Nonalcoholic Steatohepatitis is Associated with Cardiac Remodeling and Dysfunction

Tracey G. Simon1, Daniel G. Bamira2, Raymond T. Chung1, Rory B. Weiner2, and Kathleen E. Corey1

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

Methods: A retrospective cohort was identified of individuals (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 (28.6 mL/m² vs. 24.8 mL/m²; P < 0.0001) and left ventricular (LV) mass (82.6 g/m² vs. 78.6 g/m²; 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 to −0.42]; P = 0.020) and E:A (r = −0.31 [95% CI: −0.51 to −0.09]; P = 0.037). In adjusted analyses, NASH remained associated with increased LV mass index (β¹ = 7.16 [SE: 4.95]; P = 0.001) and LA volume index (β¹ = 0.19 [SE: 0.08]; P = 0.001) and reduced lateral and septal E’ (β¹ = −0.91, P = 0.015; β¹ = −0.89, P = 0.047, respectively).

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

Introduction

Nonalcoholic fatty liver disease (NAFLD) and heart failure (HF) are obesity-related conditions with high cardiovascular mortality. A growing body of data now links 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 nonalcoholic 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 patients with obesity undergoing bariatric surgery in whom perioperative liver biopsy and echocardiography enabled the assessment of hepatic histology and 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 nonischemic 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 were accompanied by intraoperative liver biopsies, which were 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, BMI, and body surface area (BSA) were recorded on the date of TTE, and measures of left atrial (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, analysis of variance (ANOVA), and linear regression models adjusted for age, sex, diabetes, hypertension, and BMI. The study was approved by Partners Human Research Committee (Institutional Review Board).

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 (45.0 kg/m² vs. 43.7 kg/m²; 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 preoperative risk assessment without recorded symptoms, 14 (21%) had dyspnea, and 3 (5%) had no recorded indication.

LV structure
Compared to non-NASH patients, NASH patients had concentric cardiac remodeling, including increased LA size, volume, and LV mass indices (Table 1). No significant differences in ejection fraction were found between groups. After adjustment for age, sex, diabetes, hypertension, and BMI, NASH remained associated with increased LV mass indexed for height (β = 7.16 [SE: 4.95]; P = 0.001) and LA size indexed for height (β = 0.17 [SE: 0.12]; P = 0.002) and BSA (β = 3.10 [SE: 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 to −0.02]; P = 0.007) and E:A (r = −0.31 [95% CI: −0.51 to −0.09]; P = 0.037) (Table 1). In multivariable analysis, NASH remained associated with reduced lateral and septal E' velocities (β = −0.91 cm/s [SE: 0.56]; P = 0.015 and β = −0.89 cm/s [SE: 0.45]; P = 0.07, respectively), E-wave (β = −0.19 cm/s [SE: 0.04]; P = 0.002), E:A (β = −4.15 [SE: 3.23]; P = 0.021), and deceleration time (β = −14.52 [SE: 9.64]; P = 0.020) (Table 2).

Sensitivity analyses
Excluding patients with diabetes, statin users (n = 4), and those undergoing TTE for clinical symptoms (n = 14) did not materially alter the effects of NASH on cardiac structure or function. Exclusion of those with postoperative 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) was compared with normal hepatic histology (n = 18), the observed effects were attenuated but remained significant (Supporting Information Table S1). When patients with NASH (n = 14) were compared with patients with steatosis (n = 33), the effects were unchanged from the primary analysis (Supporting Information 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 patients with diabetes, statin users, or those lacking preoperative 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 (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 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 <10 cm/s (lateral E') and <7 cm/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 10 cm/s and 7 cm/s, respectively, findings that 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 on 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 children with obesity (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, the authors relied on 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 adiposity.
| Variable                        | No NASH (n = 51) | NASH (n = 14) | P value |
|--------------------------------|------------------|---------------|---------|
| Age (y), median [IQR]          | 50.0 [41.0-56.5] | 46.5 [35.0-55.5] | <0.0001 |
| Female sex, n (%)              | 12 (37.5%)       | 7 (50.0%)     | 0.314   |
| Caucasian, n (%)               | 25 (78.1%)       | 12 (85.7%)    | 0.063   |
| BMI, median [IQR]              | 43.7 [40.2-49.5] | 45.0 [43.3-50.4] | 0.003   |
| Diabetes, n (%)                | 9 (29.0%)        | 6 (42.9%)     | 1.000   |
| Dyslipidemia, n (%)            | 13 (41.9%)       | 6 (42.9%)     | 1.000   |
| Hypertension, n (%)            | 14 (42.4%)       | 8 (57.1%)     | 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), n (%) | 20 (60.6%)       | 6 (42.9%)     | 0.141   |
| Family history of CAD, n (%)   | 6 (18.8%)        | 9 (64.3%)     | 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, ×1,000/mm³           | 278.0 (68.8)     | 223.1 (60.4)     | <0.0001 |

Echocardiographic parameter

| Diastolic function              | 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 [55.7-79]   | 67.0 [59.0-85.0] | 0.320   |
| Deceleration time, ms           | 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 |
| 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                    |                  |                  |         |
| • By height².⁷g/m²                | 50.5 [48.0-53.5] | 59.5 [58.0-64.0] | <0.0001 |
| • By BSA, g/m²                    | 88.0 [86.0-90.5] | 112.0 [108.0-122.0] | <0.0001 |
| LVDD, mm                         | 30.5 [28.0-33.5] | 30.5 [26.0-32.0] | <0.0001 |
| LVDD, 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/m²             | 38.0 [34.0-39.0] | 39.5 [37.5-42.5] | 0.003   |
| LA volume index                  |                  |                  |         |
| • LA volume/height, mL/cm        | 0.31 [0.30-0.35] | 0.38 [0.37-0.40] | <0.0001 |
| • LA volume/BSA, mL/m²           | 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   |

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

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

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

*LV mass index is shown by indexation for height².⁷ and by body surface area (BSA)².⁷

*LA size and LA volume are indexed for BSA (m²) as per recommendations by the American Society of Echocardiography (7). For comparison, both parameters are also indexed separately for height (cm).

