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Relationships Between Right Ventricular Function, Body Composition, and Prognosis in Advanced Heart Failure

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Objectives This study sought to examine the relationships between right ventricular (RV) function, body composition, and prognosis in patients with advanced heart failure (HF).

Background Previous studies investigating HF-related cachexia have not examined the impact of RV function on body composition. We hypothesized that RV dysfunction is linked to weight loss, abnormal body composition, and worsened prognosis in advanced HF.

Methods Subjects with advanced HF (n = 408) underwent prospective assessment of body composition (skinfold thickness, dual-energy X-ray absorptiometry), comprehensive echocardiography, and blood testing. Subjects were followed up for adverse events (defined as death, transplantation, or circulatory assist device).

Results Subjects with RV dysfunction (51%) had lower body mass index, lower fat mass index, and were more likely to display cachexia (19%). The extent of RV dysfunction correlated with greater antecedent weight loss and a lower fat/lean body mass ratio. Over a median follow-up of 541 days, there were 150 events (37%). Risk of event was greater in subjects with RV dysfunction (hazard ratio: 3.09 [95% confidence interval (CI): 2.18 to 4.45]) and cachexia (hazard ratio: 2.90 [95% CI: 2.00 to 4.12]) in univariate and multivariate analyses. Increased body mass index was associated with a lower event rate (HR per kg/m^2: 0.92 [95% CI: 0.88 to 0.96]), and this protection was mediated by a higher fat mass (0.91 [95% CI: 0.87 to 0.96]) but not a fat-free mass index (0.97 [95% CI: 0.92 to 1.03]).

Conclusions RV dysfunction and cardiac cachexia often coexist, have additive adverse impact, and might be mechanistically interrelated. Wasting of fat but not of lean mass was predictive of adverse outcome, suggesting that fat loss is either a surrogate of enhanced catabolism or adipose tissue is cardioprotective in the context of HF. (J Am Coll Cardiol 2013;62:1660–70) © 2013 by the American College of Cardiology Foundation

Although obesity is well known as a potent risk factor for incident heart failure (HF) (1,2), increased body mass is associated with lower mortality in patients with prevalent HF (3–7), a relationship that is commonly referred to as the "obesity paradox." Unintentional weight loss in HF patients, the seminal feature of cardiac cachexia, is associated with at least 2-fold higher risk of death (8,9). The impact of advanced HF on body composition and the potential mechanisms underlying the protective influence of increased body mass in HF are poorly understood. It has been suggested that cardiac cachexia is related to hemodynamic alterations of HF (10,11) and the ensuing neurohumoral and cytokine responses (12), which have in turn been implicated in impaired gastrointestinal function (13), anorexia (11), hypermetabolism, and altered substrate utilization in tissues (14).

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Previous studies examining determinants of HF-related cachexia have reported no relationship to left ventricular (LV) impairment, but, importantly, relationships with right ventricular (RV) function were not examined (15–17). Right ventricular dysfunction (RVD) is associated with worse outcome in HF (18) independent of the degree of pulmonary hypertension (19). Increased right heart filling pressure and tricuspid regurgitation have been linked to body fat depletion (10,20) and low body mass index (BMI) (7), but RV function itself was not quantified in these studies. By maintaining forward cardiac output and protecting splanchnic organs from passive venous hypertension (21), the right ventricle may play a critical role in delaying the onset of wasting in HF.

Accordingly, we investigated the relationships between RV function, body composition, and prognosis in a prospectively defined group of patients with advanced HF. We hypothesized that preserved RV function is protective against cardiac cachexia and that RVD is linked to accelerated weight loss, abnormal body composition, and worsened prognosis in advanced HF.

Methods

The study enrolled patients with chronic (>6 months) advanced systolic HF (ejection fraction <50%) electively hospitalized at a non–intensive care unit ward at The Institute for Clinical and Experimental Medicine in Prague between November 2007 and August 2011 for consideration of advanced therapies. Two cardiologists (V.M., M.K.) identified potential participants from the list of planned procedures; study coordinators then reviewed exclusion eligibility criteria and obtained written consent. Patients with acute HF decompensation, hemodynamic instability or reversible cardiac dysfunction (e.g., planned valve surgery, revascularization, tachycardia-induced cardiomyopathy), active malignancy, chronic infection, history of intentional weight loss attempts in the past year, or those unwilling to participate were excluded. The study was approved by the ethical committee of the Institute of Clinical and Experimental Medicine.

All subjects underwent morning fasting blood sampling for laboratory analysis and completed a medical history, Minnesota Living with Heart Failure questionnaire, and an anthropometric and echocardiography examination (Vivid7, General Electric Healthcare, Wauwatosa, Wisconsin). LV function and dimensions were measured according to contemporary recommendations by a physician with an expertise in echocardiography (22). Mitral and tricuspid regurgitations were assessed semiquantitatively and expressed in 3 grades (absent, insignificant, and significant). RV systolic pressure was estimated from the tricuspid regurgitation velocity (available in 75%) and right atrial pressure estimate, based on inferior vena cava diameter (22). RVD was quantified (0 to 3) in an apical 4-chamber view by using tricuspid annular systolic excursion (M-mode TAPSE) (23) and tissue systolic velocity (S_m) (24) with the following cutoffs: RVD0, normal: TAPSE >20 mm, S_m >12 cm/s; RVD1, mild impairment: TAPSE 16 to 20 mm, S_m 9 to 12 cm/s; RVD2, moderate: TAPSE 10 to 15 mm, S_m 6 to 8 cm/s; and RVD3, severe: TAPSE <10 mm, S_m <6 cm/s. In case of disagreement of criteria, qualitative visual estimation of RV motion in apical 4-chamber was also taken into account. Because RVD2-3 and RVD0-1 grades had similar prognostic impact, they were aggregated for dichotomized analyses.

