Referat zum Thema Statistische Modellbildung

Artikel: Dorbala et al. (2006): Effect of Body Mass Index on Left Ventricular Cavity Size and Ejection Fraction. American Journal of Cardiology

Betreuer: Dr. rer. nat. Sandra Freitag-Wolf (IMIS, Tel.: 597-3180, freitag@medinfo.uni-kiel.de) und Prof. Dr. med. Hartwig Siebner (Neurologie, Tel.: 597-8807, h.siebner@neurologie.uni-kiel.de)

Anhaltspunkte und Leitfragen

Ätiologie/Krankheitsbild/Symptome. Was ist die linksventrikuläre Ejektionsfraktion, wie wird sie gemessen? Welche Werte sind normal? Wodurch können Abweichungen im linksventrikulären Volumen entstehen? Welche klinische Symptomatik weisen Patienten mit einer eingeschränkten ventrikulären Pumpfunktion auf?

Studie. Was ist das Ziel dieser Studie? Welches Design wurde gewählt? Sind die Daten prospektiv oder retrospektiv erhoben, sind sie vollständig? Wie lauten die Ein- und Ausschlusskriterien? Welche Variablen wurden erfasst, welches Messniveau haben sie und wie lassen sie sich in Ziel-, Einfluss- und Störgrößen einteilen?

Statistische Verfahren. Welche statistischen Methoden wurden angewandt? Was ist ein multiples Regressionsmodell, warum wird es verwendet? Welche Voraussetzungen müssen dafür erfüllt sein? Wie wird der BMI in das Modell einbezogen? Warum wird jeweils für Männer und für Frauen ein Modell angepasst? Nach welchen Kriterien werden die Variablen in das Modell einbezogen? Was sagen die Regressionskoeffizienten aus und wie werden sie getestet? Was beschreibt das Bestimmtheitsmaß und wie lässt es sich interpretieren?

Ergebnisse. Darstellung der medizinischen und klinischen Merkmale der Patienten. Wie hoch ist die linksventrikuläre Ejektionsfraktion in den BMI-Gruppen? Wie lauten die Ergebnisse der Regressionsmodelle? Welche Einflussfaktoren beeinflussen die Zielgröße?

Diskussion. Ist die Studie repräsentativ? Ist das Studiendesign optimal? Sind alle Aspekte einbezogen oder gibt es weitere potentielle Einflussgrößen und/oder Confounder? Sind die statistischen Methoden adäquat? Gibt es Alternativen zu der statistischen Modellierung? Wie bewerten Sie die Aussagekraft der Studie? Sind Folgestudien notwendig?

Diese Fragen dienen nur der Orientierung. Die Setzung von Schwerpunkten, der Aufbau des Referats und das eventuelle Einbringen von zusätzlichen Aspekten ist den Referenten überlassen.

Effect of Body Mass Index on Left Ventricular Cavity Size and Ejection Fraction

Sharmila Dorbala, MD*, Sharon Crugnale, MS, David Yang, MA, and Marcelo Fernando Di Carli, MD

Extreme obesity is known to be associated with left ventricular (LV) systolic dysfunction. The relation of lesser degrees of obesity and LV systolic function is controversial. This study assessed the relation between body mass index (BMI; weight in kilograms divided by height in meters squared) and the LV ejection fraction (EF) and volumes in 1,806 subjects with normal technetium-99m sestamibi myocardial perfusion imaging results. BMI was evaluated as a continuous and a categorical variable (normal >18.5 and <25, overweight ≥25 and <30, obese ≥30 and <35, and severely obese ≥35 kg/m^2). The prevalence of an EF ≤50% was similar in normal, overweight, obese, and severely obese subjects. On univariate analysis, only severely obese women had mildly reduced LVEFs. LV end-diastolic and end-systolic volumes increased linearly from normal to obese men and women, respectively (each $p < 0.01$). On multiple linear regression analysis ($R = 0.5$, $p < 0.001$), BMI ($p = 0.03$) and diabetes ($p < 0.001$) influenced the EF adversely, whereas age and female gender were protective ($p < 0.001$). However, on gender-stratified analysis, diabetes, not BMI, independently predicted the EF in men and women. BMI remained an independent predictor of greater end-diastolic volumes in men and women ($p < 0.01$) even after accounting for co-morbidities. In conclusion, mild obesity was associated with LV dilatation, but the LVEF was preserved even with severe obesity. Weight control may be recommended to reduce the incidence of obesity-related co-morbidities and their impact on adverse LV remodeling. **(Am J Cardiol 2006;97:725–729)**

