OPTIMIZING IMMUNOSUPPRESSION IN PATIENTS FOLLOWING HEART TRANSPLANTATION

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ABSTRACT

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Background: Effective immunosuppression is necessary for long-term survival following heart transplantation, but it is also associated with a multitude of adverse effects. Protocols have emerged to attempt to optimize the risk-to-benefit ratio of immunosuppression. We reviewed our center's experience with two such protocols: tapering corticosteroids following heart transplantation and administering basiliximab as an induction agent.

Methods: We reviewed the records of all cardiac transplant recipients at our center between 1988 and August 2004. Patients treated with traditional triple therapy immunosuppression (cyclosporine, azathioprine, and prednisone; CAP) were compared to a similar group of patients treated with a goal of rapid (within 6 months) steroid taper and discontinuation (CAPT). Patients who received basiliximab as an induction agent were compared to a historical control group of patients who received a similar immunosuppressive protocol without basiliximab induction.

Results: Fifty-seven percent of the patients in the CAPT group were successfully withdrawn from steroids at six months post-transplantation. This group had a decreased freedom from acute rejection ($p<0.01$) and increased frequency of acute rejection ($p<0.01$) when compared to the CAP group. There was, however, no difference in freedom from transplant coronary artery disease ($p=0.53$). The CAPT group enjoyed an increased freedom from malignancy ($p=0.01$) and trended towards a decreased frequency of infection ($p=0.10$) and improved survival ($p=0.06$) when compared to the CAP group.

One hundred forty-five patients were included in the comparison between basiliximab and control. At one and two-years post-transplantation, no difference was found between groups in the rise of serum creatinine ($p=0.29$). Basiliximab induction decreased the frequency of acute rejection ($p=0.02$) and improved the freedom from first acute rejection episode ($p<0.01$) during the first two years after transplantation. It had no statistically significant effect on freedom from infection, malignancy, or overall survival in our cardiac transplant population ($p=0.52$, $p=0.85$, $p=0.27$ respectively).

Conclusions: Steroid withdrawal was possible in 57% of patients at six months post-transplantation. The institution of an early steroid taper protocol improves the overall freedom from malignancies and may decrease the frequency of infection and prolong overall survival. Basiliximab induction does not affect renal function at mid-term follow-up; however, it decreases the frequency of acute rejection and increases the freedom from first acute rejection episode. It accomplishes this without decreasing the freedom from infection, malignancy, and transplant vasculopathy. Novel medications and treatment protocols provide an opportunity for transplant teams to continue to optimize immunosuppression while simultaneously minimizing side-effects.

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PRIOR PUBLICATIONS & PRESENTATIONS

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ATGAM – purified, concentrated, and sterile gamma globulin, primarily monomeric IgG, from hyperimmune serum of horses immunized with human thymus lymphocytes.

BMI – Body mass index.

CAP – Patient group receiving cyclosporine, azathioprine, and prednisone without taper.

CAPT – Patient group receiving cyclosporine, azathioprine, and prednisone taper.

CMV – Cytomegalovirus.

ISHLT – International Society for Heart and Lung Transplantation

OKT3 – muromonab-CD3, an immunosuppressant drug that reacts with and blocks the function of CD3 in the membrane of a T cell.

PTLD – Post-transplant lymphoproliferative disorder.

CHAPTER ONE
INTRODUCTION

BALANCING RISKS AND BENEFITS OF IMMUNOSUPPRESSION FOLLOWING HEART TRANSPLANTATION

Although the first rudimentary heart transplant was performed in 1905, it was not until the introduction of immunosuppression 60 years later that heart transplantation became a feasible treatment for patients with end-stage congestive heart failure. The combination of corticosteroids and azathioprine was introduced at that time by a team at Stanford who showed that the addition of the regimen made the long-term survival of dogs after heart transplant possible.[1] The introduction of cyclosporine to the regimen in 1983[2] was a subsequent breakthrough that eventually led to the modern era of triple drug immunosuppression. The use of three different drugs, such as azathioprine, corticosteroids, and cyclosporine, allows the physician to maximize the benefit of overall immunosuppression while minimizing the risk of individual drug toxicity.

Such is the dilemma with immunosuppression. The medications are necessary in order to prevent the rejection of the transplanted heart, but they do not come without consequences. Immunosuppression leads to increased infection and malignancy as the host's immune system is compromised on a general level, not just with regard to the transplanted organ. In addition, each drug has its own individual side effects. Steroids are the most well known, leading to a plethora of complications such as osteoporosis, elevations in cholesterol and glucose levels, weight gain, diabetes, cataracts, and hypertension. Cyclosporine has also been associated with renal toxicity, hypertension, neurological toxicity, hirsutism, gingival hyperplasia, and the development of diabetes.

These side effects, along with the quest for continuing improvement in survival rates, have led to the search for medications that can deliver better benefit to risk ratios. Tacrolimus is a newer calcineurin inhibitor that offers an alternative to cyclosporine, while mycophenolate mofetil is an alternative to azathioprine as an antiproliferative agent. Biological response modifiers are also available as adjutant agents, such as anthymocyte globulin, OKT3 and the more recent IL-2 inhibitors – daclizumab and basiliximab.

Simultaneously with the addition of new agents, transplant teams have also sought the perfect mix of immunosuppressive drugs that can safely suppress life-threatening rejections while minimizing infections and malignancies. Encouraging results for decreased steroid doses was first shown by Yacoub, et al in 1985,[3] and various research teams, including our own, have sought to find the optimal level of steroid use since then. In addition, induction agents such as basiliximab have been used at the time of transplant have been used to attempt to delay the start of cyclosporine and decrease its resultant renal toxicity.

Below are two studies, one that reviews our center's experience in the long-term follow-up of patients who have been tapered off of steroids, and a second that focuses on the use of basiliximab as an induction agent. Both of them examine continuing ways to optimize the benefit to risk ratio of the immunosuppressive drugs that are administered to heart transplant patients.

CHAPTER TWO

EFFECTS OF EARLY STEROID WITHDRAWAL FOLLOWING HEART TRANSPLANTATION

BACKGROUND

In order to decrease the negative effects of prolonged steroid treatment, many transplant programs have investigated steroid free or withdrawal protocols. In the mid 1980s, Yacoub demonstrated encouraging results with a steroid free regimen.[3] This pioneering work was quickly followed with several variations of this theme by other investigators. These included attempts at complete avoidance of steroids and early or late steroid taper after initial treatment with prednisone.[4-19] Although these protocols demonstrated the feasibility of steroid withdrawal with varying effects on rejection, steroid complications, and survival, 75% of today's heart transplant recipients are still treated with chronic steroid therapy.[20]

Previously our institution reported that prednisone could be withdrawn in heart transplant recipients without jeopardizing survival and graft function.[13] Follow up, however, was insufficient to assess the full impact of early withdrawal on long-term graft function, the incidence of coronary artery disease, and other complications. This analysis explores the long-term effects of this steroid withdrawal protocol in heart transplant recipients.

METHODS

We obtained Institutional Review Board approval and retrospectively reviewed the records of 162 consecutive cardiac transplantations that were performed at our institution between the years 1988 and 1996. During this time period, nine patients suffered post-transplant in-hospital mortality and three were lost to follow up. These 12 patients were excluded from the study. The patients who underwent transplantation between 1988 and 1990 were treated with traditional

triple therapy immunosuppression (cyclosporine, azathioprine, and prednisone [CAP; n=46]). Beginning June 1990, we instituted a protocol of early steroid taper with discontinuation of steroids at six months post-transplant. There was no patient preselection. One hundred four patients were transplanted during this six-year period. Seven patients who either lived too far away from the transplant center or for various financial reasons were unable to partake in the more extensive biopsy protocol necessary for early steroid taper were excluded from the study. Another four patients were excluded from this study for the following reasons: sarcoidosis (requiring steroid treatment), single kidney (lowering cyclosporine levels if renal function deteriorated would lead to under-immunosuppression), re-transplantation, and age less than 18 years. Therefore, 93 of the 104 patients who underwent cardiac transplantation between the years 1990 and 1996 were treated with a protocol of cyclosporine, azathioprine, and prednisone taper (CAPT group).

The immunosuppressive protocol utilized by our program during this study period is outlined in detail elsewhere.[13] Briefly; both groups received cyclosporine and azathioprine during the entire study period according to an identical protocol. All patients received methylprednisolone on initiation of cardiopulmonary bypass and during the first postoperative day. On the second postoperative day, both groups were started on oral prednisone at a dose of 1 mg/kg/day. Subsequently, the steroid dose was tapered at different rates in the two groups and was completely withdrawn at six months post-transplant in the CAPT group (Table 1). CAPT patients were returned to the standard triple drug regimen if they experienced two episodes of acute graft rejection, any hemodynamically compromised rejection, acute vascular rejection, leucopenia, renal insufficiency, or any other indication for steroid treatment. Data were analyzed according to intention-to-treat.

Table 1 describes our surveillance endomyocardial biopsy protocol. The diagnosis of acute graft rejection was made according to Billingham's criteria before 1990 and the classification of the

International Society of Heart Transplantation after 1990. A coronary angiogram and left ventriculogram were obtained within six to 12 weeks from transplantation and used as a baseline with which to compare yearly followup studies.

Table 1: Steroid Taper and Biopsy Protocols

	CAP*	CAPT*
Prednisone Taper	• 1 mg/kg/day X 2 months • 0.25 mg/kg/day X 4 months • 0.15 mg/kg/day X 6 months • 0.1 mg/kg/day thereafter	• 1 mg/kg/day X 1 month • 0.25 mg/kg/day X 1 month • 0.15 mg/kg/day X 4 months • off prednisone thereafter
Biopsy Protocol	• q 2 wk X 3 months • q 1 month X 3 months • q 3 months X 1.5 years • annually thereafter	• q 2 wk X 8 months • q 1 month X 4 months • q 3 months X 1 year • annually thereafter

*CAP – cyclosporine, azathioprine, and prednisone
*CAPT – cyclosporine, azathioprine, and prednisone taper

Follow up was concluded on December 31, 2004. Serious infection was defined as any case that necessitated IV therapy or required hospital admission. A solid malignancy was defined as any malignancy in which the primary lesion was not in the skin, including oropharyngeal cancers. Continuous variables were compared with t-tests, and categorical variables were analyzed with the X^2 statistic. Two-by-two tables were analyzed using Fisher's Exact Test. Patient survival and freedom from events were analyzed with Kaplan-Meier curves and compared with the log-rank statistic. The impact of immunosuppressive therapy on body mass index (BMI) and serum creatinine values between the two groups was analyzed using a repeated-measure analysis of variance. All statistics were computed using SAS Version 9.1, and $p < 0.05$ determined significance. Data are expressed as mean ± SD.

