Heart transplantation: no longer an experiment

The therapeutic benefit of cardiac transplantation is emphasized by the high quality of life that recipient patients demonstrate. Furthermore, 20 years after the initial faltering attempts at human heart transplantation, survival rates have dramatically improved. In patients otherwise faced with a 90% probability of death within one year, transplantation often results in survival of more than 80%. Reasons for this progress include better cardiovascular surgical technique, more sophisticated immunosuppressive drugs, and increased understanding of rejection dynamics. Additionally, we have more therapeutic agents to treat complications after transplantation, and we have a better idea of which patients are likely to benefit. We review the development of the concept and science of heart transplantation, putting our present knowledge into perspective.

KEY WORDS: CARDIAC TRANSPLANTATION, HEART FAILURE, CARDIOMYOPATHY, IMMUNOSUPPRESSION.

Cardiac transplantation is now a therapeutic option for patients with end-stage heart disease. Indeed, hospitals in Austin, Dallas, Houston and San Antonio perform this procedure, and there may be over 100 heart transplant “centers” in the United States (1). Solid organ transplantation in general is quite frequent. In 1986, more than 11,000 solid organs were transplanted, including 1,430 hearts (1). Improved graft and patient survival associated with these transplants relates to new antirejection medications (including cyclosporine and OKT3), the ability to diagnose organ rejection early, lower maintenance steroid doses, and improved diagnostic techniques and treatment protocols for infection. Additionally, patient selection has become sophisticated with well-defined criteria predicting success. Development of cardiac transplantation as a therapeutic option, in many respects, resembled the progress of renal transplantation, but occurred decades later. The earliest heterotopic transplant of a cadaveric kidney, for example, occurred in 1947. This was done in an anuric pregnant woman who was in severe shock and uremic coma (2). The transplanted kidney produced urine and was removed 48 hours later. The patient recovered. Renal transplantation, however, brought much social and legal debate that spilled over into the early years of heart transplantation as well. Common problems included patient selection, finding suitable organ donors, creating new definitions of death, and handling problems of immunosuppression.

Cardiac transplantation evolved from a highly theoretical and experimental concept to a procedure of proven therapeutic benefit. Much of the basic groundwork for heart transplantation was laid in the early part of this century when Carrel published his protocols for heterotopic canine heart transplants (3,4). These studies actually were designed to pioneer vascular anastomotic technique, so important to cardiovascular surgery in general, but also demonstrated the feasibility of placing an explanted heart in heterotopic position (the animal’s neck). The problem of cell-mediated rejection of transplanted hearts was recognized in 1933 by Mann and associates (5), and Luisada’s group in 1951 first speculated seriously about the therapeutic potential of heart transplantation in humans (6): “A transplanted heart or heart-lung transplantation might be used for replacement of the diseased organ. The latter must be considered, at present, a fantastic dream and does not fall within the scope of present considerations.”

Downie in 1953 (7) demonstrated that heart transplantation in experimental animal preparations was possible with simple techniques. Between 1957 and 1959, Webb et al (8) demonstrated the effectiveness of hypothermic myocardial preservation by completing the first orthotopic canine heart transplants from which the recipient animals awoke (9). In 1958, Goldberg did the first orthotopic canine transplant utilizing cardiopulmonary bypass (10,11), and in 1959 Cass and Brock refined the implantation technique using methods that were ultimately extrapolated to human heart transplants (12). Lower and Shumway in the 1960s reported their technique for canine heterotopic transplants that allowed animals to return, for the first time, to normal function (13,14). It was their observation in 1961 that control of transplant organ rejection was now the most important challenge (15). They noted: “Observations in [our] animals suggest that, if the immunologic mechanisms of the host were prevented from destroying the graft, in all likelihood it would continue to function adequately for the normal lifespan of the animal.” This was a seminal observation, appropriately directing research toward control of the rejection problem.

Subsequent efforts in the 1960s were focused toward technique development, with Reemtsma (16) and Demikhov (17) refining heterotopic (parallel or “piggyback”) transplants. In 1965, Kondo demonstrated long-term orthotopic transplant survival in immunologically immature puppies (18), and Lower showed that exogenous immune suppression allowed long-term survival in his canine transplant model (19). It was during these experiments that a decrease in electrocardiographic QRS voltage was correlated with significant rejection.

