Evaluating ejection fraction and obesity paradox in a heart failure program

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Abstract

Objective: This study was aimed to relate the obesity paradox to ejection fraction and obesity. The obesity paradox remains controversial in the literatures. Obesity has detrimental effects on heart failure, but has been found to be paradoxically associated with improved survival. We hypothesized that a preserved ejection fraction in heart failure patients is associated with obesity.

Method: We analyzed 732 patients who were enrolled in our heart failure program and excluded those who did not follow up or patients discharged from the cardiology clinic. 688 patients who have been followed since 2013 were included. Using ACC/AHA guidelines, heart failure is classified as a reduced ejection fraction (HFrEF, EF <40), preserved ejection fraction (HFpEF, EF>50) and heart failure with an improved ejection fraction (HFpEF(i), EF≥40). BMI was classified according to NCEP-ATP III.

Results: The number of normal weight (BMI <25 kg/m²), overweight (30 kg/m² >BMI≥25 kg/m²) and obesity (BMI≥30 kg/m²) were 207(35.7%), 224(35.1%) and 208(29.1%) respectively. The number of patients in our selected populations of HFrEF, HFpEF and HFpEF(i) were 456(67.9%), 136(20.2%) and 68(11.9%) respectively. A preserved EF had a significant P-value associated with the obese group compared to our normal weight group. In addition, the absence of diabetes mellitus, an ICD (implantable cardioverter defibrillator), no prior cardiac catheterization and age over 65 were associated with a preserved EF.

Conclusion: The obesity paradox of EF applied to our study group. The obese group had a significant association with a preserved ejection fraction compared to the normal weight group. Based on the risk factors related to preserved ejection fraction, targeted management of related factors in heart failure could lead to different approaches in the future treatment of heart failure.

Background

Obesity was reported as a risk factor for cardiovascular mortality, however, it has been remained paradoxically cardioprotective in some population [1]. Although increasing BMI (body mass index) in general population, patients with heart failure and coronary artery disease were less likely to have acute myocardial infarction or stroke [2,3]. One hypothesis explaining obesity paradox showed total cholesterol had anti-an inflammatory effect related to better survival in congestive heart failure patients [4]. It would be helpful for preventing progression of cardiovascular disease. BMI defined by weight over height square did not take into consideration of body fat distribution [4]. Also, body fat distribution has been reported as an important role as visceral fat is more related to morbidity [5]. Waist circumference or abdominal imaging study were suggested for more accurate visceral fat measurement [6]. Improving left ventricular ejection fraction provided patients’ survival benefit [4]. One report said lower left ventricular systolic function in obese subjects than lean patients [4], which could be contradictory to obesity paradox. In African American and Hispanic population which is predominant in our study population, rate of obesity has been more dominant than other ethnicities however, their characteristics of heart failure have not been well defined. Moreover, ejection fraction is not reported to find the relationship with obesity paradox. Therefore, this study was conducted to relate obesity paradox to ejection fraction and obesity.

Methods

We analyzed 732 patients who were enrolled in our heart failure program and excluded those who did not follow up or patients discharged from the cardiology clinic. 688 patients who have been followed since 2013 were included. All patients with a confirmed diagnosis of heart failure were selected from January, 2013 to July 2015. Discharged patients from the cardiology clinic or expired patients were excluded. According to ACC/AHA guidelines [7], heart failure is analyzed as three types. They are heart failure with a reduced ejection fraction (HFrEF, Ejection Fraction <40), a preserved ejection fraction (HFpEF, Ejection Fraction >50) and heart failure with an improved ejection fraction(HFpEF(i), Ejection Fraction ≥40). HFrEF was also marked as systolic HF and HFpEF was termed as diastolic HF. HFpEF(i) has been established that a subgroup of patients with HFpEF had HFrEF priorly. BMI was classified according to NCEP-ATP III. BMI over 30 kg/m², 30 kg/m² > BMI≥25 kg/m² and 25> BMI≥20 were classified to obesity, overweight and normal. All characteristics were shown as numbers and frequency percentages for categorical variables. The proportions in three types of heart failure subjects were presented for anthropometric factors, social history, medications and
biochemical results. A multiple logistic regression analysis was used to figure out significant associations between the characteristics of subjects that were relevant to preserved ejection fraction. In addition, history cardiac catheterization and ICD (Implatable cardioverter defibrillator) were acquired from documented electronic medical record (EMR). All data were given as actual numbers with percentage. The demographic characteristics of the study were presented according to control of blood pressure in a heart failure program. Variables with a P<0.25 in the univariate test were selected as candidates for the multivariate model. Multivariate adjusted logistic regression was used to find our risk factors related to preserved ejection fraction and also showed non-adjusted logistic regression. Statistical analyses were performed using the SAS (Version 9.4; SAS Institute, Cary, NC). A P value <0.05 was considered statistically significant. The study protocol was approved by the Institutional Review Board at New York Medical College (Westchester, NY).