Table 2: Demographics of Heart Transplant Patients				
	Entire Study	**CAP**	**CAPT**	**p-value**
Patients	139	46	93	
Age (years)	53.1 ± 9.9	53.5 ± 8.9	52.9 ± 10.5	0.74
Gender				0.11
Male	112	41	71	
Female	27	5	22	
Ethnicity				0.58[a]
White	123	42	81	
Black	14	4	10	
Hispanic	1	0	1	
American Indian	1	0	1	
Etiology				0.68
Ischemic	81	29	52	
Idiopathic	46	14	32	
Other	12	3	9	
Acquired Valvular	3	0	3	
Congenital	2	1	1	
Alcoholic	3	0	3	
Hypertrophic	1	0	1	
Postpartum	1	0	1	
Other	2	2	0	
Ischemic Time (min)	165.7 ± 48.6	176.9 ± 51.6	160.2 ± 46.3	0.06
Creatinine at Transplant (mg/dl)	1.3 ± 0.4	1.3 ± 0.3	1.3 ± 0.4	0.77
BMI at Transplant	23.9 ± 4.1	23.3 ± 3.1	24.2 ± 4.5	0.20

[a] p value represents Caucasian versus non-Caucasian ethnicity secondary to low number of Hispanic and American Indian patients

Table 3: Demographics of CAPT Group				
	CAPT	**Tapered**	**Failed Taper**	**p-value**
Patients	93[a]	53	35	
Age (years)	52.9 ± 10.5	53.5 ± 11.7	52.2 ± 8.7	0.57
Gender				0.08
Male	71	44	23	
Female	22	9	12	
Ethnicity				0.03[b]
White	81	50	28	
Black	10	2	7	
Other	2	1	0	
Hispanic	1	0	0	
American Indian	1	1	0	
Etiology				0.38
Idiopathic	52	19	12	
Ischemic	32	31	18	
Other	9	3	5	
Acquired Valvular	3	1	2	
Congenital	1	0	1	
Alcoholic	3	2	1	
Hypertrophic	1	0	0	
Postpartum	1	0	1	
Ischemic Time (min)	160.2 ± 46.3	155.0 ± 40.5	170.7 ± 52.4	0.12
Creatinine at Transplant (mg/dl)	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.5	0.63

[a] 5 patients died before getting tapered off steroids
[b] p value represents African American versus non-African American ethnicity secondary to low number of American Indian and Hispanic patients

RESULTS

One hundred thirty-nine patients were included in this study. The CAP group included 46 patients, and the CAPT group included 93 patients. The mean follow up time was 10.8 ± 4.5 years in the CAP group and 10.0 ± 3.7 years in the CAPT group. Demographic information for the two groups is provided in Table 2.

Of the 93 patients eligible for steroid taper, 53 (57%) were successfully withdrawn from steroids at six months. Thirty-six patients continued to require steroids for multiple episodes of rejection (19), renal insufficiency (7), acute vascular rejection (5), leucopenia (4), and reactive airway disease (1). Table 3 compares the characteristics of the patients in the CAPT group who were successfully weaned with those who failed the steroid taper.

Rejection and Post-Transplant Graft Vasculopathy

Five cases of acute rejection occurred in the CAP group during the first six months post-transplant, while 41 cases occurred during the same time period in the CAPT group. During the remainder of the follow up period, 11 cases of acute rejection occurred in the CAP group, and 32 occurred in the CAPT group. During the entire follow up period, there were 0.35 ± 0.77 cases of acute rejection per patient in the CAP group versus 0.78 ± 0.87 cases per patient in the taper group ($p<0.01$). Freedom from acute rejection was greater in the CAP group than in the CAPT group (Figure 1). Interestingly, freedom from coronary artery disease was not significantly altered by early withdrawal of steroids (Figure 2).