Abbreviations and Acronyms

BMI = body mass index
BNP = B-type natriuretic peptide
CI = confidence interval
DEXA = dual-energy X-ray absorptiometry
HF = heart failure
HR = hazard ratio
LV = left ventricular
RV = right ventricular
RVD = right ventricular dysfunction

Body weight was measured by using an electronic scale (HBF-510W, Omron, Japan). Antecedent weight 6 months before the evaluation was carefully ascertained by subjects' historical recollection and by review of available medical records, as done previously (9,12,15). Four-site skinfold thickness (triplicate measurement in nondominant subscapular, bicipital, tricipital, and suprailiac areas) was measured by using Best's caliper with controlled grip strength. In 19 subjects, between-day reproducibility of skinfold measurement was excellent (r^2 > 0.9) (Online Fig. 1A). Skinfold sum was converted into total body fat by using established age- and sex-specific formulas (25), and fat mass index or fat-free mass index was obtained by indexing to square of body height (26). Mathematically, the sum of the fat mass index and the fat-free mass index then corresponds to BMI (26). In the last one-third of subjects enrolled in the study (n = 162), body composition was also measured by using dual-energy X-ray densitometry (DEXA) (Lunar prodigy, General Electric Healthcare) to externally validate results. Body fat proportion according to DEXA and the skinfold method showed good agreement ($r^2 = 0.56$) (Online Fig. 1B). Cardiac cachexia was defined by the presence of significant weight loss (>5% within 6 months), as done previously in landmark studies that defined prognostic impact of weight loss (cachexia) in HF (8,9) and by simultaneous presence of abnormal biochemistry (C-reactive protein >5 mg/l or hemoglobin <120 g/l or albumin <32 g/l) as recently recommended to enhance specificity (27).

Glomerular filtration rate was estimated by using the Modification of Diet in the Renal Disease equation (28). Plasma sodium, albumin, aspartate-aminotransferase, glucose, creatinine, and cholesterol were measured by using an automated Abbott Architect ci1600 analyzer. The B-type natriuretic peptide (BNP) concentrations were measured by using microparticle immunoassay (Architect BNP, Abbott Laboratories, Chicago, Illinois; long-term analytical CV 4.5%). Adiponectin was measured using high-sensitivity enzyme-linked immunoadsorbent assay (BioVendor, Brno, Czech Republic; CV 6.2%), leptin by using radioimmunoassay (Millipore, Billerica, Massachusetts; CV 4.7%), and cortisol by using radioimmunoassay

Table 1 Clinical, Echocardiography, and Anthropometric Parameters

	All (n = 408)	No RVD (n = 198)	RVD (n = 210)	p Value	No Cachexia (n = 330)	Cachexia (n = 78)	p Value
Age (yrs)	59 ± 11	59 ± 11	59 ± 11	0.46	59 ± 11	60 ± 11	0.35
Male (%)	84	80	89	0.014	83	90	0.35
Ischemic etiology (%)	53	52	55	0.45	52	58	0.40
NYHA functional class (I to IV)	2.8 ± 0.6	2.7 ± 0.5	2.9 ± 0.6	0.0001	2.8 ± 0.6	2.9 ± 0.5	0.04
MLHFQ sum	47 ± 22	43 ± 22	51 ± 22	0.002	45 ± 21	55 ± 24	0.003
Anorexia grade (1–5)	1.9 ± 1.6	1.6 ± 1.6	2.1 ± 1.6	0.001	1.7 ± 1.5	2.5 ± 1.8	0.001
RV lead/defibrillator (%)	75/66	76/65	75/67	0.90/0.66	75/65	78/69	0.53/0.46
Diabetes mellitus (%)	34	30	38	0.07	33	37	0.52
Systolic/diastolic BP (mm Hg)	115 ± 19/72 ± 11	119 ± 20/75 ± 11	111 ± 17/70 ± 11	<0.0001/0.0001	116 ± 19/72 ± 12	110 ± 18/69 ± 9	0.03/0.0003
Heart rate (beats/min)	77 ± 15	74 ± 14	80 ± 15	<0.0001	76 ± 15	82 ± 15	0.005
Edema present (%)	25	18	31	0.001	23	31	0.18
Furosemide daily dose (mg)	92 ± 82	82 ± 73	111 ± 88	0.0006	95 ± 82	108 ± 83	0.24
BB/ACEI or ARB/ARA use (%)	92/85/77	92/88/74	92/82/80	0.9/0.06/0.06	94/89/75	83/68/87	0.04/<0.001/0.01
Echocardiography							
LV ejection fraction (%)	25 ± 6	27 ± 7	23 ± 5	<0.0001	26 ± 6.7	24 ± 5.3	0.09
LV end-diastolic diameter (mm)	70 ± 9	69 ± 9	71 ± 8	0.04	70 ± 9	70 ± 8	0.62
Mitral regurgitation grade (0–2)	0.9 ± 0.8	0.7 ± 0.8	1.1 ± 0.8	0.0001	0.9 ± 0.8	0.9 ± 0.8	0.48
RV diameter (mm)	30 ± 6	28 ± 6	32 ± 6	<0.0001	30 ± 6.5	32 ± 5.6	0.006
RVD grade (0–3)	1.4 ± 1.0	0.6 ± 0.5	2.3 ± 0.4	<0.0001	1.4 ± 1.7	1.7 ± 0.9	0.003
Tricuspid regurgitation grade (0–2)	0.5 ± 0.7	0.2 ± 0.5	0.7 ± 0.8	<0.0001	0.5 ± 0.7	0.6 ± 0.7	0.22
Inferior vena cava diameter (mm)	20 ± 6	18 ± 5	22 ± 6	<0.0001	20 ± 5.9	21 ± 6.6	0.11
Tricuspid regurgitation gradient (mm Hg)	36 ± 12	34 ± 11	38 ± 12	0.016	37 ± 12	35 ± 12	0.19
RVSP estimate (mm Hg)	46 ± 12	43 ± 11	48 ± 12	0.001	46 ± 12	45 ± 12	0.32
Anthropometrics							
Body mass index (kg/m^2)	27.8 ± 4.8	28.6 ± 4.5	27.1 ± 4.8	0.002	28.3 ± 4.6	25.6 ± 4.3	<0.0001
Fat mass index (kg/m^2)	7.2 ± 3.8	7.8 ± 3.6	6.7 ± 3.9	0.005	7.6 ± 3.8	5.6 ± 3.2	<0.0001
Fat-free mass index (kg/m^2)	20.6 ± 3.0	20.7 ± 3.1	20.3 ± 2.9	0.21	20.7 ± 3.1	20.0 ± 2.5	0.05
Waist circumference (cm)	102 ± 13	103 ± 11	100 ± 14	0.02	102 ± 13	98 ± 12	0.008
DEXA fat mass (kg)	28 ± 11	30 ± 11	25 ± 10	0.002	29 ± 10	24 ± 11	0.02
Lean mass (kg)	54 ± 9.6	55 ± 10	54 ± 9	0.64	55 ± 9.8	52 ± 8.6	0.09
Body weight loss in 6 months (kg)	−2.8 ± 9	−1.4 ± 8	−4.0 ± 10	0.002	−0.2 ± 7.2	−13 ± 8	<0.0001
Body weight loss >5% in 6 months (%)	33	27	39	0.01	17	100	<0.0001
Cachexia (%)	19	14	24	0.01	0	100	<0.0001

