symptoms, poorer exercise tolerance, and worse prognosis, despite having a LVEF that was no different from the patients without anemia.[2] However, anemia is seen not only in severely ill patients but also in those with only moderate or mild HF, and even in asymptomatic patients.[11] In our study, men with chronic HF with low hemoglobin concentrations had the poorest exercise capacity and functional class, without significant differences in LV function.

**In this study, we found that across a broad range of severity of HF, exercise capacity is significantly dependent on hemoglobin concentrations. This relation is even stronger within the population with below normal hemoglobin levels. In the subset of patients with low hemoglobin, exercise capacity was more significantly related to LVEF than in the overall HF population.**


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# Body Composition and Prognosis in Chronic Systolic Heart Failure: The Obesity Paradox


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Although obesity has adverse effects on cardiovascular structure and function[1–11] and may be a risk factor for heart failure (HF),[12] several recent studies have suggested that in patients with chronic systolic HF, obesity is actually associated with trends for better survival.[13–15] However, these studies mostly included patients with severe functional limitations, patients who were in New York Heart Association (NYHA) class IV, and only assessed body mass index (BMI) and not body composition parameters, such as percent body fat. This study examines the impact of obesity and specific various body composition parameters on clinical outcomes in patients with chronic systolic HF and only mild to moderate (NYHA class I to III) functional limitations.

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We retrospectively studied 209 consecutive ambulatory patients with chronic systolic HF (NYHA class I to III) who were referred to our cardiac rehabilitation program for assessment of body composition parameters at the time of a standard cardiopulmonary exercise test between January 1996 and December 1998. All patients had HF for ≥6 months and were on stable doses of their medications with no increase in symptoms or need for intravenous inotropic support for ≥6 weeks before study entry.

We assessed 5 body composition parameters: body surface area, BMI, percent body fat, total fat, and lean body weight. The percent body fat was determined by the skinfold technique using the average of 3 skinfolds (thigh, chest, and abdomen in men; thigh, triceps, and suprailiac in women). Total body fat was determined by total weight multiplied by the percent body fat, and lean body weight was the total weight minus the fat weight.

All patients were followed at the Cardiomyopathy and Heart Transplant Center, and clinical events, including cardiovascular death and urgent transplantation, were collected from medical records or phone interviews. Listing for transplant was done by committee consensus based on clinical, metabolic, exercise, and hemodynamic data, and all urgent transplantations consisted of status 1 patients who were constricted to an intensive care unit requiring inotropic support.

We compared the 28 patients with major clinical events (13 cardiovascular deaths and 15 urgent transplantations) with 181 patients without major clinical


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**TABLE 1** Clinical Characteristics and Body Composition Parameters of the Study Population, Including Those With and Without Major Clinical Events (cardiovascular death or urgent transplantation)

| Characteristics | Events (n = 28) | Event-free (n = 181) | p Value |
|---|---|---|---|
| Age (yrs) | 53 ± 13 | 54 ± 12 | 0.63 |
| Men (%) | 24 (86%) | 145 (80%) | 0.45 |
| Etiology | | | |
| Ischemic | 20 (71%) | 68 (38%) | 0.001 |
| Nonischemic | 8 (29%) | 113 (62%) | |
| NYHA Class | 2.7 ± 0.5 | 2.3 ± 0.7 | 0.007 |
| I | 1 (4%) | 20 (11%) | 0.01 |
| II | 6 (22%) | 80 (44%) | |
| III | 21 (74%) | 81 (45%) | |
| Left ventricular ejection fraction (%) | 19 ± 9 | 24 ± 13 | 0.02 |
| Peak $VO_2$ (ml/kg/min) | 13.6 ± 4.4 | 16.5 ± 6.0 | 0.004 |
| Peak $VO_2$ lean (ml/kg/min) | 17.5 ± 5.1 | 22.3 ± 7.4 | <0.0001 |
| Medications | | | |
| Lanoxin | 89% | 82% | 0.37 |
| Diuretics | 93% | 81% | 0.13 |
| Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers | 93% | 95% | 0.55 |
| β blockers | 30% | 31% | 0.90 |
| Body surface area ($m^2$) | 2.0 ± 0.26 | 2.06 ± 0.24 | 0.22 |
| BMI ($kg/m^2$) | 27.7 ± 5.1 | 29.2 ± 5.4 | 0.15 |
| Percent body fat (%) | 22.5 ± 6.8 | 26.5 ± 7.7 | 0.01 |
| Total fat (kg) | 19.7 ± 9.0 | 24.5 ± 10.6 | 0.02 |
| Lean body weight (kg) | 65.5 ± 14.5 | 65.9 ± 12.5 | 0.89 |

