HEART TRANSPLANTATION: IS THERE A RELATION BETWEEN EXPERIENCE AND OUTCOME?

By

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M.D. University of Miami School of Medicine
(1980)

Submitted to the
Whitaker College of Health Sciences and Technology
in partial fulfillment of the requirements
for the degree of
Ph.D. in Health Policy and Management

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

February, 1991

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ABSTRACT

Current federal heart transplant policy is based on several unproven assumptions about the relation between experience and mortality for this procedure. To test these assumptions, I studied a data set containing information from the Registry of the International Society for Heart Transplantation and from a personally collected supplementary survey that provided additional patient, donor and center characteristics. The data set included 2,005 patients who underwent heart transplantation between 1984-1986 at one of 70 centers participating in the Registry.

This study's major conclusions are that: 1) Heart transplant centers acquire incremental experience while performing their first several transplants, and this enables them to reduce the risk of death in subsequent patients. This learning curve is most apparent in patients who have the highest mortality risk to begin with. 2) Heart transplant mortality is not related to transplant volume, transplant rate, or the year of transplantation. 3) In new heart transplant centers, prior transplant experience among cardiologists and/or transplant coordinators is associated with lower mortality.

BIOGRAPHICAL NOTE

Glenn Laffel, M.D. is an Instructor in Medicine at Harvard Medical School and Associate Physician at Brigham and Women's Hospital, where he is a staff member in the Cardiovascular Division. He has primary clinical responsibilities in the hospital's cardiac transplantation program. He is also the Director of Quality Assurance Planning at the hospital. In this role, he has helped to develop and implement a comprehensive quality management system. He has lectured extensively on the relations, at both theoretical and practical levels, between quality programs in health care and in industrial settings. He is a magna cum laude graduate of Tufts University, where he majored in Biology and Psychology. He is an Alpha Omega Alpha graduate of the University of Miami School of Medicine.

GLOSSARY

Comorbid Conditions-Any patient attribute that worsens prognosis following heart transplantation. Examples include female gender, pulmonary disease and diabetes. Patients having multiple coexisting comorbid conditions are said to have a high burden of premorbid illness.

Cumulative Experience-Skill and/or knowledge that accrues through successive repetitions of a procedure.

High Risk Patient-One who, by virtue of an excessive burden of premorbid illness, has a relatively high likelihood of death following heart transplantation.

Intertransplant Interval-A measure of the rate at which centers perform heart transplantation. It is calculated by dividing the number of days between the first and the most recent transplant by the total number of transplants performed.

Ischemic Time-The elapsed time between the moment surgeons clamp the donor aorta during harvesting and the moment the recipient aorta is unclamped after the aortic anastomosis is completed. Prolonged ischemic times can damage the donor heart.

Low Risk Patient-A transplant recipient who has few or no comorbid conditions, and who therefore has a relatively high likelihood of survival following heart transplantation.

Learning Curve-A description of the observation that initial repetitions of a procedure are associated with incrementally improved outcomes.

Left Ventricular Ejection Fraction-The percentage of blood ejected from the left ventricle (the heart's main pumping chamber) during each cardiac contraction. Normal values exceed 55%. Values less than 20% indicate severe heart failure.

GLOSSARY (ctd.)

Premorbid Burden of Illness-The accumulated risk of death secondary to the presence of one or more comorbid conditions.

Preoperative Mechanical Support-The use of intraaortic balloon pumps, left ventricular assist devices or total artificial hearts to augment heart function and maintain adequate circulation to vital organs. These devices are reserved for patients with very severe heart failure.

Transplant Volume-The total number of heart transplants performed at one center.

Transplant Rate-The number of heart transplants completed per unit time. Usually measured as the intertransplant interval.

Triple Drug Immunosuppressive Therapy-A treatment protocol for the prophylaxis of cardiac transplant rejection. It consists of Cyclosporine, Azathioprine (Imuran) and Prednisone.

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SUMMARY:

This introduction provides the rationale for a study of the relation between experience and outcome in heart transplantation.

KEY POINTS:

- In the 1980s, the number of centers offering heart transplant services proliferated at an explosive rate. This growth followed the introduction of cyclosporine and a series of favorable coverage decisions.

- This technology's proliferation has been characterized by a lack of concordance between the need for services, as defined by local population density, and the availability of these services.

- In addition, there is striking variation in the number of transplants performed per center.

- The federal government has recently attempted to regulate the proliferation of heart transplantation in order to equalize access to it and to maximize results from the scarce donor organ supply.

- Unfortunately, federal regulators have so far been unable to develop a single strategy that maximizes both goals.

- A major obstacle to the development of optimal federal heart transplant policy has been the absence of empiric data showing a relation between experience with the procedure and survival following it.

- Optimal federal policy cannot be formulated until this relation is studied and characterized.

Among recent medical innovations, heart transplantation remains one of the most highly visible and captivating. The first United States heart transplant was performed in 1967, and it attracted intense public interest. In the next two years, clinicians performed nearly 100 more heart transplants, but clinical and lay interest rapidly waned when it became clear that clinicians could not successfully prevent or treat rejection of the transplanted organ. Few heart transplants were performed over the next decade.

Widespread enthusiasm resurfaced in 1980 when a new immunosuppressive drug, cyclosporine, became available on an experimental basis. Cyclosporine quickly proved to be far more effective than first generation immunosuppressive agents in preventing rejection. It also caused fewer infectious complications. Cyclosporine was released for routine clinical use in 1984. By that time, investigators had already begun to report that a regimen combining small doses of cyclosporine with two other immunosuppressive agents (so called "triple drug therapy") was more effective in preventing rejection and infection than a regimen consisting solely of cyclosporine in high doses.

As a result of these advances in immunosuppressive management, survival following heart transplantation increased dramatically. By the mid 1980s, most centers reported one-year survival rates above 80% (1-4). This compared favorably with 80-90% six-month mortality rates among eligible patients for

whom a donor heart did not become available (1,2). In addition, investigators reported that transplant recipients experienced marked improvements in functional capacity: 81% of eligible patients were bedridden at their pre-transplant evaluation, and yet 88% of the recipients had no physical limitations following transplantation (5). These results convinced physicians that heart transplantation was reasonable therapy for patients with advanced, isolated congestive heart failure.

With the clinical efficacy of heart transplantation no longer in doubt, the mid-1980s witnessed a rapid expansion in third party coverage for heart transplantation. Most Blue Cross/Blue Shield programs chose to cover this procedure by 1986. At least 25 Medicaid programs, dozens of HMOs and most commercial insurers also followed suit in this period.

The number of heart transplant centers increased dramatically in response to these favorable reimbursement conditions. In 1982, only 8 US centers had performed this operation. By 1986, 75 centers had done so. The General Accounting Office now estimates there are approximately 130 such centers in this country (6).

The proliferation of heart transplant centers has been remarkable because of its rate and also because of the uneven geographic distribution of these centers. For example, presently there are 27 heart transplant centers within 300 miles of Chicago, and 31 centers within the same radius of

Indianapolis (2). However, there are only 12 programs on the entire west coast. Texas has 9 heart transplant centers, whereas 8 states have none. Eight of the nation's fifty largest metropolitan areas have no heart transplant centers (2).

An additional feature of this technology's diffusion has been remarkable variation in the number of transplants performed per center. In 1985 for example, ten centers performed 70% of all US heart transplants, although 60 centers performed at least one (1).

That year the number of transplants performed per center varied from 91, at the University of Pittsburgh, to one, at many centers. These variations in procedure volume continue today. They are due to variations in referral patterns, institutional commitment, population density and the geographic proximity of other centers.

Nevertheless, despite rapid public and clinical acceptance of the procedure and the rapid proliferation of facilities capable of performing it, the number of transplants performed annually equals no more than one-half the number of patients who could benefit from the procedure (4). The disappointing reality is that the number of donor organs is essentially fixed, despite numerous attempts to increase it, at about 2,300 per year (1).

These features of heart transplantation-its rapid ascension to the status of accepted medical practice, the lack of

concordance between the need for services and their geographic availability, the vast differences in procedure volume across centers, and the profound lack of donor organs-create an unquestioned need for federal regulatory intervention. The two imperatives for policymakers are to equalize access to the service, and to assure that it is offered only by centers capable of providing care of the highest quality.

Regulators are concerned about equalizing access to all medical services, but their interest is particularly acute for heart transplantation. This is because the procedure is life-saving, there is no alternative to it for patients with end-stage heart failure, and because the service is constrained by the donor organ supply.

Regulators and clinicians have long recognized that access to heart transplantation depends critically on the distance between the patient's home and the nearest transplant center. It is simply too difficult to manage the intricacies of patient care over long distances. For example in the pre-operative period, potential recipients often require prolonged hospitalization and intensive care at the transplant center. If the patient lives far from the center, family members find it difficult to accompany them. Patients frequently find such separation intolerable and refuse to be considered as transplant candidates.

In addition, transplant centers must occasionally require that outpatients wait for their transplants near the center.

This places an enormous financial burden on patients: they must pay out of pocket for temporary accommodations because these expenses are not covered by third parties. It places an equally large burden on family members: they must forego work or school in order to care for their loved ones.

Similar geographic barriers exist in the post-operative period. Most physicians are unfamiliar with the medications and protocols used to manage transplant recipients. And yet, routine post-transplant care requires very intensive follow-up with physicians who are familiar with the above protocols. Again, the necessity to receive care at the transplant center creates potentially insolvable difficulties for certain patients.

Regulators are also acutely concerned that heart transplants are performed in high quality centers. The rationale for regulatory intervention in the quality arena is straightforward. First, the donor organ supply is fixed. Second, investigators have demonstrated dramatic graft and patient survival differences across kidney transplant centers (see chapter 5), and most believe similar differences exist in heart transplantation. The regulatory imperative therefore becomes to maximize public benefits from the scarce resource.

Ideally, heart transplant policy would simultaneously equalize access and assure that transplants were performed only in high quality facilities. Unfortunately, regulators have so far been unable to develop a single policy that

maximizes both goals. This has created a major controversy among policymakers, and led to the deployment of an array of policies which lack consistency.

Consider on one hand a policy that establishes very low barriers for centers wishing to initiate transplant programs. This policy would hasten the proliferation of new centers and hence improve access[1].

This policy would simultaneously reduce the number of transplants performed per center, because the number of donor organs is fixed. Reductions in the number of transplants performed per center decelerate the learning process at each institution and create disincentives for centers to accumulate transplant expertise on site. In addition, it might increase inappropriate competition for organs or recipients, either via the manipulation of patient selection criteria or through less-than-rigorous application of patient "listing" criteria.

On the other hand, consider a policy that sets rigorous criteria for the designation of transplant centers[2]. This policy would assure that transplant services are provided by capable centers and would hence maximize outcomes from the limited donor supply. Unfortunately, this policy would simultaneously prevent many potential centers from offering

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[1] The United Network of Organ Sharing (UNOS), which operates the nation's transplantation network (see below), has designed its transplant policy with this in mind.

[2] Medicare designed its transplant coverage policy with this in mind.

transplant services, inhibit further proliferation of the technology, and hence impede access to the procedure.

To complicate matters further, regulators (wishing to designate centers on the basis of quality) face the imposing task of developing criteria that effectively distinguish the best facilities. No regulatory agency has perfected this art to date. There are two major approaches to the formulation of criteria for designation: one is to base criteria on proven success; the other is to base criteria on the presence of center characteristics that are thought to be predictive of future success.

Regulators would certainly find it appealing to designate centers on the basis of hard patient outcome data. Unfortunately, there are several problems with this approach. First, it is statistically difficult to isolate the "bad apples" when both the number of cases performed by a center and the probability of an adverse event are low, as is the case in heart transplantation[3]. Second, for new or rapidly evolving medical technologies such as heart transplantation, existing data are often unavailable or outdated. Third, isolated outcome-based designation criteria would create incentives for centers to select only low risk patients and this might inappropriately favor certain groups.

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[3] I discuss this further in chapter 5.

EXPERIENCE AS A CRITERION FOR THE DESIGNATION OF TRANSPLANT CENTERS

In the case of heart transplantation, even data regarding the proxies for future success is sparse. As a result, Medicare designation criteria are based on the best judgement of clinician advisors (3,4). The outputs of this process have been designation criteria that include, prominently, specifications for procedure volume.

These specifications are supported by a large body of research demonstrating that centers characterized by high procedure volumes are associated with relatively low mortality rates from those procedures[4]. The mechanism linking high procedure volumes to improved outcomes is thought to include the creation of incentives for high volume centers to invest in capital and to attract teams of experts who can pool their skills on behalf of patients.

Unfortunately, it is far from clear that the above studies are applicable to the case of heart transplantation. Consider for example that the above volume-outcome studies have focused on procedures for which volumes are relatively fixed over time. As a result it is not possible to determine from this literature whether outcomes in one period reflect procedure volume in that period or procedure volume in some earlier period. This is critically important to the study of heart

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[4] This literature is reviewed in detail in chapter 5.

transplantation, because most new heart transplant centers are characterized by rapidly increasing procedure volumes over time.

Beyond this, it is not clear that the presumed mechanism linking high volumes to improved outcomes is relevant for heart transplantation. First of all, centers require little or no capital investment in order to initiate a heart transplant program, because heart transplant programs use the same facilities as preexisting open-heart surgery programs. Second, providers are aware that public scrutiny inevitably surrounds the initiation and continued operations of a transplant program, so they virtually always make strong efforts to assemble the appropriate expertise before they attempt their first transplant[5].

Perhaps most important from a conceptual standpoint is that procedure volume is a rather static descriptor for institutional experience: it does not appear to capture the dynamic, accelerated learning that was taking place in US transplant centers at the time federal transplant policy was formulated (between 1984-86). During this period, many centers attempted the procedure for first time. It was a period of active experimentation: individuals varied their approach, practiced manipulative and cognitive skills, and integrated current experiences with those of the past and those of

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[5] Obviously regulations may be useful to the extent that this does not occur in <u>all</u> cases.

colleagues. Another descriptor of experience-the learning curve-appears to better capture these events.

Regulators wishing to use experience as a criterion for the designation of transplant centers face other challenging questions as well. Should prior transplant experience be a requirement for physicians wishing to initiate programs at new centers? If so, what constitutes adequate transplant experience? Should experience be vested in the transplant surgeon, the cardiologist or the coordinator? Finally, is there any benefit in shunting particularly ill recipients to the most experienced centers?

UNITED STATES HEART TRANSPLANT POLICY

Federal heart transplant policy has attempted to balance the access and quality issues and to answer the above questions as well. A brief summary of current heart transplant policy follows:

In 1984, Congress passed the National Organ Transplant Act (P.L. 98-507) in response to increasing public concern about access and equity. The act directed the Secretary of Health and Human Services to establish:

1- A Task Force on Organ Transplantation, which was charged to review medical, ethical, economic and social issues associated with organ procurement and transplantation (2), and

2- The Organ Procurement and Transplantation Network (OPTN), which matches donor organs with potential recipients (6)[6].

THE TASK FORCE AND MEDICARE POLICY

The Task Force's April, 1986 report emphasized both the costs and outcomes from transplant technology. It recommended that Medicare cover the procedure, and "that transplant centers be designated by an explicit, formal process using well-defined, published criteria (3)". Its rationale was "to prevent transplantation from being jeopardized by the uncontrolled diffusion of transplantation technology into unqualified institutions." The Task Force also reasoned that transplant center designation would result in "a more orderly, systematic process for the expansion of quality transplant centers...cost-effective organ transplantation...(and it would) minimize inappropriate competition for donor organs and transplant recipients (3).

The Task Force suggested that 13 criteria be used in the center designation process, including one stating that centers should have an "established, ongoing (4)" heart transplant

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[6] It also prohibited individuals from purchasing or distributing donor organs, and authorized grants to stimulate growth of the existing organ procurement network. A substantial part of federal transplant policy focuses on organ procurement and distribution. This document will not cover this subject in detail. See references 2,3 and 5 for further information.

program in which one year survival was 70%.

The Task Force's most controversial criterion was that centers should complete a minimum annual volume of 12 transplants per year. The volume criterion was controversial because no one had studied the volume-outcome relation in heart transplantation, and no one could demonstrate this relation in extrarenal transplantation (7-9). The Task Force felt such a recommendation was prudent given that significant volume-outcome relations had been demonstrated in the vast majority of surgical procedures for which data was available (to be discussed in chapter 5) and it did suggest the volume criterion could be waived for centers which might be desirable because of geographic location or pediatric specialization (2).

In the fall of 1986, the Health Care Financing Administration finally announced its Medicare heart transplant coverage policy (10). The policy generally follows the spirit of the Task Force recommendations. It includes criteria for patient selection and management, institutional commitment, facility plans, maintenance of data, organ procurement, and laboratory services. Medicare also requires that centers have performed at least 12 transplants per year in the two years prior to certification, plus an additional 12 transplants before this (a total of at least 36 transplants). It requires reasonable proof that the center will continue to perform at least 12 transplants per year. Finally, there are minimally

acceptable one- and two-year survival rates: 73% and 65%, respectively.

Medicare criteria do differ from Task Force recommendations in that they do not allow exceptions for geographic considerations (2). This has resulted in an uneven distribution of the 31 so-far approved centers. For example, there are five designated centers within 300 miles of Philadelphia, Chicago and St. Louis, whereas eligible patients living in Seattle or Miami have to travel nearly 700 miles (and, in the latter case, pass by a dozen programs on the way) to reach a designated center (2).

In conclusion, Medicare heart transplant coverage policy was implemented in late 1986. It is a precedent-setting federal attempt to limit the diffusion of and control federal outlays for the heart transplant procedure, and to assure high success rates by designating centers at which the service is covered. The policy has clearly not been effective in limiting diffusion because it was implemented after the period in which this technology diffused most rapidly (2). Its rationale for assuring high success rates was logical given existing volume-outcome literature for other procedures, but it was not based on empiric findings in heart transplantation.

THE OPTN AND THE UNITED NETWORK FOR ORGAN SHARING

In 1986, the Department of Health and Human Services awarded contracts to the United Network for Organ Sharing

(UNOS) to operate the transplantation network and to maintain a registry[7] of organ transplants (6). UNOS was further empowered by the Omnibus Budget Reconciliation Act of 1986 (PL 99-509) which "required hospitals performing heart transplants to be members of, and abide by the rules of, the Transplantation Network (6)".

In establishing its membership criteria, UNOS did not adopt the Task Force recommendations regarding transplant volume and other structural characteristics of the transplant center. In fact, UNOS criteria do not require prior institutional experience as a requisite for initial membership. Instead, "UNOS criteria for membership are based primarily on the experience of the transplant team (6)".[8] UNOS criteria are still undergoing modification, but in principle, they require each transplant center to have:

1- A transplant surgeon having a minimum one year formal training and one year experience at a transplant program meeting UNOS membership criteria. Alternatively, the surgeon may qualify by virtue of having 3 years

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[7] Recently, UNOS reached an agreement with the International Society for Heart Transplantation such that the latter's Registry (the one used for this study) will serve this purpose.

[8] However, UNOS does intend to review programs that perform less than 12 transplants per year and programs that do not meet Medicare survival guidelines.

experience at a UNOS-sanctioned transplant program.[9] In addition, the surgeon must be board certified by the American Board of Thoracic Surgery.

2- A transplant "physician" having a minimum one year formal training in transplantation medicine or two years documented experience at a UNOS-sanctioned transplant program. The physician must be board certified or board eligible in cardiovascular disease.

Thus, UNOS promulgated personnel-based criteria in order to stimulate the establishment of new transplant programs in underserved areas and hence to improve access to the procedure. In contrast to the Medicare criteria, UNOS criteria do not include structural attributes of transplant centers. In the context of donor shortages, UNOS also avoided volume and survival criteria so as to eliminate incentives to perform marginally necessary procedures. As of September 1988, 131 hospitals had registered with UNOS as heart transplant centers (6).

OBJECTIVES OF THIS DISSERTATION

In conclusion, current federal heart transplant policy has attempted to balance several apparently conflicting interests, particularly the trade-off between strategies to equalize access and those to maximize benefits from the scarce donor

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[9] Precise specifications for training and experience remain to be defined.

supply. Of great importance, existing policies have been formulated in the absence of data that might have informed the policymaking process. In particular, Medicare's strategy of designating transplant centers assumes, without empiric support, that high volume centers have better outcomes from the procedure. This policy may well impede access to the procedure for Medicare beneficiaries, and it exists despite a nagging feeling that the volume proxy does not accurately reflect the nature of experience with this new procedure.

In this dissertation, I intend to provide an empiric basis for the study of current heart transplant policy and for its refinement if necessary. In particular, I explore and characterize the relation between experience and outcomes in heart transplantation. To accomplish this, I analyze data from the International Registry of Heart Transplantation and data from a survey of transplant coordinators that I personally conducted. Chapter 1 of this document summarizes the methods used in this study. Chapters 2-8 summarize the study's primary results. Chapter 9 discusses the results and their implications for heart transplant policy.

CHAPTER 1

METHODS

SUMMARY:

This chapter describes the data set used in this study, the method by which data was collected, the study population and the analytic techniques used during this study.

KEY POINTS:

- The study includes more than 90% of the patients that underwent orthotopic heart transplantation in the United States between 1984-1986.

- The principal data sources for this study are the Registry of the International Society for Heart Transplantation, a personally administered supplemental survey, and the 1986 American Hospital Guide.

CHARACTERISTICS OF THE DATA SET USED IN THIS STUDY

The data set for this study contains merged information from three sources. These are: 1)the Registry of the International Society for Heart Transplantation, 2)a personally administered supplemental survey, and 3)the 1986 American Hospital Association Guide. The salient features of each source are as follows:

The Registry: The Registry is the most important source of data for this study. In May, 1987, transplant centers were not required to contribute data to the Registry. However,

approximately 95% of all U.S. heart transplant centers did voluntarily contribute the required information. Dr. Michael Kaye was at the time solely responsible for maintaining and updating the Registry's data files. He did so on an IBM AT personal computer located at the University of Minnesota.

The process by which the Registry collected information was as follows:

1) The Registry periodically mailed blank copies of its standard patient information form to transplant coordinators at each participating center.

2) Two to three times per year, transplant coordinators (or occasionally, data managers) completed these forms for every patient that had undergone heart transplantation since the last update. They then forwarded the information to the Registry.

3) Coordinators were also responsible for informing the Registry about changes or additions to the information contained in existing patient files. The most important update was the date of death for any patient that had died since the original data was entered into the Registry. This follow-up information played a critical role in determining the reliability of the Registry's actuarial analyses, as the Registry assumed all patients were alive unless it was specifically informed otherwise.

4) Dr. Kaye or his designee entered the information into

the Registry files as it was received.

The Registry's standard information form (figure 1.1) elicited details concerning gender, dates of birth, transplant and death (if appropriate), cause of death, indications for and type of transplant (orthotopic, heterotopic or retransplant), as well as some facts about the relevant donor and the immunosuppressive regimen used[1]. Although most centers submitted updated information 2-3 times per year, there was considerable variation in the update frequency. The approximate range of frequencies with which centers updated Registry files was from once per month to once per year.

The Supplementary Data Form-After reviewing the literature on the determinants of mortality following organ transplantation, I felt that it would be preferable to augment the Registry data base with additional information concerning characteristics of the transplant centers, the recipients and the donors. To do so, I designed a supplementary questionnaire and mailed it to transplant coordinators.

Part I (figure 1.2) elicited details about the structural characteristics of the transplant centers. Included were questions regarding:

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[1] The Registry has modified this form on several occasions since 1987, such that more patient, donor and immunosuppressive information is available.

- the presence of a preexisting kidney transplant program (and hence local expertise in immunosuppressive management),

- the volume of open heart surgery procedures (the skills for which might be transferrable to the heart transplant procedure)

- the volume of cardiac catheterization (which is required during routine pre- and post-transplant care)

- the clinician primarily responsible for managing immunosuppressive therapy (to compare the skills of surgeons and cardiologists in this regard), and

- the presence of prior heart transplant experience among key personnel (to test its effect on transplant mortality at new centers).

Part II (figure 1.3) elicited details about each recipient which were not available from the Registry data banks. Included were questions regarding:

- the listing status at the time of transplant[2] (to assess the relation between the severity of premorbid illness and

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[2] When a center has decided that a patient is an acceptable candidate for heart transplantation, it contacts the relevant organ procurement agency. This agency adds the patient's name to its waiting list. Then, when a donor becomes available, the agency and the transplant center use this list to select the most appropriate candidate. The selection process is influenced by several factors in addition to the original date that the patient was placed on the list. The most important of these factors is the transplant team's assessment of each patient's severity of illness and probability of death in the short term. Patients having the worst prognosis (that is, having the highest listing status), are given priority over others, even if the latter have been waiting for longer periods.

mortality following heart transplantation),

- the left ventricular ejection fraction (for the same reason),

- the presence coexisting diseases that might impact long term survival following heart transplantation.

I also used the American Hospital Association Guide (1986; AHA Press; Chicago) to determine each transplant center's admission rates and membership status in the Council of Teaching Hospitals.

DATA COLLECTION

With consent from Dr. Michael Kaye, the Director of the Registry of the International Society for Heart Transplantation, I acquired an updated copy of the Registry's patient care files on May 1, 1987. I used these files throughout the study.

In September 1986, I mailed supplementary surveys to the transplant coordinators of all centers that were participating in the Registry. I included cover letters (figures 1.4-1.5) emphasizing that the International Society For Heart Transplantation supported the additional data collection. I allowed 6 months for centers to respond. Three large, well established centers could not respond to the survey, but they permitted me to make a site visit in order to personally collect the data. These centers were: Stanford University, Presbyterian Hospital at the University of Pittsburgh, and

the University of Minnesota.

Once I had obtained the results of the supplementary survey and an updated copy of the Registry files, I merged the data, as follows. I first created data files for the supplementary information on the VAX-VMS mainframe computer at the Whitaker College of Health Sciences at Massachusetts Institute of Technology. I then converted the Registry files into an ASC-II file. After translating the file into a format compatible with the VAX, I combined the two data sets on the basis of common information on transplant center and the patient's dates of birth, death and transplant. Figure 1.6 shows a complete list of variables analyzed in this study.

STUDY POPULATION

The study population (figure 1.7) included patients that underwent orthotopic heart transplantation between January 1, 1984 and December 31, 1986 at a United States transplant center that contributed data to the Registry. In addition, recipients had to be at least 10 years old, and their 90 day mortality status had to be known. Retransplants and heterotopic heart transplants were excluded from the study.

DATA ANALYSIS

I performed statistical analyses on the Vax using Version 5.0 of SAS (Cary, North Carolina). I used PROC LIFETEST for

lifetable analysis and PROC CATMOD for logistic regression analysis.

I followed certain guidelines and made several key assumptions in analyzing the data. These were as follows:

1) To test the validity of Medicare guidelines for transplant center certification and to be consistent with previous published reports (6), I considered age to be a dichotomous variable ($\leq$50 vs. >50).

2) To test the hypothesis that preoperative mechanical support is an important predictor of mortality post-transplant, I combined patients who were classified as "Listing Status Class I" and "Class II" into one category and compared mortality in this group with patients who were classified as "Listing status 9"[3].

3) To test the relationship between transplant mortality and the existence of <u>any</u> coexisting disease (see figure 1.3), I generated a new variable, <u>Comorbid Conditions</u>, which indicated the presence of any of the coexisting diseases referred to in the supplementary survey.

4) The Indication for Transplantation (see figure 1.1) in more than 90% of transplant recipients was either cardiomyopathy or coronary artery disease. The remaining 13 indications account for less than 10% of the cases. Therefore, to simplify the analysis of the relation between transplant

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[3] The precise specifications for each listing category are described in figures 1.3 and 1.5.

indication and mortality, I aggregated all patients with a rare indication into one category.

5) I decided not to study donor organ location because only 3 coordinators responded to this question.

6) I grouped data regarding admissions, the volume of open heart surgery and the volume of cardiac catheterization into quartiles.

7) I grouped data regarding ischemic time into two categories: less than two hours and greater than or equal to two hours, as most coordinators reported the data as such.

8) Before I began to analyze data, I developed a list of 8 pretransplant attributes (including some from the patient, donor, and center) that were likely to have an impact on mortality following transplantation (figure 1.8). I chose these risk factors on the basis of a literature review and personal clinical experience. In subsequent analyses (see chapter 2, figures 2.4-2.5), I used these "risk factors" to calculate the overall burden of premorbid illness in the study population, to assess its overall impact on mortality following transplantation, and to determine whether the burden of illness in an individual patient might modulate the relation between center experience and mortality following heart transplantation[4].

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[4] A more detailed discussion of these risk factors and their role in this study appears in chapter 2.

Figure 1.1

INTERNATIONAL HEART TRANSPLANTATION REGISTRY

PATIENT DATA:

Transplant Center Number_____ Patient Number_____
Patient Chart Number_____ Sex:_____Male_____Female_____
Age_____Death_____No___Yes____ Date of Birth_____/_____/____
Date of Transplant___/___/____ Date of Death_____/_____/____
Type of Transplant: ____Orthotopic____Heterotopic____H-L
Retranplantation_____No_____Yes Other_____

Comments_____

DONOR DATA:

Age_____
Cause of Death:
_____Motor Vehicle Accident _____Suicide
_____Cerebrovascular Accident _____Other_____
Locale-Donor Heart: _____In Hospital____In Community_____Remote
Ischemic Time (hr)_____

INDICATIONS:

MAJOR
____Cardiomyopathy ____Coronary Artery Dis.
____Congenital ____Graft Rejection
____Primary Pul Hypertension

OTHER
____Pulmonary Hypertension ____Rheumatic Heart Dis.
____Congestive Heart Failure ____Myocarditis
____Valvular Disease ____Idiopathic
____Endocardial Fibro ____Carcinoma
____Emphysema ____Eisenmengers
____Other_____ Comments_____

IMMUNOSUPPRESSIVE REGIMEN:

____Cyclosporine ____ATG
____Imuran ____Prednisone
____Other_____ Comments_____

CAUSE OF DEATH:

____Acute Rejection ____Chronic Rejection
____Infection ____Ventricular Failure
____Cardiac Arrest ____Myocardial Infarct
____Pulmonary Embolism ____Carcinoma Type_____
____Other_____ Comments_____

COMMENTS_____
_____

FIGURE 1.2

INTERNATIONAL HEART TRANSPLANT REGISTRY
SUPPLEMENTARY QUESTIONNAIRE

PART I: CENTER CHARACTERISTICS

1. Did your hospital have a kidney transplantation program in the year your heart transplantation (HT) program was initiated?

   YES_____ NO_____

   If not, has a kidney transplantation program since been started?

   YES (START UP YEAR)_____ NO_____

2. Number of Coronary Bypass operations done at your hospital in:
   Year of HT program's initiation?_____
   1985?_____

3. Number of cardiac catheterizations done at your hospital in:
   Year of HT program's initiation?_____
   1985?_____

4. Your patient's immunosuppressive therapy is managed primarily by:
   Surgeons_____ Cardiologists_____ Immunologists_____

5. Did any team members have prior "Hands on" experience in the management of HT patients when your HT program was initiated? (Please state institution where the experience was obtained)

   Surgeon_____
   Cardiologist_____
   Transplant Coordinator_____
   Other_____

FIGURE 1.3

PATIENT NUMBER_____
PATIENT CHART NUMBER_____
DATE OF BIRTH_____
DATE OF TRANSPLANTATION_____
DATE OF DEATH (IF APPROPRIATE)_____

PART II: DONOR CHARACTERISTICS

1. Donor Ischemic Time:_____minutes

2. Location of donor organ relative to your institution:

   In-Hospital_____
   In same community_____
   Distant_____

PART III: PATIENT CHARACTERISTICS

1. Home address (city and state, only):_____
   _____

2. Date patient was officially listed for HT:_____

3. Date of hospital discharge following transplant:_____

4. Listing status at the time of transplant:_____

   (Note: Class I: Awaiting transplant, out of hospital;
   Class II: Hospitalized due to cardiac failure;
   Class 9: Death imminent without transplant.)

5. Coexistent diseases at the time of transplant:

   Diabetes_____
   COPD_____
   Primary Renal Dysfunction_____
   Primary Liver Dysfunction_____
   Other (specify)_____

6. Left Ventricular Ejection Fraction prior to transplant:

   less than 12%_____
   12-20%_____
   more than 21%_____

FIGURE 1.4

Glenn Laird, M.D.
Department of Medicine
Cardiovascular Division

75 Francis Street
Boston, Massachusetts 02115
(617) 732-5696

Dear Sir/Madam:

I am a cardiologist at the Brigham and Women's Hospital. Recently, I received permission from the Registry of the International Society for Heart Transplantation to examine their data base for the purpose of analyzing the effects of coexistent diseases, the severity of preexisting heart disease, and donor characteristics on the outcome from heart transplantation, and the extent (if any) to which these relations are modulated by experience with the technique.

After a review of the Registry's available data, I believe it is necessary to obtain some additional information about patients having already undergone transplantation. Dr. Kaye has granted me permission to contact you and encourage your cooperation in this project, since this data would strengthen the Registry's data base and allow additional informative data to be transmitted to the transplant community. We realize that this request will be a burden but feel that this information will prove valuable to you and your patients.

Should you agree to cooperate in this study, I would prefer to collect this data by mail. The plan is to mail you blank supplementary questionnaires, similar to the sample enclosed with this letter. I would ask that you complete them for as many patients as possible and mail them back to me. I do recognize that in some cases it will be impossible to collect data in this fashion. In these situations, although my resources are limited, it may be possible to make site visits and help collect the data.

You will note that the questionnaire has three parts. Part one requests information regarding your center. Please be assured that no information regarding any specific center will be published; all information in the Registry is considered in terms of individual and institutional rights to privacy. Part two requests information regarding donor characteristics. This information is requested on the present Registry forms, but had not been requested on older forms. Part three requests additional information about recipient characteristics in the peri-transplant period.

My plan is to wait approximately two weeks after this mailing to allow you time to consider this request and review the sample questionnaires. During this time, if you determine that you will be unable to provide any of the information, or if you will require a site visit, please contact me by phone: (617) 732-5696 beeper #1520. If I have not heard from you in two weeks, I will send you the proper number of questionnaires by mail, along with additional instructions. Under Dr. Kaye's close supervision, I will perform

initial data analysis here in Boston. Subsequently, all data will be entered into the Registry's data banks.

We thank you in advance for your cooperation.

Sincerely,

Glenn Laffel, M.D.

FIGURE 1.5

Glenn Lahey, M.D.
Department of Medicine
Cardiovascular Division

Boston, Massachusetts

Dear

Thank you for agreeing to participate in my study, which will be done in cooperation with the International Heart Transplant Registry. We plan to analyze the effects of several patient, donor, and center characteristics on the outcome from heart transplantation, and the extent (if any) to which these relations are modulated by experience with the technique.

Initial data analysis will be done in Boston, and will be supervised by Michael Kaye, M.D., the director of the International Heart Transplant Registry. Subsequently, all data will be transferred to the Registry's data banks in Minneapolis. I want to reemphasize our commitment to honoring institutional and individual rights to privacy.

I have enclosed the questionnaires which will be used for data collection. There is one form containing five questions regarding your center. Also, there are several copies of a second form requesting information about each transplanted patient. These forms contain routine biographical information from the Registry's files, (patient number, chart number, date of birth, date of transplant, date of death, if appropriate) which will allow you to provide the requested information for each patient. The forms are ordered according to the date of transplant.

One clarification on Part III, Question (4): A <u>class 9</u> listing status refers to patients who are intubated, or who have had a mechanical device inserted to maintain adequate cardiac output (i.e., intraaortic balloon, left ventricular assist device, biventricular assist device, "artificial heart," etc.). <u>Class II</u> status includes patients who are receiving any form of in-hospital medical therapy, including pressors, for the management of congestive heart failure.

In completing the questionnaires, please include the "date of death" for those patients who have passed away since you last updated your Registry files. I have included some blank questionnaires for your most recently transplanted patients, and can supply more if required (alternatively, a xeroxed copy of one of the blanks would suffice).

PLEASE NOTE: We also plan to study the use of different protocols for the management of routine immunosuppressive therapy and for acute rejection. Therefore, please include a brief summary of (or a copy of) your present protocols for the management of these issues.

Please return the completed questionnaires and protocols to me in Boston, at the above address. I will be happy to assist you in any way I can--don't hesitate to call! I can be reached at: the Brigham, (617) 732-5696 beeper #1520, or home (617) 332-1426.

Once again, thank you for your time and cooperation.

Sincerely,

Glenn Laffel, M.D.

Figure 1.6
DETERMINANTS OF SURVIVAL FOLLOWING HEART TRANSPLANTATION

PATIENT CHARACTERISTICS	FIELDS
GENDER	MALE FEMALE
AGE	≤50 >50
INDICATIONS FOR HT	CARDIOMYOPATHY CORONARY ARTERY DISEASE OTHER
PRETRANSPLANT REQUIREMENTS FOR MECHANICAL CIRCULATORY SUPPORT*	PRESENT ABSENT
LEFT VENTRICULAR (LV) EJECTION FRACTION*	≤11% >11%
COMORBID CONDITIONS*	PRESENT ABSENT
DONOR CHARACTERISTICS	
ISCHEMIC TIME*	0-120 MIN. >120 MIN.
CHARACTERISTICS OF EXPERIENCE	
PROGRAM DURATION (see chapter 3)	YEAR 1984-1986
CUMULATIVE EXPERIENCE (see chapter 4)	TRANSPLANT NUMBER 1,2,3...
TRANSPLANT VOLUME (see chapter 5)	CENTER 1-70
TRANSPLANT RATE (see chapter 6)	MEAN INTERTRANSPLANT INTERVAL #1-5, 6-10, 11-20

Figure 1.6 (ctd.)
DETERMINANTS OF SURVIVAL FOLLOWING HEART TRANSPLANTATION

CENTER CHARACTERISTICS	FIELDS
CYCLOSPORINE	USED NOT USED
TRIPLE DRUG THERAPY	USED NOT USED
KIDNEY TRANSPLANT PROGRAM*	PRESENT ABSENT
ANNUAL VOLUME-CORONARY BYPASS*	94-236 (first quartile) 240-436 467-744 775-3700
ANNUAL VOLUME-CARDIAC CATH.*	180-900 (first quartile) 900-1569 1600-2109 2169-6193
IMMUNOSUPPRESSIVE MANAGEMENT*	SURGEONS INTERNISTS
PRIOR HT TRAINING-SURGEONS*	YES NO
PRIOR HT TRAINING-CARDIOLOGISTS*	YES NO
PRIOR HT TRAINING-COORDINATORS*	YES NO
TOTAL ADMISSIONS, 1986*	9,376-17,687 (first quartile) 17,703-21,535 21,540-28,813 29,084-47,749
COUNCIL OF TEACHING HOSPITALS AFFILIATION*	YES NO

* data available only through the supplemental survey

Figure 1.7
ENTRY CRITERIA

Transplanted Between 1/1/84-12/31/86
Orthotopic Transplant (retransplants and heterotopic transplants excluded)
Age >10 Years
Performed In US
Center Contributes Data To ISHT Registry
90-Day Mortality Status Known

figure 1.8
PRIMARY RISK FACTORS
IN HEART TRANSPLANTATION

1. Age >50 Years
2. Preoperative Mechanical Support *
3. Comorbidities Present *
4. Rare Indication for Transplant °
5. Ejection Fraction <11% *
6. Gender = Female
7. Ischemic Time >150 Minutes *
8. 3-Drug Immunosuppression Not Used

* Available from Supplemental Survey only

° All indications OTHER THAN cardiomyopathy and coronary artery disease

CHAPTER 2

TRADITIONAL DETERMINANTS OF MORTALITY FOLLOWING HEART TRANSPLANTATION

SUMMARY:

This chapter reviews some general features of the data set and then it reviews the results of univariate and bivariate analyses relating heart transplant mortality to several patient characteristics, the donor ischemic time and the use of certain immunosuppressive regimens.

KEY POINTS:

- 80% of the Registry centers responded to the supplementary survey.

- Heart transplant deaths in the first 90 days account for 85% of the total first year deaths and 70% of the total deaths in the first two years.

- For several reasons, 90-day mortality is used as the outcome measure in this study.

- Univariate and bivariate analyses suggest that female gender, preoperative mechanical support, left ventricular ejection fractions less than 11%, comorbid conditions, donor ischemic times greater than 2 hours, and non-use of triple drug immunosuppressive therapy are all related to heart transplant mortality.

Studies of the experience-outcome relation for any medical procedure must first account for "traditional" determinants of mortality such as age and coexisting disease. Surprisingly, we know relatively little about these traditional determinants following heart transplantation. In part this is because the

technology is relatively young. For example, nearly half of all United States heart transplants have been performed in the last 3 years, and so long term follow-up is sparse.

It is also true that uncontrolled transplant center proliferation has prevented all but a few programs from accumulating series large enough to support research. To make matters worse, transplant centers have tended to develop unique treatment protocols and unique data collection instruments, and this complicates attempts to compare results. In addition, they have so far been unwilling to participate in multicenter randomized trials. Furthermore, until recent legislation mandated that centers contribute to the Registry of the International Society for Heart Transplantation, the Registry depended on voluntary participation.

Nevertheless, investigators have slowly begun to define relations between these traditional determinants-usually categorized into patient, donor and center attributes-and mortality. In this chapter, I review my univariate and bivariate analyses of these relations and compare these findings with existing literature on the subject. This review follows a discussion of some general features of my data set, and a discussion of the mortality variable itself.

