

Adrenergic Activation, Fuel Substrate Availability, and Insulin Resistance in Patients With Congestive Heart Failure

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- Objectives** This study sought to investigate plasma levels of glucose and free fatty acids (FFA) and their relationship with adrenergic activation and insulin resistance (IR) in patients with advanced congestive heart failure (CHF).
- Background** Adrenergic activation and IR are hallmarks of advanced heart failure. The resulting changes in fuel substrate availability and their implications for exercise capacity have not been elucidated.
- Methods** Subjects with CHF underwent maximal exercise testing. Plasma glucose, FFA, insulin, and norepinephrine (NE) levels were measured at rest and at peak exercise. Beta-receptor sensitivity to NE was assessed using the Chronotropic Responsiveness Index (CRI). Homeostasis Model Assessment Index >2.5 defined IR. Left ventricular ejection fraction was estimated by 2-dimensional echocardiography.
- Results** Ninety-six subjects were enrolled. CHF subjects without IR (CHF/No-IR), but not those with IR (CHF/IR), significantly increased glucose and insulin in response to exercise. Only CHF/No-IR subjects increased FFA in response to exercise (0.14 ± 0.27 mmol/l; $p = 0.027$). NE increased significantly less with exercise, and CRI was lower in CHF/IR subjects compared with CHF/No-IR subjects (1.3 ± 1.4 vs. 2.5 ± 2.1 ; 6.4 ± 2.6 vs. 8.5 ± 3.4 ; $p = 0.069$). CRI correlated with the exercise-induced increase in FFA ($r = 0.41$; $p < 0.005$). These results stayed the same after excluding diabetic patients from the CHF/IR group.
- Conclusions** Circulating FFA levels increased during exercise in CHF subjects without IR, but not in those with IR or DM. Increased FFA availability during exercise may represent a catecholamine-dependent compensatory fuel shift in CHF. (J Am Coll Cardiol HF 2013;1:331–7) © 2013 by the American College of Cardiology Foundation

In congestive heart failure (CHF), profound changes in the rate of whole-body free fatty acids (FFA) and carbohydrate oxidation take place, although studies examining the direction of such fuel shifts, particularly in the failing human heart, have not led to clear conclusions (1). Some investigators have reported a shift away from FFA utilization (2), whereas others have reported a shift towards FFA utilization (3). Few studies have examined overall fuel utilization in patients with CHF during exercise and in vivo (4,5). In contrast to the prevailing paradigm that glucose is the preferred fuel in humans with CHF, at least 1 study suggests that FFA utilization is critically linked to reduced cardiac efficiency (5).

Overall fuel source utilization is governed by substrate availability and the organism's ability to use the substrate, which, in patients with CHF, may be affected by comorbid conditions such as diabetes (DM) or insulin resistance (IR), as well as pharmacotherapy and adrenergic activation (6,7). The availability of circulating fuel substrates in subjects with CHF receiving standard medical therapy during exercise has not been studied in regard to their status of IR. Accordingly, we examined resting and peak exercise levels of glucose, insulin, and norepinephrine (NE), as well as FFA, in subjects with advanced CHF on optimal medical therapy.

Methods

Patient population. Subjects with CHF were recruited from consecutive patients referred for a cardiopulmonary exercise test at New York Presbyterian Hospital–Columbia University Medical Center and were included if the following criteria were met: CHF, New York Heart Association class II to IV symptoms, left ventricular ejection fraction (LVEF) $\leq 40\%$, and optimal medical therapy including

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Manuscript received October 9, 2012; revised manuscript received April 2, 2013, accepted April 15, 2013.

**Abbreviations
and Acronyms**

BMI = body mass index
CHF = congestive heart failure
CRI = Chronotropic Responsiveness Index
DM = diabetes mellitus
FFA = free fatty acids
HOMA = Homeostasis Model Assessment
IR = insulin resistance
LVEF = left ventricular ejection fraction
NE = norepinephrine
pV_O₂ = peak oxygen consumption

angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and beta-blocker for at least 3 months unless contraindicated. Subjects were considered diabetic if this diagnosis had been made previously and they were taking antidiabetic medications. Nondiabetic subjects were categorized as insulin resistant if the Homeostasis Model Assessment (HOMA) Index was >2.5. Subjects were excluded if they had been hospitalized within 3 months for cardiovascular diseases or had noncardiac exercise-limiting illnesses, such as moderate-to-severe arthritis, peripheral vascular disease, or chronic obstructive pulmonary disease.