It is apparent that a cadre of investigative information, produced over a 60-year period, was responsible for setting the stage for the first clinical trials of human heart transplantation. Early ventures...
into human heart transplantation were controver-
sial. Hardy et al. each reported the first human heart
transplantation (28). In 1964, they implan-
ted a xenograft transplanted (a chimpanzee
heart) in a patient in Jackson, Miss. The small pri-
mate heart was unable to support the patient’s cir-
culation, however, and cardiopulmonary bypass
could not be performed. In 1966, it was shown that
de unless a patient could remove a human heart from a cada-
veric renal donor, and then successfully reimplant
the organ and establish an appropriate rhythm. A
human heart was also successfully transplanted into a
baby (10).

The first orthotopic allograft heart transplant was
performed by Barnard on Dec 3, 1967, in Cape-
town, South Africa (22). The patient survived 18
days, dying of pneumonia and sepsis. The first hu-
man orthotopic heart transplant in America was
done two weeks later in Brooklyn, New York, when
Kantorowitz placed an anencephalic infant’s heart
into a 18-day-old patient with a terminal congeni-
tal cardiac anomaly (23). The recipient infant only
died two weeks later in Brooklyn, New York, when
Kantorowitz placed an anencephalic infant’s heart
into a 18-day-old patient with a terminal congeni-
tal cardiac anomaly (23). The recipient infant only
died two weeks later.

The first orthotopic allograft heart transplant was
performed by Barnard on Dec 3, 1967, in Cape-
town, South Africa (22). The patient survived 18
days, dying of pneumonia and sepsis. The first hu-
man orthotopic heart transplant in America was
done two weeks later in Brooklyn, New York, when
Kantorowitz placed an anencephalic infant’s heart
into a 18-day-old patient with a terminal congeni-
tal cardiac anomaly (23). The recipient infant only
died two weeks later.

The first orthotopic allograft heart transplant was
performed by Barnard on Dec 3, 1967, in Cape-
town, South Africa (22). The patient survived 18
days, dying of pneumonia and sepsis. The first hu-
man orthotopic heart transplant in America was
done two weeks later in Brooklyn, New York, when
Kantorowitz placed an anencephalic infant’s heart
into a 18-day-old patient with a terminal congeni-
tal cardiac anomaly (23). The recipient infant only
died two weeks later.

The first orthotopic allograft heart transplant was
performed by Barnard on Dec 3, 1967, in Cape-
town, South Africa (22). The patient survived 18
days, dying of pneumonia and sepsis. The first hu-
man orthotopic heart transplant in America was
done two weeks later in Brooklyn, New York, when
Kantorowitz placed an anencephalic infant’s heart
into a 18-day-old patient with a terminal congeni-
tal cardiac anomaly (23). The recipient infant only
died two weeks later.

The first orthotopic allograft heart transplant was
performed by Barnard on Dec 3, 1967, in Cape-
town, South Africa (22). The patient survived 18
days, dying of pneumonia and sepsis. The first hu-
man orthotopic heart transplant in America was
done two weeks later in Brooklyn, New York, when
Kantorowitz placed an anencephalic infant’s heart
into a 18-day-old patient with a terminal congeni-
tal cardiac anomaly (23). The recipient infant only
died two weeks later.

The first orthotopic allograft heart transplant was
performed by Barnard on Dec 3, 1967, in Cape-
town, South Africa (22). The patient survived 18
days, dying of pneumonia and sepsis. The first hu-
man orthotopic heart transplant in America was
done two weeks later in Brooklyn, New York, when
Kantorowitz placed an anencephalic infant’s heart
into a 18-day-old patient with a terminal congeni-
tal cardiac anomaly (23). The recipient infant only
died two weeks later.

The first orthotopic allograft heart transplant was
performed by Barnard on Dec 3, 1967, in Cape-
town, South Africa (22). The patient survived 18
days, dying of pneumonia and sepsis. The first hu-
man orthotopic heart transplant in America was
done two weeks later in Brooklyn, New York, when
Kantorowitz placed an anencephalic infant’s heart
into a 18-day-old patient with a terminal congeni-
tal cardiac anomaly (23). The recipient infant only
died two weeks later.

The first orthotopic allograft heart transplant was
performed by Barnard on Dec 3, 1967, in Cape-
town, South Africa (22). The patient survived 18
days, dying of pneumonia and sepsis. The first hu-
man orthotopic heart transplant in America was
done two weeks later in Brooklyn, New York, when
Kantorowitz placed an anencephalic infant’s heart
into a 18-day-old patient with a terminal congeni-
tal cardiac anomaly (23). The recipient infant only
died two weeks later.