Depressed left ventricular (LV) ejection fraction (EF) was found to be independently and positively associated with body mass index (BMI) in a small number of morbidly obese subjects[1–3] and also in a population-based study of hypertensive subjects.[4] However, a preserved LVEF with a lower end-systolic wall stress to end-systolic volume index (a load-independent measure of myocardial contractility) has been described in a small number of mild and moderately obese subjects.[5] Furthermore, the relation between the LVEF and the continuum of BMI is not known. It is possible that the left ventricle dilatates with greater BMI, but LV systolic dysfunction may ensue only with severe degrees of obesity. Our objective was to determine the relation of BMI to the EF and LV volumes across the spectrum of BMI in men and women separately.

Methods

Study population: We prospectively evaluated 1,806 consecutive subjects with normal rest-stress myocardial perfusion single photon-emission computed tomography (SPECT) imaging results from March 11, 2002, to September 24, 2003. Subjects with inadequate gating, poor endocardial definition, arrhythmias, and valvular heart disease were excluded. Self-reported histories of hypertension, diabetes, hyperlipidemia, smoking, family histories of premature coronary artery disease, myocardial infarction, and revascularization (percutaneous or surgical), as well as height and weight, were recorded in a database and verified by review of electronic medical records before the performance of the SPECT studies. Informed consent was obtained from the subjects, and the Human Research Committee of Brigham and Women's Hospital approved the study. Subjects were classified on the basis of their BMIs (weight in kilograms divided by height in meters squared) as normal (18.5 to <25 kg/m^2), overweight (≥25 and <30 kg/m^2), obese (≥30 and <35 kg/m^2), or severely obese (≥35 kg/m^2).

Myocardial perfusion SPECT and stress protocol: Most subjects underwent standard single-day gated rest-stress technetium-99m sestamibi (11 and 33 mCi, respectively) myocardial perfusion SPECT. Subjects with weight >250 lb underwent separate-day rest-stress studies with approximately 30 mCi technetium-99m sestamibi on each day. Attenuation correction software was not used. Subjects underwent either standard symptom-limited Bruce treadmill tests or adenosine or dobutamine stress tests per standard

Division of Nuclear Medicine, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Manuscript received July 30, 2005; revised manuscript received and accepted September 16, 2005.

* Corresponding author: Tel: 617-525-6769; fax: 617-582-6056.
E-mail address: sdorbala@partners.org (S. Dorbala).

