Heart Failure in Obesity

From early detection to the role in clinically overt disease

Yaar Aga

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Heart Failure in Obesity
From early detection to the role in clinically overt disease

Hartfalen in Obesitas
Van vroegtijdige detectie tot de rol in klinisch vastgestelde ziekte

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
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and in accordance with the decision of the Doctorate Board.
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Medicine has taught me that there is wisdom in the body.
If we would put our stethoscopes to our own chests,
we would hear the pause of diastole.
A drop in pressure. Relaxation. Expansion.
And then, with a full heart, a gush of life.

Colleen M. Farrell, JAMA 2019

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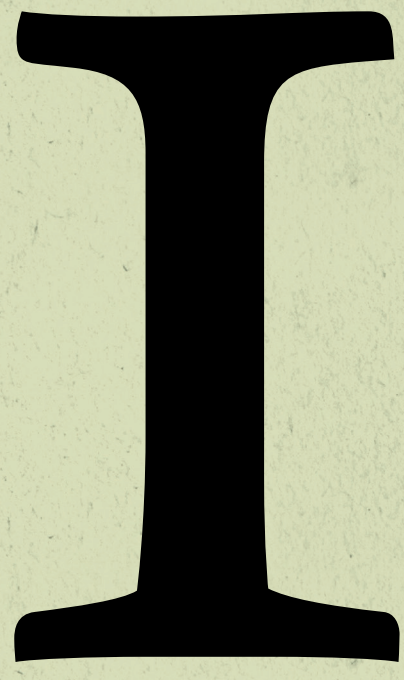
Introduction



Chapter I

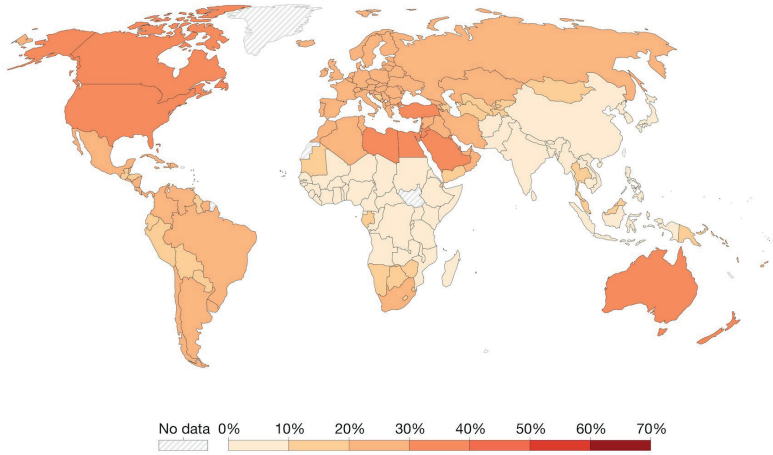
General introduction, aims and outlines of this thesis

OBESITY

Obesity is a major worldwide healthcare problem with substantial related morbidity and mortality (1). Obesity is defined with the use of the body mass index (BMI) scale, in which a BMI greater than 30 kg/m^2 is defined as obesity (2). It is estimated that in 2016, worldwide 13% of adults had a BMI ≥ 30 kg/m^2, and 39% of adults were overweight **(Figure 1)** (2). In 2017, 8% of global deaths were attributed to obesity (2). The numbers of obesity and obesity related comorbidities, and deaths are increasing, which is a cause for concern as obesity is a debilitating medical condition associated with an increased risk for cardiovascular disease and other conditions (1-4). These other conditions include diabetes mellitus type 2 (DM2), chronic kidney disease, hyperlipidaemia, hypertension, non-alcoholic fatty liver disease, certain types of cancer, osteoarthritis, obstructive sleep apnea, and depression (4, 5). The treatment for these conditions can place a large burden on healthcare systems and costs, as it is estimated that people with obesity have 30% higher medical costs than individuals without obesity (1).

Obesity is complex, multifactorial medical condition that is not yet fully understood. It involves regulation of calorie intake and physical activity, but underlying hereditary and environmental factors also play an important role (1). In addition, socio-economic status, psychological stress, and availability of health-care systems have been recognized as important factors in obesity (1). For cardiovascular disease, and in particular heart failure, systemic inflammation caused by obesity is considered as a key factor in the pathophysiological link between obesity and heart failure (3, 6).

Figure 1: Share of adults with a BMI ≥ 30 kg/m² in 2016. Source: WHO (2), Global Health Observatory, 2022

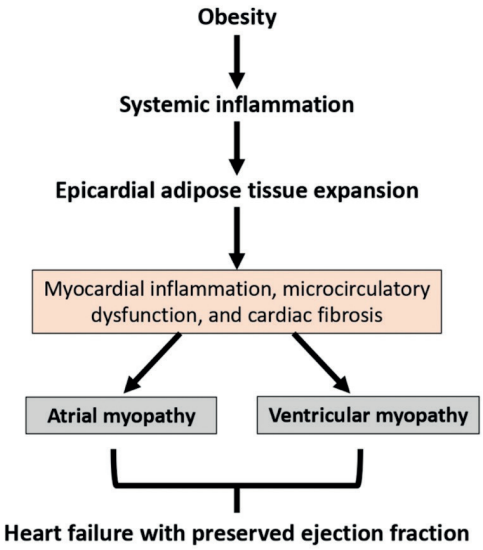


HEART FAILURE

The prevalence of heart failure (HF) is increasing and forms a major health threat that is, in part, related to the fast-growing prevalence of obesity (7, 8). A BMI ≥ 30 kg/m^2 doubles the lifetime risk of developing heart failure (9), and every one-unit increase in BMI is associated with a 7% increased risk for HF in women, and 5% in man (10). The rising number of obesity and subsequent risk for heart failure warrants efficient screening and early detection to identify those at highest risk. In obesity, the phenotype of heart failure may vary and can be manifested as heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF). Studies have shown that obesity and related cardiometabolic traits are more associated with HFpEF than with HFrEF (11). In HFpEF patients, more than 80% of patients are either overweight or obese (12). This underscores that the obesity-related HFpEF phenotype is prevalent as well as clinically relevant (13).

The pathogenesis of how obesity leads to heart failure is not yet completely understood, but in the recent years it has become clearer that systemic inflammation plays a key role in the pathophysiology, especially in HFpEF (3, 6). Moreover, the role of epicardial adipose tissue (EAT) as a mechanism of inflammation in obesity related HFpEF has gained more interest (14, 15). Obesity facilitates a state of inflammation which can lead to expansion of EAT that in turn becomes a source of pro-inflammatory and pro-fibrotic markers (6, 14, 16). In contrast to other adipose tissues that surround organs in the human body, EAT is unique because of the location, as it is in direct contact with the coronary arteries and the myocardium since there is no fascia or similar structure that separates the myocardium from the EAT (16). Inherently, this promotes an environment for direct infiltration into the myocardium of the pro-inflammatory and pro-fibrotic markers that are produced in the EAT. Depending on the location of the EAT, this may result in atrial myopathy or ventricular myopathy potentially leading to atrial fibrillation, diastolic dysfunction, and HFpEF (**Figure 2)** (16, 17). Besides the effect of systemic inflammation and EAT, obesity is also related to comorbidities, such as hypertension and diabetes mellitus, that are all independent risk factors for HFpEF (4). In addition, obesity causes hemodynamic changes that can alter cardiac structure and function, that can potentially lead to HFpEF (18, 19). Furthermore, obesity causes activation of the sympathetic nervous system, as well as the renin-angiotensin-aldosteron-system (RAAS) which alters autonomic tone (20, 21). All of these mechanisms may contribute to the pathophysiology of heart failure in patients with obesity.

Figure 2: Mechanism by which obesity promotes atrial and ventricular myopathy. Source: adapted from Packer et. al.