Results

General characteristics of three types of heart failure patients

Our study showed different factors among three groups of heart failure in terms of anthropometric, demographic, laboratory, and medications in Table 1. This study population was mainly comprised of African American and Hispanic patients. Different types of heart failure had significant association with sex, age, BMI (body mass index), DM, history of cardiac catheterization, ICD (implantable cardioverter defibrillator) insertion, compliance to medication and use of cocaine were related to types of heart failure based on ejection fraction (Table 1) (P<0.05).

Factors associated with preserved ejection fraction in a heart failure population

Table 2 showed multiple logistic regression analysis results. Basically, variables with a P<0.25 in the univariate test were selected as candidates, however, factors related to ejection fraction were included. The results were unadjusted and then adjusted by multiple variables related to preserved ejection fraction. Association between preserved ejection fraction and cardiac risk factors were as follows (Table 2). Based on adjusted logistic regression, obesity (35≥BMI≥30) was significantly associated with preserved ejection fraction compared to normal BMI (less than 25) (P<0.05). Patients with ICD were likely to have preserved ejection fraction. Compliance to medication also had positive association to have preserved ejection fraction compared to non-compliance to medication (P<0.05). Patients with DM were more related to impaired ejection fraction (P<0.05). If patients had cardiac catheterization history, they would like to have preserved ejection fraction (Table 2) (P<0.05). Diastolic blood pressure over 90 mmHg were more related to preserved ejection fraction (Table 2) (P<0.05).

Relationship between number of medications and BMI in a heart failure population

Figure 1 showed BMI were not associated with numbers of medication in each heart group. In other words, in each HFpEF, HFrEF and HFpEF(i) group, obese, overweight and normal body weight groups did not have significant relationship with numbers of medication. (P>0.05)

Association between age and BMI in a heart failure population

In Figure 2, age was significantly associated with different BMI in three types of heart failure. Especially, in HFpEF and HFpEF(i) patients over 65 years old were more prevalent (HFpEF; P<0.05 and HFpEF(i); P<0.05) in each BMI group, however, in HFrEF, patients aged between 40 and 65 had higher proportion (P<0.05) and they tended to increase according to increase of BMI.

Discussion

This is the study to analyze ejection fraction and obesity paradox among adults with diagnosed heart failure from a heart failure cohort study predominantly composed of Hispanic and African American population. In our study, obese patients had significant association with preserved ejection fraction (EF >40%) in Table 2 (P<0.05). The obese group had a larger portion of patients with a preserved EF compared to the normal weight group. This is consistent with one previous study result to show positive relationship between obesity and preserved ejection fraction [8]. Preserved ejection fraction was shown to have association with increased survival rate [9]. Even though the current study was retrospective and mortality benefit cannot be discussed, however, patients with improved EF in our study might have better survival compared to ones with reduced EF. So, the obesity paradox could be correlated to our study group. This may suggest that obese patient diagnosed with chronic heart failure had better heart function leading to improved survival rate. Effects of obesity on heart failure was consistent with previous studies showing paradoxical effect on survival [1,3]. Similarly, reverse epidemiology in congestive heart failure was reported regarding association between obesity and better survival [10]. In addition, a protective effect of obesity in patients with coronary artery disease was noted [2]. The inadequacy of BMI to predict body composition was also suggested, and then, waist circumference or waist to hip ratio was proposed to assess accurate measurement of visceral fat [1,6]. One study showed a preserved ejection in obese patients was associated with an increase of cardiac collagen and a decrease in the collagenase system of the heart. Also, inflammatory process stimulates extracellular matrix accumulation and then may result in HFpEF [9].

