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Nonalcoholic steatohepatitis (NASH) is associated with cardiac remodeling and dysfunction

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Abstract

Objective—Preliminary data suggest that nonalcoholic fatty liver disease (NAFLD) is associated with early heart failure (HF). However, whether nonalcoholic steatophepatitis (NASH) is directly associated with echocardiographic changes in cardiac structure or function remains unknown.

Methods—We identified a retrospective cohort (N=65) without known heart disease, undergoing elective bariatric surgery with perioperative liver biopsy, and available recent transthoracic echocardiography (TTE). TTE measures were evaluated by NASH status using correlation coefficients, ANOVA and linear regression, accounting for cardiometabolic factors.

Results—Median age was 47 years; 22% (n=14) had NASH. NASH patients had increased median left atrial (LA) volume (28.6mL/m^2 vs. 24.8mL/m^2, p<0.0001) and LV mass (82.6 g/m^2 vs. 78.6 g/m^2, p<0.0001), indexed for height. NASH was inversely correlated with indices of diastolic function, including septal E′ (r= −0.90 [95% CI −1.21, −0.42], p=0.020) and E:A (r= −0.31 [95% CI −0.51, −0.09], p=0.037). In adjusted analyses, NASH remained associated with increased LV mass index (ß[1] = 7.16 [SE 4.95], p=0.001), LA volume index (ß[1]= 0.19 [0.08], p=0.001), and reduced lateral and septal E′ (ß[1] = −0.91, p=0.015; ß[1] = −0.89, p=0.047, respectively).

Conclusions—In this bariatric cohort, NASH was associated with changes in myocardial structure and in loaddependent indices of LV diastolic function, suggestive of subclinical HF.

Keywords

steatohepatitis; NAFLD; heart failure; echocardiography; inflammation

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) and heart failure (HF) are obesity-related conditions with high cardiovascular mortality. A growing body of data now link NAFLD to changes in myocardial energy metabolism, and to echocardiographic measurements of cardiac morphology and function[1]. It is hypothesized that the pathogenesis of cardiac dysfunction in NAFLD is related to the release of inflammatory cytokines among those with steatohepatitis (NASH)[2]. However, data in patients with biopsy-proven NAFLD are limited, and the few published analyses of this relationship using histologically-defined NASH have yielded conflicting results[3–5]. Thus, it remains unknown whether histological NASH is associated with subclinical cardiac remodeling. Here, we present a retrospective cohort of 65 obese patients undergoing bariatric surgery, in whom peri-operative liver biopsy and echocardiography enabled the assessment of hepatic histology, cardiac structure and function.

METHODS

Among 332 patients who underwent elective bariatric surgery at a tertiary medical center between January 1, 2005 and August 1, 2016, we identified 78 patients without known heart disease, who underwent transthoracic echocardiography (TTE) within 12 months of surgery. Exclusions included viral hepatitis (n=2), alcohol abuse (n=5), chronic liver disease (n=4), or any history of ischemic or non-ischemic heart disease, including valvular disease (n=2), leaving 65 individuals eligible for analysis. Clinical data including indication for TTE were collected through review of the medical record. At this institution, bariatric surgeries are accompanied by intra-operative liver biopsy, and read by a blinded pathologist. NASH was defined by grade ≥1 steatosis, lobular inflammation and hepatocyte ballooning; all biopsies not meeting criteria for NASH (including normal liver histology) were defined as non-NASH. Steatosis was defined by grade ≥1 steatosis without ballooning or lobular inflammation, while NAFLD included either steatosis or NASH. Original TTE images were reviewed by two blinded cardiologists, trained in echocardiography, and only those images deemed adequate were eligible for inclusion. Myocardial structure and function were assessed with 2D echocardiography, and left ventricular (LV) diastolic function was evaluated with Doppler and tissue Doppler imaging. Height, body mass index (BMI) and body surface area (BSA) were recorded on the date of TTE, and measures of LA and LV size, volume and mass were indexed for height[6]. LA size and volume were also separately indexed for BSA[7]. Measures of myocardial structure and function were compared by NASH status using correlation coefficients, ANOVA and linear regression models, adjusted for age, sex, diabetes, hypertension and BMI.

RESULTS

The median age was 47 years (range 35.0–56.5). Of the 65 individuals, 18 (28%) had normal hepatic histology, 33 (51%) had steatosis without ballooning or lobular inflammation, and 14 (22%) had NASH, defined by the presence of steatosis with ballooning and lobular inflammation. Individuals with NASH had higher median BMI (45.0kg/m^2 vs. 43.7kg/m^2, p=0.003), and were more likely to have diabetes (45% vs. 29%, p=0.003), and a family

history of coronary disease (67% vs 19%, p=0.016) (Table 1). No significant differences in smoking status, hypertension or dyslipidemia were found between groups. Forty-eight patients (74%) underwent TTE for pre-operative risk assessment without recorded symptoms, 14 (21%) had dyspnea, and 3 (5%) had no recorded indication.

