Editorial
The actual meaning of "urgency" in the practice of heart transplantation

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Heart transplantation is an accepted therapeutic option for patients with severe congestive heart failure. Since the availability of heart donors fails to keep pace with the growing demand, increasing numbers of potential recipients are placed on the waiting list, resulting in longer waiting times and increased mortality rates. Data from the United Network for Organ Sharing (UNOS) Scientific Registry 1998 indicate that, while the number of transplantations decreased by 3% between 1995 and 1997, the heart waiting list more than tripled from 1988 to 1997[1]. The same source reports that waiting times are increasing for all candidates but particularly for outpatients. Status 1 candidates had an estimated waiting time of fewer than 55 days in 1997 while the median waiting time for heart transplant increased from 116 days in 1988 to 207 days in 1997. At the end of 1988, 13% of registrants had been on the waiting list for 1 year or more; at the end of 1997, this group accounted for 55% of the waiting list. Several studies have shown that when patients are correctly selected for non urgent heart transplantation listing, mortality remains high, even in those surviving the initial 6 months after listing[2]. Although a European registry for organ transplantation is not available, similar evidence comes from published data of the main European centers for heart failure management.

As the waiting lists grow longer many outpatients deteriorate and require hospitalization and urgent transplantation. The pool of hospitalized candidates, who receive priority for the limited donor hearts, is composed largely of these deteriorating patients rather than those initially listed with urgent status. Status 1 candidates made up 33% of the heart waiting list in 1997. The percentage of recipients on life support just prior to transplant increased from 17% in 1988 to 66% in 1997. Recipients with medical urgency status of 1 increased from 55% in 1991 to 69% in 1997.

These pressures on the transplant system have resulted in attempts to expand the donor pool by liberalizing donor acceptability criteria to include organs previously deemed marginal. Expanded, or high-risk, heart donors have been defined on the basis of age, previous cardiac arrest and resuscitation, use of high-dose inotropic drugs, significant wall motion abnormalities by echocardiogram, significant (> 20%) donor/recipient size disparity, presence of coronary artery disease, and total postretrieval cold ischemic time. Each of these relative contraindications has been challenged[3].

Concerns have been raised that the simultaneous trend toward liberalizing donor criteria and transplanting more patients who are in an advanced state of decompensation could result in poorer postoperative survival, a less effective use of donors and a negligible chance of transplantation for the outpatients[4,5]. The UNOS Scientific Registry reports that among recipients on life support just prior to transplant, those in the Intensive Care Unit (ICU) had similar short-term graft survival rates as those on life support but not in the ICU. However, those on life support not in the ICU had better 3- and 5-year survival rates, with 73% graft survival at 5 years posttransplant compared to 66%

for recipients on life support and in the ICU just prior to transplant. Long-term graft and patient survival rates were the highest for recipients whose donors were between the ages of 11 and 34. The Fifteenth Annual Report of the International Society for Heart and Lung Transplantation includes a multivariate analysis of risk factors for 1-year mortality after heart transplant in 17 685 recipients[6]. Recipient characteristics related to a significantly worse outcome are, among others, the need for ventilator support or mechanical circulatory assistance just prior to transplant. Donor characteristics related to worse outcome are increasing age and increasing ischemic time. These data are consistent with the results of the multivariate analysis of risk factors for 5-year mortality (n = 9536).

This setting defines a very difficult challenge: how may the limited number of donors be best used to minimize death of proposed recipients while on the waiting list and optimize postoperative survival? Although survival rates after transplantation could be better if less-sick patients were selected, the prognosis of these patients without the transplantation could be just as good as their prognosis without it. On the other hand, truly terminal patients with severe end-organ dysfunction despite maximum support may have such high complication rates after transplantation that the use of scarce donor organs for such patients is unethical.