Values are mean ± SD or %. Fat-free mass index was derived from skinfold measurements performed in all subjects.

ACEI = angiotensin-converting enzyme antagonist; ARA = aldosterone receptor antagonist; ARB = angiotensin receptor blocker; BB = beta-blocker; BP = blood pressure; CAD = coronary artery disease; DEXA = dual-energy X-ray absorptiometry (n = 162); LV = left ventricular; MLHFQ = Minnesota Living with Heart Failure questionnaire; No RVD = RVD grades 0–1; NYHA = New York Heart Association; RV = right ventricular; RVD = right ventricular dysfunction; RVD present = RVD grades 2–3; RVSP = right ventricular systolic pressure estimate (n = 306)

Table 2 Right Heart Catheterization and Laboratory Parameters

	All (N = 408)	No RVD (n = 198)	RVD (n = 210)	p Value	No Cachexia (n = 330)	Cachexia (n = 78)	p Value
Right heart catheterization							
Right atrium (mm Hg)	9.3 ± 6	8.1 ± 6	10 ± 6	0.01	9.3 ± 6.2	9.4 ± 5.7	0.92
PA mean (mm Hg)	34 ± 12	34 ± 12	36 ± 11	0.008	34 ± 12	35 ± 9	0.68
PA wedge pressure (mm Hg)	23 ± 9	22 ± 10	25 ± 8	0.02	23 ± 9	25 ± 7	0.25
Cardiac output (l/min)	4.0 ± 1.0	4.2 ± 0.9	3.9 ± 1.0	0.03	4.0 ± 0.9	4.0 ± 1.2	0.82
Biochemistry							
GFR (ml/min/1.73 m^2)	52 ± 18	54 ± 19	50 ± 17	0.20	53 ± 19	46 ± 14	0.0004
Hemoglobin (g/dl)	13.9 ± 1.7	13.9 ± 1.7	14.0 ± 1.7	0.04	14.1 ± 1.6	13.5 ± 2.0	0.04
C-reactive protein (mg/l)	8.3 ± 16	6.8 ± 12	9.8 ± 18	0.05	6.8 ± 13	15 ± 24	0.004
Alanine aminotransferase (μkat/l)	0.8 ± 0.9	0.8 ± 0.9	0.7 ± 1.0	0.7	0.8 ± 0.8	0.8 ± 1.1	0.63
Total protein (g/l)	70 ± 6.4	69 ± 6	70 ± 7	0.03	69 ± 6.3	70 ± 7	0.42
Albumin (g/l)	38 ± 4	38 ± 4	38 ± 4	0.76	39 ± 4	36 ± 5	<0.0001
Total cholesterol (mmol/l)	4.2 ± 1.1	4.4 ± 1.0	4.1 ± 1.1	0.002	4.3 ± 1.1	4.0 ± 0.9	0.03
Glucose (mmol/l)	6.3 ± 2.4	6.0 ± 2.0	6.5 ± 2.8	0.10	6.3 ± 2.5	6.2 ± 2.2	0.96
Hormones							
BNP (pg/l)	861 ± 822	612 ± 648	1094 ± 897	<0.0001	746 ± 723	1349 ± 1019	<0.0001
Cortisol (nmol/l)	513 ± 173	490 ± 170	535 ± 173	0.012	506 ± 169	544 ± 186	0.06
Leptin (μg/l)	18 ± 15	20 ± 15	16 ± 14	0.006	19 ± 15	14 ± 12	0.007
Adiponectin (mg/l)	37 ± 31	30 ± 23	43 ± 36	<0.0001	33 ± 28	53 ± 38	<0.0001

Values are mean ± SD. Right heart catheterization was available in 193 subjects.
BNP = B-type natriuretic peptide; GFR = glomerular filtration rate; PA = pulmonary artery; other abbreviations as in Table 1.

(Beckman-Coulter, Prague, Czech Republic; CV 9.2%). Right heart catheterization was performed via jugular access using a balloon-tipped thermodilution catheter (Corodyn, Braun, Melsungen, Germany) and a standard data acquisition system (MacLab, General Electric Healthcare).