0002-9149/06/$ – see front matter
doi:10.1016/j.amjcard.2005.09.122

Table 1
Baseline characteristics of the study groups by gender

Characteristic	BMI (kg/m^2)				p Value
	<25	25–30	30–35	>35	
Men (n = 709)	n = 130	n = 326	n = 171	n = 82	
Mean age (yrs)	60 ± 14	60 ± 13	59 ± 12	55 ± 13	<0.001
Height (in)	69 ± 3	69 ± 3	70 ± 3	70 ± 3	0.1
Weight (lb)	152 ± 17	181 ± 17	216 ± 20	264 ± 39	<0.001*
Body surface area (m^2)	1.8 ± 0.1	2.0 ± 0.2	2.1 ± 0.2	2.3 ± 0.2	<0.001*
BMI (kg/m^2)	22.9 ± 1.8	27.4 ± 1.4	32.1 ± 1.4	39.5 ± 4.8	<0.001
Hypertension	49%	51%	64%	74%	<0.001
Diabetes	16%	14%	21%	43%	<0.001
Dyslipidemia	35%	50%	57%	49%	0.002
LV hypertrophy	11%	6%	4%	4%	0.1
Exercise treadmill test	69%	78%	68%	68%	0.06
Women (n = 1,097)	n = 266	n = 345	n = 244	n = 242	
Mean age (yrs)	62 ± 14	65 ± 12	61 ± 12	60 ± 11	<0.001
Height (in)	64 ± 3	64 ± 3	63 ± 3	64 ± 3	0.1
Weight (lb)	126 ± 16	152 ± 15	178 ± 17	229 ± 39	<0.001
Body surface area (m^2)	1.6 ± 0.1	1.7 ± 0.1	1.8 ± 0.1	2.0 ± 0.2	<0.001
BMI (kg/m^2)	22.5 ± 2	27.3 ± 1.4	32.3 ± 1.4	41.2 ± 6	<0.001
Hypertension	50%	64%	68%	73%	<0.001
Diabetes	9%	15%	21%	38%	<0.001
Dyslipidemia	38%	47%	49%	55%	0.002
LV hypertrophy	6%	3%	4%	3%	0.1
Exercise treadmill test	63%	59%	63%	54%	0.1

p Values depict the significance of change across categories by analysis of variance or chi-square tests.
* Significant trend across study groups by trend test with p <0.05.

protocols. Poststress images were used to calculate end-diastolic and end-systolic volumes and the LVEF using QGS software (Cedars Sinai Inc., Los Angeles, California). We did not adjust LV volumes to body surface area, because we were making comparisons across categories of BMI.

Two experienced observers (SD and MDC) assessed the gated myocardial perfusion images using a standard 17-segment model,[6] using a 5-point scoring system (0 = normal, 1 = mild reduction in tracer uptake, 2 = moderate reduction in tracer uptake, 3 = severe reduction in tracer uptake, and 4 = absent tracer uptake). A summed stress score of <4 was considered to represent a normal study result.

Statistical analysis: Continuous variables are reported as mean ± SD, median (interquartile range), or as simple proportions as appropriate. Differences among the study groups were assessed by 1-way analysis of variance for continuous variables with Tukey's post hoc test for intergroup comparisons or a chi-square test as appropriate. The normal subjects were used as controls, and all results were compared with this group. Kendall's trend test was used to evaluate trends across study groups.

Multiple linear regression models were developed to predict the independent contribution of factors that influenced the LVEF and end-diastolic and end-systolic volumes. Because normal limits of the LVEF and volumes are gender specific,[7,8] separate models were developed stratified by gender. The influence of BMI was studied as a continuous and categorical variable. Variables with a univariate significance level of <0.10 were included in the model. A 2-tailed p value of <0.05 was considered significant for all analyses.

Results

Clinical characteristics of the study subjects: The baseline characteristics of the study cohort by BMI categories are listed in Table 1. There were 61% women (n = 1,097) in the study cohort. Overweight subjects (37%) constituted the largest study group. Eighteen percent of the subjects (n = 324) were severely obese, with 75% of them being women. The mean age of the subjects decreased with increasing BMI in men and women (Table 1). The prevalence of diabetes and hypertension increased with increasing BMI (Table 1).

Influence of BMI on the LVEF: The prevalence of LV systolic dysfunction (LVEF <50%) was lower in women (3.1% vs 11%, p <0.001). However, among the BMI categories of 18.5 to <25, 25 to 30, 30 to 35, and ≥35 kg/m^2, the percentage of subjects with LVEFs <50% was similar in men and women (p = NS).