There are potential explanations of the paradox. One was the endotoxin and lipoprotein hypothesis saying higher level of cholesterol are beneficial in CHF on the basis of the ability of serum lipoproteins to modulate inflammatory immune function [4]. Also, cardiopulmonary fitness is more important than percent body fat to assess prognosis of heart failure [9]. Obese patients might have better muscle strength, muscle mass and better nutritional status resulting in improved survival rate [11,12].

Factors related to a preserved EF were different in our study groups. Diabetes mellitus had negative association with preserved EF, which was consistent with previous study [12]. One study showed that diabetes mellitus-related cardiomyopathy was also described as heart failure with diastolic left ventricular(LV) dysfuction [13]. Likewise, this study population with diabetes might have the myocardium and then structural changes from the natural collagen network which was reported at one study [13]. The diabetic heart failure patients may have impaired ejection fraction, therefore, mortality could be increased compared to non-diabetic heart failure patients.

ICD insertion was also found as a significant factor for preserved EF (Table 2). Several studies showed ejection fraction improvement since device placement [1,11]. ICD has demonstrated prevention from sudden cardiac death and improvement of left ventricular EF [14]. So, ICD in our study could have survival benefit, and it means that it provided the basis for risk stratification for heart failure [15-20].

Patients with cardiac catheterization in our population were likely...
to show reduced ejection fraction (Table 2). In this study, our data did not include whether stent insertion was done or not, however, ischemic etiology with heart disease might be related to ejection fraction (Table 1). Ischemic cardiomyopathy was shown to be a significant risk factor for a mortality predictor [4]. There was no causal relationship between cardiac cath and preserved ejection fraction [21-24]. Most of patients with ischemic etiology had coronary angiography, therefore, close observation is needed to appropriately treat patients with catheterization history [25,26].

Table 1. General characteristics of heart failure patients.