Adverse outcomes were defined by the combined endpoint of death without transplantation, urgent heart transplantation, or implantation of ventricular assist device. Because time to nonurgent transplantation reflects donor availability rather than recipient's condition, those patients were censored as having no outcome at the day of transplantation. Data were analyzed by using JMP10 software (SAS Institute, Inc., Cary, North Carolina). Differences between groups were tested by using the chi-square test, unpaired Student *t* test, or analysis of variance. Logistic regression analysis was used to identify the predictors of cachexia. The impact on survival was tested by using the Cox proportional hazards model.

Results

A total of 408 predominantly male subjects with chronic HF (median duration 6.3 years; interquartile range 2.4 to 12 years) were enrolled (Table 1). Optimal medical and device therapies (45% cardiac resynchronization therapy, 66% implantable cardioverter-defibrillator) were widely used. Subjects displayed significant LV remodeling and dysfunction. Pulmonary hypertension (estimated RV systolic pressure >35 mm Hg) was present in 79%. Right heart catheterization (n = 193) (Table 2) revealed increased pulmonary artery (PA) and LV filling pressures, but RA pressures and cardiac output were relatively preserved, consistent with a reasonably compensated state (on average). Moderate or severe RVD was present in 51% of subjects. Only 2% of subjects had BMI ≤20 kg/m^2, and most (70%) were either overweight or obese. About one-half (49%) reported unintended weight loss in the past 6 months and 33% had weight loss of >5% of body weight. Cachexia, defined by weight loss and laboratory criteria, was present in 19% of subjects.

Association of RVD and cachexia. Patients with RVD had more severe HF symptoms, lower systemic blood pressures and cardiac output, more tricuspid regurgitation, and greater pressure load imposed on the right ventricle (Tables 1 and 2). Patients with RV dysfunction were leaner, had more pronounced weight loss, more often fulfilled cachexia criteria, and had lower body mass and less body fat mass than those with preserved RV function, in contrast to lean mass that was similar in both groups (Fig. 1, Table 1). In the whole cohort, there was a stepwise relation between RVD grade, weight loss, and ratio of fat mass to lean mass by DEXA (Fig. 2). Weight change and body composition also significantly (both $p < 0.001$) inversely correlated with the ratio of RV to LV function, indicating a relatively stronger link of cachexia to compromised right heart, compared with left heart impairment.

When patients were dichotomized according to the presence of cachexia, cachectic subjects displayed greater RV dilation and more severe RVD, while prevalence of tricuspid regurgitation, pulmonary hypertension, and right atrial pressures were similar in noncachectic subjects (Tables 1 and 2). Among the cardiac indexes, only RV characteristics, but not LV dimension or ejection fraction, discriminated between cachectic versus noncachetic patients. Cachectic patients had a lower quality of life, more anorexia, and higher heart rate; lower systemic blood pressure; lower use of angiotensin-converting

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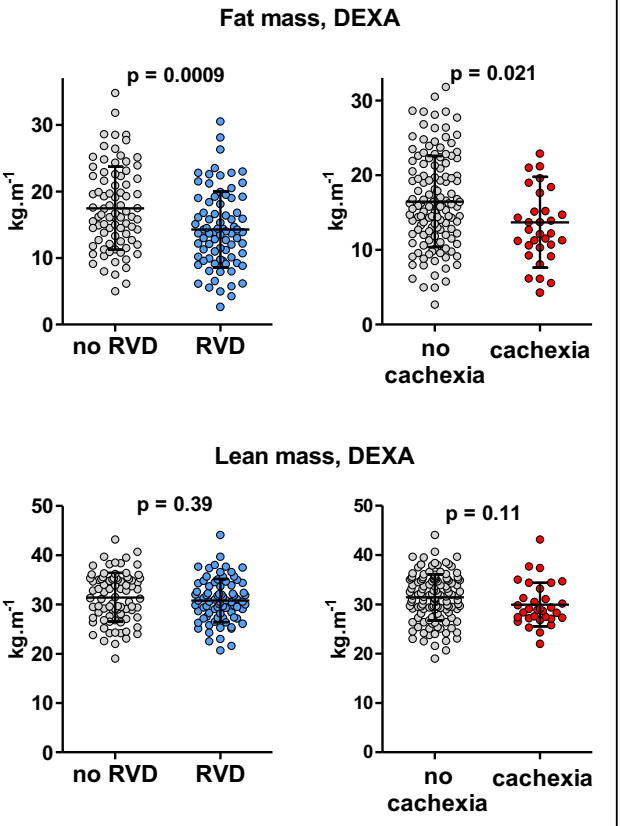

Figure 1 Body Composition by DEXA

Impact of significant right ventricular dysfunction (RVD) (moderate and severe grade) or cachexia on fat and lean mass, determined by dual-energy X-ray absorptiometry (DEXA). Values were adjusted to body height. **Lines and brackets** represent mean ± SD.

enzyme inhibitors/angiotensin receptor blockers and beta-blockers; and more renal dysfunction, anemia, and inflammatory/stress response activation. In contrast, HF etiology and duration, hemodynamics, liver function, presence of edema, and impaired glucose tolerance were similar in cachectic and noncachectic groups.

Cachectic subjects demonstrated ~2-fold higher BNP (despite similar hemodynamics), lower leptin levels, and markedly higher adiponectin levels. Adiponectin but not leptin remained significantly different when adjusted to percentage of body fat ($p = 0.018$). Skinfold-derived body composition analysis showed that the BMI difference between cachectic and noncachectic subjects was attributable mainly to low-fat mass, although fat-free mass was only marginally reduced (Table 1). The reduction in fat mass but preserved lean mass in cachectic patients was confirmed by DEXA ($n = 162$) (Fig. 1).

Logistic regression was used to delineate which cardiac, clinical, and humoral factors were independently associated with cachexia (Table 3). Among the cardiac parameters, only RVD remained significant in the multivariate model to predict cachexia. Notably, tricuspid regurgitation grade and velocity, inferior vena cava diameter, LV dimension, or ejection fraction and all other echocardiographic indexes were not predictive of cardiac cachexia in multivariate analysis. Among clinical factors, the absence of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or beta-blockers remained independently associated with cachexia. Among humoral factors, adiponectin and BNP showed strong independent relationships to cachexia.