LV structure

Compared to non-NASH subjects, NASH patients had concentric cardiac remodeling, including increased LA size, volume and LV mass indices (Table 1). No significant differences in ejection fraction (EF) were found between groups. After adjustment for age, sex, diabetes, hypertension and BMI, NASH remained associated with increased LV mass, indexed for height ($ß^1$ = 7.16 [4.95]; p=0.001), and LA size, indexed for height ($ß^1$ = 0.17 [0.12]; p=0.002), and BSA ($ß^1$ = 3.10 [1.62]; p=0.039) (Table 2).

Diastolic function

NASH was associated with impaired myocardial relaxation, including reduced lateral e′ and septal e′ velocities, and reduced mitral inflow velocity, measured by E-wave (r= −0.25 [95% CI −0.49, −0.02], p=0.007), and E:A (r= −0.31 [95% CI −0.51, −0.09], p=0.037) (Table 1). In multivariable analysis, NASH remained associated with reduced lateral and septal e′ velocities ($ß^1$ = −0.91cm/s [SE 0.56], p=0.015, and $ß^1$ = −0.89cm/s [SE 0.45], p=0.07, respectively), E-wave ($ß^1$ = −0.19 cm/s [SE 0.04], p=0.002), E:A ($ß^1$ =−4.15 [SE 3.23], p=0.021), and deceleration time ($ß^1$ = −14.52 [SE 9.64], p=0.020) (Table 2).

Sensitivity analyses

Excluding diabetics, statin users (n=4), or those undergoing TTE for clinical symptoms (n=14) did not materially alter the effects of NASH upon cardiac structure or function. Exclusion of those with post-operative TTE (n=11) did not materially alter the estimated effects, nor did the demographics of the excluded group differ significantly from the main cohort. When NAFLD (n=47) vs. normal hepatic histology (n=18) were compared, the observed effects were attenuated but remained significant (Table S1). When patients with NASH (n=14) vs. steatosis (n=33) were compared, the effects were unchanged from the primary analysis (Table S2).

DISCUSSION

Within this biopsy-proven NAFLD population, NASH was associated with significant echocardiographic abnormalities, consistent with progressive diastolic dysfunction. These relationships remained significant after adjustment for traditional cardiometabolic risk factors, and were not attenuated by the exclusion of diabetics, statin users or those lacking pre-operative TTE.

This study is the first to demonstrate an independent association between histologically-defined NASH and significantly increased LA volume. Within the general population, LA volume is a powerful predictor of cardiovascular outcomes, including risk of myocardial infarction (MI)[8] and incident HF[9]. Only one published study to date has reported a link between NAFLD and LA volume[1], but that study lacked hepatic histology, and thus was

unable to assess NASH[1]. Our study is also the first to describe a significant relationship between NASH and reduced lateral and septal e′ velocities, two robust echocardiographic measures of early impairments in myocardial relaxation[10]. Published echocardiographic guidelines recommend cutoffs of <10cm/s (lateral e′) and <7cm/s (septal e′) for the diagnosis of impaired LV relaxation[10]. Indeed, we observed that among patients with NASH, the median lateral and septal e′ velocities were 10cm/s and 7cm/s, respectively, findings which lend further support to the hypothesis that NASH may be linked to significant diastolic impairment. Additionally, our results highlight the potential clinical utility of echocardiography for assessing NAFLD-related HF risk. If validated, early cardiac abnormalities could serve as predictive biomarkers of HF risk, allowing providers to accurately identify NAFLD patients most likely to benefit from personalized interventions.

Published reports linking NAFLD to cardiac remodeling or to subclinical functional changes have largely relied upon surrogate biomarkers or radiographic definitions of NAFLD, which are unable to identify NASH[1, 11]. Only three published studies have involved hepatic histology, with conflicting results. Pacifico and colleagues reported a link between histological NAFLD severity and early LV dysfunction, but used a small cohort of obese children[3], in whom measures of diastolic dysfunction may not be directly comparable to an adult population[12]. Karabay and colleagues observed no significant differences in cardiac function among adult patients with and without NASH, however in this analysis the authors relied upon assessments of standardized mean differences between patients and controls, without accounting for potential covariates[4]. Most recently, in an analysis of 147 consecutive adults with histologically-confirmed NAFLD, no significant differences in LV mass, E:A ratio or early annular diastolic tissue velocity were found in a multivariable model comparing those with and without NASH, however that study did not include normal histological controls, and the population had a remarkably high rate of both prevalent NASH (76%) and visceral obesity (85%), suggesting advanced underlying cardiometabolic disease, which could limit the generalizability of their results[5]. Though small in size, our study benefits from the availability of comparable patient controls with normal hepatic histology.