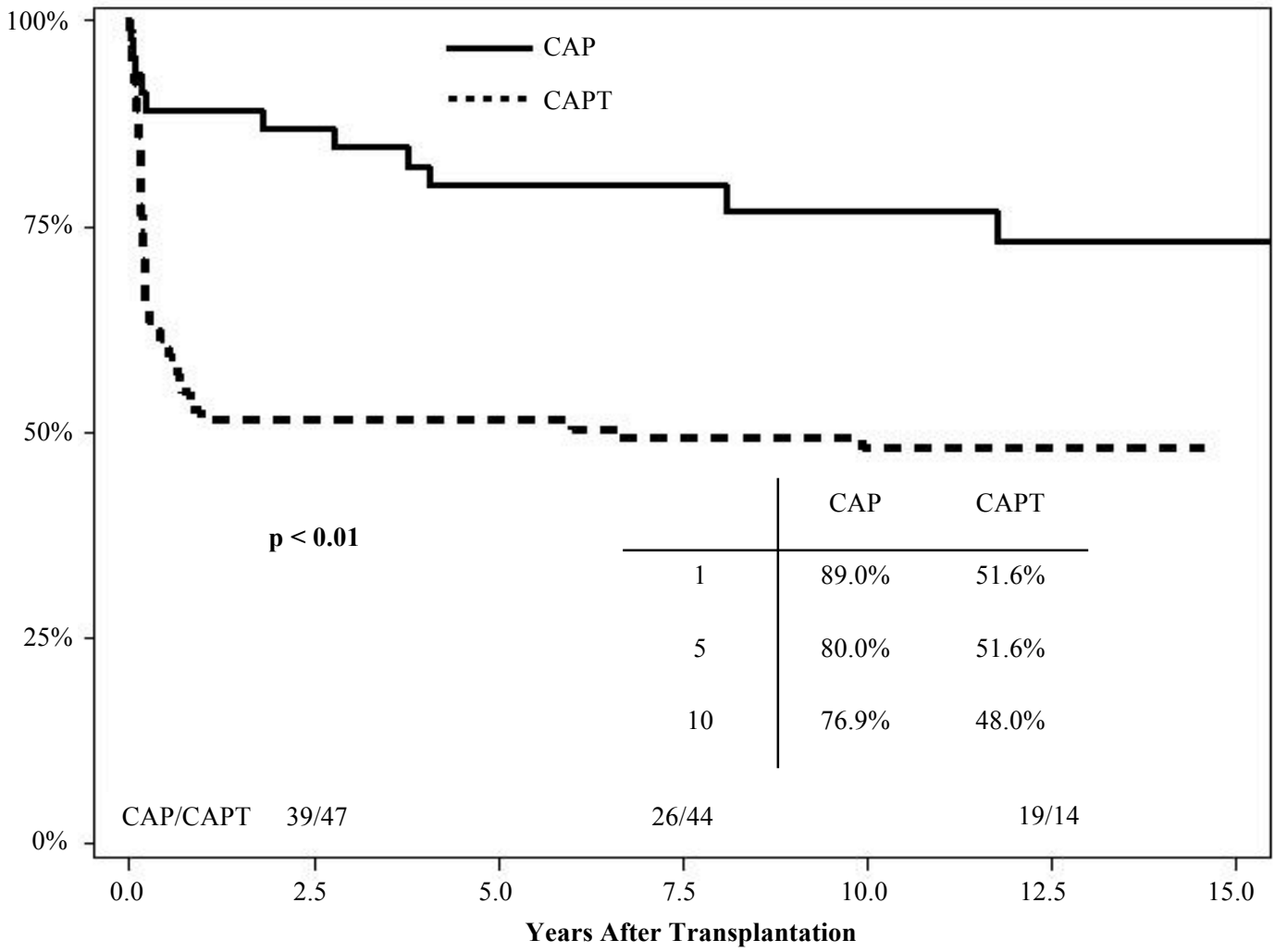

Figure 1: Freedom from Acute Rejection

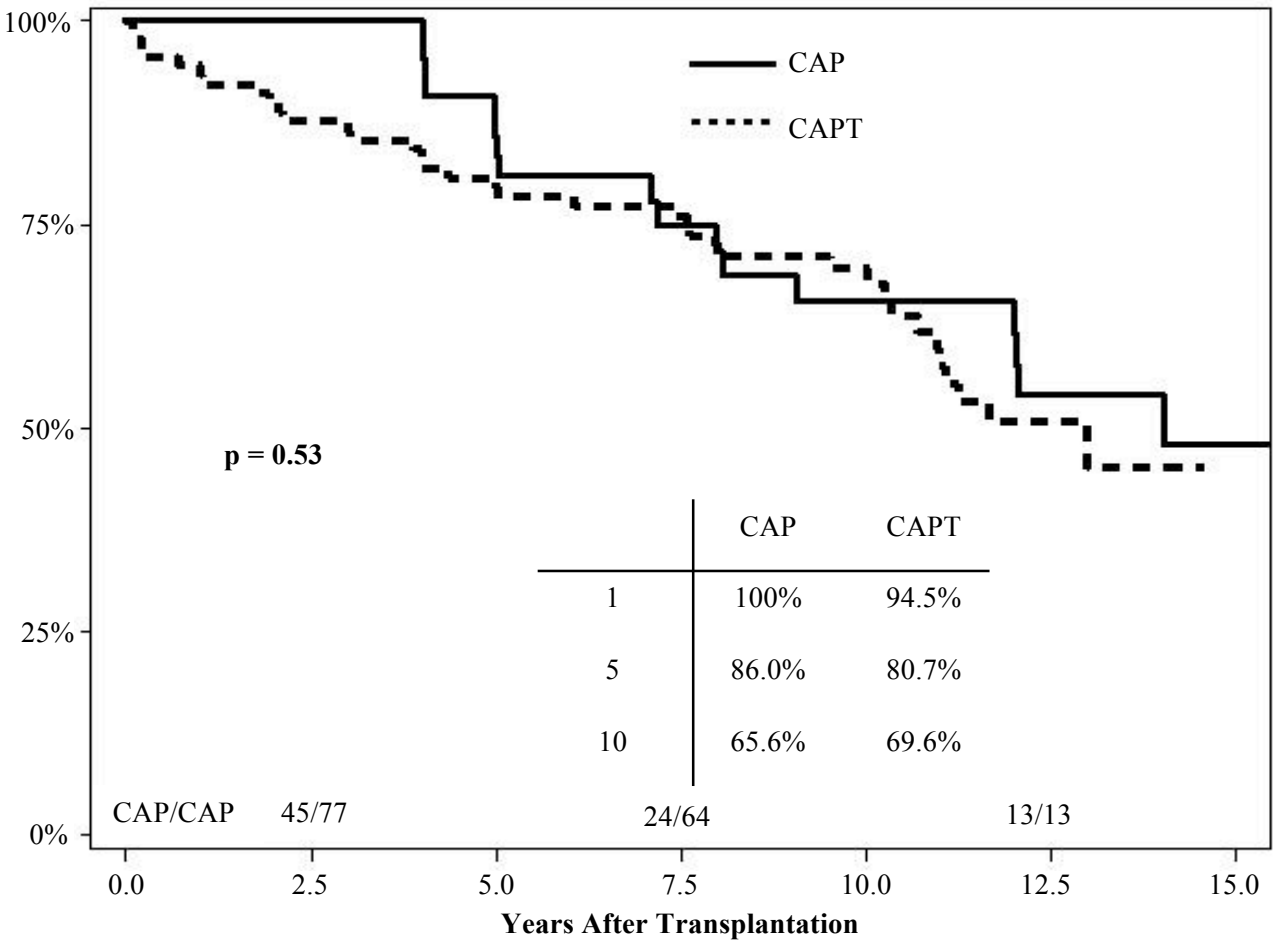

Figure 2: Freedom from Transplant Coronary Disease

Malignancy

The CAPT patients had an increased overall freedom from malignancy (Figure 3). When examining different cancer types, there was no difference in freedom from solid organ malignancy (p=0.26) or post-transplant lymphoproliferative disorder (PTLD; p=0.27); however, there was significantly increased freedom from skin cancer in the taper group (p=0.03).

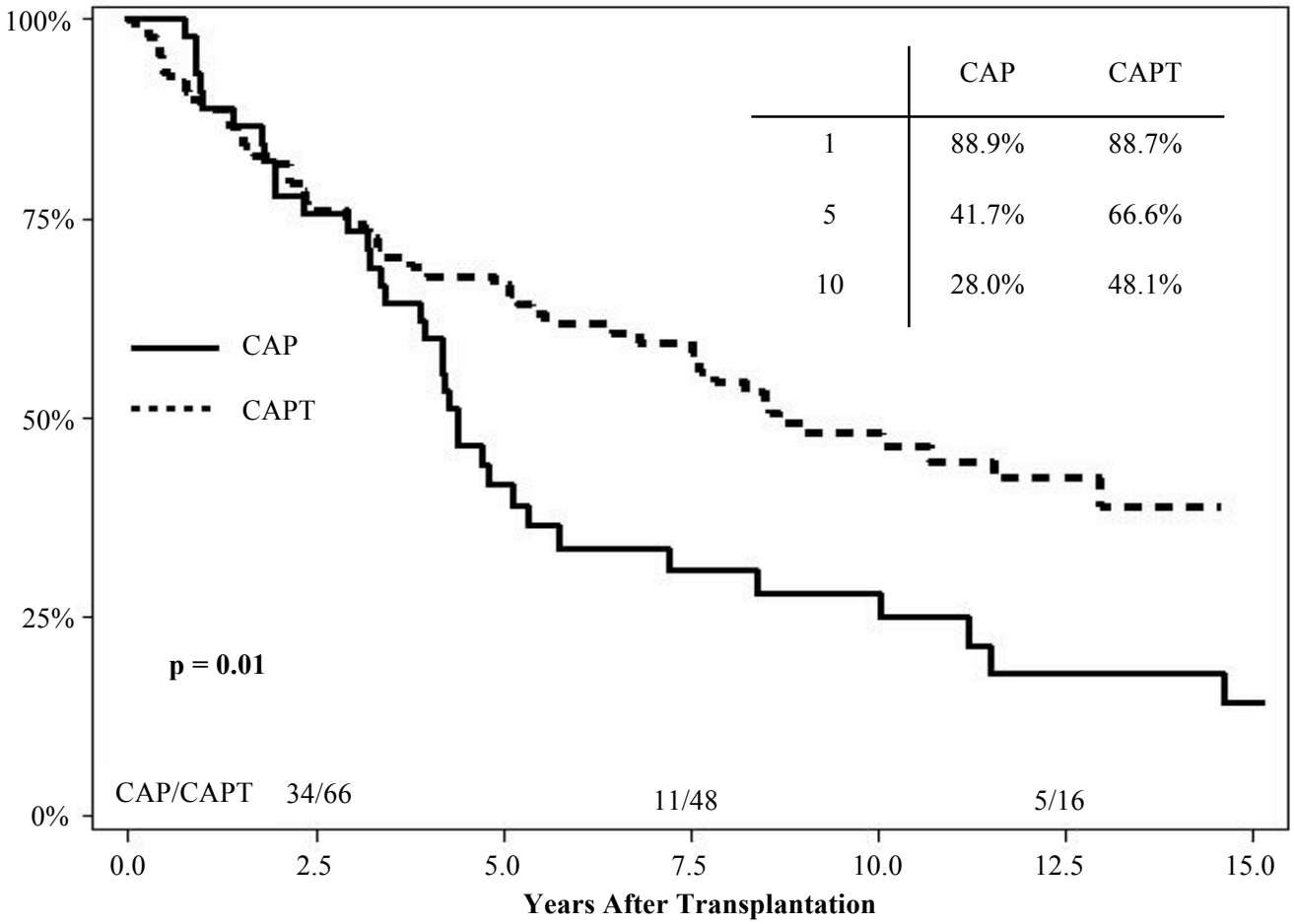

Figure 3: Freedom from any Malignancy

Infection

There were 91 versus 124 infective episodes in the CAP and CAPT groups respectively. Overall freedom from infection did not differ between the two groups (Figure 4); however, there was a trend towards increased episodes of infection in the CAP group (1.96 ± 2.72/patient versus 1.24 ± 2.19/patient; p=0.10).

Morbidity

Common post-transplant morbidities such as renal dysfunction, obesity, and diabetes were not altered by early steroid withdrawal. The freedom from diabetes, as measured by need for insulin or oral medication, did not differ between the two groups (p=0.38). Renal dysfunction, as

measured by serum creatinine level, and obesity, as measured by the patient's BMI, were not significantly different at the time of transplantation and at 1, 5, and 10 years post-transplantation (p=0.28 and p=0.22 respectively).

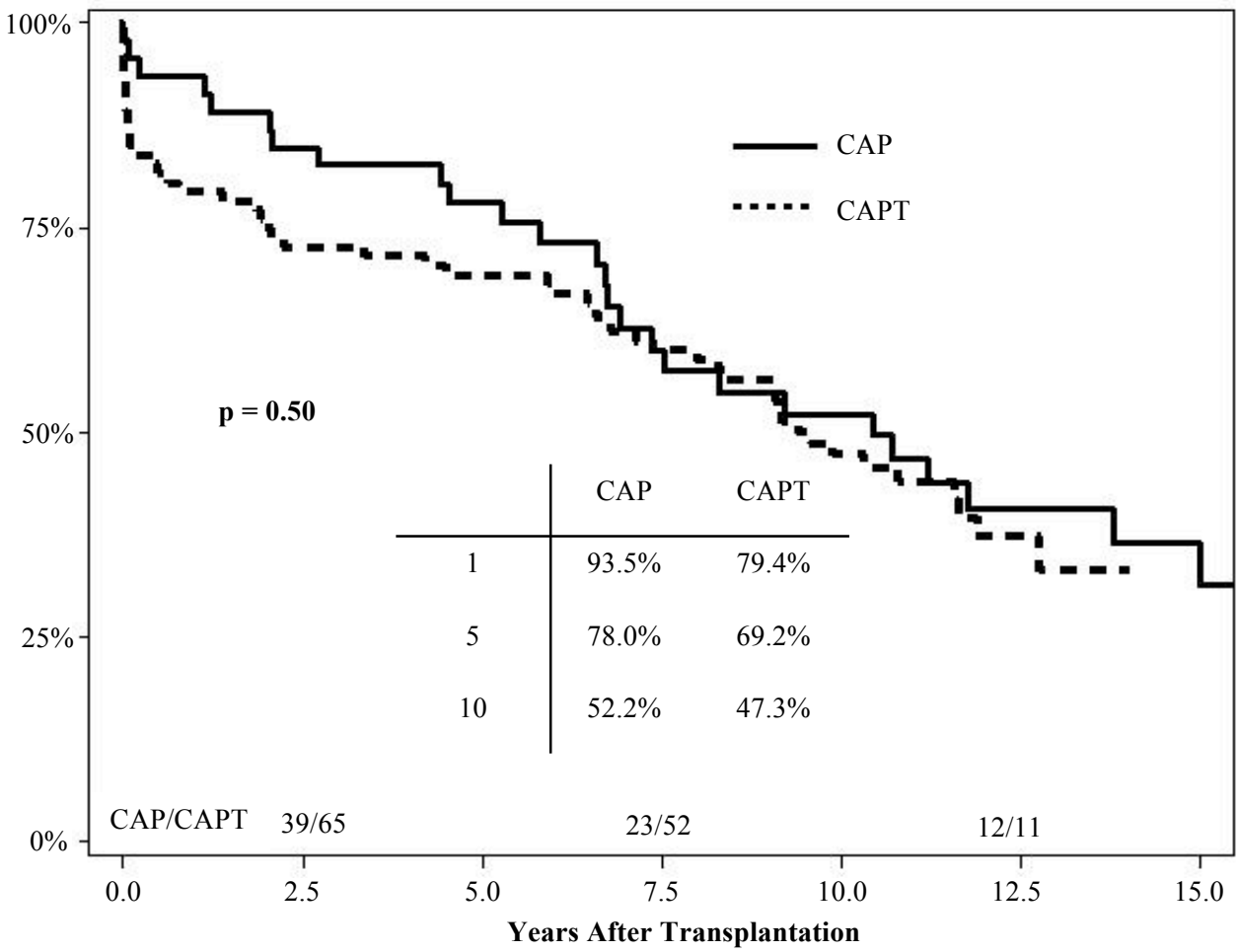

Figure 4: Freedom from Infection

Survival

Five patients died during the first six months post-transplantation in the CAPT group. One died from infection, and four patients died from sudden cardiac death. Of those four, one patient had been leucopenic from CMV infection and azathioprine had been held for almost a month. A second patient, who was known to be noncompliant with medications, was found deceased at home. A third patient suffered a cardiac arrest while in the hospital after his cyclosporine dosing

had been decreased secondary to renal insufficiency. The fourth patient was also being treated with decreased dosing of cyclosporine when he died. All four patients' causes of death were classified as acute rejection; however, in each case the patient was on a nonstandard immunosuppression protocol due to noncompliance or decreased dosing for the various previously stated reasons. Overall, the CAPT patients were found to have a very strong trend towards improved survival when compared to CAP patients (Figure 5). There was no significant difference between the two groups in frequency of death due to acute rejection, chronic rejection, or malignancy (Table 4). The CAP group tended to be more likely to succumb to infection than the CAPT group (p=0.06).