The influence of cachexia and RVD on prognosis. After a median follow-up of 541 days (interquartile range: 254 to 873 days), 150 (37%) of 408 patients had an adverse event. The presence of RVdysfunction (hazard ratio [HR]: 3.13; 95% confidence interval (CI): 2.09 to 4.79; $p < 0.0001$) or cachexia (HR: 3.56; 95% CI: 1.65 to 7.00; $p = 0.0002$) was strongly associated with adverse events, and risk was much greater if both cachexia and RVD were present (HR: 6.67; 95% CI: 4.08 to 10.9; $p < 0.0001$ vs. noncachectic patients with normal RV) (Fig. 3). In univariate Cox analysis, antecedent weight loss (>5% in past 6 months) was associated with increased events (HR: 1.85; 95% CI: 1.32 to 2.59; $p = 0.0005$) (Online Fig. 2). When the lean and fat components of BMI were separated according to skinfold-derived body composition, the protective effect of BMI on adverse outcomes (HR per kg/m^2: 0.92 [95% CI: 0.88 to 0.96]; $p < 0.001$) (Fig. 4A) was conferred by fat mass index (HR per kg/m^2: 0.91 [95% CI: 0.87 to 0.96]; $p < 0.001$) rather than fat-free mass index (HR per kg/m^2: 0.97 [95% CI: 0.92 to 1.03]; $p = 0.40$). Although fat-free mass displayed a flat relationship with events, fat mass demonstrated a steep, almost linear inverse relationship to the event risk (Fig. 4B). Multivariate Cox analysis (Table 4) incorporating all significant predictors showed that both RVD and cachexia, in addition to pulmonary hypertension, age, heart rate, and absence of neurohumoral inhibition, were independent predictors of event-free survival.

Discussion

The study shows that involuntary weight loss in advanced HF, the defining feature of cardiac cachexia, is independently associated with impaired RV function. Circulating BNP, adiponectin, absence of neurohormonal antagonist therapy, and RVD were the only independent predictors of cachexia. Body composition analysis in patients with RV dysfunction demonstrated more pronounced depletion of body fat than of lean mass. In support of their mutual interrelation, both RVD and cachexia displayed an additive adverse impact on prognosis. Higher body mass was associated with a better prognosis in keeping with previous studies documenting the obesity paradox, but interestingly, it was the amount of fat rather than lean mass that predicted better outcome. This finding is somewhat at odds with current pathophysiological models that emphasize preferential maintenance of lean mass to prevent cachexia and adverse outcomes (29).

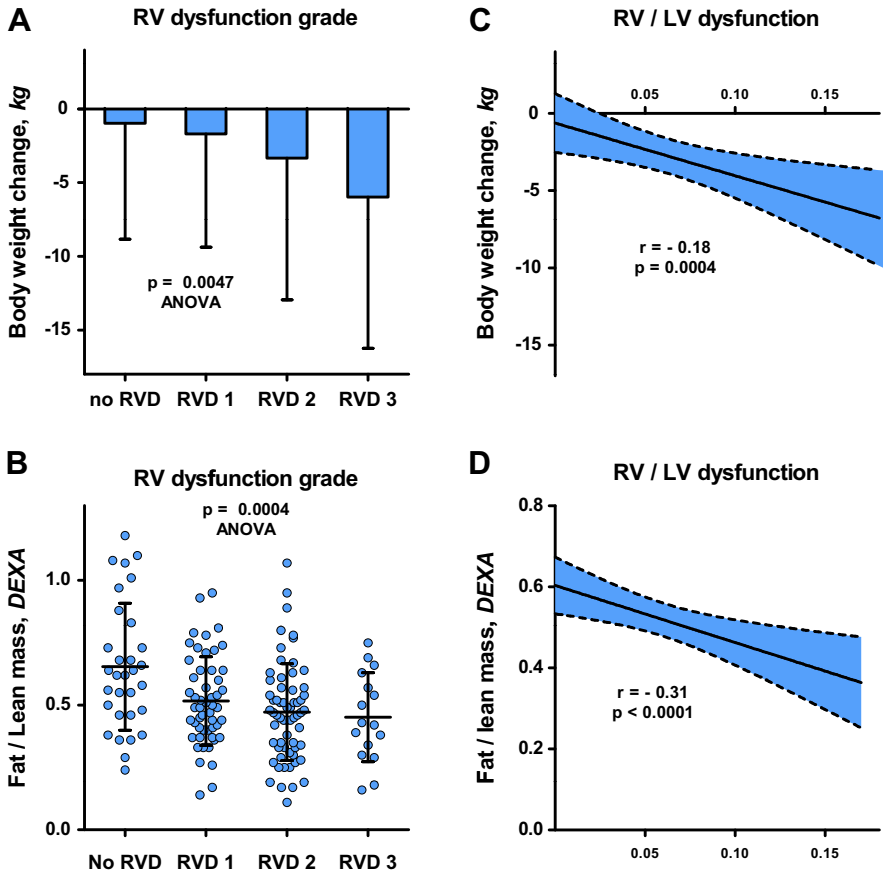

Figure 2 RV Dysfunction and Wasting in HF

The gradual relation of RVD grade (x axis) to **(A)** the extent of body weight loss in past 6 months (n = 408) and to **(B)** the body composition measured by DEXA (n = 162) in patients with advanced heart failure. The correlation between the ratio of **(C)** RVD to left ventricular (LV) dysfunction (RVD grade/LV ejection fraction %) and body weight loss in past 6 months and to **(D)** the body composition derived by DEXA. Abbreviations as in Figure 1.