DETECTION OF HEART FAILURE IN OBESITY

The growing prevalence of obesity and subsequent increase in heart failure warrant efficient screening and early detection of heart failure in patients with obesity. However, identifying heart failure in patients with obesity is challenging due to several reasons. The difficulty starts with the patient's history and physical examination, as signs and symptoms, such as dyspnea and edema, are often attributed to the extra weight and other comorbidities that are related to obesity (4). The following challenge in obesity is the use of the blood biomarker brain natriuretic peptide (BNP), which is a guideline recommended and commonly used biomarker for diagnosing heart failure (22). In obesity, BNP is decreased as obesity enhances upregulation of enzymes involved in the clearance of BNP, and obesity promotes increased renal filtration of BNP (23, 24). Alternative blood biomarkers that are specifically related to systemic inflammation and pro-fibrotic markers in obesity could potentially provide superior information than BNP on precursors and signs of early cardiac dysfunction in obesity. However, to date little is known about the role of alternative biomarkers for heart failure specifically in patients with obesity.

Another key diagnostic tool in heart failure is the use of transthoracic echocardiography. Echocardiography is a non-invasive tool that can provide assessment of cardiac

structure and function, and can offer a ton of prognostic information. Left ventricular ejection fraction (LVEF) is the most commonly used and recommended echocardiographic parameter of cardiac function (22). In the recent years, the use of speckle tracking echocardiography (STE) has emerged as a valuable echocardiographic tool for cardiac function (25, 26). For the left ventricle, global longitudinal strain (GLS) has gained interest as a measure of function as it has been shown to be more sensitive than LVEF for the assessment of early myocardial dysfunction (27-29). Moreover, GLS carries prognostic information for patients with heart failure (26). In patients with obesity, GLS could potentially identify early subclinical cardiac dysfunction, before changes in LVEF can be detected (21).

Left atrial strain (LAS) assessed by STE has also increasingly been recognized as an important parameter to identify diastolic dysfunction and HFpEF (30-32). Traditionally, the left atrium is evaluated by using left atrium volume indexed (LAVI) to body surface area (BSA) (33). The use of LAVI as a criterion in obesity is however unsuitable, as indexing to BSA overcorrects left atrial volume and potentially normalizes a pathological LA dilatation (34). Alternative indexation methods may provide a better estimate for left atrial volume in obesity. However, there is currently limited evidence regarding the clinical benefit of using alternative indexation methods for LAV in obesity and the relation of alternative indexation methods with LAS. The use of LAS could provide important diagnostic and prognostic information in patients with obesity, as recent studies have shown LAS provides superior information over LAVI , and that LAS has better correlation with invasive left ventricular filling pressures than LAVI (35-39). In addition, LAS independently predicts incident HFpEF, and LAS seems to be altered before traditional parameters of HFpEF can be detected (30-32). An in-depth exploration of the use of LAS in patients with obesity might provide a superior parameter for LA function for this important patient population.

OUTLINE OF THIS THESIS

The overall aim of this thesis is to investigate cardiac dysfunction in obesity, and to explore the role of biomarkers and speckle tracking echocardiography in the early detection of heart failure in patients with obesity.
Part I contains the introduction of this thesis. In **Chapter 1**, we describe the general introduction on obesity and heart failure. Information on the use of biomarkers and background of speckle tracking echocardiography is provided.
In **Part II**, we focus on the role of the left atrium in early detection of cardiac dysfunction. In **Chapter 2** we investigate the role of LAS in estimating left ventricular filling pressures in a patient population with chronic, stable HFrEF in whom non-invasive

estimation of LV filling pressures with echocardiography can be challenging, due to unavailable echocardiographic parameters. In **Chapter 3**, we assess the prognostic role of repeated measurements of LAS in a stable, chronic heart failure population. In **Chapter 4,** we use the knowledge gained on LAS in the previous chapters, to study whether LAS is useful to detect cardiac dysfunction in patients with obesity. In **Chapter 5**, we describe alternative methods of indexing left atrial volume in relation to LA strain, in order to improve diagnostic criteria for heart failure in patients with obesity.

In **Part III**, we describe the role of the left ventricle in early detection of cardiac dysfunction and the impact of bariatric surgery on left ventricular function. In **Chapter 6**, we assess the prognostic value of repeated measurements of GLS over the prognostic value of repeated measurements of LVEF in a stable, chronic heart failure population. In **Chapter 7**, we investigate whether weight loss achieved by bariatric surgery is associated with changes in measures of systolic function, such as GLS and LVEF. In **Chapter 8**, we describe predictors for persistent cardiac dysfunction after bariatric surgery.

The focus in **Part IV** is on cardiovascular biomarker profiles in obesity patients to gain understanding of the underlying pathophysiology and to hypothesize whether alternative biomarkers are more appropriate to use for cardiac dysfunction in obesity. In **Chapter 9** we describe differences in biomarker profiles in patients with and without obesity. In addition, we specifically focus on differences in biomarker profiles in patients with and without cardiac dysfunction. In **Chapter 10** we investigate changes in biomarker profiles before and after bariatric surgery.

In **Part V**, we describe the role of obesity in patients with diagnosed heart failure. In **Chapter 11**, we investigate the role of obesity in atrial fibrillation in patients with diagnosed HFpEF. In **Chapter 12**, we investigate differences in heart failure drug treatment in patients with and without obesity in a large cohort of chronic heart failure patients and explore whether patients with obesity receive the target dose of guideline recommended heart failure drugs, and we speculate on the possible association of this finding with the obesity paradox.

Finally, in **Part VI**, we place the results of the studies described in this thesis in a broad context and discuss the implications of the findings in **Chapter 13**. In **Chapter 14**, we provide a summary of the main findings of this thesis and give recommendations for future research.

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Part II

Early detection of cardiac dysfunction in obesity – the left atrium

2

Chapter 2

Potential role of left atrial strain in assessment of left ventricular filling pressures in heart failure with reduced ejection fraction

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ABSTRACT

Aims

In a large proportion of heart failure with reduced ejection fraction (HFrEF) patients, echocardiographic estimation of left atrial pressure (LAP) is not possible when the ratio of the peak early left ventricular filling velocity over the late filling velocity (E/A ratio) is not available, which may occur due to several potential causes. Left atrial reservoir strain (LASr) is correlated with LV filling pressures and may serve as an alternative parameter in these patients. The aim of this study was to determine whether LASr can be used to estimate LAP in HFrEF patients in whom E/A ratio is not available.

Methods

Echocardiograms of chronic HFrEF patients were analyzed and LASr was assessed with speckle tracking echocardiography. LAP was estimated using the current ASE/EACVI algorithm. Patients were divided into those in whom LAP could be estimated using this algorithm (LAPe) and into those in whom this was not possible because E/A ratio was not available (LAPne). Additionally we assessed the prognostic value of LASr on clinical endpoints.

Results

We studied 153 patients; mean age of 58 years; 76% men; 82% NYHA class I-II. 86 were in the LAPe group and 67 in the LAPne group. LASr was significantly lower in the LAPne group as compared to the LAPe group (15.8% vs. 23.8%, $p<0.001$). PEP-free survival at a median follow-up of 2.5 years was 78% in LAPe versus 51% in LAPne patients. An increase in LASr was significantly associated with a reduced risk of the PEP in LAPne patients (adjusted hazard ratio: 0.91 per %, 95% confidence interval 0.84-0.98). An abnormal LASr (<18%) was associated with a 5-fold increase in reaching the PEP.

Conclusions

In HFrEF patients who would remain uncategorized due to unavailability of E/A ratio, assessing LASr potentially carries added clinical and prognostic value.