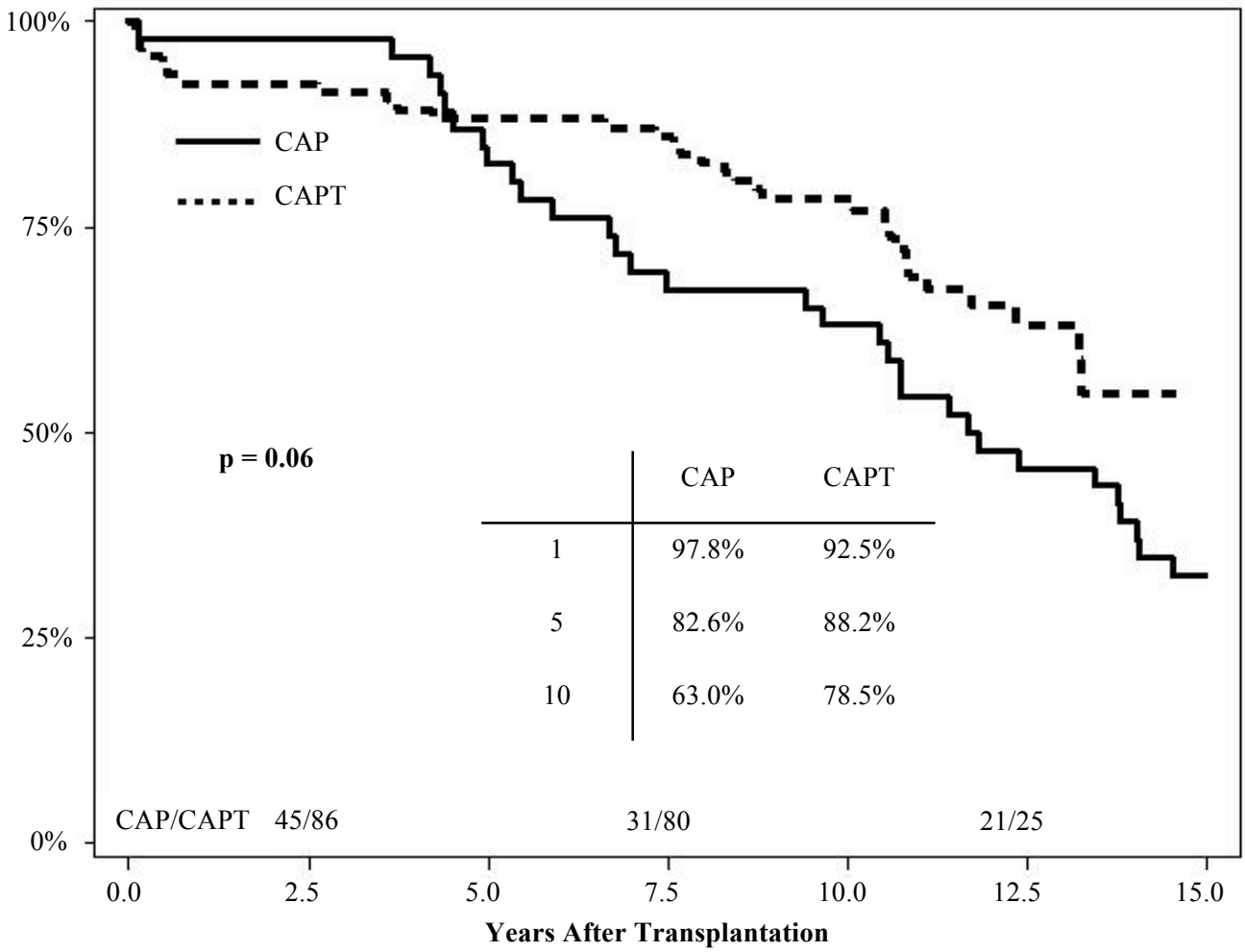

Figure 5: Overall Survival after Cardiac Transplantation

Table 4: Primary Cause of Death of CAP and CAPT Patients			
	CAP	**CAPT**	**p-value**
Infection	10	3	0.06
Malignancy	12	8	0.42
Acute Rejection	1	4	0.35
Chronic Rejection	5	7	0.75
Other	3	9	0.11
Respiratory Failure	1	1	
Renal Failure	2	3	
Multi-System Organ Failure	0	1	
Cerebrovascular Accident	0	1	
Ischemic Colitis	0	1	
Sudden Cardiac Death	0	2	
Unknown	2	0	

DISCUSSION

Several transplant centers have investigated the role of steroid free immunosuppresion over the past 20 years. The latest registry of the ISHLT demonstrates, however, that although prednisone use has been decreasing, almost 75% of patients are still receiving this drug at one year post-transplantation.[20] Many studies demonstrate that prednisone can be safely tapered in the majority of patients. Studies that have investigated the use of ATGAM or OKT3 as induction therapy have suggested that 50 - 80% of patients can either never be treated with steroids or have them successfully weaned off after initial triple drug therapy.[4-6,8-9,12,16] Other transplant centers have attempted steroid tapering without induction therapy. They have also reported a success rate of 50%-80% in weaning patients from steroid therapy.[10-11,13,19] Our results are consistent with these

reviews, and demonstrate that 57% of patients can have steroids eliminated from their immunosuppressive regimen at six months post-transplant without induction therapy.

Some patient populations are less likely to successfully wean from steroids. Taylor reported that female patients have more treated rejection episodes during the first three months after transplantation and, therefore, are less likely to tolerate steroid withdrawal.[14] African American patients have also been identified as a population that is less likely to successfully wean from steroids.[19] In our series, we noted a trend towards decreased success in steroid weaning in female patients at six months post-transplant ($p=0.08$), and a significant reduction in successful steroid weaning in African American patients ($p=0.03$).

There is some debate as to whether or not steroid withdrawal leads to an increased incidence of acute rejection. Some studies demonstrate that acute rejection is lower in patients who are successfully tapered from steroids. These studies usually exclude patients who fail the steroid taper or place them in the steroid-requiring group for analysis. Price found that rejection is lower in patients who are tapered off steroids by four months and noted that successful steroid withdrawal may select for a group of patients with a decreased propensity for rejection during the following 32 months.[8] Pritzker reported a similar incidence of acute rejection in both double and triple therapy groups.[9] Arnold found a higher incidence of acute rejection in the triple therapy group, but this was after risk stratifying patients who were at higher risk of rejection into the triple drug group.[17]

In contrast to the above studies, several reports describe an increased incidence of acute rejection following withdrawal of steroids. Keogh reported a higher incidence of rejection in a group of patients treated without steroids through the initial three months post-transplant.[6] Previous data from our institution analyzed patients on an intent-to-treat basis (leaving those patients who failed

steroid taper in the taper group for analysis) and found an increased incidence of acute rejection in the early withdrawal group.[13] Not surprisingly, our current results mirror this data.

This increased frequency of acute rejection may increase post-transplant coronary artery disease in our steroid withdrawal patients if immunologically mediated injury to the endothelium during acute rejection is an important etiological factor in chronic rejection. Olivari, however, reported that triple drug therapy with cyclosporine, azathioprine, and prednisone while effective in preventing acute rejection, does not alter the incidence of coronary lesions when compared to earlier and less effective immunosuppressive regimens.[21] In the current study, the frequency of acute rejection did not correlate with post-transplant coronary artery disease, a finding consistent with other reports.[4,8,14]

Cardiac transplant recipients are at risk for developing malignancies, especially cutaneous neoplasms.[22] Immunosuppression is considered a possible etiologic factor in the increased incidence of cancer in this patient population. Our results suggest that steroid withdrawal improves the overall freedom from malignancy in our patient population. When individual types of malignancies were considered, however, only cutaneous malignancies were affected. These findings mirror other recently published data which demonstrate that after multivariate analysis, immunosuppressive load (for cyclosporine, azathioprine, steroids, antithymocyte globulin, and OKT3) failed to emerge as independent risk factors for non-cutaneous malignancy.[23] When considering cutaneous malignancies, however, the risk may be related to cumulative immunosuppressive dosage, and sunlight exposure may exert an additive immunosuppressive effect in these patients.[24] Certainly, the etiological factors of cancer are multifactoral, and further study is needed.

Multiple reviews have examined the effects of steroid withdrawal on post-transplant infection. Several authors have reported that steroid withdrawal does not influence the incidence of infection.[4-6,25] In contrast, Pritzker and colleagues found an increased incidence of bacterial infection in patients who underwent early steroid taper.[9] That study involved a group of patients who underwent induction therapy with OKT3. Previously published data from our institution described a decreased incidence of infection in patients who underwent steroid taper at two year follow up.[13] Our current results suggest that this benefit may be lost over long-term followup (see Figure 4). Although freedom from infection is not different between our groups of patients, there is a trend towards decreased frequency of infection in the steroid tapered group.