One key to this challenge relies on better prediction of the outcome. There are extensive published reports addressing the risk factors for poor outcome in heart failure. Many risk factors validated in the broad spectrum of mild to moderate heart failure are uniformly elevated and are thus poor discriminants in advanced heart failure. Among these factors, peak VO_2 measured after optimization of maximal medical regimen is the only cardiophysiological prognostic factor routinely used as a selection criterion in heart failure patients being evaluated for cardiac transplantation. The 2-year event-free survival rate for patients with peak VO_2 • 14 ml/kg/min was 48% compared with 84% for patients with peak V O ^{2} > 14 ml/kg/min. The discriminatory power of peak VO_2 is not surprising because it is dependent on two physiological processes that are impaired in heart failure: the ability to increase forward cardiac output and the ability to dilate peripheral skeletal muscle blood vessels in response to exercise. It has not been established whether adjusting the value of VO_2 max to account for patient gender, age, weight, and conditioning status enhances the prognostic value of the absolute peak VO_2[7]. However the use of peak VO_2 as the only prognostic factor used in transplant evaluations does not do the field justice, particularly since several studies have shown that a combination of factors is more predictive. Aaronson et al.[8] examined 80 clinical characteristics at the initial evaluation of 268 ambulatory heart failure patients referred for heart transplantation to the Hospital of the University of Pennsylvania. Two predictive models were constructed: a noninvasive model with seven independent variables (cause of heart failure, resting heart rate, left ventricular ejection fraction, mean blood pressure, intraventricular conduction delay, peak VO_2, and serum sodium); and an invasive model, which added an eighth variable (mean pulmonary capillary wedge pressure). The resulting events were defined as urgent transplant or death without transplant. Low, medium, and high-risk groups were defined as 1-year event-free survival rates of 93, 72, and 43% respectively. Notably the invasive model did not perform better than the noninvasive model in predicting event-free survival. The study by Aaronson et al.[8], however, went further to validate their model in a prospective cohort of patients. The invasive and noninvasive models were applied to 199 ambulatory heart failure patients evaluated at the Columbia-Presbyterian Medical Center who were being considered for cardiac transplantation. Both models performed well in the prospective cohort. When the noninvasive model was used, the validation patients could be stratified into low, medium, and high-risk groups with 1-year event-free survival rates of 88, 60, and 35% respectively. In both the derivation and validation cohorts, patients with medium and high-risk scores had a 1-year event-free survival rate which was lower than expected for patients undergoing cardiac transplantation (82%). The authors recommended that those patients in the medium and high-risk groups be listed immediately for transplantation but that the low-risk patients be deferred. Although there are several limitations, this study is methodologically sound, meets the major criteria proposed for valid and potentially useful clinical prediction models and hence may become the new benchmark for prediction in such patients.

On the other hand, from lessons learned as a result of recent studies and from growing clinical experience the predictive importance of functional and hemodynamic responses to aggressive medical therapy can be addressed. A retrospective analysis of the V-HeFT trials found that patients with serial improvement in left ventricular ejection fraction had better survival than patients without serial improvement. Six-month reassessment of 68 patients who had been placed on the waiting list for heart transplantation on the basis of a peak VO_2 < 14 ml/kg/min resulted in the removal from the active waiting list of 31 patients who had had a Ž 2 ml/kg/min increment in VO_2 max and met the criteria for clinical stability. No deaths and only two transplants occurred over the next 2 years in the group of patients removed from the heart transplant waiting list. A reevaluation of 126 patients, on average 300 days following the initial assessment with the exercise-based heart failure survival score, demonstrated that this statistical model proved useful in guiding the dynamic process of candidate selection. These findings led to the definition of heart transplant candidacy as a dynamic status which may evolve to an improvement that renders transplantation unnecessary or to decompensation of heart failure requiring additional medical therapy or, at the end, heart replacement[9].

In conclusion, any future prediction model should be designed to optimize prediction at whatever prognostic threshold would be most helpful in this discrimination, such as the threshold at which medical prognosis equals transplant prognosis. An ideal model should apply as many independent, noninvasive, prognostic and clinical parameters as needed to maximize discrimination while permitting dynamic flexibility to allow incorporation of newly identified prognostic variables, new treatments, and changes in a patient's clinical status[10].

