to passive smoke and in young adults who smoke (Gidding et al., 1994). Children who smoke have higher levels of triglycerides, VLDL cholesterol, LDL cholesterol, and lower levels of HDL cholesterol (Gidding, Morgan, Perry, Isabel-Jones, & Bricker, 1994). Atherosclerosis and endothelial/epithelial injury serves as the primary precursor to the development of atherosclerosis among these young individuals. An immediate effect of tobacco smoke is an increase in the carboxyhemoglobin concentration. This is a by-product of the increased carbon monoxide and need for hemoglobin because of the tobacco smoking.

Smokers have been discovered to have increased platelet aggregation when compared with non-smokers. This same platelet aggregation occurs when a non-smoker is exposed to passive smoke (Gidding et al, 1994). Primary evidence linking passive tobacco smoke and atherosclerosis comes from the Patholobiological Determinants of Atherosclerosis in Youth (PDAY) study (Gidding et al., 1994). The

study demonstrated a correlation between biochemical markers (blood cotinine and thiocyanate levels) to coronary artery and arterial lesions in young adults between the ages of 15-35 years who died suddenly. Cigarette smoking increased the risk of having raised atherosclerotic plaques in all vascular beds, and included the right coronary artery and descending aorta. The potential for these raised atherosclerotic plaques was greatest in the descending aorta, which is similar to what is found in adults who smoke (Gidding et al., 1994).

Other research has addressed the association between tobacco smoke, socioeconomic status, and atherosclerosis. An experimental population of 194 children ages 4-14 years were evaluated in context to lipid levels, tobacco smoke exposure, and socioeconomic level of parents as measured by education level of parents (Iscan, Uyanik, Vurgun, Ece, & Yigitoglu, 1996). Results indicated that children in the lower socioeconomic class had higher levels of total cholesterol, LDL cholesterol, and the ratio of total cholesterol/HDL cholesterol as compared to the middle-high socioeconomic class of parents. The values for total cholesterol, LDL cholesterol, the ratio of total cholesterol/HDL cholesterol and the LDL cholesterol/HDL in the passive smoker group were found to be higher than the non-passive smoker group. The socioeconomic level in the passive smoker group was found to be lower than the non-passive smoker group, and implies that the impact of passive smoking on the lipid levels of the children was related to the socioeconomic level/status. The study concluded that passive smoking and lower socioeconomic level are important risk factors for cardiovascular disease in children.

Specific to children and adolescents, socioeconomic status, early life events, and coronary artery disease may have a basis for increased risk of atherosclerolitic heart disease later in life (Kaplan & Keil, 1993). Kaplan and Keil suggested that poor living conditions in childhood and adolescence increase the risk of arteriosclerotic heart disease later in life. In contrast, review of associations between early life experiences and cardiovascular disease was conducted by Elford, Shaper, & Whincup (1992). They concluded relationships found between early life experience, socioeconomic status, and later life cardiovascular disease may not be as statistically robust and therefore caution should be taken when interpreting this association.

Physiological and socioeconomic risk factors such as cholesterol and income level are important aspects of understanding the development and progression of coronary artery disease among children and adolescents. Psychological or behavioral factors have been suggested to be key mediators of the pathogenesis of heart disease, whether alone or through the interaction with biologic processes as major contributors for healthy or unhealthy hearts (Hunter, Bao, & Berenson, 1995; Rozanski et al., 1999). These particular factors include genetic markers, psychological variables (personality and coping style), social factors (socioeconomic status, developmental age, gender, race, and social interactions), and biological factors (blood pressure, lipoproteins) (Hunter et al., 1995).

Particular to pediatric heart transplant recipients, research as to the association between psychological/behavioral components and post transplant coronary artery disease is absent. Certain areas such as cognitive functioning and behavioral status

have been examined among pediatric heart transplant patients (Wray, Pot-Mees, Zeitlin, Radley-Smith, & Yacoub, 1994). Research conducted by Wray et al (1994) compared 65 children who had been given heart or lung transplants and two reference groups of 52 children who had other types of cardiac surgery (conventional surgery) and 45 healthy children considered cognitive functioning and behavioral status. Patients between the ages of 5-17 years, via parent's report, had significant problem behaviors at home after the transplant. Problem behaviors were described as neurotic (sleeping problems, misery, irritability, anxiety). Comparison of the transplant group to the reference groups indicated that the transplant group had more problem behaviors than healthy peers did. The prevalence of the problem behaviors (increased anxiety, depression, aggression) is supportive of other studies with chronically ill children (Wray et al., 1994).

Uzark, Sauer, Lawrence, Miller, Addonizio, & Crowley (1992) studied a pediatric heart transplant population (N=49) under the age of 16 years who were surviving three months or more after transplantation. The study utilized self report instruments for subjects older that eight years as well as parent reporting instruments relative to the subjects'/families' psychosocial functioning. As part of the assessment battery, the Child Behavior Checklist (CBCL) was implemented as a measurement of psychosocial adaptation (Achenbach & Edelbrock, 1983). The results of the study, and specifically the CBCL, indicated that the heart transplant recipients showed significantly less social competence and more behavioral problems than a normative population. The behavior problems most observed were suggestive of depression. The

study concluded that behavior problems, particularly suggesting depression and diminished social competence, were common in this population.

Todaro, Fennell, Sears, Rodrigue, and Roche (2000) reviewed the literature investigating the cognitive and psychological effects of pediatric heart transplantation. Studies investigating only cognitive and psychological outcomes, either prospectively or cross sectionally, were reviewed. This review concluded that children and adolescents generally function within the normal range on most measures of cognitive functioning post transplant. In addition, a complicated transplant course secondary to infections or rejections may place these patients at an increased risk for cognitive difficulties, and 20-24% of the recipients experienced significant psychological problems such as depression, anxiety, and behavior problems during the first year of transplant.

The literature supports both physiological and psychological risk factors for children and adolescents in the development of coronary artery disease that seems to start very early in age among the non transplant pediatric populations. Although these risk factors have not been explored within the pediatric transplant populations, they can serve as guide in understanding coronary artery disease among pediatric heart transplant recipients.

B. Coronary Artery Disease and Heart Transplantation

The study of heart transplant recipients indicates that post transplant coronary artery disease is a limiting factor to the long term survival for both adult and pediatric heart transplant populations (Valatine, 2000; Uretsky et al., 1987; Bieber, Hunt,

Schwinn, Jamieson, Reitz, Oyer, Shumway, & Stinson, 1987; Gao, Schroeder, Alderman, Hunt, Silverman, Wiederhold, & Stinson, 1987; & Gao, Schroeder, Hunt, & Stinson 1988; Pahl et al., 1990).

The Stanford Pediatric Heart Transplant Program suggested that acute rejection was one of the two most common and serious complications of heart transplantation among their pediatric population (Baum et al., 1991). These 15 years of data collection by the Stanford Pediatric Heart Transplant Program was based on a subject pool of 53 patients between the ages of 0.25 days to 19 years who received transplants at Stanford University Medical Center between 1974 and 1989. Cumulative survival rate of these patients was 79% at one year, 76% at 3 years, and 69% at five years among 31 male and 22 female patients. Specific to rejection episodes, the first three postoperative months demonstrated the highest frequency accounting for 70% of the subject pool. The time period after the first three postoperative months demonstrated a decline in rejection episodes. None of the patients surviving five years post transplant were absent of rejection episodes.

Research in support of the association between rejection episodes, post transplant coronary artery disease, and long term survival was conducted by Addonizio et al. (1990). This study incorporated 29 pediatric heart transplant patients, mean age 11 years with a range of 0.37-18 years, from the Columbia-Presbyterian Medical Center. Postoperative mortality greater than three months indicated that one-year survival rate was 91%, two-year survival rate was 77%, and a total of nine patients were marked as loss of graft. Of these nine patients, two patients received re-

transplantation and were survivors of the graft loss. There was increase in graft loss (i.e., mortality) after 20 months which was associated with noncompliance with immunosuppressive medications in four of seven patients. The etiology of graft loss in the nine patients was acute rejection in eight patients and myocardial infarction secondary to coronary disease in one patient. Interesting to the eight grafts lost due to rejection, examination revealed that two patients had rejection alone and six patients had post transplant coronary disease in addition to acute rejection.