Study approval was obtained from the institutional review board, and all subjects signed informed written consent.

Study protocol. Subjects were asked to withhold breakfast on the morning of the test and take their medication with water. After 20 min of supine rest, an 18- or 20-ga angiocatheter was inserted into a forearm vein, and blood for biochemical assessments was drawn. Subjects underwent a symptom-limited cardiopulmonary exercise test, and blood was again drawn immediately upon cessation of exercise. Samples were stored on ice after collection and promptly centrifuged at 1,550 *g* for 10 min. After separation, plasma aliquots were stored frozen at -80°C .

Study procedures. CARDIOPULMONARY EXERCISE TESTING. Peak oxygen consumption (pV_O₂) in milliliters per kilogram per min (ml/kg/min) was assessed during graded treadmill exercise. Work rate increased continuously as a ramp function by augmenting the speed and grade of the treadmill according to the Naughton protocol (8). Heart rate and electrocardiograms were recorded continuously throughout the test, and blood pressure was measured at rest, every 2 min during exercise, and immediately upon cessation of exercise. Expired gases were collected throughout exercise, and oxygen consumption was calculated on a breath-by-breath basis using a metabolic cart (Medgraphics, St. Paul, Minnesota). Subjects exercised to exhaustion, and pV_O₂ was defined as the highest value of oxygen uptake attained in the final 20 s of exercise.

Chronotropic Responsiveness Index (CRI), a measure of post-synaptic beta-receptor responsiveness to NE, was calculated using the following formula: (peak heart rate – baseline heart rate)/Log (peak norepinephrine – baseline norepinephrine) (9).

ECHOCARDIOGRAPHY. Echocardiograms were performed within 6 months of the V_O₂ study, and results were gathered from online charts. LVEF was estimated using

2-dimensional parasternal long, parasternal short, apical long, and apical short images.

BIOCHEMICAL ANALYSES. Plasma glucose was determined with a glucose oxidase method (GM7 Analyser, Analox Instruments, Hammersmith, United Kingdom). Insulin levels were determined in heparinized plasma by 2-site chemiluminescent immunometric assay (Diagnostic Products Corp., Los Angeles, California). Serum FFAs were determined with an enzymatic colorimetric method (Nefa C test, Wako Chemicals, Neuss, Germany). NE was determined by high-performance liquid chromatography separation and tandem mass spectrometric detection (API 4000, Applied Biosystems, Carlsbad, California) in the first 55 CHF patients.

We estimated IR using the HOMA Index, which is defined as fasting insulin (μU/ml) times fasting glucose (mmol/l) divided by 22.5 (10). A HOMA index >2.5 defined IR (11). Subjects using exogenous insulin were excluded from the HOMA index calculations.

Statistical analysis. Continuous variables are expressed as mean ± SD. Continuous variables were explored for normal distribution according to histograms and the Shapiro-Wilk test. In Tables 1 and 2, the comparison of quantitative variables between the CHF groups was performed using the Student *t* test for normally distributed variables and the Mann-Whitney *U* test for non-normally distributed variables. Categorical variables are expressed as number and percentage, and the chi-square test was used for comparisons with Fisher exact test when appropriate. In Figures 1 and 2, for the comparison of the change in glucose or FFA in response to exercise between diabetic patients, CHF subjects with IR (CHF/IR), and CHF subjects without IR (CHF/No-IR), we used the Kruskal-Wallis test. In Figure 3, for the comparison of the change in FFA in response to exercise according to the pV_O₂ in quartiles, we used the Jonckheere-Terpstra test for trend. For the comparison between resting and exercise measurements (response to exercise), we used the paired-samples Wilcoxon test for non-normally distributed variables. Bivariate correlations were analyzed by the Pearson correlation coefficient, and the significance test was 2-tailed. For correlation analyses that involved the HOMA Index, we excluded patients with insulin-dependent DM because we did not control the administration of exogenous insulin before the study and the possible influence of this exogenous insulin on the HOMA Index. We performed backward method linear multiple regression analysis to predict the increase in FFA during exercise with an inclusion criteria of $p < 0.05$ and an exclusion criteria of $p > 0.10$. Analysis of residuals was performed. Significance was set at $p < 0.05$ (2-tailed). SPSS version 17 was used to perform all statistical evaluations (SPSS, Chicago, Illinois).