Strictly linked to patient stratification is the issue of organ donor selection in the sense that certain factors making an organ donor unacceptable for one patient could make it desirable for another. Unfortunately, donor organ allocation schemes do not allow ad hoc donor-recipient matching. Indeed all donors and all recipients are usually regarded as equals. One issue that must be addressed soon if we are to improve organ donor utilization for heart transplant is the concept of risk adjustment to facilitate more specific organ donor allocation schemes. Importantly, one should not consider certain donors "higher risk" but rather, one should carefully consider the risk-benefit ratio of using any given donor in any clinical setting. It is doubtful that anyone would ever attempt cardiac transplantation with a donor heart that was not expected to work well postoperatively. It is even more doubtful that anyone would list a patient for heart transplant if morbidity and mortality risk without the procedure is acceptable.

Besides patient stratification, another key point is optimization of medical therapy as emphasized by the report of the Bethesda Conference on Cardiac Transplantation. All patients with chronic heart failure should undergo careful dissection and reconstruction of their medical regimen bearing in mind at least three main issues. First, continuous hemodynamic monitoring for adjustment of intravenous medications to optimize loading conditions allow for discharge and progressive clinical improvements for many patients considered to have refractory heart failure. Second, the most common target for further medical therapy is the severe elevation of ventricular filling pressures, which can often be reduced to and maintained at near normal levels, with: maximal cardiac output, minimal valvular regurgitation and resolution of congestive symptoms. Third, intensity of effort and resources devoted to follow-up on medical therapy to maximize function and minimize rehospitalization with heart failure should be comparable to those available for patients after cardiac transplant which means patient education, availability of specialized nursing staff, exercise rehabilitation and, as stated above, frequent clinical assessment. A study by Stevenson[11] reported that even patients discharged after arriving for transplantation with New York Heart Association functional class IV symptoms have a 1-year survival of 68%, compared with the earlier 54% described in 1987 for the enalapril group of the CONSENSUS trial in patients with a less clinical compromise. Both perfect patient selection and optimal medical management were the key to the successful experience by Rickenbacher et al.[12]. They studied 116 consecutive patients with symptomatic heart failure, severe left ventricular dysfunction (left ventricular ejection fraction 20 ± 7%) and duration of symptoms > 1 month referred for heart transplantation, who were acceptable candidates for the procedure but were not listed for transplantation because of relative clinical stability. During a mean follow-up of 25.0 ± 14.8 months there were 8 cardiac deaths (7%). Only 9 patients (8%) were listed for heart transplantation. Actuarial 1- and 4-year survival rates were 98 ± 1% and 84 ± 7%, respectively, and freedom from listing for transplantation was 95 ± 2% and 84 ± 7% respectively. As the impact of medical therapy for advanced heart failure continues to improve it should be emphasized that hospitalization for urgent transplantation is now to be viewed as an endpoint of medical treatment failure.

Despite optimally tailored medical therapy, an increasing number of patients decompensate requiring the addition of intravenous inotropic therapy during the pretransplant period. As reported in the current literature, a majority of these are low-cost ambulatory patients on intermediate doses of intravenous dobutamine. Whether patients requiring intermittent inotropic support should be accorded a higher transplantation priority status because of concern about the increased waiting list mortality rate is still matter for debate. The decision to use maintenance intravenous inotropic therapy in heart transplant candidates and the setting in which such therapy is administered must be weighed carefully given the differential in waiting list priority status, the higher costs of inpatient intravenous therapy and the uncertain effects of intravenous inotropic therapy on mortality rates. Findings of a retrospective study by Winkel et al.[13] suggest that in the setting of skilled outpatient surveillance in a heart failure center with rapid access to hospitalization, the waiting list mortality rate for UNOS status 2 heart transplant candidates who require intravenous inotropic therapy to maintain clinical compensation is no greater than that of UNOS status 2 candidates who can be maintained on oral therapy alone. However, further prospective studies are needed.

