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ORIGINAL RESEARCH

Cardiac Morphology, Function, and Hemodynamics in Patients With Morbid Obesity and Nonalcoholic Steatohepatitis

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BACKGROUND: The patients with nonalcoholic fatty liver disease demonstrate an increased cardiovascular risk. The adverse influence of liver abnormalities on cardiac function are among many postulated mechanisms behind this association. The aim of the study was to evaluate cardiac morphology and function in patients with morbid obesity referred for bariatric surgery with liver biopsy.

METHODS AND RESULTS: We evaluated with echocardiography 171 consecutive patients without known cardiac disease (median age 42 [interquartile range, 37–48] years, median body mass index 43.7 [interquartile range, 41.0–47.5], 67% female patients. Based on the liver biopsy results, there were 44 patients with nonalcoholic steatohepatitis (NASH), 69 patients with isolated steatosis, and 58 patients without steatosis. Patients with NASH demonstrated signs of left ventricular concentric remodeling and hyperdynamic circulation, including indexed left ventricular end-diastolic diameter [cm/m^2]: NASH 1.87 [0.22]; isolated steatosis 2.03 [0.33]; without steatosis 2.01 [0.19], P=0.001; relative wall thickness: NASH 0.49±0.05, isolated steatosis 0.47±0.06, without steatosis 0.46±0.06, P=0.011; cardiac index [L/m^2]: NASH 3.05±0.54, isolated steatosis 2.80±0.44, without steatosis 2.79±0.50, P=0.013. After adjustment for sex, age, blood pressure, and heart rate, most of the measures of the left ventricular systolic and diastolic function, left atrial size, right ventricular function, and right ventricular size did not differ between groups.

CONCLUSIONS: In a group of patients with extreme obesity, NASH was associated with left ventricular concentric remodeling and hyperdynamic circulation. Increased cardiac output in NASH may represent an additional risk factor for incident cardiovascular events in this population.

Key Words: cardiac remodeling ■ echocardiography ■ metabolic syndrome

See Editorial by Sven Francque

Patients with nonalcoholic fatty liver disease (NAFLD), especially with nonalcoholic steatohepatitis (NASH), demonstrate an increased risk of cardiovascular events.[1] The adverse influence of liver abnormalities, especially NASH, on cardiac function, are among many postulated mechanisms behind this association.[2] Although several studies demonstrated subclinical left ventricular (LV) dysfunction in patients with NAFLD when compared with healthy controls,[3–6] the data from histologically confirmed NASH cases are scarce and show conflicting results.[7–10] Moreover, various methodological limitations in those studies may be

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CLINICAL PERSPECTIVE

What Is New?

- In a population of patients with morbid obesity referred for bariatric surgery, nonalcoholic steatohepatitis diagnosed by intraoperative liver biopsy was associated with more advanced left ventricular concentric remodeling and higher cardiac index compared with patients with simple steatosis or no steatosis.

What Are the Clinical Implications?

- Hyperdynamic circulation in nonalcoholic steatohepatitis may represent an additional mechanism of the increased risk of heart failure and atherosclerotic complications found in this group of patients.

Nonstandard Abbreviations and Acronyms

DM	diabetes mellitus
ISTE	isolated steatosis
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NOSTE	no steatosis

identified, including their retrospective design, preselection of patients based on elevated transaminases, low total number of patients with NASH, or long-time intervals between liver biopsy and cardiac assessment. To avoid some of those limitations, and to provide further information about cardiac function in patients with NAFLD, we decided to evaluate cardiac morphology, function, and hemodynamics shortly before liver biopsy, in an unselected cohort of patients with morbid obesity referred for bariatric surgery.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients

We initially evaluated 195 consecutive, patients with severe obesity (body mass index [BMI] >35 kg/m^2) referred for bariatric surgery (laparoscopic sleeve gastrectomy) to the Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Poland, between June 2016 and December 2019. Cardiac diseases were excluded based on detailed clinical history, physical examination, and medical documentation screening. In exclusion criteria, we defined an excessive alcohol use as self-reported daily alcohol consumption ≥30 g for men and ≥20 g for women. During the evaluation phase, 24 patients were excluded from the study, but among them, only 2 patients were excluded because of completely inadequate cardiac visualization on echocardiography. Finally, we analyzed the total number of 171 patients.

The demographic, clinical, and laboratory characteristics of the patients are presented in Table 1. The screening evaluation, according to the Consort guidelines, is presented on Figure 1.

Liver Biopsy

The wedge liver biopsy was performed during bariatric surgery, as a part of the local routine surgical protocol. Tissue sample of ≈10×5 mm was acquired from the subcapsular part of the liver left lobe (the third liver segment according to Couinaud classification).[11] The liver biopsy specimens were fixed in formalin and embedded in paraffin. The histopathological evaluation was performed by a single experienced pathologist, who was blinded to the clinical, echocardiographic, and laboratory results. The histopathological semiquantitative assessments was done according to the recommendations of the Clinical Research Network for Nonalcoholic Steatohepatitis.[12] The results of the histopathological assessment included percentage of hepatocytes with steatosis, nonalcoholic fatty liver activity score, hepatic fibrosis stage, degree of intralobular inflammation, and the presence or absence of NASH. The liver steatosis was diagnosed, when more than 5% of hepatocytes were identified with fatty infiltration. NASH was diagnosed in patients with the NAFLD activity score ≥5 with the presence of hepatocyte ballooning and intralobular inflammation.