GENERAL FEATURES OF THE DATA SET

On May 1, 1987, 70 United States heart transplant centers were contributing information about their recipients to the

Registry of the International Society for Heart Transplantation (figure 2.1). Between the years 1984 and 1986, these centers performed a total of 2,005 heart transplants on patients that met entry criteria for this study.

These centers exhibit striking heterogeneity with respect to the total heart transplant volume per center during the three year study period. The total number of heart transplants performed per center ranges from 1 (one) to 207. These transplant centers also exhibit striking heterogeneity with respect to their 90-day mortality; center-specific death rates range from 0% to 75% (figure 2.2).

Of great interest, a preliminary display of the relation between center-specific procedure volume and mortality (figure 2.2) fails to reveal a strong correlation, as the Federal Task Force on Organ Transplantation and others thought would be present[1]. This preliminary analysis does show considerably more mortality rate variation among centers with low volumes, but such increases could be attributed to chance alone when center volume is small. Chapter 5 presents a detailed analysis of this and other issues pertaining to the volume-outcome relation in heart transplantation.

I was able to collect supplementary information from 56 of the 70 US heart transplant centers (80%) that were

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[1] See the Introduction for a further discussion of the Federal Task Force and its impact on Medicare heart transplant policy.

participating in the Registry. These 56 centers performed 1,711 (85%) transplants during the three year study period. Among the 56 participating centers, some could not provide supplementary information about certain patients. Other centers could not answer particular questions (for any of their patients) because they simply had not been collecting the appropriate data. Nevertheless, the centers did manage to provide complete supplemental information for a total of 1,123 transplant recipients.

Importantly, the characteristics of patients for whom complete supplemental data is available do not differ significantly from those for whom supplemental data is not available (figure 2.3). Specifically, the two groups are comparable with respect to mortality, the percentage of patients aged less than 50 years, gender, and the indications for transplant.

In the patients for whom complete supplementary information is available, it is possible to tally the number of risk factors[2] present in each patient, and thus to assess the overall burden of illness in the study population. The number of risk factors present ranges from zero (in 72 patients) to seven (in 1 patient), with a median of two (figure 2.4)[3].

---

[2] For a discussion of risk factors, see chapter 1.

[3] Appendix 1 (available on request) provides additional details regarding the precise mix of risk factors in each patient. This histogram is <u>not</u> meant to imply that the impact of each risk factor is the same as that for each of the other six, <u>nor</u> is it meant to imply that the effects of each risk

Of great interest, heart transplant mortality increases steadily as the number of risk factors increases. This confirms clinical suspicions about the individual impact of the risk factors[4], but multivariate analyses are required to precisely assess interactive or additive effects of these variables.

NOTE: For the purposes of later analyses, I have in certain places reaggregated the patient risk factor data from seven categories into three categories (figure 2.5). The first group includes patients that have either zero or one risk factor: I define these patients as having a "low burden of premorbid illness". The second group includes patients that have exactly two risk factors- defined as a "moderate burden of illness". The third group includes patients that have more than two risk factors. I define these patients as having a "high burden of illness". **The principal reason for reaggragating the data in this way is to generate subgroups that have**

---

factor are strictly additive to the effects of the others. Multivariate analyses are required to explore each risk factor's relative impact on mortality, its correlations with other risk factors, and the interactive effects of all risk factors on transplant mortality. Chapter 8 provides such an analysis.

[4] Note: Figure 2.12 displays univariate analyses of the relations between these variables and transplant mortality. Figure 2.13 shows bivariate analyses. These will be discussed shortly.

1)clearly different mortality risk following heart transplantation and that 2)contain enough patients in each group to permit meaningful, informative analyses. As figure 2.5 shows, these three subgroups include between 330-430 patients each, and their mortality rates are in fact distinctly different[5].

MORTALITY FOLLOWING HEART TRANSPLANTATION

Mortality (%) following heart transplantation for all patients in this study is as follows:

1 month:	10
2 months:	12
3 months:	14
12 months:	19
24 months:	25
36 months:	27

As expected, mortality rates are highest in the months immediately following transplantation. Interestingly, the mortality rate appears to be relatively constant between 3 and 24 months. This rate is well below that observed within the first three months, and well above the rate observed beyond

---

[5] The algorithm that I use to create these new categories is to some extent arbitrary. It is possible for example, that by virtue of their specific combination of risk factors, some patients in the "moderate risk" category could actually have a worse prognosis than some in the "high risk" category.

Nevertheless, the above algorithm has the advantage of being conceptually simple and consistent with clinical intuition about the burden of illness. It certainly appears to be as logical as any other approach that could be developed to create large subsets of patients that are stratified according to their risk of death.

24 months (see the lifetable analysis in figure 2.6). Deaths within the first 90 days account for 85% of the total deaths at one year, and for 70% of the total deaths at two years.

When I stratify the data donor characteristics, by the year of transplant, or by the use (or nonuse) of cyclosporine, I find a similar pattern-in which mortality risk declines with time (figures 2.7-2.11). Similar relations are demonstrable for other univariate predictors, and this information is available on request.

For this study, I have chosen mortality at 90 days to be the independent variable. There are several reasons for this:

1) 90-day mortality appears to be predictive of 1- and 2-year mortality, as shown in figure 2.6.

2) By selecting a relatively "tight" follow-up period (90 days), I maximize my ability to include data from 1986 transplants in my analyses. Had I selected mortality at one year, I would have been unable to include patients transplanted after May 1, 1986 (because I obtained the final data tapes from the Registry on May 1, 1987). It is certainly desirable to include as many 1986 transplant recipients as possible, since nearly half the study's heart transplants took place that year.

3) The 90-day endpoint covers the immediate post-operative period and (roughly) the first two months following hospital discharge. During this time, patients

are most susceptible to infection and transplant rejection. It is also the time in which clinicians rapidly taper immunosuppressive drugs towards chronic dosage regimens. Therefore it is reasonable to postulate that experience or learning would most likely have an effect on mortality in these first 90 days. I choose the 90-day endpoint in part to enhance the likelihood of detecting a learning phenomenon.

RELATIONS BETWEEN HEART TRANSPLANT MORTALITY AND PATIENT, DONOR AND IMMUNOSUPPRESSIVE THERAPY: UNIVARIATE AND BIVARIATE ANALYSES

Univariate analyses from this study (figure 2.12) show that the following attributes are associated with significantly higher mortality following heart transplantation: female gender, preoperative requirements for mechanical support, left ventricular ejection fraction less than 11%, comorbid conditions present, donor ischemic times greater than 120 minutes, and immunosuppressive management without triple drug therapy. Similar analyses fail to demonstrate a significant impact for the following variables: age, indication for transplant, and cyclosporine use.

Of great interest, bivariate analyses (figure 2.13) suggest that the above univariate predictors remain important in many patient subsets. For example, mortality is 12% for males that do not require preoperative mechanical support. It is 16% for patients who are <u>either</u> female or who require such support.

It is 31% for females requiring preoperative mechanical support. Appendix 2, available on request, displays several more two by two and three by two comparisons of this nature. These bivariate analyses suggest that the above univariate predictors have independent effects on transplant mortality, although formal multivariate analyses are required to test this assertion (see chapter 8).

A Review of the Literature-As I mentioned earlier in this chapter, the medical literature comparing these traditional determinants to mortality is surprisingly underdeveloped. However in general, the results of the above analyses are consistent with the available literature.

Among these traditional determinants, investigators have most frequently studied patient AGE. Reports from individual centers consistently show that carefully selected patients aged greater than 50 or even 60 years experience a mortality risk similar to that of younger patients (11-15). The results of this are consistent with these earlier findings.

Of note, investigators have also studied the effects of recipient age on other important outcomes from heart transplantation. They have found that age does not appear to have adverse effects on length of stay, renal function or the number of rejection episodes following transplantation. One study did note that patients aged greater than 55 years experienced a higher incidence of steroid-induced diabetes

(17% vs. 9%) and osteoporosis (13% vs. 3%), although these conditions did not significantly affect functional status[6].

Several investigators have suggested that the degree of cardiac failure prior to heart transplantation may affect mortality following the procedure. All eligible patients have depressed cardiac function, but measures of cardiac function do vary from patient to patient. For example, preoperative left ventricular ejection fraction varied from 5% to 28% (normal >55%) and left ventricular filling pressure varied from 4mm Hg to 42mm Hg (normal <12mm Hg) in a recent series (18). However until this study, no investigator had actually studied the relations between such direct measures of native heart function and mortality post-transplant. This study's univariate analyses show in fact that patients having very severely depressed left ventricular function (ejection fraction less than 11%) are characterized by higher mortality following heart transplantation[7].

On a related topic, several investigators have already studied the relations between <u>indirect</u> measures of cardiac performance, such as REQUIREMENTS FOR INOTROPIC SUPPORT or MECHANICAL ASSIST DEVICES, and mortality. The results have

---

[6] Our experience at Brigham and Women's Hospital suggests that steroid-associated osteoporosis substantially affects functional status. The effects of age on steroid-associated osteoporosis requires further investigation.

[7] However, as discussed in chapter 8, these findings are not confirmed in multivariate analyses. Reasons for this are discussed in chapter 8.

been mixed (36,37). McBride's group for example, found that patients requiring preoperative mechanical support had a 30-day survival of 33% (2/6). 63% (12/19) of patients requiring preoperative inotropic support survived 30 days. In contrast, 30-day survival in patients not requiring mechanical or inotropic support was 97% (19). However, O'Connell's group recently reported that small mortality differences notable at one month disappeared completely by one year (20), and they concluded that mortality following heart transplantation does not depend on preoperative requirements for inotropic or mechanical support.

The univariate and bivariate analyses of this study, in which the follow-up period is 90 days, suggest that preoperative mechanical support <u>is</u> an important predictor of post-transplant mortality[8]. All these studies must be interpreted with caution, as the use of such support may reflect resource availability or simply variation in practice rather than differences in the severity of underlying cardiac disease. Such discretionary utilization may underlie recent reports of excellent results with mechanical assist devices (36-37).

With respect to TRIPLE DRUG IMMUNOSUPPRESSIVE THERAPY, this

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[8] However, as with the case of left ventricular ejection fraction, these findings are not supported in multivariate analyses. These two instances represent the only important discrepancies between the findings of univariate and bivariate analyses and the findings of the multivariate analyses. I discuss these issues in more detail in chapter 8.

study's univariate and bivariate analyses support existing studies (18-21) that consistently show survival benefits for patients receiving this regimen. Earlier studies had documented markedly reduced infection and rejection rates when this regimen was used, and this undoubtedly underlies the mortality benefits.

The relations between other patient characteristics and transplant mortality have been studied less extensively. One study found a higher rate of allograft rejection among FEMALES, but no mortality differences between sexes (23). However, the Registry of the International Society for Heart Transplantation has reported higher mortality rates among females (1). The univariate and bivariate analyses of this study, using more recent data than the above, continue to show that females have higher mortality rates.

Among donor characteristics, the ISCHEMIC TIME is the most likely donor attribute to affect mortality following heart transplantation. The ischemic time is defined as the time elapsed between the moment surgeons clamp the donor aorta during harvesting and the moment the recipient aorta is unclamped after the aortic anastomosis is completed. It has long since been known that ischemic times greater than 4-5 hours cause substantial ultrastructural damage and diminished contractile function in the donor heart (27). Most transplant surgeons will not accept a donor organ if they anticipate that the ischemic time will exceed 5 hours.

However, studies of the relation between donor ischemic time and mortality have been somewhat inconclusive to date. Two groups found no relation (28-29). However, the Registry has recently reported that 30-day mortality is directly related to ischemic time. It reports that the 30-day mortality is 6% when the ischemic time is less than 2 hours, and 13% when the ischemic time is 2-5 hours (1).

Univariate and bivariate analyses in the study, in which the majority of donor ischemic time data is collected via the supplementary survey (not the Registry), and in which the follow-up period is 90 days, confirms earlier Registry findings. They suggest that transplant mortality is lower in patients having donor ischemic times less than 2 hours. Such studies assume great importance in the context of the current donor organ shortage, since the donor organ pool might be expanded by as much as 5-10% if clinicians would accept organs for which the anticipated ischemic time was 5-6 hours.

In chapters 8 and 9, I discuss further the relations between transplant mortality and these traditional attributes of patients and donors. It is worth mentioning at this time that until this study, no investigator had studied the relations between center characteristics (another "traditional" determinant) and transplant mortality. I have studied this in detail. I present the results of these analyses in chapter 7.

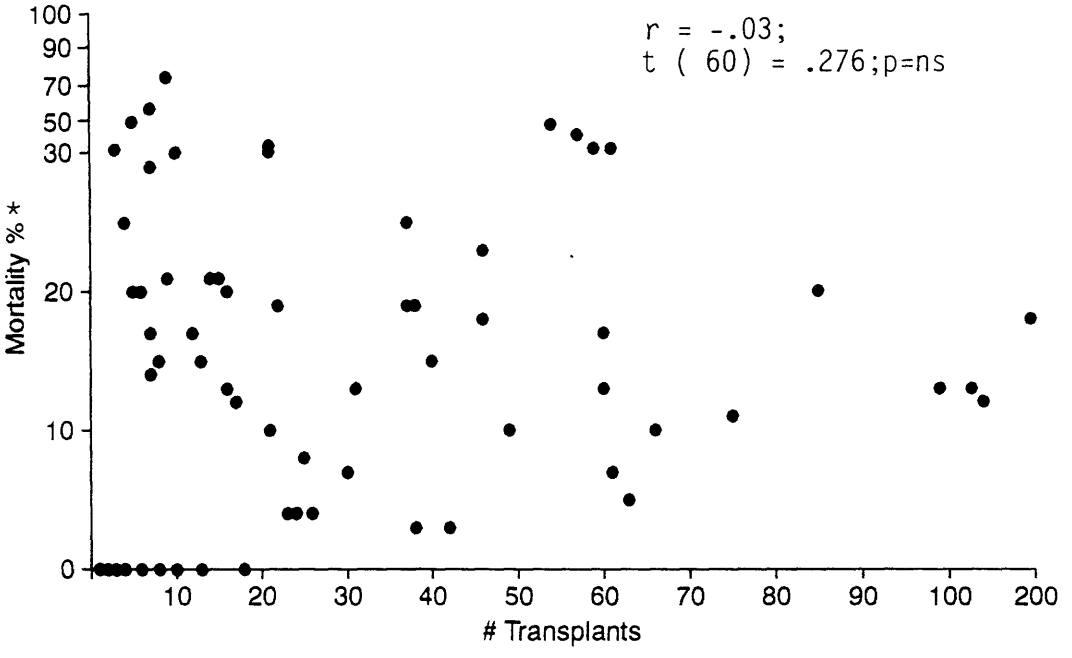
Figure 2.1

U.S. HEART TRANSPLANT CENTERS IN THE ISHT REGISTRY
(circa April, 1987)

CENTER	FIRST HT	TOTAL HT(84-86)	SUPPLEMENTAL INFORMATION
Stanford University	1968	130	Yes
Mayo Clinic	1981	0	No
St. Louis University	1972	47	Yes
Methodist Hospital (Indiana)	1982	46	Yes
University of Pittsburgh	1980	207	Yes
University of Arizona	1979	67	Yes
Texas Heart Institute	1982	145	Yes
University of Minnesota	1978	65	Yes
Columbia Presbyterian	1977	91	Yes
McGuire VA Medical Ctr.	1977	99	No
John's Hopkins Hospital	1983	62	Yes
Medical College of Virginia	1968	60	Yes
University of Alabama	1981	61	Yes
UCLA School of Medicine	1984	30	Yes
Loyola University	1984	76	Yes
Georgia Heart Institute	1984	13	Yes
Pacific Presbyterian Hosp.	1984	21	Yes
Arizona Heart Institute	1984	4	No
Brigham and Women's Hosp.	1984	30	Yes
Kansas University	1984	18	Yes
Humana Hosp. Audobon	1984	23	Yes
St. Luke's Hosp. (Milwaukee)	1984	21	Yes
University of Wisconsin	1984	24	Yes
Hartford Hospital	1984	18	Yes
Temple University	1984	51	Yes
Hershey Medical Center	1984	38	Yes
SUNY Buffalo	1984	5	No
Methodist Hospital (Baylor)	1984	40	Yes
Jewish Hospital (Louisville)	1984	23	No
Vanderbilt University	1985	7	Yes
Tennessee Heart Institute	1985	12	Yes
Henry Ford Hospital	1985	38	Yes
St. Luke's Hospital (K.C.)	1985	10	Yes
Utah Medical Center	1985	63	No
Lutheran Hosp. (Fort Wayne)	1985	15	Yes
Tampa General Hospital	1985	16	Yes
University of Florida	1985	14	Yes
Milwaukee County M.C.	1985	9	Yes
Cleveland Clinic	1984	38	Yes
St. Paul M.C. (Dallas)	1985	3	Yes
University of Michigan	1984	30	Yes
University of Chicago	1984	16	Yes
Talahassee Memorial Hosp.	1985	16	Yes
Beth Isreal Hosp. (N.J.)	1986	10	Yes
Mercy M.C. (Iowa)	1985	9	Yes
Bishop Clarkson Hosp. (Ne.)	1985	7	Yes
University of Iowa	1985	8	Yes
Barnes Hospital	1985	44	No
Loma Linda Hospital	1985	10	Yes
Sharp Memorial Hosp. (Ca.)	1985	13	Yes
Hines VA Hosp. (Il.)	1986	8	Yes
St. Anthony Hosp. (Ok.)	1985	5	Yes
University of Tennessee	1985	6	Yes
Emory Clinic	1985	42	Yes
University of Cincinnati	1985	32	Yes
Massachusetts General Hosp.	1985	5	Yes
University of Illinois	1985	4	Yes
St. Francis Hospital (Ne.)	1985	3	Yes
University of Washington	1985	5	Yes
Baptist Medical Center (Ok.)	1985	9	Yes
McGaw Medical Center (Il.)	1985	2	Yes
Indiana University	1986	6	Yes
University of New Mexico	1986	6	Yes
Oregon Health Sciences Univ.	1985	30	No
Baptist Medical Center (Al.)	1986	0	No
Seton Medical Center (Tx.)	1986	4	No
St. Francis Hospital (Ks.)	1986	3	No
Abbott Northwestern (Mn.)	1985	10	No
St. Vincent Hospital (In.)	1986	8	No
University of Miami (Fl.)	1986	1	No

figure 2.2

TOTAL NUMBER OF HEART TRANSPLANTS vs. MORTALITY (1984 - 1986)



Each point represents actual data from a transplant center participating in the Registry.

* Note: In this case and all subsequent figures, "Mortality" refers to 90-day mortality. See pp 46-48.

figure 2.3

RECIPIENT CHARACTERISTICS

	Complete Data Available	Complete Data Not Available
Number	1,123	882
90 Day Mortality (%)	14	15
% Age $\leq$50	66	67
% Male	87	85
% Cardiomyopathy	57	56
% Coronary Artery Disease	37	38
% Cyclosporine Used	94	88
% ``Triple Therapy'' Used	51	46
% Transplanted in 84	18	17
% Transplanted in 85	38	31
% Transplanted in 86	44	52

figure 2.4

RISK FACTORS PER PATIENT
(n=1123)

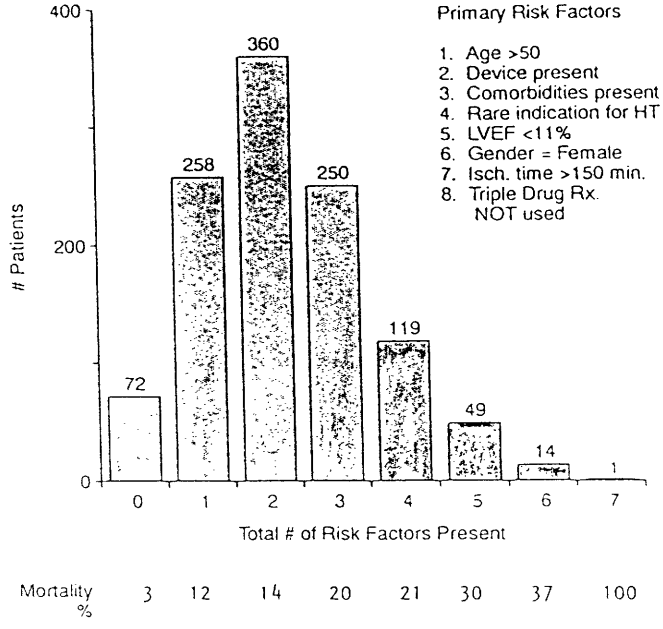


figure 2.5

THE BURDEN OF PREMORBID ILLNESS

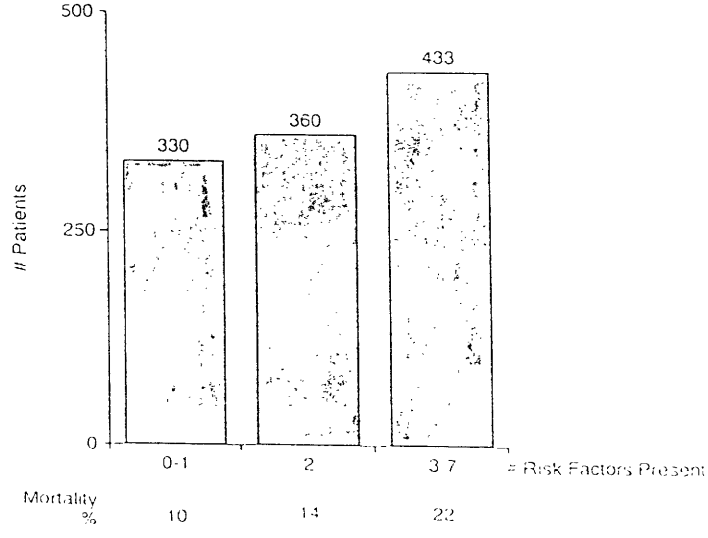


Figure 2.6

MORTALITY FOLLOWING HEART TRANSPLANTATION

All Patients

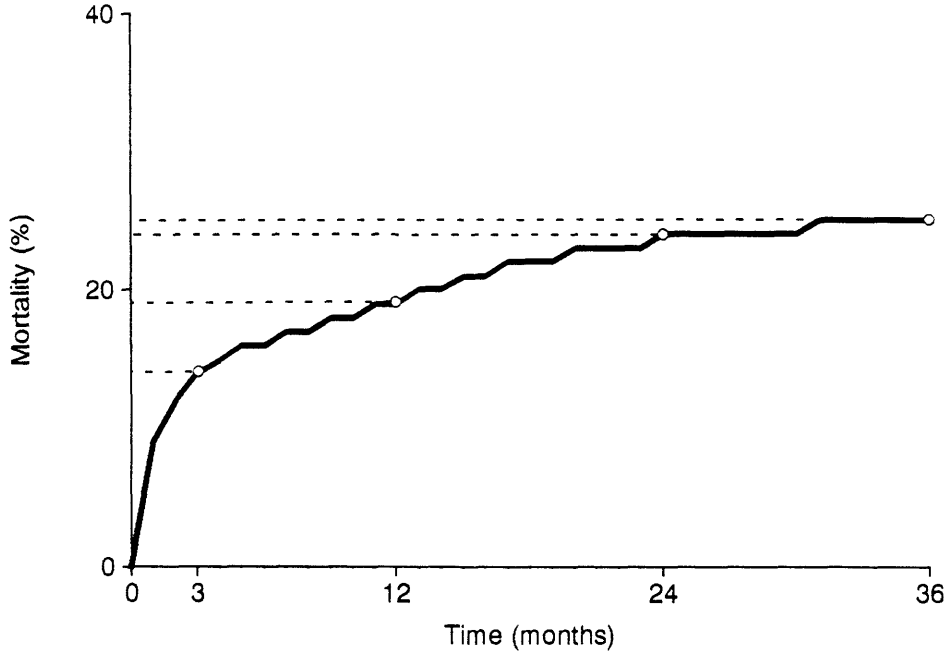


figure 2.7

MORTALITY FOLLOWING HEART TRANSPLANTATION
By Gender

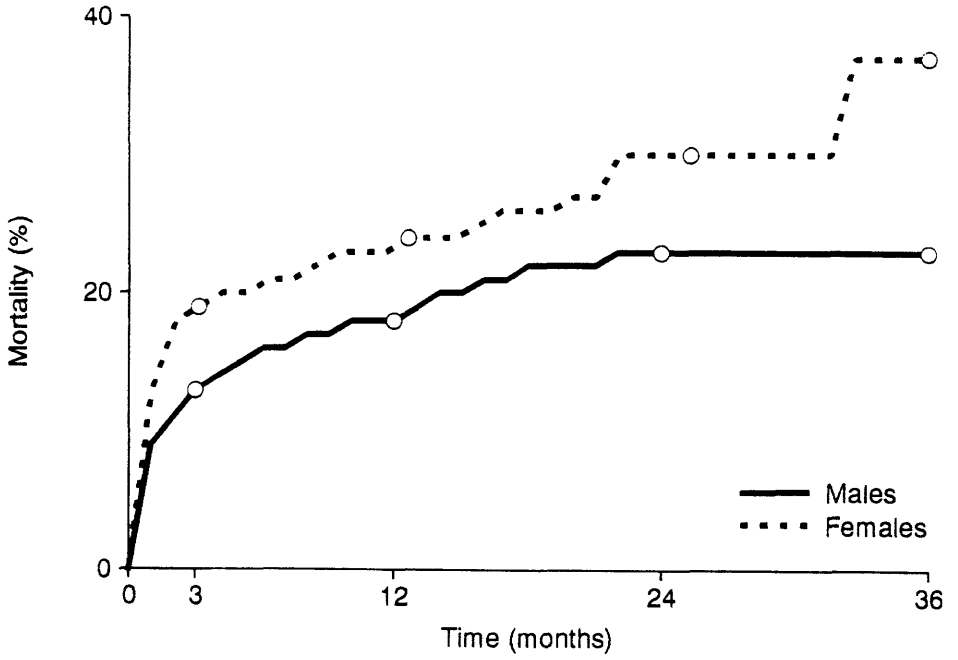


Figure 2.8

MORTALITY FOLLOWING HEART TRANSPLANTATION
By Mechanical Support

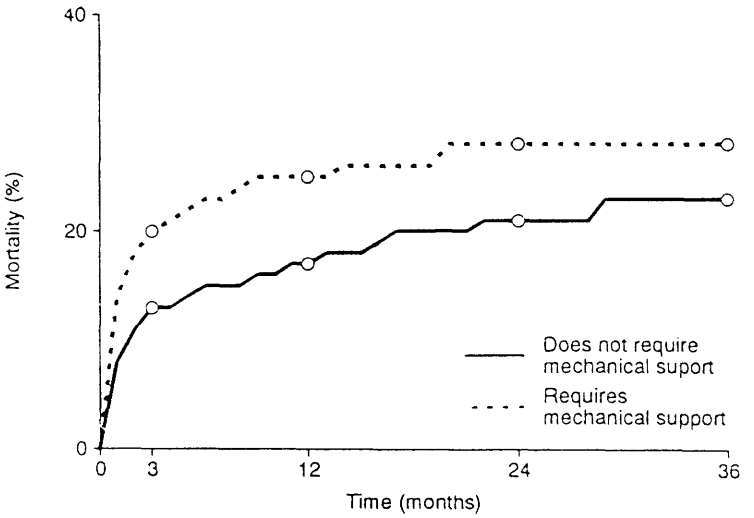


figure 2.9

MORTALITY FOLLOWING HEART TRANSPLANTATION
By Use of Cyclosporine

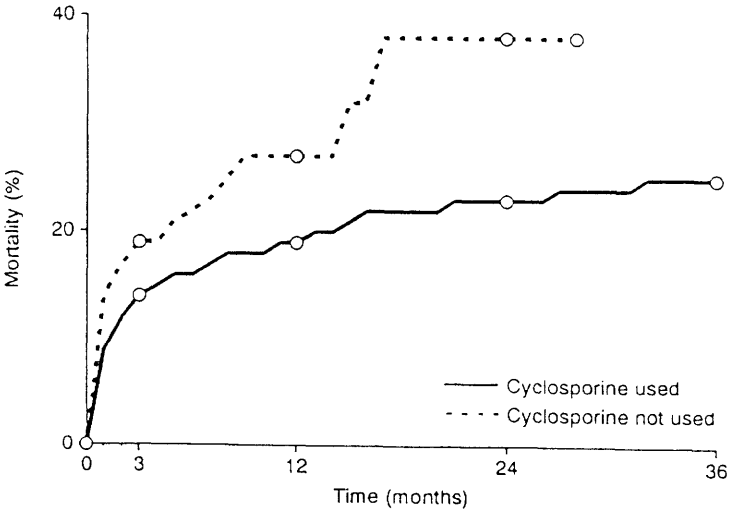


figure 2.10

MORTALITY FOLLOWING HEART TRANSPLANTATION
By Year of Transplant

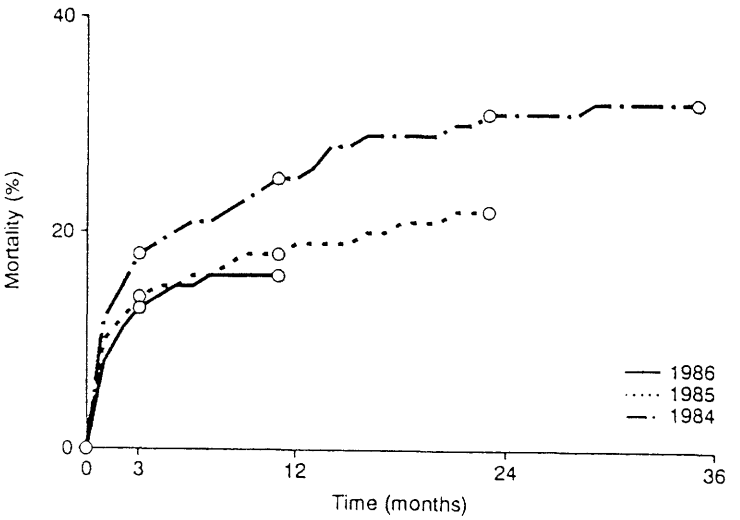


figure 2.11

MORTALITY FOLLOWING HEART TRANSPLANTATION
By Transplant Number

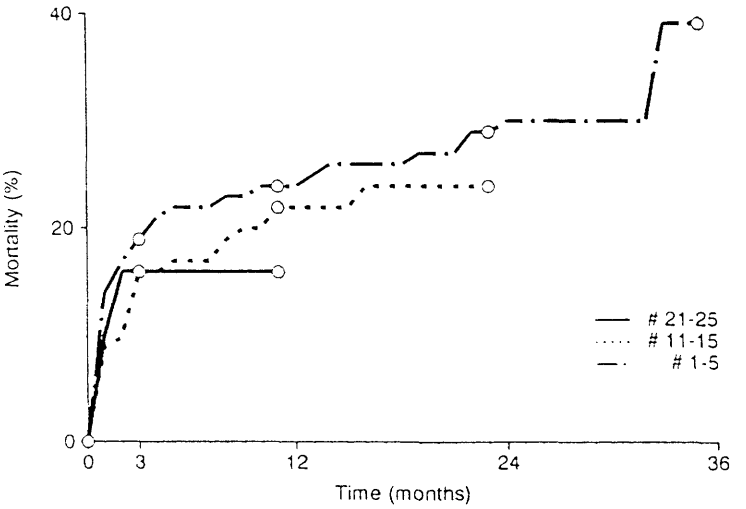


Figure 2.12

MORTALITY FOLLOWING HEART TRANSPLANTATION
UNIVARIATE ANALYSIS

CHARACTERISTIC	FIELD	MORTALITY %	# PATIENTS	
Gender	M	13	1612	p < .05 *
	F	19	304	
Age	≤ 50	14	1288	p = NS
	>50	15	699	
Indication	CRDMPY.	13	1091	
	C.A.D.	17	754	p = NS
	Other	17	218	
Mechanical Support	No	13	1301	p < .05
	Yes	20	334	
Ejection Fraction	≤ 11 %	18	417	p < .05
	≥ 11 %	13	940	
Comorbid Conditions	No	13	1724	p < .05
	Yes	20	262	
Ischemic Time	≤ 120 min	10	439	p < .05
	> 120 min	17	971	
Cyclosporine	No	19	1862	p <.05
	Yes	14	206	
Triple Drug R_x	No	18	1065	p < .05
	Yes	12	996	

* Note: "One-tailed" tests are used in this analysis.

figure 2.13

DETERMINANTS OF MORTALITY FOLLOWING HEART TRANSPLANTATION (2 x 2 Tables)

		GENDER	
		Male	Female
Mechanical Support	No	12	16
	Yes	16	31

		GENDER	
		Male	Female
Comorbid Conditions	No	13	17
	Yes	18	24

		GENDER	
		Male	Female
CRDMPY	Yes	12	16
	No	14	22

		GENDER	
		Male	Female
3-Drug Rx	Yes	13	18
	No	20	21

		MECHANICAL SUPPORT	
		No	Yes
Comorbid Conditions	No	12	16
	Yes	18	28

		MECHANICAL SUPPORT	
		No	Yes
CRDMPY	Yes	11	15
	No	20	18

		MECHANICAL SUPPORT	
		No	Yes
3-Drug Rx	Yes	10	13
	No	16	23

		COMORBID CONDITIONS	
		No	Yes
CRDMPY	Yes	12	21
	No	15	17

		COMORBID CONDITIONS	
		No	Yes
Comorbid Conditions	Yes	10	18
	No	17	21

NOTE: Figures represent 90-day mortality in patients having both characteristics as shown.

		CARDIOMYOPATHY	
		Yes	No
3-Drug Rx	Yes	10	12
	No	16	19

CHAPTER 3

YEAR OF TRANSPLANT AND MORTALITY FOLLOWING HEART TRANSPLANTATION

SUMMARY:

This chapter explores the relation between year of transplant and mortality following heart transplantation.

KEY POINTS:

- Between 1984 and 1986, clinicians altered their patient selection practices to include more patients who were older than age 50, who required preoperative mechanical support, and who had indications for the procedure other than cardiomyopathy.

-However, the overall burden of premorbid illness did not change over these three years.

- In part, this was because transplant centers also utilized triple drug immunosuppressive therapy with increasing frequency during this period.

- There was a trend toward decreased mortality during this period, but it did not reach statistical significance.

- This trend is explained primarily by the increasing use of triple drug immunosuppressive therapy and by a learning phenomenon at new centers.

The years 1984-1986 (the period of this study) can be described as the "renaissance" era of heart transplantation. These were the years during which the technology swept into the public eye as a newly effective, life-saving and enormously compelling symbol of high-tech medicine. It was a

period of unprecedented growth and optimism as the overall volume of procedures doubled annually and the number of transplant centers increased from 32 to 70 (figure 3.1). The vast increases in procedure volume generated an explosion of new data about the procedure, and new journals, forums, professional societies and conferences founded during this period facilitated the dissemination of this information. And of great significance, it was during this period that clinicians adopted "triple drug immunosuppressive therapy" for the prophylaxis of transplant rejection. Triple drug therapy remains to this day the primary immunosuppressive strategy for heart transplant recipients[1].

This growth in transplant volume was fueled a tendency to relax patient selection criteria and to accept patients that would have been excluded in the past[2]. Specifically, there were significant increases in (figure 3.2):

- The number of transplant recipients who were older than age 50: Between 1984 and 1986, there was an 800% growth in this group, but "only" a 200% growth among transplant recipients who were younger than age 50.
- The number of patients who required preoperative mechanical support: This group grew three times faster

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[1] The events surrounding the maturation of heart transplantation into a generally accepted medical practice are summarized in the Introduction and in chapter 9.

[2] And presumably by the increased availability of donor organs.

than the overall growth in transplant volume[3].

- The number of recipients requiring transplantation for indications other than cardiomyopathy (the "classic" indication): This group grew twice as fast as the group requiring transplantation for cardiomyopathy.

Interestingly, the overall burden of premorbid illness-calculated according to the formula in chapter 2 (see figures 2.4-2.5)-did not change appreciably during this period. This is illustrated in figure 3.3, where for example one sees that the percentage of transplant recipients having a high burden of illness remains essentially constant from 1984 to 1986.

The reason why overall burden of illness does not change despite the above trends in patient selection is that the "non-use" of triple drug therapy-another patient risk factor (see figure 1.8)-decreases dramatically during the study period (figure 3.4). By 1984, several groups had reported that recipients treated with small doses of three immunosuppressive agents-cyclosporine, prednisone and azathioprine-had fewer and less fulminant episodes of cardiac rejection and fewer side effects than patients treated with high dose cyclosporine alone[4]. These reports triggered a massive, nationwide change

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[3] Growth in the number of transplant recipients requiring preoperative mechanical support undoubtedly also reflects the diffusion of (and improvements in) mechanical support technology.

[4] See Introduction and chapter 9 for details.

in immunosuppressive protocols such that usage of triple drug therapy nearly quadrupled from 15% in 1984 to 57% in 1986.

As patient selection practices and immunosuppressive management strategies changed, overall mortality following heart transplantation decreased from 18% in 1984 to 14% in 1985, to 13% in 1986 (figure 3.5). This trend approaches, but does not quite achieve statistical significance ($p=.06$).

This strong trend certainly requires further investigation. Specifically, three questions require further analysis:

1) What is the possibility that a very strong trend toward reduced mortality between 1984-1986 does not achieve statistical significance because it is masked by another trend, in which clinicians tended to select sicker patients in the later years of this study?

2) To what extent is the trend towards reduced mortality explained by the increasing use of triple drug immunosuppressive therapy during this period?

3) What is the possibility that a very strong trend toward reduced mortality is hidden by the vast expansion in the number of new, inexperienced transplant programs that began during the study period?

I analyze these questions below.

YEAR OF TRANSPLANT, PATIENT CHARACTERISTICS AND THE MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY

Univariate analyses described earlier (figure 2.12) reveal that several patient attributes confer survival benefits in this study. For example, gender is a univariate predictor of mortality following heart transplantation: males have significantly lower mortality rates than females. Similar survival benefits are demonstrated among patients not requiring mechanical support and patients without comorbid conditions.

The year of transplant does not affect these primary univariate relationships. As shown in figures 3.6 and 3.7, the expected relation is found in 11 of the 12 samples when the data is stratified by year of transplant: males have lower mortality in all three years, patients without comorbid conditions have lower mortality in all three years, and so forth. Five of these 12 comparisons reach statistical significance (as shown). This pattern is very unlikely to have occurred by chance ($p<.005$)[5], and it provides additional support for the conclusion that the above patient characteristics are indeed important predictors of transplant mortality.

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[5] If these patient characteristics were not correlated with transplant mortality, the chances of observing 11 of 12 events in this pattern are equal to $12/(1/2)^{12}$, or 12/4,096.

GIVEN THAT the above patient characteristics are important predictors of transplant mortality, it is now possible to test the hypothesis that year of transplant is another important predictor. IF THIS WERE THE CASE, one would expect to see stepwise reductions in transplant mortality by year in each of the patient subsets. However, this pattern is not seen: the year of transplant has no consistent effect. For example, when I stratify by gender, the trend towards a decline in mortality between 1984-1986 is maintained in females, but it is less apparent in males (figure 3.6). [Neither trend achieves statistical significance ($X^2_{(females)}$ =1.89; p=NS. $X^2_{(males)}$=0.73; p=NS].

When I stratify by comorbid conditions, there is an insignificant trend ($X^2_{(not\ present)}$=0.65; p=NS), towards reduced mortality in patients having no comorbidities, and no trend at all in the group featuring the presence of comorbid conditions (figure 3.6). Similarly, there are no clear patterns in either subset when the data is stratified by the presence or absence of preoperative mechanical support.

And interestingly, yet a different pattern is visible when I stratify the mortality-by-year data by the use or non use of triple drug immunosuppressive therapy (figure 3.7). A trend toward declining mortality with time, consistent with the overall trend in the data set, is apparent in patients who did not receive triple drug therapy (however this trend does not reach statistical significance, as shown). The opposite trend,

towards higher mortality in later years, is seen for the patients treated with triple drug therapy! Further analyses of this sort (available on request) fail to reveal any clearcut relation between year of transplant and mortality.

Taken together, these findings suggest that the above patient characteristics and the decision to use triple drug immunosuppressive have a greater impact on transplant mortality than the year of transplant itself. And since clinicians tended to select sicker patients over these three years (older, more mechanical support, etc.), the data also suggests that the choice of triple drug immunosuppressive therapy has a powerful impact on transplant mortality-enough perhaps to be responsible (at least in part) for the trend towards reduced transplant mortality seen between the years 1984-1986. Further confirmation of this suspicion requires multivariate analysis (see chapter 8)[6].

PROGRAM DURATION AND MORTALITY

In examining the trend towards reduced heart transplant mortality between 1984-86, I must also account for the considerable role played by the new transplant centers-those that began operation during the study period. During this

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[6] A somewhat less plausible hypothesis to explain the above findings is that clinicians did in fact learn to select candidates who were more likely to survive the transplant procedure, and that the cues they learned to use were not detectable in the present study. This hypothesis cannot be tested directly using this data set.

period, the number of transplant centers increased from 32 to 70 (figure 3.1), and it is reasonable to suppose that this influx of inexperienced centers could have an impact on overall mortality following heart transplantation. If this were true, then the trend towards reduced mortality over the study period would assume greater significance.

Interestingly, centers beginning programs in 1984 and in 1985 tended to select patients with risk profiles similar to their established counterparts (see figure 3.8-NOTE: THIS FIGURE APPEARS ON THE SAME PAGE AS FIGURE 3.4)[7]. However, centers beginning in 1986 selected significantly more high risk patients than their established counterparts.