|                | Reduced ejection fraction (HFrEF, EF <40) | Improved ejection fraction (HFpEF,i,EF≥40) | Preserved ejection fraction (HFpEF, EF>50) | P value |
|----------------|------------------------------------------|-------------------------------------------|------------------------------------------|---------|
| **Sex**        |                                          |                                           |                                           |         |
| Male           | 296(64.9)                                | 72(52.9)                                  | 44(55)                                   | <0.001  |
| Race           |                                          |                                           |                                           |         |
| African American | 182(39.9)                               | 42(42.5)                                  | 34(30.8)                                 | 0.154   |
| Hispanic       | 242(53.1)                                | 84(45.0)                                  | 36(61.8)                                 |         |
| Asian          | 24(5.3)                                  | 6(10.0)                                   | 8(4.4)                                   |         |
| Caucasian      | 8(1.8)                                   | 4(2.5)                                    | 2(2.9)                                   |         |
| **Age(years)** |                                          |                                           |                                           | <0.001  |
| ≥65            | 266(77.3)                                | 44(12.8)                                  | 22(32.4)                                 |         |
| BMI(kg/m²)     |                                          |                                           |                                           | <0.001  |
| ≥35            | 54(11.8)                                 | 28(15.0)                                  | 44(20.6)                                 |         |
| 35-30          | 33(14.5)                                 | 30(7.5)                                   | 18(22.1)                                 |         |
| <25            | 176(38.6)                                | 42(22.5)                                  | 6(30.9)                                  |         |
| SBP (mmHg)     |                                          |                                           |                                           |         |
| ≥125           | 128.9 ± 21                               | 124.4 ± 18                                | 127.1 ± 17.7                             | 0.875   |
| DBP (mmHg)     | 74.6 ± 13.5                              | 68.6 ± 9.8                                | 70 ± 11.6                                | 0.154   |
| DM (%)         | 184(40.4)                                | 78(47.5)                                  | 38(57.4)                                 |         |
| HTN (%)        | 412(90.4)                                | 116(85.3)                                 | 66(82.5)                                 |         |
| Hyperlipidemia | 312(68.4)                                | 94(69.1)                                  | 46(57.5)                                 | 0.139   |
| ESRD on HD (%) | 264(77.3)                                | 44(12.8)                                  | 22(32.4)                                 |         |
| **Etiology**   |                                          |                                           |                                           |         |
| ISCP           | 298(65.3)                                | 102(75)                                   | 33(41.2)                                 | 0.121   |
| NISCQ          | 158(34.7)                                | 33(25)                                    | 47(58.8)                                 |         |
| LDL (mg/dl)    |                                          |                                           |                                           | 0.237   |
| ≥150           | 102(22.4)                                | 40(29.4)                                  | 20(25)                                   |         |
| <150           | 354(77.6)                                | 96(75.0)                                  | 60(75)                                   |         |
| TG (mg/dl)     |                                            |                                           |                                           | 0.795   |
| ≥150           | 108(23.7)                                | 36(26.5)                                  | 20(25)                                   |         |
| <150           | 348(76.3)                                | 100(75.0)                                 | 60(73.5)                                 |         |
| HDL (mg/dl)    |                                          |                                           |                                           | <0.001  |
| ≥150           | 250(54.8)                                | 100(73.5)                                 | 40(50)                                   |         |
| <150           | 206(45.2)                                | 36(26.5)                                  | 40(50)                                   |         |
| Cath (%)       |                                          |                                           |                                           | <0.001  |
| ≥150           | 230(55.4)                                | 66(48.5)                                  | 64(80)                                   |         |
| <150           | 92(20.2)                                 | 10(7.4)                                   | 14(17.5)                                 | 0.002   |
| Aspirin (%)    |                                          |                                           |                                           | 0.259   |
| ≥150           | 328(71.9)                                | 90(66.2)                                  | 52(65)                                   |         |
| <150           | 344(75.4)                                | 98(72.1)                                  | 58(72.5)                                 |         |
| ACEi or ARB (%)|                                          |                                           |                                           | 0.970   |
| ≥150           | 230(50.4)                                | 70(51.5)                                  | 42(52.5)                                 |         |
| <150           | 160(35.1)                                | 36(55.0)                                  | 12(26.5)                                 | 0.124   |
| Active Smoking |                                          |                                           |                                           | 0.762   |
| ≥150           | 108(23.7)                                | 36(26.5)                                  | 20(25)                                   |         |
| <150           | 62(13.6)                                 | 8(5.9)                                    | 12(15)                                   | 0.039   |
| Past alcohol (%)|                                          |                                           |                                           | <0.001  |
| ≥150           | 120(26.3)                                | 14(10.2)                                  | 16(20.0)                                 |         |
| <150           | 60(13.2)                                 | 6(7.5)                                    | 6(4.4)                                   | 0.009   |

Abbreviation: ACEi: Angiotensin-converting-enzyme inhibitor, ARB: Angiotensin-receptor II antagonist B-Blocker, BMI: Body mass index, Cath: Cardiac catheterization, DBP: Diastolic blood pressure, DM: Diabetes Mellitus, ESRD: End stage renal disease, HD: Hemodialysis, HDL: High density lipoprotein, ICD: Implantable cardioverter defibrillator, ISCP: Ischemic cardiomyopathy, LDL: Low density lipoprotein, NISCQ: Nonischemic cardiomyopathy, SBP: Systolic blood pressure, TG: Triglyceride

In heart failure patients, poor compliance should be identified and modified because it is reversible causes of a worsening heart failure [1]. This finding was corresponding to our study. Patients with compliance to medical therapy were more having preserved ejection fraction [27]. Especially, our study population was mostly elderly, therefore, it may suggest that simple education about CHF or self-management training alone may not be effective [9]. Practitioners should consider that developing effective and comprehensive method based on complexity of CHF medication. Numbers of medication in our heart failure
patients was not related to BMI (Figure 1). Obese patients may not need more medication compared to normal weight ones [28].

BMI was related to age groups in HFrEF and HFpEF(i) (Figure 2), which might suggest age could be an important factor in each type of heart failure. Compared to one study in United States [11], the proportion of obesity was decreased according to increased age. This is overall similar to our study. In HFrEF and HFpEF(i) of our study, patients’ obesity were less prevalent as age increases. It might suggest that elderly with certain types of heart failure might have less impact of obesity [29,30].