Previous data from our institution demonstrated that at one year post-transplant, the incidence of diabetes was significantly higher in patients who remained on steroids.[13] Other series found no effect on post-transplant diabetes after steroid withdrawal.[5,19] In the current study, we find no difference in freedom from diabetes in patients who undergo steroid withdrawal and also no significant difference in BMI between the CAP and CAPT groups. Only one series demonstrated that those patients who are treated with triple therapy gain more weight.[8] Most authors have noted that cardiac transplant recipients regain their premorbid weight after surgery and that there is no difference in obesity between those patients managed with or without steroids.[9,11,13,18-19] Lake suggested that post-transplant weight gain is more dependent on genetic factors than immunosuppressive medications.[26]

Survival tended to be improved in our CAPT patients. This is an interesting finding given the observed increased frequency of acute rejection and absence of any difference in post-transplant coronary artery disease and freedom from solid malignancy between the two groups. The improved survival could be attributed to the increased freedom from cutaneous malignancies, although malignancy as a cause of death is not significantly different between the two groups.

The trend towards increased incidence of infective episodes may lead to decreased survival in the CAP group, a hypothesis supported by the observation that infection tended to more often be a cause of death in this group when compared to the CAPT group. Taylor also demonstrated improved survival in patients who could be weaned off of steroids.[14] He suggested that those who are successfully tapered off steroids are "immunologically privileged" and have a low risk of long-term mortality.

In addition to the increased survival of the CAPT patients, there is evidence that these patients enjoy an improved quality of life as well. Jones reported that patients who are managed on double therapy (i.e. without steroids) have a better sense of physical well-being, are less anxious, more sexually satisfied, and financially more secure than their triple therapy counterparts. In addition, double therapy patients demonstrated a lower frequency of and less distress from therapeutic side effects.[27]

We acknowledge the limitations inherent in this nonrandomized retrospective study. It is certainly possible that the decreased freedom from and increased frequency of acute rejection that is seen in the tapered patients is due to the increased frequency of biopsies. However, when the steroid taper protocol was first instituted, it was felt that these patients must be closely monitored with increased biopsy frequency, and we still use this biopsy protocol today. It is difficult to assess the effects that a more frequent biopsy schedule during the first two years post-transplant may have on long-term outcomes, but it is possible that it biases our results. Additionally, the improved survival that is seen in the steroid tapered patients could be due to the era in which these patients received their transplantation. Unfortunately, we can only analyze variables that are available in the medical records. Subtle changes in surgical technique and post-operative care that evolve over time cannot always be captured. However, the years that define our CAP and CAPT patients (1988-1990 and 1990-1996) overlap three eras as defined by the latest registry of the International

Society of Heart and Lung Transplantation (1982-1988, 1989-1993, and 1994-1998).[20] Therefore, the increased survival of the CAPT patients cannot be explained exclusively by the era in which their transplantation was performed. Finally, it is difficult to assess the effects of steroid withdrawal on other important postoperative morbidities such as hypercholesterolemia and hypertension, when almost all heart transplant patients are routinely placed on lipid lowering and antihypertensive therapies. Our study is strengthened, however, by its large size, long follow up, and statistical analysis by intention-to-treat. Those patients who failed steroid withdrawal were included in the analysis in their original (CAPT) group, adding validity to our data. Additionally, our patients, in contrast to many previous studies, were not preselected and received otherwise identical care.

CHAPTER THREE
EFFECTS OF BASILIXIMAB INDUCTION THERAPY AT MID-TERM FOLLOW-UP FOLLOWING HEART TRANSPLANTATION

BACKGROUND

The introduction of cyclosporine into the immunosuppressive regimen of solid organ transplantation greatly reduced rejection episodes and improved results.[28,29] However, nephrotoxicity is a well-recognized complication of calcineurin inhibitor use and contributes to the significant rate of post-operative renal dysfunction in cardiac transplant recipients.[30,31]

Given the potential renal toxicity of cyclosporine, we instituted a protocol of basiliximab induction therapy with delayed cyclosporine use until post-operative day four. This allowed for the stabilization of acute post-operative hemodynamic changes prior to cyclosporine introduction. We demonstrated that basiliximab induction allows delayed initiation of cyclosporine and minimizes the short-term risk of post-operative renal dysfunction in those cardiac allograft recipients who are at high-risk of renal dysfunction.[32] Given these promising short-term results, we performed a review of all patients who received basiliximab at our institution from September 1998 through August 2004 in order to investigate the mid-term effects of basiliximab induction on our entire cardiac transplant population.

METHODS

We obtained Institutional Review Board approval and retrospectively reviewed the records of all patients who underwent cardiac transplantation with basiliximab induction at our institution from September 1998 through August 2004. Informed consent was waived due to the retrospective nature of the study. Follow-up was concluded at the end of two-years post-

transplantation or at the end of December 2005; whichever came first. Seventy-one patients underwent cardiac transplantation with basiliximab induction during this period. Basiliximab was initially only given to patients who were thought be at an increased risk of post-transplant renal dysfunction; however, we have subsequently included basiliximab induction in the immunosuppressive regimen of all of our cardiac allograft recipients. Five patients were excluded secondary to non-routine basiliximab dosing (3) and 30 day mortality (2). The three patients who received non-routine dosing were transplanted during a time of protocol adjustment and, therefore, were not exposed to the same dosing strategy. The remaining 66 patients were compared to a historical control group that underwent cardiac transplantation and received a similar immunosuppressive protocol without basiliximab induction from May 1996 though May 2001 (n=82; 30 day mortality = 3; final n=79).

Our immunosuppressive protocol has been detailed elsewhere.[5] Briefly, basiliximab induction consisted of 20 mg IV immediately prior to heart transplantation and a second 20 mg dose on post-operative day (POD) four. Cyclosporine was started on POD four at a dose of 1-2 mg/kg and then titrated to 2-6 mg/kg until targeted serum levels were reached (trough blood levels of 225-325 ng/ml during the first 3 months, 150-275 ng/ml during the second three months, 100-225 ng/ml during the remainder of the first year, and 75-150 ng/ml thereafter). The broad range in targeted serum levels is secondary to dosing based on serum creatinine level. In contrast, the historical control group received no basiliximab, and cyclosporine was started pre-operatively at 1-3 mg/kg and titrated to the aforementioned serum levels. A total of 11 patients were switched from cyclosporine to tacrolimus at various points during their follow-up (seven control and four basiliximab patients). All patients received methylprednisolone upon initiation of cardiopulmonary bypass and during the first postoperative day. On the second postoperative day, they were started on oral prednisone and begun on a taper protocol, as detailed elsewhere, with the goal of having patients off steroids at six months post-transplantation.[33] Mycophenolate mofetil dosing varied during the period of this study as our experience with this agent grew. All

patients received 1-2 gm of mycophenolate mofetil preoperatively and were maintained on 1-3 gm daily without monitoring for serum levels.

Acute rejection was graded according to the International Society of Heart and Lung Transplantation guidelines. Acute rejection without hemodynamic compromise was treated with methylprednisolone for three days (1 gm IV), and oral prednisone was restarted at 0.3 to 0.5 mg/kg/day and tapered from there. Rejection associated with hemodynamic compromise and second rejections were treated with methylprednisolone for three days (1 gm IV), and prednisone was restarted at 0.5 mg/kg/day and tapered to 0.1 mg/kg over 30 days.

Follow-up was concluded on December 31, 2005. Continuous variables were compared with t-tests, and categorical variables were analyzed with the X^2 statistic. Two-by-two tables were analyzed using Fisher's Exact Test. Patient survival and freedom from events were analyzed with Kaplan-Meier curves and the log-rank statistic for categorical variables. Cox proportional hazard models and the X^2 statistic were used to analyze freedom from events for continuous variables. A multivariate Cox proportional hazards model was used to determine the independent impact of mycophenolate mofetil dosing and basiliximab use on the freedom from acute rejection. Multivariate stepwise regression was used to determine the independent impact of mycophenolate mofetil dosing and basiliximab use on the frequency of acute rejection. Serial serum creatinine values and cyclosporine levels were compared between the two groups with a repeated-measure analysis of variance. Data are expressed as mean ± SD. All statistics were computed using SAS Version 9.1, and $p < 0.05$ determined significance.

RESULTS

One hundred forty-five patients were included in this review (79 control and 66 basiliximab). The patients' demographics are represented in Table 1. The median follow-up time was 1.9±0.3 years (p=0.87) in both groups. The follow-up did not reach a full two years in both

groups secondary to a few deaths in each group as detailed later as well as a lack of a full two years follow-up in seven of the basiliximab-treated patients. Cyclosporine levels were no different between the two groups from three months post-transplantation through two years of follow-up (Table 2).

Table 5: Demographics of Heart Transplant Patients

	Entire Study	Control	Basiliximab	P-value
Patients	145	79	66	
Age	53.6 ± 11.5	53.7 ± 11.9	53.5 ± 11.2	0.92
Gender				0.19
Male	120	62	58	
Female	25	17	8	
Ethnicity				0.83
White	116	65	51	
Black	25	13	12	
Other	4	1	3	
Etiology				0.40
Idiopathic	35	18	17	
Ischemic	91	53	38	
Other	19	8	11	
Acquired Valvular	5	2	3	
Congenital	4	2	2	
Alcoholic	1	1	0	
Restrictive	1	1	0	
Postpartum	2	1	1	
Other	6	1	5	
Ischemic Time	180.7 ± 51.3	183.4 ± 50.9	177.5 ± 51.9	0.49
Creatinine at Transplant	1.3 ± 0.5	1.3 ± 0.6	1.4 ± 0.5	0.09
IABP	13	7	6	1.00
VAD	28	11	17	0.09

Creatinine

Creatinine was not significantly different between the two groups at baseline (control: 1.3±0.6 vs. basiliximab: 1.4±0.5; p=0.09). At one and two-years post-transplantation, no difference was found between groups in the rise of serum creatinine. The control group had

values of 1.8±0.7 and 1.7±0.6, while the basiliximab group had values of 1.8±0.5 and 1.8±0.6 at one and two-years respectively (p=0.29).