When I stratify transplant mortality by program duration and the year of transplant, several interesting observations emerge (figure 3.9). First, for each calendar year, centers beginning programs in that year experienced higher mortality rates than their established counterparts, as follows:

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[7] In this analysis, "new centers" began programs in the calendar year shown. "Established centers" had begun transplant operations before that calendar year.

1984		
TRANSPLANTS:	New center mortality	23% (n=56)
	Established center mortality	14% (n=147)
	z=1.53; p=NS	
1985		
TRANSPLANTS:	New center mortality	20% (n=66)
	Established center mortality	14% (n=340)
	z=1.26; p=NS	
1986		
TRANSPLANTS:	New center mortality	19% (n=24)
	Established center mortality	14% (n=470)
	z=0.64; p=NS	

And when I reaggregate the above data, I find that transplant mortality is significantly higher at new centers:

ALL		
TRANSPLANTS:	New center mortality	20% (n=146)
	Established center mortality	14% (n=957)
	z=2.13; p<.05	

Second, the mortality difference between new and established centers is particularly notable in patients having a moderate or a high burden of illness. In such patients, stepwise increments in program duration are correlated with stepwise reductions in mortality (figure 3.9) in all three years. This relation is not evident among patients having a low burden of illness. Although none of these relations reaches statistical significance by itself, the presence of such a stepwise relation in six independent samples (1984-moderate, 1984-high, 1985-moderate, 1985-high, 1986-moderate,

1986-high) would be exceedingly unlikely to occur by chance.

To summarize the pertinent observations on program duration:

1) New centers select patients with characteristics similar to those chosen by the established centers[8].

2) Regardless of the year of transplant, new centers are associated with higher mortality rates.

3) Increases in program duration are associated with mortality reductions in moderate and high risk patients.

The most logical explanation for these observations is that new transplant centers are able to improve their performance in the sickest patients as a result of having learned from their own past experience with the transplant procedure. Furthermore, at least some of the skills and/or knowledge that centers obtain through repetitions of the transplant procedure cannot be obtained vicariously (if it been possible for new centers to learn by observing or reading about the practice of other centers, then new centers should have demonstrated mortality rates equal to their more established counterparts).

The results of these analyses suggest that the trend towards reduced transplant mortality between 1984-1986 is

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[8] With the 1986 high risk exception mentioned above.

mediated (at least in part) by increases in the use of triple drug immunosuppressive therapy and by a learning phenomenon that occurred at new transplant centers. The learning phenomenon will be analyzed in chapter 4.

figure 3.1

TRANSPLANT VOLUME (1984 - 1986)

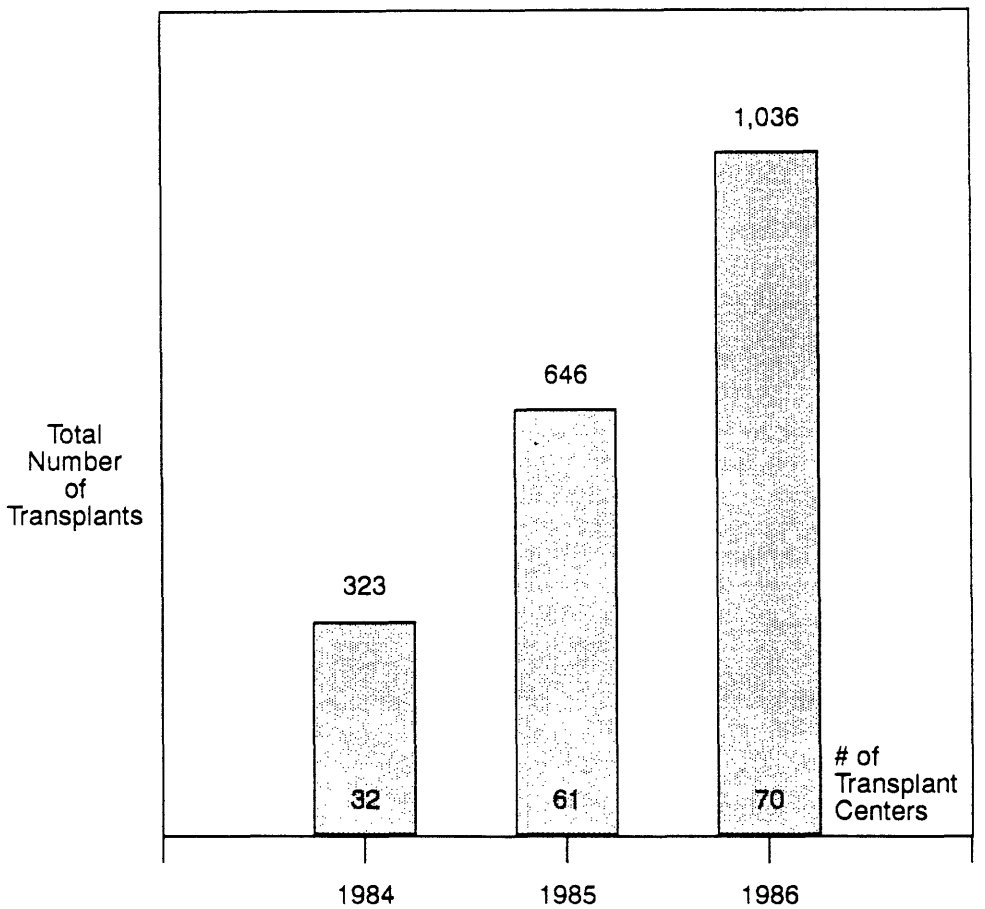


figure 3.2

TRENDS IN PATIENT AND DONOR CHARACTERISTICS
AND IN IMMUNOSUPPRESSIVE MANAGEMENT
(1984 - 1986)

Figure 3.3

TRENDS IN THE BURDEN OF ILLNESS
1984-1986

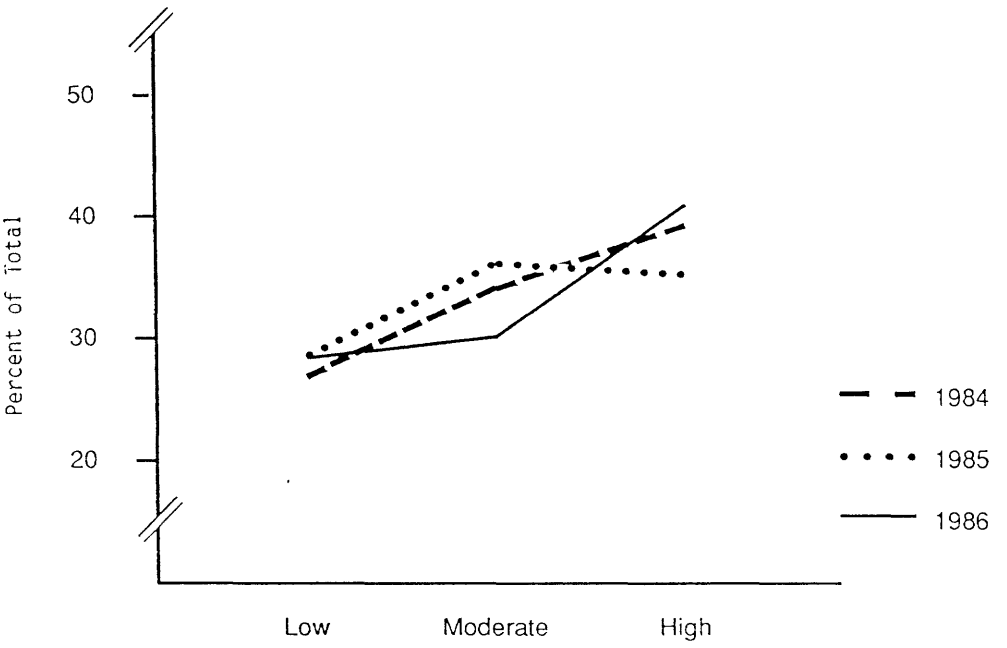


figure 3.5
MORTALITY FOLLOWING HEART TRANSPLANTATION
(1984 - 1986)

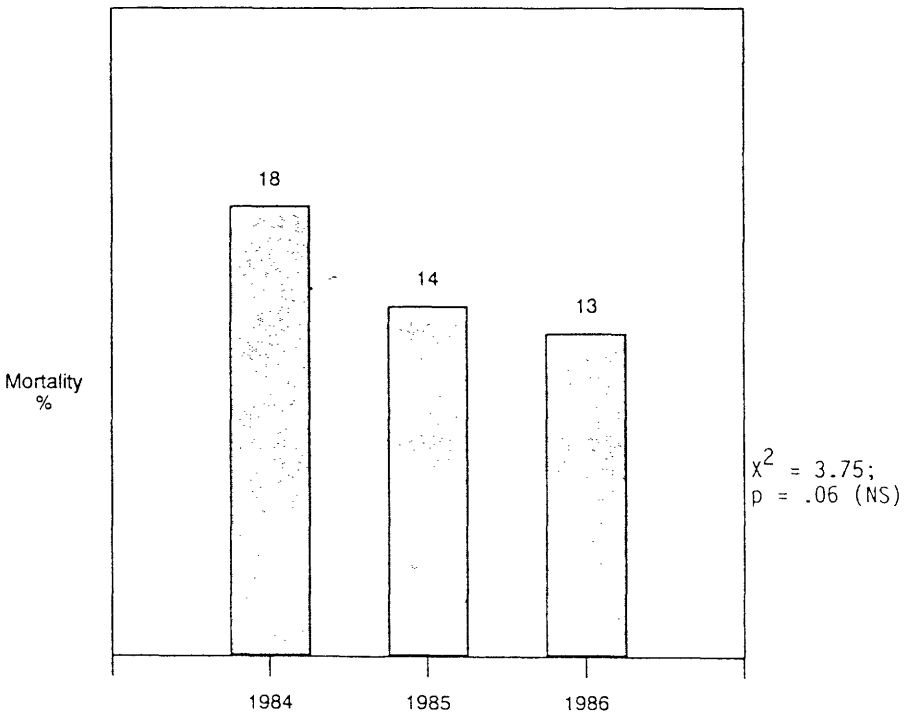


Figure 3.6

YEAR OF TRANSPLANT AND MORTALITY %

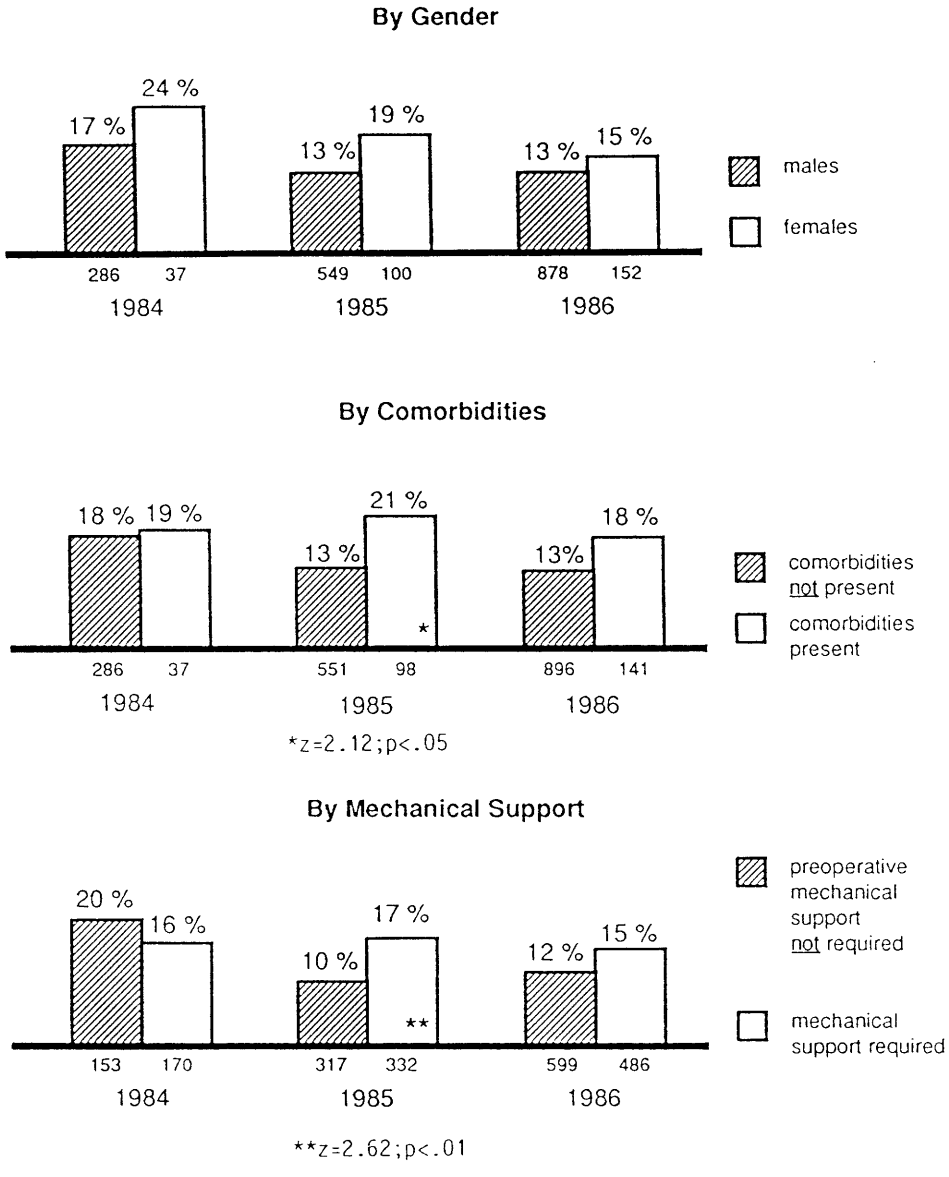


Figure 3.7

YEAR OF TRANSPLANT AND MORTALITY

By Triple Drug Immunosuppressive Therapy

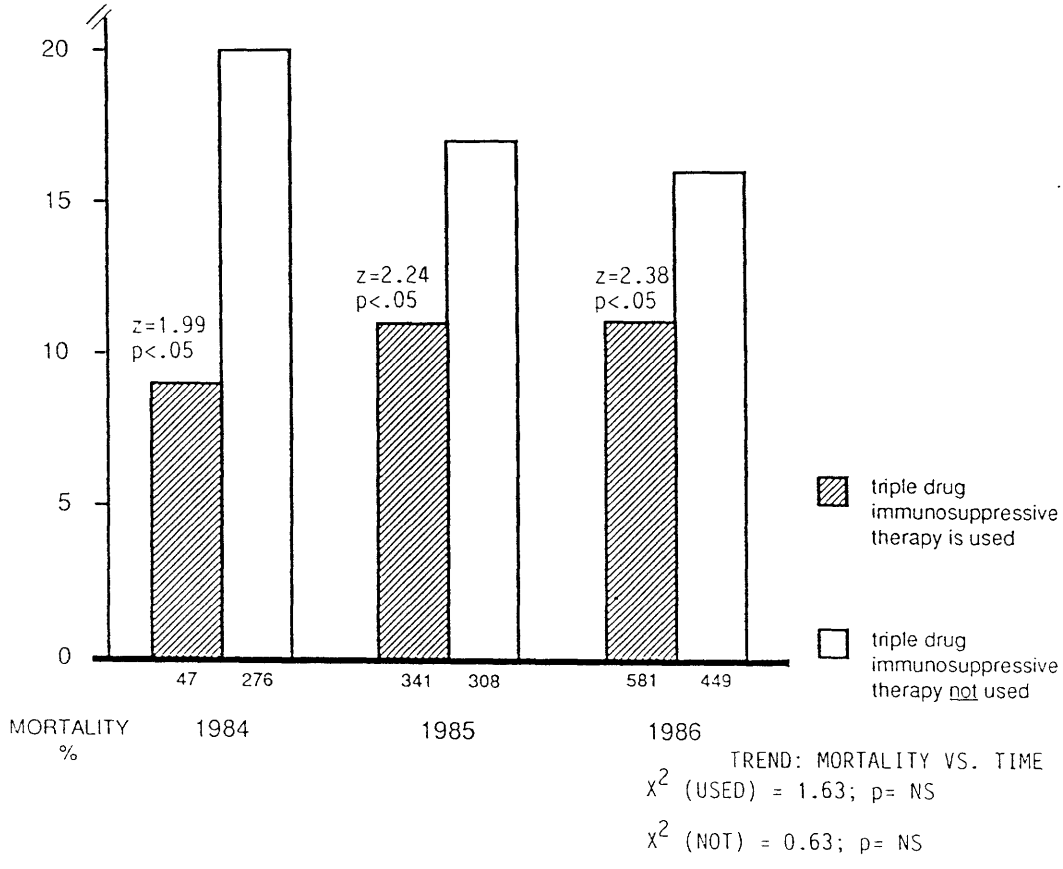


Figure 3.8

SELECTION CRITERIA IN NEW AND ESTABLISHED TRANSPLANT PROGRAMS

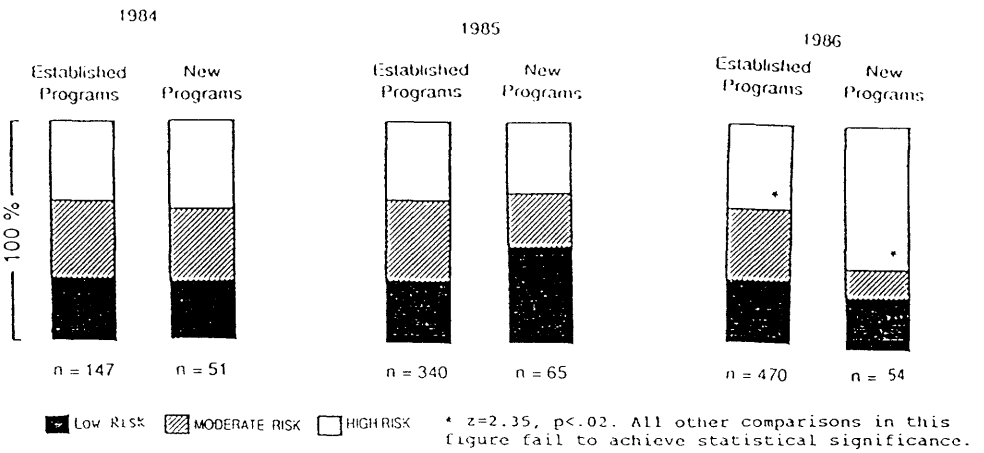


figure 3.4

TRENDS IN THE USE OF TRIPLE DRUG THERAPY (1984 - 1986)

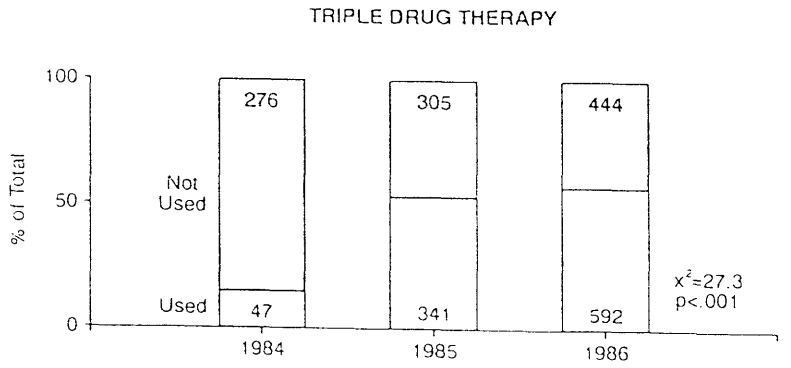


Figure 3.9

PREMORBID BURDEN OF ILLNESS AND MORTALITY
NEW vs. OLD CENTERS

1984 Transplants

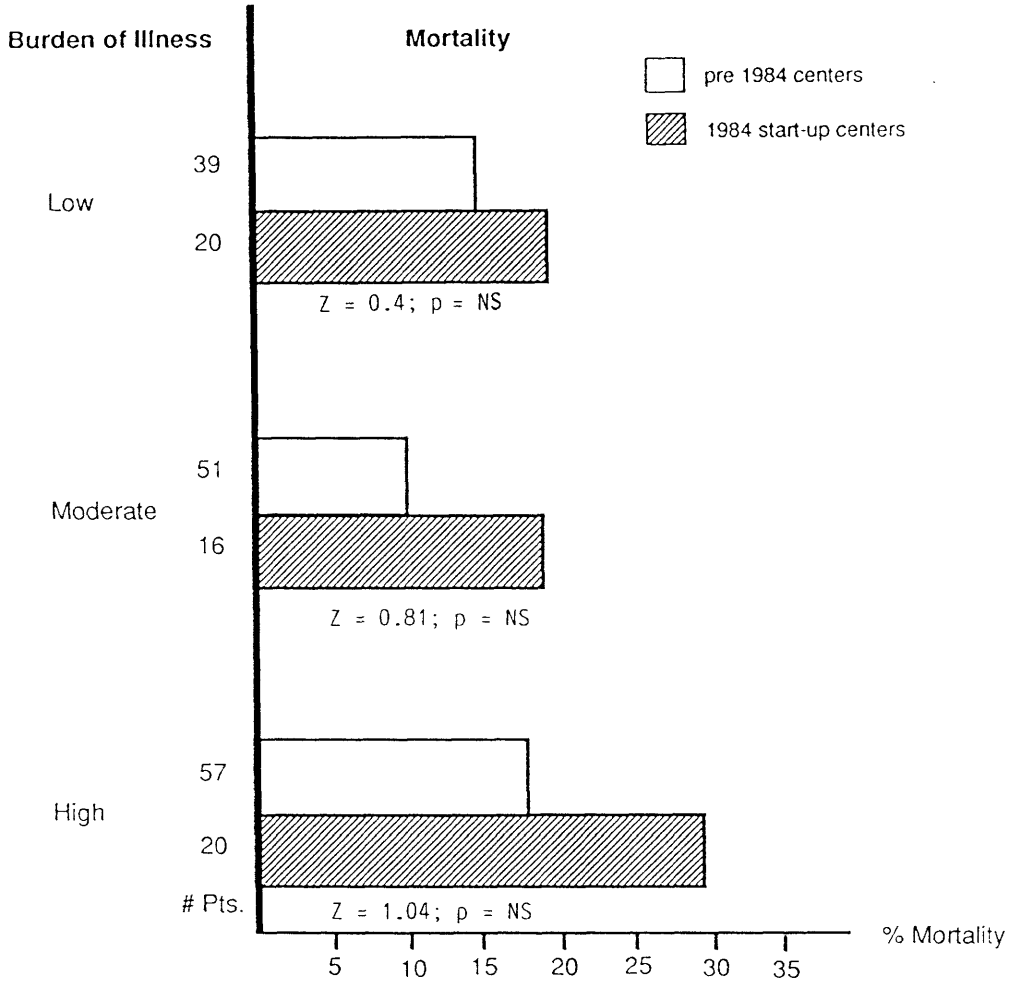
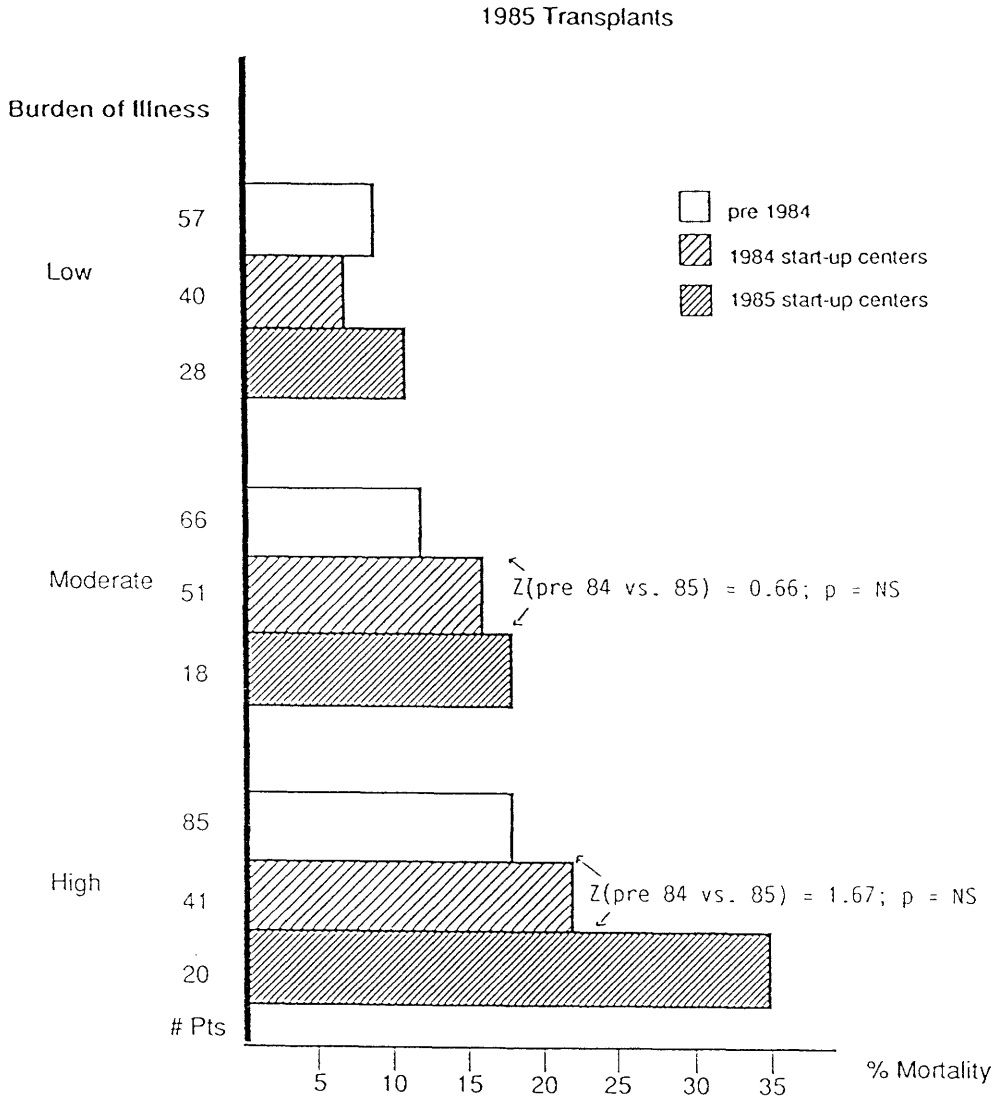


Figure 3 9 (Ctd)

PREMORBID BURDEN OF ILLNESS AND MORTALITY
NEW vs. OLD CENTERS



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CHAPTER 4

CUMULATIVE EXPERIENCE AND MORTALITY FOLLOWING HEART TRANSPLANTATION (the "Learning Curve")

SUMMARY:

This chapter investigates the hypothesis that knowledge and skills acquired during initial repetitions of the heart transplant procedure lead to decrements in mortality risk.

KEY POINTS:

- Mortality following heart transplantation is highest among the first several patients to receive the procedure at any particular center.

- As centers repeat the procedure, they achieve better results in moderate and high risk patients. This relation is less well defined in low risk patients.

- The rate of decline in mortality risk and the number of transplants over which mortality decrements can be demonstrated vary by category of high (or moderate) risk patient.

- Skills and knowledge obtained through the management of low risk patients are applicable to the management of moderate or high risk patients.

In chapter 3, the analysis of transplant program duration revealed that mortality following heart transplantation is significantly higher at new centers than it is at established centers. The analysis also revealed that when transplant programs are stratified by the number of years in which they

have performed the procedure, there are successive mortality reductions for each additional year of experience (figure 3.9). These findings suggest that centers acquire knowledge and/or skills by performing the heart transplant procedure and that the centers can translate these experiences into improved outcomes in future repetitions of the transplant procedure. In other words, they "learn by doing".

When one considers the multiplicity and complexity of the care processes required to provide heart transplant services, one might reasonably expect learning curve phenomena to exist. In this regard, it is interesting to note that current heart transplant policy fails to account for this possibility[1]. Of course it is also true that to date no investigator has attempted to demonstrate such phenomena in heart transplantation, and in fact empirical studies documenting the presence of learning curves in health care are quite rare.

In this chapter, I will provide an overview of learning curve theory, review what limited literature exists on learning curves in health care, and then present the results of my study of learning curve phenomena in heart transplantation.

AN OVERVIEW OF LEARNING CURVES

The learning curve was originally described as a

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[1] The Introduction and chapter 9 provide an overview of heart transplant policy.

logarithmic decline in labor costs as a function of cumulative production experience. It was first observed in aircraft production during wartime (40). Similar relations have been described for the production of integrated circuits, high-grade aluminum and benzene (40). More recently, learning curves have been demonstrated in the acquisition of second languages (41), and in the acquisition of cognitive and manipulative skills by children (42,43).

Health care providers routinely refer to "learning curves" in medicine. Most implicitly believe they exist for a very broad range of clinical activities: from simple phlebotomy to the interpretation of radiologic images, to the performance of complex operations such as open heart surgery[2]. In addition, professional organizations routinely require that providers perform procedures while being supervised before they can become certified to perform them independently[3]. In the context of these beliefs and policies, it is striking to find how little empiric support there is in the medical literature that documents or characterizes in any way learning curve phenomena in health care.

Fortunately the literature is relatively well developed for one technology, and it happens that this technology is in some

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[2] ...in the author's personal experience.

[3] For a summary of practice guidelines and standards in health care, see: Leape, L; Practice Guidelines and Standards; An Overview; Quality Review Bulletin; (16)42-50; 1990.

ways similar to heart transplantation. The technology is Percutaneous Transluminal Coronary Angioplasty (PTCA). In PTCA, cardiologists use balloon-tipped catheters to dilate coronary arteries that have become narrowed due to atherosclerosis. The similarities between PTCA and heart transplantation are as follows: 1) they both gained acceptance in the mid-1980s. 2) The number of centers offering both services has exploded in recent years. 3) Rapidly improving outcomes from these procedures could be reasonably attributed to both increasing professional skill and associated innovations in related fields (for PTCA, it was catheter design; for heart transplantation, it was immunosuppressive therapy). I will now review the literature on PTCA learning curves and use it to introduce some general discussion points about the learning curve phenomenon.

The first account of a PTCA learning curve appeared in 1984. In a study published in the American Journal of Cardiology, Kelsey used results from the National Heart, Lung and Blood Institute's PTCA registry to determine whether learning curves were present for this procedure (44). He found that cardiologists had 55% success rates during their first 50 cases and 77% success rates after case number 150. Kelsey showed that improved results were secondary to improved manipulative skills rather than the year in which the PTCA was performed or the attributes of the lesions that were dilated.

In the period between 1982-1986, there were many important breakthroughs in the design of dilation catheters and the guidewires that were used to advance the catheters into proper position. First, several companies introduced steerable catheters which improved catheter maneuverability. Then they introduced so called "low profile" catheters, which performed the same functions as the older versions, but they offered better torque control and they were much thinner, thus enabling operators to advance these catheters beyond proximal stenoses.

These advances changed the characteristics of the PTCA learning curve (45-46). Cardiologists with no prior PTCA experience began to report outstanding results as soon as they began to use the new catheters. In one report, previously untrained cardiologists successfully dilated 85% of the first 20 lesions they attempted (46). In another report, cardiologists successfully dilated 94% of their first 100 lesions (47). This group noted their failures occurred sporadically; there was no demonstrable learning curve! The explanation for such results was that advances in catheter design had reduced task complexity to the point where excellent performance could be expected on the very first attempt.

Factors That Influence Learning Curves-Thus in the case of PTCA, innovation in a related area (catheter design) affected the shape of the learning curve by markedly simplifying a

previously complex task. Other factors may determine whether learning curves will be present or mediate their shape. Task complexity per se is one such factor. Activities requiring complex cognitive or manipulative skills, or for whatever reason generate a multitude of situations that operators must handle, are likely to be associated with prolonged learning phases. Those which are relatively simple will manifest a steep learning curve or none at all.

Preexisting skills or knowledge in related areas are a third factor that may modulate the shape of learning curves. Individuals having skills which are transferable to the new task are likely to master the new task more rapidly than those without such skills. This observation provides the rationale for requirements that new heart transplant centers have preexisting open heart surgical programs (10). Skills and teamwork mastered during routine open heart surgery are certainly applicable to the heart transplant procedure, and they allow individuals to focus learning efforts on its unique aspects.

A fourth factor that can modulate the learning curve is the RATE at which the relevant task is performed (40). If this rate is low, individuals may not be able to practice newly acquired skills intensively enough to master them, and there may be extinction of these acquired skills. At the other extreme, it is possible that very high performance rates may impair the assimilation of new knowledge by providing

insufficient time to internalize knowledge and skills.

Learning curves may also be modulated by a fifth factor, the time period in which learning takes place. This was also demonstrated in the PTCA example. Clinicians that began performing PTCA after innovations in catheter design had starkly different learning curves than those who began before. The learning curves of late starters are also affected by better teaching (from the pioneers) and better support processes (again, fashioned by the pioneers)[4].

A sixth factor that can impact the presence and shape of learning curves is the choice of measures used to detect it. If investigators select an outcome measure that is relatively insensitive, then they may not be able to detect a learning curve phenomenon. For example, mortality rates associated with PTCA have not dropped notably since PTCA was introduced, but success rates and other more sensitive measures have shown improvement.

A final point concerning the medical literature on learning curves is that it is focused on individual, as opposed to organizational performance. This literature has yet to document, much less characterize learning curves at the organizational level [although outside health care there is evidence that learning curve phenomena can be observed at this

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[4] It would appear that innovations in related fields, task complexity, preexisting skills, performance rate and program start time could all modulate volume-outcome relations as well, although these interactions have not been studied.

level (40)].

This omission is important because the success of heart transplant technology almost certainly depends on organizational, not individual performance. And while few would find it implausible that learning curves could exist for heart transplantation, it remains a major challenge to isolate and describe these phenomena given that new transplant centers are also likely to exhibit variations in their patient selection and patient care protocols, their transplant team structure, and in the degree of institutional support for their program.

LEARNING CURVES IN HEART TRANSPLANTATION: THE RESULTS OF THIS STUDY

To investigate whether transplant centers accumulate knowledge and/or skill during their initial repetitions of the transplant procedure, and whether they can translate this into reduced mortality in subsequent procedures, I:

1- Created a new data set consisting of centers that began transplant programs in the years 1984-1986.

2- Grouped all patients in this data set according to their "transplant number". For example, all the patients who happened to be the first transplant recipient at their respective centers were grouped (transplant number 1), as were all patients who happened to be the second (transplant number 2), and so on.

Figure 4.1 shows the relation between transplant number and mortality for the first 50 transplants at these "new" transplant centers. Mortality is consistently high in the earliest phases of this sequence (approximately the first four transplants). As the transplant number increases from number four to approximately number 20, a somewhat lower steady state mortality is reached, although sporadic peaks and valleys are common. Beyond (about) transplant number 20, the sequence is characterized by large variations in mortality from observation to observation. When both parametric and non-parametric statistical tests are applied to this sequence of 50 transplants[5], a statistically significant trend toward mortality reduction is <u>not</u> demonstrable.

Figure 4.2 shows the same relation, but it displays data for the first 20 transplants only. This figure is meant to highlight possible mortality reductions as centers accumulate skills and/or knowledge <u>from their initial experiences</u> with the procedure. Of great interest, there <u>is</u> a significant trend toward reduced transplant mortality as transplant number increases from one to 20 (see figure).

Therefore, one can demonstrate a significant trend for the

---

[5] Parametric method: Chi-Square Test for the comparison of more than two proportions in independent samples.

Non-parametric method: Spearman's Rank Correlation Test to determine the degree of relationship between two variables.

For further information see: Colton, T; <u>Statistics In Medicine</u>; Little, Brown and Co.; Boston, Ma.; 1974; p174-9, 223-7.

first 20 transplants, but the trend is no longer apparent when the sequence is extended to 50 transplants. There are two possible explanations for these findings (which are not mutually exclusive). First, it is possible that centers achieve the maximal benefits from learning relatively early in their sequence of heart transplant procedures, and so extending the sequence out to 50 transplants dilutes the effect. Second, it is possible that sample sizes for the higher transplant numbers are too small to allow a real difference to be detected.

To explore these possibilities, I reaggregated the data into larger groups by transplant number. For example, to create figure 4.3[6], I combined individuals having transplant numbers from 1-5 into one group, those with transplant numbers from 6-10 into a second group, etc. In this figure, one can see that mortality is highest in the first group (the earliest transplants in the sequence). There is considerable variation after this first group, but it is noteworthy that of the 10 observations in figure 4.3, the first 5 observations contain 4 of the highest mortality rates, and the last 5 observations contain 4 of the lowest mortality rates. However, as shown, this trend does not reach statistical significance.

Importantly, figure 4.3 also shows that even after reaggregating the data as described, sample size becomes

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[6] In these figures, and all subsequent histograms in this chapter, the mortality rate is shown $\pm$ 1 standard error.

relatively small as transplant number increases beyond about number 30. Therefore, for a second analysis I grouped the data into multiples of ten transplant numbers (figure 4.4). This analysis again reveals that mortality is higher in the first group (transplant numbers 1-10). It also shows that mortality is lowest in the last group (transplant numbers 40-50). Although this trend does not quite reach significance using a non-parametric test, the chi-square analysis does suggest this pattern is unlikely to have occurred by chance.

To pursue these findings further, I then reaggregate transplant number into two groups (figure 4.5): the first group consists of transplant numbers 1-5 and the second consists of all transplant numbers greater than 5. Mortality in the former group is 20%, and mortality in the latter group is 12%. This difference is highly significant ($p<.002$). I subsequently aggregate transplant number into different groups, as follows:

	Group A	Group B
Transplant Number	1-10	>10
Mortality (%)	17.0	12.2
Sample Size	413	483
	Z=2.13; p<.05	

Transplant Number	1-15	>15
Mortality (%)	16.5	12.0
Sample Size	540	346
	Z=1.83; p=NS	

Thus, the significant relation between transplant number and mortality disappears after about the 10th transplant.

If one could attribute this relation to improvements in the execution of patient care processes, then one would in fact be describing a learning curve phenomenon in heart transplantation. However, the above relations could also be explained by changes in patient selection or in the use of triple drug immunosuppressive therapy as transplant number increases.

I investigate these possibilities by studying the relations between transplant number and: 1) patient characteristics shown by univariate analysis (figure 2.12) to be significant predictors of mortality, b) immunosuppressive practices, and c) the premorbid burden of illness. These relationships are displayed in figures 4.6-4.8.

Transplant number is not related to any of the univariate predictors of mortality (analyses available on request) [Of peripheral interest however, transplant number is related to recipient age-a patient characteristic <u>not</u> found to be a strong predictor of transplant mortality (figure 4.6). The relation is characterized by a tendency to select patients older than age 50 years as transplant number increases].

Of greater importance, there is a modest positive relationship between transplant number and the use of triple drug immunosuppressive therapy (figure 4.7). However, this relation is characterized by an increasing tendency to use

this more effective regimen as transplant number increases[7]. This effect enhances, rather than confounds, the central observation that mortality is higher among patients with low transplant numbers.

Equally important, the data does not indicate a tendency to select patients with a low burden of illness as transplant number increases (figure 4.8).

These observations essentially rule out the possibility that the inverse relationship between transplant number and mortality is due to underlying trends in patient selection or in the management of immunosuppressive therapy. The remaining hypothesis is that a learning curve exists in heart transplantation:

> Transplant centers are able to improve the execution of their patient care processes as a result of their early experiences with the procedure. These improvements translate into reduced transplant mortality in subsequent cases.

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[7] I use the word "modest" because the non-parametric test for correlation reaches conventional standards for statistical significance, while the chi-square test does not suggest the relation is significant. This implies a very consistent trend of very small magnitude, as can be seen in figure 4.7.

CHARACTERISTICS OF THE HEART TRANSPLANT LEARNING CURVE

Now that I have identified the heart transplant learning curve, I proceed by characterizing it more fully. Several questions come to mind in this respect, and I will answer each of them.

What is the relation between the year in which transplant programs are initiated and the learning curve? Interestingly, the data shows significant learning curve phenomena for transplant programs that began operations in 1984 and 1985 (figures 4.9-4.10), but nothing even remotely resembling a learning curve in 1986 start-up centers (figure 4.11).

The learning curves for 1984 and 1985 have different characteristics. The curve for 1984 shows strikingly and consistently high mortality through the first 6 transplants followed by a rather abrupt reduction in mortality which is maintained throughout the remainder of the sequence. The overall trend reaches statistical significance by parametric tests but not by non-parametric tests (the latter presumably because of the notable uniformity in the sequence beyond transplant number 6).

In contrast, the curve for 1985 start-up centers (figure 4.10) is characterized by a gradual reduction in transplant mortality which is more or less evident over the entire 20-transplant sequence. This curve reaches significance at the .05 level using the Chi-Square Test and the Spearman Rank Correlation test (the latter presumably because the of the

near perfect correspondence between transplant number and "mortality rank" at both the beginning and the end of the 20-transplant sequence).

For 1986 start-up centers, the relation between transplant number and mortality is not at all reminiscent of a learning curve (figure 4.11). When compared to the curves for 1984 and 1985 centers, the 1986 data is characterized by unexpectedly high mortality in transplant numbers 8-10. The data set used in this study includes relatively little information about transplant recipients from centers that began programs in 1986 (see figure 2.1), and it would certainly be worthwhile to reexplore this relation with more complete information regarding 1986 start-up centers.