The implications of this and previous mentioned studies is that rejection episodes are associated with post transplant coronary artery disease and subsequently to long term survival of the heart transplant recipient. Although these studies offer a better understanding of post transplant survival, rejection episodes, and post transplant coronary artery disease, other possible factors have been explored and are discussed below.

One of the larger and more comprehensive studies was conducted by Pahl et al (1994). In this study, 17 centers were surveyed on patient outcome and incidence of post transplant coronary artery disease performed between 1974 and 1993. A second questionnaire was sent to 17 centers in order to determine patient age at transplantation, age at death, time to diagnosis of post transplant coronary artery disease, and rejection episode history. In addition, information was gathered regarding angiography and autopsy results specific to post transplant coronary artery disease.

These 17 centers performed a total of 815 pediatric heart transplants, which included 188 neonates, and 560 survivors (69%). Post transplant coronary artery

disease was identified in 58 of the 815 heart transplant patients by angiography, autopsy, or both. Additional demographic information was available for 45 of these 58 identified post transplant coronary artery patients. In 45 of the total 58 patients, angiography was performed and was normal in 15 of the patients who subsequently died of post transplant coronary artery disease. Autopsy performed in 36 of the 49 patients who died, showed severe (> 75% narrowing) coronary artery stenosis in 28 of the 36 recipients (78%), and concurrent cellular rejection in 26 of these 36 autopsy recipients (72%).

Additional demographic data indicated that the study population mean age at date of diagnosis for post transplant coronary artery disease was 9.9 years (0.2-26 years), and the time from the date of transplant to date of diagnosis for post transplant coronary artery disease was a mean of 2.2 years (0.1-7.7 years). Mean age at transplantation was 7.6 (1 day to 18 years), and recipients were predominately male (70%). Among these 45 recipients, 16 (37%) of the deaths were sudden and unexpected.

Further information obtained from this study indicated that post transplant coronary artery disease was diagnosed in 16 of the original 58 patients who received transplants before the age of two. Also, out of the 58 patients with the diagnosed post transplant coronary artery disease, only nine were surviving which included five that had a second heart transplant.

This study suggests that a number of factors need to be considered in context to post transplant coronary artery disease among pediatric heart transplant patients.

This multi center study indicated that post transplant coronary artery disease is similar to that in the adult heart transplant populations, and that patients with post transplant coronary artery disease had a significant rejection history. This conclusion is similar to that found in other studies which indicated that post transplant coronary artery disease accounted for 36% of deaths from one to seven years after transplantation, and that cellular rejection was common at autopsy (Uretsky, Kormos, Zerbe, Lee, Tokarczyk, Murali et al, 1992; Kertesz, Towbin, Clunie, Fenrich, Friedman, Kearney, Dreyer et al, 2003).

This multi center study implied that all ages of patients were subject to post transplant coronary artery disease, and that non-compliance among teenage patients may be an antecedent to post transplant coronary artery disease. Pahl et al. (1994) concluded that alternative methods must be developed to allow for early detection, prevention, and treatment of coronary artery disease among pediatric heart transplant recipients.

The implications from this study and others are that post transplant coronary artery disease is related to a history of rejection episodes, and seemingly a precursor to the death of the recipient. The exploration of other possible risk factors and evaluation of established cardiovascular risk factors among pediatric heart transplant patients would help develop preventive and effective intervention strategies for post transplant coronary artery disease. Empirical data to this point clearly indicates the need for additional research in understanding post transplant coronary artery disease.

This proposed study is to ascertain and seek out psychosocial and physiological variables associated with pediatric post transplant coronary artery disease. Most of the measurement variables to employ in this study are known as well-established risk factors for coronary artery disease among the general public and non-transplant population. The understanding of how these established heart disease risk factors play a role in pediatric post transplant coronary artery disease can hopefully lead to effective prevention and treatment, and improve the survival of pediatric heart transplant recipients.

CHAPTER 3

METHOD

A. Study Design

The study utilized retrospective data from identified transplant recipients and survey data only among parents. A cross sectional design was used to collect descriptive data and determine the strength of association of post transplant coronary artery disease to coronary artery disease risk factors among pediatric heart transplant patients at Loma Linda Heart Institute.

B. Subjects

The subjects were 194 children/adolescents (deceased and alive) from Loma Linda University Medical Center (LLUMC) transplanted from 1984 to August 1998 (168 months) between the ages of five to 18 years, one-year post transplant. The subjects were 116 males (59.8%) and 78 females (40.2%).

C. Inclusion Criteria

1. Child/Adolescent

Child/adolescents between 5-18 years of age (n=194), one-year post transplant, who received a heart transplant at LLUMC who were either surviving or deceased at the time of data abstraction were included.

2. Parents

Parent(s) of children/adolescents currently between the age of 5-18 years (n=173), one year post transplant, who consented to participate and return survey.

D. Exclusion Criteria

1. Parents

All parents/guardians of the heart transplant recipients between the age of 5-18 years, one year post transplant, whose child/adolescent died (n=21, 10.8%) were excluded from prospective data collection.

E. List of Study Variables

1. Demographic Data of Heart Transplant Patients

Age, height, weight, gender, age at transplant, number of years post-transplant, and ethnicity were obtained through archival data at LLUMC.

2. Physiological Data of Heart Transplant Patients

The mean total number of rejection episodes, lipid levels (HDL, LDL, total cholesterol, triglyceride), systolic and diastolic blood pressure measurements, and diagnosed coronary artery disease (grade 1-4) were obtained through archival data at LLUMC.

3. Demographic and Behavioral Data of Parents

Specific data regarding parental socioeconomic status (level of income)

and smoking and exercise behavior were collected through a Demographic Information Form developed by the primary investigator (see appendix B).

4. Psychological Variables/Child Behavior Checklist

Child Behavior Checklist (CBCL). Designed to measure behavior problems, the CBCL (Achenbach & Edelbrock, 1983) is one of the most widely used standardized measures of child psychopathology. The total problem score is considered analogous to the construct of general ability as represented by total scores on intelligence tests, with lower scores reflecting less psychopathology. Overall, correlations among total problem scores for the CBCL and other instruments have been found to be as high as correlations reported for different measures of general intelligence. In terms of criterion-related validity, different scale scores and total scores for the CBCL consistently discriminate clinical and non-referred samples after demographic effects are partialled out.

Although three forms of the CBCL (i.e., Teacher Report Form, Parent Report Form, and Youth Self Report Form; Achenbach & Edelbrock, 1983) are available, this study examined only the Parent Report Form.

F. Procedures

Abstraction of specific physiological data for surviving and deceased heart transplant recipients (n=194) were provided by computer archival database with the help of departmental research staff at Loma Linda University Medical Center/Pediatric

Heart Transplantation. Multiple measures of all variables used were calculated as a mean for statistical analysis.

Informed Consent (see appendix A), Questionnaires (Demographic Information Form & Child Behavior Checklist), incentive (five-dollar gift certificate from Toys-R-Us), and a self-addressed stamped envelope were mailed to the parents of surviving (n=166) heart transplant patients. All mailings were returned to Loma Linda Pediatric Heart Institute. Questionnaires/instruments were evaluated, scored, and checked for missing data. Follow-up phone calls (see appendix C) to parents to gather missing information occurred within one week after the primary investigator sent out the questionnaire.

Follow-up telephone calls by hospital support staff and primary investigator were also conducted for individuals who had not responded to the CBCL and Demographic Information Form within an eight-week period (beginning from the mailing date). Parents who did not respond in the first two weeks were called and asked to mail the completed CBCL and Information Form. Parents, when called, who stated that they did not receive a Child Behavior Checklist and Information Form (N=6), were mailed another packet. Returned mailings due to incorrect addresses (N=15) were not re-mailed. Received mailings (83/166, 50% response rate) were evaluated and scored by primary investigator.