Echocardiographic Examination

Echocardiography was performed 1 to 2 days before bariatric surgery with liver biopsy by a single, dedicated physician experienced in echocardiography. Images were acquired using GE Vivid E9 cardiac ultrasound system, with M5S-D (1.7/3.3 MHz) probe, GE Healthcare, Horten, Norway) and stored on the Echopac workstation (GE Healthcare, Horten, Norway). The images were analyzed offline by another experienced echocardiographer, blinded to the liver biopsy results. LV end-diastolic dimension, LV wall thickness, aortic root dimension, and left atrial anteroposterior dimension were all measured in parasternal long axis views. All patients included in the final analysis had adequate visualization, after 2 people were excluded from the study at the screening phase. The right ventricular end-diastolic diameter and left atrial area were measured in apical 4-chamber view. If technically possible, left atrial volume and LV ejection fraction by Simpson biplane method were measured in apical views. However, because of the image quality,

Table 1. Demographic, Clinical, and Laboratory Characteristics of Patients

Variable	NASH (n=44)	ISTE (n=69)	NOSTE (n=58)	*P* Value
Age, y	41.5 [11.5]	42.00 [9.00]	39.00 [15.00]	0.148
Female sex, n (%)	27 (61.36%)*	39 (56.52%)*	49 (84.48%)	0.002
Body mass index, kg/m^2	44.18 [5.21]	43.40 [7.65]	43.81 [5.62]	0.354
Body surface area, m^2	2.49 [0.37]*	2.41 [0.44]	2.37 [0.28]	0.014
Height, m	1.72 [0.16]*	1.70 [0.18]	1.68 [0.10]	0.020
Weight, kg	132.00 [32.50]*	125.00 [34.00]	119.50 [24.00]	0.028
HTN, n (%)	30 (68.18%)	49 (71.01%)*	28 (48.28%)	0.021
Use of anti-HTN medications n (%)	28 (62)*	49 (71)*	25 (43)	0.005
Beta blockers	12 (27)	23 (33)	15 (26)	0.599
Angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker	18 (40)	33 (48)	21 (36)	0.399
Diuretics	13 (29)	15 (22)	14 (24)	0.684
Diabetes mellitus, n (%)	18 (40.91%)*,†	12 (17.39%)	8 (13.79%)	0.002
Dyslipidemia, n (%)	17 (38.64%)	24 (34.78%)	20 (34.48%)	0.892
Smoking, n (%)	6 (13.64%)	19 (27.54%)	13 (22.41%)	0.514
Metabolic syndrome, n (%)	37 (84.09%)*	51 (73.91%)*	23 (39.66%)	<0.001
Steatosis, %	60.00 [30.00]*,†	20.00 [15.00]*	2.00 [2.00]	<0.001
Fibrosis stage n (%)				
0	6 (13)	12 (17)	17 (29)	0.108
1	17 (39)*,†	49 (71)	38 (66)	0.001
2	14 (32)*,†	8 (12)	3 (5)	<0.001
3	7 (16)*,†	0 (0)	0 (0)	<0.001
4	0 (0)	0 (0)	0 (0)	
Systolic blood pressure, mm Hg	140.50 [14.50]*	138.00 [17.00]*	132.50 [17.00]	0.005
Diastolic blood pressure, mm Hg	86.50 [10.50]*	84.00 [10.00]*	80.50 [10.00]	0.002
Heart rate, 1/min	74.32±8.29	72.58±9.95	72.10±9.62	0.478
AST, U/L	37.00 [24.00]*,†	25.00 [13.00]	23.00 [7.00]	<0.001
ALT, U/L	55.50 [41.50]*,†	32.00 [24.00]*	26.00 [16.00]	<0.001
Elevated AST, ALT, n (%)	24 (54.55%)*,†	14 (20.29%)	4 (6.90%)	<0.001
GGT, U/L	48.00 [43.00]*,†	33.00 [32.00]*	22.50 [11.00]	<0.001
Elevated GGT, n (%)	20 (45.45%)*	19 (27.54%)	8 (13.79%)	0.002
Bilirubin, mg/dL	0.65 [0.31]†	0.53 [0.30]	0.51 [0.28]	0.008
C-reactive protein, mg/dL	6.20 [8.80]	5.70 [4.95]	5.25 [6.10]	0.452
Creatinine, mg/dL	0.76 [0.19]	0.80 [0.24]	0.76 [0.13]	0.506
Glucose, mg/dL	107.50 [49.50]*	97.00 [17.00]	92.00 [12.00]	<0.001
Glycated hemoglobin, %	6.90 [1.05]*	5.80 [0.70]*	5.40 [0.50]	<0.001
Insulin, IU/mL	26.80 [22.86]*	19.50 [18.10]*	14.15 [9.30]	<0.001
Homeostatic model assessment of insulin resistance	8.66 [6.99]*	4.66 [5.27]*	3.19 [1.95]	<0.001
Total cholesterol, mg/dL	178.59±35.01	179.14±37.11	182.62±32.86	0.807
Low-density lipoprotein, mg/dL	107.03±32.76	101.86±32.42	108.16±26.91	0.522
High-density lipoprotein, mg/dL	39.55±10.12*	43.86±11.00*	50.20±12.46	<0.001
Triglycerides, mg/dL	152.00 [121.00]*	160.00 [96.00]*	116.50 [62.00]	<0.001
Albumin, g/dL	4.15±0.37	4.22±0.41	4.17±0.39	0.665
Platelets, 1000/mm^3	247.45±58.17	272.80±73.57	272.69±58.66	0.087

Differences between groups were analyzed using ANOVA for normally distributed variables (mean±SD), and Kruskal-Wallis test for nonnormal distributed variables (median and interquartile range)—*P* value in column 5. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HTN, hypertension; ISTE, isolated steatosis; NASH, nonalcoholic steatohepatitis; and NOSTE, no steatosis.