The association between RVD and cachexia has not received attention because previous studies examining the prognostic role of RV function in HF did not report anthropometric data (19,30,31), and, conversely, studies of cardiac cachexia have provided no details regarding RV function (3,4,8,9,15). Two small (10,20) and one larger (7) study found that cachexia was associated with increased right atrial pressure (10) or tricuspid regurgitation (7,10,20), pointing toward the role of right heart impairment; however, in these studies, RV function was not assessed. Despite the fact that patients with RV dysfunction also have more left heart dysfunction due to shared myocardial disease (32), our data indicate that cachexia is linked more specifically to right than left heart impairment (Fig. 2).

Impaired RV function can promote weight loss and cachexia by several potential pathways. RV dysfunction leads to systemic venous congestion in the hepatic and splanchnic beds, which may be associated with anorexia, intestinal dysmotility, fat malabsorption (33), and increased intestinal permeability (13), with ensuing protein loss (34) and endotoxin translocation (35). Despite that our patients had relatively low filling pressure at the time of examination, it is likely that during periods of decompensation, venous congestion would have been more dramatic, potentially contributing to promotion of cachexia. RV dysfunction also contributes to reduced forward cardiac output that begets neurohormonal activation and pro-catabolic effects. Higher cortisol, lower cardiac output, and increased BNP found in patients with RVD endorse these mechanisms. The likely contribution of natriuretic peptide–related metabolic effects is supported by the fact that BNP emerged as one of the strongest predictors of cachexia in our study. Previously, we have demonstrated that bioactive BNP is able to strongly stimulate lipolysis of adipose tissue in patients with HF (36). Natriuretic peptides can also act indirectly by inducing secretion of adiponectin that promotes substrate utilization (37), weight loss, and, perhaps, HF mortality (38).

In multivariate regression analysis, RVD predicted cachexia even after adjusting for tricuspid regurgitation, estimated right atrial pressure and PA pressure, emphasizing

Table 3 Logistic Regression Analysis of Hormonal, Cardiac, and Clinical Factors Associated With Cachexia in All HF Subjects (n = 408)

	Univariate				Multivariate			
	HR	95% CI	Chi-Square	p Value	HR	95% CI	Chi-Square	p Value
Hormones						*All model*	*36.4*	
BNP (pg/l)	1.0007	0.99–1.001	28.2	<0.0001	1.0006	1.0002–1.0009	10.9	0.0009
Cortisol (nmol/l)	1.001	0.99–1.003	2.6	0.10	1.0008	0.99–1.01	0.9	0.35
Leptin (μg/l)	0.97	0.95–0.99	5.4	0.02	0.98	0.95–1.01	1.8	0.18
Adiponectin (mg/l)	1.02	1.010–1.023	19.6	<0.0001	1.009	1.0001–1.019	4.0	0.047
Cardiac characteristics						*All model*	*13.1*	
RV diameter (mm)	1.04	1.01–1.08	5.9	0.015	1.008	0.95–1.06	0.1	0.77
LV end-diastolic diameter (mm)	0.99	0.97–1.02	0.2	0.63	0.98	0.94–1.01	1.5	0.22
LV ejection fraction (mm)	0.97	0.92–1.01	2.3	0.13	0.97	0.92–1.03	0.9	0.36
Tricuspid regurgitation gradient (mm Hg)	0.98	0.96–1.01	1.8	0.18	0.98	0.96–1.01	1.8	0.18
Inferior vena cava diameter (mm)	1.03	0.99–1.08	2.8	0.09	1.02	0.96–1.08	0.4	0.54
RVD grade (0–3)	1.48	1.14–1.94	8.7	0.003	1.52	1.07–2.20	5.1	0.020
Tricuspid regurgitation grade (0–2)	1.53	0.77–3.0	0.2	0.21	0.81	0.50–1.28	0.8	0.37
Mitral regurgitation grade (0–2)	1.10	0.82–1.5	0.5	0.50	0.95	0.63–1.43	0.1	0.81
Clinical variables						*All model*	*40.3*	
Age (yrs)	1.01	0.98–1.03	0.8	0.36	1.02	0.95–1.01	1.4	0.24
HF duration (yrs)	0.98	0.95–1.03	0.3	0.56	—	—	—	—
NYHA functional class (I to IV)	1.56	0.99–2.48	3.7	0.05	1.13	0.53–1.47	0.2	0.63
Diabetes mellitus, present	1.18	0.70–1.97	0.4	0.52	—	—	—	—
ACEI/ARB therapy, present	0.26	0.14–0.47	18.9	<0.001	0.29	0.15–0.55	14.1	0.0002
BB therapy, present	0.30	0.14–0.66	8.7	0.003	0.35	0.16–0.80	6.0	0.014
Systolic blood pressure (mm Hg)	0.98	0.97–1.03	5.0	0.026	1.01	0.99–1.02	2.0	0.16
Heart rate (beats/min)	1.02	1.01–1.03	7.9	0.005	0.98	0.97–1.01	2.8	0.09
GFR (ml/min/1.73 m)	0.98	0.96–0.99	9.9	0.002	1.01	0.99–1.03	1.7	0.20
Ischemic HF etiology	0.80	0.49–1.33	0.7	0.40	—	—	—	—
Male	1.8	0.86–4.21	2.3	0.13	1.09	0.48–2.73	0.04	0.84