Results

Ninety-six subjects age 52.5 ± 12.5 years were enrolled. The etiology of CHF was ischemic cardiomyopathy in

Table 1 Baseline Characteristics

	CHF/DM (n = 18)	CHF/IR (n = 31)	CHF/No-IR (n = 47)	p Value		
				IR vs. No-IR	IR vs. DM	No IR vs. DM
Age, yrs	56.6 ± 9.9	51.6 ± 14.0	52.1 ± 12.0	0.871	0.186	0.125
Male	15 (83)	20 (65)	30 (65)	0.950	0.160	0.168
BMI, kg/m ²	31.3 ± 3.8	33.2 ± 6.5	25.6 ± 3.9	<0.001*	0.540*	<0.001*
Beta-blocker	16 (89)	28 (90)	44 (96)	0.560	0.624	0.189
CHF etiology				0.740	0.142	0.291
Ischemic	9 (50)	9 (29)	16 (33)			
Nonischemic	9 (50)	22 (71)	31 (67)			
LVEF, %	19.8 ± 8.7	25.8 ± 10.6	24.4 ± 10.8	0.620*	0.042*	0.103*
pV _{O₂} , ml/kg/min	14.4 ± 4.6	15.6 ± 3.8	18.2 ± 5.7	0.001*	0.152*	0.004*
pV _{O₂} , l/min	1.37 ± 0.51	1.58 ± 0.57	1.36 ± 0.52	0.089*	0.255*	0.958*
RER, beats/min	1.04 ± 0.11	1.06 ± 0.10	1.04 ± 0.11	0.972	0.708*	0.972
Resting HR	75 ± 12	73 ± 12	69 ± 14	0.148	0.667	0.113
Peak HR	116 ± 20	120 ± 21	126 ± 24	0.311	0.400*	0.056*

Values are mean ± SD or n (%). For comparison of quantitative variables between groups, we used the Student *t* test except as noted. For comparison of categorical variables between groups, we used the chi-square test, with the Fisher exact test when appropriate. *Mann-Whitney *U* test used for the comparison.

BMI = body mass index; CHF = congestive heart failure; DM = diabetes mellitus; HR = heart rate; IR = insulin resistance; LVEF = left ventricular ejection fraction; pV_{O₂} = peak oxygen consumption; RER = respiratory exchange ratio.

33 (34%) patients. The mean LVEF was 23.5 ± 10.5%, and pV_{O₂} was 16.7 ± 5.2 ml/kg/min. Eighteen (17%) patients had been previously diagnosed with diabetes and were receiving insulin and/or oral anti-hyperglycemic agents. In addition to the 18 diabetic patients (CHF/DM), 31 CHF subjects had IR (CHF/IR), and 47 CHF subjects did not have IR (CHF/No-IR). There was no difference in the etiology of CHF between CHF/IR, CHF/DM, and CHF/No-IR subjects. CHF/IR subjects had a higher body mass index (BMI) compared with

CHF/No-IR subjects. Only 7 patients were not receiving a beta-blocker (2 CHF/No-IR and 5 CHF/IR). Type and dose of beta-blocker were similar in the CHF groups (Table 1).

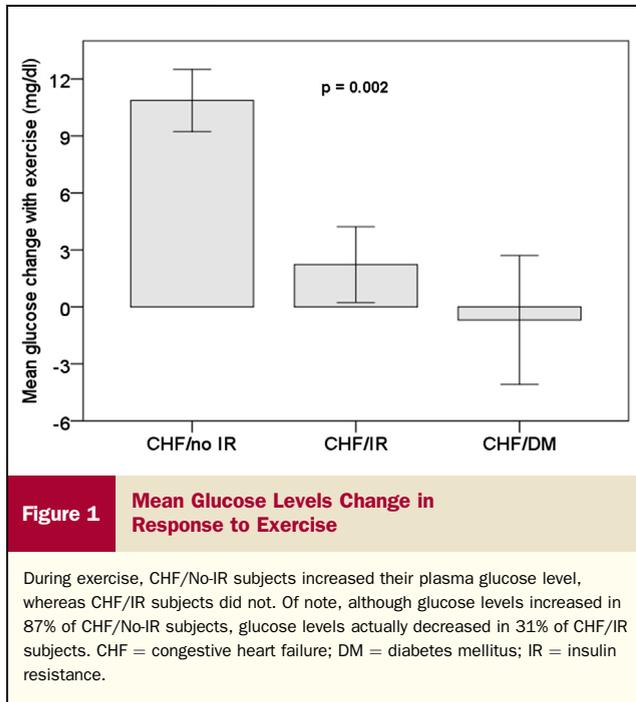
Resting levels of circulating fuel substrate. Resting levels of glucose and insulin were significantly lower in CHF/No-IR compared with CHF/IR and CHF/DM; NE levels were lower as well in CHF/No-IR, but this did not reach statistical significance (Table 2). There was no difference in resting FFA levels between the groups.