*$P<0.05$ vs NOSTE for post hoc analysis.

†$P<0.05$ vs ISTE.

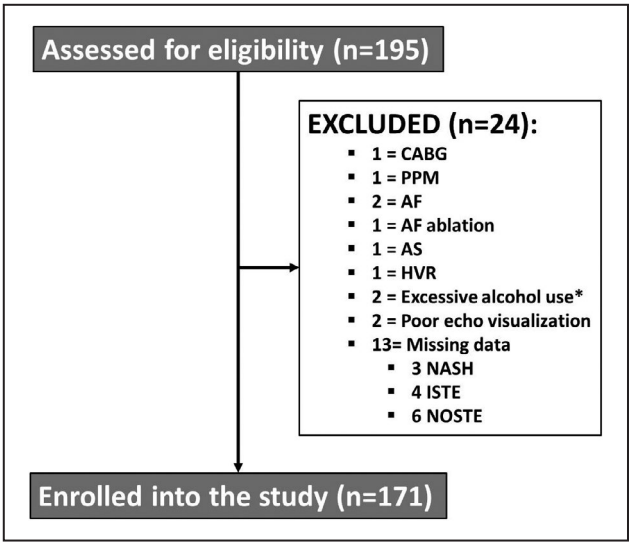

Figure 1. Study sample.
*Excessive alcohol use was defined as ≥30 g/day in men and ≥20 g/day in women. AF indicates atrial fibrillation; AS, aortic stenosis; CABG, coronary artery bypass grafting; HVR, heart valve replacement; ISTE, isolated steatosis; NASH, nonalcoholic steatohepatitis; NOSTE, no steatosis; and PPM, permanent pacemaker.

the volumetric measurements were possible in only 76% and 33% of patients, respectively. Therefore, for the feasible echocardiographic assessment of the LV systolic function, the additional echocardiographic parameters were implemented. Fractional shortening was used for transverse LV systolic function assessment. It included calculation of the difference between end-diastolic and end-systolic LV diameter acquired from the parasternal long axis view. Tissue Doppler imaging was used for longitudinal systolic LV function assessment, with the mean of maximal systolic velocity of the lateral and medial part of the mitral annulus measured from apical 4-chamber view. LV diastolic function was assessed combining the standard use of the ratio of the early-to-late pulse wave Doppler velocities of the mitral inflow and the mean of tissue Doppler early diastolic velocities of the lateral and medial part of the mitral annulus. The ratio of the transmitral E wave velocity to mean tissue Doppler E′ wave velocity was calculated. Stroke volume was calculated by measurement of time velocity integral with Doppler method in the LV outflow tract. Stroke volume index represented stroke volume indexed for body surface area (BSA). Cardiac output was calculated as the product of stroke volume and heart rate, and cardiac index, as cardiac output indexed for BSA. The results of Doppler recordings were averaged from 5 consecutive cardiac cycles. Blood pressure was measured at the end of the echocardiographic examination using an automated oscillometric monitor (Microlife, Watch BP Office, Switzerland), with the size of the cuff appropriately adjusted to the arm circumference.

Biochemistry

A 12-hour overnight fasting blood sample was taken before surgery to determine laboratory parameters related to liver function and metabolic status. They included serum levels of alanine transaminase, aspartate transaminase, and gamma-glutamyl transferase; total bilirubin; C-reactive protein; cholesterol levels (total, low-density lipoprotein, high-density lipoprotein); triglycerides; plasma glucose; insulin; albumin; glycated hemoglobin level; and platelet count. Insulin resistance was determined according to the homeostasis model assessment method, using the formula homeostatic model assessment of insulin resistance=Fasting insulin (IU/mL)×Fasting glucose (mg/dL)/405.[13]

Statistical Analysis

The study design was an observational analysis. First, data were analyzed for normality using the Shapiro-Wilk test. For variables with normal distribution, data were expressed as mean±SD. For variables with nonnormal distributions, data were expressed as median and interquartile range. Categorical data were presented as number of cases in each category and percentages. Analysis of the impact of liver disease on the echocardiographic parameters was done in 2 steps. First, differences in the echocardiographic parameters between groups of patients with NASH, isolated steatosis (ISTE), and no steatosis (NOSTE) were analyzed using ANOVA for normally distributed variables and Kruskal-Wallis test for nonnormal distributed variables (Table 2). In case of a significant difference between groups, an appropriate post hoc analysis was performed using the Tukey HSD test for normally distributed variables and the Dunn test for nonnormally distributed variables. For the categorical variables, the chi-square test was used, with Bonferroni correction for multiple comparisons. In the second part of the analysis, series of multivariable linear regressions were fitted to explore impact of the histopathological liver changes on the value of each echocardiographic parameter separately, after controlling for potential confounding factors. In the analysis of morphological and volumetric parameters, models were adjusted for sex. In the analysis of systolic and diastolic function, models were adjusted for age, heart rate, and systolic blood pressure, as these factors are known to significantly influence cardiac functional parameters. The model equation had the form:

$$\mathrm{ECHO}_i = b_0 + b_1 \cdot I(\text{ISTE vs NASH}) + b_2 \cdot I(\text{NOSTE vs NASH}) + b_3 \cdot X_3 + \ldots$$

where ECHO_i indicates i-th echocardiographic parameter; I, indicator function for dummy variable ISTE versus NASH and NOSTE versus NASH; b_0, intercept; and b_3…, coefficient for confounding variables. Coefficients