G. Data Analysis

Means, frequencies, standard deviations, and percentages were calculated for physiological and demographic variables from archival data for recipients with and

without post transplant coronary artery disease. Psychological and parent health behavior variables as determined by Child Behavior Checklist and Demographic Information Form among surviving recipients with and without post transplant were included in the analysis. Chi Square, independent T-test, and regression analysis were computed for determining differences and associations among physiological, psychological, parent health behavior, and demographic variables for recipients with and without post transplant CAD.

CHAPTER 4

PUBLISHABLE PAPER

Journal of Pediatric Psychology

Pediatric Heart Transplantation: Physiological and Psychological Differences Among Recipients With and Without Post Transplant Coronary Artery Disease

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Abstract

The purpose of this research was to examine children/adolescents (n=194), between 5-18 years old, one-year post heart transplant. **Objective**: Determine specific physiological and psychological/behavioral differences between recipients with (n = 28) and without post transplant coronary artery disease (n = 166). **Method**: Archival (physiological) data were abstracted from Loma Linda Heart Institute computer database and a mailed survey sent to parents to assess psychological/behavioral variables. **Results**: Total number of rejection episodes and mean triglyceride levels were higher for recipients with post transplant coronary artery disease. Psychological variables anxious/depression, aggression, and thought problems were higher for recipients without post transplant coronary artery disease. Recipients whose parents smoked in the past or currently smoke had a higher rate of total number of rejection episodes.

Conclusions: The results indicate that rejection episodes, triglyceride levels, and parental smoking behavior generate a greater risk for developing post transplant coronary artery disease. Focal point to lifestyle wellness dynamics such as nutrition, smoking cessation, and successful long-term behavior change in conjunction with transplant medical care will offer recipients the best chance for a long and better quality of life.

Introduction

Pediatric heart transplantation is now a widely accepted medical therapy for children with end-stage heart disease (Luikart, 2001; Suddaby, 1999; Duitsman, Suddaby, & Masterson, 1999; Baum, Berstein, Starnes, Oyer, Pitlick, Stinson, & Shumway, 1991). Transplantation has been used in the treatment of children with acquired and congenital heart disease and performed successfully as early as the neonatal period (Webber, 1997; Baum et al., 1991). Heart transplantation in children at Loma Linda University began in the laboratory in 1978. This beginning research involved the use of animal models in context to cross species' transplant of the heart. Loma Linda University Medical Center entered the medical world arena in 1984 when an infant known as "Baby Fae" received the heart of a baboon due to the unavailability of a human donor heart. Since that point, Loma Linda has become a world leader in human to human infant heart transplantation.

The development and implementation of heart transplantation procedures has been successful in offering an extended life for both adults and children suffering from end stage cardiac disease. Although this surgical procedure is life saving, it is not without complications relative to the short and long-term outcomes of the patient. Complications associated with the survival of the pediatric heart transplant patient include infection, hypertension, tumors, chronic rejection, non-compliance, hyperlipidemia, and more recently post transplant coronary artery disease (Suddaby, 1999; Pahl, Fricker, Armitage, Griffith, Taylor, Uretsky, Beerman, & Zuberbuhler, 1990; Pahl, Zales, Fricker, & Addonizio, 1994; Waldo, Behrman, Kliegman, & Arvin,

1997; Addonizio, Hsu, Smith, Gersony, & Rose, 1990; Uretsky, Murali, Reddy, Rabin, Lee, Griffith, Hardesty, Trento, & Bahnson,1987).

Very little research has addressed the possible association between risk factors and post transplant coronary artery disease. Research designed to understand post transplant coronary artery disease among pediatric heart transplant recipients has identified possible demographic and physiological variables that may contribute to post transplant coronary artery disease. Pahl, Zales, Fricker, and Addonizio (1994) attempted to understand the mechanisms and possible risk factors for post transplant coronary artery disease in the pediatric heart transplant population. These efforts provide support that specific risk factors, such as rejection episodes, are associated with post transplant coronary artery disease among this population. In addition, this research suggests that exploration of other risk factors for post transplant coronary artery disease is needed. Further investigation of rejection episodes and other possible risk factors for post transplant coronary artery disease is imperative to increase understanding, treatment, and prevention of post transplant coronary artery disease. Classical risk factors for coronary artery disease have been identified for adult and pediatric healthy populations. Exploration of physiological and psychosocial risk factors will provide insight for interventions in a preventive and rehabilitative context in this special medical population.

Literature Review

Cardiovascular Risk Factors and Non-Transplant Children/Adolescents

While there has been an association between certain physiological and psychosocial risk factors and coronary artery disease within adult populations (Rozanski & Blumenhal, & Kapln, 1999; Farmer & Gotto, 1997), these same risk factors for the development of coronary artery disease have also been explored in child/adolescent populations (American Heart Association web site, 2004; Kwiterovich, 1995). Certain risk factors associated with the development of early lesions of coronary artery disease in youth include elevated plasma levels of total cholesterol and its major carrier low density lipoprotein (LDL); increased levels of triglyceride, and very low density lipoprotein (VLDL); a low level of high density lipoprotein (HDL), obesity, high blood pressure, cigarette smoking, and diabetes (American Heart Association web site, 2004).

The landmark article supporting the idea that coronary artery disease begins to develop in childhood/adolescents was supplied by Enos et al (Enos, Beyer, & Holmes, 1955). In this article the authors described the high frequency of advanced coronary artery lesions in young US soldiers killed in the Korean War. Evidence of coronary artery disease, primarily in the aorta, was observed in 77 percent of these soldiers whose average age was 22 years.

In support of the work by Enos et al (1955), the International Atherosclerosis Project (IAP) evaluated the pathology of atherosclerosis in 23,000 sets of aortas and coronary arteries collected from individuals in 14 countries. The IAP findings

indicated that after 10 years of age early onset of fatty streaks in the aorta and the rapid increase of these streaks occur in all geographic locations (American Academy of Pediatrics Part 2, 1992).

Research supports the idea that coronary artery disease begins early in life and is possibly associated with lipid levels. A post-mortem study of the aorta and coronary arteries of 150 male persons between the ages of 6-30 by Berenson, Wattigney, Tracy, Newman, Srinivasam, and Weber et al (1992) found a relationship between certain antecedent risk factors and the development of coronary artery disease (Berenson, Wattigney, Tracy, Newman, Srinivasam, Weber, & Dalferes, 1992). The authors of this study concluded that the physiological condition of these aortas was associated to antemortem levels of total and LDL cholesterol and to ponderal index (weight/height). Also, fatty streaks in the coronary arteries were related to levels of VLDL cholesterol and triglyceride, systolic and diastolic blood pressure, and fatty streaks (Berenson et al., 1992). The authors suggested that lipid levels as well as other classical risk factors might be implicated in the development and progression of coronary artery disease at an early age.

Research as to the influence of lipids as well as other risk factors associated with coronary artery disease has been addressed. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study was overviewed in context to the influence of several risk factors on the progression of atherosclerosis in young people in the United States (Wissler, 1995). The assessment of the risk factors of hyperlipidemia, diabetes, smoking, and hyperglycemia were considered in context to the development of

atherosclerosis in a young population. Specific conclusions of the study were that coronary artery disease develops in young people. In relationship to risk factors for the development and progression of coronary artery disease, smoking can damage the arteries of young individuals, hypertension is associated with an increased risk of accelerated atherosclerosis in all parts of the arterial system, and obesity increases the risk for coronary disease (Wissler, 1995).

Psychological or behavioral factors have been suggested as key mediators of the pathogenesis of heart disease, whether alone or through the interaction with biologic processes as major contributors for healthy or unhealthy hearts (Hunter, Bao, & Berenson, 1995; Rozanski et al., 1999). These particular factors include genetic markers, psychological variables (personality and coping style), social factors (socioeconomic status, developmental age, gender, race, and social interactions), and biological factors (blood pressure, lipoproteins) (Hunter et al., 1995).