Table 6: Cyclosporine Levels (ng/ml) at Follow-Up*

	Entire Study	Control	Basiliximab
3 Months	325.10 ± 69.9 (N=138)	331.29 ± 73.79 (N=76)	317.52 ± 64.59 (N=62)
6 Months	282.10 ± 66.17 (N=134)	291.45 ± 69.10 (N=75)	270.20 ± 60.75 (N=59)
1 Year	220.27 ± 55.70 (N=128)	226.00 ± 57.83 (N=72)	212.89 ± 52.42 (N=56)
2 Years	169.55 ± 47.57 (N=115)	183.19 ± 51.89 (N=64)	152.43 ± 35.06 (N=51)

*Cyclosporine levels were compared between the two groups with a repeated-measure analysis of variance (p =0.73)

Acute Rejection and Post-Transplant Coronary Vasculopathy

Univariate analysis demonstrated that basiliximab induction was responsible for a decreased frequency of acute rejection after transplantation. The six-month and two-year frequency of acute rejection per person in the basiliximab group was less than in the control group (0.06 ± 0.3 and 0.2 ± 0.56 vs. 0.19 ± 0.46 and 0.44 ± 0.69; p=0.04 and 0.02 respectively). Multivariate step-wise analysis demonstrated that the varying doses of mycophenolate mofetil, pre-op or maintenance, did not significantly affect the frequency of acute rejection episodes during the two-year follow-up period (pre-op: p=0.54 and maintenance: p=0.67 respectively). Therefore, the observed differences in the frequency of acute rejection were due to basiliximab induction. Additionally, basiliximab induction was responsible for a prolonged freedom from acute rejection (Figure 1; p<0.01). Again, multivariate analysis demonstrated that the varying doses of mycophenolate mofetil, pre-op or maintenance, did not affect the freedom from acute rejection episodes independent of basiliximab (pre-op: p=0.61 and maintenance: p=0.66). However, multivariate analysis confirmed that basiliximab induction was responsible for the prolonged freedom from acute rejection (p<0.03). Figure 1 demonstrates that the majority of the

benefit of basiliximab induction is seen during the first three months post-transplantation. This is the time of highest risk of acute rejection.

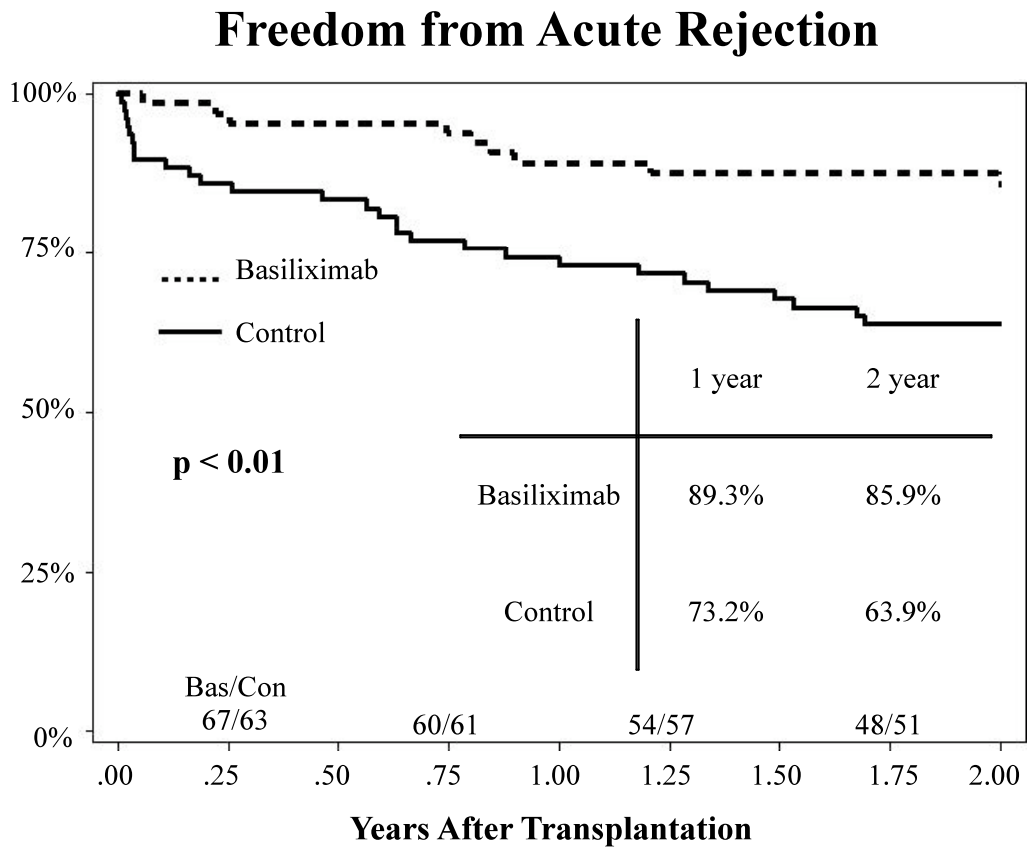

Figure 6: Freedom From Acute Rejection
Bas – Basiliximab, Con - Control

Infection

Infection was defined as the need for hospital admission or IV antibiotic therapy. In the first six months post-transplantation, there were 1.03 ± 1.37 infectious episodes per patient in the control group, while in the basiliximab group, there were 0.88 ± 1.05 episodes per patient (p= 0.47). During the entire follow-up period, there were 1.57 ± 1.93 episodes per patient and 1.15 ± 1.27 episodes per patient in the control and basiliximab groups respectively (p=0.12). There was no difference in freedom from first infection between the two groups (Figure 2).

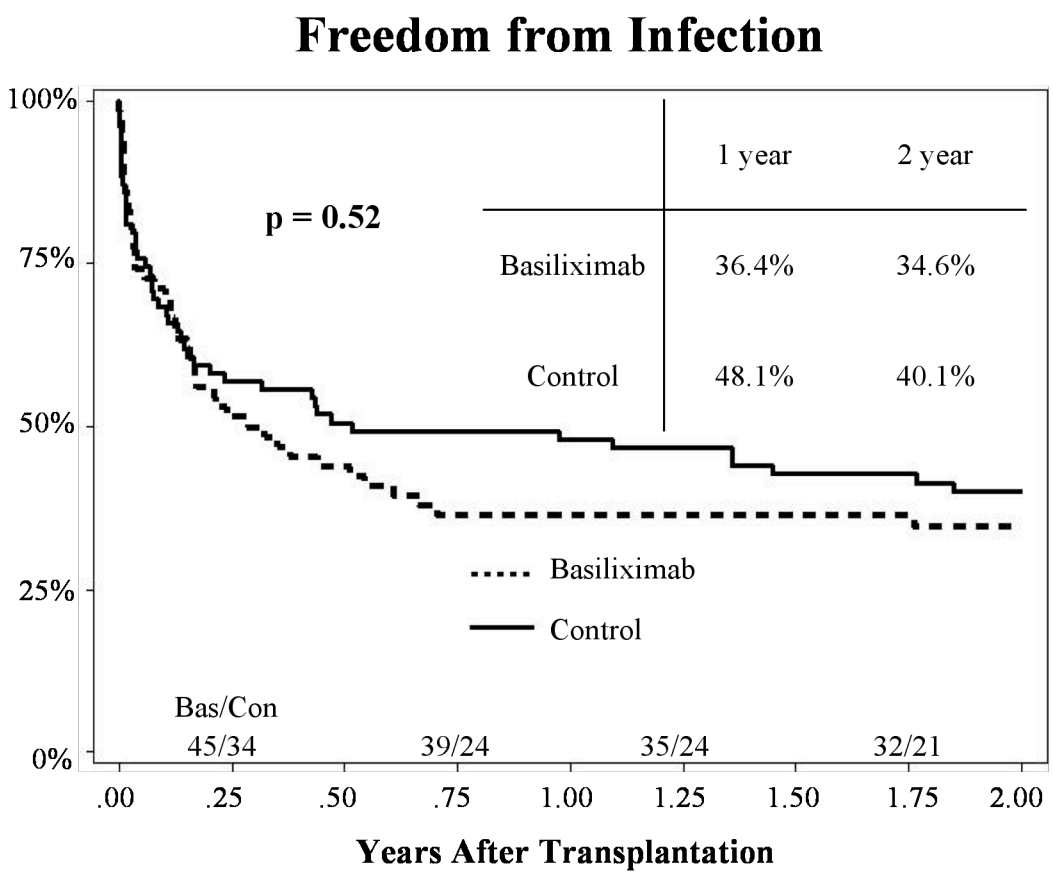

Figure 7: Freedom From Serious Infection
Bas – Basiliximab, Con - Control

Malignancy

There was no difference in freedom from first malignancy in the two groups of patients (Figure 3). When examining specific cancer types (post-transplant lymphoproliferative disorder [PTLD], skin, solid organ), no difference in freedom from disease was noted. There were no cases of PTLD in either group during the first two years of follow-up. The freedom from skin cancer at two years was 89% and 89% (p=0.92) in the control and basiliximab groups respectively. The freedom from solid organ malignancy at this same time point was 93% and 95% (p=0.64) in the respective groups.