In the current data set however, a hint at the explanation for this unexpected result comes from a previous analysis (figure 3.4), which revealed that 1986 start-up centers selected unusually high numbers of high risk patients to begin with. Further exploration of this finding reveals the following results:

MORTALITY IN 1986 START-UP TRANSPLANT CENTERS

TRANSPLANT #	# PATIENTS	# DEATHS	DEATHS BY RISK GROUPS		
			High	Mod.	Low
1-5	33	2	2/19	0/3	0/11
6-10	17	8	6/14	1/1	1/2
11-15	4	1	1/2	0/2	0/0
TOTAL	54	11	9/35	1/6	1/13

From this table, it is apparent that several factors contribute to the unusually high mortality rates seen between transplants 6-10 in these 1986 start-up centers. These factors include 1) the selection of a disproportionately high number of high risk patients between transplant numbers 6-10, 2) unusually low mortality rates among high risk patients transplanted between numbers 1-5, and 3) the apparently coincidental deaths of one patient from both the moderate and low risk groups that occurred in group of transplants from 6-10[8]. I can think of no clinically plausible explanation for the concurrence of these events, but given the small numbers of patients that underwent heart transplantation at 1986 start-up centers, I recommend further investigation of the learning curve phenomenon using a more complete data set before I would reject the possibility that a learning curve could exist in 1986 start-up centers.

Is the learning curve demonstrable after the data is stratified by important patient characteristics or immunosuppressive management protocols? The results suggest that learning curve phenomena are demonstrable in moderate and high risk patients (figures 4.16-18, 4.20, 4.22-23) but not in low

[8] Another explanation-regarding the trend toward treating transplant recipients with triple drug immunosuppressive therapy-is discussed below.

risk patients (figures 4.13-15, 4.19, 4.21).

For this analysis, I use three methods to stratify patients according to risk: univariate predictors of mortality, bivariate predictors, and the burden of illness classification system (these three methods are described in chapter 2). Figures 4.13 to 4.15 display the relation between cumulative transplant experience and mortality in three categories of low risk patients identified through univariate analysis (see figure 2.12): these are males, patients receiving triple drug immunosuppressive therapy, and patients having comorbid conditions. In two of these three low risk groups, mortality is slightly higher in the earliest transplant recipients, but the mortality difference between these earliest recipients and subsequent recipients is small. In the third case, mortality is lower for transplant numbers 1-5 than it is for transplant numbers 6-10. Both parametric and non-parametric tests suggest there are no significant relations between transplant number and mortality in these low risk groups. The results of similar analyses involving other univariate predictors of low risk also fail to reveal a learning curve phenomenon. These analyses are available on request.

Figures 4.16 to 4.18 show the above relations for corresponding categories of (univariate) high risk patients. Learning curve phenomena are demonstrable in these three high risk groups: mortality is highest among the earliest transplant recipients and it declines subsequently. As noted

in previous analyses, this family of learning curves displays considerable variation in both the rate at which mortality declines and the length of the transplant sequence over which declines can be measured.

In the case of females (figure 4.16) there is a striking, rapid decline in mortality over the first 8-10 transplants, and this relation is highly significant. In the case of patients not receiving triple drug therapy (figure 4.17) the learning curve exhibits a more gradual decline, with evidence for improvements almost through the completion of the 20-transplant sequence. This relation also achieves statistical significance using either parametric or non-parametric tests. In the case of patients having comorbidities (figure 4.18) the learning curve is difficult to appreciate over the 20-transplant sequence, but the marked variation from transplant to transplant suggests that sample sizes are to small to detect a significant trend. Interestingly, when transplant numbers are aggregated into groups of 5 in the accompanying histogram, the learning curve phenomenon becomes apparent (and achieves statistical significance using parametric tests).

The observation that a learning curve exists for patients who <u>do not</u> receive triple drug immunosuppressive therapy, and that it does not exist for patients who <u>do</u>, **is very important.** Recall that in chapter 3, I noted that over the years 1984-86, there was a significant trend toward the adaptation of triple drug therapy. This trend provides another reasonable

explanation for the failure to document a learning curve in 1986 start-up centers (figure 4.11) and further emphasizes the need to restudy the 1986 learning curve issue using a more complete data set (see previous discussion)[9]. And assuming that the trend toward using triple drug therapy continued beyond 1986[10], this finding also raises questions about the applicability of these findings to current heart transplant experience.

Figures 4.19 and 4.20 are examples of bivariate analyses. The results of these analyses are consistent with the above univariate analyses. Bivariate analyses generate, in a rough sense, three strata of risk: patients can have neither, one, or both of the "high risk" attributes. In the example shown, the two high risk attributes are prolonged ischemic times and preoperative mechanical support. Therefore in this analysis, low risk patients have ischemic times less than 2 hours and no need for preoperative mechanical support. There is no apparent relation between cumulative experience and mortality in these low risk patients (figure 4.19).

In the corresponding analysis for moderate risk patients (those having exactly one of the two "high risk" attributes), mortality declines as cumulative experience increases (figure

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[9] However, the explanation provided earlier in this chapter appears sufficient to describe observations seen in figure 4.11.

[10] Based on personal experience, this is almost certainly true. It would be easy to verify using updated Registry files.

4.20). This relation is almost imperceptible in the original 20- transplant sequence, but when the data are aggregated into groups of five, the trend is easy to detect and achieves significance using both the Chi-Square test and the Spearman Rank Correlation Test.

Unfortunately, only 43 patients qualify as "high risk" in this bivariate analysis[11]. This extremely small sample size does not permit one to detect a learning curve using the above methods: there are, on average only slightly more than two patients per transplant number.

The results of other bivariate analyses show similar patterns: learning curves are generally not demonstrable in low risk patients; a family of learning curves is demonstrable in moderate risk patients; and small sample sizes prevent the use of this methodology for high risk patients.

The sample size problem for high risk patients in bivariate analyses can be overcome by using the premorbid burden of illness classification system (developed in chapter 2) to generate new risk classifications. When patients are stratified according to their premorbid burden of illness, and the above methodology is used to identify learning curves, distinct patterns can be seen for each of the three strata. In the low risk group (figure 4.21), there is no discernable relation between cumulative experience and mortality. In the

[11] This undoubtedly reflects clinical attempts to control the overall mortality risk in transplant recipients.

moderate risk group (figure 4.22), there is a steep drop in mortality after the first 5 transplants, with no further changes seen beyond this point. This learning curve reaches statistical significance when the data are aggregated into groups of five, as shown. In the high risk group (figure 4.23), there is a continuous and relatively gradual decline in mortality over the first twenty transplants. This finding is somewhat obscured by variation in mortality from transplant number to transplant number due to small sample sizes, but when the data are aggregated into groups of five, the learning curve is easy to visualize. Once again I have demonstrated the presence of learning curves in high and moderate risk patients, and not in low risk patients.

Are the skills and/or knowledge obtained from the management of low risk patients transferrable to high risk patients? I have devised two tests for this question. Both suggest that learning acquired while managing low risk patients is applicable to, and can be used reduce mortality in, high risk patients.

The two tests are based on the creation of a series of new data sets. These sets consist of high risk patients only, with careful attention to maintain their original transplant sequence. To accomplish this, I use the methodology shown in figure 4.24. The first of the two tests involves simply displaying data from the newly created sets using the same

format as in previous analyses throughout this chapter. By examining the shapes of the learning curves generated in the new data sets, I can infer whether learning from the (currently excluded) low risk patients is transferrable to high risk patients. If learning was transferrable, learning curves in the new data sets would appear truncated when compared to the curves in the original set. If learning was not transferrable, the new learning curves would appear similar to, or even more gradual in their slope than those in the original data set.

The curves so generated from these new data sets (figure 4.25-4.27) in fact demonstrate that the first one or (at most) two transplant procedures have higher mortality risk than subsequent procedures. Beyond these very early procedures, there appears to be no relation between transplant number and mortality risk. As above, these truncated learning curves suggest that knowledge and skills acquired during the management of low risk patients is being successfully applied to the patients high risk patients.

The second test is a somewhat stronger test of the hypothesis that learning from low risk patients is transferrable to the high risk population. For this test, I used the following methodology:

1) I create subsets of high risk patients according to their sequence in the new data set: for example, one subset consists of all high risk patients who are first in the new

sequence (so called "H1" patients).

2) Then, I determine the place of each such patient in the original sequence. Patients in all these subsets-homogenous with respect to their position in the new data set-exhibit striking heterogeneity with respect to their position in the original data set[12]. For example, among the subset of H1 patients having comorbidities (figure 4.25), the range of their appearance in the original data set is from transplant number 1 to transplant number 16 (this will be denoted as $H1_{(1)}$ and $H1_{(16)}$ in analyses below).

3) Because of small sample size in each subset of high risk patients, I then create 3 groups: those whose position in the original sequence is from 1-5, those whose original position is from 6-10, and those whose original position is >10. For the H1 subgroup, the denotation for these groups is as follows: $H1_{(1-5)}$, $H1_{(6-10)}$, and $H1_{(>10)}$.

4) I then determine mortality rates for each subgroup, as shown presently:

[12] The "original" data set is entire data set. It is the one containing low and high risk patients.

PATIENTS W/COMORBIDITIES

	Transplant Number in Original Sequence			
	1-5	6-10	>10	Total (%)
Deaths/Transplants H1:	10/21	4/16	1/4	15/41 (.37)
H2:	5/12	3/14	0/6	8/32 (.25)
H3:	0/1	2/8	3/14	5/23 (.22)

FEMALES

	Transplant Number in Original Sequence			
	1-5	6-10	>10	Total (%)
Deaths/Transplants H1:	10/25	2/13	0/1	12/39 (.31)
H2:	3/12	3/12	0/9	6/33 (.17)
H3:	1/5	2/10	2/8	5/23 (.22)

PATIENTS W/HIGH BURDEN OF ILLNESS

	Transplant Number in Original Sequence			
	1-5	6-10	>10	Total (%)
Deaths/Transplants H1:	9/15	7/28	1/5	17/48 (.35)
H2:	3/7	10/30	3/8	16/45 (.35)
H3:	2/2	5/21	3/17	10/40 (.25)

I performed similar analyses for the other 4 univariate predictors of poor outcome (see figure 2.12) and these analyses are available on request.

The second test of the hypothesis that learning from low risk patients is transferrable to high risk patients is derived from this data.

Test 2: If learning was <u>not</u> transferrable, then one would expect that mortality in $H1_{(1-5)}$ would not be significantly

different from mortality in $H1_{(6-10)}$ or $H1_{(>10)}$. However, in the above three examples, $H1_{(1-5)}$ mortality is greater than or equal to the latter two subgroups. These differences do not reach statistical significance in any of these three examples but they warrant further investigation:

When the above two univariate analyses (comorbidities and females) are combined with data from the remaining four univariate analyses (mechanical support, ejection fraction, ischemic time, and triple drug therapy; see figure 2.12), it turns out that **$H1_{(1-5)}$ mortality is greater than $H1_{(6-10)}$ and $H2_{(>10)}$ mortality in 10 of the 12 cases.** The probability that this observation could have occurred given no transferrable learning is .015[13], and this strongly mitigates for rejecting this hypothesis (and supporting the hypothesis that learning is transferrable).

Similar analyses can be performed for the H2 and H3 subsets, and indeed for any subset beyond H3 (HX). However, the number of patients in the $HX_{(1-5)}$ category rapidly diminishes to zero as X grows past numbers two or three. This phenomenon substantially reduces the analytical power of this

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[13] The calculation for the chance of x successes in n independent trials with z chance of success in each trial (x=10, n=12, z=.5) is:

$$(1/2)^{10}(1/2)^{2}[12!/10!(2)]=66/2^{12}=.015$$

method. Nevertheless, for the H2 subset, the data shows that $H2_{(1-5)}$ mortality exceeds that of $H2_{(6-10)}$ and $H2_{(>10)}$ in 9 of 12 opportunities. The probability that this could have occurred in the absence of transferrable learning is .054. It is therefore reasonably unlikely to have occurred by chance alone.

In the H3 data set, $H3_{(1-5)}$ exceeds the remaining two categories in only 7 of the 12 cases. This event would occur fully 20% of the time if indeed there were no differences between the three groups, and there is hence no reason to suspect transferrable learning has affected the H3 data set. For data sets beyond H3, there is no clearcut benefit for any of the three subsets (that is, $HX_{(1-5)}$, $HX_{(6-10)}$ and $HX_{(>10)}$ are equally likely to exhibit the highest mortality rates).

This pattern of highly significant declines in mortality in the H1 data set, declines of borderline significance for the H2 data set, and no clear relation for data sets H3 and beyond, is consistent with the earlier findings (figures 4.25-27) and provides strong support for the hypothesis that learning in low risk patients is transferrable to the high risk patients.

In summary, it is possible to demonstrate learning curves in heart transplantation. These learning curves manifest themselves as progressive reductions in mortality with increasing center-specific transplant experience. This

phenomenon is readily apparent in moderate and high risk patients, but it cannot be demonstrated in low risk patients. The learning curve phenomenon is easy to appreciate in 1984 and 1985 centers, but is not present in 1986 centers. Although this latter finding may be caused by small sample sizes, the findings that:

1) learning curves are not present in patients treated with triple drug immunosuppressive therapy, and

2) the increasing trend to use this therapy in 1986 and beyond,

strongly warrant follow-up studies with complete, recent data.

Finally the experience of performing heart transplantation in low risk patients appears to improve subsequent mortality rates in high risk patients. The mechanisms and policy implications of these important findings are reviewed in chapter 9.

figure 4.1

CUMULATIVE EXPERIENCE AND MORTALITY
FOLLOWING HEART TRANSPLANTATION

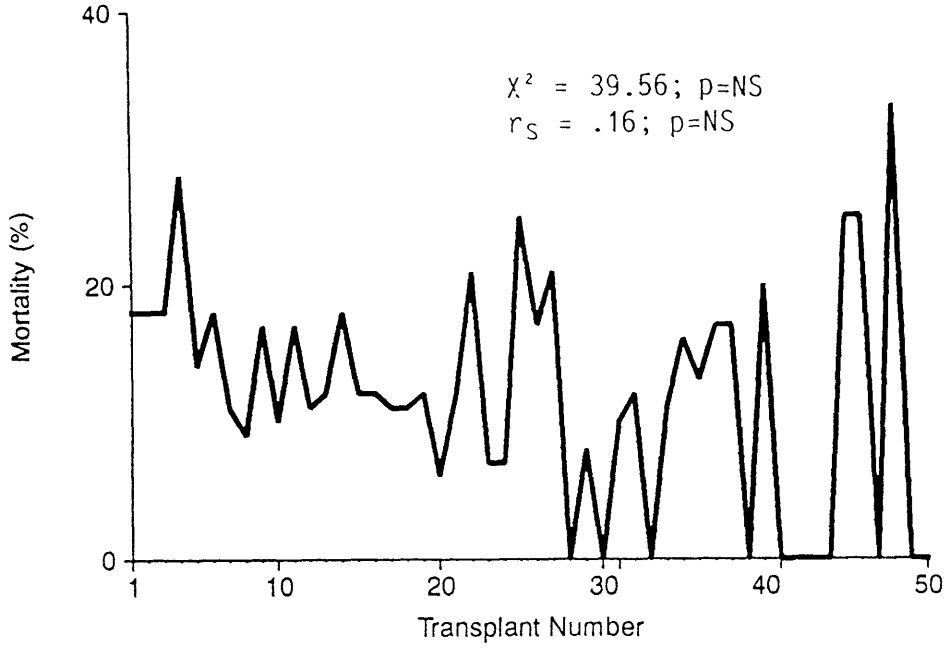


figure 4.2

CUMULATIVE EXPERIENCE AND MORTALITY
FOLLOWING HEART TRANSPLANTATION

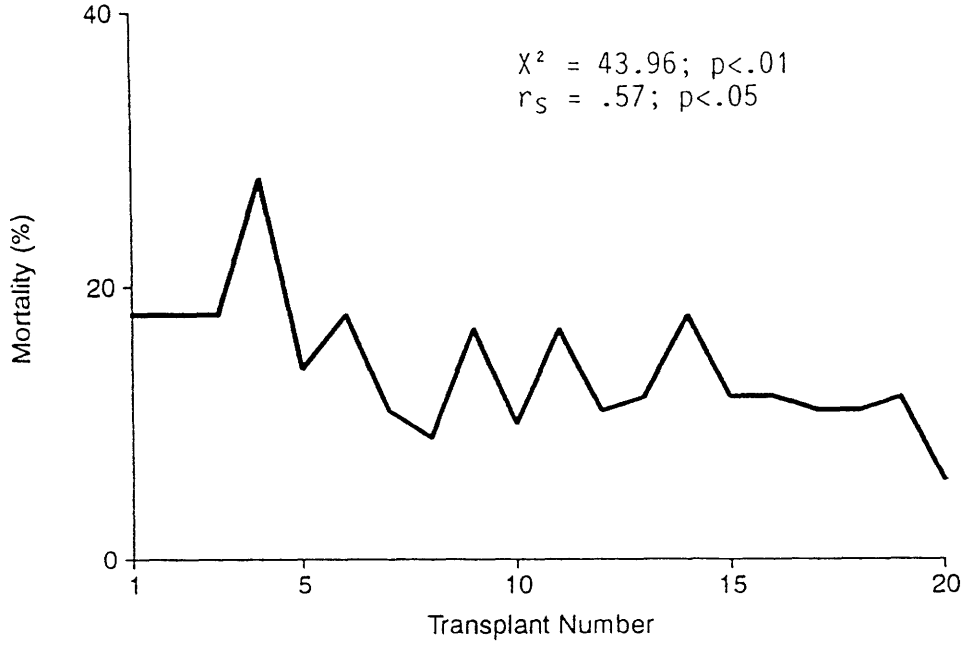


figure 4.3

CUMULATIVE EXPERIENCE AND MORTALITY
FOLLOWING HEART TRANSPLANTATION

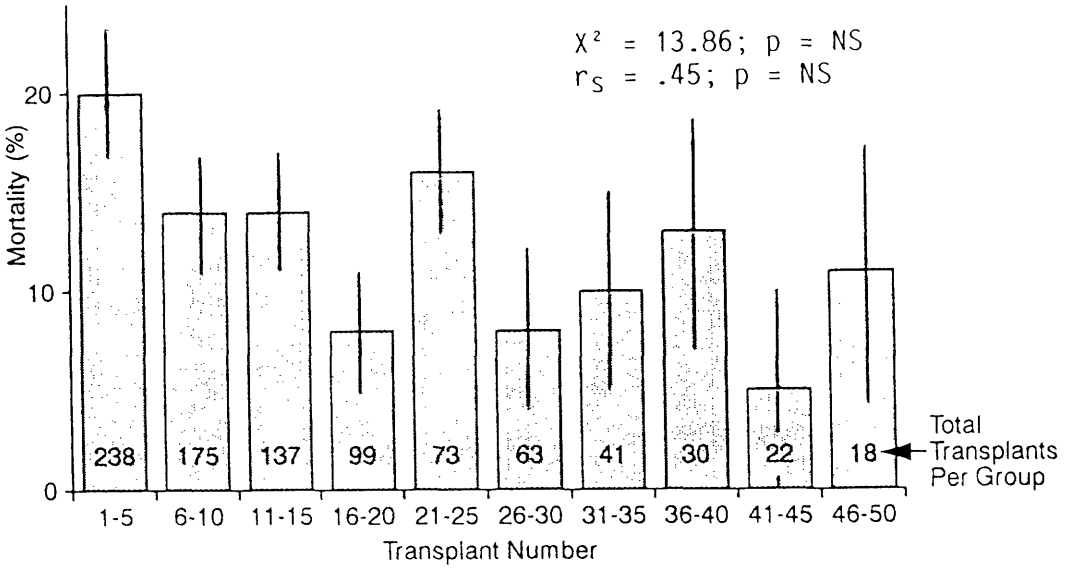


figure 4.4

CUMULATIVE EXPERIENCE AND MORTALITY
FOLLOWING HEART TRANSPLANTATION

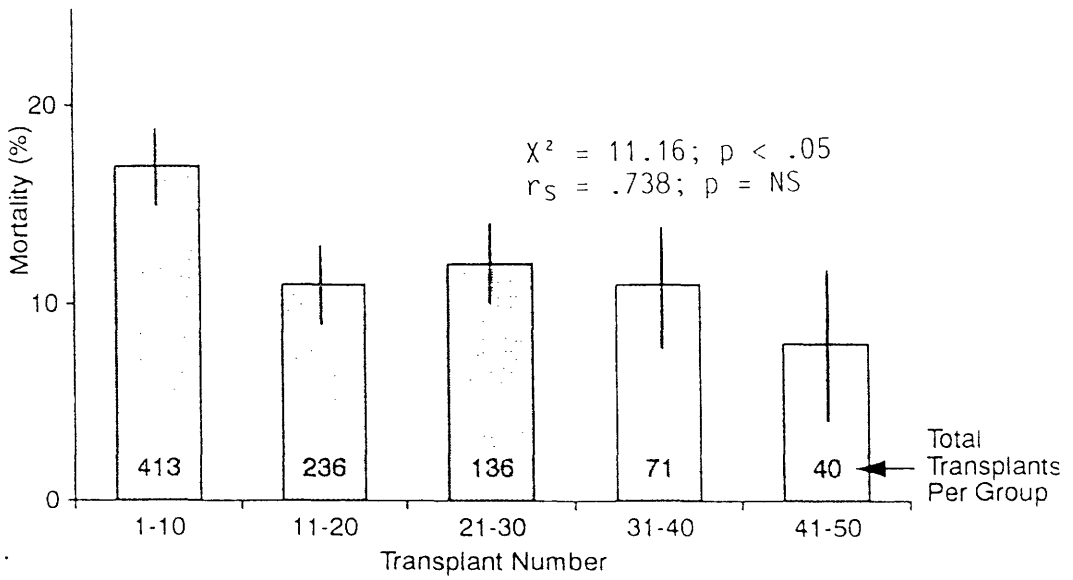


figure 4.5

CUMULATIVE EXPERIENCE AND MORTALITY FOLLOWING HEART TRANSPLANTATION

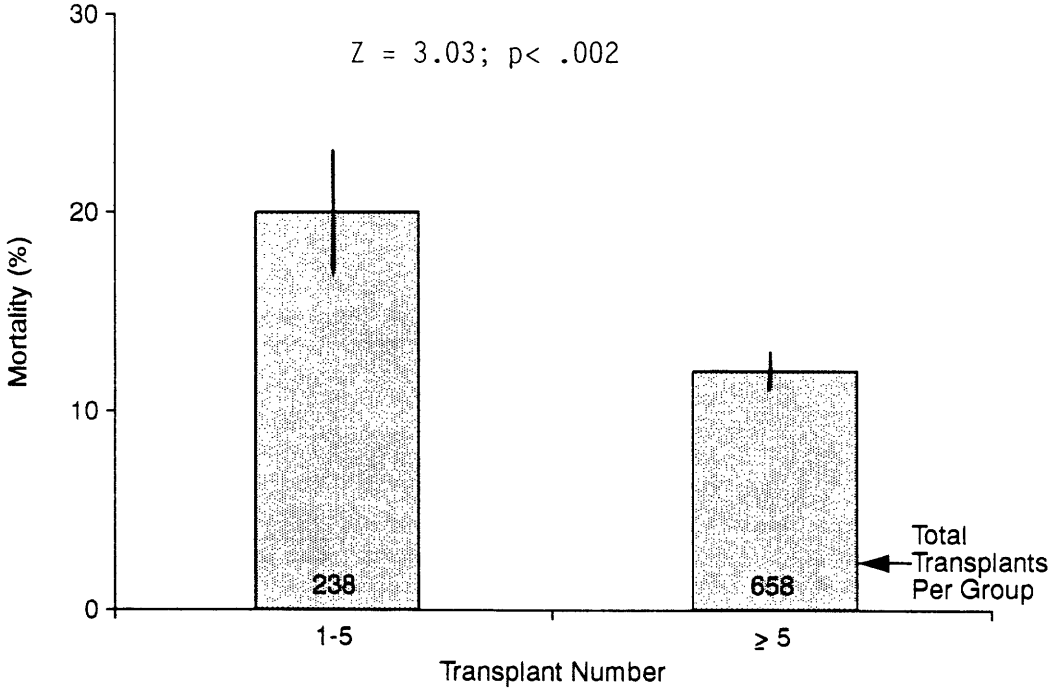


figure 4.6

TRANSPLANT NUMBER AND RECIPIENT AGE

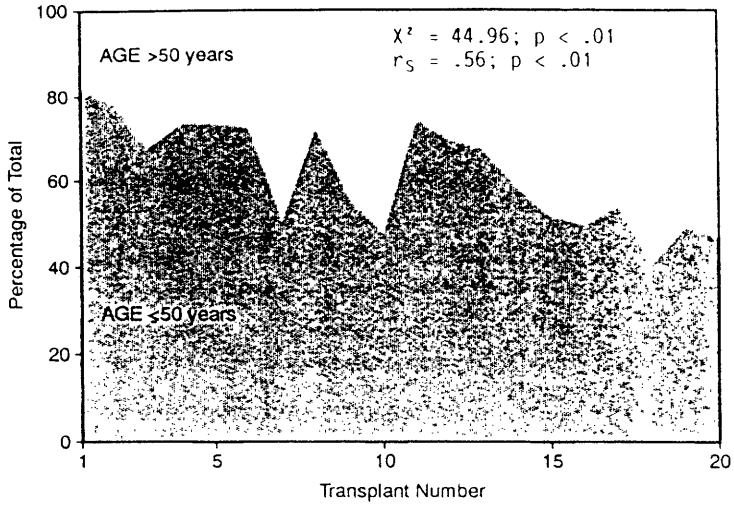


figure 4.7

TRANSPLANT NUMBER AND IMMUNOSUPPRESSIVE THERAPY

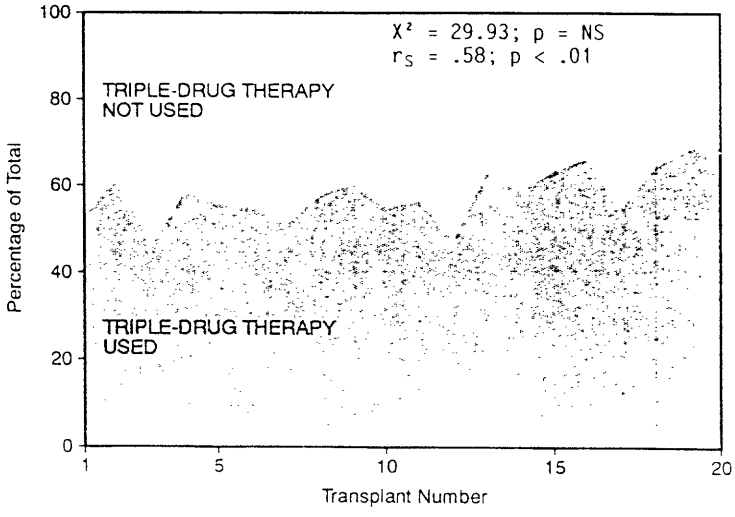
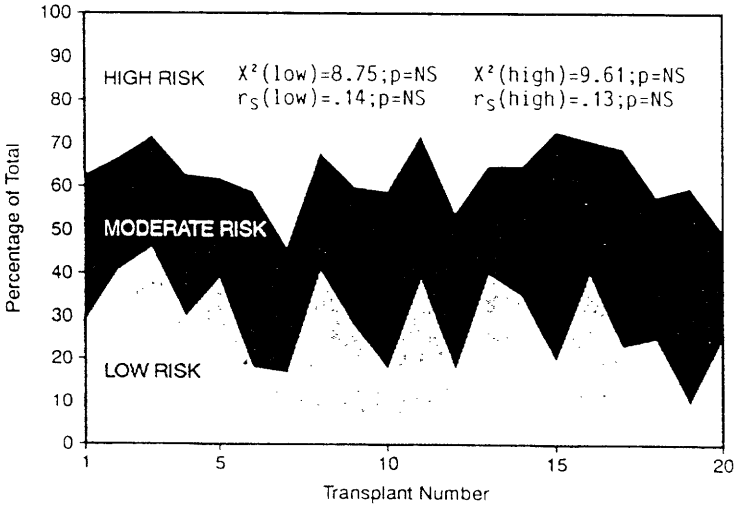


figure 4.8

TRANSPLANT NUMBER AND THE PREMORBID BURDEN OF ILLNESS



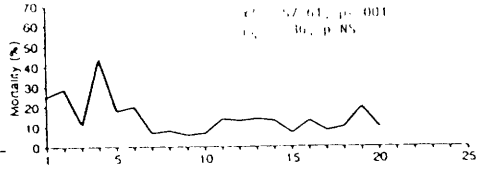
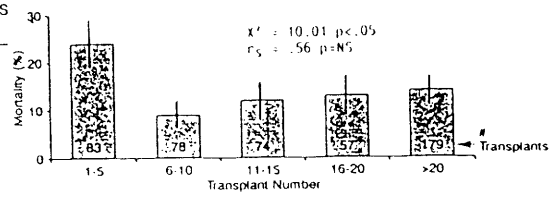


figure 4.9

CUMULATIVE EXPERIENCE
IN CENTERS THAT BEGAN TRANSPLANT PROGRAMS
IN 1984



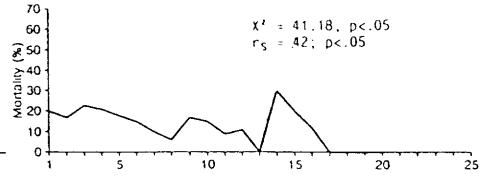
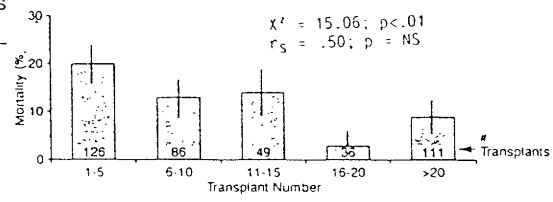


figure 4.10

CUMULATIVE EXPERIENCE
IN CENTERS THAT BEGAN TRANSPLANT PROGRAMS
IN 1985



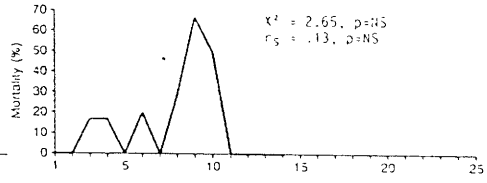


figure 4.11

CUMULATIVE EXPERIENCE
IN CENTERS THAT BEGAN TRANSPLANT PROGRAMS
IN 1986

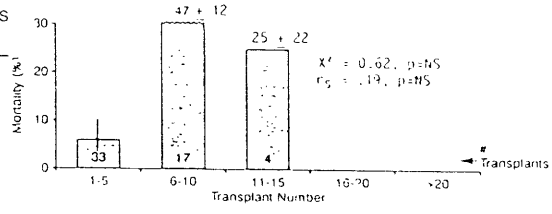


figure 4.13

CUMULATIVE EXPERIENCE
IN MALES

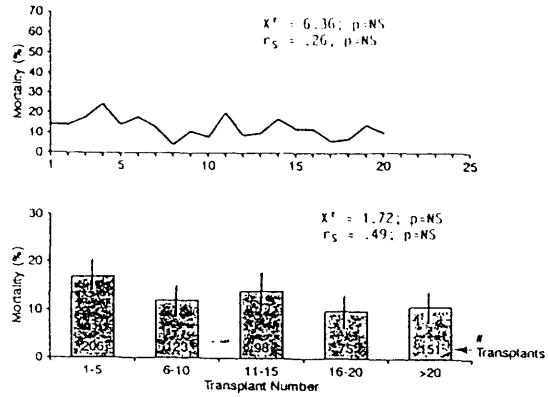


figure 4.14

CUMULATIVE EXPERIENCE
IN PATIENTS RECEIVING
3-DRUG IMMUNOSUPPRESSIVE THERAPY

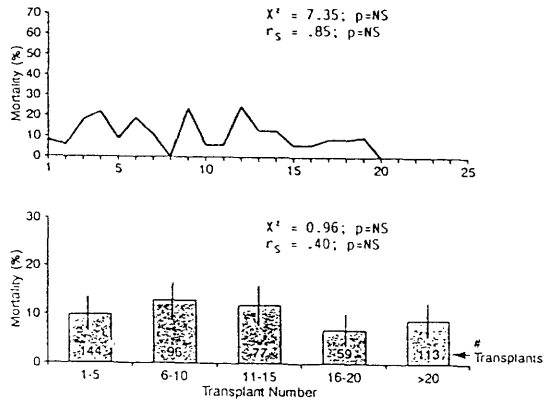


figure 4.15

CUMULATIVE EXPERIENCE
IN PATIENTS
HAVING NO COMORBIDITIES

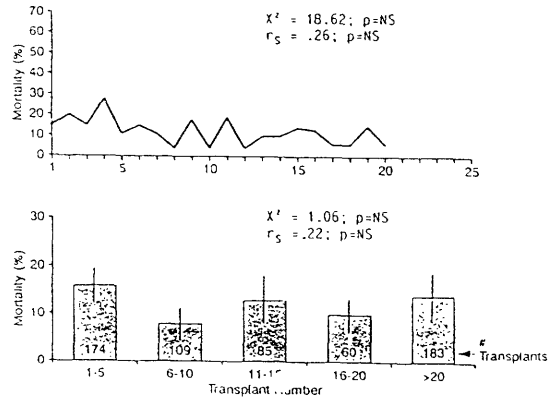


figure 4.16

CUMULATIVE EXPERIENCE
IN FEMALES

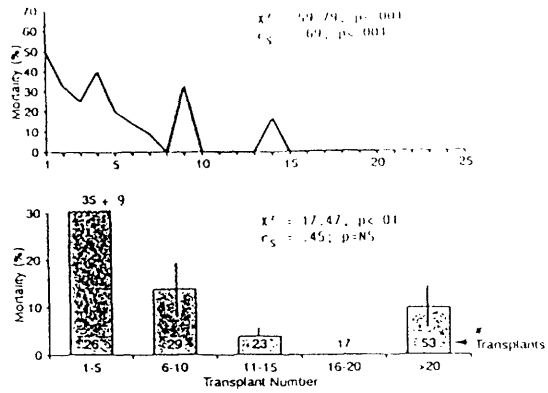


figure 4.17

CUMULATIVE EXPERIENCE
IN PATIENTS NOT RECEIVING
3-DRUG IMMUNOSUPPRESSIVE THERAPY

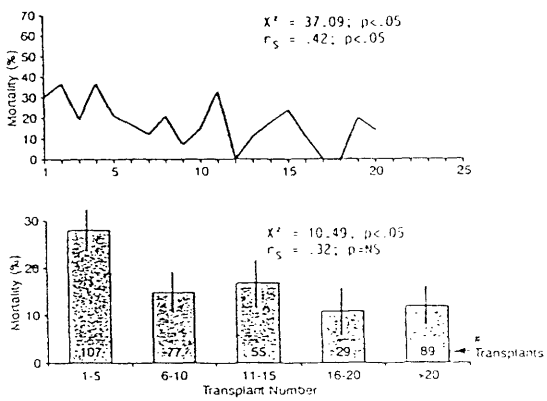


figure 4.18

CUMULATIVE EXPERIENCE
IN PATIENTS HAVING COMORBIDITIES

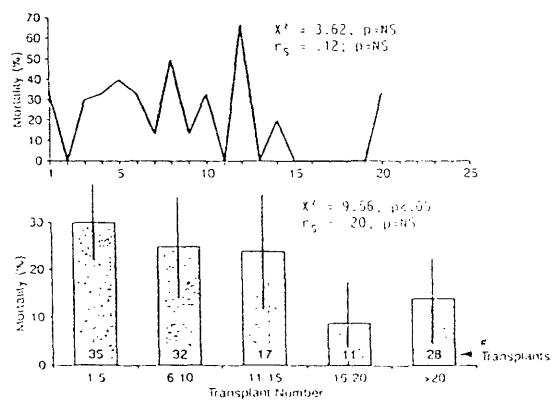


figure 4.19

CUMULATIVE EXPERIENCE
IN PATIENTS WITH SHORT ISCHEMIC TIMES AND
WITH NO PREOPERATIVE MECHANICAL SUPPORT

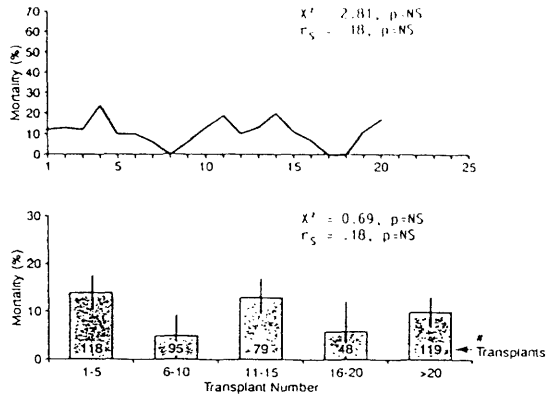


figure 4.20

CUMULATIVE EXPERIENCE
IN PATIENTS WITH LONG ISCHEMIC TIMES OR
PREOPERATIVE MECHANCIAL SUPPORT

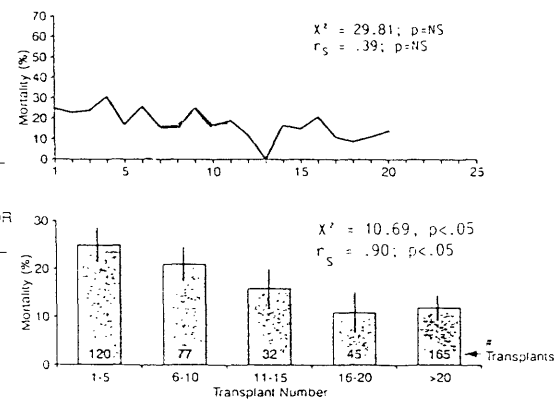


Figure 4.21

CUMULATIVE EXPERIENCE
IN LOW RISK PATIENTS

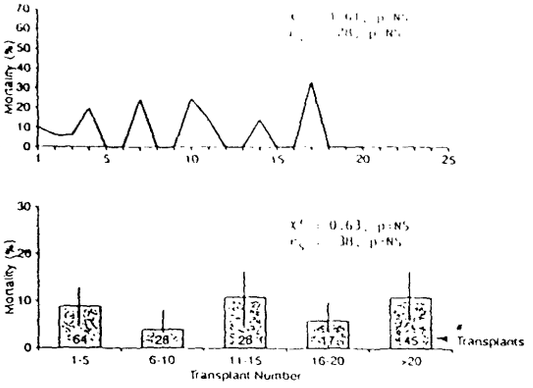


Figure 4.22

CUMULATIVE EXPERIENCE
IN MODERATE RISK PATIENTS

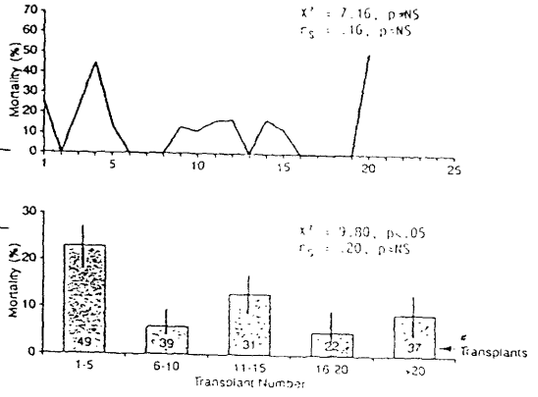


Figure 4.23

CUMULATIVE EXPERIENCE
IN HIGH RISK PATIENTS

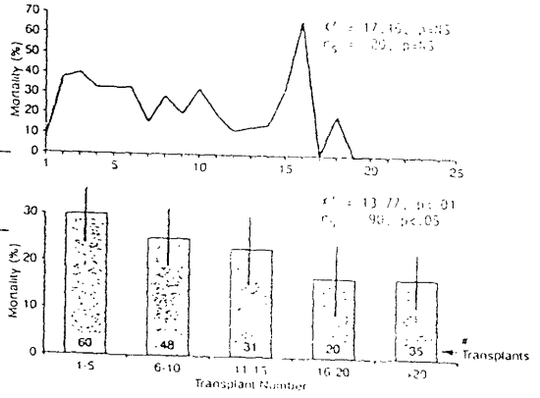


figure 4.24

RESEQUENCING TO ANALYZE HIGH RISK PATIENTS (an illustration)

CENTER A

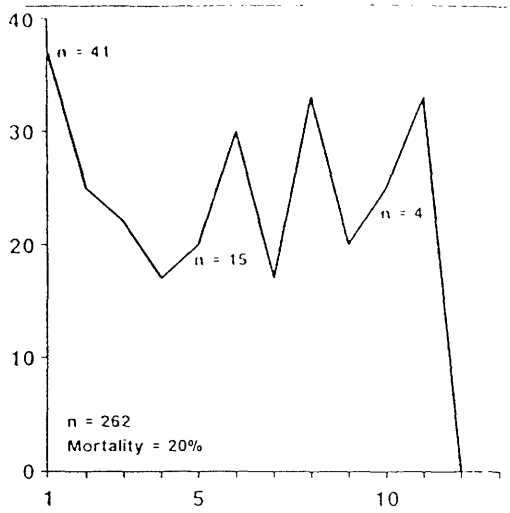
Existing Sequence	1	2	3	4	5	6	7	8	9	10	...
Risk	L	L	H	L	H	H	L	L	L	H	...
New Sequence			1		2	3				4	...

