second revascularization procedure than were those assigned to CABG. Subsequent major events occurring in such patients would not be reported. This would bias the mortality and myocardial infarction rates in favor of PTCR.

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REFERENCE


REPLY

We disagree with the comments made by Dr. F. James Brennan that major events were underreported in our recent Journal article (1). Although we used a composite end point that included death, myocardial infarction, cerebrovascular accident and myocardial revascularization, we also separately reported mortality, myocardial infarction, repeat revascularization procedures and stroke (1).

For example, as outlined in the Results section, there were thirteen 30-day deaths in the coronary artery bypass graft (CABG) group and two deaths in the percutaneous transluminal coronary angioplasty (PTCR) group. After one month, five patients died in the PTCR group and four in the CABG group. These deaths are reflected in the Kaplan-Meier survival curves shown in our Figure 2, demonstrating a better survival in the PTCR group compared with CABG group (96.9% vs. 92.5%, respectively, p < 0.017).

We employed the Kaplan-Meier method to estimate length of survival, freedom from myocardial infarction, freedom from repeat revascularization procedures and freedom from combined events for patients treated with CABG and with PTCR (see our Figs. 2–4). Comparison between groups was performed using the log-rank test. The Kaplan-Meier method is an appropriate means of estimating survival and other major events in our study. Because each of the events (mortality, myocardial infarction and repeat revascularization procedures) was analyzed separately using the Kaplan-Meier method, there was no under-reporting of major events. Although a given patient may have experienced a nonfatal primary end point, he or she was not excluded from the analysis of the other events. The Kaplan-Meier method allows the estimation of survival time of each patient who dies and provides exact survival proportions; this is because it uses exact survival times. The same principle was applied in the calculation of freedom from myocardial infarction and freedom from repeat revascularization procedures.

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Lean Tissue Adjusted Peak Oxygen Consumption in Congestive Heart Failure

Osman et al. (1) recently reported data on the prognosis of 225 patients with heart failure. In their analysis they sought to test the hypothesis that peak oxygen uptake gains prognostic power when expressed per lean body mass. Taking the present and other available data (2,3), we entirely agree that this may in fact be possible. However, we also see a number of problems in the present article with regard to exercise testing, the patient group itself and its very low event rate, as well as the statistical analysis. Therefore, we cannot consider their article to offer proof of its conclusion.

The mean peak oxygen uptake (VO2) of their population of heart failure patients was 16 ml/kg/min. The mean anaerobic threshold was 12.7 ml/kg/min, and the peak heart rate was only 126 beats/min. Although mentioned in their Methods section, the investigators’ data for respiratory exchange ratio at peak exercise, a marker of metabolic stress, are not given anywhere in their report. The investigators chose to present event rates based on 14 deaths and 15 urgent transplants. In other words, the total mortality rate in this population was about 7% during 19 months of follow-up. This study group appears on average to have been in mild heart failure. This low mortality rate is surprising given the mean peak VO2 of 16 ml/kg/min. Even if urgent transplant is included in the end point, the 12-month event rate in patients with peak VO2 ≤14 ml/kg/min is still only about 15%, which seems very low. Using the same cutoff, Mancini et al. (4) reported a mortality rate of 30% to 53% in 12 months. Taken together, this raises concern about the validity of their exercise tests, suggesting that an adequate VO2 may not have been reached.

Whichever way one examines the data, the total event number of 29 appears too small to perform extensive statistical analyses. The main statistical analysis in the Osman et al. (1) article is concerned with comparing peak VO2/weight versus peak VO2/lean weight as a continuous or dichotomous variable, respectively. Unfortunately, the receiver-operator curves (ROCs) for the two continuous variables are not presented, and the arguments are based on somewhat different chi-square (20.53 vs. 17.17) and p values (0.0001 vs. 0.0007). No statistical comparison for the two continuous variables is provided. Also, the comparison of the two cutoffs appears difficult to interpret.

First, the data in their Table 2 (1) do not specify the follow-up period to which they relate. Second, calculation of the ROC is reserved for variables with many different levels. In their Table 2,
because in each case there is only one cutoff, it is not possible to calculate an area under the curve (AUC) for ROC as one has only one data point of corresponding sensitivity and specificity. 

Further explanation is necessary. It would be worthwhile to know how the p values for the differences between the AUCs were obtained, as the p values seem very small (Table 2) for the comparison between the two peak VO₂ measures.

Additionally, it remains arguable whether the comparison to Mancini’s cutoff is justified at all, as the cutoff was established in a much sicker population, whereas the lean cutoff was specifically designed for this population. Does selection of the optimal peak VO₂/weight cutoff change the predictive power of this variable? Finally, we cannot consolidate the fact that the confidence interval for the RR values in their Table 5 (1) encompasses 1.0, yet all p values are highly significant.

The literature reviewed for the Osman et al. article appears somewhat incomplete. Using the DEXA-scan, previous studies have found that absolute peak VO₂ (in ml/min) closely relates to lean tissue mass in patients with congestive heart failure (CHF) (5,6). That peak VO₂/weight underestimates true exercise capacity in obese patients with CHF (7) and overestimates it in cachectic patients with CHF (8) has been suggested some years ago.

Finally, the investigators (1) conclude that peak VO₂/lean weight is the cardiopulmonary exercise parameter that provides “the best risk stratification across the heterogeneous systolic heart failure cohort.” The presented data do not justify this conclusion. First, this is due to the above problems, but more importantly this is because the VE/VCO₂-slope (which is automatically provided by the equipment the authors used) was ignored for all analyses. For several years now the latter is known to be a strong prognosticator (9,10) independently of peak VO₂. In mild CHF, the VE/VCO₂-slope is even superior to peak VO₂ in predicting prognosis (11). Again, we believe the report by Osman et al. (1) examines an important subject, and we agree that peak VO₂/lean weight is better than peak VO₂/weight, but we also believe this message has not been proven by these investigators, and that the points we addressed above could have been beneficially optimized during the review process.

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REFERENCES

REPLY
We appreciate the opportunity to respond to the concerns raised by Drs. Wensel and Anker, which in our opinion do not affect the major results and conclusions of our study (1).

Of the 225 patients we studied, 170 (75%) reached anaerobic threshold (mean VO₂ at AT 12.28 ± 3.97 ml/kg/min). Additionally, at peak oxygen consumption, the mean respiratory exchange ratio was 1.09 ± 0.14, suggesting an adequate effort for the study population.

The authors also point out the low mortality rate of our population, and they compare our major event rate to that of the smaller and sicker population studied by Mancini et al. (2). Whereas 46% of our patients were in New York Heart Association (NYHA) functional class III, 40% in class II and 14% in class I, 70% of the population in Mancini’s study were in NYHA functional class III, and even 13% in class IV, with only 17% in class II. In addition, owing to many years separating patient selection for these two studies, there may be major differences in overall medical management, including aggressive revascularization of patients with ischemic cardiomyopathy, adequate use of angiotensin-converting enzyme (ACE) inhibition (95% of our patients) and an evolving mandated use of beta-blockers (31%), which have likely reduced the morbidity and mortality for our heart failure patients. However, we believe that our population is representative of heart failure and cardiac transplant patients currently presenting to large referral centers in the United States. In addition, the relatively high percentages of women and, particularly, obese patients—with both groups having strong trends for lower major event rates—further contribute to the low overall event rate noted in our cohort.

The authors refer to several studies that corroborate the evidence that lean body mass correlates better to peak oxygen consumption. We regret not having mentioned Dr. Anker’s study using DEXA scanning, an accurate technique but one that has not gained wide practical acceptance. In our study we used a simple anthropometric