Particular to pediatric heart transplant recipients, research on the association between psychological/behavioral components and post transplant coronary artery disease is absent. Certain areas such as cognitive functioning and behavioral status have been examined among pediatric heart transplant patients (Duitsman, Suddaby, & Masterson, 1999; Suddaby, 1999; Wray, Pot-Mees, Zeitlin, Radley-Smith, & Yacoub, 1994). Todaro, Fennell, Sears, Rodrigue, and Roche (2000) reviewed the literature on the cognitive and psychological effects of pediatric heart transplantation. Studies investigating only cognitive and psychological outcomes, either prospectively or cross sectionally, were reviewed. The authors concluded that children and adolescents

generally are within the normal range on most measures of cognitive functioning post transplant. In addition, a complicated transplant course secondary to infections or rejections may place these patients at increased risk for cognitive difficulties, and 20-24% of the recipients experienced significant psychological problems such as depression, anxiety, and behavior problems during the first year of transplant.

Uzark, Sauer, Lawrence, Miller, Addonizio, and Crowley (1992) studied a pediatric heart transplant population (N=49) under the age of 16 years who were surviving three months or more after transplantation. The study utilized self report instruments for subjects older that eight years as well as parent reporting instruments relative to the subjects'/families' psychosocial functioning. As part of the assessment battery, the Child Behavior Checklist (CBCL) was implemented as a measurement of psychosocial adaptation. The results of the study, and specifically the CBCL, indicated that the heart transplant recipients showed significantly less social competence and more behavioral problems than a normative population. The most frequent behavior problems observed were suggestive of depression and diminished social competence.

Coronary Artery Disease and Heart Transplantation

Research in support of the association between rejection episodes, post transplant coronary artery disease, and long term survival was conducted by Addonizio et al. (1990). This study included 29 pediatric heart transplant patients, mean age 11 years with a range of 0.37-18 years, from the Columbia-Presbyterian Medical Center. Postoperative mortality greater than three months indicated that one-year survival rate was 91%, two-year survival rate was 77%, and a total of nine

patients were marked as loss of graft. Of these nine patients, two patients received re-transplantation and were survivors of the graft loss. There was increase in graft loss (i.e., mortality) after 20 months, which was associated with noncompliance with immunosuppressive medications in four of seven patients. The etiology of graft loss in the nine patients was acute rejection in eight patients and myocardial infarction secondary to coronary disease in one patient. Interesting to the eight grafts lost due to rejection, examination revealed that two patients had rejection alone and six patients had post transplant coronary disease in addition to acute rejection. Thus, post transplant coronary artery disease in conjunction with acute rejection seems to be associated with a higher incidence of graft loss than acute rejection alone.

One of the larger and more comprehensive studies was conducted by Pahl et al (1994). In this study, 17 centers were surveyed on patient outcome and incidence of post transplant coronary artery disease performed between 1974 and 1993. A second questionnaire was sent to 17 centers in order to determine patient age at transplantation, age at death, time to diagnosis of post transplant coronary artery disease, and rejection episode history. In addition, information was gathered regarding angiography and autopsy results specific to post transplant coronary artery disease.

These 17 centers performed a total of 815 pediatric heart transplants, which included 188 neonates, and 560 survivors (69%). Post transplant coronary artery disease was identified in 58 of the 815 heart transplant patients by angiography, autopsy, or both. Additional demographic information was available for 45 (78%) of these 58 identified post transplant coronary artery patients. In 45 of the total 58

patients, angiography was performed and was normal in 15 (33%) of the patients who subsequently died of post transplant coronary artery disease. Autopsy performed in 36 (73%) of the 49 patients who died, showed severe (> 75% narrowing) coronary artery stenosis in 28 (78%) of the 36 recipients, and concurrent cellular rejection in 26 (72%) of these 36 autopsy recipients. Additional demographic data indicated that the study population mean age at date of diagnosis for post transplant coronary artery disease was 9.9 years (0.2-26 years), and the time from the date of transplant to date of diagnosis for post transplant coronary artery disease was a mean of 2.2 years (0.1-7.7 years). Mean age at transplantation was 7.6 years (1 day to 18 years), and recipients were predominately male (70%). Among these 45 recipients, 16 (37%) of the deaths were sudden and unexpected.

Further information obtained from this study indicated that post transplant coronary artery disease was diagnosed in 16 of the original 58 patients who received transplants before the age of two. Also, out of the 58 patients with the diagnosed post transplant coronary artery disease, only nine were surviving which included five that had a second heart transplant.

Thus, Pahl et al (1994) study demonstrates that a number of factors need to be considered in context to post transplant coronary artery disease among pediatric heart transplant patients. These factors include that post transplant coronary artery disease is similar to that in the adult heart transplant populations, and that patients with post transplant coronary artery disease had a significant rejection history. This conclusion is similar to that found in other studies which indicated that post transplant coronary

artery disease accounted for 36% of deaths from one to seven years after transplantation, and that cellular rejection was common at autopsy (Uretsky, Kormos, Zerbe, Lee, Tokarczyk, Murali et al, 1992). Pahl et al (1994) also concluded that alternative methods must be developed to allow for early detection, prevention, and treatment of coronary artery disease among pediatric heart transplant recipients.

The implications from this study and others are that post transplant coronary artery disease is related to a history of rejection episodes, and seemingly a precursor to the death of the recipient. The exploration of other possible risk factors and evaluation of established cardiovascular risk factors among pediatric heart transplant patients would help develop preventive and effective intervention strategies for post transplant coronary artery disease. Empirical data to this point clearly indicate the need for additional research in understanding post transplant coronary artery disease.

The proposed study is to determine psychosocial and physiological variables associated with pediatric post transplant coronary artery disease in a pediatric population. Most of the measurement variables in the proposed study are well-established risk factors for coronary artery disease among the general public and non-transplant population. An understanding of how these established heart disease risk factors play a role in pediatric post transplant coronary artery disease is central to the proposed study. Hopefully this study will lead to effective prevention and treatment of post transplant coronary artery disease, and improve the survival and quality of life of pediatric heart transplant recipients.

Method

Study Design The study utilized retrospective data from identified transplant recipients and survey data of parents. A cross sectional design was used to collect descriptive data and determine the strength of association of post transplant coronary artery disease to risk factors among pediatric heart transplant patients at Loma Linda Heart Institute.

Subjects The subjects were 194 children/adolescents (deceased and alive) from Loma Linda University Medical Center (LLUMC) transplanted from 1984 to August 1998 (168 months) between the ages of five to 18 years, one-year post transplant. The subjects were 116 males (59.8%) and 78 females (40.2%).

Inclusion Criteria

Child/Adolescent Child/adolescents between 5-18 years of age (n=194), one-year post transplant, who received a heart transplant at LLUMC, who were either surviving or deceased at the time of data abstraction.

Parents Parent(s) of surviving children/adolescents between the age of 5-18 years (n=173), one year post transplant, who consented to participate and return survey.

Exclusion Criteria

Parents All parents/guardians of the heart transplant recipients between the age of 5-18 years, one year post transplant, whose child/adolescent died (n=21, 10.8%) were excluded from prospective data collection.

List of Study Variables

1. Demographic Data of Heart Transplant Patient: Age, height, weight, gender, age at transplant, number of years post-transplant, and ethnicity were obtained through archival data at LLUMC.

2. Physiological Data of Heart Transplant Patient: The mean total number of rejection episodes, lipid levels (HDL, LDL, total cholesterol, triglyceride), systolic and diastolic blood pressure measurements, and diagnosed coronary artery disease (grade 1-4) were obtained through archival data at LLUMC.

3. Demographic and Behavioral Data of Parent: Specific data regarding parental socioeconomic status (level of income) and smoking and exercise behavior were collected through a Demographic Information Form developed by primary investigator.

4. Psychological Variables/Child Behavior Checklist: Data regarding child/adolescent psychological variables were obtained from parents as measured by the Child Behavior Checklist (Achenbach & Edelbrock, 1983).

Procedures

Abstraction of specific physiological data for surviving and deceased heart transplant recipients (n=194) were provided by computer database with the help of departmental research staff at Loma Linda University Medical Center/Pediatric Heart Transplantation. Multiple measures of all variables were calculated as a mean for statistical analysis.