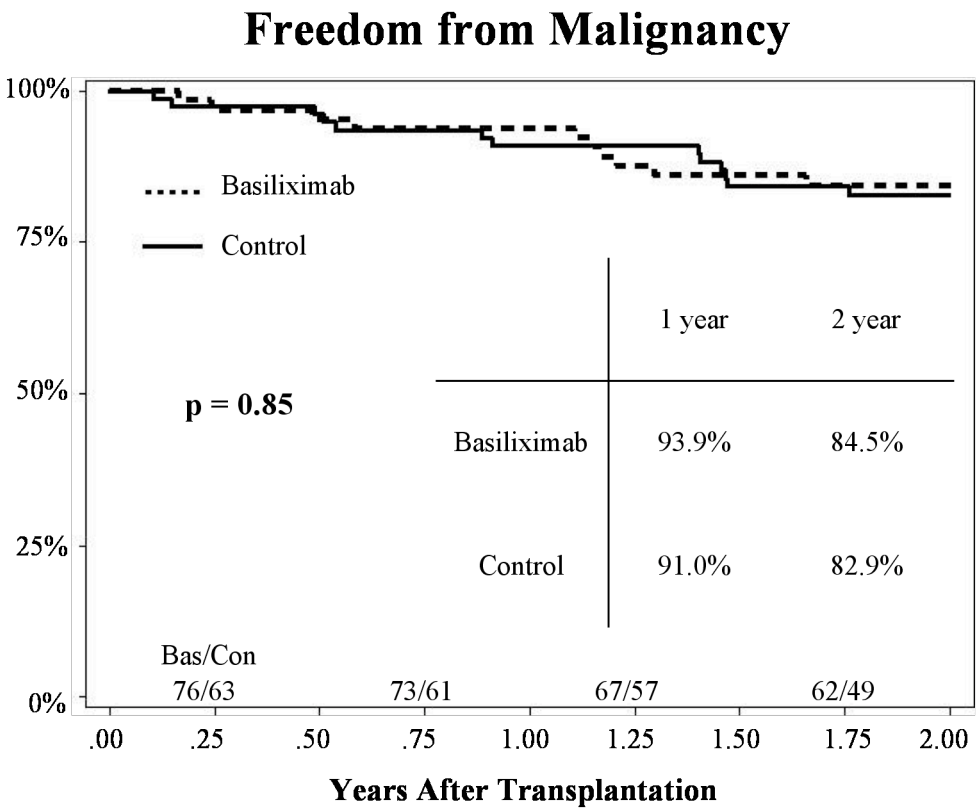

Figure 8: Freedom From Malignancy
Bas – Basiliximab, Con - Control

Survival

Nine patients died in the control group during the follow-up period, and four died in the basiliximab group. Basiliximab induction did not alter the cause of death between the two groups; however, the small number of deaths makes analysis difficult (Table 3). Additionally, it did not improve mid-term overall survival in cardiac allograft recipients when compared with control patients (Figure 4). The 2-year survival in the basiliximab group was 94% and in the control group, it was 89%. This observation, however, was not statistically significant.

Table 7: Cause of Death Data			
Cause of Death	**Control**	**Basiliximab**	**P-value**
Acute Rejection	4	0	NS
Myocardial Infarction	1	1	NS
Infection	2	1	NS
Sudden Cardiac Death	0	1	NS
Unknown	2	1	NS

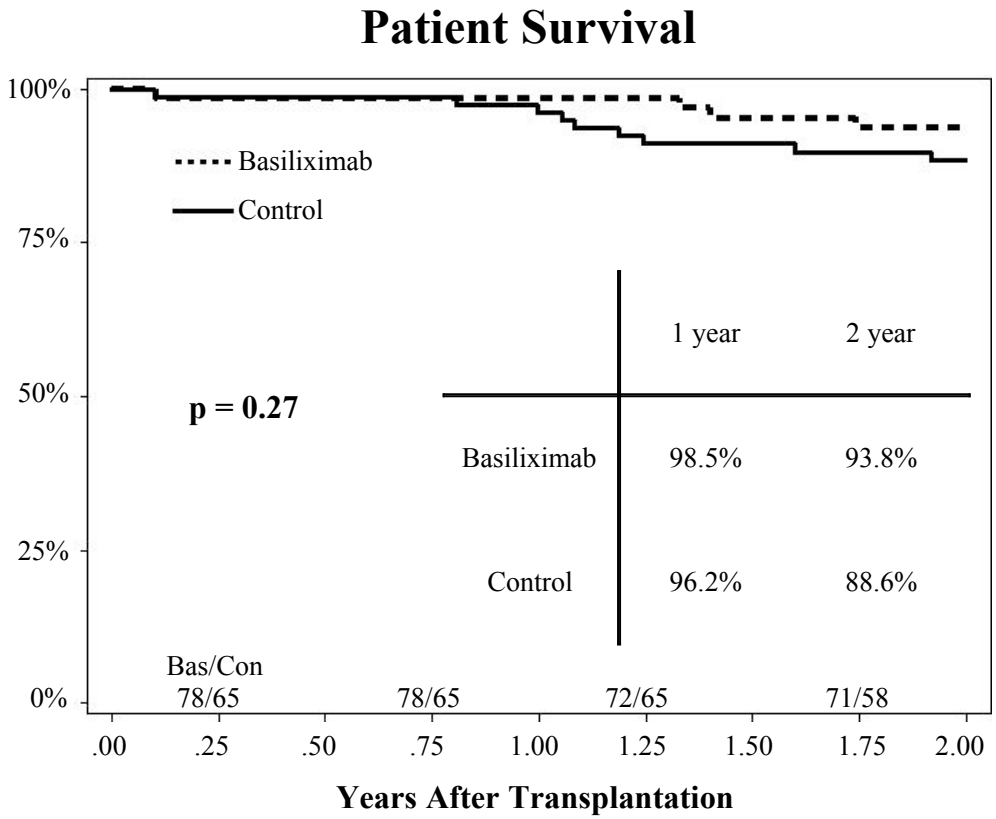

Figure 9: Overall Survival
Bas – Basiliximab, Con - Control

DISCUSSION

Our results demonstrate that basiliximab induction and delayed cyclosporine introduction does not help maintain pre-transplant renal function at mid-term follow-up. However, it does delay the first episode of acute rejection as well as decrease the overall frequency of acute rejection episodes in the heart transplant population.

The risk of developing high-grade rejection after heart transplantation is predicted by the presence of IL2 – dependent T-cell infiltration in the allograft.[34] IL-2 receptor-targeted therapy selectively inhibits T-cell proliferation and has been investigated as a means for improving post-transplant outcomes.[35] Basiliximab is a chimeric monoclonal antibody directed against the alpha chain of the IL-2 receptor that selectively inhibits T-lymphocyte proliferation. The mean duration of receptor saturation in adult renal transplant recipients receiving 20 mg of basiliximab on days zero and four was 36-49 days.[36] Mehra and colleagues verified that in cardiac transplant recipients, basiliximab has an average of 38 days of IL-2 receptor saturation with the day zero and day four dosing strategy.[37] They demonstrated basiliximab is well-tolerated and has a safety profile comparable with placebo during the first year post-transplantation.

We recently demonstrated that induction therapy with basiliximab allowed delayed initiation of cyclosporine therapy and minimized the risk of renal dysfunction in patients who were at high-risk of developing azotemia during the immediate post-operative period.[32] Delgado demonstrated similar results with basiliximab induction in at-risk patients. His group found improved serum creatinine levels early after transplantation that were sustained up to six months post-transplantation.[38] However, our current results suggest that when treating all patients with basiliximab induction, not just those at risk of renal dysfunction, there is no benefit of preserved renal function at mid-term follow-up.

Multiple studies have demonstrated the efficacy of basiliximab in reducing acute rejection after renal transplantation.[39-41] They demonstrate a 28-32% reduction in the proportion

of patients with biopsy-confirmed acute rejection episodes without an increase in the incidence of infections when compared to placebo.[39,40] Cardiac allograft literature describing the use of daclizumab for induction supports this data. Daclizumab, another IL-2 receptor antagonist, has demonstrated efficacy in decreasing acute rejection episodes after cardiac transplantation without increasing infectious complications.[42-44] Carlsen demonstrated that when compared with anti-thymocyte globulin, daclizumab induction led to an increase of Grade I acute rejections but a similar number of ≥ Grade 2 acute rejections and significantly fewer bacterial infections. The long-term medical and financial consequences of increased Grade 1 acute rejections but fewer infections were not addressed.[45]

Basiliximab induction has demonstrated similar early results. We previously reported a trend towards a lower incidence of acute rejection early after heart transplantation with basiliximab induction; however, the finding was not statistically significant.[32] Additionally, Mehra demonstrated a trend towards an increased freedom from first rejection of grade 3A or greater when compared to placebo during the first six months post-transplantation.[37]

Our current results are the first to demonstrate a statistically significant improved freedom from and decreased frequency of acute rejection through the first two years post-transplantation in cardiac allograft recipients treated with basiliximab induction immunosuppression. The decrease in acute rejection appears to be most evident during the first three months post-transplantation. This benefit in increased immunosuppression was accomplished without decreased freedom from infection or malignancy. The decreased frequency of acute rejection did not translate into a statistically significant improvement in overall survival. However, there was a trend towards improved 2-year survival in the basiliximab-treated patients when compared to historical controls (94% vs. 89%; p=0.27). Long-term follow-up will determine if there is a survival benefit to basiliximab induction therapy.

This study is limited by its nonrandomized retrospective nature and is, therefore, vulnerable to unintentional bias. Our historical group of patients was well matched in multiple

demographic areas to the basiliximab group; however, the immunosuppressive protocols were not perfectly standardized between the groups. This is most notable with the varied doses of mycophenolate mofetil. However, multivariate analysis did not demonstrate that the different mycophenolate mofetil doses (either pre-operative or maintenance) affected acute rejection episodes in the control and basiliximab groups of patients.

The rejection rates reported in this review are lower than those typically observed in cardiac transplantation recipients. Historically, our rejection frequency has been quite low. This may reflect an inherent referral bias, a more favorable donor pool or unrecognized surgical and/or treatment practices that mitigate the risk of rejection in our patient population.

CHAPTER FOUR
Conclusions and Recommendations

Topic A

Conclusions:

Steroid withdrawal is possible in almost 60% of patients by six months post-transplantation. Despite an increased frequency of acute rejection, early steroid withdrawal improves the freedom from malignancy and may decrease the frequency of infection, and improve long-term survival in the cardiac transplant population.

Recommendations:

A longer follow-up or larger study should be done to confirm the improvement in long-term survival suggested by the study. Steroid withdrawal should be considered as a superior alternative to continuous administration of corticosteroids. Further research should continue to be done to minimize risk of immunosuppressive drug combinations while efficiently suppressing the patient's immune system to prevent fatal rejection.

TOPIC B

Conclusions:

In the first two years of follow-up, basiliximab induction therapy appears to decrease the frequency of acute rejection and prolong the duration to first acute rejection episode without decreasing the freedom from infection, malignancy, and transplant vasculopathy. The use of basiliximab to delay the initiation of cyclosporine did not continue to have a protective renal effect past the initial post-transplant period.

Recommendations:

Long-term follow-up is needed to determine if basiliximab induction confers either a survival advantage or a continued freedom from rejection benefit further out from transplant. A prospective, randomized trial should be performed to confirm the findings of this retrospective study. Continued monitoring should be done to ensure that the benefits of basiliximab do not come at the expense of any additional, yet to be determined, side-effects.