Abbreviations: BSA, body surface area; CAD, coronary artery disease; HbA1c, hemoglobin A1c; IVS, interventricular septum; LA, left atrial; LV, left ventricle; LVEF, left ventricular ejection fraction; LVDD, left ventricular diameter, diastole; LVDD, left ventricular diameter, systole; NASH, nonalcoholic steatohepatitis.
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<sup>a</sup> β<sup>1</sup> [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<sup>+</sup>                      | −0.91 [0.56]                           | 0.015   |
| Septal E<sup>+</sup>                       | −0.89 [0.45]                           | 0.047   |
| Deceleration time                          | −14.52 [9.64]                          | 0.020   |
| Myocardial structure                       |                                        |         |
| LV mass index                              |                                        |         |
| LV mass/height, g/m<sup>2</sup>            | 7.16 [4.95]                            | 0.001   |
| LV mass/BSA, g/m<sup>2</sup>               | 4.22 [3.39]                            | 0.029   |
| LA size index                              |                                        |         |
| LA size/BSA, mm/m<sup>2</sup>              | 3.10 [1.62]                            | 0.039   |
| LA size/height, mm/cm                      | 0.17 [0.12]                            | 0.002   |
| LA volume index                            |                                        |         |
| LA volume/BSA, mL/m<sup>2</sup>            | 4.10 [2.18]                            | 0.001   |
| LA volume/height, mL/cm                    | 0.19 [0.08]                            | 0.001   |
| IVS, mm                                    | 0.64 [0.41]                            | 0.040   |
| LVIDS, mm                                  | −0.45 [0.39]                           | 0.015   |

<sup>a</sup> Multivariable linear regression model, adjusted for age, sex, diabetes, BMI, and hypertension. For echocardiographic measurements indexed for BSA, BMI was not included as a covariate.

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

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 HF remain largely uncharacterized, although 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 and 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, as 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 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 therefore subject to residual confounding, and we were not able to fully account for all putative risk factors for HF or confounders of NAFLD; we also lacked more detailed functional assessments of cardiac output and filling pressures. Additionally, only 54 bariatric patients underwent preoperative 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.

© 2017 The Obesity Society

References

1. Van Wagner LB, Wilcox JE, Colangelo LA, et al. Association of nonalcoholic fatty liver disease with subclinical myocardial remodeling and dysfunction: a population-based study. *Hepatology* 2015;62:773-783.
2. Targher G, Bertolini L, Rodella S, et al. NASH predicts plasma inflammatory biomarkers independently of visceral fat in men. *Obesity (Silver Spring)* 2008;16:1394-1399.
3. Pacifico L, Di Martino M, De Merulis A, et al. Left ventricular dysfunction in obese children and adolescents with nonalcoholic fatty liver disease. *Hepatology* 2014;59:461-470.
4. Karabay CY, Kocabay G, Kalayci A, et al. Impaired left ventricular mechanics in nonalcoholic fatty liver disease: a speckle-tracking echocardiography study. *Eur J Gastroenterol Hepatol* 2014;26:325-331.
5. Petta S, Craxi A. Epicardial fat in patients with non-alcoholic fatty liver disease. *J Hepatol* 2015;62:1215. doi:10.1016/j.jhep.2015.01.012
6. Cuspidi C, Giudici V, Negri F, et al. Improving cardiovascular risk stratification in essential hypertensive patients by indexing left ventricular mass to height (2.71). *J Hypertens* 2009;27:2465-2471.
7. Pritchett AM, Jacobsen SJ, Mahoney DW, et al. Left atrial volume as an index of left atrial size: a population-based study. *J Am Coll Cardiol* 2003;41:1036-1043.
8. Beinart R, Boyko V, Schwammenthal E, et al. Long-term prognostic significance of left atrial volume in acute myocardial infarction. *J Am Coll Cardiol* 2004;44:327-334.
9. Meris A, Amigoni M, Uno H, et al. Left atrial remodelling in patients with myocardial infarction complicated by heart failure, left ventricular dysfunction, or both: the VALIANT Echo study. *Eur Heart J* 2009;30:56-65.
10. Nagaseh SF, Smithe OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016;17:1321-1360.
11. Forbici H, Yakar T, Duman D, et al. Impairment of the left ventricular systolic and diastolic function in patients with non-alcoholic fatty liver disease. *Cardiol J* 2010;17:457-463.
12. Bonci E, Chiesa C, Versacci P, et al. Association of nonalcoholic fatty liver disease with subclinical cardiovascular changes: a systematic review and meta-analysis. *Biomed Res Int* 2015;2015:213737. doi:10.1155/2015/213737
13. Lautamaki R, Borra R, Iozzo P, et al. Liver steatosis coexists with myocardial insulin resistance and coronary dysfunction in patients with type 2 diabetes. *Am J Physiol Endocrinol Metab* 2006;291:E282-E290.
14. Kane GC, Karon BL, Mahoney DW, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA* 2011;306:856-863.