Informed Consent, Questionnaires (Demographic Information Form & Child Behavior Checklist), incentive (five-dollar gift certificate from Toys-R-Us), and a self-addressed stamped envelope were mailed to the parents of surviving (n=166) heart transplant patients. All mailings were returned to Loma Linda Pediatric Heart Institute. Questionnaires/instruments were evaluated, scored, and checked for missing data. Follow-up phone calls to parents to gather missing information occurred within one week after the primary investigator sent out the questionnaire.

Follow-up telephone calls by hospital support staff and primary investigator were also conducted after the first week for individuals who had not responded to the CBCL and Demographic Information Form. CBCL and Demographic Information Form returned within an eight-week period (beginning from the mailing date) were included.

Parents who did not respond in the first two weeks were called and asked to mail the completed CBCL and Information Form. Parents, when called, who stated that they did not receive a Child Behavior Checklist and Demographic Information Form (N=6), were mailed another packet. Returned mailings due to incorrect addresses (N=15) were not re-mailed. Received mailings (83/166, or 50% response rate) were evaluated and scored by primary investigator.

Data Analysis

Means, frequencies, standard deviations, and percentages were calculated for physiological and demographic variables from the archival data base for recipients with and without post transplant coronary artery disease. Psychological and parent

health behavior variables as determined by Child Behavior Checklist and Demographic Information Form among surviving recipients with and without post transplant were included in the analysis. Chi Square, independent t-test, and regression analysis were computed for determining differences and associations among physiological, psychological, parent health behavior, and demographic variables for recipients with and without post transplant CAD.

Results

Demographic Variables of Total Study Population: Recipients and Parents

Total post heart transplant patients included in the study were 194 (alive=173, 89.2%, deceased=21, 10.8%). The parent who completed the Child Behavior Checklist and Demographic Information Form were predominately the child's mother (n=71/85, 83.5%). Age, race, and gender of study population with and without post transplant coronary artery disease (PTxCAD) were compared (see Table 4.1). Age of the surviving transplant study group (n=173) was a mean of 8 years. No significant difference among recipients with and without post transplant coronary artery disease was found for age, race, and gender. Mean time since date of transplant for study group was 7 years. A significant difference ($p \leq .01$) was found in that older recipients were more likely to have PTxCAD (M=8.58 years) as compared to non PTxCAD recipients (M= 6.87 years) with respect to time since transplant.

Table 4.1

Demographics of All Recipients. PTxCAD vs Non-PTxCAD

Variable	n	PTxCAD	SD	n	N-PTxCAD	SD	p-value
Age (yrs)	14	M=9.5	2.01	159	M=8.35	2.67	.115
Gender							
Male	17	60.7%		99	59.6%		.914
Female	11	39.3%		67	40.4%		
Race							
Caucasian	16	57.1%		99	59.6%		.910
Hispanic	8	28.6%		48	28.9%		
Others	4	14.3%		19	11.4%		
Time since transplant (yrs)	14	M=8.58	1.54	159	M=6.87	2.34	.008 *

PTxCAD=post transplant coronary artery disease
Non-PTxCAD=no post transplant coronary artery disease
yrs=years
Chi Square (gender, race)
T-Test (age, time since transplant),

Physiological Data. Recipients With PTxCAD vs Non-PTxCAD

Results for recipients with and without post transplant CAD for all physiological variables included in the comparisons are listed (see Table 4.2). Recipients with and without post transplant coronary artery disease (PTxCAD) correspond to deceased and surviving child/adolescents with obtainable physiological variables abstracted from Loma Linda University Medical Center databases.

A significant difference ($p \leq .05$) was found between PTxCAD and non-PTxCAD recipients for total number of rejections ($p \leq .02$), where recipients with PTx CAD had a much higher mean of 4.88 rejections versus a mean for non PTxCAD recipients of 2.88 rejections. A significant difference was also noted with respect to triglycerides ($p \leq .05$), where recipients with PTxCAD had a mean of 115.50 versus non-PTxCAD recipients with a significantly lower mean of 85.90.

Psychological variables as measured by the Child Behavior Checklist (CBCL) were compared between surviving recipients with (n=6) and without (n=77) post transplant CAD (see Table 4.3). Specific variables shown to be significantly different between recipients with and without PTxCAD were aggression (51.33 vs 54.26), anxious/depressed (50.67 vs 54.58), and thought problem scales (50.00 vs 55.32) of CBCL, which shows higher levels of these variables among those without PTxCAD.

Physiological variables were evaluated in context to past smoking behavior of the parents. Children with PTxCAD had higher mean number of rejection episodes (see table 4.2).

Independent t-test indicated that recipients with at least one parent who smoked in the past had a significantly higher mean total number of rejection episodes (m=4.82) compared to recipients whose parent(s) did not smoke (m=2.58, $p \leq .01$).

Table 4.2

Physiological Variables of All Recipients. PTxCAD vs Non-PTxCAD

Variables	n	PTxCAD (M)	SD	n	N-PTxCAD (M)	SD	p-value
Total cholesterol	16	148.46	30.71	102	151.14	28.96	.73
HDL cholesterol	12	34.00	11.53	87	38.04	9.85	.19
LDL cholesterol	12	104.64	32.93	85	100.90	25.08	.64
Triglyceride	14	115.50	76.93	130	85.90	47.59	.05 *
Total rejections	25	4.88	3.79	93	2.88	1.90	.01 *
BMI	14	15.28	1.55	78	16.99	6.85	.35
Systolic BP	7	115.28	21.96	51	109.78	14.47	.38
Diastolic BP	7	73.85	16.90	51	69.01	11.07	.31

Independent t-test * Significant $p \leq .05$
PTxCAD=post transplant coronary artery disease
Non-PTxCAD=no post transplant coronary artery disease

Table 4.3

Child Behavior Checklist Variables. Surviving PTxCAD vs Non-PTxCAD

Variable	n	PTxCAD (M)	SD	n	N-PTxCAD (M)	SD	p-value
Internal	6	49.50	6.53	77	53.55	11.54	.40
External	6	47.33	5.43	77	50.49	10.46	.46
T-CBCL	6	51.67	2.73	73	53.64	11.81	.27
T-competence	5	39.40	9.76	58	39.79	12.08	.94
Comp/activity	6	46.17	7.63	64	43.17	9.06	.43
Comp-school	6	35.67	11.81	60	36.43	9.69	.85
Comp-social	6	44.00	9.47	63	41.17	9.95	.50
Anxious/depressed	6	50.67	1.03	77	54.58	7.77	.01 *
Aggression	6	51.33	1.97	77	54.26	6.90	.01 *
Attention problem	6	57.50	5.99	77	57.94	10.11	.91
Delinquent	6	52.83	3.25	77	53.62	5.93	.74
Social problem	6	59.83	9.81	77	57.19	8.93	.49
Somatic problem	6	55.50	6.06	77	60.49	9.41	.20
Thought problem	6	50.00	.00	77	55.32	7.04	.01 *
Withdrawn	6	54.83	5.49	77	54.75	7.52	.98

Independent t-test

Statistical analysis was conducted to account for the possibility that this difference is due to the length of time since that parent had smoked (i.e. time since transplant), which may result in a greater accumulation of rejection episodes. An independent t-test demonstrated a significant difference regarding the current age of the recipient and those parents who reported smoking in the past (M=10.18) and those parents who did not smoke in the past (M=7.56, $p \leq .01$). Regression analysis was employed to consider total number of rejection episodes as the dependent variable, and smoking in the past and current age as the independent variables. The regression analysis indicated that the overall model was significant ($p \leq .01$) and smoking in the past was significant ($p \leq .02$) as was current age ($p \leq .01$). Therefore, past parental smoking, not just current age of the recipient (i.e. time since transplant), seems to be contributing to the total number of rejection episodes that a recipient experiences.

A Pearson correlation matrix was computed for continuous variables, which are presented in Table 4.4. Results indicate various significant linear associations between physiological (i.e. rejection episodes), demographic (i.e., time since transplant and recipient age), and current parent smoking behavior. Total number of rejection episodes had a positive correlation with the number of cigarettes (M=8.3) that a parent currently smoked (.587 $p \leq .05$), time since transplant (.325 $p \leq .01$), and current age (.301$p \leq .01$).