Table 2. Echocardiographic Characteristics of Patients

Variable	NASH (N=44)	ISTE (N=69)	NOSTE (N=58)	*P* Value	*P* Value for Trend
LVEDD, cm	4.81±0.41	4.93±0.43	4.80±0.32	0.135	0.448
LVEDD/BSA, cm/m^2	1.89±0.17*,†	2.00±0.21	2.01±0.16	0.001	0.001
LVM, g	239.65 [77.43]†	225.42 [90.49]†	191.94 [48.88]	0.003	0.002
LVM index, g/m^2	90.50 [20.50]	91 [26.00]†	81.50 [17.00]	0.011	0.029
LVM/height, g/m$^{2.7}$	50.79 [11.78]	52.50 [18.08]	49.05 [11.94]	0.117	0.146
Relative wall thickness	0.49±0.05†	0.47±0.06	0.46±0.06	0.011	0.001
LA, cm	4.20 [0.45]	4.20 [0.40]	4.05 [0.40]	0.029	0.005
LA/BSA, cm/m^2	1.68±0.17	1.72±0.17	1.73±0.15	0.383	0.086
LA area, cm^2	19.28±3.16	19.07±3.12	18.26±3.40	0.220	0.047
LA area/BSA, cm^2/m^2	7.52 [0.97]	7.69 [1.36]	7.55 [1.36]	0.643	0.452
Ao, cm	3.40 [0.45]	3.40 [0.60]†	3.20 [0.30]	0.004	0.006
Ao/BSA, cm/m^2	1.38 [0.20]	1.39 [0.14]	1.36 [0.19]	0.204	0.496
SV, mL	106.50 [23.00]†	92.00 [24.00]	87.50 [21.00]	<0.001	<0.001
SV index, mL/m^2	40.33 [8.76]	38.50 [9.19]	38.15 [8.31]	0.048	0.011
Cardiac output, L	7.90 [1.66]*,†	6.78 [1.84]	6.42 [1.57]	<0.001	<0.001
Cardiac index, L/m^2	3.05±0.54*,†	2.80±0.44	2.79±0.50	0.013	0.004
Left ventricle fractional shortening,%	38.59±5.71	39.5±6.15	40.68±5.91	0.213	0.103
Mean peak systolic velocity of mitral annulus by tissue Doppler, m/s	0.09 [0.03]	0.08 [0.03]	0.09 [0.03]	0.176	0.342
Ratio of the transmitral E wave velocity and A wave velocity	1.13±0.28	1.09±0.26	1.20±0.26	0.081	0.062
Mean tissue Doppler E′ wave velocity, m/s	0.10±0.20	0.09±0.02†	0.10±0.02	0.003	0.011
Ratio of the transmitral E wave velocity to mean tissue Doppler E′ wave velocity	8.00 [2.44]	8.42 [2.45]	8.06 [2.29]	0.326	0.453
Right ventricular end-diastolic diameter, cm	3.78±0.46	3.69±0.54	3.64±0.49	0.404	0.112
Tricuspid annular plane systolic excursion by M–mode, cm	2.33±0.32	2.30±0.40	2.37±0.32	0.591	0.219

Differences between groups were analyzed using ANOVA for normally distributed variables (mean±SD), and Kruskal-Wallis test for nonnormal distributed variables (median and interquartile range); *P* value in column 5. Ao indicates aortic root diameter; BSA, body surface area; ISTE, isolated steatosis; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVM, left ventricular mass; NASH, nonalcoholic steatohepatitis; NOSTE, no steatosis; and SV, stroke volume.

*P<0.05 vs ISTE.

†P<0.05 vs NOSTE for post hoc analysis. In column 6, the *P* value for trend calculated using Jonckheere-Terpstra test.

b_1 and b_2 with respective CIs and *P* values describe strength and direction of the impact of liver status (b_1 ISTE versus NASH, b_2 NOSTE versus NASH) on the change in the value of each of the cardiac parameters and are reported in Table 3. Results for confounding variables were not reported. Additionally, among rising grades of NAFLD, analysis of the trend in the change of the key parameters of cardiac morphology and function was performed using the Jonckheere-Terpstra test.

The group characteristics consisted of 35 different variables, and echocardiographic comparisons were performed using 23 parameters of cardiac morphology and function. However, multiplicity adjustment was deemed not feasible because of the exploratory character of the study. All computations were performed using STATISTICA 13.1 (StatSoft, Tulsa, OK, USA), with code programmed in R 3.4.0 environment for statistical computations (R Foundation for Statistical Computing, Vienna, Austria).[14] The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the local Institutional Review Committee, and all patients gave informed consent for study participation.