INTRODUCTION

Elevated left atrial pressure (LAP) in patients with heart failure with reduced ejection fraction (HFrEF) is common and can be a sign of disease progression or trigger of worsening HF (1). The main reason to noninvasively estimate LAP in HFrEF is that it can be used to guide medical treatment and can affect clinical outcomes (2, 3) . Currently, echocardiographic estimation of LAP in HFrEF is performed by evaluating a combination of parameters related to left ventricular (LV) diastolic function (4). Potential complicating factors in estimating LAP in HFrEF, are that the algorithms as proposed by the ASE/EACVI guidelines are relatively complex and that crucial parameters, such as the ratio of the early (E) to late (A) ventricular filling velocities (E/A ratio), are often affected by heart rhythm abnormalities and/or mitral valve disease (4). An emerging echocardiographic parameter that may be used to estimate LAP in HFrEF, is left atrial reservoir strain (LASr) (5-7). Previous studies have shown that LASr is impaired in HFrEF (8, 9), and that an abnormal LASr is associated with increased LAP, as measured invasively in patients with moderately and severely reduced LV ejection fraction (EF) (10). An important advantage of measuring LASr, as opposed to traditional echocardiographic estimation of LAP, is that LASr is not affected by atrial fibrillation (AF) and mitral valve disease, conditions that are frequently present in patients with HFrEF (11, 12). Therefore, assessment of LASr in HFrEF patients in whom estimation of LAP cannot be performed due to these comorbidities and in whom E/A ratio is subsequently missing, could help to estimate LAP and herewith to guide treatment and provide prognostic information. The algorithm as proposed by the ASE/EACVI guidelines for estimation of LAP is not applicable in HFrEF patients in whom E/A ratio is not available. It is unknown whether LASr may be of added value in these patients. Therefore, the aim of this study is to determine whether LASr may be a useful parameter in this specific patient group.

METHODS

Study design

For this study, data was used from the Bio-SHiFT study (Serial Biomarker Measurements and New Echocardiographic Techniques in Chronic Heart Failure Patients Result in Tailored Prediction of Prognosis). Details on the design of the Bio-SHiFT study have been published previously (13). In short, Bio-SHiFT is a prospective, observational cohort of stable patients with chronic heart failure (CHF), conducted in the Erasmus MC, Rotterdam, and Northwest clinics, Alkmaar, The Netherlands. The main inclusion criteria were diagnosis of HF according to the then prevailing guidelines of the European Society of Cardiology (14) and age ≥18 years. Patients were

recruited during their regular outpatient visits while in clinically stable condition (i.e., they had not been hospitalized for HF in the 3 months prior to inclusion). Patients were followed for a maximum of 30 months by tri-monthly study visits. During the study, the routine outpatient follow-up by the treating physician also continued for all patients. A total of 398 patients were included in the entire Bio-SHiFT cohort. Out of these, 175 patients were included in an echocardiography substudy at the Erasmus MC (15) of whom 2 patients had insufficient image quality, leaving a total of 173 patients for the substudy. All the patients from the Erasmus MC were eligible to enter the echocardiographic substudy. The study was approved by the medical ethics committees, conducted in accordance with the Declaration of Helsinki, and registered in ClinicalTrials.gov (NCT01851538). All patients signed informed consent for the study.

Echocardiography measurements and evaluation

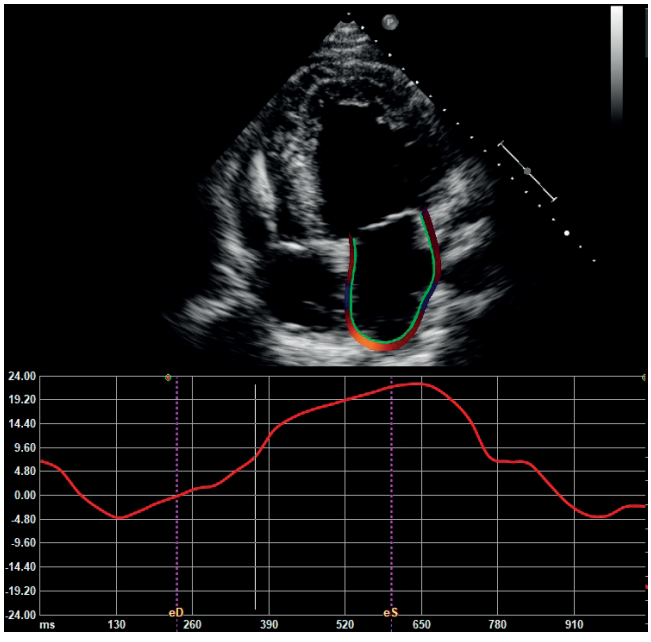
Two-dimensional grey-scale harmonic images were obtained in the left lateral decubitus position. Conventional and speckle tracking echocardiography was performed on all participants. Standard apical four-, three-, and two-chamber views were recorded. A commercially available ultrasound system was used (iE33, Philips, Best, The Netherlands), equipped with a broadband (1-5 MHz) S5-1 transducer (frequency transmitted 1.7 MHz, received 3.4 MHz). Images were stored in the echo core lab of Erasmus MC. All acquisitions, and measurements were performed according to the ASE/EACVI guidelines (16) using Philips Excellera version R4.1 (Philips Medical Systems, The Netherlands) or TomTec Imaging Systems. Diastolic parameters were assessed, and grading occurred according to the ASE/EACVI guidelines (4). All echocardiographic measurements were performed blinded to biomarker and clinical event data. LA strain was measured with speckle tracking and analysed offline with dedicated software (2D Cardiac Performance Analysis version 4.5; TomTec Imaging Systems, Unterschleissheim, Germany). Measurement of LA strain was performed retrospectively by a single operator. The apical 4-chamber view was used preferably for the analysis. LA endocardial borders were automatically traced using end-diastole as reference. When tracking was suboptimal, fine-tuning was performed manually. If the 4-chamber view was of poor image quality, the 2-chamber view was used. Patients with images of insufficient quality to perform LA strain analysis or patients with an atrial pacemaker were excluded. LA strain was assessed according to the three phases of the LA cycle: LA reservoir strain (LASr) which starts at the end of ventricular diastole (mitral valve closure) and continues until mitral valve opening, LA conduit strain (LAScd) which occurs from the time of mitral valve opening through diastasis until the onset of LA contraction, and LA contractile strain (LASct) which occurs from the onset of LA contraction until the end of ventricular diastole (mitral valve closure). LASr was used for the analysis. All strain values are reported as absolute

values for improved readability and data interpretation (17). An example of a LA strain curve is provided in Figure 1.

Classification based on available or not available LAP estimation

Patients in whom E/A ratio was available, were pooled in the group 'LAP estimation available' (LAPe). Patients in whom E/A ratio was not available to estimate LAP (lack of an A-wave due to AF, fusion of E- and A-wave, and/or moderate/severe mitral valve disease) were pooled in the group 'LAP estimation not available' (LAPne). General and echocardiographic characteristics were compared between the LAPe and LAPne group to provide information on severity of disease.

Figure 1: Example of left atrial strain measurement. LASr, left atrial reservoir strain; LAScd, left atrial conduit strain; LASct, left atrial contractile strain.