The pathophysiologic mechanisms linking NAFLD to heart failure (HF) remain largely uncharacterized, however it has been hypothesized that systemic inflammatory activation, ectopic fat deposition and insulin resistance collectively impair myocardial insulin sensitivity, promoting oxidative damage and ventricular stiffening, increasing the risk of both pressure and volume overload[1, 2, 13]. NASH has been shown to predict levels of interleukin-6, tumor necrosis factor-α, and high-sensitivity C-reactive protein independently of visceral adiposity, and increased circulating cytokines may contribute to cardiac remodeling[2]. In this analysis, we found that NASH was strongly associated with markers of diastolic dysfunction and also with ventricular wall thickening, indicative of early hypertrophy. Such findings carry important clinical implications, for diastolic dysfunction is a well-described predictor of future HF risk within the general population[14]. Whether diastolic dysfunction similarly portends a risk of future HF among patients with NAFLD and/or NASH remains unknown, and we therefore eagerly await well-designed, prospective studies to characterize this relationship.

It is important to highlight that the generalizability of our study was limited by a small, selected patient sample and a retrospective design; our study is thus subject to residual confounding, and we were not able to fully account for all putative risk factors for HF or confounders of NAFLD, nor did we have available more detailed functional assessments of cardiac output or filling pressures. Additionally, only 54 bariatric patients underwent pre-operative TTE, thus raising the possibility of ascertainment bias. We attempted to minimize this through manual review of the medical records and by conducting careful sensitivity analyses. Despite these limitations, our study provides evidence that the pathogenesis of subclinical heart failure may relate to progressive NASH. Future studies with well-phenotyped populations and defined cardiovascular outcomes are needed, to more fully define the risk of heart failure in patients with NAFLD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is known about the subject

- Nonalcoholic fatty liver disease (NAFLD) and heart failure (HF) are obesity-related conditions with significant cardiovascular mortality.
- Mounting data suggest a link between NAFLD and changes in myocardial energy metabolism, and in echocardiographic measurements of cardiac morphology and function, suggestive of early, subclinical HF.
- While it is hypothesized that the pathogenesis of HF in NAFLD may relate to inflammatory cytokines related to progressive, inflammatory steatohepatitis (NASH), data in patients with biopsy-proven NASH are limited, and it is unknown whether histological NASH is associated with early markers of HF.

What this study adds

- This is the first study in a well-characterized population of obese patients undergoing elective bariatric surgery to demonstrate an independent relationship between histological NASH and increased left atrial (LA) volume indexed for height, a well-described predictor of incident heart failure risk, within the general population.
- This is also the first published study in a bariatric cohort to demonstrate an association between biopsy-proven NASH and impaired LV relaxation indicative of progressive diastolic dysfunction, as marked by multiple well-characterized echocardiographic indices, including E′, lateral and septal e′ velocity, E:A ratio and deceleration time.

Table 1

Demographic, clinical and echocardiographic features of included subjects (N=65), according to the presence of histological NASH

Variable[1]	No NASH (N=51)	NASH (N=14)	p-value
Age, median (range)	50.0 [41.0, 56.5]	46.5 [35.0, 55.5]	<0.0001
Female sex, %	12 (37.5%)	16 (50.0%)	0.314
Caucasian, %	25 (78.1%)	29 (90.6%)	0.063
BMI, median [IQR]	43.7 [40.2, 49.5]	45.0 [43.3, 50.4]	0.003
Diabetes, %	9 (29.0%)	14 (45.2%)	0.029
Dyslipidemia, %	13 (41.9%)	13 (41.9%)	1.000
Hypertension, %	14 (42.4%)	20 (62.5%)	0.202
Systolic blood pressure, mmHg[¥]	127.9 (13.7)	130.2 (10.1)	0.414
Diastolic blood pressure, mmHg[¥]	88.5 (8.4)	90.1 (9.6)	0.650
Smoking (any vs. never), %	20 (60.6%)	13 (40.6%)	0.141
Family history of CAD, %	6 (18.8%)	12 (66.7%)	0.016
Laboratory parameters			
Creatinine, mg/dL, median [IQR]	0.85 [0.72, 1.03]	0.97 [0.71, 1.20]	0.473
HbA1c%	5.9 (1.4)	6.1 (0.5)	0.001
Alanine aminotransferase, U/L	28.3 (15.8)	41.0 (57.2)	<0.0001
Aspartate aminotransferase, U/L	26.3 (12.7)	31.3 (20.5)	<0.0001
Albumin, g/dL	4.3 (0.4)	3.9 (0.5)	<0.0001
Platelets, ×1000/mm^3	278.0 (68.8)	223.1 (60.4)	<0.0001
Echocardiographic parameter[*]			
Diastolic function			
E:A ratio	1.16 [1.05, 1.32]	1.03 [0.88, 1.42]	<0.0001
E wave, cm/s	86.0 [73.0, 96.0]	76.0 [70.0, 89.0]	<0.0001
A wave, cm/s	70.0 [5.5, 78.0]	67.0 [59.0, 85.0]	0.320
Deceleration time, msec	195.0 [170.0, 210.0]	180.0 [170.0, 220.0]	<0.0001
E:e′ ratio	10.5 [8.0, 12.4]	9.2 [7.7, 10.1]	0.001
Lateral E′, cm/s	12.0 [10.0, 13.0]	10.0 [8.0, 11.5]	<0.0001