Table 2 Change in Circulating Substrate Levels as a Function of IR

	Diabetic (n = 18)	CHF/IR (n = 31)	CHF/No-IR (n = 47)	p Value		
				IR vs. No-IR	IR vs. DM	No-IR vs. DM
Glucose, mg/dl						
Rest	188.56 ± 71.30	113.03 ± 18.00	97.63 ± 11.16	<0.001	<0.001	<0.001
Peak exercise	183.31 ± 68.28	115.26 ± 17.14	108.43 ± 15.0	0.270	<0.001	<0.001
ΔGlucose	-0.69 ± 13.61	2.23 ± 11.13	10.87 ± 10.99	<0.001	0.770	0.005
FFA, mmol/l						
Rest	0.56 ± 0.25	0.65 ± 0.29	0.60 ± 0.25	0.275	0.312	0.506
Peak exercise	0.61 ± 0.21	0.66 ± 0.28	0.75 ± 0.33	0.694	0.519†	0.136
ΔFFA	0.043 ± 0.14	-0.008 ± 0.16	0.14 ± 0.27	0.030	0.081	0.064†
Insulin, μU/ml						
Rest	51.83 ± 69.4	28.19 ± 26.02	6.13 ± 1.55	<0.001	0.626	<0.001
Peak exercise	52.74 ± 68.97	24.57 ± 13.06	8.10 ± 4.71	<0.001	0.297	<0.001
ΔInsulin	0.91 ± 28.37	-3.79 ± 20.26	1.91 ± 4.35	0.041	0.749	0.288
NE, nM*						
Rest	4.75 ± 4.90	3.56 ± 2.57	3.07 ± 1.72	0.516	0.882	0.507
Peak exercise	6.55 ± 5.34	4.71 ± 2.64	5.61 ± 3.39	0.301	0.790	1.000
ΔNE	1.79 ± 1.77	1.15 ± 1.26	2.53 ± 2.09	0.004	0.328†	0.428
CRI	6.06 ± 2.75	7.12 ± 2.57	8.49 ± 3.38	0.175†	0.405†	0.098†