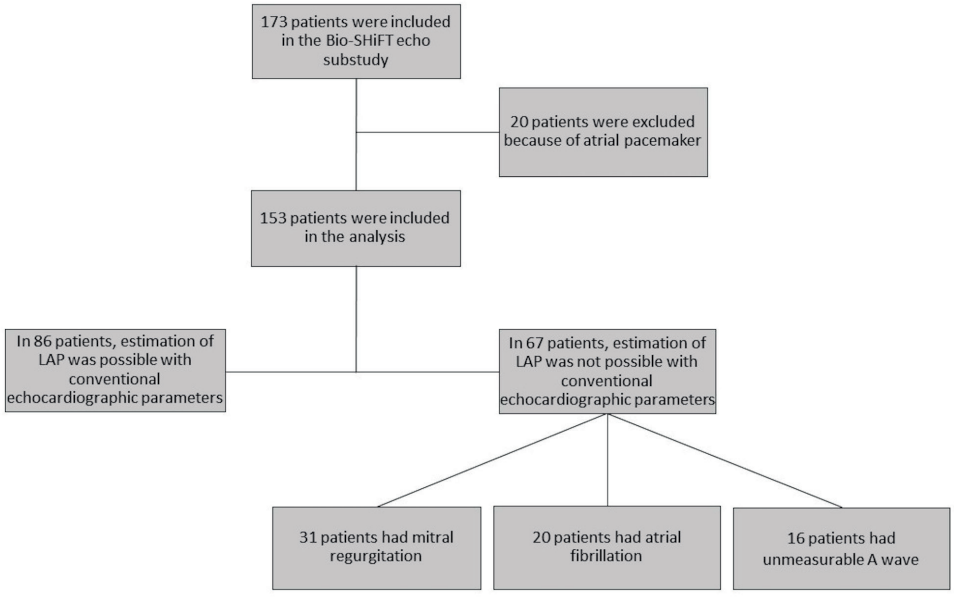
Clinical Study Endpoints

The primary endpoint (PEP) comprised the composite of hospitalization for the management of acute or worsened HF, LV assist device (LVAD) implantation, cardiac transplantation, and cardiovascular death, whichever occurred first in time. All events were adjudicated by a clinical event committee blinded for the echocardiographic assessments and biomarker measurements, after reviewing corresponding hospital records and discharge letters.

Statistical Analyses

Distributions of continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed continuous variables are presented as mean ± standard deviation (SD), and nonnormally distributed variables as median and 25^{th}-75^{th} percentile. Categorical variables are presented as numbers and percentages. Differences in baseline characteristics between patients in the different LAP groups were tested using ANOVA and the Kruskal-Wallis test, according to variable distributions, for continuous variables, and χ^2-tests and Fisher's exact tests, when appropriate, for categorical variables. In order to evaluate the association between LASr and the PEP, Cox proportional hazards regression was performed. First, we studied the unadjusted association between LASr (model 1) as well as conventional diastolic echocardiographic parameters and the incidence of the PEP (Supplementary material). Next, we used multivariable models to adjust for age, sex, HF duration, and NT-proBNP (18, 19) (model 2), additionally for left atrial volume index (LAVI) and the E/e' ratio (model 3), and additionally for global longitudinal strain (GLS) and EF (model 4). We report our findings as hazard ratios (HRs) and the corresponding 95% confidence intervals (CI). The HRs are given per one unit increase in LASr. In addition, we dichotomized LASr to study the effect of a normal versus abnormal LASr. For this purpose, we used a cut-off value of 18% (7). All analyses were performed with R Statistical Software using package survival (18). All tests were two-tailed, and P values < .05 were considered statistically significant.

Figure 2: Overview of the study population. LAP, left atrial pressure.



RESULTS

Baseline characteristics

From October 2011 to January 2018, 175 patients were included in an echocardiography substudy at the Erasmus MC (15) of whom 2 patients had insufficient image quality, leaving a total of 173 patients for the substudy. Twenty patients had an atrial pacemaker and were therefore excluded from the analysis. In the remaining 153 patients, 86 patients (56%) were assigned to the LAPe group. In the remaining 67 patients (44%), E/A ratio was not available and these patients formed the LAPne group. In the LAPne group, in 31 patients had moderate/severe mitral regurgitation, 20 patients had AF during the echocardiogram, and 16 patients had unmeasurable A wave due to fusion of the E and the A wave. None of the patients had mitral stenosis. Figure 2 provides an overview of the included patients and their categorization. Baseline and echocardiographic characteristics of the study population are shown in Tables 1 and 2. In the total study population, 76% patients were male, mean age was 58.0 years ± 11.1 years, and mean LVEF was 28.6% ± 10.2%. Most patients were often in NYHA class I or II (26% and 56% respectively), and ischemic heart disease was the most common HF etiology (44%).

When comparing the LAPe and LAPne groups, a similar proportion was male, and the groups did not significantly differ in age. However, patients in the LAPne group did have a higher NT-proBNP (233 pmol/L (122 pmol/L – 419 pmol/L) vs. 73 pmol/L (27 pmol/L – 188 pmol/L), p<0.001), and were in a higher NYHA class (NYHA III 29% vs. 10%, p=0.009). Also, mean systolic blood pressure was lower (104 mmHg ± 17.9 mmHg vs. 110 mmHg ± 17.1 mmHg, p=0.039) and the proportion of prior occurrence of atrial fibrillation was higher (43% vs. 20%, p=0.003). As for medication use, in the LAPe group there was a higher proportion of ACE-inhibitor use (77% vs. 60%, p=0.037) (Table 1).

Conventional echocardiographic parameters

The echocardiographic characteristics are shown in Table 2. Patients in the LAPne group had a lower mean LVEF (25% ± 9.9% vs. 31% ± 9.9%, p=0.001) and a lower mean GLS (-7.8% ± -3.6% vs. -9.8% ± -3.5%, p<0.001). As for diastolic parameters, patients in the LAPne group had a higher median E/e' ratio (18.7 (12.5 - 21.6) vs. 14.1 (7.8 - 19.2), p=0.007), and a larger mean LAVI (46.2 mL/m^2 ± 19.6 mL/m^2 vs. 35.3 mL/m^2 ± 14.6 mL/m^2, p<0.001).

Left atrial strain parameters

In the total study population, mean LASr was 20.6% ± 11.3%, mean LAScd 10.9% ± 5.8%, and median LASct 8.8% (3.2%-14.0%). Patients in the LAPne group had

significantly lower LASr, LAScd, and LASct compared to patients in the LAPe group (resp. 15.8% ± 9.7% vs. 23.8% ± 11.4%, p<0.001; 8.6% ± 4.8% vs. 12.5% ± 6.0%, p<0.001; 4.2% (2.1% - 11.0%) vs. 11.0% (4.9-15.8%), p<0.001).

Clinical endpoints

Median follow-up time was 2.5 years (25^{th}-75^{th} percentile: 2.3-2.6 years). In total, 50 patients reached the PEP, out of whom 37 patients were re-hospitalized for acute or worsened HF, six patients received a heart transplantation, four patients received an LVAD implantation, and three patients died due to cardiovascular causes. The number of PEPs in the LAPe group was 19 (22%). In the LAPne group, a total of 31 patients (46%) reached the PEP(Figure 3). The LAPne group had a significantly lower event-free survival time compared to the LAPe group (p<0.001). The event-free survival probability at the median follow-up time was 78% for the LAPe group and 51% for the LAPne group.

Table 1: Clinical characteristics of the study population.

