Does Cardiac Transplantation Prolong Life?

A Reassessment

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Analysis of survival data from two studies on cardiac transplantation suggests that the assignment method used favored the transplanted group and that the improved survival in the transplanted group could be explained solely in terms of selection bias. Several alternative experimental designs are proposed.

TWO RECENT REPORTS of experience with cardiac transplantation conclude that this procedure appears to prolong life in carefully selected patients (1-2). In our opinion, the data do not warrant even this guardedly optimistic assessment, since the observed differences in survival can be explained in terms of probable selection bias.

Methods and Results

Figure 1 contains four survival curves calculated by applying the actuarial methods in Cutler and Ederer (3) to the data of Messmer and associates (1) and Clark and colleagues (2). All time is measured in months from when the patient was first accepted as a potential transplant recipient. Percent survival is plotted on a log scale so that the force of mortality (slope of the log survival plot) can be seen. The data of Messmer and associates (1) (hereafter called study 1) are represented by solid symbols, and those of Clark and colleagues (2) (hereafter called study 2) are represented by open symbols. For both studies circles depict survival of the transplanted group and triangles that of the nontransplanted group. The median survival of the transplanted group exceeds that of the nontransplanted group by about 4 months in study 1 and 8 months in study 2. We now ask if this difference in survival is an effect of treatment or only reflects bias in the assignment of subjects to the transplanted or nontransplanted groups.

In both study 1 and study 2 the patient is assigned to the nontransplant group by default. That is, a potential transplant recipient becomes a member of the nontransplant group because no suitable donor becomes available before the potential recipient dies (or before the end of the study). We now present a hypothetical example that illustrates how this assignment method biases the results in favor of the transplanted group.

Dr. Edgeworth decided to conduct a study of the efficacy of cardiac transplantation, and he accepted three patients, A, B, and C into his pool of potential recipients. Patient A was agonal with, at most, days to live; Patient B was a bad operative risk, having had debilitating cardiac disease for years; and Patient C was comparatively healthy. Unfortunately no allograft became available for 40 days. Patient A had died 3 days after acceptance into the recipient pool; he was assigned to the nontransplanted group. Patient B, too, had died, after 31 days, and was assigned to the nontransplanted group. Only Patient C survived the 40-day waiting period. He received a transplant and had an uncomplicated postoperative course until he died during a rejection crisis 100 days later (which was 140 days after his initial acceptance as a potential transplant recipient). Although Dr. Edgeworth was tempted to compare the survival of Patient C, the transplantee, with that of Patients A and B, the nontransplanted group, he reasoned as follows:

"My assignment procedure introduced important

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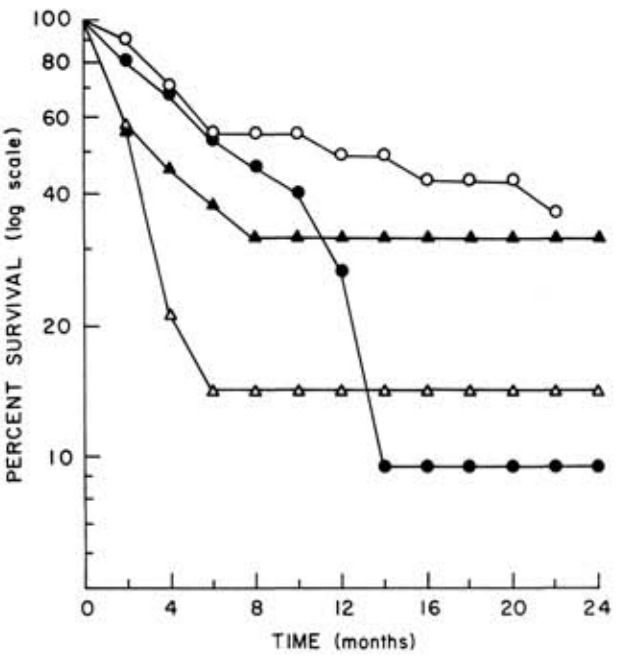

Figure 1. Percent survival (log scale) versus time in months from initial acceptance into the recipient pool. Solid symbols depict data of Messmer and associates (1) and open symbols those of Clark and colleagues (2). Circles represent transplanted groups and triangles nontransplanted groups. (All 14 patients in the nontransplanted group described by Clark are included.)

biases. After all, A, the sickest patient, never had much chance to be transplanted anyway. And in general, most of my sickest subjects will get thrown into the nontransplanted group. Also, this waiting period will tend to filter out the bad risks like Patient B, so I'll only have to operate on comparatively healthier patients like C. This should at least reduce my early mortality, and maybe it will help in the long run too. And if I had randomized the initial assignment to the transplant group, surely some of the patients in this group would have died while awaiting a donor. In effect I have given my transplantee survival curve an artificial boost by guaranteeing survival at least to the time of transplantation."