The first orthotopic allograft heart transplant was
performed by Barnard on Dec 3, 1967, in Cape-
town, South Africa (22). The patient survived 18
days, dying of pneumonia and sepsis. The first hu-
man orthotopic heart transplant in America was
done two weeks later in Brooklyn, New York, when
Kantorowitz placed an anencephalic infant’s heart
into a 18-day-old patient with a terminal congeni-
tal cardiac anomaly (23). The recipient infant only
died two weeks later.

The first orthotopic allograft heart transplant was
performed by Barnard on Dec 3, 1967, in Cape-
town, South Africa (22). The patient survived 18
days, dying of pneumonia and sepsis. The first hu-
man orthotopic heart transplant in America was
done two weeks later in Brooklyn, New York, when
Kantorowitz placed an anencephalic infant’s heart
into a 18-day-old patient with a terminal congeni-
tal cardiac anomaly (23). The recipient infant only
died two weeks later.

The first orthotopic allograft heart transplant was
performed by Barnard on Dec 3, 1967, in Cape-
town, South Africa (22). The patient survived 18
days, dying of pneumonia and sepsis. The first hu-
man orthotopic heart transplant in America was
done two weeks later in Brooklyn, New York, when
Kantorowitz placed an anencephalic infant’s heart
into a 18-day-old patient with a terminal congeni-
tal cardiac anomaly (23). The recipient infant only
died two weeks later.

The first orthotopic allograft heart transplant was
performed by Barnard on Dec 3, 1967, in Cape-
town, South Africa (22). The patient survived 18
days, dying of pneumonia and sepsis. The first hu-
man orthotopic heart transplant in America was
done two weeks later in Brooklyn, New York, when
Kantorowitz placed an anencephalic infant’s heart
into a 18-day-old patient with a terminal congeni-
tal cardiac anomaly (23). The recipient infant only
died two weeks later.

The first orthotopic allograft heart transplant was
performed by Barnard on Dec 3, 1967, in Cape-
town, South Africa (22). The patient survived 18
days, dying of pneumonia and sepsis. The first hu-
man orthotopic heart transplant in America was
done two weeks later in Brooklyn, New York, when
Kantorowitz placed an anencephalic infant’s heart
into a 18-day-old patient with a terminal congeni-
tal cardiac anomaly (23). The recipient infant only
died two weeks later.

The first orthotopic allograft heart transplant was
performed by Barnard on Dec 3, 1967, in Cape-
town, South Africa (22). The patient survived 18
days, dying of pneumonia and sepsis. The first hu-
man orthotopic heart transplant in America was
done two weeks later in Brooklyn, New York, when
Kantorowitz placed an anencephalic infant’s heart
into a 18-day-old patient with a terminal congeni-
tal cardiac anomaly (23). The recipient infant only
died two weeks later.

The first orthotopic allograft heart transplant was
performed by Barnard on Dec 3, 1967, in Cape-
town, South Africa (22). The patient survived 18
days, dying of pneumonia and sepsis. The first hu-
man orthotopic heart transplant in America was
done two weeks later in Brooklyn, New York, when
Kantorowitz placed an anencephalic infant’s heart
into a 18-day-old patient with a terminal congeni-
tal cardiac anomaly (23). The recipient infant only
died two weeks later.
to 8,000 individuals per year in the United States who would be suitable candidates for cardiac transplantation but there may only be 1,000 to 3,000 donor organs available each year (39). These figures highlight the critical importance of choosing the best available candidate and indicate the reason why a large number of patients die prior to transplantation. Additionally, early identification and evaluation of candidates for cardiac transplantation are important, so that one is not faced with the problem of trying to evaluate and prepare for transplant a dying patient not requiring maximum cardiovascular support in a short period of time.

2. Absolute contraindications to cardiac transplantation

Absolute contraindications to cardiac transplantation are listed in Fig 2. Age is only a relatively important factor so that generally one can accept patients over the age of 60. These figures highlight the critical importance of choosing the best available candidate and indicate the reason why a large number of patients die prior to transplantation. Additionally, early identification and evaluation of candidates for cardiac transplantation are important, so that one is not faced with the problem of trying to evaluate and prepare for transplant a dying patient not requiring maximum cardiovascular support in a short period of time.

Significant coronary artery disease.