Male, *n (%)*	116 (76)	67 (78)	49 (73)	0.6
Age, *years*	58.0 ± 11.1	56.9 ± 11.4	59.3 ± 10.7	0.2
BMI, *kg/m²*	27.6 ± 4.6	27.8 ± 4.9	27.2 ± 4.3	0.5
Mean heart rate, *bpm*	68 ± 13	68 ± 15.4	67 ± 10.5	1
Systolic BP, *mmHg*	107 ± 18.1	110 ± 17.1	104 ± 17.9	0.039
Diastolic BP, *mmHg*	67 ± 9.6	69 ± 9.9	66 ± 9.6	0.2
NYHA class, n (%)				0.009
NYHA class I	40 (26)	25 (29)	15 (22)	
NYHA class II	84 (56)	52 (61)	32 (49)	
NYHA class III	27 (18)	8 (10)	19 (29)	
NT-proBNP, *pmol/L*	140 (39 - 262)	73 (27 – 188)	233 (122 – 419)	<0.001
HF etiology				
Ischemic heart disease, *n (%)*	67 (44)	38 (44)	29 (43)	1
Hypertension, *n (%)*	2 (1)	2 (2)	0 (0)	0.6
Cardiomyopathy, *n (%)*	58 (38)	32 (37)	26 (39)	1
Valvular heart disease, *n (%)*	4 (3)	2 (2)	2 (3)	1
Unknown, *n (%)*	9 (6)	6 (7)	3 (5)	0.8
Medical history				
Myocardial infarction, *n (%)*	65 (43)	38 (44)	27 (40)	0.8
PCI, *n (%)*	58 (38)	33 (38)	25 (37)	1
CABG, *n (%)*	15 (10)	8 (9)	7 (10)	1
Atrial fibrillation, *n (%)*	46 (30)	17 (20)	29 (43)	0.003
Diabetes Mellitus, *n (%)*	37 (24)	20 (23)	17 (25)	0.9
Chronic renal failure, *n (%)*	61 (40)	30 (35)	31 (46)	0.2
COPD, *n (%)*	22 (14)	11 (13)	11 (16)	0.7
Medication				
Beta blockers, *n (%)*	145 (95)	81 (94)	64 (96)	1
ACE inhibitors, *n (%)*	106 (70)	66 (77)	40 (60)	0.037
ARB, *n (%)*	43 (28)	21 (24)	22 (33)	0.3
Loop diuretics, *n (%)*	143 (94)	77 (90)	66 (99)	0.059
Aldosteron antagonists, *n (%)*	110 (72)	58 (67)	52 (78)	0.2

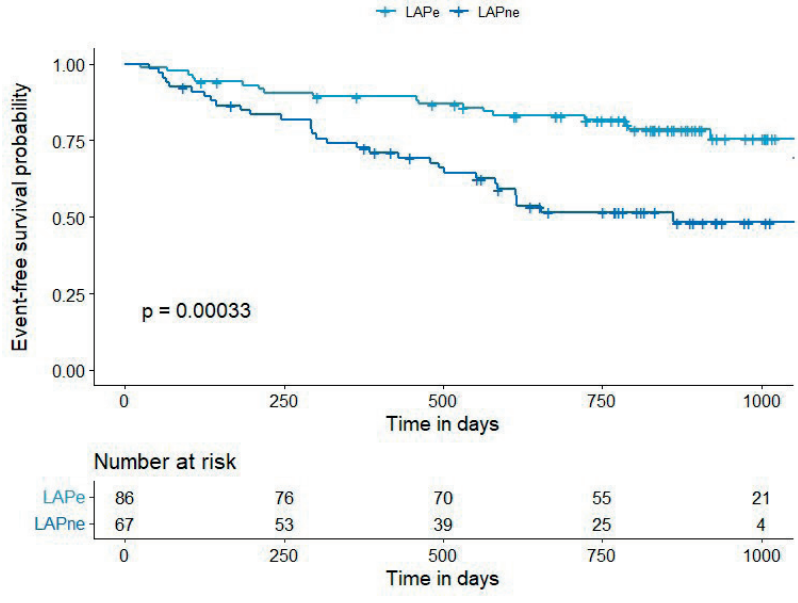
LAPe, left atrial pressure grading available; LAPne, left atrial pressure grading not available; BMI, body mass index; bpm, beats per minute; BP, blood pressure; NYHA, new york heart association; HF, heart failure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker. Normally distributed data are presented as mean ± sd, non-normally distributed data are presented as median (25^{th} – 75^{th} percentile). P-values represent overall comparison between LAPe and LAPne.

Table 2: Echocardiographic characteristics of the study population.

	Total (n=153)	LAPe (n=86)	LAPne (n=67)	p-value
LASr, *%*	20.6 ± 11.3	23.8 ± 11.4	15.8 ± 9.7	<0.001
LAScd, *%*	10.9 ± 5.8	12.5 ± 6.0	8.6 ± 4.8	<0.001
LASct, *%*	8.8 (3.2 - 14.0)	11.0 (4.9 - 15.8)	4.2 (2.1 - 11.0)	<0.001
LV GLS, *%*	-8.9 ± 3.7	-9.8 ± 3.5	-7.8 ± 3.6	<0.001
LVEF, *%*	28.6 ± 10.2	31.1 ± 9.9	25.1 ± 9.9	0.001
E/e' ratio	15.7 (9.5 - 19.7)	14.1 (7.8 - 19.2)	18.7 (12.5 - 21.6)	0.007
TR velocity, *m/s*	2.5 (2.1 - 2.8)	2.4 (2.0 - 2.7)	2.7 (2.4 - 3.2)	0.01
LAVI, mL/m^2	39.6 ± 17.4	35.3 ± 14.6	46.2 ± 19.6	<0.001
Mitral regurgitation, *n (%)*				<0.001
None	48 (31)	40 (47)	8 (14)	
Mild	61 (40)	46 (54)	15 (27)	
Moderate	25 (16)	0 (0)	25 (45)	
Severe	8 (5)	0 (0)	8 (14)	

LAPe, left atrial pressure estimation available; LAPne, left atrial pressure estimation not available; LASr, left atrial reservoir strain; LAScd, left atrial conduit strain; LASct, left atrial contractile strain; LV GLS, left ventricular global longitudinal strain; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation; LAVI, left atrial volume indexed. Normally distributed data are presented as mean ± sd, non-normally distributed data are presented as median (25^{th} – 75^{th} percentile). P-values represent overall comparison between LAPe and LAPne.

Figure 3: Kaplan – Meier survival curves displaying the survival probabilities for both groups (Logrank test). LAPe, left atrial pressure estimation available; LAPne, left atrial pressure estimation not available.



Association of LASr with the composite endpoint

In LAPne patients, LASr was significantly associated with reduced incidence of the PEP (unadjusted HR was 0.84 per 1% absolute increase; 95% CI 0.78 - 0.90; p-value <0.001). After adjustment for age, sex, HF duration and NT-proBNP (model 2) the association remained statistically significant, as well as after additional adjustment for conventional diastolic (model 3) and systolic (model 4) echocardiographic parameters (Table 3). Abnormal LA strain was associated with a 5-fold increase in risk of reaching the PEP (HR 5.2, 95% CI, 1.4 - 18.9). An overview of the associations of LASr with the PEP is presented in Table 3.

Supplementary Table 1 shows the univariable associations of echocardiographic parameters with the PEP in the LAPne group. LASr showed the strongest association (HR 0.84, 95% CI, 0.78 – 0.90).

Table 3: Associations of left atrial reservoir strain with the primary endpoint.

	LAPe (n=86)		LAPne (n=67)	
	HR (95%CI)	**p-value**	**HR (95%CI)**	**p-value**
Model 1	0.90 (0.85 - 0.97)	<0.001	0.84 (0.78 - 0.90)	<0.001
Model 2	0.85 (0.77 - 0.93)	<0.001	0.91 (0.85 - 0.97)	0.01
Model 3	0.87 (0.79 - 0.96)	<0.001	0.91 (0.84 - 0.98)	0.02
Model 4	0.88 (0.79 - 0.97)	0.03	0.88 (0.79 - 0.98)	0.03

Model 1: univariable analysis

Model 2: corrected for age, sex, HF duration, and NT-proBNP

Model 3: corrected for age, sex, HF duration, NT-proBNP, left atrial volume index, E/e' ratio (log transformed)

Model 4: corrected for age, sex, HF duration, NT-proBNP, global longitudinal strain, left ventricular ejection fraction

DISCUSSION

In the present study, we have demonstrated that assessment of LASr has added clinical and prognostic value in the large proportion of HFrEF patients in whom estimation of LAP is not possible with conventional echocardiographic parameters due to unavailable E/A ratio. A decrease in LASr was associated with an increased risk of the PEP, even after adjusting for potential confounders. Therefore, in HFrEF patients with limited prognostic information due to missing E/A ratio and consequently unavailable LAP estimation, LASr can provide important information on prognosis, which may help monitor HF severity and guide medical treatment.