In an earlier era of medical therapy the "wait and see" strategy of selection was shadowed by the relatively high risk of sudden death early after referral. Today progressive pump failure accounts for 46% of all deaths on the waiting list, whereas about 30% of all deaths occur suddenly. The increasing use of angiotensin-converting enzyme inhibitors, the avoidance of class 1 antiarrhythmic agents and perhaps the increasing use of amiodarone appear to have contributed to the improved survival in advanced heart failure. A study on 737 patients referred for heart transplantation over a 7-year period relates an improvement in 1-year survival to changes in drug therapy[11]. Although the baseline clinical profiles did not change significantly, 1-year mortality declined from 33 to 16% over the 7-year period,

with a decrease in sudden death to 8%. It should also be recognized that some of the decrease in sudden deaths might also result from the closer surveillance and improving ability to detect and address early signs of recurrent hemodynamic decompensation. Monitored terminal cardiac electrical activity in patients dying while awaiting transplantation reveals that bradyarrhythmias and/or electromechanical dissociation are involved in 68% of cases and ventricular tachyarrhythmias in 32% of cases[14]. Patients with a history of aborted cardiac arrest are at a higher risk of recurrent malignant arrhythmias. The implantable cardioverter defibrillator (ICD) is the most effective therapy for preventing sudden cardiac death from ventricular tachyarrhythmias. Pooled data from a total of 75 sudden death survivors listed for cardiac transplantation demonstrate that ICD therapy can be applied with low mortality, low morbidity, and high efficacy, with up to 94% of the patients receiving appropriate shocks during the waiting period. The implanted device does not adversely affect subsequent heart transplant and posttransplant survival. However, there is concern that this early survival benefit conferred by the ICD may be nullified by the competing risk of death due to terminal pump failure, as the waiting list and waiting time to transplantation lengthen. In advanced heart failure, risk stratification for sudden tachyarrhythmic death is only of limited value. Therefore, although sudden tachyarrhythmic death appears to constitute only a minor fraction of total cardiac death in patients awaiting heart transplantation, prophylactic ICD implantation as an electronic bridge to transplantation may be considered. Prospective randomized studies are needed to properly define the prophylactic role of ICD therapy.

Besides pharmacological and electrical bridging methods, the wide discrepancy between possible recipients and available donors generates a realistic need for circulatory assist devices for cardiac support and replacement. A patient who will probably survive until transplantation but present major risk factors for progressive multiorgan failure in the perioperative period may eventually be considered to be at a lower total risk after circulatory support and recovery of secondary organ function before transplantation. Patient and device selection and correct timing probably are the most important factors in determining success with mechanical circulatory assistance, and are still under evolving debate. Options for mechanical support include intraaortic balloon counterpulsation, centrifugal pumps, and pulsatile implantable ventricular assist devices. The intraaortic balloon pump is increasingly coming to be regarded as a short-term option to allow further decisions, essentially a bridge to the bridge. Controversies remain as to whether major benefit is derived from this support, particularly in patients without epicardial coronary artery disease. The centrifugal pumps are also short-term options that require a less extensive operation than more complex devices but do not allow major patient mobility nor an extended "physiological" support period. The individual success rate of all the commonly used implantable assist devices ranges between 81-94%[15]. This shows their efficacy in bridging a patient to heart transplant. The fact that the rates are similar should serve to improve the selection criteria for the use of devices, and patients' needs may one day dictate what device should be used. Such success in terms of survival and quality of life has led to the application of the assist devices as a permanent support alternative to heart transplant. Extended indication of mechanical devices is mainly supported by three different evidences. First of all although mechanical bridging to transplantation is an effective therapeutic option it is suitable only for a limited number of selected patients at the expense of major alterations in waiting list priority. On the other hand, analysis of the International Society for Heart and Lung Transplantation Registry has clearly identified two different classes of patients in which mechanical assistance represents a better option than transplantation: 1) among heart transplant candidates, the older Zero blood group outpatients with a high body surface area or with high rates of preformed antibodies since they have a low chance of receiving an organ, and 2) among those already transplanted, the non-white females since they have a poor outcome. Finally patients on the waiting list represent only a small percentage of those affected by terminal heart failure who may benefit from mechanical support.

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