The mean LVEF was significantly greater and LV volumes significantly smaller in women than in men in each BMI category (p <0.001 for each comparison; Table 2). On univariate analyses, there was a small (likely not clinically significant) but statistically significant decrease in the LVEF across BMI categories in women (Table 2). A similar trend was observed in men that was not statistically significant,

Table 2
Gated myocardial perfusion imaging data by body mass index category

Characteristic	BMI (kg/m^2)				p Value
	<25	25–30	30–35	>35	
Men	n = 130	n = 326	n = 171	n = 82	
LVEF (%)	61 ± 11	61 ± 10	60 ± 9	59 ± 8	0.1
LV end-diastolic volume (ml)	99 ± 42	107 ± 42	110 ± 34	120 ± 34	≤0.001
LV end-systolic volume (ml)	42 ± 32	45 ± 35	46 ± 23	51 ± 21	0.1
Women	n = 266	n = 345	n = 244	n = 242	
LVEF (%)	71 ± 11*	70 ± 11*	70 ± 11*	68 ± 9*	<0.001
LV end-diastolic volume (ml)	64 ± 25*	67 ± 22*	72 ± 23*	82 ± 27*	<0.001
LV end-systolic volume (ml)	20 ± 19*	21 ± 16*	23 ± 17*	28 ± 18*	<0.001

Data are presented as mean ± SD. p Values depict the significance of change across the groups.
* p <0.001 compared with mean values in men.

Table 3
Independent predictors of left ventricular ejection fraction

Variable	Age	BMI	Hypertension	Diabetes	Female Gender
LVEF, overall study cohort, model R = 0.5, F = 158, p <0.001					
β coefficient	0.14	−0.08	−1.0	−3.6	+9.7
p value	<0.001	0.03	0.06	<0.001	<0.001
Men, model R = 0.2, F = 4.7, p = 0.01					
β coefficient	0.07	−0.08	−1.4	−2.1	
p value	0.01	0.3	0.09	0.04	
Women, model R = 0.3, F = 27, p <0.001					
β coefficient	0.2	−0.09	−0.79	−4.5	
p value	<0.001	0.08	0.24	<0.001	

likely because of the small effect and smaller number of subjects.

Independent predictors of the LVEF across categories of weight: We performed multiple linear regression analysis (Table 3) to further evaluate the relation between BMI and the LVEF, adjusting for age, gender, hypertension, and diabetes, factors known to influence the LVEF (multiple R = 0.5, F = 158, p <0.001). Overall, female gender and age were independent predictors of a greater LVEF (p <0.001), whereas diabetes was an independent predictor of a smaller LVEF. There was an inverse relation between BMI and the LVEF (p = 0.03). However, the magnitude of this effect was very small and not statistically significant after stratifying the results by gender (Table 3).

On analysis stratified by gender, diabetes was a significant independent predictor of a smaller LVEF in men and women. Similarly, increasing age was a significant independent predictor of a greater LVEF in men and women. However, after accounting for differences in age, hypertension, and diabetes, BMI was not an independent predictor of a smaller LVEF in men or women.

Influence of BMI on LV volumes in men: The influence of BMI on LV volumes by univariate analysis in men and women is summarized in Table 2. LV end-diastolic volume increased across BMI categories (p ≤0.001, chi-square test). Obese (p = 0.03) and severely obese (p = 0.002) subjects had significantly larger LV end-diastolic volumes compared with men in the normal group. There was no significant difference in LV end-systolic volume on the basis of BMI.

On multiple linear regression analysis, larger BMI and hypertension were significant independent predictors of greater LV end-diastolic volume, while hypertension alone was an independent predictor of LV end-systolic volume. Only hypertension, not diabetes mellitus, was an independent predictor of larger LV volumes in men. Age was inversely related to LV end-diastolic and end-systolic volumes.

Influence of BMI on LV volumes in women: LV end-diastolic and end-systolic volumes increased across categories of BMI (Table 2). LV volumes were significantly greater in obese (p <0.001) and severely obese (p <0.001) women compared with women in the normal group.

On multiple linear regression analysis, in addition to BMI, diabetes remained an independent predictor of greater LV end-diastolic and end-systolic volumes. In contrast to their effects in men, hypertension was not an independent predictor of larger LV volumes in women. Age was again inversely related to LV end-diastolic and end-systolic volumes.