Table 4.4

Correlations of Recipient Physiological, Demographic, Psychological, and Parental Smoking Data

Variable (DV)	Variable (IV)	Pearson r	p value
Total number of rejections	Current age	.301**	.01
	Number of cigarettes	.587*	.05
	Time since transplant	.325**	.01

Discussion

This article presents results of comparisons between recipients with and without PTxCAD for physiological variables. Significant differences were that recipients with PTxCAD had a higher number of rejection episodes and mean triglyceride levels than recipients without PTxCAD. Previous and current research (Pahl et al, 1994; Webber, Naftel, Parker, Mulla, Balfour, Kirklin, & Morrow, 2003) established that rejection episodes are statistically associated with post transplant CAD, and the current research supports that association. In this study, the mean triglyceride levels for recipients with PTxCAD was 115 mg/dl, which is in the 95th percentile for increased risk of CAD when compared to normative samples.

Elevated triglyceride levels have been shown to be an independent risk factor in graft coronary artery disease (Chin, Rosenthal, & Bernstein, 2000). These authors found that among 28 pediatric heart transplant recipients on immunosuppressive therapy, 90% had abnormalities (>75th percentile) of either triglycerides or HDL. As part of the study, Chin, Rosenthal and Bernstein demonstrated that converting recipients from the immunosuppressive medication cyclosporine to tacrolimus allowed for these lipoprotein levels to remain statistically unchanged.

The elevated triglyceride levels of recipients with PTxCAD versus non PTxCAD found in this study are likely due to similar research findings regarding immunosuppressive therapy regimens and elevated lipoprotein levels of heart transplant recipients. Even though the association between elevated lipoprotein levels and immunosuppressive therapy exists, the fact remains that these elevated lipoprotein

levels are seemingly a risk factor for development of post transplant coronary disease and subsequently long term survival of recipient. As well, the fact that elevated triglyceride levels can increase the risk for coronary artery disease in the general population, should be given consideration in context to other factors that have a positive influence on lipid levels such as dietary habits and physical activity behaviors (Kraus, Houmard, Duscha, Knetzger, Wharton, et al, 2002; Kris-Etherton, Pearson, Wan, Hargrove, Moriarty, Fishell, & Etherton et al, 1999)

Specific psychological variables, as indicated by the Child Behavior Check List, were noted to be significantly different among recipients with and without PTxCAD. Levels of anxious/depressed, aggression, and thought problem scales were higher for recipients without post transplant coronary artery disease. This finding was unanticipated and expectation was that recipients with PTxCAD would have more psychological and behavioral problems as compared to recipients without PTxCAD. However, in light of the fact that only six children had PTxCAD conclusions regarding this finding are limited. In addition, other research has noted that behavioral/psychological problems are not foreign to pediatric post heart transplant populations, as well as data that suggests that not all recipients experience significant behavioral/psychological problems post transplant (Todaro, Fennell, Sears, Rodrigue, & Roche, 2000; Ikkos, Lask, Whitehead, Rees, & Graham, 1999; Uzark et al., 1992).

Todaro et al review of literature indicated that a complicated transplant course such as infections or rejections might place recipients at an increased risk for post transplant behavioral difficulties. More specifically, the review indicated that

approximately 20-24% of pediatric heart transplant recipients experienced significant symptoms of anxiety, depression, and behavior problems during the first year post transplant. In contrast, this same review of the literature acknowledged that children and adolescents generally functioned within the normal range on most measures of behavioral functioning post transplant.

The notion that most recipients do well and/or function within normal behavioral measurements coincides with the findings of this study. The overall mean scores for psychological/behavioral factors, in both PTxCAD and non PTxCAD groups, were not indicative of clinical pathology, just significantly different with higher scores for the non PTxCAD group. The unexpected results with this study lies in the finding that PTxCAD recipients were found to have less psychological/behavioral problems in comparison to non PTxCAD recipients. This finding is unanticipated based on the concept that a more complicated post transplant history (i.e. post transplant CAD) would likely result in more psychological distress, not less in comparison to a non PTxCAD group. This study was unique in that comparison was made between PTxCAD and non PTxCAD recipients. An explanation for this finding is reason for further research and inquiry. New research could focus to non-physiological explanations such as parental social desirability, exasperation with the child, parental psychopathology, and other psychosocial dynamics of recipient and family.

Physiological variables were evaluated in context to past smoking behavior of the parents. T-test results indicated that recipients with parents who smoked in the past

had a significantly higher mean total number of rejection episodes (M=4.82) as compared to those parents who did not smoke in the past (M=2.58, p≤.01). Analysis was conducted to account for the possibility that this difference was due to the length of time since that parent had smoked (i.e., time since transplant) in the past resulting in a greater accumulation of rejection episodes. A t-test demonstrated a significant difference regarding the current age of the recipient and those parents who reported to smoke in the past (M=10.18) and those parents who did not smoke in the past (M=7.56, p≤.00). Thus, recipients whose parents smoked in the past seem to be at greater risk for more rejection episodes than recipients whose parents did not smoke in the past.

Regression analysis was employed with total number of rejection episodes as the dependent variable, and smoking in the past and current age as the independent variables. The regression analysis indicated that the overall model was significant (p≤.00), smoking in the past was significant (p≤.025) as was current age (p≤.009). Therefore, not just current age (i.e. time since transplant) pointed toward this significant difference, but rather parents smoking behavior also contributed to PTxCAD recipients higher number of total rejection episodes.

In support of previous findings with respect to parent smoking and increased rejection episodes, a Pearson correlation matrix was computed for continuous variables. Results indicate linear associations between certain physiological (i.e. rejection episodes), demographic (i.e. time since transplant and recipient age), and parental factors (i.e., smoking). Results indicate that total number of rejection episodes

had a positive correlation with the number of cigarettes that a parent smoked (.587, $p \leq .05$), time since transplant (.325, $p \leq .01$), and current age (.301,$p \leq .01$).

Studies with respect to second hand smoke have shown an increased risk for various health problems for children (World Health Organization, June 1999). Problems such as lower respiratory infections, middle ear diseases, chronic respiratory symptoms, asthma, lung function, and Sudden Infant Syndrome (SIDS) have been associated with environmental tobacco smoke and children. Additional information from World Health Organization summaries indicate that ETS is also associated with the acceleration of cardiovascular disease in children, adolescents, and young adults.

Although no research in the pediatric heart transplant field has examined parent's smoking behavior, and association is being accounted for by parents smoking behavior and total number of rejection episodes experienced by the child/adolescent. With data that supports the impact of environmental tobacco smoke on children's health, the possibility of environmental tobacco smoke on heart transplant recipients is plausible and supportive of the findings of this study.

Conclusion

Heart transplantation for children and adolescents is a life offering surgical procedure. One of the primary factors limiting long-term survival of heart transplant recipients is post transplant coronary artery disease. This study was designed to address physiological, psychological, and demographic variables in context to recipients with and without PTxCAD. The study showed that differences existed between these two groups, and suggested that total number of rejection episodes and

mean triglyceride levels were higher for recipients with PTxCAD. From the psychological segment of the study, parents reported that anxious/depression, aggression, and thought problems were higher for recipients without PTxCAD. Although unexpected, these variables were not at a clinical level among PTxCAD recipients.

One of the more compelling findings of the study was that parental smoking behavior increased the risk/frequency of post transplant rejection episodes. This is an important finding to be noted because this study, as well as other studies, has demonstrated an association between rejection episodes and PTxCAD. Therefore, parental smoking behavior could be playing a role in the frequency of post transplant rejection episodes, and subsequently an increased risk for developing PTxCAD. These findings provide the base for additional research on the consequences of parental smoking behavior and the need to explore other parental lifestyle behaviors that could be increasing the risk of recipient post transplant medical and health problems. Future research should include multi site centers, with the prospect of replicating these findings on a larger scale, and developing a better understanding of other lifestyle risk factors that could have a negative effect on the quality and length of life for children/adolescents who receive a heart transplant.