CENTER B

Existing Sequence	1	2	3	4	5	6	7	8	9	10	...
Risk	H	L	H	L	L	L	L	L	H	L	...
New Sequence	1		2						3		...

figure 4.25

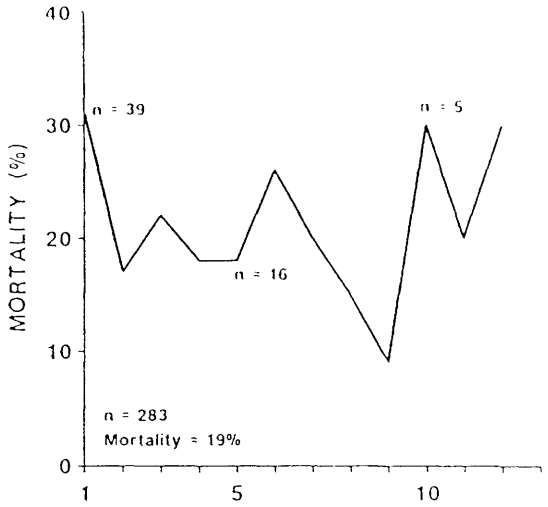
CUMULATIVE EXPERIENCE: LIMITED STUDY ONLY PATIENTS WITH COMORBIDITIES



On average, the first transplanted patient with comorbidities present corresponded to patient number 4 in the complete sequence (see figure 4.24). The range was from patient number 1-16

figure 4.26

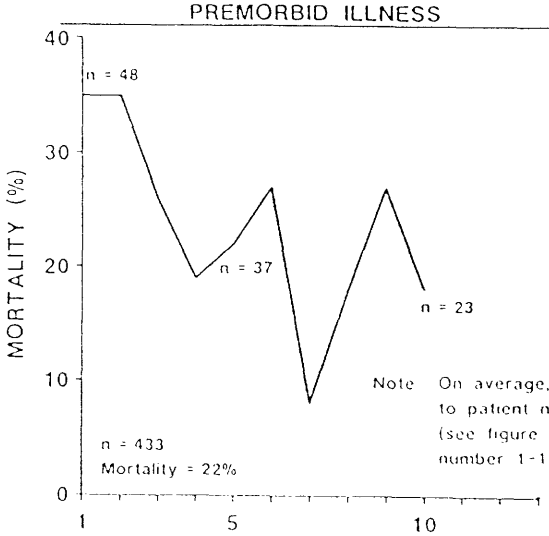
CUMULATIVE EXPERIENCE: LIMITED STUDY ONLY FEMALES



Note: On average, the first female to be transplanted corresponded to patient number 3 in the complete sequence (see figure 4.24) The range was from patient number 1-8

figure 4.27

CUMULATIVE EXPERIENCE: LIMITED STUDY ONLY PATIENTS WITH HIGH BURDEN OF PREMORBID ILLNESS



Note On average, the first such patient corresponded to patient number 4 in the complete sequence (see figure 4.24) The range was from patient number 1-11.

CHAPTER 5

TRANSPLANT VOLUME AND MORTALITY FOLLOWING HEART TRANSPLANTATION (the "Volume-Outcome Relationship")

SUMMARY:

This chapter investigates the hypothesis that there is a relation between the performance of large quantities of heart transplant procedures and mortality following heart transplantation.

KEY POINTS:

- There is no relation between heart transplant volume and mortality.

The results of chapter 4 indicate there is a heart transplant learning curve: transplant centers acquire skills and/or knowledge as they perform their initial procedures, and this experience allows them to improve performance in subsequent procedures.

Recall however that the methods used to identify learning curves lose their analytic power if they are applied to procedures beyond the very earliest in the transplant sequence. One is reminded for example, that the above methods easily detected (in fact, rigorously demonstrated) a learning curve when they were applied to an initial 20 transplant sequence (figure 4.2). However, when these same methods were applied to an extended sequence of 50 initial transplants from

the same data set (figure 4.1), they were unable to detect the phenomenon.

Beyond this, it is important to recognize that learning curves are not the only way to conceive of experience: other descriptors, or proxies, exist as well. One of the simplest and most commonly used proxy for experience is volume, the total number of repetitions of a function or task. Although these two proxies reflect in many cases the same manifestations of experience, there are some important conceptual differences between them. Learning curves tend to emphasize a dynamic process by which providers acquire skills and/or knowledge: the provider learns with each repetition, but the increment learned decreases as the level of accumulated knowledge and/or skills grows. In this model, incremental learning eventually decays to zero and a steady state performance results.

The volume proxy in effect assumes the provider has already achieved this steady state, and instead it tends to emphasize scale: centers that have produced high volumes of certain procedures (and that are likely to produce high volumes in the future) can reorganize their care processes, hire or train specialists and make capital investments that in combination result in improved outcomes.

As one considers these conceptual differences, it is well to remember that Federal heart transplant policy (as it relates to experience) focuses on volume-not learning curves-

as the proxy for experience. Federal heart transplant policy focuses on volume for the compelling reason that the volume-outcome phenomenon has been intensively studied and well documented for many activities in health care[1]. Investigators in this field have focused primarily on surgical procedure volume and its relation to procedure-specific mortality. Most of these investigators have demonstrated that "high volume" centers are characterized by relatively low mortality rates for the procedures in question (32-35).

However, no study has to date documented such a relation in heart transplantation, or for that matter in any form of organ transplantation. Obviously there is a need to document the existence of such a relation in heart transplantation, and if it does exist, to distinguish it in some way from the previously documented learning curve phenomena. Therein lies the goal of this chapter.

I will begin by briefly reviewing the "volume-outcome" literature in health care, and then continue by analyzing my data set to determine whether a volume-outcome relation exists in heart transplantation. I conclude with some further

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[1] And, as mentioned in chapter 4, the medical literature on learning curves is not nearly as well developed. I cannot explain <u>why</u> the latter proxy has received comparatively little attention from the research community. Certainly simple analytical methods exist to study learning curves, as shown in chapter 4. It is equally clear that health care providers implicitly believe learning curves do exist for countless varieties of procedures in health care. I can only comment that this appears to be a fruitful area for research in the future.

observations about volume-outcome relationships in non-cardiac organ transplantation.

VOLUME-OUTCOME STUDIES IN MEDICINE: A REVIEW OF THE LITERATURE

Investigators have found inverse correlations between procedure volume and procedure-specific mortality (the classical, expected "volume-outcome" relationship) to exist for a wide variety of surgical procedures. These include: abdominal aortic aneurysm repair, vascular surgery, biliary tract surgery, appendectomy, coronary artery bypass grafting, total hip replacement, prostatectomy, gastric operations, intestinal operations and hysterectomy. Similar correlations have also been found for non-surgical conditions such as cardiac catheterization and acute myocardial infarction (although as discussed below, the findings are not as compelling for non-surgical conditions-see reference 31)[2].

The nature of this inverse relation varies by procedure. For example, Luft (32) has shown that for coronary artery bypass grafting, the relation is linear: centers that perform low volumes of bypass have the highest mortality; as center

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[2] Luft and colleagues recently reviewed the entire volume-outcome literature in detail. To obtain more detail, the reader should refer to this superb review:
Luft HS, Garnick DW, Mark D, McPhee SJ; Evaluating Research on the use of Volume of Services Performed in Hospitals or by Physicians as an Indicator of Quality; Contractor Document: Office of Technology Assessment; U.S. Congress; Washington, D. C.; 1987.

volume increases, mortality decreases steadily over the entire range of center volumes. For other procedures such as appendectomy, the relation is curvilinear (35): as center volumes increase from very low to low levels, the above inverse relation between volume and mortality is apparent; however, as appendectomy volumes increase from moderate to high levels, no further mortality reductions can be demonstrated.

In characterizing procedures for which a linear volume-outcome relation can be demonstrated, Luft and others (32-37) point out that the slope of this line is procedure dependent. For vascular surgery, eg, the slope is -0.00016 deaths/procedure: on average, a 100 procedure volume increment results in a 1.6% mortality decrease. For transurethral resection of the prostate, the slope of this line is -0.000015 deaths/procedure: the "volume effect" is less apparent.

In characterizing procedures for which curvilinear relations can be demonstrated, investigators point out that the inflection point varies by procedure. For abdominal aortic aneurysm repair, eg, centers performing an annual volume of 50 procedures have roughly the same mortality as centers performing any number greater than this, but an inverse volume-outcome relation is apparent below 50 procedures. For pyloroplasty, this inflection is reached at a procedure volume of about five.

Interestingly, these studies also suggest that:

1) Procedure complexity does not predict the relation between volume and outcome. Thus on one hand, complex operations such as coronary artery bypass graft surgery and vascular procedures and simple operations such as prostatectomy are characterized by a linear relation. On the other hand, other operations-both simple and complex-are associated with curvilinear relations.

2) The type of surgery also does not predict the form of the volume-outcome relation. Thus, coronary artery bypass grafting and abdominal aortic aneurysm repair are both vascular procedures, but the former displays a linear relation, and the latter displays a curvilinear relation.

Perhaps overshadowing these observations, investigators using different data sets have not been able to replicate all the findings mentioned above. Consider coronary artery bypass grafting, the procedure examined most commonly in volume-outcome studies. Most investigators have demonstrated a linear volume-outcome relation for this procedure. However, three studies have demonstrated a curvilinear relation, two have demonstrated a parabolic relation (in which mortality declined, then increased as volume increased) and two were unable to demonstrate any relation between volume and outcome

(31). Equally important, there remain some surgical procedures (repair of femoral fractures and herniorrhaphy, for example) for which investigators have failed more often than not to demonstrate any volume-outcome relation (31).

Volume-Outcome Relations and the Regionalization of Medical Care-Health care planners and policymakers are particularly interested in the results of volume-outcome studies. If these studies had demonstrated consistent, reproducible patterns, then policymakers would have a strong rationale to regionalize care and so increase volume at specified centers.

Unfortunately the above inconsistencies in the literature have to date prevented policymakers from generating an airtight case-at least as it relates to the quality of care-for regionalization. Another rationale for regionalizing certain medical procedures (and simultaneously increasing procedure volume at the designated centers) is that this would result in cost savings due to economies of scale. However despite its obvious appeal, there is little empirical evidence in health care to support this rationale.

But whatever the rationale for regionalization, proponents of the regionalization of health care technologies face several important implementation challenges. First, existing volume-outcome studies have not enabled investigators to determine whether these relationships are due to increased experience ("practice makes perfect") or whether the existing referral system directs patients to providers proven to have

better outcomes (31, 37-39).

This unanswered question carries enormous implications for health care policymakers, and particularly those who have struggled to formulate heart transplant policy[3]. Had investigators demonstrated that "practice made perfect", then regionalization strategies should include a process for selecting centers on a geographical basis and then assuring that they perform large numbers of procedures. Had investigators demonstrated selective referral patterns, then regionalization strategies should simply identify the most proficient centers and designate them (2,31).

The second major challenge facing regionalization strategies (that maximize the "volume benefit") is that procedure volume simply does not tell the whole story about health care outcomes. Not all high-volume centers have good outcomes, and not all low volume centers have poor outcomes (see for example, figure 2.2, chapter 2). The phenomenon in which a cohort of centers having similar procedure volumes displays considerable variation in outcomes is particularly evident among cohorts having low procedure volumes (see figure 2.2).

The explanation for this effect is that there is inherent variability across patients-even with similar diagnoses and treatments-and when this inherent variability is coupled with

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[3] I provide details of heart transplant policy in the Introduction and in chapter 9.

the relatively low rate of adverse outcomes, it becomes statistically difficult (at the level of the individual center) to separate poor performance from random noise in the data. Thus while large data sets and advanced statistical methods can be used to identify the correlation between volume and outcome, they in many cases do not explain performance at the individual center[4].

Yet a third issue on the subject of implementing regionalization policies: it is unclear that centers could cope with the relatively sudden increases in procedure volume that would follow the implementation of such policies. Centers that have achieved excellent results have done so precisely because they have implemented processes that can be executed flawlessly given a certain procedure volume. Stepwise increases in volume could place pressures on these processes that they were not designed to handle.

Policymakers would also require answers to several additional questions before they could effectively use the volume-outcome literature as a basis to formulate regionalization policy. For example, what is the mechanism by which volume-related outcome benefits are mediated? Do high volumes improve performance of the surgeon, the anesthesiologist, recovery room staff, or other personnel in

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[4] A thorough explanation of this issue appears in: Luft HS, & Hunt SS; Evaluating Individual Hospital Quality Through Outcome Statistics; Journal of the American Medical Association; (255)2780-84.

the hospital (31)? Do they simply justify the purchase of specially designed equipment and materials, the recruitment of specialized or highly trained personnel? Or do they encourage hospital personnel to spend time analyzing and improving the processes by which care plans are executed?

The Volume-Outcome Relationship in Heart Transplantation: More Unanswered Questions-The above literature leaves two more questions unanswered, and these questions are particularly relevant to heart transplantation. The first question is, "What is the relation between volume and outcome in 'medical' (i.e. non-surgical) patients?"

The volume-outcome literature is nearly devoid of articles that demonstrate such relations for medical patients. For example, there are only four published articles concerning volume-outcome relations in acute myocardial infarction. Two of these show that high volume centers do better, one shows that high volume centers do worse, and the final one shows no correlation at all (31).

One explanation for the inability to demonstrate volume-outcome relations in medical conditions is that methodological problems prevent them from being detected. It is far more difficult to code the medical records of non-surgical patients than it is to do so for surgical patients. This makes it hard for investigators to develop the precise classification systems required to carry out volume-outcome research. Coding difficulties arise because "medical" patients have more

complex and less predictable courses in the hospital. In addition, they are characterized by multiple diagnoses, coexisting conditions, and reasons for admission to the hospital.

Another explanation is that the confounding features of "medical" conditions and the intricate, highly individualized medical care processes they engender, fundamentally change the relation between experience and outcome such that the expected volume-outcome relations simply do not exist.

The reason why this is important is that the management of heart transplant recipients is dominated after the first several days by non-surgical issues. Recall for example that such patients require lifetime therapy with toxic immunosuppressive drugs, and that the major causes of death following heart transplantation are infection and rejection-conditions which are treated medically[5].

The second question is, "What is the effect of experiences that are acquired during the performance of technically similar procedures?" Recall that most "heart transplant surgeons" perform many more coronary artery bypass operations each year than they do heart transplants. Bypass procedures are technically similar to the heart transplant procedure (and

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[5] An obvious place to look for insights regarding this question is the volume-outcome literature for non-cardiac organ transplantation. In fact, there is a rather well-developed volume-outcome literature for kidney transplantation. I have chosen to review this (at the end of this chapter) following a review of this study's results.

most cardiovascular surgeons believe the former are actually more demanding than the latter). It is extremely likely that "transplant surgeons" generate knowledge and/or skills as a result of performing bypass operations that can be generalized to the transplant procedure. This certainly could affect the relation between heart transplant volume and mortality following the transplant procedure. It is with these ideas and concepts in mind that I now present the findings of this study.

THE VOLUME-OUTCOME RELATIONSHIP IN HEART TRANSPLANTATION: RESULTS OF THIS STUDY

During the years 1984-1986, United States heart transplant centers displayed wide variation in transplant volume-the total number of transplants performed per center (figure 5.1). Specifically, transplant volume per center ranged from 207, at the University of Pittsburgh, to one at several centers.

As shown in figure 2.2 (chapter 2), center-specific transplant volume during the three year study period is not correlated with mortality ($r=-.04$; $t_{(df=60)}=.276$; $p=.78$[NS]). This finding is extremely important in that it is not consistent with the majority of findings in the literature, and that it does not support Medicare guidelines for the certification of heart transplant centers. Therefore, I will explore this finding in some detail, and in particular I will explore the possibility that a true volume-outcome relation

may somehow be hidden in this broad analysis.

It is possible, for example, that the effects of cumulative experience (discussed in chapter 4) may have biased this analysis. This is because low volume centers will have a higher proportion of recipients that have undergone transplantation before the centers have accumulated skills and knowledge pertaining to the transplant procedure. I explore this possibility by omitting the results from the first 10 transplants at all centers, and then repeating the above analysis. The resulting scatter diagram (figure 5.2) also shows no clear relation between total transplant volume and mortality, and the correlation coefficient remains extremely low and not significant[6].

It is also possible that a valid volume-outcome relation could be present in certain subsets of the data set, but not in others. I explore this possibility by performing separate analyses for several representative subsets, and the results again show no demonstrable volume-outcome relationship. I will review these results in detail presently.

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[6] NOTE: The remaining scatter diagrams in this chapter include <u>all</u> patients, not just those beyond transplant number 10. However in all cases, I did run similar analyses in which I omitted these first 10 transplants. <u>In no case</u> did this technique expose a volume-outcome relation when it was not present in the analysis of the complete data set. In one case, discussed below, omitting the first 10 transplants from the analysis actually obliterated a strong trend towards a significant volume-outcome relation.

Figures 5.3 and 5.4 show separate analyses for centers that began performing heart transplants in 1984 and 1985, respectively. There is no volume-outcome correlation in either subset. Interestingly, there is a strong trend in the expected direction (low volumes, high mortality) in the 1985 data set ($r=-.36$; $t_{(df=27)}= 1.99$; $p=.06$[NS]). However, when I eliminate transplant numbers 1-10 and repeat the analysis, the strong trend disappears to a large degree ($r=-.29$; $t_{(df=12)}=1.44$; $p=.21$[NS]).

As discussed earlier, the technique of removing from the analysis all transplants that were performed early in each center's sequence has the effect of eliminating the confounding effects of the learning curve phenomenon. As demonstrated in this particular case, it also reduces sample size by eliminating all centers that performed less than ten transplants in total. It is worth repeating that at these low volume centers, it is statistically difficult to separate poor performance from random noise in the data and this provides another reason to run parallel analyses (such as this one) that specifically eliminate this "end effect".

Figures 5.5 and 5.6 are scatter diagrams displaying once again a lack of correlation between heart transplant volume and mortality. In this case, the subsets are males and females, respectively. Interestingly, there is a strong trend towards a <u>direct</u> relation (high volume, high mortality) in the female subgroup ($r=.25$; $t_{(df=53)}=1.85$; $p=.07$[NS], see figure

5.6). However, it is apparent that this "trend" is largely driven by one aberrant observation. When I eliminate this observation and repeat the analysis, the "trend" vanishes completely ($r=.06$; $t_{(df=52)}=.49$; $p=.63$[NS]).

This aberrant observation comes from the University of Pittsburgh, which had the highest total transplant volume during the study period. I doubt this represents a coding error, but I can think of no plausible explanation for high mortality among females at this particular center.

Figures 5.7 to 5.13 provide additional proof that there is no relation between heart transplant volume and mortality. These figures represent further subset analyses, including patients treated with and without triple drug immunosuppressive therapy, patients having and not having comorbid conditions, and patients with a low, moderate and high burden of illness. Analyses of other patient subsets also show no relationship, and these are available on request.

As a final test of the relation between total transplant volume and mortality, I reaggregate the center-specific data into three larger groups: high volume centers, moderate volume centers, and low volume centers. This technique minimizes the statistical difficulties (described earlier) associated with the assessment of quality at low volume centers.

In the "high volume" category, I include the top five centers in terms of transplant volume during the study period (see figure 5.1). These five centers performed between 91-207

transplants per center over the study period (for a total of 643), and all had completed at least 20 transplants prior to 1984. In the "low volume" category, I include the 40 centers that performed the fewest transplants per center over the study period. No center in this category performed more than 25 transplants in total, and 24 of them performed less than 10 transplants in total. This group transplanted a total of 410 patients during the study period. The remaining 25 centers constitute the "moderate volume" category. This group performed 952 transplants between 1984-1986.

The results are as follows:

MORTALITY FOLLOWING HEART TRANSPLANTATION (%): HIGH, MODERATE AND LOW VOLUME CENTERS

OVERALL MORTALITY:

High Volume	**15 (643)**
Moderate Volume	**12 (952)**
Low Volume	**19 (410)**

VOLUME CATEGORY	MALE	FEMALE
High	13 (558)	28 (85)
Moderate	12 (818)	20 (134)
Low	19 (346)	22 (64)

	USE 3 DRUG	NOT USED
High	11 (266)	19 (377)
Moderate	10 (576)	20 (376)
Low	15 (230)	25 (180)

-CONTINUED ON NEXT PAGE-

	NO COMORBIDITIES	COMORBIDITIES
High	15 (572)	17 (371)
Moderate	13 (678)	24 (274)
Low	17 (362)	29 (48)

	LOW BURDEN	MODERATE BURDEN	H I G H BURDEN
High	13 (94)	12 (147)	19 (156)
Moderate	14 (144)	15 (119)	18 (130)
Low	11 (92)	17 (94)	25 (147)

As one can see, overall mortality is 15% in the high volume centers, 12% in the moderate volume centers and 19% in the low volume centers. There are no significant differences between the mortality rates in these groups, and the absence of a trend toward decreasing mortality with increasing transplant volume is yet another piece of evidence mitigating against a significant volume-outcome relation in heart transplantation.

Upon closer inspection, one notes that low volume center mortality rates are highest in all but two of the subcategories shown (females, and low burden of illness). However, based on previous analyses, it is reasonable to attribute this effect to learning curve phenomena. And of great importance, these subgroup analyses reveal no consistent relation between mortality rates at moderate and high volume centers, respectively. Once again, there is no evidence to support the existence of a volume-outcome relation in heart transplantation.

In sum, there is little doubt that volume-outcome relations do not exist in this data set. This finding is to some extent unexpected, as most studies of surgical procedures suggest that such relations are present. It carries important implications for Medicare heart transplant center designation policies, because they are based on an apparently invalid assumption that such relations do exist. Should this finding have come as such a surprise? Perhaps not!

It turns out that there is a relatively well-developed volume-outcome literature covering the field of non-cardiac organ trans-plantation (primarily kidney transplantation), and not one study in this literature could demonstrate significant correlations. (In fairness to Medicare policymakers, several of the most important articles in this field became available after they formulated their policies)[7].

For example Opelz et. al. (9a) in an early study, found no evidence that one-year graft survival rates were lower in low volume kidney transplant centers. Many centers in this study

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[7] A detailed review of this literature is provided in: Sloan FA, Shayne MW, Doyle MD; Is There a Rationale for Regionalizing Organ Transplantation Services?; in Blumstein JF, Sloan FA, eds.; Organ Transplantation Policy; Duke University Press; Durham, 1989. My review of this subject is largely based upon this reference.

was characterized by low transplant volumes and hence high variations in outcomes. Opelz' group attributed these variations to random fluctuations. The authors did not account for other factors that could affect graft survival in this study.

Krakauer et. al. (9b, 9c) used a Cox proportional hazards model and found significant "center effects" existed and these persisted after controlling for patient and donor characteristics such as the use of cyclosporine, race, recipient age, blood transfusions prior to transplantation and tissue match. However, these effects could not be attributed to volume differences between centers.

Cicciarelli (7) assessed graft survival at 80 centers that had performed at least 100 kidney transplants. He classified centers into three categories according to their graft survival rates-excellent (>55%), good (45-55%), and fair (<45%). He found that "excellent" centers utilized pretransplant blood transfusions more frequently, tissue typed at the DR locus in a higher percentage of their patients, and matched HLA-A,B histocompatibility loci comparatively frequently[8]. These procedural differences were sufficient to explain the "center effect" in this group of centers that was

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[8] In a parallel finding of great interest, Cicciarelli found that cyclosporine therapy resulted in an increase in graft survival in excellent centers, but had a neutral effect in fair centers. This finding suggests that excellent centers are characterized by learning curves with respect to the use of cyclosporine.

relatively homogenous with respect to volume.

Benlahrache et. al. (9d) applied methodologies similar to Cicciarelli's, but they used a data set that was more recent and that included more low volume centers. They were able to confirm Cicciarelli's findings using this data set, and they also showed that center-specific graft survival was not affected by center-specific (first) transplant volume.

Finally, Held et. al. (9) very directly assessed the effect of kidney transplant volume on patient and graft survival after controlling for more than a dozen characteristics of patient, donor and center. The authors used a set of binary variables to represent the number of transplants performed per year at each center. The parameter estimates for the volume variables were small, and in all cases the standard errors exceeded the parameter estimates.

With this literature in mind, the results of the present study appear somewhat less surprising. In fact, given that:

1) heart transplant surgeons readily admit that these procedures are technically simpler than the coronary bypass procedures and that,

2) they perform the latter with far more regularity than heart transplantation, and that

3) medical follow-up for heart transplant recipients is complex and prolonged,

it might be reasonable to classify heart transplantation <u>not</u> as an exception to the otherwise consistent volume-outcome

literature for surgical procedures, but as another example of a medical procedure for which volumes and outcomes do not appear to be correlated. I will develop this discussion further in chapter 9.

figure 5.1

TRANSPLANT VOLUME VARIATIONS IN U.S. HEART TRANSPLANT CENTERS (1984 - 1986)

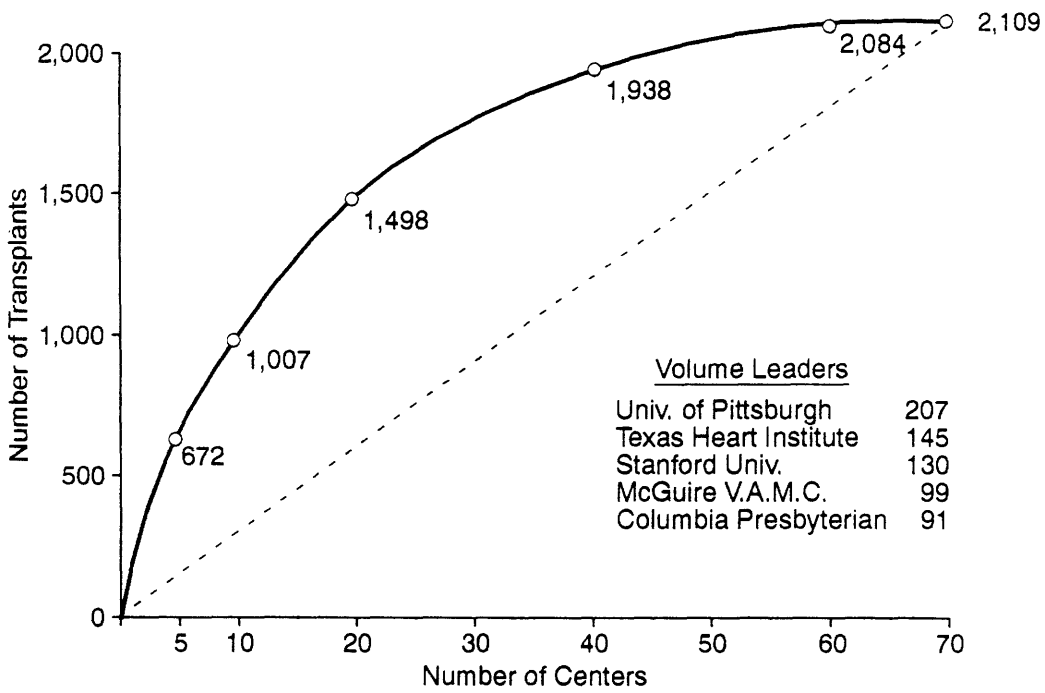
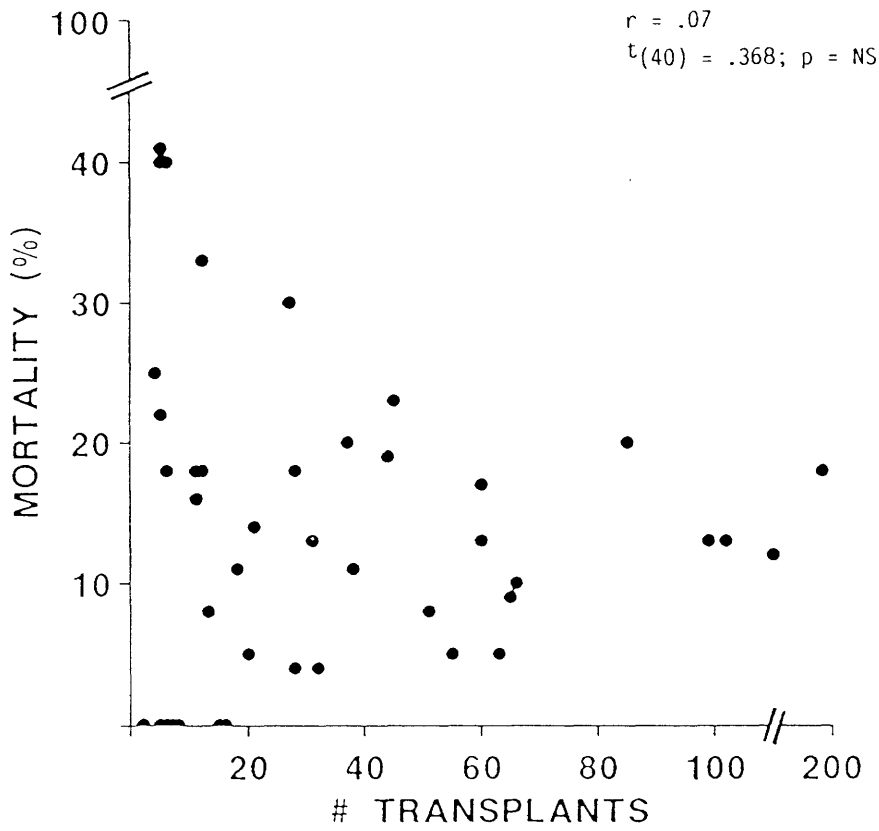


figure 5.2

TRANSPLANT VOLUME AND MORTALITY*



*does not include data from first 10 transplants at each center

figure 5.3

TRANSPLANT VOLUME AND MORTALITY

(1984 Start-up Centers)

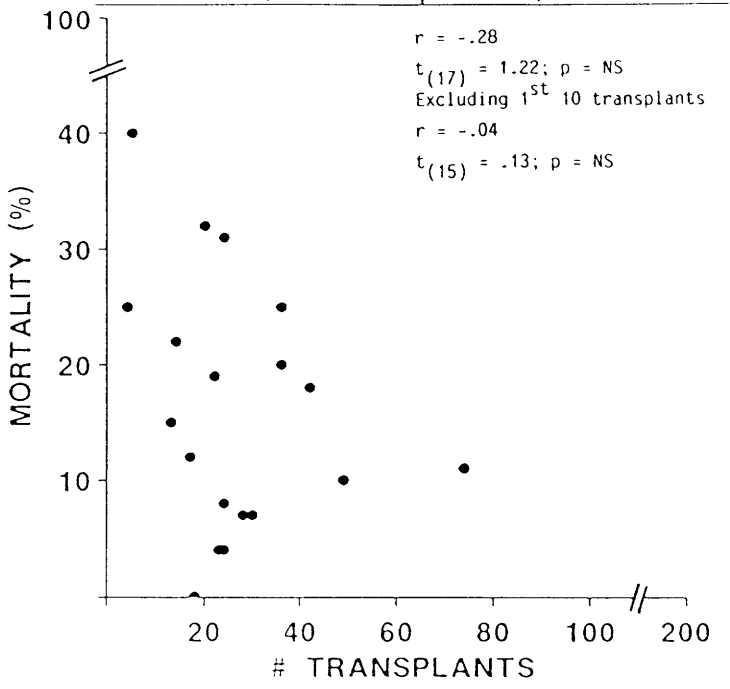


figure 5.4

TRANSPLANT VOLUME AND MORTALITY

(1985 Start-up Centers)

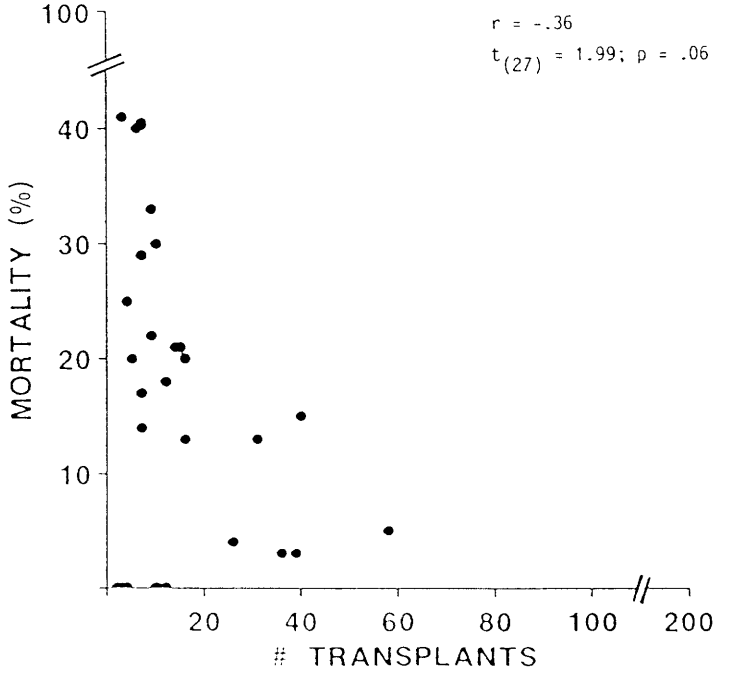


figure 5.5

TRANSPLANT VOLUME AND MORTALITY
(in Males)

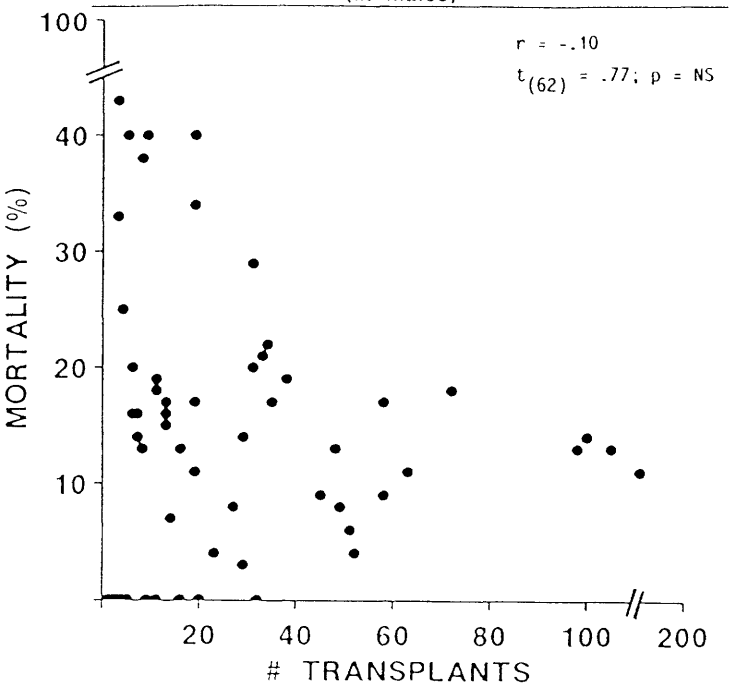


figure 5.6

TRANSPLANT VOLUME AND MORTALITY
(in Females)

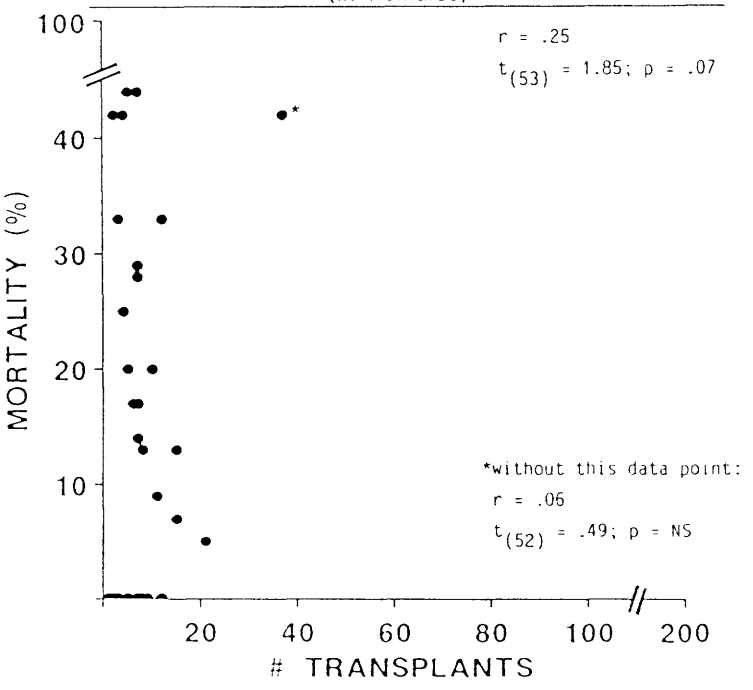


figure 5.7

TRANSPLANT VOLUME AND MORTALITY

(in patients receiving triple drug immunosuppressive therapy)

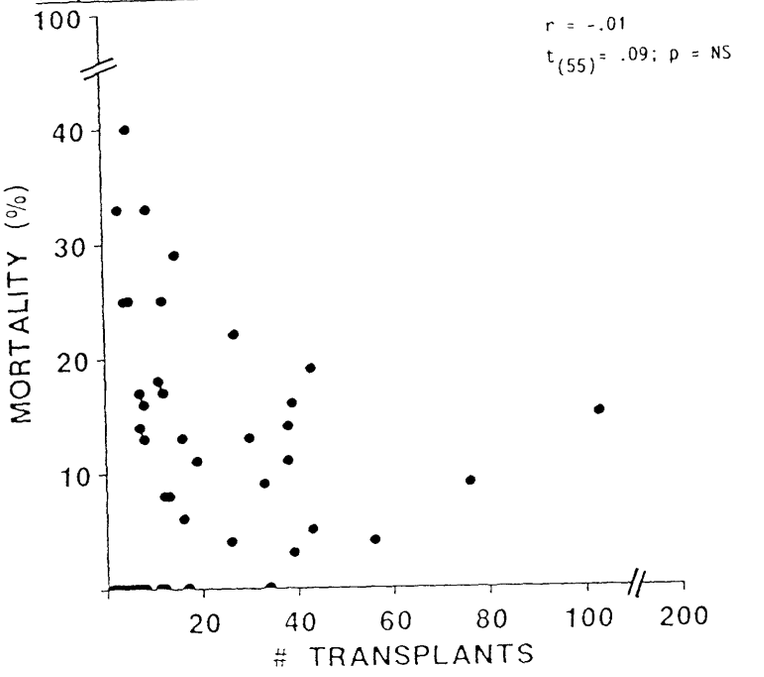


figure 5.8

TRANSPLANT VOLUME AND MORTALITY

(in patients not receiving triple drug immunosuppressive therapy)

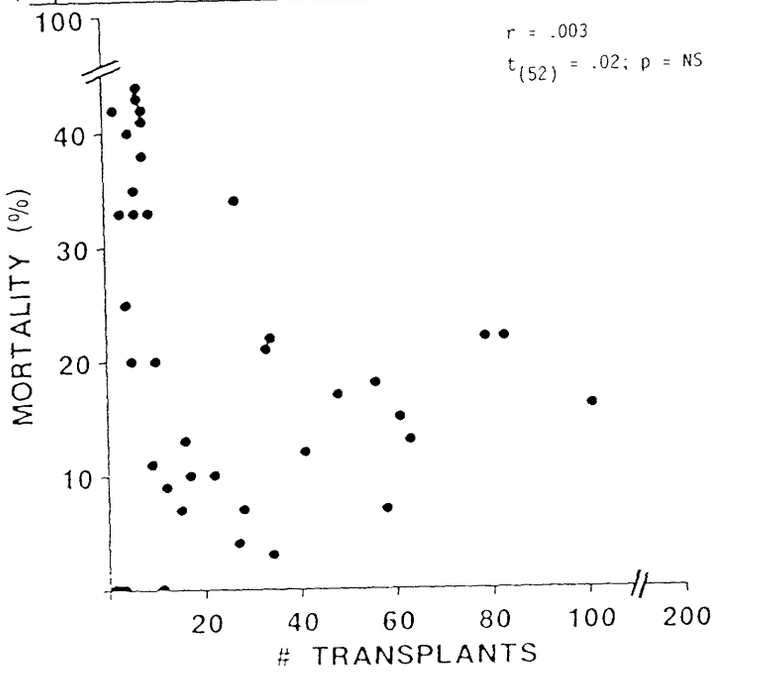


figure 5.9

TRANSPLANT VOLUME AND MORTALITY

(in patients without comorbidities)

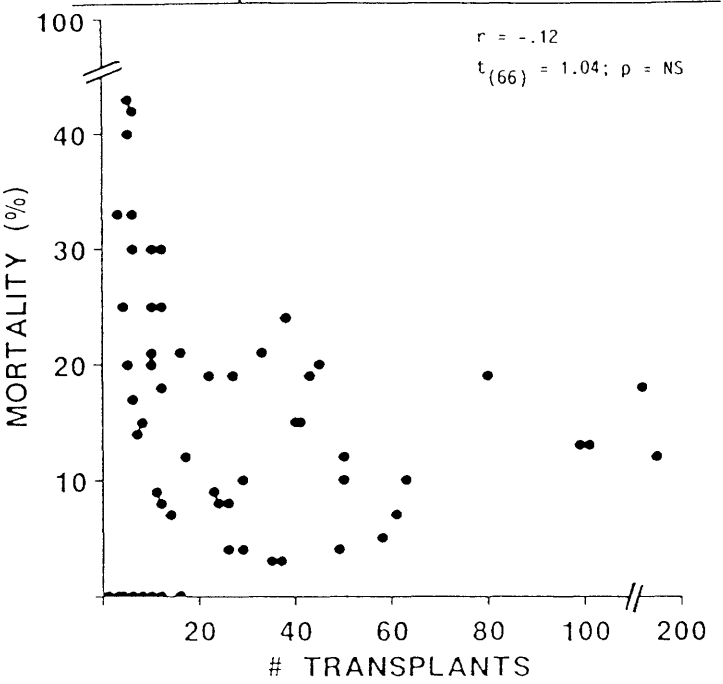


figure 5.10

TRANSPLANT VOLUME AND MORTALITY

(in patients with comorbidities)

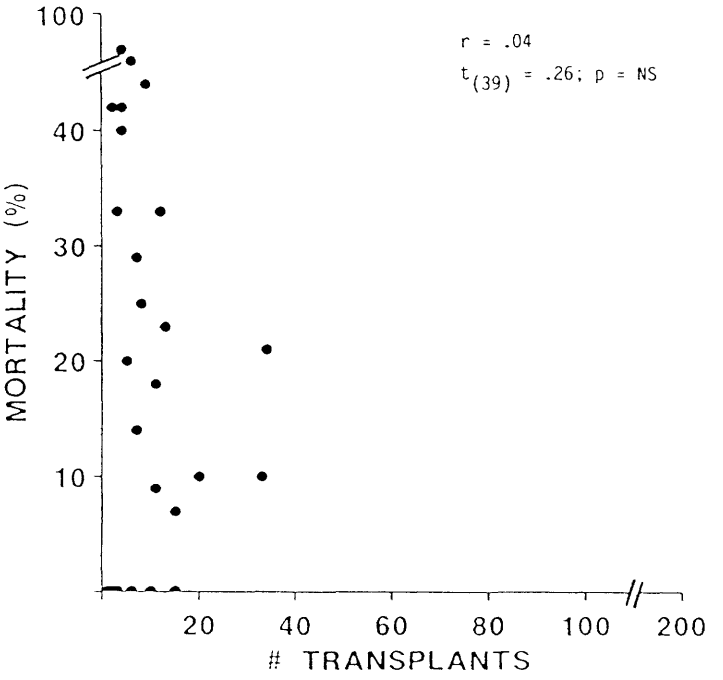


figure 5.11

TRANSPLANT VOLUME AND MORTALITY

(low burden of illness)

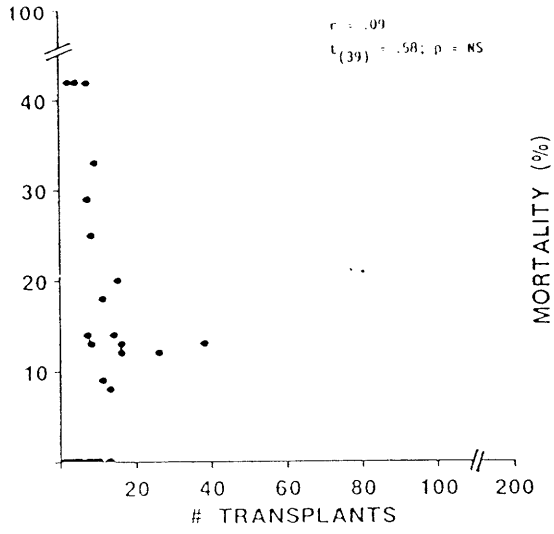


figure 5.12

TRANSPLANT VOLUME AND MORTALITY

(moderate burden of illness)

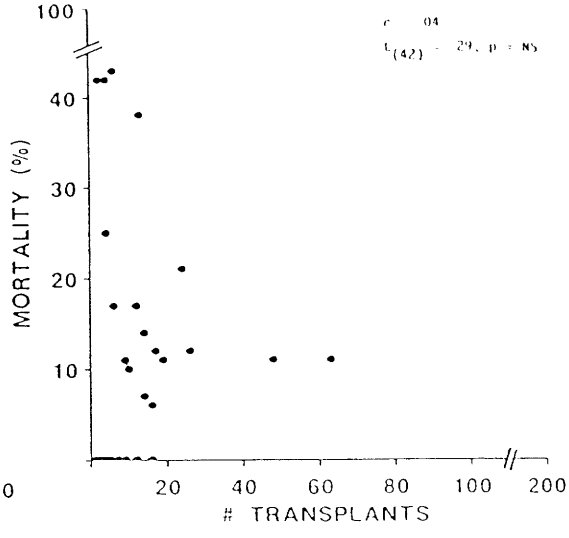
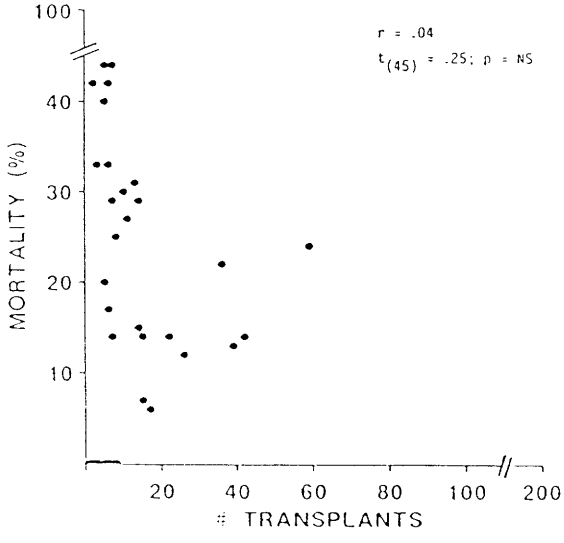


figure 5.13

TRANSPLANT VOLUME AND MORTALITY

(high burden of illness)



CHAPTER 6

PROCEDURE FREQUENCY AND MORTALITY FOLLOWING HEART TRANSPLANTATION

SUMMARY:

This chapter investigates the hypothesis that the rate at which heart transplants are performed is associated with mortality.