Discussion

This study represents the largest systematic evaluation of the relation of BMI and the LVEF and volumes in a large

number of men and women. The findings of our study using subjects with normal BMIs as a reference group add to previous observations[9,10] that greater BMI is associated with LV enlargement. LV enlargement was evident at even mild degrees of obesity in men and women. However, LV volumes and the EF even in the severely obese women were smaller than in normal men. Further, the LVEF was not adversely affected even with severe degrees of obesity. Small decrements in the LVEF seen in severely obese women appear to be due not to a greater BMI per se but rather to a higher prevalence of diabetes. Diabetes was the major correlate of depressed LV systolic function in men and women. In women, diabetes was also a correlate of LV enlargement, while hypertension was an independent correlate of LV enlargement in men. Gender advantages of smaller LV volumes and a greater EF were seen even with large BMIs and severe obesity.

Elevated BMI may result in LV dilatation from many factors,[11] including hemodynamic overload from increased blood volume and capillary flow,[12] neurohormonal activation,[13] and increased oxidative stress.[14] An interesting finding in our study was LV dilation in obese (mild or severe) but not overweight men and women. This suggests that the "threshold BMI" beyond which the left ventricle fails to accommodate greater blood volumes without dilatation is likely the same in men and women and likely greater than the overweight range. Our findings contrast with those of a number of previous studies limited either by small or selected study cohorts that demonstrated smaller LVEFs in severely obese subjects[1–3,5,15,16]; the difference is likely explained by our evaluation of a large number of unselected subjects. However, our results are akin to a few other reports describing normal LVEFs in obese subjects.[4,16,17] There was no independent relation between BMI and a smaller LVEF in our study, despite a higher prevalence of hypertension and diabetes with greater BMIs. This finding adds to and expands on the results of a previous report showing that obesity alone, in the absence of glucose intolerance, hypertension, and dyslipidemia, seems to be associated only with an impairment of diastolic function and hyperkinetic systole.[15] The "protective effect" of a greater BMI against systolic dysfunction despite a higher prevalence of diabetes and hypertension could be a potential mechanism for the paradoxical lower mortality risk described in subjects with heart failure with greater BMIs.[18]

The prevalence of LV systolic dysfunction in our cohort was lower in women than in men and similar to that described previously.[19] Women are known to have larger LVEFs and smaller LV volumes compared with men in multiple clinical settings.[8–10] These differences could be attributed in part to differences in body stature. Yet, surprisingly, the mean LVEF and volumes even in severely obese women were smaller than in normal men. These findings suggest an inherent difference in LV remodeling between men and women that may be independent of BMI.[20]

We evaluated subjects with clinical indications to document coronary artery disease, and the results of this study will be most applicable to subjects with similar characteristics. However, because we included only subjects without scan evidence of coronary artery disease, the results may be extrapolated to asymptomatic subjects. Self-reported height and weight correlate highly with measured height and weight.[21] A systematic error in the underestimation of BMI in the overweight and obese subjects may be seen, as described previously. However, these errors are usually small and thus not likely to have influenced our results.[21] The observed differences in LV volumes may be a result of smaller LV volumes in normal subjects, as opposed to greater LV volumes in obese subjects. However, this is not likely the case, because >50% of normal subjects in our cohort had hypertension, and mean LV volumes in normal subjects were greater than the gender-based normal limits for LV volumes from our laboratory.

