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Editorial Comment

Optimal Candidates for Heart Transplantation: Is 14 the Magic Number?*

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> As no two faces, so no two cases are alike in all respects, and unfortunately it is not only the disease itself which is so varied, but the subjects themselves have peculiarities which modify its action.
>
> William Osler, 1928

During the past decade, the number of patients awaiting heart transplantation has steadily grown. This impressive growth has not been paralleled by an equal growth in the number of heart transplantations performed as a result of an unchanging donor pool. In 1990, 2,108 heart transplantations were performed in the United States. In 1993, the number had risen to 2,399, a modest increase of 13.8%. As of January 1995, an impressive 2,965 patients were awaiting heart transplantation (1). Other current issues concerning heart transplantation are also worth noting. Because of recent changes in United Network of Organ Sharing (UNOS) listing criteria, the number of patients undergoing transplantation as "Status 1" (inotropic dependent in intensive care unit settings) has increased, whereas the number of patients undergoing transplantation as "Status 2" (waiting at home or in non–intensive care unit settings) has decreased (2). Consequently, Status 2 patients may have a longer waiting time before transplantation and a greater chance of succumbing to their disease while they wait. Although it is true that many listed patients undergo changes in listing status once symptoms deteriorate, others continue to die suddenly.

Transplantation: evaluation criteria. With these observations in mind, and as more patients with advanced heart failure approach the doors of heart transplantation centers, selection of the most appropriate candidates is paramount to properly allocate this very precious resource (i.e., donor hearts). The mission of the transplant center is therefore not only to identify the most suitable candidates among those referred, but more specifically those with the greatest risk of dying. These facts have prompted the reexamination of criteria used for the selection of appropriate transplant candidates, as noted by Wilson et al. (3) in this issue of the Journal.

Standard transplant evaluation criteria usually include a measure of left ventricular ejection fraction, rest hemodynamic variables and oxygen uptake, among others. For the most part, ejection fraction may be the most common reason for patient referral and is generally <25% (4,5). Although a strong marker of survival (6), ejection fraction may lose its prognostic value in the very low ranges <25% (7). In addition, hemodynamic variables, often markedly altered in this population with advanced heart failure, have also not consistently been useful in predicting early prognosis (4).

Assessment of function. Evidence linking exercise capacity with outcome in patients with heart failure has led to the frequent use of peak oxygen consumption (Vo_2) in evaluations of transplant candidates (4,6). Functional impairment has thus become an important criterion in the selection of heart transplant candidates. Some investigators (4,8) have found that values of peak Vo_2 <10 ml/min per kg identify a group of patients with a significantly poor prognosis. In contrast, Vo_2 values >14 ml/min per kg have identified patients whose 1-year survival is comparable to that after heart transplantation (4,6). However, these studies have not consistently defined the timing of the test in relation to optimization of medical therapy nor have they taken into consideration the level of deconditioning of patients with severe heart failure. There is at the present time no consensus on the timing of the "index" exercise test used in transplant evaluation vis a vis optimization of medical therapy.

Poor functional capacity has to date implied an abnormal circulatory response to exercise. This implication has led Wilson et al. (3) to explore the presence or absence of circulatory dysfunction in a group of patients with reduced exercise capacity who would be considered for heart transplantation. Should circulatory dysfunction not be present, Wilson et al. imply that these patients should not immediately be referred for transplantation. Alternatively, they suggest that the source of exercise limitation be explored with hemodynamic measurements or by enrolling the patients in a conditioning program to determine whether improvements in functional capacity can occur.

The search for correlations between hemodynamic variables and exercise Vo_2 to better define functional impairment is not a new one. Several investigators (9,10) have attempted to link abnormal Vo_2 to cardiac output during exercise. Previous work by Weber et al. (9) described at least four levels of functional impairment and correlated each of these to cardiac reserve observed during exercise. They further observed (9) that rest hemodynamic variables did not reliably predict cardiac reserve but that Vo_2 was a useful index of cardiac output response to exercise. Sullivan et al. (10) found that peak cardiac output was positively correlated to peak Vo_2 in a heterogenous group of patients with heart failure.

