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Physical and Psychological Attributes of Fatigue in Female Heart Transplant Recipients

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Background: The attributes of fatigue after orthotopic heart transplantation (OHT) are poorly understood. We conducted this study to assess the prevalence, severity and correlates of fatigue among female OHT survivors.

Methods: Fifty women (age 54.7 ± 13.0 years) from a single heart transplant center, who underwent OHT 5.1 ± 4.4 (mean ± SD) years earlier, completed a battery of questionnaires including the Profile of Mood States–fatigue sub-scale to assess levels of fatigue, the Beck Depression Inventory to measure depression, and the Short Form-36 to measure functional status and mental health. Demographic and clinical data were obtained from self-reports and medical chart reviews.

Results: Women reported mean scores of 15.7 ± 6.8 (range 3 to 27), 13.2 ± 8.2 (range 0 to 38), 37.2 ± 10.8 (range 22 to 62) and 41.5 ± 11.2 (range 17 to 60) for fatigue, depression, functional status and mental health, respectively. Univariate analyses revealed that sociodemographic and clinical variables (e.g., age, employment status, anemia, renal insufficiency) were significantly related to fatigue ($p < 0.001$). Likewise, depression, functional status and mental health were also significantly related to fatigue ($p < 0.001$). In a multivariate model, age (adjusted $R^2 = 0.23$, $p < 0.001$), anemia (adjusted $R^2 = 0.39$, $p < 0.001$), functional status (adjusted $R^2 = 0.60$, $p < 0.001$) and depression (adjusted $R^2 = 0.69$, $p < 0.001$) were significant predictors of fatigue. The model explained 69% of the variance in fatigue ($p < 0.001$).

Conclusions: Fatigue is common in women after OHT and is associated with both physiologic and psychologic factors. Clinicians should evaluate all female recipients for symptoms of fatigue, especially those with anemia, renal insufficiency, poor functional status and depression. Other potential mediators of fatigue, such as the denervated donor heart and type of immunosuppressive regimen, may also play a role and require further study. J Heart Lung Transplant 2004;23:614–9.

Over the last 2 decades, orthotopic heart transplantation (OHT) has become a widely used treatment for end-stage heart failure that has influenced survival rates[1] and quality of life[2,3] of patients with advanced heart disease. Likewise, studies on the effect of OHT on functional and psychologic outcomes show that, overall, OHT recipients report dramatic improvements in functional outcomes but continue to report psychologic distress several years after OHT surgery.[4,5] More recently, investigators[6,7] have judiciously examined factors associated with psychologic distress and disorders among OHT survivors that have led to a better understanding of OHT survivorship. However, few investigators have examined factors associated with fatigue among OHT recipients after surgery.

Fatigue has been implicated in decreased self-care ability in older women with heart failure.[8] Likewise, OHT recipients have reported low satisfaction with their level of energy to conduct daily activities at 1 year after surgery.[9] However, the role of fatigue is poorly understood in OHT patients. Among liver transplant recipients, fatigue has been viewed as a multidimensional construct that contains both physical and psychologic aspects,[10] but little is known about fatigue among female OHT recipients. Likewise, no empirical studies have been conducted that examine interventions to prevent and treat fatigue among women after OHT.

The purpose of the current investigation was to describe the prevalence, severity and correlates of fatigue in female OHT survivors. The overall goal of the study was to determine whether fatigue experienced by

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female OHT survivors is primarily physical or psychologic. Knowledge of the nature of fatigue experienced by this vulnerable population could provide information on the type of intervention needed to cope with long-term recovery after surgery and the challenges associated with OHT survivorship.

METHODS

Study Design and Subjects

The study design was cross-sectional. The convenience sample included 50 female OHT survivors (>1 year after surgery) followed up at a single outpatient transplant clinic. Patients were included in the study if they were >18 years old; alert and oriented; and able to read, write and understand English. Patients were excluded if they had major or acute physical or psychologic traumas, including major stressors or major injuries, within the previous 6 months before data collection (i.e., additional surgery requiring general anesthesia, acute renal failure).