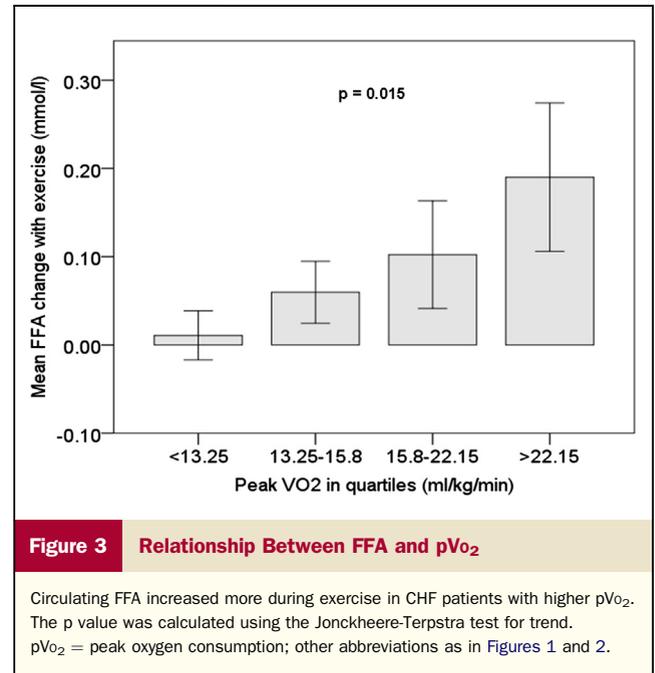
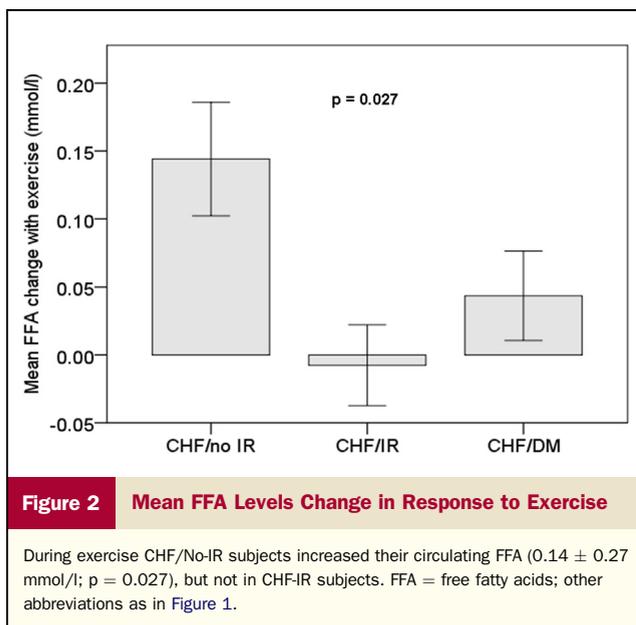
Values are mean ± SD. *NE levels were measured only in the first 55 patients: 6 CHF/DM, 20 CHF/IR, and 29 CHF/no IR. For all comparisons between groups, we used the Mann-Whitney *U* test, except as noted. †We used the Student *t* test because the variables followed a normal distribution.

CRI = Chronotropic Responsiveness Index; FFA = free fatty acids; NE = norepinephrine; other abbreviations as in Table 1.



Response to exercise. CHF/IR and CHF/DM patients did not at all increase glucose or insulin in response to exercise ($p > 0.05$) and had the smallest increase in NE ($p = 0.001$ in CHF/IR and $p = 0.03$ in CHF/DM). By contrast, CHF/No-IR increased glucose ($p < 0.001$), insulin ($p = 0.002$), and NE ($p < 0.001$) in response to exercise.

Of note, although glucose levels increased in 87% of CHF/No-IR subjects, glucose levels actually decreased in 31% of CHF/IR and CHF/DM subjects (Fig. 1).



Similarly, FFA increased in CHF/No-IR subjects (0.14 ± 0.27 mmol/l; $p = 0.027$), but not in CHF/IR and CHF/DM subjects (Fig. 2).

Relationship of pV_{O_2} , IR, CRI, and changes in circulating fuel substrate in CHF subjects. CHF/IR and CHF/DM subjects had lower pV_{O_2} compared with CHF/No-IR subjects (Table 1), and pV_{O_2} and HOMA Index were inversely correlated ($r = -0.254$; $p = 0.026$). Age, sex, LVEF, and etiology of cardiomyopathy did not differ between CHF/IR, CHF/DM, and CHF/No-IR subjects.

NE was lower and CRI was higher in CHF/No-IR subjects. Furthermore, CRI was correlated with delta FFA ($r = 0.41$, $p < 0.005$), and FFA increased more during exercise in those with higher pV_{O_2} (Fig. 3).

In order to evaluate what factors were associated with an increase in FFA levels during exercise in CHF, we performed backward multivariate linear regression analysis using the following variables: HOMA Index, CRI, age, pV_{O_2} , and BMI. In this analysis, only CRI remained significant in the model (Beta = 0.027; $p = 0.039$).

Discussion

We measured plasma levels of FFA, glucose, NE, and insulin at rest and following maximal exercise in stable outpatients with CHF. Our principal findings are as follows:

First, IR was present in 50% of the CHF patients, and its severity was inversely correlated with pV_{O_2} .

Second, CHF/IR and CHF/DM subjects had higher resting levels of glucose, insulin, and NE.