1. Alpert MA, Terry BE, Mulekar M, Cohen MV, Massey CV, Fan TM, Panayiotou H, Mukerji V. Cardiac morphology and left ventricular function in normotensive morbidly obese patients with and without congestive heart failure, and effect of weight loss. *Am J Cardiol* 1997;80:736–740.
2. Alaud-din A, Meterissian S, Lisbona R, MacLean LD, Forse RA. Assessment of cardiac function in patients who were morbidly obese. *Surgery* 1990;108:809–818.
3. Ferraro S, Perrone-Filardi P, Desiderio A, Betocchi S, D'Alto M, Liguori L, Trimigliozzi P, Turco S, Chiariello M. Left ventricular systolic and diastolic function in severe obesity: a radionuclide study. *Cardiology* 1996;87:347–353.
4. Devereux RB, Bella JN, Palmieri V, Oberman A, Kitzman DW, Hopkins PN, Rao DC, Morgan D, Paranicas M, Fishman D, et al. Left ventricular systolic dysfunction in a biracial sample of hypertensive adults: the Hypertension Genetic Epidemiology Network (HyperGEN) study. *Hypertension* 2001;38:417–423.
5. Garavaglia GE, Messerli FH, Nunez BD, Schmieder RE, Grossman E. Myocardial contractility and left ventricular function in obese patients with essential hypertension. *Am J Cardiol* 1988;62:594–597.
6. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;105:539–542.
7. Ababneh AA, Sciacca RR, Kim B, Bergmann SR. Normal limits for left ventricular ejection fraction and volumes estimated with gated myocardial perfusion imaging in patients with normal exercise test results: influence of tracer, gender, and acquisition camera. *J Nucl Cardiol* 2000;7:661–668.
8. De Bondt P, Van de Wiele C, De Sutter J, De Winter F, De Backer G, Dierckx RA. Age- and gender-specific differences in left ventricular cardiac function and volumes determined by gated SPET. *Eur J Nucl Med* 2001;28:620–624.
9. Danias PG, Tritos NA, Stuber M, Kissinger KV, Salton CJ, Manning WJ. Cardiac structure and function in the obese: a cardiovascular magnetic resonance imaging study. *J Cardiovasc Magn Reson* 2003; 5:431–438.
10. Wong ND, Gardin JM, Kurosaki T, Anton-Culver H, Sidney S, Roseman J, Gidding S. Echocardiographic left ventricular systolic function and volumes in young adults: distribution and factors influencing variability. *Am Heart J* 1995;129:571–577.

11. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N Engl J Med* 2002;347:305–313.
12. Alexander JK, Dennis EW, Smith WG, Amad KH, Duncan WC, Austin RC. Blood volume, cardiac output, and distribution of systemic blood flow in extreme obesity. *Cardiovasc Res Cent Bull* 1962;1:39–44.
13. Engeli S, Sharma AM. The renin-angiotensin system and natriuretic peptides in obesity-associated hypertension. *J Mol Med* 2001;79:21–29.
14. Herrera MF, Deitel M. Cardiac function in massively obese patients and the effect of weight loss. *Can J Surg* 1991;34:431–434.
15. Iacobellis G, Ribaudo MC, Leto G, Zappaterreno A, Vecci E, Di Mario U, Leonetti F. Influence of excess fat on cardiac morphology and function: study in uncomplicated obesity. *Obes Res* 2002;10:767–773.
16. Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial characteristics associated with obesity. *Circulation* 2004;110:3081–3087.
17. Devereux RB, Roman MJ, Liu JE, Welty TK, Lee ET, Rodeheffer R, Fabsitz RR, Howard BV. Congestive heart failure despite normal left ventricular systolic function in a population-based sample: the Strong Heart Study. *Am J Cardiol* 2000;86:1090–1096.
18. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 2001;38:789–795.
19. Hedberg P, Lonnberg I, Jonason T, Nilsson G, Pehrsson K, Ringqvist I. Left ventricular systolic dysfunction in 75-year-old men and women; a population-based study. *Eur Heart J* 2001;22:676–683.
20. Hayward CS, Kalnins WV, Kelly RP. Gender-related differences in left ventricular chamber function. *Cardiovasc Res* 2001;49:340–350.
21. Stevens J, Keil JE, Waid LR, Gazes PC. Accuracy of current, 4-year, and 28-year self-reported body weight in an elderly population. *Am J Epidemiol* 1990;132:1156–1163.