**TABLE 2** Clinical, Cardiopulmonary, and Event Data in Obese (BMI ≥30 $kg/m^2$) and Lean (BMI <25 $kg/m^2$) Patients

| Parameter | Obese (n = 76) | Lean (n = 43) | p Value |
|---|---|---|---|
| Age (yrs) | 51 ± 12 | 57 ± 14 | <0.02 |
| Men (%) | 56 (74%) | 33 (77%) | 0.71 |
| BMI ($kg/m^2$) | 34.6 ± 4.3 | 22.7 ± 1.8 | <0.0001 |
| Body fat (%) | 31 ± 8 | 20 ± 5 | <0.0001 |
| Peak $VO_2$ (ml/kg/min) | 14.5 ± 4.9 | 17.7 ± 7.3 | <0.01 |
| Anaerobic threshold (ml/kg/min) | 11.8 ± 3.6 | 14.2 ± 5.0 | 0.02 |
| Peak $VO_2$ lean (ml/kg/min) | 20.9 ± 6.5 | 22.2 ± 9.0 | 0.36 |
| Major events | 8 (10.5%) | 9 (21%) | 0.11 |

events. We also evaluated quintiles of each body composition parameter for major events. Regarding BMI, we also analyzed characteristics of obese (BMI ≥30 $kg/m^2$) versus nonobese (BMI <30 $kg/m^2$) and versus lean (BMI <25 $kg/m^2$) patients.

Continuous variables are expressed as mean ± 1 SD, whereas discrete variables are shown as percentages. Categorical variables were compared using the likelihood ratio chi-square test. With continuous variables, group means were compared with the unpaired Student's *t* test or Wilcoxon rank sum test if the variables did not follow the normality assumption. Event-free survival curves were also constructed using the Kaplan-Meier product limit method for quintiles 1 and 5, and were compared with the log-rank test.

Cox proportional hazard regression analysis was performed to determine the independent predictors of event-free survival, and included 1 obesity parameter (either BMI, percent body fat, or total fat) and 6 clinical parameters (age, gender, ischemic vs nonischemic cardiomyopathy, functional classification, left ventricular ejection fraction, and peak oxygen consumption [$VO_2$]).

The baseline clinical characteristics of the study population are listed in Table 1, including differences between those with clinical events versus event-free survivors. Patients with major events were more likely to have ischemic cardiomyopathy, higher NYHA classification, slightly lower ejection fraction, and lower peak $VO_2$, as well as peak $VO_2$ corrected for lean body mass (peak $VO_2$ lean). Both groups were statistically similar regarding age, gender, and baseline medications.

The body composition parameters are listed in Table 1. Patients with clinical events had lower body surface area and BMI, but these differences were not statistically significant. However, patients with events had significantly lower percent body fat ($p = 0.01$) and total body fat ($p = 0.02$) compared with event-free survivors. In contrast, lean body weight was statistically similar and almost identical in those with events and event-free survivors.

When we compared obese versus lean patients (Table 2), obese patients were significantly younger and had higher percent body fat, whereas peak $VO_2$ and the anaerobic threshold were statistically lower than in the lean patients. However, when peak $VO_2$ was corrected for lean body mass (peak $VO_2$ lean), both groups were similar statistically. The lean patients had a twofold higher incidence of clinical events, although this was not statistically significant ($p = 0.11$). Both obese and lean patients were similar with regard to gender as well as classification of HF, functional class, ejection fraction, and medications. When the obese group was compared with the nonobese patients (n = 133), the same trends were apparent for the parameters listed in Table 2. Obese patients had slightly lower incidence of events (10.5% vs 15%), which was not statistically significant.

Data regarding body composition quintiles and major clinical events are presented in Table 3 and Figure 1. In general, there were trends for better event-free survival with higher body composition quintiles. Patients in quintile 1 generally had more major events than patients in quintile 5: BMI ($p = 0.09$), percent body fat ($p < 0.02$), and total fat ($p = 0.05$). As demonstrated in Figure 2, patients in quintile 5 had better event-free survival than patients in quintile 1: percent fat ($p = 0.029$), BMI ($p = 0.047$), as well as total body fat ($p = 0.033$).