Third, in response to exercise, different patterns of change in circulating hormones and fuel substrate occurred; the stress response in CHF/No-IR was characterized by

increases in NE, insulin, and glucose, as well as FFA levels. CHF/IR and CHF/DM patients did not have increased glucose, insulin, or FFA and had the lowest increase in NE. Importantly, all subjects provided similar effort and maximal effort as evidenced by nearly identical respiratory exchange ratios averaging 1.04 during metabolic testing. At this similar stage of metabolic effort, changes in circulating substrate were statistically significantly different between groups. This remained the case after excluding diabetic patients.

Lastly, an increase of circulating FFA was associated with better exercise capacity and better CRI, which may indicate that FFA release is important for exercise capacity and possibly mediated by preserved sympathetic activation.

Many studies have described an association of DM and CHF: in the Framingham Heart Study, diabetes mellitus was an independent risk factor for the development of CHF, with a 2.4-fold risk increase in men and a 5-fold risk increase in women (12). In the UKPDS (UK Prospective Diabetes Study), for every 1% increase in glycosylated hemoglobin (HbA_{1c}), the risk of developing CHF rose by 16% (13). Although this potentially causal relationship of DM and CHF is now well described, evidence is mounting that heart failure itself can cause IR. Swan *et al.* (14) demonstrated that CHF is associated with marked IR, and the adverse association of IR and exercise capacity has also been established (15).

Our data on the prevalence of IR and DM, as well as their association with diminished exercise capacity, are concordant with the previously cited studies (12–15). We tried to further characterize this metabolic phenotype and/or the root cause of IR in CHF. Our study, although cross sectional in nature, is the first to explore changes in both resting and exercise-induced levels of circulating fuel substrate, and simultaneously investigate the relationship between fuel substrate availability, IR, and adrenergic activation. Adrenergic activation is extremely well studied in CHF, and our observations regarding higher resting NE levels, diminishing NE release in response to exercise, and reduced beta receptor sensitivity (CRI) in patients with more advanced CHF (*i.e.*, lower pV_{O₂}) were not only expected (9,16), but underscore a well-established paradigm of compensatory, but ultimately detrimental, neurohormonal activation in CHF (17). Clearly, the ability of the end-stage CHF patients to release NE is diminished, and our data seem to suggest a similar phenomenon for glucose and FFA.

Resting levels of glucose were higher, apparently resulting in an “exhausted” mechanism for glucose release during exercise (much like what is seen with NE and possibly linked to it). We believe that in this setting, FFAs are mobilized to serve as a complimentary fuel; thus, exercise-induced increases in FFA are seen. This increase in FFA is probably mediated by NE, and the fact that CRI and not the HOMA Index predicted the exercise-induced increase in FFA after correcting for age, pV_{O₂}, and BMI supports this. Although this compensatory mechanism is activated, it is outweighed

by the loss of glucose utilization, and consequently, exercise capacity decreases. The inverse relationship of HOMA Index (or other measures of IR) and exercise capacity shown in our study and previously by others (15) are consistent with a dominant role of glucose utilization in determining exercise capacity.

We observed nominally higher resting FFA levels in CHF/IR versus CHF/No-IR subjects, possibly by increased lipolysis due to rising catecholamine levels, a phenomenon some have referred to as the “hyperadrenergic free fatty acid load in CHF” (18). Regrettably, we were unable to demonstrate a statistically significant difference in FFA resting levels in the nondiabetic CHF patients with and without IR. Interestingly, diabetic patients with CHF had the lowest levels of FFA, indicating either a completely different pathophysiology or even higher reliance on FFA. It is equally speculative, but conceivable, that the very high insulin levels in this group suppressed lipolysis at rest.

Given the paucity of data in the fuel-availability arena, a recent study by Melenovsky *et al.* (4) is noteworthy. In an experimental setup similar to ours, the authors identified circulating pyruvate—a product of glycolysis—as closely associated with pV_{O₂}. Although we did not measure pyruvate, our data on increased resting levels of insulin, glucose, and FFA are concordant with their findings. Interestingly, these authors observed very high resting FFA levels and a sharp decrease following exercise in diabetic patients, an observation concordant with our hypothesis on higher reliance of FFA in diabetic patients. With regard to other findings, some of them discordant, it is of note that Melenovsky *et al.* (4) in their intriguing study compared diabetic and nondiabetic CHF patients with an average HOMA Index of 4, whereas we separated nondiabetics according to HOMA Index <2.5. Ultimately, it is important to emphasize that circulating substrates such as FFA and glucose are not necessarily indicative of tissue utilization, and neither Melenovsky *et al.* nor we examined the production of FFA or glucose by the liver or its consumption by heart and skeletal muscle (19,20). Future studies should build on the current evidence and simultaneously study fuel availability and utilization.