Assessing LAP in HFrEF

Although the treatment of HF has improved over the last decade, the mortality due to HF remains high and repeated hospitalizations for HF occur frequently (19). Categorization of HF is mainly based on systolic function, and less on diastolic determinants (20). However diastolic determinants are essential in HFrEF, as they can provide information on LAP that can be used to guide prognosis (2, 3, 21, 22). Cardiac catheterization remains the gold standard for assessing LV pressure and subsequent LAP. Nevertheless, cardiac catheterization is less attractive for routine assessment of LAP because its invasive nature carries a non-negligible risk and adds significant costs (23). Using echocardiography, a rough estimation of LAP can be made along with grading of diastolic function, using a combination of several echocardiographic parameters (4). A limitation of this approach is that a large number of HFrEF patients may remain uncategorized because of the absence of a reliable E/A ratio. A common comorbidity in HFrEF that limits measurements of the E/A ratio, is AF during the echocardiogram. The prevalence of concomitant AF in HFrEF patients is high, and assessment of diastolic determinants in AF is limited by the variability in cycle length, the absence of organized atrial activity and subsequent missing A wave, as well as the frequent occurrence of LA enlargement regardless of filling pressures (4, 24). The co-existence of mitral valve disease also restrains the usability of echocardiographic assessment of LAP. Moderate to severe mitral regurgitation (MR) or stenosis (MS) leads to an elevation in peak E velocity and LA enlargement and thus the evaluation of LAP is hindered (4, 25). LASr is not affected by these conditions and could therefore provide a clinical solution to estimate LAP in these HFrEF patients (10-12). Our study is the first to investigate the potential role of LASr in HFrEF patients in whom echocardiographic assessment of LAP is not possible due to lack of one or more of the required echocardiographic parameters. The importance of measuring LAS in patients with HFrEF is illustrated by the observation that LAS is associated with invasively measured LV filling pressure (7, 10). In a study consisting of 322 patients with various cardiovascular diseases, LASr and LASct predicted LV filling pressure better than conventional echocardiographic markers (7). In the same study, LASr <18% supported elevated LV filling pressure in patients with reduced HFrEF. In our cohort, LASr was 15.8% in the LAPne group, while in the LAPe group this was 23.8%. Since LASr has been shown to correlate with LAP (5, 7, 10), this observation indicates that in the LAPne group LAP was more increased, a finding in-line with several other clinical and echocardiographic parameters that pointed at a more severe disease stage in these patients. We

Role of conventional diastolic parameters and LASr in clinical outcomes of HFrEF patients

Only a few studies have previously investigated the role of parameters of LV diastolic function on outcomes in HFrEF patients (26, 27). In a study consisting of 2018 HFrEF and HF patients with mid-range EF (HFmrEF), severe diastolic dysfunction was associated with increased all-cause mortality (27). A study by Benfari et al. investigated the mortality associated with diastolic echocardiographic measures in patients with HFrEF, and found that elevated E/e' was associated with substantially reduced short-term survival (26). However, these studies did not include LASr in their analysis, and focused specifically on patients in whom estimation of LAP was possible with conventional echocardiographic parameters.

Studies that have focused on the prognostic value of LASr in HFrEF, have demonstrated that measurement of LASr is predictive of clinical outcomes in these patients (9, 28, 29). The strength of our study is that it is the first to investigate the potential role of LASr specifically in patients in whom grading of LAP with the current guideline algorithm is not possible due to conditions such as AF and MR. We demonstrated that in this LAPne group, a decrease in LASr was associated with an increased risk of PEP, even after adjusting for multiple confounders. Moreover, an abnormal LASr <18% was associated with a 5-fold increased risk in reaching the primary endpoint in the LAPne group. In addition, we showed that LASr was significantly associated with the primary outcome, while conventional echocardiographic parameters, such E/e' and LAVI, were not. We also found that LASr was associated with the PEP in the LAPe group, which suggests that LASr also carries prognostic information in this group. However additional prognostic information is essential for the LAPne group, while sufficient prognostic information may already be available in the LAPe group by using the ASE/EACVI algorithm.

Study limitations

Treating physicians were not blinded to the echocardiograms and conventional parameters derived from the echocardiograms. Therefore, echocardiographic characteristics may have influenced treatment. However, LAS values were not available to the treating physicians because they were measured after completion of follow-up. Second, the sample size of this study was modest and so was the number of endpoints, which limits statistical power. Also, consequently, the number of variables that could be entered into the Cox models was limited, and therefore residual confounding may be present. However, we adjusted for the most important confounders, we also adjusted for the duration of HF at baseline, to control for possible lead time or length time bias. Furthermore, the patients in this echo sub-study were relatively young and there was a relatively high proportion of HF patients in NYHA classes I and II. This may be because older patients with worse condition were less likely to participate in the echo

sub-study of Bio-SHiFT. The results may therefore not be extrapolated to patients in more advanced stages of HF. Finally, inherent to the design of this study, patients in the LAPne group were in worse condition than those in the LAPe group. Nonetheless, there is currently no estimate for LAP in this group of patients, further stressing the importance for an appropriate parameter for LAP estimation in this group and underscoring the relevance of our study.

Conclusion

In patients with HFrEF in whom LAP cannot be estimated using the conventional algorithm due to an unavailable E/A ratio, LASr is able to provide clinical and prognostic information that may help monitor HF severity and guide medical treatment.

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SUPPLEMENTARY CONTENT

Supplementary Table 1: Univariable associations of conventional echo parameters with the primary endpoint.

	LAPe (n=86)		LAPne (n=67)	
	HR (95%CI)	**p-value**	**HR (95%CI)**	**p-value**
LASr, *%*	0.91 (0.85 - 0.96)	0.002	0.84 (0.78 - 0.90)	<0.001
E/e' ratio	0.91 (0.87 - 0.95)	<0.001	0.97 (0.94 - 1.01)	0.1
LAVI, ml/m^2	0.94 (0.92 - 0.97)	<0.001	1.01 (0.99 - 1.03)	0.2
TR velocity, *m/s*	0.41 (0.19 - 0.90)	0.03	0.70 (0.36 - 1.38)	0.3
LV GLS, *%*	0.59 (0.47 - 0.73)	<0.001	0.86 (0.76 - 0.97)	0.01
LVEF, *%*	0.89 (0.84 - 0.94)	<0.001	0.97 (0.93 - 1.02)	0.2

LAPe, left atrial pressure estimation available; LAPne, left atrial pressure estimation unavailable; LASr, left atrial reservoir strain; LAVI, left atrial volume indexed; TR, tricuspid regurgitation; LV GLS, left ventricular global longitudinal strain; LVEF, left ventricular ejection fraction.

3

Chapter 3

Prognostic value of longitudinal repeated measurements of left atrial strain in patients with heart failure with reduced ejection fraction

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Submitted

ABSTRACT

Background

We investigated whether repeatedly measured left atrial reservoir strain (LASr) in heart failure with reduced ejection fraction (HFrEF) patients provides incremental prognostic value over a single baseline LASr value, and whether temporal patterns of LASr provide incremental prognostic value over temporal patterns of other echocardiographic markers and NT-proBNP.

Methods

In this prospective observational study, 153 patients underwent 6-monthly echocardiography. During a median follow-up of 2.5 years, a median of 3(25th-75th percentile:2-4) echocardiograms were obtained per patient. Hazard ratios (HRs) were calculated for LASr from Cox models (baseline) and joint models (repeated measurements). The primary endpoint (PEP) comprised HF hospitalization, left ventricular assist device, heart transplantation, and cardiovascular death.