Procedures

Institutional review board approval for protection of human subjects was received before contact with patients. Patients who expressed an interest in participating in the study signed an informed consent during their routine clinic visit and were given a battery of self-administered study instruments to complete. Questionnaire completion took 10 to 15 minutes. Sociodemographic data (e.g., gender, age, race, income, education, marital status and employment status) and health history specific to their heart disease and current clinical status (e.g., etiology of heart failure, time since OHT, left ventricular ejection fraction and laboratory tests) were obtained from patient self-reports and verified by medical records. The presence of anemia was confirmed when hemoglobin levels were ≤11 g/dl; renal insufficiency was identified as creatinine ≥1.2 mg/dl.

Instruments

Profile of Mood States–Fatigue (POMS-F). The POMS-F is a 7-item sub-scale obtained from the 65-item Profile of Mood States instrument developed to assess transient distinct mood states specific to fatigue-inertia. Participants were asked to rate their feelings related to being "worn out," "listless," "fatigued," "exhausted," "sluggish," "weary" and "bushed" on a 0 (not at all) to 4 (extremely) scale. Summative scores range from 0 to 35, with a higher score denoting greater fatigue. The mean POMS-F raw scores for 5 diagnostic groups were found to be as follows: 12.3 (psychoneurosis); 11.6 (personality disorder); 10.5 (psychosis); 8.1 (psychophysiologic); and 8.4 (no disorder).[11] Reliability of the POMS-F was 0.91 (mean 6.80) in a sample of 428 cancer patients.[12] Cronbach's alpha of the scale for the current study was 0.88.

Beck Depression Inventory (BDI). Depression was measured using the BDI, which has been used widely in chronically ill populations and is well validated.[13] The BDI was chosen because its wide acceptance and frequent use in medically ill populations allows comparison across studies. It is a self-report inventory designed to measure severity of depressive mood or symptoms. The 21-item tool consists of a Likert-type scale from 0 (absence of symptom) to 3 (severe or persistent presence of the symptom). Eight of the BDI items pertain to somatic symptoms of depression (e.g., loss of appetite and sleep disturbance) and 13 of the items reflect cognitive-affective symptoms of depression (e.g., hopelessness and social withdrawal). Scores on the BDI range from 0 to 63. Patients with BDI scores of 0 to 9 are considered as having no symptoms of depression, scores 10 to 16 mild, scores 17 to 29 moderate, and scores 30 to 63 as having severe symptoms of depression.[14] Meta-analyses of internal consistency for the BDI have yielded alpha coefficients of 0.86 for psychiatric patients and 0.81 for non-psychiatric patients.[20] Cronbach's alpha of the scale for the current study was 0.82.

Short Form Health Survey (SF-36). Functional status and mental health for the current study were measured using the multidimensional SF-36, a generic measure of quality of life.[15] This 36-item self-report evaluates 8 health concepts (physical functioning, bodily pain, role limitations due to physical health, role limitations due to emotional problems, emotional well-being, social functioning, vitality/fatigue and general health perceptions). The time frame for all items is within the last 4 weeks. Higher scores indicate better quality of life. Items in each of the scales are added and averaged to create normed scale scores for physical function (functional status) and mental health.[16] The validity and reliability of each of the scales of the SF-36 in various patient populations has been confirmed in the United States.[17] Estimates of scale score reliability (internal consistency, test-retest, and alternate form) were reported in 14 studies. The median coefficients were ≥0.76.[18] Cronbach's alphas of the physical and mental component scales in the current study were 0.83 and 0.84, respectively.

Data Analysis

Data were analyzed using SPSS for Windows (version 10.0, SPSS, Inc., Chicago, IL).[18] Descriptive statistics were used to characterize the study population. Pearson product-moment correlation coefficients were used for variables that were normally distributed and on an

Table 1. Total Fatigue, Depression, Functional Status and Mental Health Scores ($N = 50$)