HF = heart failure; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

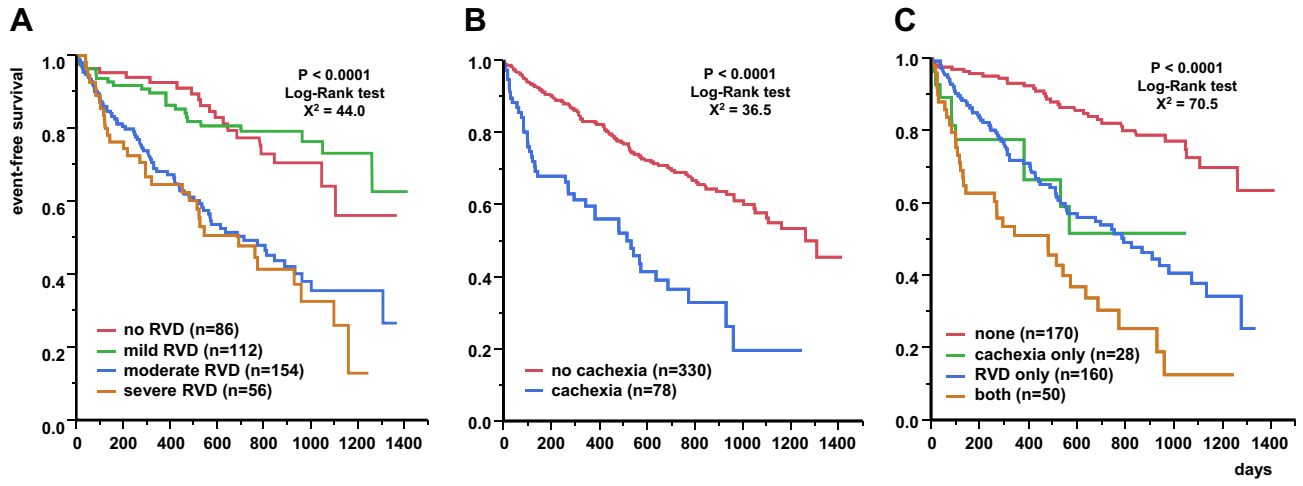

Figure 3 RV Dysfunction, Cachexia, and Survival

Kaplan-Meier plots displaying the effect of **(A)** RVD grade, **(B)** presence of cachexia, or **(C)** both on freedom of adverse event (combined endpoint of death without heart transplantation, urgent transplantation or assist device implantation). In **C**, RVD integrated moderate and severe grade. Cachexia was defined by history of >5% body weight loss in past 6 months and abnormal laboratory findings (see the Methods section). Abbreviation as in Figure 1.

the role of RV functional response to pressure overload (21,39), rather than the degree of pressure overload itself. Persistent RV impairment may be a consequence of load/perfusion mismatch or it may integrate transient episodes of overloading that can occur during exercise or of hypervolemia (21). Conversely, causal links between cachexia and RVD may be bidirectional in nature; that is, cytokines and metabolites released during wasting may adversely influence cardiac performance (Fig. 5) (40). Tumor necrosis factor–alpha, a cytokine elevated in cardiac cachexia (41), has potent negative inotropic effects (42) and is correlated with RV ejection fraction, but not LV ejection fraction, in patients with biventricular HF (43). Future studies should examine whether improvement in RV function may alleviate cardiac cachexia or vice versa. Indeed, recent studies have reported that the phosphodiesterase 5 inhibitor sildenafil enhances RV function (44) and may attenuate weight loss in advanced HF (45).

Subjects with cardiac cachexia in this study were notably in the upper range of normal BMI. Normal body habitus does not exclude ongoing wasting, particularly in previously obese HF subjects. The relatively larger depletion of fat in

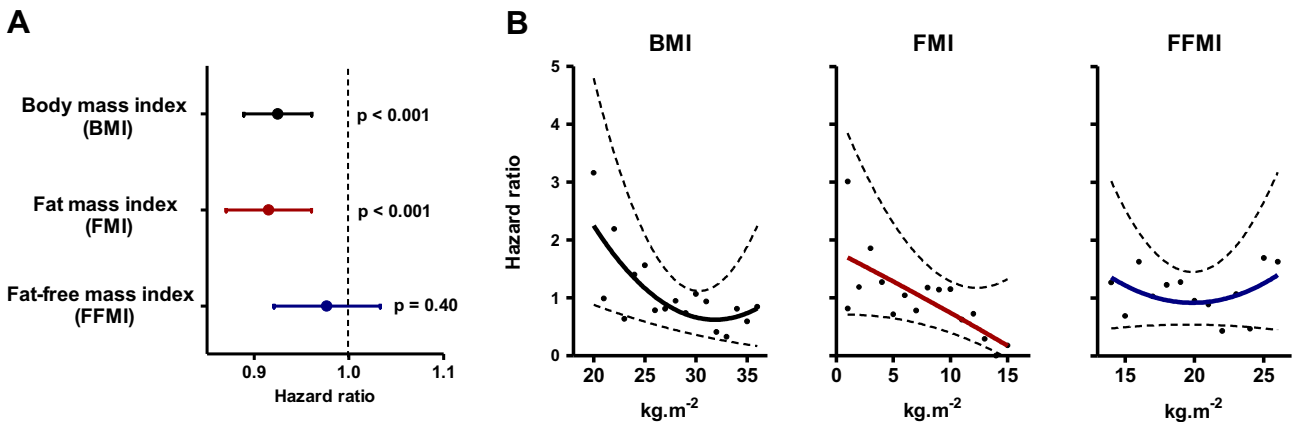

Figure 4 Body Composition and Outcome in HF

The effect of body mass index (BMI) and its components (BMI = fat mass index [FMI] + fat-free mass index [FFMI]) derived from anthropometric measurements of skinfold thickness (26) on risk of adverse outcome (death without transplantation, urgent transplant or assist device implantation) in univariate Cox proportional hazards model. **(A)** Risk ratios (and 95% confidence interval) for the whole population, **(B)** risk ratios **(dots + solid line)** and 95% confidence interval **(interrupted line)** per integers of variables; second degree polynomial fit.