Results

Mean age was 58±11 years, 76% were men, 82% were in NYHA class I/II, mean LASr was 20.9%±11.3%, and mean LVEF was 29%±10%. PEP was reached by 50 patients. Baseline and repeated measurements of LASr (HR per SD change (95% CI): 0.20(0.10-0.41) and (0.13(0.10-0.29), respectively) were both significantly associated with the PEP, independent of both baseline and repeated measurements of other echo-parameters and NT-proBNP. Although LASr was persistently lower over time in patients with PEP, temporal trajectories did not diverge in patients with versus without the PEP as the PEP approached.

Conclusion

LASr was associated with adverse events in HFrEF patients, independent of baseline and repeated other echo-parameters and NT-proBNP. Temporal trajectories of LASr showed decreased but stable values in patients with the PEP, and do not provide incremental prognostic value for clinical practice compared to single measurements of LASr.

INTRODUCTION

Most of the contemporary risk scores for heart failure with reduced ejection fraction (HFrEF) focus on systolic echocardiographic determinants, while the influence of diastolic determinants on prognosis has been studied less extensively [1]. Categorization of HFrEF patients based on diastolic determinants is mainly used to non-invasively estimate left atrial pressure (LAP), which can be useful to guide medical treatment and provide information on prognosis [2,3]. However, the algorithm currently in use for estimating LAP carries an important limitation; it requires multiple parameters that are often affected by cardiac rhythm and/or mitral valve disease, with the consequence that a substantial part of HFrEF patients remain uncategorized [4,5].

Recently, there has been an emerging interest in the use of left atrial reservoir strain (LASr) as a measure of left atrial (LA) function and as a derived measure for LAP in HFrEF patients [4,6-8]. Studies have demonstrated that LASr is decreased in HFrEF patients and that an abnormal LASr is associated with increased LAP [8]. Additionally, LASr is not affected by atrial fibrillation and mitral valve disease [4,9,10]. Only a few studies have demonstrated that LASr may have prognostic value in HFrEF [11-13]. These studies only examined single ('baseline') measurements of LASr, which merely represent a snapshot of a patient's condition, and related these measurements to clinical endpoints occurring over several years thereafter. The prognostic value of repeatedly measured LASr has never been examined before, and has never been compared to that of other echocardiographic parameters in chronic HFrEF patients.

Therefore, we investigated whether repeatedly measured LASr provides incremental prognostic value over a single baseline LASr value in stable chronic HFrEF patients. In addition, we hypothesized that temporal patterns of LASr are associated with adverse clinical events, and that temporal patterns of LASr may provide incremental prognostic value to temporal patterns of other prognostic markers.

METHODS

Study Design

The design of the Serial Biomarker Measurements and New Echocardiographic Techniques in Chronic Heart Failure Patients Result in Tailored Prediction of Prognosis (Bio-SHiFT) study has previously been described [14]. Bio-SHiFT is a prospective, observational study of stable patients with chronic heart failure (CHF), conducted at the Erasmus MC, Rotterdam, and Northwest clinics, Alkmaar, The Netherlands. Recruitment was conducted during the patient's regular outpatient visits while in

clinically stable condition (i.e., they had not been hospitalized for HF in the 3 months prior to inclusion). The main inclusion criteria were diagnosis of HF according to the then prevailing guidelines of the European Society of Cardiology 3 or more months before inclusion and age ≥18 years [15]. Patients with an atrial pacemaker were excluded from the current analysis. Patients were observed for a maximum of 30 months, with follow-up visits scheduled every 3 months (a window of 1 month was allowed). A brief medical examination and blood samples were taken at each visit. All patients' usual outpatient follow-up with their treating physician continued throughout the study, independently of the study visits. This study was approved by the medical ethics committees, conducted in accordance with the Declaration of Helsinki, and registered in ClinicalTrials.gov (NCT01851538). Informed consent was obtained from all patients. In total, 398 patients were included in Bio-SHiFT. The repeated echo study that we currently report was performed at the Erasmus MC only, and consisted of 175 HFrEF patients with echocardiographic assessment every 6 months during follow-up [16]. Two patients had insufficient image quality, and therefore the remaining 173 patients were included in the current study.

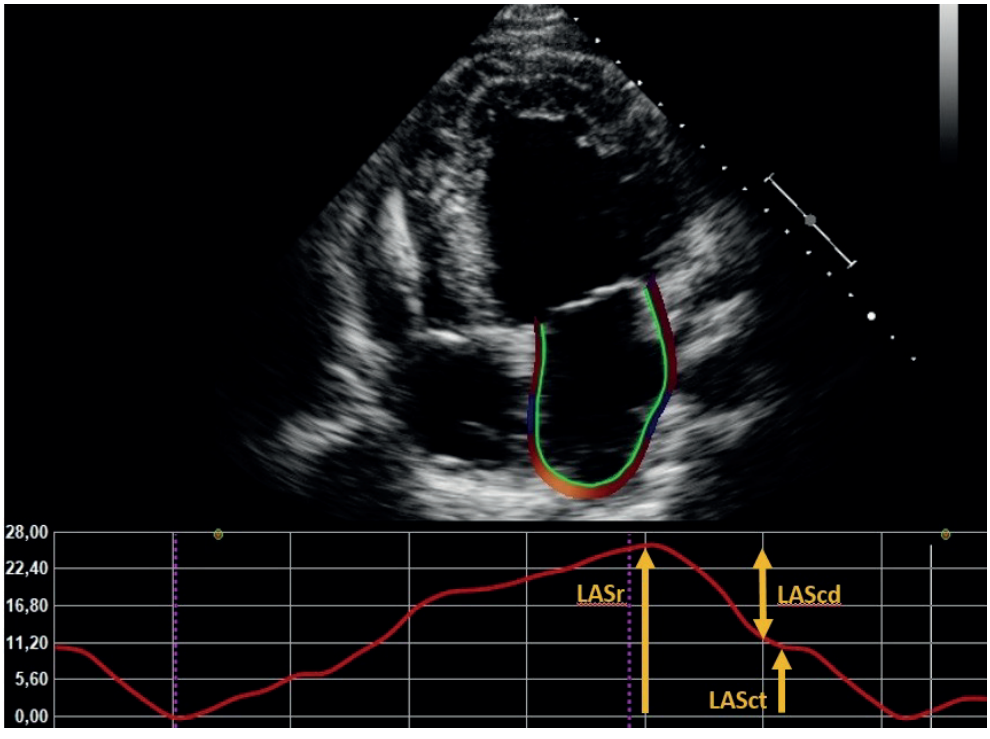
Echocardiography Measurements and Evaluation

Two-dimensional gray-scale harmonic images were obtained in the left lateral decubitus position. Standard apical four-, three-, and two-chamber views were recorded. A commercially available ultrasound system was used (iE33, Philips, Best, The Netherlands), equipped with a broadband (1-5 MHz) S5-1 transducer (frequency transmitted 1.7 MHz, received 3.4 MHz). Images were stored in the echo core lab of Erasmus MC (13). Using specialized software (2D Cardiac Performance Analysis version 4.5; TomTec Imaging Systems, Unterschleissheim, Germany), LVEF, tricuspid regurgitation (TR) velocity, and the function of the mitral valves were assessed. The diastolic parameters were evaluated using Philips Excellera version R4.1 (Philips Medical Systems, The Netherlands) or TomTec Imaging Systems. To assess diastolic function, indexed left atrial volume (LAVI), the peak early filling velocity (E)/late filling velocity (A) ratio (E/A ratio) and the ratio of the E and early diastolic mitral annular velocity (e') (E/e´ratio) were calculated [5]. For the e', we used the mean of the lateral and medial e' when available; however, if only one of the two was available, this value was used. All echocardiographic measurements were performed blinded to biomarker and clinical event data [14].