Variable[1]	No NASH (N=51)	NASH (N=14)	p-value
Septal E′, cm/s	8.5 [7.5, 10.0]	7.0 [6.5, 9.5]	0.010
LA and LV structure			
LVEF, %	65.0 [61.0, 71.5]	68.5 [67.0, 72.0]	<0.0001
LV mass index (LVMI)			
○ LVMI by height$^{2.7}$, g/m$^{2.7}$ǂ	50.5 [48.0, 53.5]	59.5 [58.0, 64.0]	<0.0001
○ LVMI by BSA, g/m^2	88.0 [86.0, 90.5]	112.0 [108.0, 122.0]	<0.0001
LVIDS, mm	30.5 [28.0, 33.5]	30.5 [26.0, 32.0]	<0.0001
LVIDD, mm	47.0 [43.0, 52.0]	45.5 [42.5, 52.0]	<0.0001
LA size index§			
○ LA size/height, mm/cm	0.32 [0.30, 0.35]	0.37 [0.35, 0.39]	<0.0001
○ LA size/BSA, mm/m^2	38.0 [34.0, 39.0]	39.5 [37.5, 42.5]	0.003
LA volume index§			
○ LAV/height, ml/cm	0.31 [0.30, 0.35]	0.38 [0.37, 0.40]	<0.0001
○ LAV/BSA, ml/m^2	24.8 [19.3, 32.5]	28.6 [22.3, 35.0]	<0.0001
IVS (mm)	11.0 [10.0, 13.0]	12.0 [10.5, 13.0]	0.002

Abbreviations: NASH, nonalcoholic steatohepatitis; BMI, body mass index; CAD, coronary artery disease; HbA1c, hemoglobin A1c; LVEF, left ventricular ejection fraction; LV, left ventricle; LVIDS, left ventricular diameter, systole; LVIDD, left ventricular diameter, diastole; LA, left atrial; BSA, body surface area; IVS, interventricular septum

[1]All variables are presented as mean (SD), with the exception of age, BMI and Creatinine which were not normally distributed and are thus presented as median [IQR].

*All echocardiographic values are presented as median [IQR].

¥Systolic and diastolic blood pressure values were obtained at the time of transthoracic echocardiography

ǂLV mass index is shown by indexation for heightˆ2.7, and by body surface area (BSA)[7].

§LA size and LA volume are indexed for body surface area (BSA, m^2) as per recommendations by the American Society of Echocardiography[7]. For comparison, both parameters are also indexed separately for height (cm).

Table 2

Relationship between histologically-defined NASH and changes in echocardiographic markers of myocardial structure and diastolic function, among bariatric surgery patients (N=65)

Echocardiographic measure	Adjusted* ß[1] [SE]	p-value
Left ventricular systolic function		
• LVEF	−1.83 [1.08]	0.009
Left ventricular diastolic function		
• E-wave	−0.19 [0.04]	0.002
• E:A ratio	−4.15 [3.23]	0.021
• Lateral E′	−0.91 [0.56]	0.015
• Septal E′	−0.89 [0.45]	0.047
• Deceleration time	−14.52 [9.64]	0.020
Myocardial structure		
LV mass index (LVMI)		
○ LV mass/height, g/m$^{2.7}$	7.16 [4.95]	0.001
○ LV mass/BSA, g/m^2	4.22 [3.39]	0.029
LA size index		
○ LA size/BSA, mm/m^2		
○ LA size/height, mm/cm	3.10 [1.62]	0.039
	0.17 [0.12]	0.002
LA volume index		
○ LA volume/BSA, ml/m^2		
○ LA volume/height, ml/cm	4.10 [2.18]	0.001
	0.19 [0.08]	0.001
Interventricular septum, mm		
LVIDS, mm	0.64 [0.41]	0.040
	−0.45 [0.39]	0.015

Abbreviations: SE, standard error; LVEF, left ventricular ejection fraction; LV, left ventricle; LA, left atrium; BSA, body surface area; IVS, interventricular septum; LVIDS, left ventricular diameter, systole

*Multivariable linear regression model, adjusted for age, sex, diabetes, body mass index (BMI) and hypertension. For echocardiographic measurements indexed for body surface area (BSA), BMI was not included as a covariate.