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Vitae

EDUCATION

2004 – present

University of Texas Southwestern Medical School

- Doctor of Medicine with Distinction in Research anticipated May 2008
- GPA: 4.0
- Passed USMLE Step 1 with a score of 255 (99) in June, 2006
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Johns Hopkins University

- Bachelor of Science, Biomedical Engineering and Mathematical Sciences, *cum laude*
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HONORS / AWARDS

Medical School

- Vice President of UTSW chapter of Alpha Omega Alpha, 2007-2008
- Southwestern Medical Foundation Scholarship for Academic Achievement, 2004-2007
- Texas Medical Liability Trust Memorial Scholarship, 2006

Military Awards

- Bronze Star Medal - Awarded for merit, Operation Enduring Freedom, 2002
- Distinguished Honor Graduate, Field Artillery Officer Basic Course, 2001

Undergraduate Awards

- Tau Beta Pi (National Engineering Honor Society), 1998-2000
- President of Johns Hopkins chapter of Tau Beta Pi, 1999-2000
- General George C. Marshall Award - top military graduate from the university, 2000
- U.S. Field Artillery Association Award - awarded to the top graduating cadet in the country entering the Field Artillery branch, 2000
- National Duet Trick Drill Champion, 1998

WORK EXPERIENCE

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Pharmacology and Clinical Medicine Tutor

Office of Medical Education, UT Southwestern Medical Center

- Plan, prepare and present review sessions for MS IIs prior to exams. Design and construct additional test preparation material as needed.

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Database Analyst

Cardiothoracic Surgery Department, UT Southwestern Medical Center

- Maintain research databases, perform statistical analysis of data, assist in manuscripts, and help determine direction of future research.

2004-2005; 1999-2000

MCAT/DAT/OAT Instructor

Kaplan, Dallas, TX; Baltimore, MD

- Planned and taught classes to pre- medical, dental, and/or optometry students covering such topics as biology, chemistry, and physics.

2000-2004

Field Artillery Officer, United States Army

1 - 319th Field Artillery Regiment, 82nd Airborne Division, Fort Bragg, NC

- Pioneered the use of Air Force simulation software to account for weather conditions in ballistic computations during deployment to Operation Enduring Freedom.
- Ensured the accuracy and efficiency of all battalion fire direction elements and coordinated the response to incoming mortar and rocket fire during Operation Iraqi Freedom.
- Assisted C/1-319th in achieving the best battery certification in seventeen years as cited by the Division Artillery Commanding Officer.
- Certified as airborne, ranger, and jumpmaster.

1998-2000

Computer Instructor

Computer Tutor, Reisterstown, MD

- Taught first time users of computers how to use common applications and the internet.
- Taught experienced users how to use such applications as Adobe Photoshop.

1996-1997

Data Manager

Study on Social Network of IV Drug Users, Johns Hopkins University School of Public Health

- Responsible for entering, cleaning, and managing data.

VOLUNTEER EXPERIENCE

2008-present

Head Coach

U6 Girl's Soccer Team, Duncanville Soccer Association

- Responsible for leading practices and games during the Spring 2008 season.

2008-present

Project Lead

Obesity Outreach Program, UT Southwestern Medical Center

- Help develop, organize, and implement student led nutrition and exercise presentations to Dallas ISD 5th graders.
- Serve as liaison between DISD executives, UT Southwestern executives, and student volunteers.

2006-present

Committee Chair
United to Serve, UT Southwestern Medical Center

- Chair the committee responsible for planning and implementing the "Medical Museum" portion of the 2008 United to Serve Health Fair at TJ Rusk Middle School.
- Lead the committee in designing and building new interactive and educational displays for teaching children about how the body works and the importance of health and exercise.
- Served on the planning committee for the 2007 United to Serve Health Fair at TJ Rusk Middle School. Primary responsibilities involved brainstorming ideas for prizes/awards and soliciting local businesses for donations

2006-present
Community Service Representative
Class of 2008 Class Officer, UT Southwestern Medical Center

- Serve as point of contact for community service activities for the Class of 2008. Acted as liaison between the class and the administration.
- Assist with such projects as medical school tours and curriculum talks for interested pre-med students.

2004, 2006
Planning Committee
Christmas in the Park, Texas Medical Association, UT Southwestern Medical Center

- Helped plan and prepare the athletic activities available to children attending the annual Christmas in the Park celebration co-hosted by the UT Southwestern TMA in 2004.
- Assisted with photography and manning booths at the annual event in 2006.

RESEARCH

2005
Medical Student Summer Research Program **Supervisor: Michael DiMaio, M.D.**
Cardiothoracic Surgery Department, UT Southwestern Medical Center, Dallas, TX

- Created a research database for cardiac transplant recipients from 1988-2004.
- Performed statistical analysis on survival and other endpoints for different immunosuppressive protocols.

2004
Medical Student Summer Research Program **Supervisor: Sherwood Brown, M.D., Ph.D.**
Psychoneuroendocrine Lab, UT Southwestern Medical Center, Dallas, TX

- Reviewed data collected from three longitudinal studies on cocaine and/or alcohol dependent bipolar patients and did a statistical analysis of their comorbid disorders and other features.

1997-2000
Undergraduate Research Assistant **Supervisor: Nitish Thakor, Ph.D.**
Biomedical Instrumentation Lab, Johns Hopkins University, Baltimore, MD

- Served as project lead in the design of a wheelchair for tetraplegics steered by eye movement.
- Worked on a research team exploring methods for operating on a beating heart.

ACTIVITIES AND ORGANIZATIONS

Medical School

- Texas Medical Association/American Medical Association, 2004-present
- American College of Physicians, 2004-present
- Laparoscopic Surgery Research Participant, 2005-2007
- Dartos Soccer, 2005-2006

Undergraduate

- Battalion Commander, ROTC, 1996-2000.
- Captain, Pershing Rifles (National Military Honor Society and Drill Team), 1996-2000.
- Community service projects including Adopt-A-Highway, food drives for Sara's House, and tutoring sessions, 1996-2000.
- Officer Christian Fellowship, 1996-2000

PUBLICATIONS

Gupta S, **Mitchell JD**, Markham DW, Mammen PP, Patel P, Kaiser PA, Ring WS, DiMaio JM, Drazner MH. Utility of the Cylex assay in tailoring immunosuppression after cardiac transplantation. Journal of Heart and Lung Transplantation. 2008; in press.

Gupta S, **Mitchell JD**, Markham DW, Mammen PP, Patel P, Kaiser PA, Ring WS, DiMaio JM, Drazner MH. High incidence of CMV disease in D+/R- heart transplant recipients shortly after completion of three months of valganciclovir prophylaxis. Journal of Heart and Lung Transplantation. 2008; in press.

Mitchell JD, Brown ES, Rush AJ. Comorbid Disorders in Patients with Bipolar Disorder and Concomitant Substance Abuse or Dependence. Journal of Affective Disorders. 2007; 102(1-3):281-7.

Rosenbaum DH, Adams BC, **Mitchell JD**, Kaiser PA, Paul MC, Meyer DM, Jessen ME, Wait MA, Drazner MH, Yancy CW, Ring WS, DiMaio JM. Effects of Early Steroid Withdrawal After Heart Transplantation. Annals of Thoracic Surgery. 2006;82(2):637-44.

Mitchell JD. A Case for Howitzers in Afghanistan. Field Artillery, November-December 2003, 6-9.

Mitchell JD. Afghanistan: Firing Artillery Accurately with Air Force MET Support. Field Artillery, January-February 2003, 38-41.

PRESENTATIONS AND POSTERS

Rosenbaum DH, **Mitchell JD**, Adams BC, Kaiser PA, Meyer DM, Jessen ME, Wait MA, Drazner MH, Ring WS, DiMaio JM. Utility of Basiliximab Induction at Mid-Term Follow-Up. *The International Society for heart and Lung Transplantation, Annual Meeting.* Accepted for presentation in Spring, 2008.

Rosenbaum DH, **Mitchell JD**, Adams BC, Paul MC, Kaiser PA, Meyer DM, Jessen ME, Wait MA, Rosenberg P, Drazner MH, Yancy CW, Ring WS, DiMaio JM. Does Basiliximab Decrease Acute Rejection and Improve Renal Function in Cardiac Transplant Recipients at Mid-Term Follow-Up? *The International Society for Heart and Lung Transplantation, Annual Meeting*. April 2006.

Rosenbaum DH, **Mitchell JD**, Adams BC, Kaiser PA, Paul MC, Meyer DM, Jessen ME, Wait MA, Drazner MH, Yancy CW, Ring WS, DiMaio JM. Does Basiliximab Decrease Acute Rejection and Improve Renal Function in Cardiac Transplant Recipients at Mid-Term Follow-Up? *6th Annual American Society of Transplant Surgeons State of the Art Winter Symposium*. January, 2006.

Mitchell JD, Rosenbaum DH, Adams BC, Paul MC, Kaiser PA, Meyer DM, Jessen ME, Wait MA, Rosenberg P, Drazner MH, Yancy CW, Ring WS, DiMaio JM. Does Basiliximab Decrease Acute Rejection and Improve Renal Function in Cardiac Transplant Recipients at Mid-term Follow-Up. *44th Annual UT Southwestern Medical Student Research Forum*. January, 2006.

Adams BC, Rosenbaum DH, **Mitchell JD**, Kaiser PA, Paul MC, Meyer DM, Jessen ME, Wait MA, Drazner MH, Yancy CW, Ring WS, DiMaio JM. Early Steroid Withdrawal Improves Late Survival After Heart Transplantation. *44th Annual UT Southwestern Medical Student Research Forum*. January, 2006.

Rosenbaum DH, Adams BC, **Mitchell JD**, Kaiser PA, Paul MC, Meyer DM, Jessen ME, Wait MA, Drazner MH, Yancy CW, Ring WS, DiMaio JM. Early Steroid Withdrawal Improves Late Survival After Heart Transplantation. *52nd Annual Meeting of the Southern Thoracic Surgical Association*. November, 2005.

PERSONAL

Married Nikki Mitchell on July 18, 1998

- Daughter, Hannah, born January 12, 2002
- Daughter, Lillian, born July 27, 2005

Hobbies and Interests

- Soccer, photography, gardening/landscaping, reading with my daughters