KEY POINTS:

- The rate at which centers perform heart transplants accelerates with increasing transplant number.

- Over the range of observed transplant rates, there is no relation between transplant rate and mortality.

Results presented in chapter 5 suggest there is no relation between heart transplant volume (defined as the total number of transplant procedures) and mortality. Transplant rate is a measure of experience that is closely related to transplant volume. It is defined as the number of transplants performed per unit time. In this chapter, I explore the relation between heart transplant rate and mortality following the procedure.

Many investigators have appropriately chosen not to distinguish between these two indices of experience. It is not necessary to make the distinction when studying technologies for which indications have been well established, and for which utilization does not change over time. When procedure

volumes remain constant over time, one gleans no additional information by using the rate proxy (volume/time) versus the volume proxy alone[1].

In a study of heart transplantation between the years 1984-86 however, it is necessary to distinguish between these two proxies. This is because utilization nearly doubled over this three year period (figure 3.1) and as shown below, this overall increase reflects in part an accelerating transplant rate at existing centers[2]. In addition, there is reason to believe that the rate at which centers perform heart transplants can affect their ability to benefit from previous experience. For example, high transplant rates may afford providers the opportunity to practice transplant-specific skills, and diminish the possibility that these skills will extinguish over time. In addition, high rates may encourage providers to experiment with new procedures and techniques that could lead to improved outcomes. They may stimulate

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[1] Interestingly, Luft and colleagues actually utilized a measure of procedure rate in their seminal article on the "volume-outcome" relationship (4)! They compared "annual procedure volume" with mortality.

[2] From an analytical standpoint, technologies exhibiting a changing procedure rate are difficult study because there is no easy way to determine whether outcomes in a particular period are referable to volumes in that period or to volumes in an earlier period. This problem is, of course, eliminated when procedure volume remains constant over time.
(Again one is struck by the excellent fit, at a conceptual level, between the learning curve proxy and the dynamic events surrounding heart transplant technology circa 1984-86.)

providers to learn about the technology more quickly and more thoroughly than they otherwise would have done. They may provide justification for providers to purchase specially designed equipment and materials. Finally, they may facilitate the recruitment of specialized or highly trained personnel, or the development of better protocols for the management of transplant recipients.

On the other hand, high transplant rates may place excessive demands on transplant team members and increase the likelihood that miscommunications will occur and that critical information will be overlooked or misinterpreted.

To investigate the relation between heart transplant procedure rate and mortality, I calculate the MEAN INTERTRANSPLANT INTERVAL for each center. This measure of procedure rate is equal to the number of days between the first and last transplant divided by the total number of transplants performed during the study period. Short intertransplant intervals reflect high transplant rates.

After determining the mean intertransplant interval for each center in the data set, I find that indeed there is a strong positive correlation between this interval and center-specific mortality, as shown in figure 6.1 ($r=.35$; $t_{(df=65)}=2.98$; $p<.005$): mortality declines as procedure rate increases.

However, as was the case in chapter 5, I must generate secondary analyses which control for the concurrent effects of cumulative experience. This is because transplant rate and

cumulative experience are almost certainly related to each other[3].

For these secondary analyses, I again limit study to "new" transplant centers: those first offering the transplant service during 1984-86. In this cohort, I generate subsets having identical levels of cumulative experience. I then divide each subset into quartiles according to their transplant rates, and calculate mortality for each quartile. I repeat this analysis of rate in subsets matched for the experience gained through transplant numbers 6 , 11, and 21.

For example, a group of transplant centers can be thought of as having achieved identical levels of cumulative experience at the point when each has completed its sixth transplant[4] (regardless of the specific date when this occurs and regardless of the date when each center began its program). However, the centers in this group will differ in the rate at which they achieved this level of experience. If

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[3] To understand why these variables are almost certainly related, recall that many centers have patients awaiting heart transplantation. When a donor organ becomes available, an organ procurement agency determines which patient should receive it. The agency selects the "proper" patient on the basis of its careful review of the waiting lists from all transplant centers affiliated with that agency. New transplant centers have relatively few candidates on their waiting lists, so a patient from these centers is not likely to be chosen. As a consequence, new centers are likely to experience low transplant rates. However as these new centers evaluate and list more patients, someone from their lists is more likely to be selected, and hence their transplant rate increases.

[4] The equivalent of five intertransplant intervals.

rate is an important determinant of mortality, then the mean intertransplant interval should be correlated with mortality in these centers that are matched for cumulative experience.

The results of this analysis are as follows:

1) Intertransplant intervals vary dramatically from center to center. Figure 6.2, a sample of raw data from 1984 start-up centers, shows this variation. Figure 6.3 summarizes the results of this analysis for the entire set. The latter shows for example, that over the period in which centers performed their first six heart transplants (five intertransplant intervals), 1984 start-up centers had a mean intertransplant interval of 56 days, with a range of 23-83 days.

2) Despite this considerable variation, centers display a significant decrease in the mean intertransplant interval over the three periods mentioned above (transplant intervals 1-6, 6-11, 11-21, see figure 6.3)[5]. Further evidence in support of this finding includes:

- Of the 19 centers for which intertransplant intervals can be determined for all three periods, 12 exhibit a pattern of continuing transplant rate acceleration over these periods.
- All but 2 centers experience their longest intertran-

[5] $Z\ (u_{(1-6)}-u_{(6-11)}) = 2.26$; $p<.05$. Other comparisons of the mean intertransplant intervals presented in figure 6.3 also show that the results are highly unlikely to have occurred by chance.

splant intervals in the first period (transplants 1-6).

- Of the 12 centers for which data is available only through the second period, 9 exhibit accelerating transplant rates from the first to the second period.

3) The relative rates at which centers perform transplants do not remain fixed from period to period (figure 6.4). For example, the intertransplant interval of center 30 is among the shortest during the second period (transplant numbers 6-11), but it is among the longest during the subsequent period (transplant numbers 11-21).

4) <u>There is no apparent relation between the intertransplant interval (ie. transplant rate) and mortality when the effects of cumulative experience are controlled</u>. This is seen most clearly in figure 6.4. This figure shows six separate analyses of the relation between transplant rate and mortality in subgroups having identical levels of cumulative experience. If transplant rate did have an independent effect on mortality, then one would expect a fairly consistent pattern such that centers in the fastest quartile (those with the fastest transplant rates) would have the lowest mortality.

This pattern is not present. In fact, in only one of the six analyses (1985 start-up centers, transplants number 1-6) do centers in the fastest quartile experience the lowest mortality rates. In the remaining five analyses, centers in the remaining three quartiles all share honors at least once

for having the lowest mortality rates. At the other extreme, centers having the longest intertransplant intervals did have the highest mortality in three of the six analyses, but in another, these centers exhibited the lowest mortality[6].

In conclusion, there is a correlation between transplant rate and mortality (figure 6.1). This correlation is mediated by cumulative transplant experience. There is no evidence to suggest that transplant rate has an independent, causal effect on mortality following heart transplantation. The evidence suggests in contrast, that cumulative experience affects both transplant rate and transplant mortality. The relations between transplant number (the marker for cumulative transplant experience), transplant rate and transplant mortality are summarized in figure 6.5.

It remains possible that transplant rates faster or slower than those registered between 1984-1986 might yet be associated with transplant mortality, and this possibility should be investigated using more recent data sets.

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[6] This inconsistent relation between transplant rate and mortality is not clarified by simply selecting a different range of transplants over which to measure the transplant rate. For example, I performed the above analyses for transplant intervals such as 1-11, 5-16, and 1-21 (these are available on request). As expected from result #3 above, such changes do scramble the quartiles in which centers fall. However, the mortality figures for these newly defined quartiles still do not suggest there is a consistent relation between transplant rate and mortality.

figure 6.1

TRANSPLANT RATE AND MORTALITY

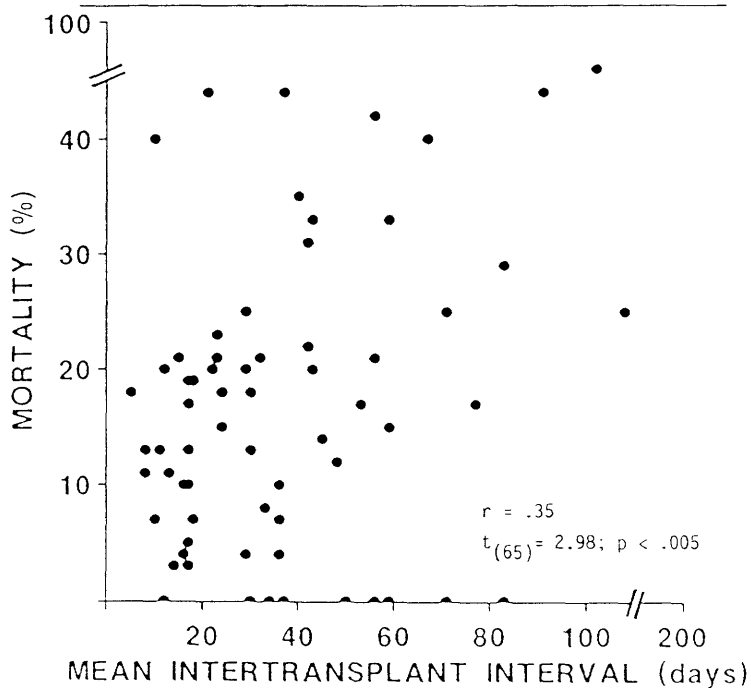


FIGURE 6.2
INTERTRANSPLANT INTERVALS:
A SAMPLE OF THE DATA

CENTER:	INTERTRANSPLANT INTERVAL (in days)			
	1-6	6-11	11-21	<---transplant number
31:	83	---*	---	
32:	35	41	---	
33:	31	25	18	
34:	71	---	---	
35:	16	13	12	
36:	35	28	---	
37:	56	27	14	
38:	36	21	18	
39:	43	---	---	

* "---" Indicates that data is not available for this particular transplant sequence. Missing data may indicate that a center that has not completed the specified sequence. It may also result from a center that has completed the sequence but has not sent updated information to the Registry.

FIGURE 6.3
INTERTRANSPLANT INTERVALS
(summary statistics)

	1984	1985
Transplant Number 1-6		
Mean:	56	50
Median:	51	48
Range:	23-83	15-136
St. Dev.:	18	24
Transplant Number 6-11		
Mean:	39	26
Median:	35	25
Range:	12-72	9-72
St. Dev:	17	15
Transplant Number 11-21		
Mean:	24	14
Median:	18	13
Range:	12-41	8-19
St.Dev.:	9	4

FIGURE 6.4
TRANSPLANT RATE AND MORTALITY

1984 Start-Up Centers

Transplant Number 1-6

Quartiles	Center Number	90-day mortality % (transplants 6-8)
1 (fastest):	21, 22, 30, 40	9 (n=12)
2	16, 18, 19, 25	0
3	20, 23, 26, 27	15
4 (slowest):	15, 17, 24, 43	22

Transplant Number 6-11

Quartiles	Center Number	90-day mortality % (transplants 11-13)
1 (fastest):	16, 26, 27, 30	27 (n=12)
2	15, 18, 22, 40	8
3	20, 23, 25, 43	9
4 (slowest):	17, 21, 24,	11

Transplant Number 11-21

Quartiles	Center Number	90-day mortality % (transplants 21-25)
1 (fastest):	16, 24, 27,	17 (n=12)
2	20, 26, 40,	18
3	15, 18, 23,	17
4 (slowest):	22, 29, 30,	18

1985 Start-Up Centers

Transplant Number 1-6

Quartiles	Center Number	90-day mortality % (transplants 6-8)
1 (fastest):	35, 49, 55, 56, 65	7 (n=15)
2	32, 33, 36, 38, 61	8
3	37, 39, 44, 46, 51	15
4 (slowest):	31, 34, 48, 50 54, 47	17

Transplant Number 6-11

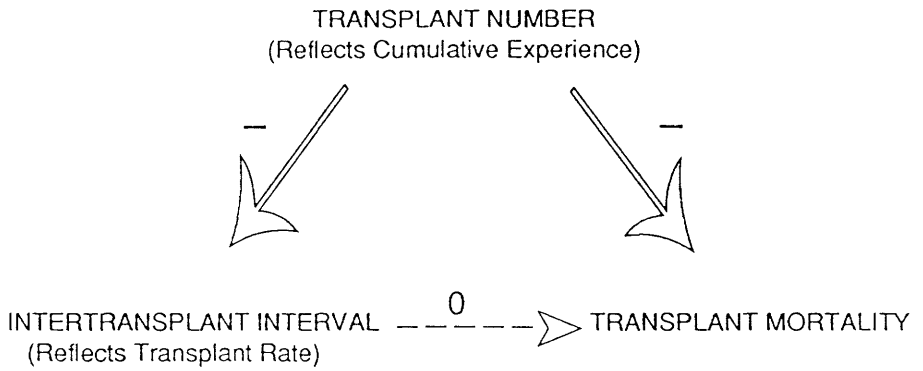
Quartiles	Center Number	90-day mortality % (transplants 11-13)
1 (fastest):	35, 44, 56, 65	7 (n=12)
2	33, 38, 49,	17
3	36, 37, 51, 55	23
4 (slowest):	32, 50, 61,	0

Transplant Number 11-21

Quartiles	Center Number	90-day mortality % (transplants 21-25)
1 (fastest):	56,	7 (n=8)
2	35, 55,	8
3	33, 49,	0
4 (slowest):	65,	15

Figure 6.5

RELATIONS BETWEEN CUMULATIVE EXPERIENCE, TRANSPLANT RATE AND MORTALITY



CHAPTER 7

CENTER CHARACTERISTICS AND MORTALITY FOLLOWING HEART TRANSPLANTATION

SUMMARY:

This chapter investigates the hypothesis that structural characteristics of new transplant centers are related to mortality following heart transplantation.

KEY POINTS:

- Structural characteristics of transplant centers vary considerably.

- Of the 9 center characteristics tested in this study, all but two are not related to mortality following heart transplantation. The two characteristics of transplant centers that are related to mortality are: prior training of transplant cardiologists, and prior training of transplant coordinators.

Modern medical quality science asserts that structural elements of health care organizations have a direct bearing on the outcomes of patient encounters with that organization[1]. In attempting to apply this logic to the field of heart transplantation, one might reasonably expect that several characteristics of transplant centers would affect outcomes

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[1] There is ample proof of this assertion. See for example:
Donabedian A; Explorations in Quality Assessment and Monitoring; Volumes I-III; Health Administration Press; Ann Arbor, Mi.; 1980.

from the transplant procedure. These characteristics might include, among others, the presence of sophisticated diagnostic equipment, broad-based consultative services, expertise in transplant immunology, and large, active catheterization laboratories and open heart surgical programs.

In fact, Medicare's designated center coverage policy, which is designed to maximize outcomes from the scarce donor organ supply, is based on the assumption that there is a relation between certain such characteristics and mortality following heart transplantation. For example, it contains criteria regarding transplant team structure, interactions with allied subspecialties, the volume of open heart surgery and cardiac catheterization programs, and the presence of certain laboratory facilities (10). Unfortunately, to date there exists no empirical data to support these assumptions[2].

This set of circumstances (ample proof outside the field of heart transplantation that there is a relation between the structural characteristics of health care providers and their outcomes, combined with federal policies based on the assumption that such relations exist for heart transplantation) is reminiscent of the volume-outcome situation described in chapter 5. However, as I described in that chapter, I found no empiric support for the putative

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[2] I discuss Federal heart transplant policies in the introduction and in chapter 9.

heart transplant volume-outcome relation. This underscores a necessity to study the relation between the structural characteristics of heart transplant centers and transplant mortality, and this is indeed the goal of the present chapter.

I have chosen once again to focus my analyses on "new" heart transplant centers-those that initiated their programs during the study period (1984-86). I do so to test the validity of the "gatekeeper" function of the aforementioned federal regulations which require that new centers meet certain criteria before they are designated for reimbursement by Medicare.

Not surprisingly, the structural characteristics of these new centers are strikingly variable (figure 7.1). Among the notable findings:

1) 70% of these centers had preexisting kidney transplant programs at the time their heart transplant programs began,

2) 63% were members of the Council of Teaching Hospitals,

3) Their annual open heart surgical volumes varied from 94-3,700 cases,

4) Their annual cardiac catheterization volumes varied from 180-6,193 cases,

5) Hospital admissions in 1985 ranged from 9,376 to 47,779,

6) Surgeons managed transplant recipients'

immunosuppressive therapy in 63% of new transplant programs[3],

7) The percentage of transplant centers that began programs with cardiologists, surgeons, or transplant coordinators possessing prior transplant experience was 25%, 43%, and 22%, respectively.

Interestingly, of the nine structural characteristics for which data is available, univariate analyses reveal that only one is significantly correlated with heart transplant mortality: this variable is the presence or absence of prior training on the part of transplant cardiologists (mortality with prior training: 7%, without prior training: 16%, $p<.001$; see figure 7.2).

A closely related variable, the presence of prior training on the part of transplant coordinators, exhibits a strong trend in the same direction, but it does not quite reach conventional standards for statistical significance (mortality with prior training: 11%, without prior training: 16%, $p=.07$) in this univariate test[4]. The comparable analysis of prior training among transplant surgeons reveals no significant effect.

To confirm and extend these findings, I perform bivariate

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[3] It would be more precise to describe this as a procedural (not a structural) characteristic of transplant centers, much like the use or non-use of triple drug therapy. However, I discuss it in this chapter because it is an attribute that is clearly referable to transplant centers.

[4] However, bivariate analyses described below do suggest that prior training of transplant coordinators is significant.

analyses in which I stratify each center characteristic by the overall burden of illness, the year of transplant, cumulative experience and (for the "prior training" variables) certain patient characteristics (figures 7.3-7.11). These analyses reveal that:

- PREEXISTING KIDNEY TRANSPLANT PROGRAMS do not confer mortality benefits to new transplant centers, despite their implied institutional knowledge of transplant immunology. In this case, the univariate analysis (figure 7.2) fails to reveal a relation, and the bivariate analyses (figure 7.3) confirm this finding.

- OPEN HEART SURGICAL VOLUMES do not have a linear relation with heart transplant mortality in new transplant centers. However, the univariate analysis (figure 7.2) suggests that centers having extremely high or extremely low volumes of open heart surgical procedures have higher mortality rates. The accompanying bivariate analyses (figure 7.4) lend considerable support to this finding: they demonstrate the same U-shaped relation in fully 5 of the 7 groups. The results are particularly striking for subgroups characterized by advanced levels of cumulative experience (transplant numbers 11-15 and $\geq$21) and by a low burden of illness.

This U-shaped phenomenon is clinically plausible, albeit slightly unexpected. Centers featuring extremely high volumes of non-transplant open heart surgery have surely developed and perfected a care process enabling them to deliver high quality

care to their routine open heart surgical patients. However, by necessity these programs must emphasize rapid patient transfer out of intensive care settings, and a highly standardized approach to patient care. These attributes may not provide the best milieu for the management of heart transplant recipients.

High volumes of routine cases may in addition place excessive demands on laboratories and health care professionals or at the very least prevent them from identifying the care of transplant recipients as a priority. Because of the unexpected nature of this finding and the fact that Medicare certification guidelines do not account for it, this issue should be investigated further.

- CARDIAC CATHETERIZATION VOLUMES are related to transplant mortality by a U-shaped pattern similar to that for open heart surgery. In this case, the univariate analysis (figure 7.2) is very strongly confirmed by the bivariate analyses (figure 7.5) which reveal the expected U-shaped pattern in all 7 subgroups.

At first blush, the relation between cardiac catheterization programs and heart transplant mortality seems obtuse at best, especially when compared to the rather obvious relation between open heart surgery programs and transplant

mortality[5]. However, the explanation for these very striking findings follows the exact same logic as that used to explain the open heart surgery phenomenon. These findings suggest that cardiologists are indeed critical to the success of heart transplant programs. Evidence presented below lends further credence to this observation.

- HOSPITAL ADMISSIONS are not related to heart transplant mortality in univariate (figure 7.2) or in bivariate analyses (figure 7.6).

- AFFILIATION WITH THE COUNCIL OF TEACHING HOSPITALS appears to offer a mild reduction in heart transplant mortality, but this trend does not reach statistical significance (univariate analysis-figure 7.2-mortality=13% vs. 18%; Z=1.68; p=NS). Bivariate analyses (figure 7.7) support the conclusion that this characteristic is not an important determinant of mortality following heart transplantation.

- CARDIOLOGIST/INTERNIST MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY confers an insignificant mortality reduction compared to situations in which surgeons manage these medications (12% vs. 15%, Z=1.15; p=NS). Of considerable interest however, bivariate analyses (figure 7.8) reveal a significant reduction in transplant mortality when cardiologists or internists manage immunosuppressive therapy <u>in the group of patients who</u>

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[5] The most palpable relation is that cardiac biopsies, required frequently in the post-operative period to diagnose and manage transplant rejection, require cardiac catheterization.

are among the first to undergo heart transplantation (transplants number 1-5). This significant difference disappears with increasing cumulative experience[6]. There is a similar trend favoring cardiologists in 1984 (but it does not achieve significance) and this trend is also eradicated by 1986.

The most likely explanation for these findings is that, when compared with transplant surgeons, the cardiologists associated with new transplant programs tend to with bring with them slightly higher levels of skills and/or knowledge in the management of immunosuppressive drugs. However, surgeons catch up quickly as a result of direct, hands on experience with their initial transplant recipients. This explanation seems reasonable from a clinical standpoint. Prior direct training in immunosuppressive management aside, cardiologists do tend to use these drugs more frequently[7].

- As mentioned above, univariate analysis reveals that centers featuring CARDIOLOGISTS WITH PRIOR HANDS-ON TRAINING IN HEART TRANSPLANTATION have significantly lower mortality rates than centers not featuring cardiologists so trained

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[6] See transplants 11-15, and $\geq$21 (figure 7.8).

[7] Cardiologists are first trained as internists. Internists use prednisone to manage collagen vascular diseases, asthma and certain allergic phenomena. They use azathioprine (Imuran) to treat certain malignancies. And although they have no direct exposure to cyclosporine, they are exposed to patients with reversible, drug-induced nephropathy, the major side-effect of cyclosporine.

(figure 7.2). Bivariate analyses (figure 7.9) strongly confirm this phenomenon, as one observes the expected relationship in all 7 subgroups.

The effect is particularly significant for transplants performed in 1984 ($Z>4.0$; $p<.001$). However, the expected ordinal relationship is maintained even as centers achieve high levels of cumulative experience (see the analysis of transplant number, figure 7.9). In the latter circumstance, the subgroups characterized by prior cardiologist training have relatively small sample sizes, and this makes interpretation difficult. This is indeed unfortunate because one would like to know how much "on site" experience is required to offset the effect of prior training.

Of note, when I stratify the effect of prior cardiologist training by various patient subsets, I can demonstrate the expected ordinal relationship in <u>both</u> high and low risk groups (figure 7.9). Interestingly, this effect achieves statistical significance consistently in the <u>low</u> risk groups (males, no comorbidities, no mechanical support, triple drug therapy used), but never in the high risk groups.

The obvious problem in interpreting these positive findings is that my supplementary survey provides no details concerning the prior training of cardiologists. Therefore it is not clear which feature of this prior training is responsible for the improvements in subsequent outcomes. Many features could prove critical, including the duration of training, the activities

performed and responsibilities maintained during training, and even the particular site of training. Now that this study has documented the importance of prior hands-on training for transplant cardiologists, further studies are needed to maximize its beneficial effects[8].

- In stark contrast to the above positive findings, PRIOR HANDS-ON HEART TRANSPLANT TRAINING FOR THORACIC SURGEONS does not confer mortality reductions in new transplant centers. Thus, when I use a univariate analysis (figure 7.2) to compare centers featuring such previously trained surgeons with centers not having this feature, I find no significant difference in mortality (12% vs. 15%; p=NS). This finding is supported by bivariate analyses, which show no consistent relationship between surgical training and outcomes in new transplant centers (figure 7.10).

Thus to summarize, heart transplant mortality reductions are associated with prior training of cardiologists but not transplant surgeons. This finding may surprise some given that long term survival following heart transplantation involves, first and foremost, major cardiovascular surgery. However it is relatively easy to explain and in fact consistent with modern clinical experience.

The explanation for the <u>lack</u> of an association between prior surgical training and transplant mortality is that the

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[8] This subject is covered in more detail in chapter 9.

"transplant" surgeons have already mastered the performance of closely allied procedures such as coronary artery bypass and valve replacement. In terms of manipulative skills and intra- and post-operative decisionmaking skills, the heart transplant procedure is quite similar to these routine procedures, and many believe it is actually simpler in terms of the physical, manipulative aspects. Therefore, above noted lack of association occurs because surgeons have successfully generalized their skills to the heart transplant procedure.

The explanation for an association between mortality and prior cardiologist training then becomes straightforward. Once "surgical" mortality is reduced to a minimum, the overall success with heart transplantation becomes dependent on medical issues such as the management of rejection and infection. These issues are handled in the majority of transplant centers by cardiologists, coordinators, and other non-surgeons.

- In a related finding of interest, the univariate analysis presented earlier showed a strong trend towards reduced mortality among centers featuring TRANSPLANT COORDINATORS WITH PRIOR TRAINING (figure 7.2). Because this trend did not quite achieve statistical significance (p=.07), it is particularly important to review the relevant bivariate analyses (figure 7.11) in this case. These reveal the expected ordinal relation in 13 of the 15 subgroups, and the results achieve statistical significance for patients with a high burden of illness, for

patients who have transplant numbers 1-5, and for patients requiring preoperative mechanical support. Taken together, the weight of evidence from univariate and bivariate analyses suggests that prior training of transplant coordinators is associated with mortality reductions in new transplant centers. Again, this is consistent with clinical experience. Transplant coordinators have an enormously complex job, and unlike the above case of the transplant surgeon, few things other than direct training would prepare a coordinator to perform this job effectively.

Transplant coordinators orchestrate many or most of the complex processes associated with the management of patients pre-and post-transplant. They coordinate the flow of information between physicians affiliated with the transplant program and specialists consulting to it. They directly participate in the evaluation of candidates for transplantation. They are actively engaged in the diagnosis and treatment of recipients' medical conditions, especially on an outpatient basis. And they perform the absolutely critical follow-up function, in which details of lab values, diagnostic tests, and biopsy results-along with clinical recommendations for action-are communicated to patients.

In summary, as was the case with the putative volume-outcome relation, this study fails to provide strong empiric support for the belief that mortality following heart transplantation is a function of the structural

characteristics of heart transplant centers. As a result, this study does not support existing federal heart transplant policies, which are based on the assumption that such relations exist. The notable exception is the finding in this study of a strong relation between mortality and the prior training of cardiologists and/or transplant coordinators. This latter finding has important implications for federal heart transplant policy, and I will discuss it further in chapter 9.

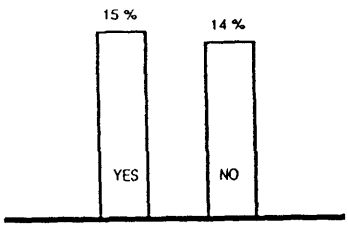
Figure 7.1

CHARACTERISTICS OF NEW TRANSPLANT CENTERS

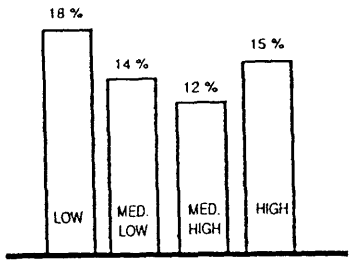
	Fields	# Centers	Total Heart Transplants 1984-1986
Established kidney transplant programs	yes	28	589
	no	12	174
Open heart surgery Annual volume	94-236	10	236
	240-436	10	129
	467-744	10	138
	755-3,700	10	209
Cardiac Catherization Annual Volume	180-900	10	171
	900-1,569	10	146
	1,600-2,109	10	236
	2,169-6,193	10	155
Hospital Admissions	9,376-17,687	10	219
	17,703-21,535	10	239
	21,540-28,830	10	195
	29,084-47,779	10	278
Member Council of Teaching Hospitals	yes	25	800
	no	15	163
Who Manages Immunosuppressive Therapy?	Cardiologists/ Internists	14	343
	Surgeons	24	382
Prior Training: Cardiologists	yes	10	236
	no	30	726
Prior Training: Surgeons	yes	17	265
	no	23	697
Prior Training: Transplant Coordinators	yes	9	201
	no	31	761

Figure 7.2

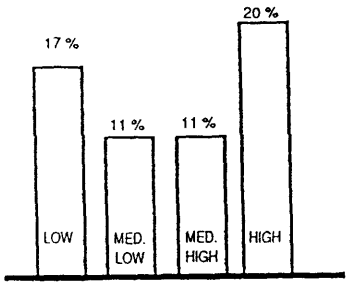
CHARACTERISTICS OF NEW TRANSPLANT CENTERS AND MORTALITY %



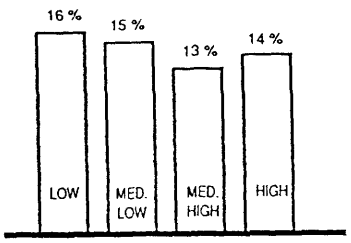
Established Kidney Transplant Programs



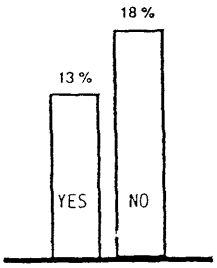
Open Heart Surgery Annual Volume



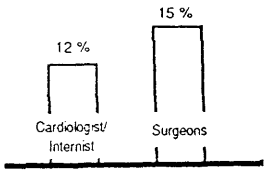
Cardiac Catherization Annual Volume



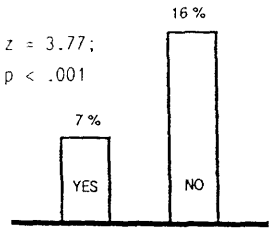
Hospital Admissions



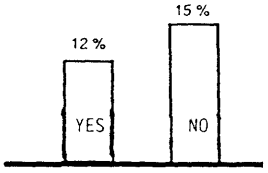
Council of Teaching Hospital Affiliation



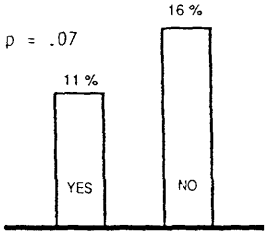
Who Manages: Immunosuppresive Therapy



Prior Training: Cardiologists



Prior Training: Surgeons



Prior Training: Transplant Coordinators

Figure 7.3

PRE EXISTING KIDNEY TRANSPLANT PROGRAMS AND MORTALITY % FOLLOWING HEART TRANSPLANTATION

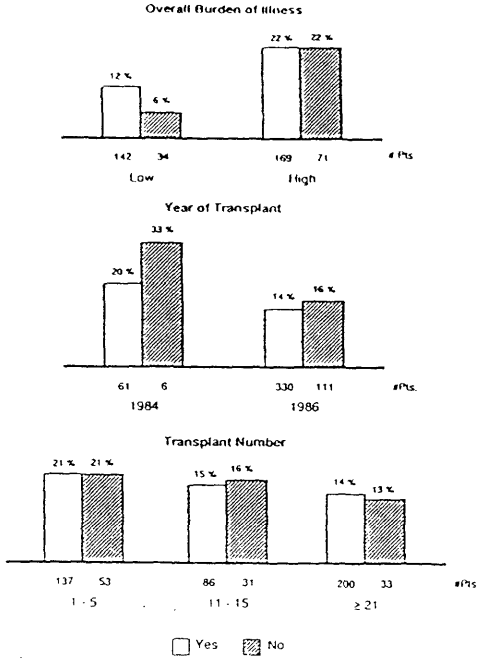


Figure 7.4

VOLUME OF OPEN HEART SURGERY AND MORTALITY % FOLLOWING HEART TRANSPLANTATION

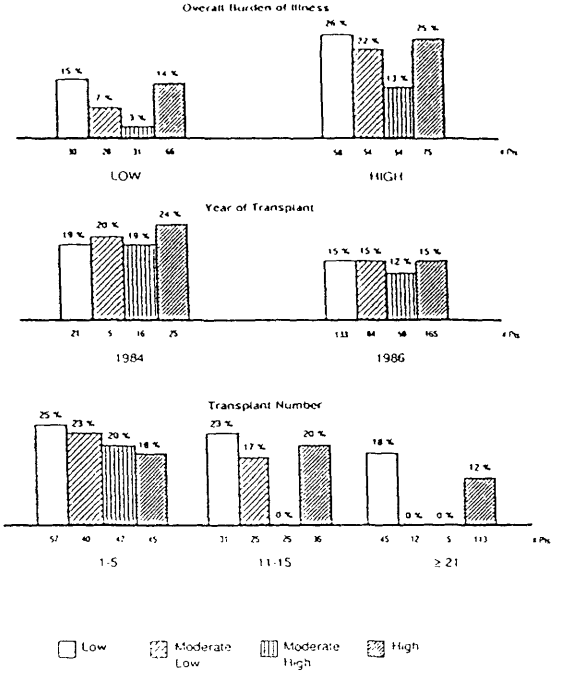


Figure 7.5

VOLUME OF CARDIAC CATHETERIZATION AND MORTALITY % FOLLOWING HEART TRANSPLANTATION

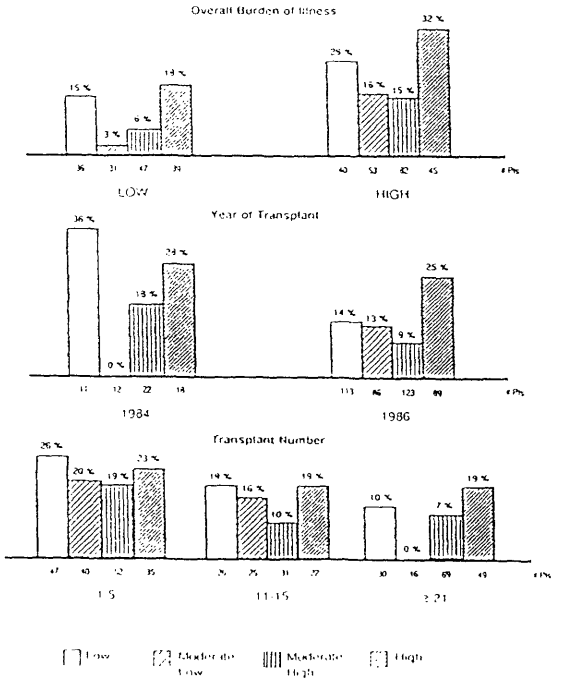


Figure 7.6

HOSPITAL ADMISSIONS AND MORTALITY % FOLLOWING HEART TRANSPLANTATION

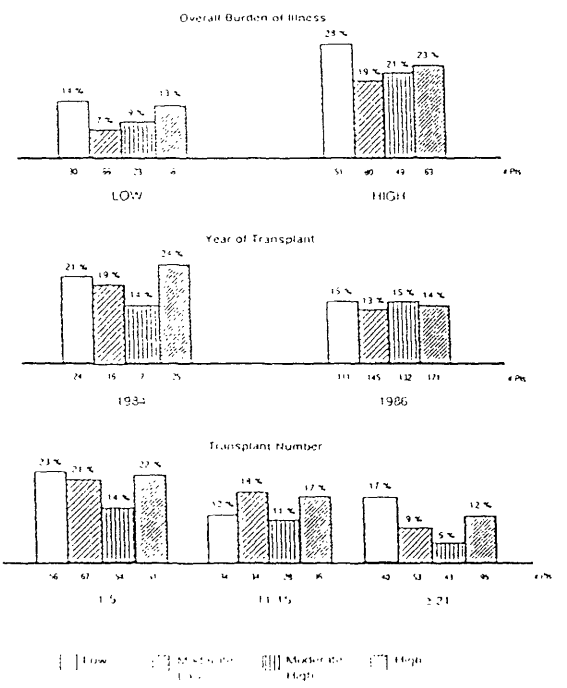


Figure 7.7

COUNCIL OF TEACHING HOSPITALS AFFILIATION AND MORTALITY % FOLLOWING HEART TRANSPLANTATION

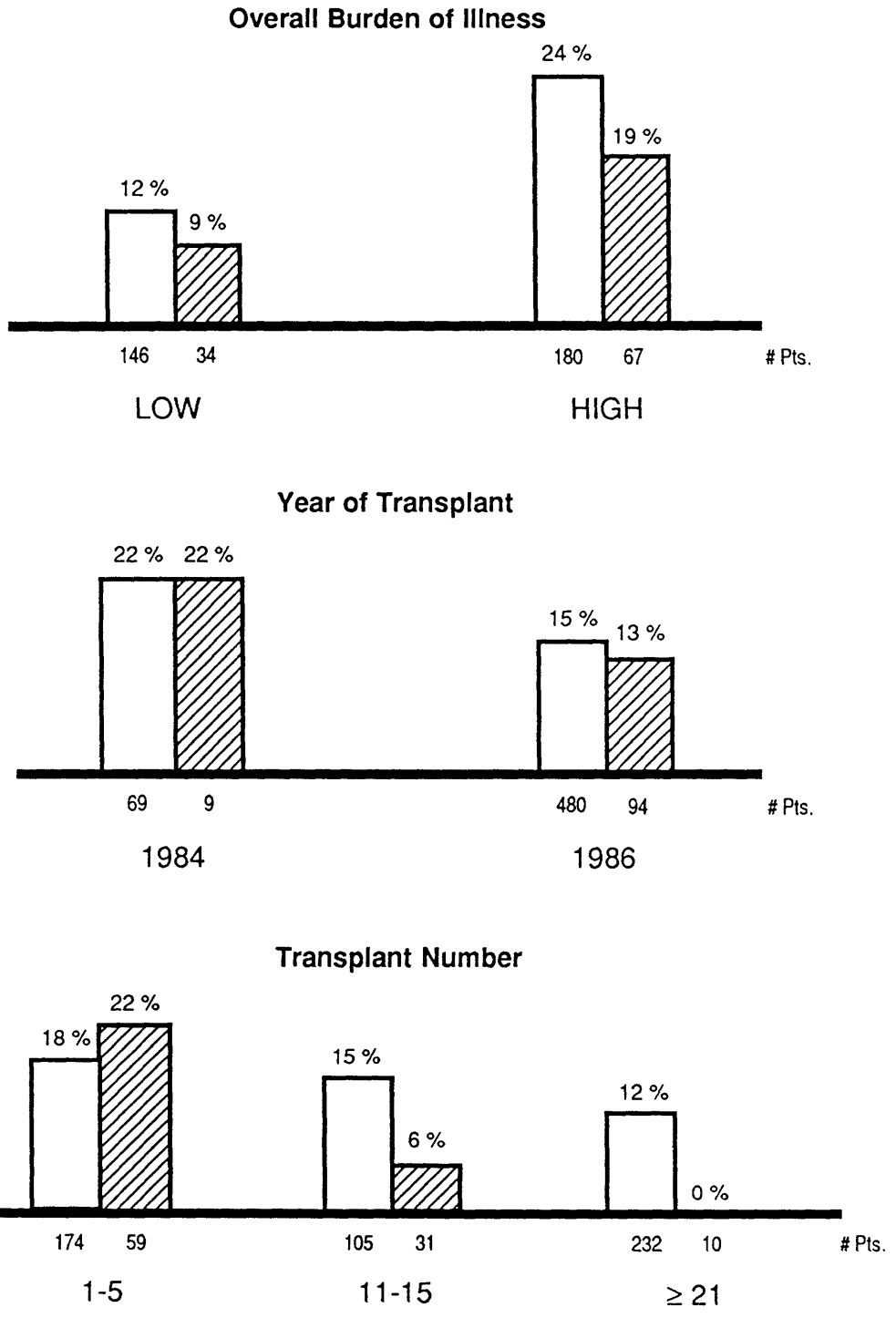


Figure 7-8

MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY
AND MORTALITY % FOLLOWING HEART TRANSPLANTATION

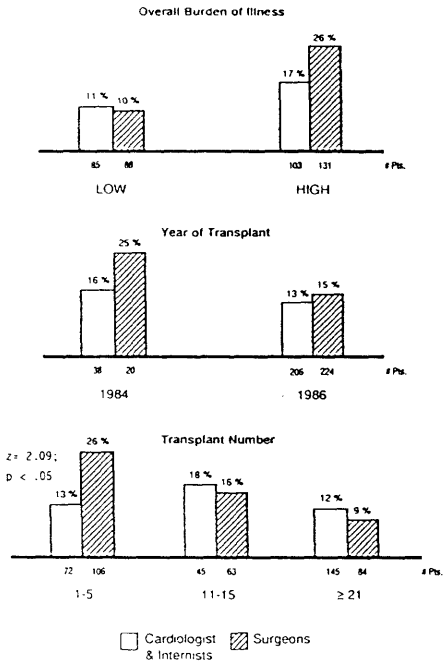


Figure 7-8 (Cont)