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CHAPTER 5

DISCUSSION

This study examined comparisons between recipients with and without PTxCAD for physiological variables. Significant differences were that recipients with PTxCAD had a higher number of total rejection episodes and mean triglyceride levels than non PTxCAD recipients. Previous and current research has established that rejection episodes are associated with PTxCAD (Webber, Naftel, Parker, Mulla, Balfour, Kirklin, & Morrow, 2003; Pahl et al., 1989, 1994). This present study parallels other research that demonstrates an association between rejection episodes and PTxCAD.

Mean triglyceride level for recipients with PTxCAD was 115 mg/dl (95th percentile), while the non PTxCAD group had a significantly lower mean triglyceride level of 85.90 mg/dl. Even though the non PTxCAD group had a significantly lower mean triglyceride level as compared to PTxCAD group, the fact remains that a triglyceride level of 85.90 mg/dl increases the risk for development of CAD.

Particular to heart transplant recipients, elevated levels of triglycerides have been shown to be an independent risk factor in graft coronary artery disease (Chin, Rosenthal, & Bernstein, 2000). These authors established within a sample of 28 pediatric heart transplant recipients, on immunosuppressive therapy, that 90% of the recipients had abnormalities (>75th percentile) of either triglycerides or HDL. In conjunction with these findings, the authors showed that converting recipients from

the immunosuppressive medication cyclosporine to tacrolimus allowed for these lipoprotein levels to remain statistically unchanged.

Explanation for elevated triglyceride levels of recipients with PTxCAD versus non PTxCAD found in this study are likely due to the variety of immunosuppressive therapy regimens recipients must endure to prevent rejection of the transplanted organ (Valatine, 2000). Even though the association between elevated triglyceride levels and immunosuppressive therapy exists, the fact that elevated triglyceride levels can increase the risk for post transplant coronary artery disease remains.

A better understanding for why recipients have elevated triglyceride levels, and how to intervene, besides immunosuppressive therapy regimens and adjustments, may come from our knowledge base of lipoproteins within the normal population. Interventions that have a positive influence on lipoprotien levels such as improvements in dietary habits and physical activity may provide help in the management and/or decrease of an elevated risk for coronary artery disease (Kraus, Houmard, Duscha, Knetzger, Wharton, et al, 2002; Kris-Etherton, Pearson, Wan, Hargrove, Moriarty, Fishell, & Etherton, 1999).

Particular psychological scales of the Child Behavior Checklist List were significantly different among recipients with and without PTxCAD. The anxious/depressed, aggression, and thought problem scales had unexpectedly higher scores for recipients without PTxCAD than those with PTxCAD. However, the overall mean scores for anxious/depressed, aggression, and thought problem scales were not indicative of any clinical pathology.

Other research has noted that behavioral/psychological problems are not unusual to pediatric post heart transplant populations (Todaro, Fennell, Sears, Rodrigue, & Roche, 2000). In contrast, some research suggests that not all recipients experience significant behavioral/psychological problems post transplant (Todaro, Fennell, Sears, Rodrigue, & Roche, 2000; Ikkos, Lask, Whitehead, Rees, & Graham, 1999; Uzark et al., 1992). Todaro et al review of literature found that a transplant course complicated by infections or rejections may place recipients at an increased risk for post transplant behavioral difficulties. Todaro et al review denotes that approximately 20-24% of pediatric heart transplant recipients experienced significant symptoms of anxiety, depression, and behavior problems during the first year post transplant. In contrast, this same meta review of the literature acknowledged that a good proportion of children and adolescents generally functioned within the non clinical range on most measures of behavioral functioning post transplant.

The results of this study are analogous to the findings of Todaro et al that heart transplant recipients can do well and/or function within non clinical range on behavioral measurements. The unexpected results with this study are that PTxCAD recipients were found to have less psychological/behavioral problems in comparison to non PTxCAD recipients. This finding is unanticipated based on the notion that a more complicated post transplant history (i.e. post transplant CAD) would result in more medical care and subsequent increased psychological distress, not less in comparison to a non PTxCAD group (Todaro, Fennell, Sears, Rodrigue, & Roche, 2000).

Explanation for this finding may link to the mean time since transplant for this study population. Mean time since transplant for this study group was seven years. Todaro et al findings suggest that psychological/behavioral difficulties were more likely to occur within the first year of transplantation, and therefore recipients who are beyond that first year since transplantation are at decreased risk for developing emotional and behavioral problems. In addition, the finding that none of this study group was found to have clinical levels of psychological/behavioral problems may also be the consequence of seven years since transplant.

Parental smoking behavior was associated with increased rejection episodes of the recipient. Specifically, parents who had smoked in the past, and parents who currently smoke, increased the risk of their child experiencing more rejection episodes. In determining the strength of this finding, time since transplant was considered to account for possible differences being attributed just to that factor, i.e., more time and thus more rejection episodes. However, regression analysis indicated that smoking in the past by a parent is significant for the total number of rejection episodes even when controlling for time since transplant.

Explanation for this finding is not available in the pediatric heart transplant literature. Clarification of this result will likely come from additional research and data specific to second hand smoke exposure. Research indicates that children exposed to environmental tobacco smoke have associated health troubles such as respiratory problems, asthma, and risk for accelerated cardiovascular disease processes (World Health Organization, June 1999). Although data from the World Health Organization

regarding second hand smoke and children relates to non-transplant populations, one could conclude that similar ill health effects are possible for heart transplant recipients.

In conclusion, the discovery that parental smoking behavior could increase the risk/frequency of post transplant rejection episodes is an important finding to be noted because this study, as well as other studies, have demonstrated an association between rejection episodes and PTxCAD. In addition, elevated triglyceride levels seem to increase the risk for developing PTxCAD. These findings provide the base for further research on the consequences of parental smoking behavior, triglyceride levels, and post transplant health and mortality of the recipients. Future research should likely include additional multi site centers, with the prospect of replicating these findings on a larger scale, and developing a better understanding of other lifestyle risk factors that could have an negative effect on the quality and length of life for children/adolescents who receive a heart transplant.

CHAPTER 6

SUMMARY/CONCLUSIONS

The purpose of this study was to provide a better understanding of pediatric heart transplant recipients, and explore the physiological and psychosocial aspects of a heart transplant recipient in context to the known presence of post transplant coronary artery disease. Findings of this study demonstrated that differences exist between PTxCAD and non PTxCAD recipients, in particular that total number of rejection episodes and mean triglyceride levels were higher for recipients with PTxCAD. Psychological, anxiety/depression, aggression, and thought problems were higher for recipients without PTxCAD. Finally, parental smoking behavior likely increases the risk/frequency of post transplant rejection episodes. These results provide a foundation of understanding pertaining to post transplant coronary artery disease, risk factors such as parental smoking, rejection episodes, recipient triglyceride levels, and a conduit to develop more effective preventive and intervention strategies to confront this life ending post transplant occurrence.

A. Preventive Care and Psychology

Preventive Care Practitioners and Psychologists can and should be an integral part of providing health care to pediatric heart transplant recipients and family. An essential part of pre/post surgical evaluation for heart transplant patients, both adult and child/adolescent is evaluation of lifestyle behaviors, psychosocial history and uniqueness, and emotional stability. The Preventive Care Specialist and

Clinical Psychologist, in conjunction with one another, possess the comprehensive mind and body knowledge to provide expected insight when completing this essential aspect of the transplantation process.

Assessment of recipients, when age appropriate and family is a standard component of transplantation with today's insurance carriers and medical teams. Transplant recipients, pre and post surgically, require behavior strategies, education, and emotional care to have the best chance of an improved quality of life and mortality. Many behavioral based factors that can be barriers to post surgical success such as poor nutrition, lack of exercise, emotional instability, lack of social network, and inadequate medication adherence rely on a strong psychological and lifestyle focus for remediation (Balestroni, Bosimini, Centofanti, Di Summa, Giannuzzi, & Zotti, 2002). The Preventive Care Practitioner and Psychologist's solid foundation in biomedical and epidemiological science, physiological and behavioral lifestyle risk factor study, encourage and provide comprehensive thinking for the betterment of patient, family, and transplant team. The issue of post transplant coronary artery disease is serious for the quality and mortality of life for recipients. Coronary artery disease in general is influence by many factors such as emotions, activity levels, nutrition, and genetics (Rozanski, Blumenthal, & Kaplan, 1999).