Significant peripheral or cerebrovascular disease.

Significant chronic bronchitis or chronic obstructive pulmonary disease.

Unresolved pre-existing malignancy.

Co-existing irreversible medical conditions which may preclude the patients from any future medical therapy for the rest of the patient's life. Similarly, patients with recent pulmonary infarction are particularly predisposed to the development of cavitory lung abscesses. High-dose steroids used for immunosuppression may make control of diabetes difficult, and in our opinion, insulin dependence becomes an absolute exclusion since these problems can have an adverse effect on patients' long-term outcome. Acute right heart failure of the transplanted heart accounts for a significant proportion of mortality in 5% of patients dying. Since acute peptic ulcer disease may be exacerbated by postoperative stress and corticosteroid therapy for the rest of the patient's life. Similarly, patients with recent pulmonary infarction are particularly predisposed to the development of cavitory lung abscesses. High-dose steroids used for immunosuppression may make control of diabetes difficult, and in our opinion, insulin dependence becomes an absolute exclusion since these problems can have an adverse effect on patients' long-term outcome. Acute right heart failure of the transplanted heart accounts for a significant proportion of mortality in 5% of patients dying. Since acute peptic ulcer disease may be exacerbated by postoperative stress and corticosteroid therapy, early identification and evaluation of candidates for cardiac transplantation are important, so that one is not faced with the problem of trying to evaluate and prepare for transplant a dying patient not requiring maximum cardiovascular support in a short period of time.

Active peptic ulcer disease may be exacerbated by postoperative stress and corticosteroid therapy, early identification and evaluation of candidates for cardiac transplantation are important, so that one is not faced with the problem of trying to evaluate and prepare for transplant a dying patient not requiring maximum cardiovascular support in a short period of time.

Significant pulmonary hypertension (resistance > 600 dynes cm sec^-1).

Significant peripheral or cerebrovascular disease.

Significant chronic bronchitis or chronic obstructive pulmonary disease.

Unresolved pre-existing malignancy.

Co-existing irreversible medical conditions which may preclude the patients from any future medical therapy for the rest of the patient's life. Similarly, patients with recent pulmonary infarction are particularly predisposed to the development of cavitory lung abscesses. High-dose steroids used for immunosuppression may make control of diabetes difficult, and in our opinion, insulin dependence becomes an absolute exclusion since these problems can have an adverse effect on patients' long-term outcome. Acute right heart failure of the transplanted heart accounts for a significant proportion of mortality in 5% of patients dying. Since acute peptic ulcer disease may be exacerbated by postoperative stress and corticosteroid therapy, early identification and evaluation of candidates for cardiac transplantation are important, so that one is not faced with the problem of trying to evaluate and prepare for transplant a dying patient not requiring maximum cardiovascular support in a short period of time.

Successful heart transplantation is dependent upon donor organ referral and adequate medical management of these cases. Successful amputation of the donor heart is performed with appropriate cardioplegic technique, and the recipient patient must be stabilized preoperatively, sometimes with aggressive measures that include intravenous vasodilator and inotropic support or a variety of perfusion assist devices. Immediately before surgery, we routinely perform right heart catheterization of the recipient to ensure that normal pulmonary pressure and resistance and inotropic support or a variety of perfusion assist devices. Immediately before surgery, we routinely perform right heart catheterization of the recipient to ensure that normal pulmonary pressure and resistance. Since active peptic ulcer disease may be exacerbated by postoperative stress and corticosteroid therapy, early identification and evaluation of candidates for cardiac transplantation are important, so that one is not faced with the problem of trying to evaluate and prepare for transplant a dying patient not requiring maximum cardiovascular support in a short period of time.

Operative approaches

Successful heart transplantation is dependent upon donor organ referral and adequate medical management of these cases. Successful amputation of the donor heart is performed with appropriate cardioplegic technique, and the recipient patient must be stabilized preoperatively, sometimes with aggressive measures that include intravenous vasodilator and inotropic support or a variety of perfusion assist devices. Immediately before surgery, we routinely perform right heart catheterization of the recipient to ensure that normal pulmonary pressure and resistance.
compensation and are capable of doing extraordinary work. In the early postoperative period, patients often need assistance and monitoring. It is rare for an early postoperative period. Patients also receive high-dose immunosuppressive therapy. Circulation 31(Supp 1):181-187, 1965.


For additional resources on this topic, see the MORE ON THE SUBJECTS department in this issue.