RESULTS

In the final analysis, we studied 171 patients, at the median age of 42 (interquartile range, 37–48) years. There were 44 patients with NASH, 69 patients with steatosis, but without NASH (ISTE group). These 2 groups belonged to nonalcoholic fatty liver disease (NAFLD) population. The third group of 58 subjects had no liver steatosis (NOSTE group). This last group was younger and had a higher proportion of women. Members of this group had significantly lower blood

Table 3. Multivariable Linear Regression Analysis Assessing the Influence of NASH on Echocardiographic Markers of Myocardial Structure and Systolic and Diastolic Function

Variable	RC	RC Value (95% CI)	*P* Value	Adjusted R^2
LVEDD*	NOSTE vs NASH	0.063 (–0.084 to 0.209)	0.400	0.137
	ISTE vs NASH	0.102 (–0.037 to 0.241)	0.149	
LVEDD/BSA*	NOSTE vs NASH	0.087 (0.019 to 0.155)	0.013	0.212
	ISTE vs NASH	0.121 (0.056 to 0.185)	<0.001	
LVM*	NOSTE vs NASH	–7.162 (–23.629 to 9.305)	0.392	0.444
	ISTE vs NASH	0.870 (–14.739 to 16.480)	0.912	
LVM index*	NOSTE vs NASH	–0.251 (–6.451 to 5.948)	0.936	0.211
	ISTE vs NASH	3.683 (–2.193 to 9.560)	0.218	
LVM/height*	NOSTE vs NASH	0.210 (–4.044 to 4.464)	0.922	0.061
	ISTE vs NASH	2.544 (–1.489 to 6.577)	0.215	
Relative wall thickness*	NOSTE vs NASH	–0.025 (–0.048 to – 0.003)	0.029	0.172
	ISTE vs NASH	–0.023 (–0.044 to – 0.002)	0.035	
LA*	NOSTE vs NASH	–0.084 (–0.213 to 0.045)	0.202	0.199
	ISTE vs NASH	–0.072 (–0.195 to 0.050)	0.244	
LA/BSA*	NOSTE vs NASH	0.017 (–0.045 to 0.078)	0.592	0.105
	ISTE vs NASH	0.038 (–0.020 to 0.096)	0.201	
LA area*	NOSTE vs NASH	–0.433 (–1.649 to 0.783)	0.483	0.129
	ISTE vs NASH	–0.327 (–1.480 to 0.826)	0.576	
LA area/BSA*	NOSTE vs NASH	0.015 (–0.448 to 0.478)	0.949	–0.010
	ISTE vs NASH	0.170 (–0.269 to 0.609)	0.446	
Ao*	NOSTE vs NASH	–0.022 (–0.133 to 0.089)	0.698	0.448
	ISTE vs NASH	0.012 (–0.093 to 0.117)	0.818	
Ao/BSA*	NOSTE vs NASH	0.029 (–0.027 to 0.086)	0.311	0.008
	ISTE vs NASH	0.056 (0.002 to 0.109)	0.042	
Right ventricular end-diastolic diameter*	NOSTE vs NASH	–0.022 (–0.204 to 0.160)	0.812	0.192
	ISTE vs NASH	–0.108 (–0.281 to 0.065)	0.218	
SV*	NOSTE vs NASH	–9.683 (–17.005 to – 2.360)	0.010	0.165
	ISTE vs NASH	–9.546 (–16.487 to – 2.605)	0.007	
SV index*	NOSTE vs NASH	–2.610 (–5.349 to 0.129)	0.062	0.006
	ISTE vs NASH	–2.100 (–4.697 to 0.496)	0.112	
Cardiac output*	NOSTE vs NASH	–0.888 (–1.412 to – 0.365)	<0.001	0.188
	ISTE vs NASH	–0.914 (–1.410 to – 0.418)	<0.001	
Cardiac index*	NOSTE vs NASH	–0.264 (–0.460 to – 0.068)	0.009	0.034
	ISTE vs NASH	–0.250 (–0.436 to – 0.064)	0.009	
Left ventricle fractional shortening†	NOSTE vs NASH	1.562 (–0.836 to 3.960)	0.200	0.022
	ISTE vs NASH	0.757 (–1.519 to 3.033)	0.512	
Mean peak systolic velocity of mitral annulus by tissue Doppler†	NOSTE vs NASH	0.000 (–0.006 to 0.006)	0.975	0.154
	ISTE vs NASH	–0.003 (–0.009 to 0.003)	0.291	
Ratio of the transmitral E wave velocity and A wave velocity†	NOSTE vs NASH	0.037 (–0.044 to 0.117)	0.369	0.448
	ISTE vs NASH	–0.014 (–0.090 to 0.063)	0.727	
Mean tissue Doppler E′ wave velocity†	NOSTE vs NASH	0.007 (0.000 to 0.014)	0.065	0.371
	ISTE vs NASH	–0.003 (–0.010 to 0.003)	0.352	
Ratio of the transmitral E wave velocity to mean tissue Doppler E′ wave velocity†	NOSTE vs NASH	0.005 (–0.827 to 0.837)	0.990	0.158
	ISTE vs NASH	0.304 (–0.485 to 1.094)	0.448	
Tricuspid annular plane systolic excursion by M–mode†	NOSTE vs NASH	0.030 (–0.114 to 0.174)	0.681	–0.020
	ISTE vs NASH	–0.028 (–0.165 to 0.108)	0.681	

Ao indicates aortic root diameter; BSA, body surface area; CI, cardiac index; CO, cardiac output; ISTE, isolated steatosis; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVM, left ventricular mass; NASH, nonalcoholic steatohepatitis; NOSTE, no steatosis; RC, regression coefficient; and SV, stroke volume.

*Multivariable linear regression model adjusted for sex.