Characteristic	Mean	SD	Range
Fatigue (POMS-F)	15.74	6.76	3–27
Depression (BDI)	13.16	8.23	0–38
Functional status (SF-36, PCS)	37.20	10.78	22–62
Mental health (SF-36, MCS)	41.49	11.20	17–60

interval scale. Variables that were not normally distributed because of outliers were analyzed using Spearman's rank sum correlation coefficient. Fatigue scores in depressed and non-depressed patients were compared by *t*-test. Univariate linear regression was used to identify the variables significantly related to fatigue. Multivariate stepwise regression analyses were then used to identify which combination of variables provided the most predictive power for overall fatigue. Variables significant at an $\alpha < 0.10$ in the univariate analysis were included in the regression model. To reflect the context variables, the age and employment status of the patients were the first variables added to the model. Next, to depict the impact of psychologic adjustment on fatigue of patients in the sample, depression, functional status and mental health were added as a second set. Clinical variables (presence of anemia and renal insufficiency) were added last. Criteria for entry and removal of variables were based on the likelihood ratio test with enter and remove limits set at $p \leq 0.05$ and $p \geq 0.100$.

RESULTS

Mean age of the sample was 54.68 ± 12.98 years (range 18 to 78). Seventy percent of the women were white, 12% were African American, and the remaining 18% were of other races, including Hispanic and Asian. Approximately half (52%) of the women were married and a majority had a low socioeconomic status as reflected by high unemployment (80%) and low educational attainment (48% completed high school or less) and income (46% reported <$15,000 annual gross income). On average, the women in our sample had their OHT surgery 5.2 ± 4.4 years before enrollment. Etiology of heart failure was ischemic (35.3%), dilated (56.0%) or other causes (9.7%), including idiopathic, valvular, congenital and post-partum.

Mean scores for fatigue, depression, functional status and mental health are displayed in Table 1. Ninety-eight percent of the women in our sample reported some degree of fatigue (only 1 woman reported having no symptoms of fatigue). Likewise, we found that a majority of patients experienced moderately high levels of fatigue compared with mean average fatigue scores for patients with no disorders, which was 8.4.[11] Depression was detected in >60% of women in the sample by the BDI questionnaire; 18 (33.3%) had mild depressive symptoms, and 15 (27.8%) had moderate–severe depressive symptoms. Because a large percentage of women in the sample were depressed, we performed a sub-group analysis to compare non-depressed women ($n = 17$) and depressed women ($n = 33$) and found significant differences ($p < 0.000$) in mean fatigue scores between the 2 groups (10.9 ± 0.61 and 18.2 ± 5.7, respectively). Because the BDI contains somatic items that might contribute to fatigue, we also used the cognitive–affective sub-scale of the BDI to evaluate fatigue symptoms. Because no cut-points for depression have been established for BDI cognitive-affective items alone, we used median splits to compare fatigue scores. Fatigue did not differ in women with higher and lower cognitive-affective symptoms of depression. The physical component score and mental component score were moderately low compared with national norms for women in the general U.S. population and comparable to national norms for women with congestive heart failure and myocardial infarction (Figure 1).[14]

Univariate analysis revealed that the only sociodemographic characteristics that correlated with fatigue were age ($r = 0.494, p < 0.001$) and employment status ($r = -0.332, p < 0.05$); older women and those who were unemployed had higher levels of fatigue than their younger and employed counterparts. To further define the role of age in predicting fatigue, we compared patients under and over the age of 65 years. Patients <65 years ($n = 41$) reported a mean fatigue level of 14.5 ± 6.7, whereas patients ≥65 years ($n = 9$) reported a mean fatigue level of 21.4 ± 3.3 ($p < 0.004$). Clinical variables associated with higher levels of fatigue were presence of anemia ($r = -0.391, p < 0.001$) and renal insufficiency ($r = 0.489, p < 0.001$). Cardiac factors, including etiology of advanced heart failure, time since OHT and left ventricular ejection fraction, were not related to fatigue levels. We observed a strong correlation between fatigue, depression, functional status and mental health scores (Table 2).

The predictors of fatigue in the current study were age, anemia, functional status and depression (Table 3). These 4 predictors accounted for 69% of the variance in fatigue scores of women in the sample. There was evidence of a linear fit for each variable in the final model. Post hoc analysis was done to test for multicollinearity among the variables and demonstrated that each of the predictors had unique effects on fatigue.