MANAGEMENT OF IMMUNOSUPPRESSIVE THERAPY
AND MORTALITY % FOLLOWING HEART TRANSPLANTATION

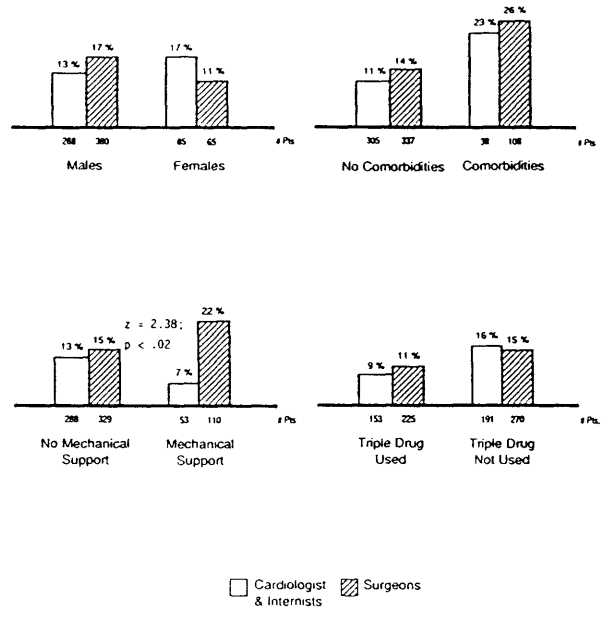


Figure 7-9

PRIOR TRAINING: CARDIOLOGIST AND
MORTALITY % FOLLOWING HEART TRANSPLANTATION

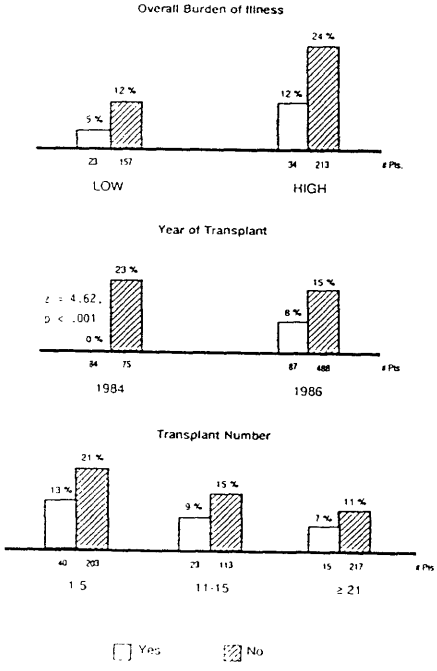


Figure 7-9 (Cont)

PRIOR TRAINING CARDIOLOGIST AND
MORTALITY % FOLLOWING HEART TRANSPLANTATION

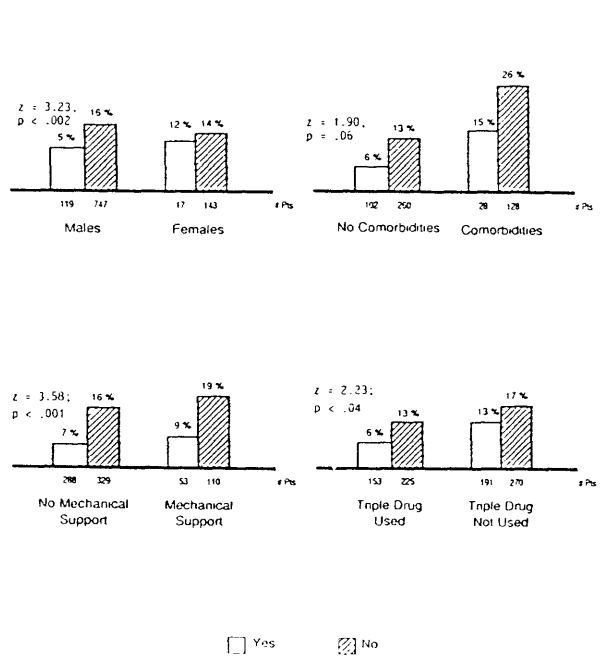


Figure 7.10

PRIOR TRAINING: THORACIC SURGEON AND MORTALITY % FOLLOWING HEART TRANSPLANTATION

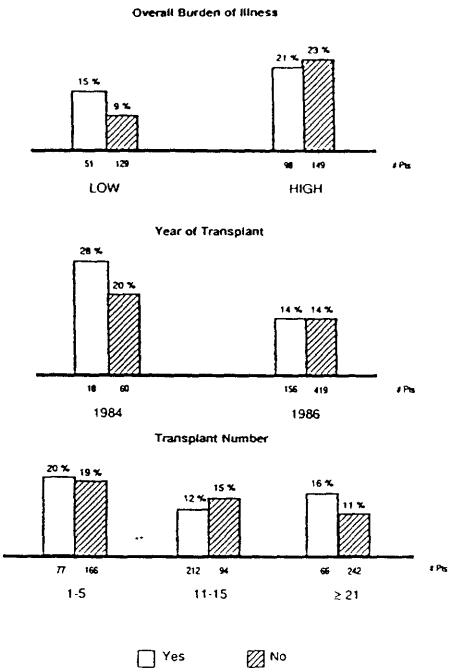


Figure 7.10 (Cont)

PRIOR TRAINING: THORACIC SURGEON AND MORTALITY % FOLLOWING HEART TRANSPLANTATION

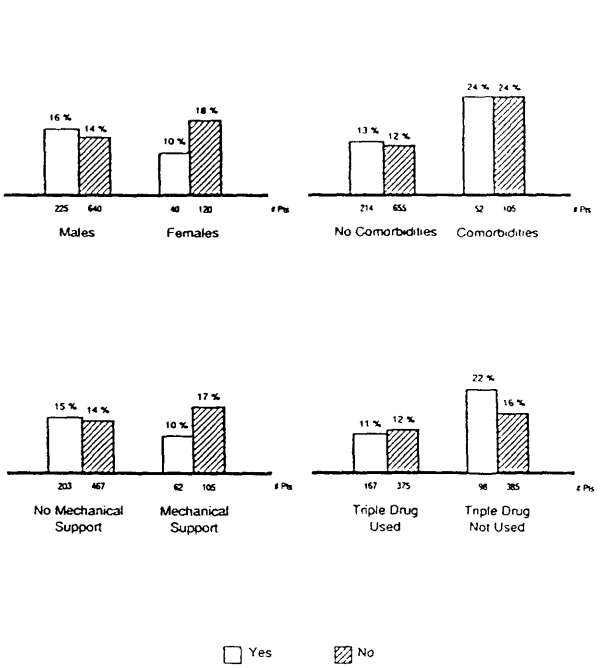


Figure 7.11

PRIOR TRAINING: COORDINATOR AND MOTRTALITY % FOLLOWING HEART TRANSPLANTATION

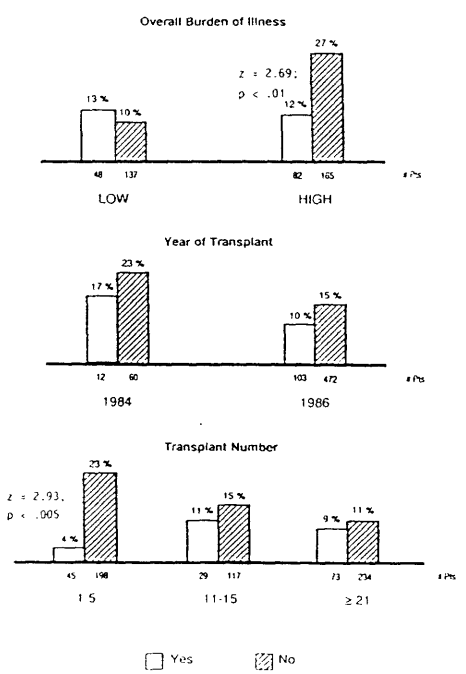
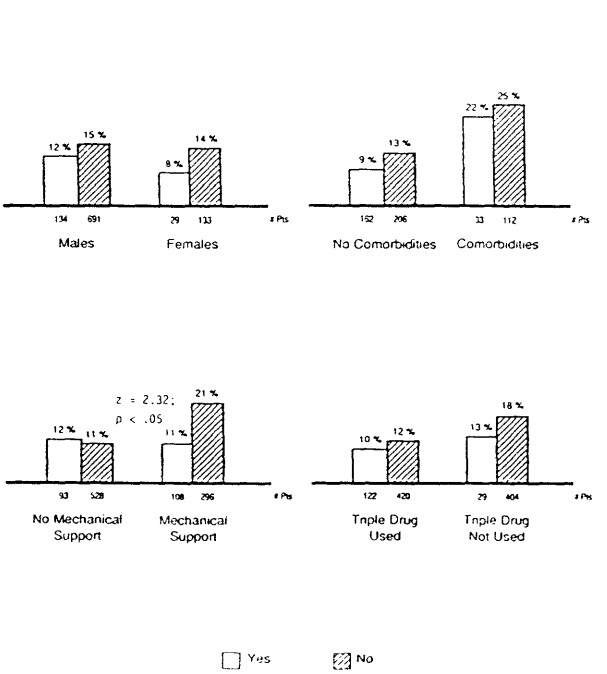


Figure 7.11 (Cont)

PRIOR TRAINING: COORDINATOR AND MORTALITY % FOLLOWING HEART TRANSPLANTATION



CHAPTER 8

EVIDENCE FROM THE LOGISTIC REGRESSION

SUMMARY:

This chapter uses logistic regression to study relations between characteristics of the patient, donor and center, various measures of experience, and heart transplant mortality.

KEY POINTS:

- Findings from this analysis support the findings of previous analyses.

This study's data set contains many variables that could reasonably be expected to impact mortality following heart transplantation. In chapters 2-7, I study these putative relationships using standard univariate and bivariate techniques. These analyses do in fact suggest that certain variables are associated with heart transplant mortality, and that others are not. Unfortunately, the above techniques are limited by their capacity to assess these relations for at most a few variables at a time. Yet just as it is reasonable to assume that many variables impact heart transplant mortality, so it is reasonable to assume that these variables produce their effects via complex interactions with each other.

Clearly therefore, it is desirable to reexamine this data set using statistical methods that have the capacity to assess correlations between the variables themselves, and between these variables and heart transplant mortality per se. I use logistic regression analysis for this purpose.

As with other multiple regression techniques, the logistic regression assigns weights to each independent variable (predictor) and produces an equation that most closely replicates variations in the dependent variable. Like some but not all regression techniques, logistic regression is applicable when the dependent variable is binary, and so for this analysis I use 90-day mortality status (dead or alive) as the dependent variable.

Theoretical and empirical observations both suggest that the response function (the relation between dependent and independent variables) is frequently curvilinear when the dependent variable is binary[1], and to be sure logistic regression is first and foremost a curve-fitting technique. The response function for the "tilted S" shaped logistic function is given as:

$$Y = \exp(B_0 + B_1X_1 + B_2X_2 + \ldots B_nX_n)/[1 + \exp(B_0 + B_1X_1 + B_2X_2 + \ldots B_nX_n)]$$

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[1] For a further discussion of these issues, see: Neter J, Wasserman W, Kutner MH; Applied Linear Statistical Models; Richard Irwin, Inc; Homewood, Illinois; 2nd ed; 1985; 357-67.

Of course, the fundamental assertion that a curvilinear response function best describes the relation between 90-day mortality and the relevant independent variables is difficult to prove. More importantly, the myriad assumptions made during routine computerized calculations of the response function may not be defensible from a clinical standpoint. And of great importance, the iterative, model-building process (by which one reduces the original list of independent variables to a relatively small number that in combination predict a relatively high percentage of the variation in outcomes) inevitably requires judgement and clinical experience. These considerations inject a certain degree of subjectivity into the logistic regression analysis. Therefore, interpretation of its results requires caution just as does interpretation of the uni- and bivariate analyses mentioned above.

Nevertheless, it is apparent from the previous discussion that the logistic regression technique and the analyses found in chapters 2-7 effectively complement each other. The strengths of one approach correspond to the weaknesses of the other. When one utilizes both methodologies to analyze the same data set, the combination provides a balanced approach and a prudent means to confirm and support conclusions.

I use PROC CATMOD from Version 5.0 of SAS to perform logistic regression analysis[2]. I study the combined effects of the following variables on 90-day heart transplant mortality:

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[2] PROC CATMOD is a procedure for categorical data modeling. It fits linear models to functions of response frequencies, and it can easily be used for logistic regression (as well as linear modeling, log-linear modeling and repeated measurement analysis). CATMOD uses maximum-likelihood estimation of parameters for log-linear models and for the analysis of generalized logits. For more information about PROC CATMOD, please refer to:

SAS User's Guide: Statistics: Version 5 Edition; SAS Institute, Inc.; Box 8000; Cary, N.C. 27511-8000; pp171-253.

(Note: The text in this footnote is excerpted from the SAS Guide)

PATIENT CHARACTERISTICS	VARIABLE NAME
Gender	SEX
Age	AGE
Coronary Artery Disease	CAD
Cardiomyopathy	CRDMPY
Comorbid Conditions	COMORBID
Preoperative Mechanical Support	DEVICE
Left Ventricular Ejection Fraction	LVEF
DONOR CHARACTERISTICS	
Ischemic Time	ITIME
PROCEDURAL CHARACTERISTICS	
Triple Drug Therapy	TRPDRG
CENTER CHARACTERISTICS	
Kidney Transplant Program	HTKT
Annual Volume-Coronary Bypass	BYPASS
Annual Volume-Cardiac Catheterization	CATH
Who Manages Immunosuppressive Therapy	DRUGMD
Prior Transplant Experience-Surgeons	EXPSUR
Prior Transplant Experience-Cardiologists	EXPCRD
Prior Transplant Experience-Coordinators	EXPTC
Total Admissions, 1985	ADMIT
Council of Teaching Hospital Affiliation	COTH
CHARACTERISTICS OF EXPERIENCE	
Year of Transplant	YOT
Total Number (volume)	VOL
Cumulative Experience (learning curve)	LC

Preparing To Perform Logistic Regression-Before I began to assemble the model, I chose to eliminate the variable coding for the use or non-use of cyclosporine. Cyclosporine use is obviously correlated to the use of triple drug therapy, as the latter regimen includes cyclosporine. But whereas the use of cyclosporine remains steady and extremely high throughout the study period (figure 3.2), the use of triple drug therapy increases steadily. Because cyclosporine use per se is so consistently high, it is unlikely to have contributed to the changing mortality during the study period. In addition, because its use is correlated with the use of triple drug therapy, a decision to include a variable coding for it might reduce the apparent mortality impact of triple drug therapy.

I also chose at this point to eliminate the variable coding for transplant rate. I did so because earlier analyses had shown that: a) cumulative experience is strongly correlated with transplant rate, and that, b) when transplant rate can be adequately distinguished from cumulative experience, it does not affect transplant mortality (see especially figure 6.5). Once again I felt that it would be wise to exclude a variable that is known to be correlated with another variable, and that appears to have little impact on its own; a decision to include such a variable might impair the capacity of the

model to assess the effects of that second variable[3].

Thirdly, to simplify the analysis, I chose dichotomous variables to represent the learning curve, ischemic time and transplant volume. The definitions for these variables and my rationale for doing so are as follows:

- The learning curve variable divides patients according to whether or not they are among the first five to receive transplants at a particular center. The split at transplant number five is consistent with previous analyses (see for example figures 4.3, 4.5 and 4.9-4.23) and is also based on visual inspection of the data (see figure 4.2) which suggests that the learning curve is most easily documented through about the fifth transplant[4].

- The ischemic time variable divides patients according to whether or not their donor ischemic times are greater than two hours. The most important reason for so doing is that most transplant coordinators report their ischemic time data with

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[3] Interestingly, after I built the final model (described below), I ran two additional iterations. In the first iteration, I substituted the cyclosporine marker for the triple drug therapy marker. The results in fact suggested that use or non use of cyclosporine was not a significant predictor of 90-day mortality. Similarly, transplant rate, when it was substituted for the learning curve, did not contribute in significant fashion to the predictive capacity of the model.

[4] As described below, I do rerun the final model using different "splits" for the learning curve variable (ie. at transplant #6, #7, etc.) to assess the length of the transplant sequence over which the effect is still significant.

this degree of specificity. They tend not to indicate ischemic times down to the minute.

- The transplant volume variable divides patients into two groups according to their center's transplant volume. I have already used categorical-type variables in certain analyses to represent the volume proxy (see chapter 5). In this case, after visual inspection of the data (figure 2.2), I initially define the split to occur at a volume of 50 transplants. However, I recognize that this is a somewhat arbitrary cutoff point, so I have chosen to rerun the analysis using several different cutoffs before reaching any conclusions about its effect (see footnote 5).

Beginning Logistic Regression Analysis-The first iteration of the logistic regression model reveals the following results:

LOGISTIC REGRESSION: MODEL 1

VARIABLE	ESTIMATE	ST. ERROR	CHI-SQUARE	PROB.
INTERCEPT	2.056	.978	4.41	.035
SEX	- .585	.221	6.99	.008
AGE	- .201	.207	0.02	.892
CAD	- .620	.279	4.47	.035
CRDMPY	- .132	.280	0.22	.647
COMORBID	- .619	.201	9.45	.002
DEVICE	- .358	.228	2.46	.117
LVEF	- .160	.184	0.76	.384
ITIME	- .003	.001	4.05	.044
TRIPDRG	1.088	.389	7.80	.005
HTKT	- .075	.277	0.07	.785
BYPASS	.054	.378	0.02	.885
CATH	.446	.395	1.28	.258
DRUGMD	1.008	.250	0.35	.555
EXPSUR	.361	.277	1.69	.193
EXPCRD	-1.126	.451	6.23	.013
EXPTC	- .906	.360	6.32	.012
ADMIT	.201	.288	0.49	.485
COTH	.270	.318	0.72	.397
YOT	.203	.229	0.79	.374
VOL	.067	.089	0.67	.413[5]
LC	.751	.357	4.44	.035

[5] I repeat this iteration of the model several times using center volume cutoffs of 10, 30 and 70 transplants. In no case does this variable have a significant impact on 90-day mortality.

This first model suggests that eight variables have a significant impact on mortality. These are:

VARIABLE	STATE THAT INCREASES MORTALITY
Gender	Female
Coronary Artery Disease	Present
Comorbid Conditions	Present
Ischemic Time	>2 hours
Triple Drug Therapy	Not Used
Prior Experience-Cardiologists	Not Present
Prior Experience-Coordinators	Not Present
Learning Curves	Transplant # >5

Refining the Model-Then as is routinely done, I proceed to make successive refinements of this first model based on clinical judgement, analysis of correlations, and a review of coefficients and their associated standard errors. I now review the major aspects of this iterative process. I give special attention to my decisionmaking process as it relates to the generation of the second model. This provides an excellent example of the thinking I use in subsequent iterations.

Several features of the first model require closer investigation. These are:

- The "large center" effect: Several of this study's center characteristics seem to reflect center size. There is reason to suspect they are correlated with each other. If so, then including all of them in the model might diminish the model's

capacity to detect an effect of any one. The relevant variables are: the presence of a kidney transplant program, annual volume of coronary bypass, annual volume of cardiac catheterization, total 1985 admissions, and affiliation with the Council of Teaching Hospitals.

In fact, the relevant correlation matrix confirms that strong correlations exist between catheterization volume and bypass volume, and between the presence of kidney transplant programs and council of Teaching Hospital Affiliation. It also suggests a mild correlation between catheterization volume and the presence of kidney transplant programs:

"LARGE CENTER" EFFECT: CORRELATION MATRIX

	HTKT	BYPASS	CATH	ADMIT	COTH
HTKT	----	.04	.20	.07	.54
BYPASS	.04	----	.52	.13	.12
CATH	.20	.52	----	.04	.02
ADMIT	.07	.13	.04	----	.04
COTH	.54	.12	.02	.04	----

Because they are correlated with other "large center" variables, I choose to eliminate the cardiac catheterization and kidney transplant variables from the model's next iteration. And, because the 1985 admissions variable is <u>both</u> not correlated with other variables <u>and</u> not shown to be a significant predictor of 90-day mortality, I choose to eliminate this variable as well.

- The "Professional Training" effect: It is reasonable to suppose that centers choosing to train one member of their transplant team (prior to initiating their program) might choose to train other members of the team as well. Therefore, the variables representing training of the cardiologist, coordinator and surgeon might be expected to be correlated. If they were, a decision to include them all might interfere with the capacity of this analysis to detect an effect of training per se[6].

In fact, the relevant correlation matrix confirms that strong correlations exist between the training of the surgeon and the training of both the cardiologist and the coordinator. It also displays a mild correlation between the training of the cardiologist and the coordinator:

"PROFESSIONAL TRAINING" EFFECT: CORRELATION MATRIX

	EXPSUR	EXPCRD	EXPTC
EXPSUR	----	.41	.41
EXPCRD	.41	----	.17
EXPTC	.41	.17	----

Based on these findings, I choose to run a series of models for the next iteration: each version includes only one of the

[6] Of course, the first model found that two of these variables-training of cardiologists and coordinators-are significant regardless of any correlations between them. Thus, this analysis boils down to my attempt to unmask any possible effect of transplant surgeon training.

training variables. I do this in an attempt to isolate the training effect for each individual. (My presentation of the second model, below, will reflect this).

The "Hemodynamic" Effect-Clinical experience suggests that the variables representing left ventricular ejection fraction and the use or non use of mechanical support should be correlated. Clinicians are aware that mechanical circulatory support devices are associated with frequent, often severe complications, so they reserve them for cases of severely decompensated left ventricular function. In fact, the correlation coefficient for these two variables is .18. Although this is a rather modest correlation, I choose in any case to eliminate-for the time being-the LVEF variable from further iterations of the model.

I do so because I: a)have a strong, persistent clinical suspicion that the two variables are correlated, b)recognize that measurements of left ventricular function have a large margin of error, c)recognize there are many methods for measuring left ventricular function, so data from different centers may not be comparable, d)recall that nearly 25% of patients in the data set do not have available data on LVEF, as compared to superb reporting of the DEVICE variable in the data set[7].

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[7] And as above, once I generated the final model, I reinserted the LVEF variable. It did <u>not</u> significantly contribute to the model's predictive power. This is an important finding in that it conflicts with the results of

The "Indication" effect: The presence of one indication for heart transplantation would be expected to be inversely correlated to the presence of other indications (occasionally people have more than one indication, but this is rare). Therefore I suspect that the presence of coronary artery disease and cardiomyopathy would be correlated. In fact, the correlation coefficient for these variables is -.78. I choose to eliminate the cardiomyopathy variable from further iterations of the model.

To summarize the above decisions, the model's second iteration omits 5 variables that were present in the first iteration. In addition, it actually consists of three separate analyses, each containing only one of the training variables.

Of great interest, the results of this second model (see below) are remarkably similar to those of the first. The same eight variables remain significant, and no new variables achieve significance.

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prior univariate analyses. I discuss this below.

LOGISTIC REGRESSION: MODEL 2

VARIABLE	ESTIMATE	ST. ERROR	CHI-SQUARE	PROB.
INTERCEPT	2.081	.825	6.36	.012
SEX	- .424	.221	3.98	.046
AGE	- .007	.007	1.05	.306
CAD	- .490	.171	4.95	.004
COMORBID	- .642	.198	9.51	.001
DEVICE	- .169	.190	1.48	.373
ITIME	- .003	.001	5.35	.020
TRIPDRG	.743	.299	6.20	.013
BYPASS	.285	.270	1.12	.291
DRUGMD	.152	.177	0.74	.391
EXPSUR	.209	.216	0.95	.331[8]
EXPCRD	-1.164	.418	7.74	.005
EXPTC	- .723	.293	6.11	.013
COTH	.252	.256	0.97	.325
YOT	.293	.220	1.77	.183
VOL	.312	.346	2.09	.170
LC	.783	.350	5.01	.025

It is particularly important that the following variables do not achieve statistical significance, as this model is designed to maximize their potential impact: prior training of surgeons, volume of bypass surgery, affiliation with the Council of Teaching Hospitals, and mechanical support devices.

Approaching Final Form-To achieve the final form of the model, I run more than twenty subsequent iterations. The

[8] As I describe above, I ran three separate analyses in this, the second iteration. For each of the three analyses, I included one, and only one, of the training variables (prior training of surgeons, cardiologists and coordinators). I did this to isolate the effects of training for each of the three professions.

highlights of this process include:

- None of the so-called "large center" variables contribute importantly to 90-day mortality. I say this with confidence because none achieve significance in any of the iterations despite my continual efforts to substitute one for the other, and to isolate them from each other.

- Year of transplant also does not contribute to 90-day mortality. Certainly this variable never achieves significance when it is maintained in the analysis along with the triple drug therapy variable. However, recall that earlier analyses (figure 3.4) showed that triple drug therapy usage was correlated with year of transplant. To further resolve this issue, I stratify the entire data set according to the use or non-use of triple drug therapy, and then reassess whether year of transplant is significant in either of these subsets. It is not.

- Transplant volume does not contribute to 90-day mortality. This variable does not achieve significance even after I change the cutpoint definition from 50 transplants to 10, or 30, or 70 transplants (see footnote 5).

- Patient age and "who manages the immunosuppressives?" are also not important predictors of 90-day mortality. These variables do exhibit occasional correlations with other variables, but these correlations do not make sense from a clinical standpoint. Nevertheless, attempts to isolate these variables from these with which they are correlated fails to

reveal that these variables are them-selves important.

- Prior training of transplant surgeons never does achieve a statistically significant impact on 90-day mortality. In contrast, models including both prior training among cardiologists and coordinators consistently show that both variables are significant, despite the fact that these two variables are moderately correlated with each other. I have decided to include both predictors in the final model, because the skills and responsibilities of these professionals differ. However, because these variables are correlated, the final model probably somewhat underestimates the magnitude of their individual impact[9].

- The logistic regression analysis detects a significant effect of cumulative experience through the ninth transplant. As I mentioned above, the learning curve variable initially divides patients according to whether they are among the first five transplants at each center. This variable is consistently an important predictor of 90-day mortality. Once the final model is in hand, I experiment with different definitions of this learning curve variable. This experimentation shows that the learning curve variable remains a significant predictor up to a cut point of transplant number 9: When the first 9

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[9] A strategy I chose not to use is to create a single variable representing training of either the cardiologist or the coordinator. This would increase the apparent significance of the training variable, but the meaning of this variable is less clear from a clinical standpoint.

transplants are separated from the remainder, this variable has significant predictive effects. When the first 10 transplants are separated from the remainder, it loses these effects.

In sum, the final model (below) suggests that the following attributes are associated with significantly higher heart transplant mortality: female sex, transplant indication: coronary artery disease, comorbidities present, non-use of triple drug immunosuppressive therapy, prolonged ischemic times, no prior training among cardiologists, no prior training among coordinators, and a lack of cumulative experience. In all cases, this evidence is consistent with earlier findings.

LOGISTIC REGRESSION: FINAL MODEL

VARIABLE	ESTIMATE	ST. ERROR	CHI-SQUARE	PROB.
INTERCEPT	2.069	.741	7.80	.005
SEX	- .515	.212	5.87	.015
CAD	- .503	.168	8.90	.003
COMORBID	- .683	.191	12.78	.001
ITIME	- .003	.001	5.11	.023
TRIPDRG	.941	.296	6.94	.002
EXPCRD	- .929	.400	5.38	.020
EXPTC	- .578	.282	4.20	.040
LC	.830	.340	5.94	.015

A useful attribute of the logistic regression analysis is that it is possible to use the final model's coefficient estimates and their standard errors to calculate the relative

risk of death at 90 days. This is accomplished by using the following formulae:

$$\text{Relative Risk} = e^{B}$$
$$\text{95\% Confidence Limits} = e^{B \pm (1.96*SE)}$$

The results of these calculations are:

	RELATIVE RISK	95% CONFIDENCE LIMITS
FEMALE	1.6	1.1-2.4
CORONARY ARTERY DISEASE	1.6	1.2-2.2
COMORBID CONDITIONS	2.1	1.4-3.0
TRANSPLANT #1-5 (Vs. >#5)	2.2	1.6-3.4
TRIPLE DRUG THERAPY	2.0	1.5-2.8
ISCHEMIC TIME	1.2	1.1-1.4
PRIOR EXPERIENCE: TRANSPLANT COORD.	2.0	1.1-3.4
PRIOR EXPERIENCE: CARDIOLOGIST	2.7	1.3-5.9

The final model also suggests that several notable variables are not related to transplant mortality. These include:

1) Total transplant volume. This is consistent with earlier findings.

2) Program start-up year. Improved mortality over the three year study period is more appropriately attributed to increasing use of triple drug immunosuppressive therapy and to decreasing proportions of patients transplanted at new transplant centers.

Again, these findings are consistent with earlier analyses.

3) Use of preoperative mechanical support. Earlier univariate and bivariate analyses (chapter 2) had suggested that patients requiring such support did experience higher mortality rates. This minor lack of congruence in the findings of the two statistical methods may reflect physicians ability to select patients who are otherwise at low risk for the procedure (and that at least some of the cues used by physicians are not captured as effectively in the univariate and bivariate analyses as they are in the multivariate analysis).

In considering this minor discrepancy, it is also worth recalling that the existing literature (19,20) on the relation between preoperative mechanical support and transplant mortality is inconclusive (see chapter 2 for a discussion of this subject). All previously published studies of this subject have used simple univariate analyses, but despite similar statistical methods, the above studies reached

opposite conclusions. My study is the first to analyze preoperative mechanical support using multivariate techniques. Clearly the putative relation between preoperative mechanical support and post-transplant mortality requires further investigation.

In my opinion, such investigations would be greatly enhanced by efforts to distinguish between the various forms of mechanical support and to use multivariate analyses. My clinical experience suggests that patients requiring support via intraaortic balloon counterpulsation have different characteristics from patients requiring left or biventricular support devices. For example, they are less likely to be female and less likely to have peripheral vascular disease. These differences may affect the relation between preoperative mechanical support and transplant mortality. My study has the benefit of multivariate analysis, but I am unable to differentiate patients according to the particular form of preoperative mechanical support.

4) Pre-operative left ventricular function. As with the use of preoperative mechanical support, univariate and bivariate analyses had suggested that patients with preoperative left ventricular ejection fractions less than 11% had a worse prognosis. In this case, the incongruence between the results of the two statistical methods probably reflects inaccuracy in the measurement of left ventricular function. The ejection fraction can be calculated using at least four different

technologies. Each one is imperfect to some extent, and their results are not strictly comparable. Undoubtedly, contributing transplant centers used different technologies to make this calculation (I did not collect data on the technique used to make it). Variation in technique across centers considerably reduces the value of the data collected on left ventricular function, and considerably reduces my ability to rigorously analyzed its effects on transplant mortality.

It is remarkable that these latter two cases are the only instances in which there is a lack of agreement between the results of this logistic regression and the results of the conventional univariate and bivariate analyses of chapters 2-7. The vast majority of the findings are the same regardless of the analytical method used. This lends great strength to the findings themselves. In chapter 9, I discuss the results of this study and its implications for heart transplant policy.

CHAPTER 9

DISCUSSION

SUMMARY:

This chapter reviews theoretical, methodological and data reliability issues associated with the present study. It then discusses this study's implications for transplant policy and makes recommendations for future research.

KEY POINTS:

- Prior to this study, no one had attempted to analyze the relation between mortality following heart transplantation and:
    * the characteristics of transplant centers, or
    * experience with the procedure.

  In addition, data linking mortality with recipient and donor characteristics was not conclusive.

- This study shows that several patient and donor attributes are related to mortality following heart transplantation. Other study results appear below:

- Among center characteristics, prior transplant experience in cardiologists and coordinators confers substantial mortality reductions in new transplant centers.

- There is a learning curve for heart transplantation: As centers perform each of their first 5-10 transplants, mortality risk decreases for subsequent transplants.

- There is no relation between transplant mortality and transplant volume, rate or year.

- The results of this study should be considered in the context of several methodological issues.

- The results of this study have several policy implications, discussed below.

OUTLINE FOR CHAPTER 9

INTRODUCTION

Long before heart transplantation was demonstrated to be a viable therapy for patients with end-stage heart failure, it was apparent that this technology would be extraordinarily expensive and that its success would depend on teams of highly skilled individuals that could deliver intensive, meticulous, and comprehensive care to each recipient. By the mid-1980s, many centers had demonstrated that heart transplantation was indeed efficacious, and in fact that it was a lifesaving therapy for a small group of individuals who were otherwise certain to die within months. It had also become clear that the scarce donor organ supply would limit the availability of the transplant procedure to a number substantially less than the number of patients who could benefit from the procedure.

Thus by mid-decade, policymakers were compelled to address several key issues regarding heart transplantation. How could they assure equitable access to the technology? How could they maximize the benefits derived from the scarce donor supply? How could they control the costs of this procedure?

The challenge facing policymakers was that strategies designed to address any one of the above issues appeared to conflict with strategies designed to address the others. For example, third parties recognized that a decision to cover heart transplantation was necessary to assure access, but such a decision would result in enormous program costs. In this case, public pressure forced them to do so, and in any event

the conflict was not overly daunting because third parties could simply pass on the program costs in the setting of such strong public sentiment.

The conflict raised between strategies designed to increase access and those designed to maximize benefits from the scarce donor supply was more pointed, however. On one hand, attempts to enhance access required that more centers be certified to perform it. This was the case because there was a clear relation between geographic proximity to a transplant center and the probability that a patient in need could actually receive a transplant. Transplant centers and their patients could simply not manage the complex care process in instances where patients lived far from transplant centers.

On the other hand, maximizing social benefits from the scarce donor organ supply meant-to some-that only a few centers could be designated to perform heart transplantation. The strategy of limiting heart transplant center diffusion was designed to accelerate learning about the procedure, centralize and coordinate what limited expertise there was, and to increase the volume of procedures at these few centers. Volume increases, the logic went, would likely lead to mortality and cost reductions, as had been shown for other medical procedures.

Unfortunately, policymakers were forced to face this pointed conflict in the absence of data that could have informed their strategies. Specifically, no one had studied

the relation between experience and outcomes in heart transplantation. Did centers with high transplant volumes enjoy better outcomes from the procedure? Is volume in fact the proper proxy for experience with new or rapidly emerging technologies? What constitutes adequate transplant experience for physicians or centers that wish to initiate programs? Should experience be vested in the transplant surgeon, the cardiologist or the coordinator, or in fact is it the center as a whole that accumulates experience? No one knew.

Policymakers did their best in the absence of such data. Medicare, which was also concerned about program costs, heeded the advice of an expert panel and chose to limit diffusion through a designated center strategy. UNOS, the United Network for Organ Sharing, adopted personnel-based experience criteria that effectively facilitated the establishment of transplant programs in geographic areas of need[1].

This dissertation has informed the above debate. Specifically, by exploring and characterizing the relations between heart transplant experience and outcomes, it has provided an empirical basis for the study and refinement of current heart transplant policy.

I present the major findings of this dissertation in chapters 2-8. In this chapter, I summarize, compile and analyze these findings, address methodological issues raised

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[1] These issues are discussed in more detail in the Introduction.

by the study and conclude by reviewing the policy implications of this study.

EXPERIENCE IN HEART TRANSPLANTATION: DEFINITIONS AND CHARACTERISTICS

The major goal of this dissertation is to explore and characterize the relation between experience and outcome following heart transplantation. "Experience" is defined in Webster's New Collegiate Dictionary as "the fact or state of having been affected by or gained knowledge through direct observation or participation (30)." Experience increases through repetition of a particular function or task. In health care, both professionals and patients value experience highly. For example, experience forms the most important criterion in deciding whether to promote health care professionals to positions of authority. Patients routinely seek care from professionals who are felt to have gained "experience" treating their particular medical condition.

People value the experience of providers because they assume it is correlated with improved results. However, this is not always the case. First, if perfection or near perfection in performance can be achieved vicariously, then repetition of that activity will not result in further improvement. Many simple activities associated with management of transplant recipients fit this description. Consider the standard evaluation received by transplant recipients who

present with fever. A transplant physician learns how to perform this evaluation by reading a "fever work-up" protocol. Once the physician reads that protocol, he or she gains little knowledge about the protocol through subsequent repetitions of the fever work-up[2].

Another mechanism by which experience may not lead to improved outcomes is if the operator misinterprets or fails to learn from his experiences. A third mechanism for a disconnect between experience and improved outcomes occurs when knowledge or skill gained through experience plays an insignificant role in determining the outcomes of a particular activity. This is the case in Percutaneous Transluminal Coronary Angioplasty (see chapter 4) where innovations in catheter design overshadow the importance of operator experience.

It is therefore possible to conceive of situations in which the relation between experience and outcome is direct, indirect or nonexistent. In heart transplantation, any of these relations could plausibly exist.[3] Hence it is necessary

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[2] Of course, the interpretation of these diagnostic tests depends heavily on experience.