†Multivariable linear regression model adjusted for age, systolic blood pressure, and heart rate.

pressure, glycated hemoglobin values, and insulin activity and resistance (homeostatic model assessment of insulin resistance) and higher levels of high-density lipoprotein cholesterol and lower levels of triglycerides, when compared with the patients with any form of NAFLD (Table 1). As expected, the patients with NASH showed significantly increased laboratory markers of hepatic injury and more pronounced glucose metabolism abnormalities, when compared with the 2 other groups of patients. Forty-one percent of patients with NASH had diabetes mellitus (DM), and more than 80% had metabolic syndrome, according to National Cholesterol Education Program Adult Treatment Program III 2001 criteria.[15] The incidence of significant fibrosis (stages 3 and 4) in patients with NASH was relatively low. Stage 3 fibrosis was present in 16% of patients with NASH, and there were no patients with stage 4 fibrosis. All groups had similar BMI, above 40 kg/m^2. After indexation for BSA, patients with NASH had smaller LVEDD compared with both ISTE and NOSTE groups. Also, relative wall thickness was increased in NASH, indicating a tendency toward concentric LV remodeling in this group. Median absolute LV mass was significantly higher in both NAFLD groups, compared with patients with NOSTE. However, an indexation for BSA or height led to the lower differences between groups. Consequently, in the regression analysis, there was no influence of NASH either on LV mass or on LV mass index. The absolute left atrial anteroposterior diameter and the aortic root dimension were both smaller in the NOSTE group, compared with the NASH and the ISTE groups. However, after indexation for BSA, there was no significant difference in the left atrial diameter and in the aortic diameter between the groups (Tables 2 and 3). The right ventricular dimension and the longitudinal systolic function were similar in all groups. Also, the LV systolic function parameters (LV fractional shortening, mean S) were similar between groups. However, the patients with NASH demonstrated larger cardiac output and cardiac index. This was mainly owing to increased systolic volume, considering that the mean heart rate was only slightly increased in this group. These findings persisted in the regression analysis after adjusting for beta blocker use, sex, and the presence of DM. Among LV diastolic function parameters, the ratio of the transmitral E wave velocity to mean tissue Doppler E′ wave velocity and the ratio of the early-to-late pulse wave Doppler velocities of the mitral inflow were similar in the groups, and E` was significantly lower in the ISTE group and only marginally lower in NASH, compared with NOSTE (Tables 2 and 3). There were no cardiovascular complications at the time of surgery and during the postoperative period until the discharge from the hospital.

DISCUSSION

The main findings of our study show that in the relatively young patients with morbid obesity referred for bariatric surgery, NASH was not associated with overt systolic or diastolic cardiac dysfunction when assessed with the standard 2-dimensional and Doppler echocardiography. However, the patients with NASH demonstrated significantly increased cardiac output and the echocardiographic signs of the LV concentric remodeling, when compared with the ISTE and NOSTE groups (Figure 2, Table 2).

Cardiac Output in NASH

The observation of an increased cardiac output and cardiac index in NASH is especially intriguing, because NASH is regarded as an early step in the development of hepatic cirrhosis, the disease that is classically associated with the presence of a hyperdynamic systemic circulation. It is currently believed that increased hepatic vascular resistance and subsequent portal hypertension play a central role in the initiation of this phenomenon, but without fully known mechanisms.[16,17] In several reports, both in animal models and in humans, it was shown that portal hypertension may be present in patients with significant steatosis and steatohepatitis, even before the development of evident hepatic fibrosis.[18–21] Therefore, it may be hypothesized that in some patients with NASH, the increased portal pressure may be associated with pathophysiological changes leading to increased cardiac output. The patients with more advanced liver disease tend to be hypotensive because of arterial vasodilatation and decreased peripheral vascular resistance. To the contrary, the patients with NASH often demonstrate elevated blood pressure. It may be speculated that in NASH, with less advanced liver dysfunction compared with cirrhosis, the predominance of prohypertensive factors (abdominal obesity, insulin resistance, sympathetic overactivity, coexistence of obstructive sleep apnea) can dominate over the hypotensive effect of decreased peripheral resistance. However, in medical literature there are few data on detailed cardiac hemodynamics in NASH. In one recent study on patients with NAFLD , with about half of them having NASH, their cardiac output was not increased compared with healthy controls. But it was only indirectly measured by the thoracic impedance method,[22] the accuracy of which may be significantly hampered by severe obesity.[23] In other studies, cardiac output was increased in NAFLD, but there were no data on liver histology.[6,24] Thus, more studies are needed to elucidate the presence of hyperdynamic circulation in NASH. If confirmed, it could explain one of the potential mechanisms facilitating the development of heart failure or atherosclerotic complications in this important group of patients. Although we found