Wilson et al. (3) set up an objective definition of the severity of hemodynamic dysfunction using both pulmonary wedge

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pressure and cardiac output. They tested a group of patients with heart failure who were relatively homogenous with regard to level of mean peak V_{O_2}, although individual values ranged from 8.4 to 19.6 ml/min per kg. Patients with a relatively preserved exercise capacity were appropriately excluded. Peak V_{O_2} correlated neither to cardiac output nor to pulmonary wedge pressure at each work load. Moreover, 20% of the patients fell into the mild impairment group, and as many as 36% of the patients had a normal cardiac output response and an abnormal wedge pressure with exercise. To further underscore their observation of the need for a better criterion than a simple cutoff value of 14 ml/min per kg, patients were classified into those with a V_{O_2} above or below this value. In fact, 44% of patients with mild or moderate hemodynamic abnormalities had V_{O_2} values ≤14 ml/min per kg, and 25% of the patients with severe hemodynamic abnormalities had values above >14 ml/min per kg. All of these findings were observed in a group of patients who exercised to a similar respiratory exchange ratio, although the group with severe hemodynamic abnormalities had a greater level of lactate production. The study by Wilson et al. (3) did not include follow-up, and therefore no statement can be made concerning the predictive value of each level of hemodynamic exercise dysfunction.

At first glance, these observations seem to contrast with that of previous reports. Such may not be the case. Weber et al. (9) studied patients with more heterogenous levels of V_{O_2}, and only a subset of these patients underwent hemodynamic exercise measurements. Although the mean values for cardiac index with exercise were different, considerable overlap existed among the groups. Sullivan et al. (10) observed a significant difference in peak cardiac output in a group of patients with heart failure compared with that in a group of normal subjects. The values of cardiac output and V_{O_2} at each stage were remarkably similar in both patients and control subjects.

Nonetheless, the conclusions of the study by Wilson et al. (3) must be taken cautiously. There is little argument that patients with preserved exercise capacity (peak V_{O_2} >18 to 20 ml/min per kg) have a good prognosis. Similarly, it is clear that those patients with a marked reduction in exercise capacity <10 ml/min per kg have a significantly poor prognosis. The population whose function lies between these two clear cutoff points is precisely the population often referred for transplantation. It is impractical at this time to assess exercise hemodynamic variables in each and every patient to determine the source of exercise limitations. Indeed, one of the advantages of exercise testing using gas exchange for evaluation of functional capacity is its reproducibility in repeated testing and its noninvasive nature. Furthermore, repeated testing can identify patients whose cardiac status is deteriorating and move them from a nonlisted to a listed status. In contrast, the suggestion of enrolling patients in a cardiac rehabilitation program followed by repeated testing to assess improvement is perhaps at this time the most practical, notwithstanding the reluctance of third-party payors to reimburse these costs.

Wilson et al. (3) emphasize two very important limitations to their study: 1) They observed that reduced muscle perfusion, not cardiac output, could obviously account for exercise limitations, but this was not measured in their study. Reduction in muscle blood flow and changes in peripheral muscle metabolism have been observed in patients with heart failure and may be the source of exercise limitations by other "circulatory factors" (10-13). 2) Oxygen uptake is related not only to age and gender, but also to body size and, more specifically, muscle mass. Yet, values of functional impairment are consistently applied across all age groups and body sizes. Furthermore, there has been a lack of a current normal data base inclusive of sedentary older adults that could be used as reference for predicting maximal V_{O_2}. In a very heterogenous population, application of percent predicted values may better show correlations between V_{O_2} and other variables of cardiac function (5).

Finally, the study by Wilson et al. (3) underscores the complexity of exercise intolerance in patients with heart failure and that a single variable of function should not make the decision for or against transplantation in such patients. Although their study does not deal with outcomes in the population studied, it should encourage further work to determine the best criteria needed for optimal selection of heart transplant candidates.

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