This example emphasizes the types of biases inherent in the assignment method used in study 1 and study 2 by depicting a very inhomogeneous recipient pool and a long waiting period. But, although this example was chosen mainly to highlight the biases, the biases are real enough, and it is the experimenter (not the gadfly) who must prove that adequate precautions were taken to eliminate bias. Indeed, since the average waiting time was about 20 days in study 1 and 26 days in study 2, and since the initial attrition rate is so high (Figure 1), these biases are undoubtedly important.

We summarize Dr. Edgeworth's objections as follows: [1] the survival time of the nontransplanted group is shorter than would have been observed with a random assignment method, because the method used assigns an unfair proportion of the sicker patients to this group (bias); [2] the survival time of the transplanted group is longer than would have been observed with a random assignment method for two reasons. First, an unfairly large number of good-risk patients have been assigned to this group, introducing a bias. Second, the patients in this group are guaranteed (by definition) to have survived at least until a donor was available, and his grace period has been implicitly added into the survival time of the transplanted group.

Discussion

Messmer and co-workers (1) and Clark and colleagues (2) conclude that cardiac transplantation "appears" to increase survival in suitably selected patients. Figure 1 shows an "apparent" increase in median survival (in comparing transplanted and nontransplanted groups) of about 4 months for study 1 and 8 months for study 2. Our analysis of selection bias allows us to state with some assurance that these figures overestimate the "true increase" in survival attributable to transplantation. (By "true increase" we mean the increase in survival that would have been observed had the original pool of potential recipients been *randomly* assigned to the transplantation and nontransplantation groups at the outset.) Part of the apparent increase in survival (perhaps 2 to 4 weeks) is a waiting period before transplantation. Part of the apparent increase is probably caused by selection bias, as described above. Indeed, the transplantation procedure may contribute nothing to the survival increase in the transplanted group. Clark pointed out that the nontransplanted group was not a "true control" group, but he failed to note, as we have, that the patient assignment method used in these studies almost certainly introduced a selection bias that favored survival of the transplanted group.

Since the difference in survival times between the transplanted and nontransplanted groups is not striking, and since a part of this difference probably results from selection bias and not from treatment method, further large-scale evaluation of the efficacy of cardiac transplantation may not be deemed necessary. Should such studies be planned, however, we suggest three alternative approaches, each answering a slightly different question.

One could pair potential recipients at their mutual time of acceptance as transplant candidates and immediately—and at random—assign one to the transplant group and one to the control group. Survival should be measured from time of acceptance into the

study. This study would measure the overall effectiveness of transplantation therapy, including the practical difficulty of waiting for a suitable donor.

If one were interested in assessing survival from the time of transplantation (rather than from the time of admission as a transplant candidate), one could randomly assign an available heart to one of a pair of living recipients (perhaps that pair that had waited longest). Then the survival of the two groups, transplantees and control subjects, could be measured from the time of operation. This design partially answers the ethical imperative of giving available hearts on a first-come, first-served basis, and it is acceptable if one is prepared to disregard histocompatibility studies in assigning the heart.

If suitable histocompatibility matching is a *sine qua non* of transplantation, one could define several cohorts of transplant candidates, each cohort consisting of subjects accepted as candidates at approximately the same date. A newly available heart would then be assigned to a cohort on a next-in-line basis. From that cohort the two members with best histocompatibility to the donor would be selected, and one would be randomly chosen for transplantation, the other becoming a control. Survival would be measured from the time of operation. If the cohorts were large enough, the two best matches would almost certainly be "suitable" for transplantation.

Each of the previous designs has distinctive desirable (and undesirable) features. The first measures the effectiveness of transplantation in current practice, and the last two the effectiveness of the operation itself in prolonging life. The second alternative partially preserves a first-come, first-served queuing discipline. The third alternative sacrifices this discipline to assure suitable histocompatibility. Other designs are conceivable, but they must all share with these three the feature of randomization to guard against selection bias.

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