[3] Positive relation: A physician becomes more skilled managing rejection he sees more episodes of it. Negative relation: Errors increase because the coordinator cannot keep up with the flow of data generated by an increasing recipient pool. No relation: A new immunosuppressive drug is introduced. This drug has no kidney toxicity. This obviates prior experience balancing the renal side-effects of immunosuppressive drugs with the risk of rejection.

to determine this relation empirically (for heart transplantation).

The challenge is that the word, "experience" connotes several different concepts: there is more than one proxy for "experience". The two most widely recognized models-or proxies-for experience are volume and the learning curve.

Volume is simply the total number, or amount of repetitions of a particular function or task. Procedure volume would appear to be an ideal descriptor of experience in circumstances where individuals have already mastered a particular skill or function; they have long since developed a standard approach to that procedure. In such circumstances, the increment learned by any single performance of that procedure is a) small compared to the high skill levels that have already been achieved, and b) about the same as the increment learned by the next, or the preceding performance. These conditions are met for the mature, long accepted surgical procedures that have been studied in the medical volume-outcome literature (reviewed in chapter 5).

In contrast, procedure volume does not capture the dynamic, accelerated process by which individuals gain proficiency as they attempt a procedure for the first several times. In these circum-stances, individuals actively experiment each time they perform the procedure: they vary their approach, practice manipulative or cognitive skills, and integrate current experiences with those of the past and those of colleagues.

Of course with each repetition, the individual faces fewer unfamiliar situations or decisions, and performs activities which become less and less unique. Therefore, individuals gain considerably more skill per repetition as a result of their first attempts than they do from subsequent repetitions. Eventually they reach a "steady state" proficiency; they have mastered that procedure.

To review, when individuals first attempt a procedure, each isolated performance results in an increment of learning that is, a) relatively large compared to existing skills, and b) greater than the increment gained through subsequent repetitions. This type of learning, more dynamic than the volume proxy has the capacity to describe, holds true whether the procedure itself is new (heart transplantation, using VCR machines, etc.) or whether individuals first try to perform an established procedure (obtaining blood specimens, driving a car). TO THE EXTENT THE SKILLS AND KNOWLEDGE ACQUIRED DURING EARLY REPETITIONS OF THE PROCEDURE ARE TRANSLATED INTO IMPROVED OUTCOMES OR REDUCED COSTS, A LEARNING CURVE IS GENERATED.

When compared with the volume proxy, it would appear that the learning curve proxy describes more precisely the events surrounding heart transplant technology circa 1984-86 (the period of the present study). During this period, a very substantial proportion of transplants were performed at centers where few or none had previously been performed. These

new transplant centers are implementing many unique care processes, and their professional staff is gaining skill in many new areas.

Nevertheless empirical studies, such as this dissertation, are required not only to identify the proper proxy for experience but to determine the key factors that modulate, or influence the relation between experience and outcome. These factors include, for example prior training of key individuals, preexisting attributes of the transplant centers, and the transplant community's ever deepening understanding of the requirements for successful heart transplantation.

THE RESULTS OF THIS STUDY

I now review the findings of this study. I begin by reviewing the relations between "traditional" determinants-characteristics of patients, donors and centers-and transplant mortality. I then review relations between experience and transplant mortality.

TRADITIONAL DETERMINANTS

As first presented in chapters 3 and 7, this study confirms that several patient, donor and center characteristics are related to mortality following heart transplantation, and that several others are not. I discuss the following attributes:

Gender
Type of Preexisting Heart Disease
Age
Preoperative Mechanical Support
Preoperative Left Ventricular Function
Comorbid Conditions
Donor Ischemic Time
Immunosuppressive Regimens
Prior Experience among Coordinators
Prior Experience among Cardiologists
Prior Experience among Surgeons
Volume of Allied Procedures
Who Manages Immunosuppressive Therapy?

FEMALES HAVE A 60% GREATER RISK OF DEATH FOLLOWING HEART TRANSPLANTATION THAN MALES[4]. One other study (25) reached a similar conclusion. Another study (23) found no relation between gender and survival, but noted that females had higher rates of transplant rejection. One theory to explain these findings is that females are exposed to their spouse's gene pool during childbirth, and this modulates their future immune responsiveness. It would be easy to test this theory because

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[4] NOTE: I derive the estimate of 60% from the logistic regression analysis (described in detail in chapter 8). The results of univariate analyses (figure 2.12) suggest nearly a 70% mortality reduction in females. In the following discussion, I continue to provide estimates from the logistic regression only for the sake of simplicity and consistency (the reader may refer to figure 2.12 in order to calculate mortality reductions based on univariate analyses). By doing so, I do not intend to suggest that the logistic regression is more reliable or compelling than the other statistical analyses in this document. As I discussed in chapter 8, all of the available tests have strengths and weaknesses, and so their results should be considered to complement each other.

clinicians routinely obtain antigen sensitivity panels during routine pretransplant evaluation. Testing the above theory would involve studying the effects of parity on antigen sensitivity, rejection rates and mortality.

PATIENTS WHO HAVE CORONARY ARTERY DISEASE AND REQUIRE TRANSPLANTATION HAVE A 60% HIGHER RISK OF DEATH than those with other indications for the procedure. One earlier study (26) reported similar findings. Patients having coronary artery disease frequently have had bypass surgery at an earlier stage of their disease. Prior thoracic surgery increases the technical difficulty of the heart transplant procedure, and this may lead to higher mortality rates. It is also possible that transplant recipients with coronary artery disease have a higher incidence of other conditions (such as peripheral vascular disease, chronic cigarette smoking, or chronic pulmonary disease) that affect mortality following transplantation. A third possibility is that the multiple blood transfusions associated with bypass surgery expose recipients to foreign antigens and so alter immune responsiveness. If the data were available (it is not, currently, in the Registry) one could test the latter hypothesis by stratifying transplant recipients with coronary artery disease into two groups according to the presence or absence of prior bypass surgery. Similarly, it would be useful to stratify all recipients according to the presence of a prior history of blood transfusion.

Another group of findings that carries major implications for the patient selection process are that RECIPIENT AGE DOES NOT CONFER INCREASED RISK, whereas the presence of COMORBID CONDITIONS[5] CONFERS A MORTALITY RISK EQUAL TO TWICE THAT OF PATIENTS WITHOUT SUCH CONDITIONS.

These findings are grouped together because clinicians commonly use them to assess whether an individual should be accepted as a candidate for heart transplantation. Clinicians are certainly aware that there is a profound shortage of donor organs. As a result, they screen patients using the above (and other) criteria to assure that the donor organ will be given to patients having a reasonable chance for long term survival. They all recognize such measures are imperfect, however, and inevitably they must rely on clinical judgement and a consensus-development process in which teams of experts assess risks and the probability of long-term survival.

The fact that age is not correlated with post-transplant mortality has been reported before (11-15). However in previous studies, small sample sizes made it difficult to determine whether age was truly not correlated or whether clinicians could effectively counter a real "age-effect" by selecting patients who were otherwise at low risk for the procedure. In this study, the large sample size permits

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[5] This is a proxy that combines the presence of any one of the following into one category: preexisting diabetes, chronic obstructive pulmonary disease, primary renal dysfunction or primary liver dysfunction.

multivariate analysis with sufficient analytic power to address this question. The results indeed show that age is not correlated with post-transplant mortality.

The fact that comorbid conditions is associated with increased mortality risk will come as no surprise to clinicians. It provides strong empiric support for current screening practices, which rely heavily on evaluations to exclude the presence of these conditions.

As discussed in chapter 8, this study is somewhat inconclusive with respect to the impact of MECHANICAL CIRCULATORY SUPPORT and LEFT VENTRICULAR EJECTION FRACTION on mortality post-transplant. Specifically, univariate and bivariate analyses suggest that these two variables are predictive of mortality, whereas the logistic regression does not suggest they are predictive.

In the former case, the inconclusive findings probably reflect the fact that patients requiring different levels of mechanical support (ie: intraaortic balloon pumps versus left and biventricular assist devices) are lumped into one variable. These patients almost certainly have different characteristics (different gender, incidence of peripheral vascular disease) and these differences themselves have large potential effects on transplant mortality. As a result, the patients captured in the "mechanical support present" category represent an unacceptably heterogeneous group.

In the latter case, the lack of concordance probably

reflects the fact that left ventricular ejection fraction is simply not a sensitive, accurate measure of cardiac performance: the signal-to-noise ratio in this data is so low as to render it largely useless (see chapter 8 for a further discussion of these issues).

DONOR ISCHEMIC TIME HAS A SMALL BUT SIGNIFICANT EFFECT ON TRANSPLANT MORTALITY. Patients for whom the donor ischemic time is greater than 2 hours have 20% higher mortality risk than patients with shorter ischemic times. Thus, previously noted ultrastructural and functional derangements associated with prolonged ischemic times (27) can now be linked with increased mortality.

In addition to the above results correlating patient and donor attributes with transplant mortality, this study reveals several interesting correlations between (the characteristics of) transplant centers and mortality following heart transplantation. I review these presently:

PATIENTS NOT RECEIVING TRIPLE DRUG IMMUNOSUPPRESSIVE THERAPY HAVE A MORTALITY RISK EQUAL TO TWICE THAT OF PATIENTS WHO ARE RECEIVING IT. Immunosuppressive therapy is a relatively fixed characteristic of transplant programs. Typically, transplant programs develop a single immunosuppressive protocol and use it for all recipients. Protocols can be modified to meet the needs of individual patients, but this is rare. When centers do modify their protocol, the change is generally implemented for all

recipients. Between 1984 and 1986, transplant centers increasingly adopted triple drug therapy protocols, this had a major impact on transplant mortality. In fact, this procedural modification is the principal reason for the improved transplant survival seen during these years. This point is illustrated by data from this study showing that 1984 transplant recipients who did not receive triple drug therapy experienced the same probability of survival as similarly treated patients who underwent transplantation in 1986 (see chapter 3).

When compared to older regimens involving high dose cyclosporine, or first generation immunosuppressive drugs in the absence of cyclosporine, triple drug therapy is associated with fewer rejection episodes and with a decreased susceptibility to infection (13-22). These are certainly responsible for the improved survival associated with triple drug therapy.

PRIOR HANDS ON TRAINING OF CARDIOLOGISTS OR TRANSPLANT COORDINATORS are characteristics of new transplant centers that confer a major positive impact on outcomes. CENTERS THAT BEGIN TRANSPLANT PROGRAMS WITH NEITHER OF THESE FEATURES HAVE MORTALITY RISK APPROXIMATELY 2.5 TIMES GREATER THAN CENTERS THAT BEGIN WITH AT LEAST ONE. These findings persist in all subgroup analyses, and are particularly striking in patients having the worst prognosis.

Except perhaps for the magnitude of their effect, these

findings will not surprise cardiologists or coordinators. In many centers, these individuals orchestrate all aspects of pre- and post-transplant management. They decide who to list for transplant, diagnose and treat recipients' medical conditions, coordinate input from other transplant team members, and follow-up the details of lab values, diagnostic tests, and biopsy results.

In striking contrast, TRANSPLANT PROGRAMS THAT BEGIN WITHOUT PRIOR TRAINING OF THE TRANSPLANT SURGEON HAVE RESULTS THAT ARE NO DIFFERENT FROM THOSE THAT BEGIN WITH THIS FEATURE. This finding is somewhat counterintuitive given that the field was pioneered by surgeons and that it obviously features cardiovascular surgery of mythical proportion. However it is in fact consistent with modern clinical experience. The likely explanation is twofold:

1) Surgeons that attempt heart transplantation have already mastered the intraoperative and postoperative skills associated with routine open heart surgery (coronary artery bypass, valve replacement), and they generalize these skills to the heart transplant procedure[6].

2) The component of intra- and post-operative mortality that is due to the technical skills of the surgeon has already

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[6] In fact, most surgeons believe that the heart transplan-tation is technically less demanding than coronary bypass surgery, because the latter involves suturing together diseased vessels, whereas the former involves a pristine (sic) surgical field.

been reduced to a minimum as a result of the above, so overall success with heart transplantation becomes dependent on medical issues such as the management of rejection and infection. These issues are handled in the majority of transplant centers by cardiologists, coordinators, and other non-surgeons.

The relations between two other center characteristics and mortality should be mentioned:

1) Centers with relatively low AND relatively high VOLUMES OF OPEN HEART SURGICAL PROCEDURES have HIGHER mortality following heart transplantation. A similar U-shaped relation exists between CARDIAC CATHETERIZATION VOLUME and transplant mortality. This finding is of interest because Medicare has set as one of its designation criteria minimally (but not maximally) acceptable volumes for these allied procedures (10). The rationale for this Medicare criterion is that transplant programs will need support from individuals and delivery systems that produce these services. The finding that LOW allied procedure volume is associated with high transplant mortality appears to justify such requirements. However, the finding that HIGH allied procedure volume is associated with high transplant mortality raises speculation that the delivery systems and communication patterns designed to produce high volumes of allied procedures cannot adapt to the unique and intensive needs of a transplant program.

2) Centers in which CARDIOLOGISTS OR INTERNISTS MANAGE

IMMUNOSUPPRESSIVE THERAPY have insignificantly lower (12% vs. 15%) transplant mortality when compared with centers in which surgeons do this. Interestingly however, the former group does significantly better in caring for patients who are among the first to under go heart transplantation (transplants 1-5), although this difference disappears completely as surgeons manage more patients (figure 7.8).

Because of the previously described results showing that prior transplant experience makes a difference for cardiologists and coordinators but not surgeons, these findings require further discussion. It is important to recognize that most cardiology and cardiovascular surgery fellowship programs do not prepare individuals to prescribe immunosuppressive drugs. On the other hand, most of these fellows have received some relevant training during their residencies. Internal medicine residents in fact get extensive opportunities to manage patients with prednisone (for asthma, allergic reactions, immune system diseases, etc.), and this drug is responsible for many of the immunosuppressive-related complications following heart transplantation. They also get reasonable exposure to patients taking azathioprine for the treatment of solid tumors, and to patients experiencing drug-induced renal toxicity as is commonly seen with cyclosporine. On balance, cardiologists probably do have more extensive prior experience with these drugs than surgeons, but the data suggests that surgeons catch up quickly.

It is also important to recognize that in this study, all but one of the transplant centers in which surgeons manage immunosuppressive therapy also feature a KIDNEY TRANSPLANT PROGRAM. This latter feature does not independently impact mortality following heart transplantation, but it is likely that surgeons utilize this on-site expertise as they began to manage immunocompromised patients.

EXPERIENCE AS A DETERMINANT

The results of this study suggest there is a heart transplant LEARNING CURVE. That is, in centers initiating heart transplant programs between 1984-86, recipients who are among the very first to undergo the procedure have higher mortality risk than those who subsequently undergo transplantation. This phenomenon is detectable through (about) the ninth transplant. Beyond (about) the ninth transplant, it is not possible to demonstrate further reductions in transplant mortality as a function of increasing repetitions of the transplant procedure. The heart transplant learning curve has several features:

1- The relation is consistently present in patients who are at high risk from the procedure. It is not consistently present in low risk patients.

2- The exact shape of the curve depends on the subgroup analyzed[7]. However as a general rule, patients who are among the first five transplants at a particular center have twice the mortality risk of those who are transplanted after the 10th procedure.

3- The relation is readily apparent in centers beginning programs in 1984 and 1985. The data set contains very small numbers of patients who underwent heart transplantation at centers beginning programs in 1986. It is thus not possible to demonstrate learning curves for these centers (see chapter 4 for a detailed discussion of this issue).

4- Knowledge and skills gained through the management of low risk patients are transferable to the management of high risk patients. For example, center A transplants a high risk patient after several low risk patients. That high risk patient has a lower mortality risk than he would have, had center A transplanted him without the benefits accrued through its prior experience with low risk patients.

5- The learning curve is visible in centers regardless of whether their cardiologists, coordinators or surgeons have obtained prior experience.

It is by no means a complete surprise that this study has identified a heart transplant learning curve. After all, the

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[7] Shape includes, a)the slope of the line correlating transplant number with mortality, and b)the number of transplants over which this correlation can be demonstrated.

successful performance of heart transplantation requires that centers implement many new care processes, and that many professionals gain skill in new areas. It is nevertheless of great interest that a learning curve can be demonstrated using an outcome measure as insensitive to the quality of care as 90-day mortality.

From the information in this study, it is not possible to identify which of the many patient care processes are affected by early experience and hence mediate the learning curve. Nevertheless, as a basis for speculation and future research, it is useful to divide the overall care process into the following phases[8].

1) Before Transplantation: With practice, transplant centers might reasonably improve their skills in the evaluation of the underlying heart failure and the coexisting conditions which may well dominate the post-transplant course. They may become more adept at evaluating the needs for social support post-transplant, and making arrangements for these needs in a timely fashion. In addition, they may well learn how to make better decisions about whether and when listed

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[8] Sloan, et. al., developed the following analytic framework to support their review of the volume-outcome relation in organ transplantation. It first appeared in: "Is There a Rationale for Regionalizing Organ Transplantation Services?"; Organ Transplant Policy; Blumstein, Sloan eds.; Duke University Press; 1989. The framework applies equally well to a discussion of learning curves.

patients should be hospitalized for inotropic or mechanical support.

2) Immediate Post-Transplant Period (hospital stay): This period is initially characterized by major physiologic and hemodynamic abnormalities, and later by intense patient rehabilitation and education. There is undoubtedly considerable opportunity to improve care through practice in this phase. Many unique diagnostic and therapeutic procedures must be executed and their results interpreted. New conditions must be diagnosed and responded to appropriately. In these instances, both the reaction time and judgement might benefit from experience. Even the decision to discharge the patient can have a major impact on outcomes, at least in the short term.

3) Post Discharge Management of the Patient-As mentioned earlier, transplant recipients must take immunosuppressive medications for the rest of their lives to prevent or reduce the severity of rejection. These medications place patients at high risk for serious infection. In addition, they can cause osteoporosis, renal failure, diabetes and hypertension. Therefore the supreme challenge in modern transplant management is to taper the doses of these medications so as to minimize adverse side effects while not allowing the risk of rejection to become too high. Physicians unquestionably can improve their abilities through practice in immunosuppressive management.

Less obvious but equally important in this phase are the processes for scheduling the frequent outpatient visits and biopsies, processing the accumulated laboratory data, and informing patients about medication changes. And no less important are processes for supporting patients and families through the emotional highs and lows that routinely accompany convalescence from this life-saving procedure. Here too, there is little doubt that early experiences can allow transplant centers to improve their performance.

While this study does not elucidate the specific care processes which are characterized by learning curves, it does suggest that the mechanism underlying the phenomenon includes at least two of the variables discussed earlier (see chapter 4). First of all, learning curves are more easy to demonstrate in patients with high pretransplant burdens of illness. The likely explanation is that the marginal skills obtained from managing an initial cohort of recipients are critical for high risk patients, but not as important in managing uncomplicated patients.

Interestingly, the marginal skills required to improve outcome in the high risk patients can be gleaned from the management of low risk patients (see figures 4.24-25). This suggests that improved outcomes in high risk patients depend more on mastery of the basic care processes encountered during treatment of routine recipients (rejection management, the response to abnormal kidney function tests, etc.) than on

familiarity with the unique situations encountered during the management of critically ill patients. The correct execution of routine care processes, accomplished through repetition, appears to be the key determinant of survival in high risk transplant recipients.

Second, the heart transplant learning curve is influenced by the advent of triple-drug therapy. A learning curve is easy to demonstrate in patients treated without this innovation (figure 4.17), but it is not present in those that did receive triple-drug therapy. Thus, as advances in catheter design simplified the task of PTCA, so has an immunosuppressive drug innovation reduced the importance of learning in heart transplantation.

This finding is of critical importance, because the trend towards the use of triple drug immunosuppressive therapy has clearly continued beyond 1986, the end of the study period. This suggests that the results of this study (as they apply to the learning curve) may not easily be applied to heart transplant practice in 1990. It is absolutely essential to restudy this learning curve phenomenon using more recent data sets[9].

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[9] Of course as described below, an offsetting phenomenon here is that mortality, this study's outcome measure, is extremely insensitive. It is quite possible that other studies using more sensitive indices of outcome (such as post-transplant renal function, hospital days, functional status or the frequency of rejection) will detect learning phenomena even in patients receiving triple drug therapy.

Other measures of experience do not have an impact on transplant mortality. For example, mortality declines with each successive YEAR OF TRANSPLANT, but the decline is due to increasing use of triple drug therapy[10] and to an increasing proportion of patients transplanted at centers that had already achieved benefits attributable to the heart transplant learning curve.

TRANSPLANT VOLUME, the total number of transplants performed at a particular center, also has no effect on mortality. This is an extremely important finding because Medicare maintains a volume criterion in its certification process: it requires that a center perform at least 36 procedures before it will designate that center to receive reimbursement for transplant-related services.

As reviewed in chapter 5, this study is the first of its kind to analyze the volume-outcome relation in heart transplantation.

Interestingly, investigators have demonstrated such relations for a wide variety of surgical procedures (see review in chapter 5), but no investigator has been able to demonstrate them in kidney transplantation[11].

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[10] 1984 transplant recipients who were treated with triple drug therapy had mortality rates equal to 1986 transplant recipients who were treated similarly.

[11] As noted in chapter 5, much of the volume-outcome literature in kidney transplantation became available after Medicare set the above policies.

In fact, this study's findings can be thought of as confirming and extending the findings referable to kidney transplantation. Both involve the implementation of highly unique care processes and an unusual degree of cooperation between allied professionals-especially surgeons and medical specialists. Both are characterized by relatively simple surgical procedures followed by lifelong, complex medical follow-up.

Perhaps this last feature suggests an explanation for the lack of a demonstrable volume-outcome relation in organ transplantation. Surgical expertise in organ transplantation has been perfected to the point that survival following a transplant has come to depend primarily on the medical follow-up received by the patient. And although the volume-outcome relation has not been extensively studied in non-surgical conditions, it has turned out to be far more difficult to document such relations when they have been sought after (see chapter 5).

TRANSPLANT RATE also has no effect on mortality, at least over the range of rates noted during this study. Transplant rates are thus high enough to let individuals maintain skills and familiarity with the complex processes by which transplant care is delivered. These rates also do not occur with a frequency that would overwhelm caretakers or the intricate transplant care processes. It is important to reexamine the relation between rate and outcome using more recent data,

since many transplant centers now perform transplants at rates below the lowest rates recorded in this data set.

RELIABILITY AND VALIDITY OF THE RESULTS

The results of this study should be interpreted in light of the following facts:

RELIABILITY OF THE DATA

The principal source of data for this study is the Registry of the International Society for Heart Transplantation. During the mid-1980s, this Registry was personally maintained on an IBM XT personal computer by Dr. Michael Kaye at the Minnesota Heart Institute. Until recently, heart transplant centers were not required to submit data to the Registry. However, during the period of this study approximately 95% of all US transplant centers, including the 20 most active centers, voluntarily contributed data to the Registry. There is no reason to suspect that data from the remaining centers would have changed the results of this study.

At most transplant centers, the responsibility for preparing and mailing data to the Registry falls to the transplant coordinators. This task is time-consuming and frequently interferes with the coordinator's routine patient care responsibilities. Furthermore, coordinators are not paid to prepare Registry forms. Thus, variation in the frequency

with which files are updated and in the completeness of reports is to be expected. However, there is no reason to suspect that certain types of centers systematically underreport or omit data from the forms. Therefore there is no reason to suspect a reporting bias in the data. In any event, the selection of a 90-day mortality endpoint for this study (as opposed to a one year endpoint, which has been used by many centers in reporting their own findings) minimizes the potential for reporting bias by decreasing the interval over which follow-up is required.

The supplementary survey contributed important data on patient and center characteristics. 80% of the Registry centers responded to requests for the supplemental information. They provided data on a total of 85% of all recipients. Supplemental information was available for the top ten centers by volume (although it was necessary for the author to make site visits to Stanford, the University of Pittsburgh, and the University of Minnesota to accomplish this) and all but two of the top 20 centers. Contributing centers did not differ from non-contributors with respect to 90-day mortality or other parameters. Similarly, patients for whom supplemental information was available had outcomes that were no different from those for whom supplemental data was available.

As with the original Registry forms, transplant coordinators were responsible for completing supplemental

surveys. However, as above, there is no reason to suspect a reporting bias with respect to data collected via the supplemental survey.

A second issue referable to data reliability is the fact that information contained in certain variables is imprecise. The variables in question concern the management of immunosuppressive therapy, prior experience and comorbid conditions.

WHO MANAGES IMMUNOSUPPRESSIVE AGENTS?-The supplemental survey requested that centers respond to this question by circling one of the following: surgeons, cardiologists or other internists. In some centers, this question cannot be answered so simply. For example at Brigham and Women's Hospital, surgeons write the orders on patients who are in the immediate post-operative period, although they frequently solicit advice from cardiologists. After the immediate post-operative period and for all outpatients, cardiologists manage immunosuppressive therapy. In other centers, interdisciplinary teams make treatment decisions, and in many instances, transplant coordinators are allowed to manipulate certain agents with supervision (!).

Nevertheless, a)most centers do delegate this responsibility to one of the above groups, and b)it is likely that centers featuring non-traditional approaches to immunosuppressive management would distribute themselves between the three possible answers to this question. This

would minimize the risk of bias, but of course the larger issue is that the present study cannot examine whether teams of physicians can more effectively manage immunosuppressive therapy than can individuals.

PRIOR HANDS-ON EXPERIENCE-This study's supplemental survey allows one to determine whether cardiologists, coordinators and/or surgeons had obtained prior experience before initiating new transplant programs. Unfortunately the survey provides no room for respondents to characterize their prior experiences. Obviously, some detail concerning the duration of prior training, the degree of involvement in direct patient care, and the types of patients treated would be desirable.

This study has shown that learning curves are present at new heart transplant centers. It cannot be inferred from this study that individual learning curves (presumably manifesting themselves during the period of prior training) would follow the same pattern, although clinical experience suggests that individual learning curves would be related to the degree of involvement in direct patient care.

COMORBID CONDITIONS-The supplemental survey did not provide precise definitions for each comorbid condition, so coordinators had to use personal judgement in answering this question. This may have introduced biased overreporting of comorbid conditions among recipients who died. However, it is just as possible that respondents would overreport these

conditions for surviving recipients. In fact, the overall incidence of reported comorbidities (7%) is clinically believable, and the magnitude of their negative effects are consistent with clinical expectations.

MISSING DATA

Information regarding several areas of interest is captured by neither the Registry nor the supplemental survey. Among the uncaptured information that would be most interesting, there are:

Traditional Determinants of Mortality

Unfortunately, the Registry collects no data from the routine preoperative right heart catheterization. This pre-transplant catheterization contains many objective parameters of preoperative hemodynamic function such as the cardiac output, right heart filling pressures, and the pulmonary capillary wedge pressure. All transplant centers routinely collect this information during their pre-transplant evaluations, and it would not be difficult for the Registry to gather this data. These measures would provide far more insight into preoperative hemodynamic status than currently collected information (listing status, presence of preoperative mechanical support) because the latter can be influenced by physician discretion or variations in the use of mechanical support devices.

In particular, such data would enable the Registry to

assess the effects of elevated pulmonary vascular resistance (PVR) on mortality following heart transplantation. Elevated PVR is a common sequelae of advanced cardiac disease. It has been known for 15 years that elevated PVR can cause right heart failure in the donor heart shortly after transplantation (16). Irreversible and severely elevated PVR is therefore an absolute contraindication to heart transplantation. However, there is considerable controversy about the risks of cardiac transplantation in patients who have reversible elevations or who have mild to moderate elevations. For the record, the most common practice is to interdict heart transplantation for patients who have fixed PVR measurements greater than 6-8 wood units (3-4 times the upper limit of normal) (17).

Details of Immunosuppressive Therapy

Registry data banks contain minimal information regarding immunosuppressive therapy. The data collected is simply a list of the agents used for rejection prophylaxis in each patient. There is no information regarding the dosages used, the parameters used to adjust dosages, or even the times at which each drug is initiated and/or discontinued. In the transplant community, it is widely accepted that recipient mortality and morbidity are affected by the above decisions, and so this represents a major failing of the current study. Two other aspects of immunosuppressive therapy should also be mentioned:

A) OTHER IMMUNOSUPPRESSIVE DRUGS-In 1987, many centers began to use OKT3, a monoclonal antibody, for the prophylaxis

and acute treatment of rejection. Antithymocyte Globulin is also used at certain centers. Other centers are experimenting with vincristine, cytoxan, total lymphoid irradiation and other approaches. The Registry data banks do not permit evaluation of these new approaches.

C) THE TREATMENT OF REJECTION-Once rejection occurs, it requires immediate therapy. As with rejection prophylaxis, centers have developed unique approaches that could have major effects on transplant mortality. Variations in the drugs of choice, routes of administration, duration of therapy and the approach to recurrent rejection are among the more important elements in rejection treatment, but unfortunately the Registry contains no information on this subject.

Details of the Care Process

The data sets used in this study contain no information regarding diagnostic and treatment protocols, communication patterns and teamwork. The present study suggests that such details are important determinants of transplant mortality. For example, learning curves are present even at centers that feature prior training of key transplant personnel. Thus, there is a component of "institutional learning" (ie getting the above care processes right) that cannot be avoided by simply training key personnel. Among the most interesting processes to study are: the diagnosis and treatment of rejection, transplant biopsy protocols, patient education and rehabilitation protocols. Others include the quantity and

quality of communication between patient and transplant team, between team and consultants, and between team members themselves.

Miscellaneous Data

The study does not include transplants in children, heterotopic transplants or retransplants, and so results may not apply to these groups. Patient characteristics such as the presence of peripheral vascular disease, a history of tobacco, drug or alcohol abuse, or socioeconomic status may impact outcomes, but they are also not studied. And of course, the study is based on transplants between 1984 and 1986. It is remotely possible that the findings of this study might not be applicable to heart transplant technology in 1990.

POLICY IMPLICATIONS

As outlined above, the heart transplant policies of the United Network for Organ Sharing (UNOS), Medicare and other groups were formulated in the context of a paradox. The paradox was that policies aimed at increasing access to the procedure (such as those which stimulated the proliferation of transplant centers) appeared to conflict with policies aimed at maximizing social benefit from the scarce donor pool (such as those which designated a small number of centers for reimbursement).

Policymakers found it difficult to approach this paradox logically because there existed no data to inform the debate.

On one hand, there was no data to support the belief that transplant center proliferation improved access to the technology. On the other hand, there was no data to support the belief that designating centers and hence increasing procedure volumes at the designated centers would improve outcomes.

In the absence of such data, heart transplant policy has been inconsistent. Medicare has chosen to designate a small number of centers for reimbursement; one of its principal reasons for doing so has been to increase transplant volume and centralize expertise at these designated centers. UNOS has chosen to adopt policies that encourage the proliferation of heart transplant centers.

This study provides data that for the first time can inform the heart transplant policymaking process as it relates to the above paradox. It demonstrates that patient, donor and center characteristics, as well as learning curve phenomena, all affect mortality following heart transplantation. And critically, it shows that there is no relation between transplant volume and mortality. The implications of these findings for current and future heart transplant policy include the following:

IMPLICATIONS FOR UNOS-In 1990, heart transplant centers are required by federal law to comply with UNOS membership criteria. The UNOS criteria focus on the experience of the transplant surgeon and transplant cardiologist. They do not

require prior institutional experience nor do they specify any structural criteria[12] for institutions to qualify. In effect, UNOS criteria encourage physicians to become trained and then to establish new transplant programs (hopefully in geographic areas of need).

This study provides strong support for the UNOS personnel-based criteria, because it shows that prior training at the individual level is an important predictor of survival following heart transplantation. However, this study shows specifically that it is the prior experience of cardiologists and transplant coordinators that affects outcomes; prior experience of transplant surgeons does not affect outcomes. UNOS criteria emphasize prior experience on the part of cardiologists and transplant surgeons. UNOS should certainly not delete the criteria for surgeons on the basis of this study alone, but it might consider relaxing them, especially for surgeons who wish to initiate programs in geographic areas of need. In addition, UNOS should maintain current standards for cardiologists and it should develop criteria for the prior training and experience of transplant coordinators.

The UNOS policy not to require that institutions maintain certain features (such as kidney transplant programs,

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[12] These might include the presence of a kidney transplant program or written protocols for the management of transplant recipients.

affiliation with medical schools, or a high volume open heart surgical program) is also supported by this study. None of these features was found to have an impact on mortality following heart transplantation. Of course it remains possible that other structural features are important determinants of survival, and it would appear reasonable to study these if questions persist.

IMPLICATIONS FOR MEDICARE-Heart transplant centers wishing to be designated by Medicare must meet its criteria which, as opposed to those of UNOS, focus on institutional experience and other structural characteristics of institutions. Medicare criteria do not include guidelines for prior professional experience with the procedure.

The results of this study suggest that Medicare should revise its heart transplant policy in many important aspects. Most importantly, this study was unable to demonstrate a volume-outcome relation in heart transplantation, but a cornerstone of Medicare policy is based on the assumption that one exists. Medicare's premise is that reimbursing for the procedure only when it is performed at high volume centers would redirect patients towards those centers and hence improve the survival of Medicare beneficiaries from the procedure. This premise is not valid.

Interestingly, Medicare was correct in assuming there would be a relation between experience and outcome in heart transplantation; it simply chose the wrong model for

experience! As described above, the proper descriptor for experience in heart transplantation is the learning curve.

As Medicare considers how it should revise its institutional-based experience criterion, it might well consider this study's finding that the benefits of experience have peaked after approximately the 9th transplant, and they are at most minimally important in low risk patients. Medicare should therefore revise its experience criterion from the present minimum of 36 transplants to at most, 10 to 15 cases[13]. Furthermore, it should require that the first several heart transplants performed at any center should be performed on low risk patients.

Other results of this study have implications for Medicare heart transplant policy. Specifically, this study shows that transplant center characteristics have no impact on survival. Medicare's designated center policy includes several of these characteristics, including the annual open heart surgical volume and the annual volume of cardiac catheterizations. It would appear reasonable to drop these criteria from the designation process and to study the remaining criteria that have not been addressed in this study.

THE LEARNING CURVE AND TRANSPLANT POLICY-One of the most important contributions of this study is its documentation and

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[13] In addition, UNOS should abandon its plans to review centers that fail to perform 12 transplants per year, so long as their survival rates conform with standards.

characterization of the heart transplant learning curve. In effect, this study shows that transplant centers "learn by doing" up to about the 9th transplant, but this phenomenon is far more apparent for high risk patients than it is for low risk patients. First and foremost, this finding must be reexamined using more recent data sets (for the reasons mentioned above and in chapter 4) If these learning curves continue to be demonstrable, then both Medicare and UNOS should incorporate guidelines that:

1-Assure that the new centers transplant low risk patients exclusively in their initial 7-10 experiences, and,

2-Recognize that poor outcomes are more likely to occur initially[14],perhaps by establishing survival standards for the first 7-10 transplants which are lower than standards for any subsequent transplants.

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[14] But as above, these poor outcomes may not be inevitable. One can reasonably expect to see important mortality reductions to the extent that new centers transplant only low risk patients during their initial 10 transplant sequence.

RECOMMENDATIONS FOR FUTURE RESEARCH

Confirming and Extending the Results

This study utilized Registry data from 1984-1986. Heart transplant technology has progressed in the four subsequent years (though not with the blinding speed that characterized the mid-1980s), so it is necessary to reconfirm the relations between mortality and all measures of experience. Even without updated supplementary surveys, the Registry contains enough data to confirm this study's major findings.

In addition, it would be useful to study relations between experience and other outcomes besides mortality. Mortality is an insensitive outcome measure. Measures of functional status, quality of life, number of hospital-days per year, frequency of rejection, complication rates and the functioning of critical organs (including the transplanted heart) are likely to provide additional insight. Possibly, the variables in this study would exhibit different relations with other outcome measures (for example, the learning curve might be demonstrable over the first 20 transplants when serum creatinine is the outcome measure. As another example, perhaps there is a relation between center volume and complication rates). Most centers already collect data regarding multiple outcomes (13), and it may not require unreasonable effort to collate this centrally.

A third area that merits investigation is the relation

between experience at the level of the individual physician and outcomes (31). Center experience does not necessarily correlate with physician experience. In many transplant centers, several physicians share responsibilities, so center experience proceeds more rapidly. In contrast, physicians occasionally care for transplant recipients at different centers. It is plausible (and many findings in this study suggest) that individual experience is a more important determinant of outcomes than center experience.

The fourth and perhaps most publicly visible issue is the relation between experience and costs of heart transplantation. Cost control has rightfully been at or near the top of third parties' heart transplant agenda, and it is a principal rationale for the Medicare designated center strategy. There is extensive evidence to suggest a relation between volume and cost in industrial settings (40), but it has been difficult to document similar savings in health care due to methodological difficulties in the quantification of health care costs (49)[15]. Although no empirical proof is available, it is certainly true that the capital costs of transplant programs are low because they use the facilities already in place for open heart surgical programs.

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[15]No one doubts that heart transplantation is expensive. However, its cost per year of life saved is comparable to other generally accepted medical technologies such as renal transplantation and dialysis.

Beyond Center Characteristics: The Heart Transplant Care Process

Most heart transplant centers have modern diagnostic and therapeutic equipment, and they have subspecialists that can lend expertise when necessary. This study suggests that transplant mortality depends not on their mere presence, but upon the communication patterns, handoffs and protocols by which these structural elements are integrated. These care processes are extremely diverse, and they mature and change in response to learning, increasing volume, or changes in transplant rate. Analysis of these care processes may provide insights that could enhance results at new and established programs.

Consider the following example, which illustrates the complex processes by which transplant centers care for recipients:

> Patient X is 3 months status-post heart transplantation. He develops a fever of 102 degrees. He notifies a transplant coordinator who in turn notifies a transplant staff physician. The physician instructs the coordinator to tell the patient to come to the EW for evaluation. The EW physician who sees the patient suspects he has a viral pneumonia. He notifies the transplant physician. The latter calls an infectious disease expert to inquire about proper viral titers and the appropriateness of

starting empiric antiviral therapy.

In this case, certain attributes of the transplant center enable it to provide optimal care for the patient. These include an EW physician and an infectious disease expert who are skilled in the evaluation of immunocompromised patients, a laboratory with the capacity to perform sophisticated viral studies, and a pharmacy that stocks rarely used antiviral drugs. Regulators can easily determine whether a transplant center possesses such characteristics.

Far more difficult to ascertain, but equally vital to the quality of patient care is the skill with which the center coordinates these features; the accuracy and efficiency with which the above process is executed. The complex interactions, information handoffs and nuances of protocol become apparent when one considers the errors that could occur as this relatively simple process is executed:

The patient might not know that he should call when he develops a fever. He might not know who to call, or how to contact that person. The coordinator might be unreachable as a result of a broken beeper or a missed communication with the page operator. The same is true of the transplant physician and the infectious disease expert. The transplant physician might forget to alert the EW that the patient is immunocompromized. The pharmacy might be temporarily out of the antiviral drugs. The laboratory that routinely runs

antiviral titers might be closed when the specimen arrives, or might forget to tell EW personnel that special protocols must be followed in order to assure proper handling of the blood specimen, etc.

In this analysis of care processes, two phenomena require investigation in particular:

PROGRAM GROWTH AND CARE PROCESSES: The care of each transplant recipient requires meticulous follow-up and the full cooperation of several services beyond the core transplant team. This is relatively easy when the number of recipients is small and a degree of novelty still surrounds the program. However, as programs grow to even moderate size, they place a surprisingly large burden on the cardiac catheterization laboratory, the pathology department and various consultative services. The possibility for miscommunication and incomplete follow-up increases rapidly, and this may indeed explain why this study did not find a relation between volume and outcome. The transplant team must find ways to prevent this[16]. Unfortunately, we know little about how transplant teams manage growth and even less about optimal strategies to do so. Enumeration of optimal strategies may well enhance performance at our largest transplant

[16]At Brigham and Women's Hospital for example, we added a second coordinator to handle inpatient issues, and solicited assistance from interested 2nd year cardiology fellows around the 80th transplant. We also updated all protocols and renewed in-service training sessions for nurses.

centers.

TRANSLATING EXPERIENCE INTO IMPROVED CARE PROCESSES: This study has documented a learning curve for heart transplantation, but it has not elucidated its mechanism. Do physicians modify their patient selection strategy? Do they become more vigilant observers for complications, or do they treat them differently? Do they modify rejection prophylaxis strategies or strategies for the management of acute rejection? Is it the surgeon, cardiologist or coordinator that is most critical?

Similarly, this study has documented that prior experience (on the part of cardiologists and coordinators) is strongly associated with improved results from heart transplantation. What features of this prior experience confer survival benefits? How long must the training period be? What "parent" programs provide the most effective training? A deeper understanding of the mechanisms underlying experience might well lead to enhanced performance at our newest transplant centers.

Related Topics of Interest to Policymakers

The transplant policymakers' dilemma has long been that policies designed to improve access may compromise outcomes from the scarce donor supply. By documenting and characterizing the relations between experience and outcomes, this study has provided approximately half the data that the

policymakers need in order to set truly rational transplant policy.

It remains for researchers to study the relation between transplant center proliferation and access to the procedure. Empirical studies are required because it is not immediately clear that policies designed to stimulate transplant center proliferation would enhance access. For example, access might be determined primarily by the extent to which physicians caring for patients with end stage congestive heart failure were aware of the transplant opportunity or were willing to refer such patients.

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