We believe our data support the following sequence of events: CHF ensues, catecholamine levels rise, catecholamines stimulate gluconeogenesis and lipolysis, glucose and FFA levels rise, glucose and FFA stores are depleted, impaired exercise tolerance ensues, and the less efficient fuel FFA is utilized to compensate (CHF/No-IR phenotype). Eventually, FFA and glucose stores are depleted, and circulating substrate fails to increase during demand situations (CHF/IR or CHF/DM phenotypes).

Although such a hypothesis cannot solely explain the complex syndrome of CHF and is somewhat speculative based on our data alone, at least 3 prior studies conducted in different settings support this concept. Nikolaidis *et al.* (21) studied the changes in resting plasma levels of NE, FFA, glucose, and insulin in 12 dogs during the evolution from

a normal state to advanced CHF. With the induction of heart failure by pacing, NE and FFAs progressively increased and IR worsened. Of note, these metabolic changes preceded changes in cardiac output and left ventricular dilation. Examining the role of FFA as a fuel in exercise in humans, Tuunanen et al. (5) attempted to facilitate glucose uptake by suppressing FFA production during exercise using acipimox, a lipolysis inhibitor. Suppression of FFA resulted in decreased cardiac work and efficiency in CHF patients. Although this result was entirely unanticipated, it supported findings by Augustus et al. (22), previously made in a lipase-deficient mouse model, where deprivation of lipase-derived FFA resulted in cardiac dysfunction. We are the first, to our knowledge, to demonstrate an association of better exercise capacity (pV_{O_2}) and higher exercise-induced FFA increases in CHF. Our finding is concordant with the aforementioned observations by Nikolaidis et al. (21) in dogs, Augustus et al. (22) in mice, and by Tuunanen et al. (5) in humans, and further underscores the importance of FFA availability in CHF.

The overall goal of studies in fuel metabolism in CHF is to develop new therapeutic approaches. How does the current data compliment and/or expand existing knowledge in this regard? Our main contribution is that we have identified FFA availability as a potentially critical element of exercise intolerance in advanced CHF. Furthermore, we have begun to elucidate mechanisms underlying FFA release in CHF and identify adrenergic activation as a possible root cause for IR in CHF. The latter finding may be of particular interest, given recent efforts to treat CHF with parasympathetic stimulation, which may counteract adrenergically mediated IR development via a mechanism different from beta blockade (23).

Study limitations. Our study is limited mainly by its cross-sectional nature and the lack of a healthy control group, but our data clearly demonstrate different patterns in circulating fuel substrates at rest and in response to exercise between CHF/IR, CHF/DM, and CHF/No-IR subjects. These differences in metabolic phenotype have not previously been reported. That said, only tracer studies can elucidate whether, for example, FFA production by the liver and adipose tissue and/or clearance by muscle is altered in CHF. Our data should prove helpful to design such studies, which would add fundamental insights into the pathophysiology of CHF. Similarly, although our results may suggest a progressive worsening of IR with detrimental effects on functional capacity, we cannot exclude that physical inactivity and increased BMI resulted in IR rather than vice versa. In this context, it is of note that Sokos et al. (24) recently demonstrated a remarkable improvement of LVEF and pV_{O_2} after 5 weeks of chronic administration of glucagon-like peptide, a naturally occurring peptide with both insulinomimetic and insulinotropic actions (24). Here, restoration of insulin effects preceded improvement in functional parameters. We believe that, conversely, and similar to the observation made by Nikolaidis et al. (21) in dogs, the development of IR in

CHF precedes a decrease in exercise capacity. Longitudinal studies are needed to prove this assertion.

Conclusions

IR was present in 50% of the CHF patients, and its severity was inversely correlated with pV_{O_2} . Patients with CHF/IR and CHF/DM had higher resting levels of glucose, insulin, and NE. These patients did not increase glucose, insulin, or FFA and had a lower increase in NE with response to exercise.

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Key Words: free fatty acids ■ glucose ■ heart failure ■ insulin resistance.