DISCUSSION

The present study was conducted to describe the prevalence and severity of fatigue among female OHT survivors and identify correlates of fatigue in this spe-

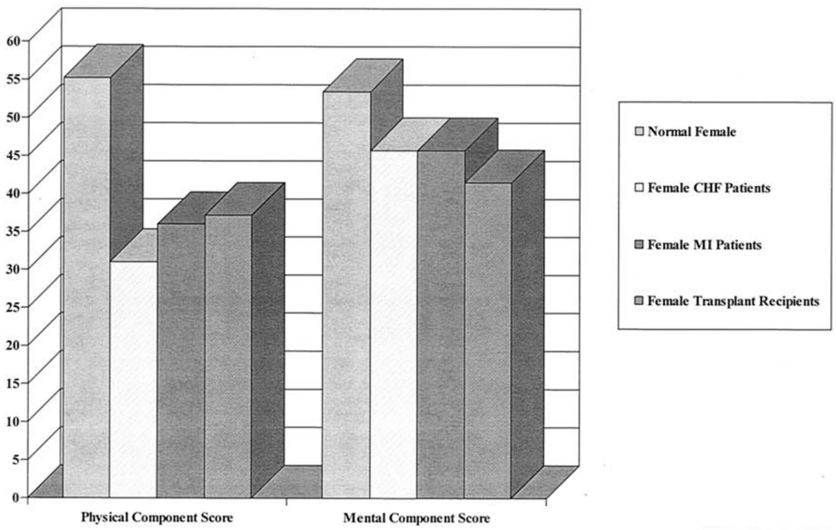

Figure 1. Physical component and mental component scores of women in the sample compared with female norms in the population.[14]

cific population. Our results showed that female OHT survivors experienced moderately high levels of fatigue and depression and moderately low levels of functional status and mental health. We also found that women in the sample continued to experience both functional and psychologic symptoms after OHT that presumably contributed to increased levels of fatigue.

Older age contributed to feelings of fatigue among women in our sample. This implies that fatigue may increase due to normal aging or that older women may be more inclined to report fatigue than younger women. The former explanation appears more likely. Data on older women with heart failure showed that fatigue was a reflection of physiologic states associated with age.[8] Likewise, physical and emotional function in liver transplant patients decreased significantly with age.[19]

We also found an association between employment status and fatigue; unemployed women experienced more fatigue than women who continued to work. A sense of control associated with working may provide a plausible explanation for this finding. It may also be that women who are employed remain more physically active because of their occupation than women who are retired. Finally, it may be that these patients were able to work because they were less fatigued. Work status after liver transplant was also associated with post-operative functional status and fatigue.[19] All of these proposed explanations require further testing in future research.

Table 2. Correlational Matrix for the Key Variables ($N = 50$)

Variable	1	2	3	4
1. Fatigue	1.000			
2. Depression	0.506*	1.000		
3. Functional status	−0.663*	−0.217	1.000	
4. Mental health	−0.545*	0.731*	0.462*	1.000

*$P < 0.001$.

Table 3. Predictors of Fatigue ($N = 50$)

Variable	Adjusted R^2	F	p-value
Age	0.229	15.53	0.000
Anemia	0.385	16.35	0.000
Functional status	0.603	25.80	0.000
Depression	0.688	28.06	0.000

Physiologic factors associated with immunosuppressive therapy may explain the impaired functional status and associated fatigue that we observed in our sample. Fatigue may not be an independent side effect of immunosuppressive medications, but may occur secondary to other documented side effects, such as osteoporosis and muscle weakness.[19] Likewise, impaired functional status may follow from such side effects as weight gain and fluid retention.[20]

Our data support that anemia is an independent predictor of fatigue. Intuitively, it would make sense that anemia and fatigue are related. However, we do not have evidence from other chronically ill populations to support the association between anemia and fatigue. On the contrary, McCann and Boore reported a lack of association between anemia and fatigue in patients with chronic renal failure.[21] Although data support that hemoglobin levels of <11 g/dl are associated with increased morbidity and mortality among renal failure patients,[22] additional studies are needed to examine whether there is a dose response between anemia and fatigue.