Half of the study cohort had NYHA functional

| TABLE 3 Body Composition Quintiles (Q) and Major Clinical Events (cardiovascular death and urgent transplantation; n = 209) | | | | | | |
|---|---|---|---|---|---|---|
| Parameter | $Q_1$ | $Q_2$ | $Q_3$ | $Q_4$ | $Q_5$ | p Value* |
| Body surface area | | | | | | |
| Mean ($m^2$) | 1.7 ± 0.1 | 1.9 ± 0.0 | 12.1 ± 0.0 | 2.2 ± 0.0 | 2.4 ± 0.1 | |
| Events | 10 (24%) | 6 (15%) | 3 (7%) | 4 (9%) | 5 (12%) | 0.15 |
| BMI | | | | | | |
| Mean ($kg/m^2$) | 22.6 ± 1.8 | 26.0 ± 0.6 | 28.0 ± 0.7 | 31.0 ± 1.0 | 37.3 ± 4.2 | |
| Events | 8 (20%) | 7 (17%) | 4 (10%) | 6 (14%) | 3 (7%) | 0.09 |
| Percent body fat | | | | | | |
| Mean (%) | 16.4 ± 2.5 | 21.3 ± 1.1 | 24.9 ± 0.8 | 28.9 ± 1.6 | 37.7 ± 4.5 | |
| Events | 9 (22%) | 7 (18%) | 4 (9%) | 6 (15%) | 2 (5%) | <0.02 |
| Total fat | | | | | | |
| Mean (kg) | 12.0 ± 2.5 | 17.3 ± 1.3 | 22.3 ± 1.1 | 27.0 ± 1.7 | 40.5 ± 8.1 | |
| Events | 9 (22%) | 9 (21%) | 2 (5%) | 5 (12%) | 3 (7%) | 0.05 |
| Lean body weight | | | | | | |
| Mean (kg) | 48.3 ± 6.2 | 59.4 ± 2.1 | 65.1 ± 1.6 | 71.3 ± 2.3 | 84.5 ± 6.2 | |
| Events | 7 (17%) | 8 (19%) | 2 (5%) | 4 (10%) | 7 (17%) | 0.96 |

*$Q_1$ versus $Q_5$.

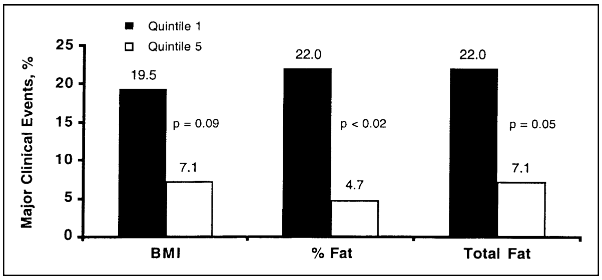


**FIGURE 1. Summary of body composition quintiles comparing major clinical events (cardiovascular death and urgent transplantation) during an average of 19 months of follow-up in the first quintile versus the fifth quintile for BMI, percent body fat (% Fat), and total fat in the total cohort (n = 209).**

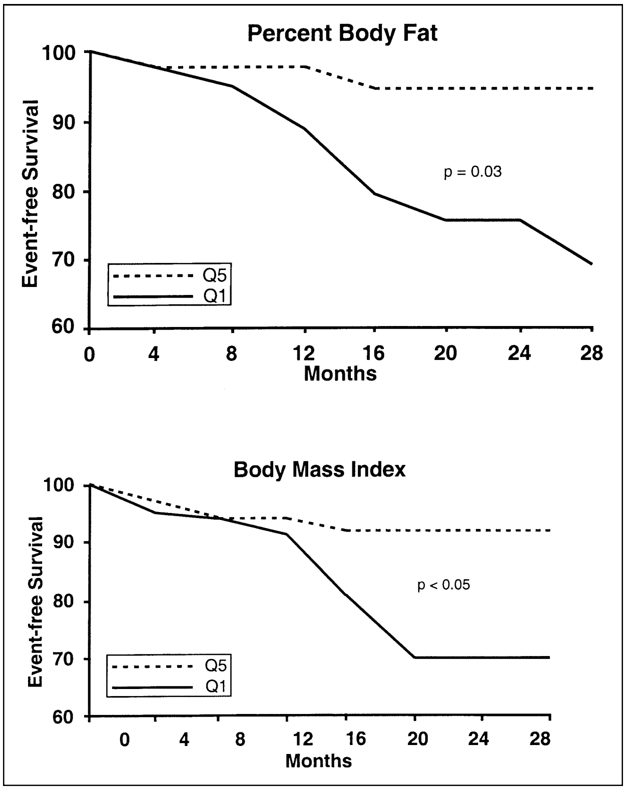


**FIGURE 2. Kaplan-Meier major event-free survival curves (freedom from cardiovascular death or urgent transplantation) in patients in quintiles (Q) 1 and 5 for percent body fat *(upper panel)* and BMI *(lower panel)*.**

class III, and these patients accounted for 3/4 of the total events in our study cohort. When just analyzing this subgroup of patients (n = 102), the same trends were apparent (Figure 3). Patients in the first tertile had more events than did those in tertile 3: BMI (p = 0.2); percent body fat, and total body fat (both p <0.05).