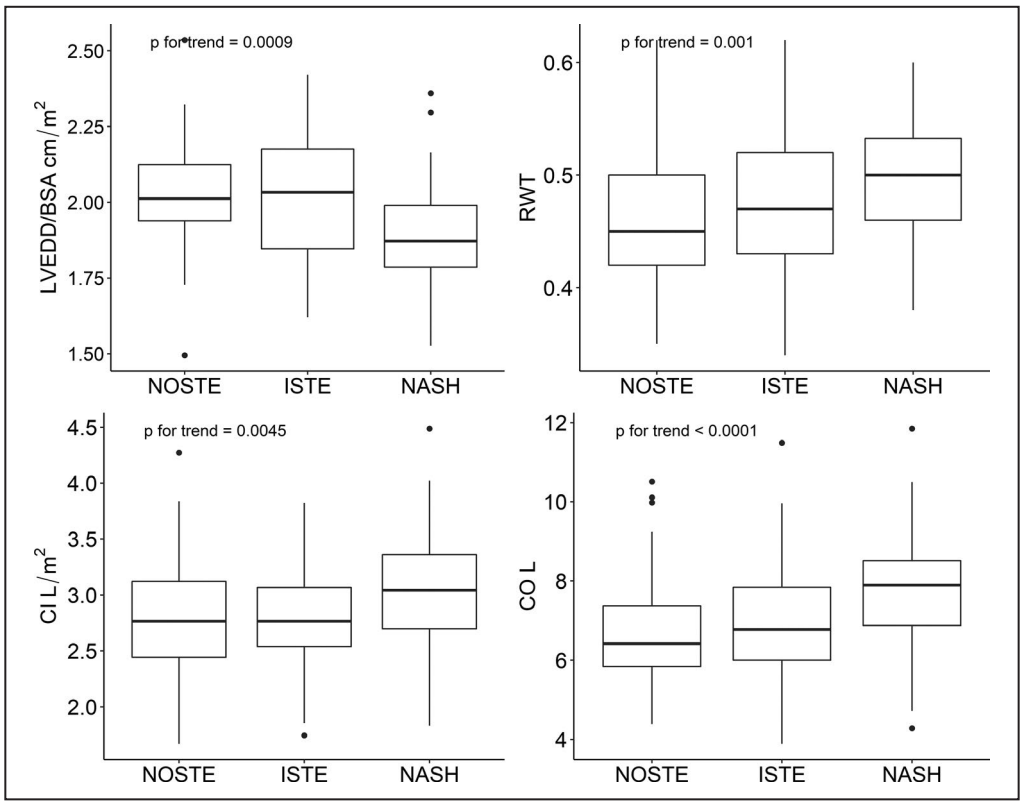

Figure 2. Trend in the change of morphological and functional cardiac parameters among rising grades of NAFLD.

Boxplots showing trend in the change of LVEDD/BSA, RWT, CI, and CO in respect to rising grades of liver steatosis from NOSTE to NASH. The analysis of trend performed using Jonckheere-Terpstra test. On each boxplot midline corresponds to the median of the parameter, with the upper and lower limits of the box being the third and the first quartile. The whiskers indicate variability outside the upper and lower quartiles. The dots beyond whiskers represent outliers. CI indicates cardiac index; CO, cardiac output; ISTE, isolated steatosis; LVEDD/BSA, left ventricular end-diastolic diameter indexed for body surface area; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NOSTE, no steatosis; and RWT, relative wall thickness.

positive association between cardiac output and the presence of NASH, the cross-sectional design of our study does not permit drawing firm conclusions about the causality of these relationships. The hypothesis of the NASH-related increase in portal pressure, as a cause of hyperdynamic circulation is attractive; however, other causes of increased cardiac output may play a role. They include sympathetic activation because of hyperinsulinemia, unrecognized obstructive sleep apnea, or other still unknown factors.

Cardiac Remodeling and Function in NASH

In our study the patients with NASH demonstrated signs of the LV concentric remodeling, as showed by the increased relative wall thickness and lower LVEDD corrected for BSA, when compared with other groups (Figure 2, Table 2). Apparently, this is a rather unexpected finding, especially with the concomitant hyperdynamic circulation in NASH. Although concentric remodeling is a well-known adaptation of the left ventricle to the elevated blood pressure, in our study relative wall thickness was higher in NASH, compared with the ISTE group, despite similar blood pressure in both groups. One of the possible explanations is the higher prevalence of DM in NASH. This could further contribute to the presence of relatively smaller LV size in this group. We performed secondary analysis, adding DM and glycated hemoglobin to the regression model, and for the relative wall thickness parameter, the relation between NASH and NOSTE, as well as NASH and ISTE, became insignificant. That may further indicate the detrimental role of DM in the cardiac remodeling. It was previously demonstrated, that DM is typically associated with concentric remodeling, with smaller LV volumes after indexation for BSA.[25–27] It is in line with the concept of diabetic cardiomyopathy, with metabolic factors like hyperglycemia, insulin resistance/hyperinsulinemia, and inflammation, acting through

various mechanisms promoting myocardial hypertrophy, increased stiffness, and concentric remodeling of the left ventricle.[28,29] Concomitant hypertension and increased aortic stiffness further contribute to this type of remodeling through increased afterload. All these abnormalities can set the stage for the insidious development of incident heart failure with preserved ejection fraction—the main heart failure phenotype in the diabetic population.[28]

The coexistence of increased cardiac output with the LV concentric remodeling in patients with NASH and obesity may seem at first paradoxical. Historically, in obesity, an increased cardiac output has been associated with dilatation of the cardiac chambers and with eccentric remodeling, leading to the so-called "obesity cardiomyopathy."[30] However, nowadays there is a significant amount of evidence that in patients with obesity and DM, in spite of increased cardiac output, the concentric remodeling or concentric hypertrophy can be the main pattern of cardiac adaptation.[31–35] Additionally, in these 2 frequent clinical scenarios heart failure with preserved ejection fraction is the dominating phenotype of incident heart failure.[34,36]

Importantly, current data indicate that cardiovascular events associated with NAFLD are mostly related to the atherosclerotic complications, especially coronary artery disease and stroke.[37,38] Unfortunately, unequivocal prospective data on the association between NASH and incident heart failure are still lacking. Some studies had indirectly suggested this association, demonstrating the presence of metabolic syndrome or increased gamma-glutamyl transferase as independent risk factors for incident heart failure.[39–42] Accordingly, a recent analysis showed an independent association of incident heart failure with fatty liver index in a large population of healthy subjects.[43]