Data related to the high incidence of depressive symptoms in our sample are similar to several earlier studies that confirmed the presence of psychologic distress after OHT that persists several years beyond OHT surgery.[6,7] In a previous report, we attributed the increased psychologic distress experienced by women after OHT to ongoing feelings of uncertainty, unpredictability and lack of control.[23] Intuitively, these feelings contribute to emotional distress. Similarly, women with breast cancer reported feelings of fatigue closely linked to depression; in this instance, fatigue was strongly associated with bodily pain and sleep disturbance.[24] In our study, fatigue was higher in women with BDI scores that indicated moderate-to-severe depression. However, when somatic items that might overlap with fatigue were removed from the BDI, fatigue did not differ between women with and without cognitive-affective symptoms of depression. This finding suggests that depressive symptoms in women after OHT may be attributed more to somatic symptoms than to other forms of depressive symptomatology. Further study is needed to confirm this hypothesis.

Generalized deconditioning due to chronic illness and recovery after surgery is common to almost all patients undergoing an OHT. In addition, the unique physiology of the transplanted heart is known to limit exercise capacity in heart transplant recipients.[25] Much of the abnormal exercise capacity in these patients has been attributed to the complete surgical denervation of the transplanted heart due to surgical interruption of post-ganglionic sympathetic fibers.[26] Although partial re-innervation of the transplanted heart occurs in some patients late after OHT, this re-innervation does not occur in all patients, is usually restricted to portions of the anterior wall, and still does not allow for a normal exercise capacity.[27,28] We acknowledge that the unique physiology of the transplanted heart may contribute to the subjective feelings of fatigue experienced by some of the patients in our study; however, these variables are beyond the scope of our study and have been investigated in previous literature.[28,29]

The limitations of this study are 2-fold. First, the small sample size limits the statistical validity of our findings. Furthermore, participant enrollment from a single heart transplant clinic resulted in a fairly homogeneous sample that may not necessarily represent the entire population of female OHT survivors, particularly those >10 years post-OHT. Nevertheless, the data strongly support the need for clinicians to evaluate the presence of fatigue associated with OHT and the ensuing recovery phase after surgery.

Suggestions for future research would be to include subjects from various heart transplant clinics. This approach will allow for enrollment of a more diverse population that could increase the generalizability of the findings to all OHT survivors. Likewise, a comparative study that includes a sample of post-transplant men is also needed to examine gender differences in perceptions of fatigue. An assessment of other factors that could potentially influence fatigue, including pre- and post-transplant disease severity and type of immunosuppressive regimen prescribed after OHT, are needed to provide a more comprehensive understanding of fatigue in OHT recipients. Finally, the role of environmental and psychosocial factors on fatigue requires further study in this patient population.

Our study is the first to elucidate the concept of fatigue in the OHT population. Ninety-eight percent of women reported some degree of fatigue and the majority reported moderately high levels. Our finding that fatigue is a multidimensional construct that contains both physical and psychologic components emphasizes the need for early recognition and treatment of fatigue among OHT survivors. Because fatigue is a subjective symptom, clinicians need to investigate its dimensions, much like pain assessment. The duration, intensity, quality, preceding factors and distress have to be addressed to properly manage this symptom. Assessment and treatment of fatigue may be key to the successful rehabilitation of OHT recipients beyond the immediate recovery phase and throughout long-term survivorship.