### Table 2. Risk factors associated with preserved ejection fraction in a heart failure program.

| Covariates                      | Preserved ejection fraction | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|---------------------------------|-----------------------------|------------------------|----------------------|
| Age≥65 vs. Age < 65             | 2.48(1.77-3.46)             | 2.44(1.61-3.69)        |
| Sex (Male vs. Female)           | 1.60(1.15-2.22)             | 0.99(0.66-1.51)        |
| BMI≥35 vs. 25< BMI              | 0.76(0.483-1.20)            | 0.63(0.274-1.47)       |
| 35≤BMI<30 vs. 25≤ BMI           | 1.56(1.04-2.18)             | 1.81(1.60-3.59)        |
| 30≤BMI<25 vs. 25≤BMI            | 0.78(0.55-1.13)             | 0.78(0.10-5.32)        |
| SBP≥140 vs. SBP<140            | 1.39(0.95-2.04)             | 1.22(0.74-2.02)        |
| DBP≥90 vs. < 90                | 2.65(1.32-5.32)             | 3.27(0.89-9.01)        |
| DM (yes vs. no)                | 0.27(0.11-0.67)             | 0.27(0.11-0.67)        |
| ICD (yes vs. no)               | 2.02(1.24-3.27)             | 2.92(1.29-6.65)        |
| Cardiac Cath (yes vs. no)       | 0.67(0.49-0.94)             | 0.50(0.27-0.93)        |
| HTN (yes vs. no)               | 1.75(1.82-2.83)             | 1.34(0.71-2.49)        |
| HDL (male: HDL<40 vs. HDL≥40)   | 0.66(0.47-0.92)             | 0.69(0.45-1.05)        |
| (female: HDL<50 vs. HDL≥50)     |                            |                       |
| LDL (LDL≥100 vs. LDL<100)      | 0.75(0.51-1.09)             | 0.78(0.48-1.24)        |
| Active smoking (yes vs. no)     | 0.45(0.23-1.12)             | 0.35(0.18-1.35)        |
| Active alcohol (yes vs. no)     | 2.57(1.35-4.89)             | 1.99(0.94-4.21)        |
| ACEi (yes vs. no)               | 0.95(0.68-1.31)             | 0.70(0.46-1.08)        |
| Beta-blocker (yes vs. no)       | 1.18(0.82-1.70)             | 1.26(0.75-2.53)        |
| Active Cocaine (yes vs. no)     | 2.82(1.17-6.82)             | 0.90(0.33-2.45)        |
| Compliance (yes vs. no)         | 1.89(1.03-3.47)             | 1.49(1.12-3.56)        |

Abbreviation: ACEi: Angiotensin-converting-enzyme inhibitor, BMI: Body mass index, Cardiac Cath: Cardiac catheterization, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, DM: Diabetes Mellitus, ICD: Implantable cardioverter defibrillator, HTN: hypertension, HDL: High density lipoprotein, LDL: Low density lipoprotein

### Figure 1. Comparison of numbers of medications among different BMI groups according to types of heart failure. Proportion of numbers was presented as percentage. Numbers of medication in any types of heart failure was not associated with BMI (P>0.05).

### Conclusions

In summary, this study results showed that obesity is associated with preserved ejection fraction which means our study might be consistent with obesity paradox. In addition, targeted management of related factors in heart failure could lead to different approaches in the future treatment of heart failure.

### Limitation

Our study is a cross-sectional study and all date were reviewed...
resectively. To find out the relationship and scientific explanation between preserved ejection fraction and risk factors, long-term prospective trial studies are necessary.

Disclosure

Ethics (and consent to participate) New York Medical College IRB approved, consent to participate was waived

Consent to publish: There is no any personal data such as individuals details, images or videos.

Competing interests: The authors declare that they have no competing interests

Authors’ contributions: Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. HSL is a first author to wrist manuscript and did statistical analysis. GP, FV and SM helped design and coordination and helped to draft the manuscript and revised manuscript. BN helped all data base collection, study design and discussion. All authors read and approved the final manuscript.

Availability of data and materials: data will not be shared, and state the reason.

List of abbreviations used (if any): HFrEF: heart failure with reduced ejection fraction, HFrEF(i): heart failure with improved ejection fraction, BMI: body mass index, ICD: Implatable cardioverter defibrillator, CHF: congestive heart failure, EF: ejection fraction

Conflict of interest: The authors declared no conflict of interest.

Acknowledgement

I would like to thank all co-authors to complete this article.

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