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Table 4 Predictors of Adverse Outcome by Cox Proportional Hazards Analysis in All HF Subjects (N = 408)

	Univariate				Multivariate (Chi-Square = 92, p < 0.001)			
	HR	95% CI	Chi-Square	p Value	HR	95% CI	Chi-Square	p Value
Natremia (mmol/l)	0.90	0.86–0.94	22	**<0.0001**	0.96	0.91–1.02	1.9	0.16
Age (yrs)	0.98	0.96–0.99	6.8	**0.009**	0.97	0.95–0.99	7.2	**0.007**
Male	2.37	1.35–4.66	9.7	**0.002**	1.13	0.57–2.33	0.1	0.73
NYHA functional class (I to IV)	1.77	1.31–2.40	14	**0.002**	1.26	0.86–1.83	1.4	0.24
Systolic blood pressure (mm Hg)	0.98	0.97–0.99	26	**<0.0001**	0.99	0.98–0.99	4.4	**0.036**
Heart rate (beats/min)	1.01	1.004–1.02	6.9	**0.009**	0.99	0.98–1.01	1.0	0.32
Inferior vena cava diameter (mm)	1.05	1.03–1.08	16	**<0.0001**	0.97	0.94–1.01	2.0	0.16
RVD present	3.09	2.18–4.45	43	**<0.0001**	2.00	1.24–3.33	8.3	**0.003**
Tricuspid regurgitation gradient (mm Hg)	1.02	1.01–1.03	6.7	**0.010**	1.02	1.006–1.04	7.5	**0.006**
ACEI or ARB use, present	0.37	0.25–0.55	21	**<0.0001**	0.49	0.30–0.81	7.5	**0.006**
BNP (pg/ml)	1.0006	1.0004–1.0007	39	**<0.0001**	1.0003	1.0001–1.0006	8.6	**0.003**
LV ejection fraction (%)	0.97	0.94–0.99	4.2	**0.04**	1.01	0.98–1.05	0.6	0.44
Cachexia present	2.90	2.00–4.12	28	**<0.0001**	1.68	1.02–2.70	4.1	**0.041**
GFR (ml/min/1.73 m)	0.98	0.97–0.99	13	**0.0004**	0.99	0.97–1.01	2.5	0.11
Leg edema, present	1.62	1.14–2.29	7.0	**0.008**	1.17	0.48–0.76	0.5	0.48

Composite adverse outcome was defined as death without transplantation, urgent transplantation, or implantation of ventricular assist device. **Bold** p values are < 0.05.
Abbreviations as in Tables 1 through 3.

cachexia noted in this study does not necessarily contradict the important role of lean tissue wasting in the pathophysiology of advanced HF (29). During increased stress and metabolic demand, fat can be preferentially mobilized and lean tissue relatively spared. Fat loss may thus precede lean mass depletion, as has been shown in cancer-related cachexia (46,47). Increased adiposity may also lead to greater muscle strength, which may facilitate some clinical benefits (48). Fat mass displayed a stronger correlation with prognosis than fat-free mass, confirming previous observations in a smaller, less morbid HF cohort (6); however, in patients with stable coronary disease, both higher fat and lean mass correlated with a better prognosis (49,50). If fat loss is simply an early surrogate of a pro-catabolic phase in HF preceding loss of lean mass, or whether fat tissue provides some cardioprotective effects in HF, is currently unknown and deserves further inquiry.

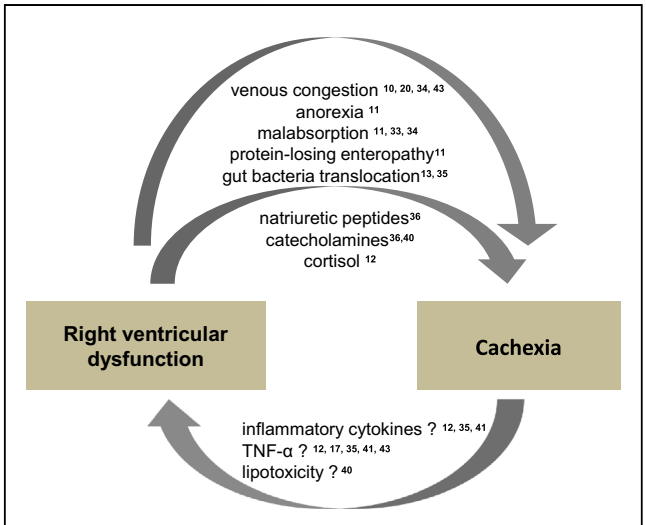

Figure 5 RVD and Cardiac Cachexia

Possible bidirectional mechanisms linking RVD to cardiac cachexia in patients with advanced heart failure. TNF = tumor necrosis factor; other abbreviation as in Figure 1.

Study limitations. This prospective study was observational and cross-sectional; therefore, causality cannot be addressed. Due to potential referral bias, our cohort may not reflect a general HF population. The definition of cachexia itself is evolving (27), and we might have obtained slightly different results if we had used a definition incorporating body composition (10,16). Not accounting for fluid loss secondary to diuretics may confound our analysis, but most of the patients had already been using diuretics for a long time, and average right atrial pressures were not markedly elevated. In addition, the presence of edema in the 6 months preceding examination (29% of subjects) had no impact on outcome (HR: 1.1; 95% CI: 0.7 to 1.5; p = 0.8) in striking contrast to reported weight loss, suggesting that the two are unrelated. If patients with antecedent edema were excluded, cachexia remained highly predictive of adverse outcome (HR: 3.5; 95% CI: 2.2 to 5.4; p < 0.0001).

Conclusions

This study showed that RVD and cardiac cachexia frequently coexist, may be mechanistically linked, and additively affect prognosis in patients with advanced HF. Strategies improving RV function might prevent cardiac cachexia, and, conversely, reversal of the wasting state may allow for enhanced RV function. Wasting of fat mass, but not of lean mass, was predictive of adverse outcome, suggesting that fat mass loss is either a surrogate of enhanced catabolism or adipose tissue confers some inherent cardioprotection in advanced HF.

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Key Words: body composition ■ cachexia ■ heart failure ■ obesity paradox ■ right ventricular function.

APPENDIX

For supplementary figures, please see the online version of this article.