REFERENCES

1. Hertz MI, Taylor DW, Trulock EP, et al. The registry of the International Society for Heart and Lung Transplantation: nineteenth official report. J Heart Lung Transplant 2002; 21:950–70.
2. Grady KL, Jalowiec A, White-Williams C. Improvement in quality of life in patients with heart failure who undergo transplantation. J Heart Lung Transplant 1996;15:749–57.
3. Dew M, Switzer G, Goycoolea J, et al. Does transplantation produce quality of life benefits. Transplantation 1997;64:1261–73.
4. Dew M, Simmons R, Roth L, et al. Psychological predictors of vulnerability to distress in the year following heart transplantation. Psychol Med 1994;24:929–45.
5. Dew MA, DiMartini AF, Switzer GE, et al. Patterns and predictors and risk of depressive and anxiety-related disorders during the first three years after heart transplantation. Psychosomatics 2000;41:191–2.
6. Dew M, Kormos R, DiMartini A, et al. Prevalence and risk of depression and anxiety-related disorders during the first three years after heart transplantation. Psychosomatics 2001;42:300–13.
7. Dew MA, Kormos RL, DiMartini AF, et al. Prevalence and risk of depression and anxiety-related disorders during the first three years after heart transplantation. Psychosomatics 2001;42:300–13.
8. Friedman M, King KB. Correlates of fatigue in older women with heart failure. Heart Lung 1995;24:512–8.
9. Grady K, Jalowiec A, White-Williams C. Predictors of quality of life in patients at one year after heart transplantation. J Heart Lung Transplant 1999;18:202–10.
10. Smets EMA, Garssen B, Bonke B, de Haes JC. The Multidimensional Fatigue Inventory (MFI). Psychometric qual-

ities of an instrument to assess fatigue. J Psychosom Res 1995;39:315–25.
11. McNair D, Lorr M, Droppleman L. EITS manual for the Profile of Mood States 1971. San Diego, CA: Educational and Industrial Testing Center.
12. Baker F, Denniston M, Zabora J, Polland A, Dudley W. A POMS short form for cancer patients: psychometric and structural evaluation. Psycho-Oncology 2002;11:273–81.
13. Beck AT, Rial W, Rickels K. Short-form of depression inventory: cross validation. Psychol Rep 1974;34:1184–6.
14. Beck AT. Depression: clinical, experimental and theoretical aspects1967. New York: Hoeber.
15. Ware JE. Conceptualizing and measuring generic health outcomes. Cancer 1991;67:774–9.
16. Stewart A, Greenfield S, Hays R, et al. Functional status and well-being of patients with chronic conditions. JAMA 1989;262:907–13.
17. Ware JE, Kosinski M, Keller SD. SF-36 physical and mental health summary scales: a user's manual, 5th ed, 1994. Boston: Health Assessment Lab, New England Medical Center.
18. 3rd ed, 1998. Chicago, IL: SPSS.
19. Aadahl M, Hansen BA, Kirkegaard P, Groenvold M. Fatigue and physical function after orthotopic liver transplantation. Liver Transplant 2002;8:251–9.
20. Rickenbacher P, Hunt S. Handbook of cardiac transplantation 1996. Philadelphia: Hanley and Belfus, 201–16.
21. McCann K, Boore J. Fatigue in persons with renal failure who require maintenance hemodialysis. J Adv Nurs 2000; 32:1132.
22. Brunier GM, Graydon J. The influence of physical activity on fatigue in patients with ESRD on hemodialysis. Am Nephr Nurses Assoc J 1993;20:457–61.
23. Evangelista L, Doering L, Dracup K. Meaning and life purpose: the perspectives of post-transplant women. Heart Lung (in press).
24. Bower J, Ganz P, Desmond K, Rowland J, Meyerowitz B, Belin T. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. J Clin Oncol 2000;18:743–53.
25. Givertz MM, Hartley LH, Colucci WS. Long-term sequential changes in exercise capacity and chronotropic responses after cardiac transplantation. Circulation 1997; 96:232–7.
26. Cooper T, William VL, Jellinek M, Hanlon CR. Heart autotransplantation: effect on myocardial catecholamine and histamine. Science 1962;138:40–1.
27. Uberfuhr P, Ziegler S, Schwaiblmair M, Reichart B, Schwaiger M. Incomplete sympathetic reinnervation of the orthotopically transplanted human heart: observation up to 13 years after heart transplantation. Eur J Cardiothorac Surg 2000;17:161–8.
28. Bengel FM, Uberfuhr P, Schiepel N, Nekolla SG, Reichart B, Schwaiger M. Effect of sympathetic reinnervation on cardiac performance after heart transplantation. N Engl J Med 2001;345:731–8.
29. Coyle CP, Santiago MC, Shank JW, Ma GX, Boyd R. Secondary conditions and women with physical disabilities: a descriptive study. Arch Phys Med Rehabil 2000;81: 1380–7.