Interestingly, although concentric remodeling together with increased cardiac output, hypertension, and DM may predispose to heart failure, in our patients with NASH, we did not find either significant alterations in cardiac function, especially LV diastolic dysfunction, or an increased left atrial size. However, our group was relatively young and therefore with short duration of the disease, which may be one of the explanations for a less deleterious effect on cardiac morphology and function. Of note, in one longitudinal study, the left atrial volume was not associated with the presence of DM at 5 years of follow-up but did so after 20 years of observation.[44] In a recent cardiac magnetic resonance imaging study, indexed left atrial volume was even decreased in patients with uncomplicated DM suggesting the possibility of negative atrial remodeling in early DM.[45] Moreover, simultaneous low values of ratio of the transmitral E wave velocity to mean tissue Doppler E′ wave velocity found in our patients suggest no significant elevation of the left atrial pressure and therefore no direct hemodynamic substrate for its dilatation. It is important to add that, in a very recent study, presence of subclinical diastolic dysfunction in patients with NAFLD was completely attenuated, when measures of general (BMI) or visceral adiposity were added to multivariable analysis.[24] This suggests an important role of obesity in mediating the previously reported associations between NAFLD and cardiac remodeling and function. Fortunately, in our a priori population with obesity, the mean BMI did not significantly differ between NASH, ISTE, and NOSTE groups; therefore, the potential confounding effect of the obesity on cardiac morphology and function was avoided. This significant homogeneity of our 3 liver histological phenotypes in terms of BMI and age, as well as no preselection of patients, allowed us to avoid various confounders and should be regarded as the strength of this study.

Our findings are in contrast to the results of the recent study by Simon et al that demonstrated significantly increased left atrial volume and LV mass, as well as impaired LV diastolic function in patients with NASH and morbid obesity, compared with combined groups of patients with ISTE and NOSTE.[10] However, the reported discrepancies may have resulted from the differences in design, including the retrospective observation, small number of patients with NASH (n=14), their older age, selection of patients, and significant time interval between echocardiographic and histologic evaluation.

There may be concerns that the bariatric population is not an optimal model to study cardiac changes in NAFLD. This may seem to be partially true with echocardiography used in patients with extreme obesity. In fact, some commonly used echocardiographic parameters of the LV systolic function could not be reliably measured in a significant number of our patients. In particular, the standard assessment of systolic function, including the Simpson's biplane LV ejection fraction and global longitudinal strain, were severely compromised because of poor definition of the endocardial borders, mostly from the standard apical views. This may be related to the long distance between the skin surface and the LV apex in severe obesity.[46] Additionally, it was not possible to measure the left atrial volume in every patient in our group. However, most of the routine cardiac measures, as well as the Doppler-based parameters, were possible to perform in practically all patients, except for only 2 subjects.

On the other hand, the surgical treatment of our patients gave us a unique opportunity to study liver histology with the wedge biopsy. However, it is important to notice, that different techniques of liver

biopsy (wedge and needle) may produce discrepant results because of different locations of the sampling material.[47,48] The main advantage of the surgical biopsy is about 20- to 40-fold larger tissue sample, when compared with the needle biopsy. Therefore, it is potentially more representative of the liver tissue, as a larger sample of the organ structure. However, the subcapsular origin of the wedge biopsy sample tissue may overestimate stage of fibrosis. In our population, the incidence of significant liver fibrosis was low; thus we believe that the technique of biopsy did not lead to significant bias of the histopathological results.

Study Limitations

Unfortunately, we did not have access to data on objective measures of the patients' level of daily activity. This is one of the potential factors that could influence cardiac morphology and function in people who have extreme obesity.

The predominance of female patients is typical for cohorts of patients undergoing bariatric surgery and in our study, there were significantly more female patients in the NOSTE group. Sex is an important determinant of the parameters of cardiac morphology and function.[49] However, it is also important for liver histological characteristics in NAFLD.[50] Therefore, adjustment for sex was done in the regression analysis models (Table 3) and reported values of cardiac morphology and hemodynamic parameters are adjusted for the effect of sex.

We did not have measures of waist-to-hip ratio, that could correlate with liver histology. Although, patients with extreme obesity have waist circumference always over the recommended values, the patterns of fat distribution may still be related to the level of steatosis and metabolic abnormalities. However, even simple waist measurement, approached according to accepted methodology, is not that simple and reproducible in patients with morbid obesity and downward displacement of the redundant fat tissue.

The patients were not screened for obstructive sleep apnea, which is common in obesity and can adversely affect both liver steatosis and cardiac function through hypoxia and sympathetic activation.[51–53] Considering the Doppler echocardiography performance in people with obesity, its precision was not widely tested in individuals with morbid obesity. However, it is an acceptable noninvasive measure of cardiac output, with high concordance with invasive hemodynamic evaluation.[54,55] Therefore, with adequate visualization of LV outflow tract from the parasternal long axis view and good quality of the Doppler signal in most of our patients, we believe, that the value of transthoracic echocardiography in cardiac output assessment is not significantly impaired in this population.

CONCLUSIONS

In conclusion, in this cohort of unselected, relatively young patients with extreme obesity, the presence of NASH was associated not only with severe metabolic abnormalities and increased blood pressure but also with signs of the LV concentric remodeling and hyperdynamic circulation. If confirmed in future studies, the increased cardiac output may represent an additional, NASH-specific risk factor for incident heart failure and atherosclerotic complications in this group of patients.

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