In a logistic regression analysis to determine independent predictors (Table 4), a higher percent body fat was the strongest independent predictor of event-free survival (chi-square 9.1; p = 0.002). In this model, other independent predictors of event-free survival were nonischemic cardiomyopathy and higher peak $VO_2$. When other obesity parameters were substituted for percent body fat in this model, both BMI (chi-square 6.2; p = 0.01) and total fat (chi-square 9.0; p = 0.003) were independent predictors of event-free survival. In this multivariate analysis, for every 1% absolute reduction in percent body fat, clinical events increased by >13%.

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Despite the adverse effects that obesity exerts on cardiac structure and function, including marked diastolic and systolic abnormalities,[1–12] recent studies have suggested that in patients with severe chronic systolic HF, obesity is actually associated with trends for better survival.[13–15] It is postulated that lower body weight is associated with a heightened catabolic state, which is associated with higher levels of tumor necrosis factor and other cytokines and increased cortisol/dehydroepiandrosterone balance.[16,17] Clearly, in advanced HF, cachexia and wasting appear to be independent predictors of increased mortality.[18]

Our study is unique, however, in that we assessed various body composition parameters, including percent body fat and total fat in addition to BMI. Also, our study cohort included patients with chronic systolic HF with only mild to moderate functional limi-

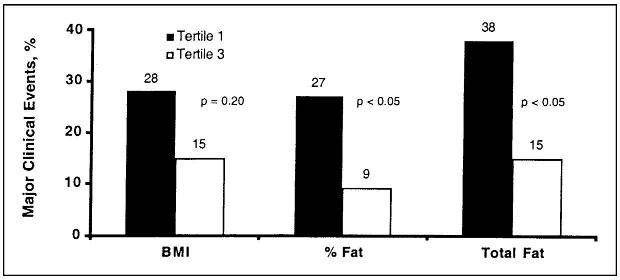


**FIGURE 3. Summary of body composition tertiles comparing major clinical events (cardiovascular death and urgent transplantation) during an average of 19 months of follow-up in the first tertile versus the third tertile for BMI, percent body fat (% Fat), and total fat in patients in NYHA class III (n = 102).**

**TABLE 4** Multivariate Analysis to Determine Independent Predictors of Event-free Survival

| Parameter | Chi-square | p Value |
|---|---|---|
| Percent body fat | 9.1 | 0.002 |
| Nonischemic cardiomyopathy | 7.7 | 0.006 |
| $VO_2$ | 5.2 | 0.02 |
| Left ventricular ejection fraction | 2.4 | 0.12 |
| Lower age | 2.3 | 0.13 |
| Lower NYHA class | 1.8 | 0.19 |
| Women | 0.6 | 0.45 |

tations at baseline, whereas most of the other studies assessed BMI and clinical prognoses in considerably sicker patients who were in NYHA class IV. A recent study by Horwich et al[13] of 1,203 patients with HF, including >60% with NYHA class IV functional status, demonstrated that patients with various categories of BMI had similar overall survival. Like our study, however, higher BMI was associated with better survival in the multivariate analysis. In a study of 181 patients with HF from The Netherlands, a higher BMI was an independent predictor of a more favorable prognosis.[14] A preliminary report from a retrospective analysis of 589 patients with HF also had similar findings: that survival was not impaired in obese patients with HF.[15] Unlike our study, however, they reported that mildly obese patients had the most favorable prognosis, whereas we found the lowest event rates in the patients with the highest BMI and percent body fat measurements. Even in our cohort of patients in the lowest quintiles of body composition parameters, the BMI and percent body fat values were at levels generally considered to be "healthy," and certainly not at levels consistent with a cachectic state. Nevertheless, patients in quintile 1 generally had the highest percentage of major clinical events, and had considerably more major events than did patients in the highest quintiles. In addition, in patients with chronic systolic HF, indexes of obesity and body composition, including BMI, total fat, and, especially, percent body fat, were strong and independent predictors of event-free survival. In our study, a higher percent body fat was the strongest independent predictor of event-free survival, with the multivariate analysis showing that every 1% absolute increase in percent body fat in the population was associated with a >13% reduction in major clinical events.

**In conclusion, although our study demonstrated an inverse relation between indexes of obesity and body composition and subsequent clinical outcome in patients with chronic systolic HF, whether this is causal or merely an association is speculative and cannot be answered by our data.[19,20] Further studies are needed to better elucidate this and the possible mechanisms for this relation.**


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