It is likely that post transplant coronary artery disease is influenced by some if not all of these factors as well. The pediatric heart transplant recipient and family is no exception to this and in reality will be served with a better-quality of care with such

perspicacity. The Preventive Care Practitioner and Psychologist can integrate what is essential in helping transplant recipients avert post transplant coronary artery disease.

B. Recommendations for Future Research

Recommendations for future research are specific to gaining a better understanding of this special population. This study was limited with various components of data collection, subject numbers, comprehensive evaluation of psychological, physiological, and demographic domains. Specific recommendations are:

1. Psychometric personality assessment of child/adolescent, when age appropriate, in conjunction with parent report
2. Addition of patients from multi site centers to increase sample size
3. Evaluation of recipient activity levels, when age appropriate, with activity logs to determine levels of exercise as risk factors for post transplant coronary artery disease
4. Evaluation of nutritional lifestyle of recipient with food logs to determine dietary intake as a risk factor for increased triglyceride levels and post transplant coronary artery disease

The findings of this study should be replicated with a larger sample size. The focus should be to collaborate with other centers to gain a better understanding of the population, and develop interventions and management strategies that are effective in diminishing/resolving post transplant coronary artery disease among this special group of people.

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Appendix A:

Informed Consent Letter

LOMA LINDA UNIVERSITY

Graduate School
Department of Psychology

11130 Anderson Street
Loma Linda, California 92350
(909) 558-8577
FAX: (909) 558-0171

Dear Parent/Guardian:

You are invited to participate in a study on understanding behavior, activity, and heart function among pediatric heart transplant patients. This study will help identify factors that may be related to the development of coronary artery disease among pediatric heart transplant patients. The purpose of this study to help us understand how parents and caregivers feel about the development of their child or adolescent who has had a heart transplant, and to assist Public Health/Mental Health Care workers in providing service to families whose child has undergone a heart transplant.

The Department of Psychology and International Infant Heart Transplant Center is requesting that you fill out two questionnaires. One of the questionnaires pertains to your child's behavior and activity or sport participation. The other is two short demographic information forms. Participation in this study will take approximately 45 minutes to complete the questionnaires (Child Behavior Checklist & Demographic Information Form).

There are minimal risks for participating in this study. There is no direct benefit to you by participating. The information you will provide may help us to better understand ways to provide more effective health care for children who receive heart transplants. Participation in this study is entirely voluntary. Your decision whether or not to participate or terminate at any time will not affect your or your child's present or future medical care. All results are anonymous. All data are kept in a locked filing cabinet at the Department of Psychology, Loma Linda University. Your name will be kept separate from data and coded to coincide with your address. In this way we can contact you in the future if necessary relative to additional research. There is no cost to you for participating in this study. A small token of appreciation in advance is offered. You may keep this even if you decide not to participate.

If you wish to contact an impartial third party not associated with this study regarding any concern you may have about the study, then you may contact The Office of Patient Relations, Loma Linda University Medical Center, Loma Linda, CA 92354, phone (909) 558-4647 for information and assistance. If you have any questions you may contact Dr. Kiti Freier at (909) 478-8577. The return of the Child Behavior Checklist and Demographic Form assumes voluntary participation in this study. You may keep this letter for your records.

Thank You

LOMA LINDA UNIVERSITY
INSTITUTIONAL REVIEW BOARD
APPROVED [illegible] AND EFFECTIVE [illegible]
[illegible] CHAIR [illegible]

Appendix B:

Demographic Information Form

DEMOGRAPHIC INFORMATION FORM

Please provide the following confidential information, which is necessary to complete this study.

Please have this form filled out by the primary caregiver of the child/adolescent who received a heart transplant. If this is a two-parent home, then this form may be completed by either the father or mother of the child. If neither the father or the mother is present, the person who provides the main care of the child may complete this form.

(Please Print):Your name

_____

Your relationship to child/adolescent who received heart transplant.

_____

1. Do you currently smoke any of the following?

Cigarettes	Yes_1	No_2	If yes, cigarettes/per day
Cigars	Yes_1	No_2	If yes, cigars/per day
Pipe	Yes_1	No_2	If yes, pipefuls/per day

2. If you are not currently smoking, have you ever smoked in the past?

Yes_1 If yes, when did you stop?

_____

Month Year

No_2

3. Please state which of the following people have ever regularly smoked in your home in the past fifteen years:

Mother of heart transplant child/adolescent

Yes_1 No_2

Father of heart transplant child/adolescent

Yes$_1$ No$_2$

Other primary caretaker of heart transplant child/adolescent

Yes$_1$ No$_2$

Siblings of heart transplant child/adolescent

Yes$_1$ No$_2$

Friends

Yes$_1$ No$_2$

Other relatives

Yes$_1$ No$_2$

4. For each of the following health problems please indicate whether they apply to the biological mother and/or father of the child/adolescent who received a heart transplant.

Mother

High blood pressure$_a$	Yes$_1$	No$_2$	Don't know$_3$
Low blood pressure$_b$	Yes$_1$	No$_2$	Don't know$_3$
Stroke$_c$	Yes$_1$	No$_2$	Don't know$_3$
Heart attack$_d$	Yes$_1$	No$_2$	Don't know$_3$
High cholesterol$_e$	Yes$_1$	No$_2$	Don't know$_3$
Diabetes (Type 1 or 2)$_f$	Yes$_1$	No$_2$	Don't know$_3$
Overweight$_g$	Yes$_1$	No$_2$	Don't know$_3$
Little/no physical activity (< 30 min x 3 times/week)$_h$	Yes$_1$	No$_2$	Don't know$_3$

Father

High blood pressure$_a$	Yes$_1$	No$_2$	Don't know$_3$
Low blood pressure$_b$	Yes$_1$	No$_2$	Don't know$_3$

Stroke$_c$	Yes$_1$	No$_2$	Don't know$_3$
Heart attack$_d$	Yes$_1$	No$_2$	Don't know$_3$
High cholesterol$_e$	Yes$_1$	No$_2$	Don't know$_3$
Diabetes (Type 1 or 2)$_f$	Yes$_1$	No$_2$	Don't know$_3$
Overweight$_g$	Yes$_1$	No$_2$	Don't know$_3$
Little/no physical activity (< 30 min x 3 times/week)$_h$	Yes$_1$	No$_2$	Don't know$_3$

5. What is the total household income, prior to taxes? (Please check one)

Under 10,000$_1$
$10,000-19,000$_2$
$20,000-39,000$_3$
$40,000-59,000
$60,000-79,000$_5$
$80,000-99,000$_6$
Over 100,000$_7$

If you have any additional comments or clarifications regarding the questions on this survey, please feel free to use the space below.

Thank you for your participation!

Appendix C:

Phone Script

Phone Format for Non-Responders: Telephone calls made to non-respondents are to be conducted after two weeks.

Format: Hello Mr./Mrs. (parent of child/adolescent). My name is Mark Randall and I am calling from the Department of Psychology in conjunction with the Loma Linda International Heart Transplant Institute at Loma Linda University/Medical Center. I was calling with reference to information that was sent to you regarding a study that includes parents of children/adolescents that received a heart transplant at Loma Linda University Medical Center. I was wondering if you have received the information and if you had any questions regarding the completion of the form and questionnaire. I was also calling to ask if you were willing to return the form and questionnaire for the study. Thank you.

Phone Format for Responders with Missing Data: Phone calls to be completed within 1-3 days after receiving Questionnaire and Demographic Form.

Format: My name is (Mark Randall/research assistants name) and I am calling from the Department of Psychology in conjunction with the Loma Linda International Heart Transplant Institute at Loma Linda University/Medical Center. I want to thank you for responding to the information I sent you, it is greatly appreciated. When going through the questionnaire and or Demographic Form I noticed that these particular items were missing. I was wondering if I could ask you this/these particular question(s) in order to complete your responses. Thank you again for responding to the information that I sent you.

Note: All phone calls are to be made in a professional and encouraging manner. No responding or non-responding subject is to be verbally harassed in order to obtained information. Phone calls are to be conducted in a courteous and non-threatening manner.