Strain parameters were measured with speckle tracking echocardiography (also using TomTec Imaging Systems) by a single operator. The apical 4-chamber view was used preferably for the analysis. LA endocardial borders were automatically traced using end-diastole as reference. Fine-tuning was performed manually if the tracking was suboptimal. If the quality of the 4-chamber view was of poor, the 2-chamber view

was used. Patients with insufficient image-quality to perform LA strain analysis or patients with an atrial pacemaker were excluded. LA strain was assessed according to the three phases of the LA cycle: LA reservoir strain (LASr) which starts at the end of ventricular diastole (mitral valve closure) and continues until mitral valve opening, LA conduit strain (LAScd) which occurs from the time of mitral valve opening through diastasis until the onset of LA contraction, and LA contractile strain (LASct) which occurs from the onset of LA contraction until the end of ventricular diastole (mitral valve closure) [17]. All strain values are reported as absolute values for improved readability and data interpretation. An example of a LA strain curve is provided in Figure 1. Global longitudinal strain (GLS) was assessed in 18 LV segments on the standard apical four-, three-, and two-chamber views, where the endocardial border was traced manually at end-systole. The mean GLS from the three apical views was considered the LV GLS.

Figure 1 Example of LA strain measurement. LASr, left atrial reservoir strain; LAScd, left atrial conduit strain; LASct, left atrial contractile strain.



Patients underwent echocardiographic assessment at baseline and every 6 months during follow-up. Due to logistic reasons, 58% of the first available echoes were performed at baseline (follow-up time zero), 15% of the first available echoes were performed during the first follow-up visit (target follow-up time 3 months), 18% during the second follow-up visit (target 6 months), and the remaining 9% thereafter (Supplementary figure 1). Missing echocardiograms occurred due to logistic circumstances (e.g., the unavailability of an ultrasound technician during the study visit). Intra-observer reproducibility was assessed by re-measuring GLS in 20 echocardiograms and calculating the intraclass correlation coefficient. The intraclass correlation coefficient was 0.93 for LASr.

Clinical Study Endpoints

The primary endpoint (PEP) comprised the composite of hospitalization for the management of acute or worsened HF, left ventricular assist device (LVAD) implantation, cardiac transplantation, and cardiovascular death, whichever occurred first in time. All events were adjudicated by a clinical event committee blinded to the echocardiographic assessments and biomarker measurements, after reviewing corresponding hospital records and discharge letters [16].

Statistical Analyses

Distributions of continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed continuous variables are presented as mean ± standard deviation (SD), and non-normally distributed variables as median and 25^{th}-75^{th} percentile. Categorical variables are presented as numbers and percentages. Differences in baseline characteristics between patients who experienced the PEP and those who did not were tested using the t-test and Mann-Whitney test, according to variable distributions, for continuous variables. For categorical variables, χ^2-tests and Fisher's exact tests were used.

First, we examined single measurements of LASr and other echo parameters of interest in relation to the PEP using Cox models (only the first available echo was used), and we adjusted for age, sex, duration of HF and N-terminal pro b-type natriuretic peptide (NT-proBNP). In addition, we calculated the Pearson correlation coefficients for the echo variables of interest to assess the correlation of LASr with other common echocardiographic parameters and NT-proBNP.

Then, we assessed the value of repeated strain measurements for prediction of the PEP, as well as their incremental value to sole, baseline measurements. For this purpose, joint models for longitudinal and survival data were used [18]. In these joint models, a linear mixed effects (longitudinal) model provided estimates of the individual tem-

poral trajectories of the echo parameters, and in combination with a relative risk model, the association of the trajectories with the risk of the PEP was estimated. The associations between the temporal evolutions of LASr and the PEP, resulting from the relative risk model, were first only adjusted for age, sex and duration of HF (model 1). Thereafter, baseline NT-proBNP (model 2), GLS and LVEF (model 3) were added consecutively. Furthermore, we adjusted for the diastolic parameters (E/A ratio, E/e ratio, LAVI) in model 4. Lastly, all variables with significant differences between those with and without the PEP were added (model 5). To investigate the incremental value of repeatedly measured LASr to repeatedly measured echo parameters and NT-proBNP, multivariable joint models were used.

To enable comparisons of effect sizes of different variables, we calculated the Z-scores for all investigated echo parameters, and NT-proBNP. NT-proBNP and E/e' were first log transformed to achieve a normal distribution. Hazard ratios were obtained from both the Cox as the joint models. Thus, the results of the regression analyses of the Cox and joint models can be directly compared and are presented as HRs, which represent risk per Z-score unit, along with the corresponding 95% confidence interval (CI).

To investigate whether repeatedly measured LASr carries incremental predictive value to repeatedly measured echo parameters and NT-proBNP, we presented our results solely as adjusted HRs and did not combine them with C-statistics. Pepe et al. have demonstrated that testing for improvement in prediction performance is redundant if a variable has already been shown to be an independent risk factor, and that standard testing procedures for C-indices are very conservative and thus insensitive to improvements in prediction performance [19].

Missing values in LASr and the other echo parameters (besides the A wave) were due to poor image quality and were therefore considered missing completely at random. Accordingly, we chose to perform a complete case analysis. Missing values for the A wave were due to atrial fibrillation during the echo or due to mitral valve replacement or clipping. In these patients the A wave can never be measured, thus imputation of missing values is inappropriate. Therefore, we again chose for a complete case analysis here.

All analyses were performed with R Statistical Software using packages nlme [20] and JMbayes [18]. All tests were two-tailed, and P values < .05 were considered statistically significant.

RESULTS

Baseline characteristics

Between October 2011 to January 2018, 173 patients were included in the Bio-SHiFT echo study. Twenty patients had an atrial pacemaker and were therefore excluded from the current analysis. In the remaining 153 patients, 76% of the patients were male, mean age was 58 ± 11 years, and mean BMI was 27.5 kg/m^2 ± 4.6 kg/m^2. A total of 27% were in NYHA class I, and 55% were in NYHA class II. Ischemic heart disease was the most prevalent HF etiology (44%). The median time between diagnosis of HF and inclusion in the study was 6.5 (6.1-7.3) years.

During a median follow-up time of 2.5 (2.3-2.6) years, a total of 50 patients (33%) reached the PEP, out of whom 37 were re-hospitalized for acute or worsened HF, 6 patients received a heart-transplantation, 4 patients received an LVAD, and 3 patients died from a cardiovascular cause. Patients who reached the composite PEP had lower systolic and diastolic blood pressure (resp. 101 ± 17 mmHg vs. 110 ± 18 mmHg, p=0.008; 69 ± 10 mmHg vs. 64 ± 8 mmHg, p=0.009), had a higher NT-proBNP (303, 180 – 540 pmol/L vs. 71 26 – 166 pmol/L, p<0.001), and comorbidities such as atrial fibrillation and renal failure were more prevalent in this group (resp. 46% vs. 21%, p=0.009; 58% vs. 30%, p=0.003). An overview of the baseline characteristics of the study population is provided in Table 1.

Echocardiographic characteristics

During a median follow-time of 2.5 years, 410 echocardiograms were performed with a median of 3 (2–4) per patients. Patients had up to 8 consecutive echocardiographic

Table 1 Baseline patient characteristics of the total study population

	Overall	No PEP	PEP	p-value
N	153	103	50	
Demographics				
Male, *n (%)*	116 (76)	79 (76)	37 (73)	0.9
Age, *years*	57.7 ± 11.2	57 ± 11.3	60 (11.1)	0.2
Clinical characteristics				
Duration of HF, *years*	6.5 (6.1 - 7.3)	6.2 (5.9 - 6.9)	8.1 (7.0 - 9.3)	0.01
Body mass index, *kg/m²*	27.5 ± 4.7	27.8 ± 4.9	26.9 ± 4.2)	0.3
Mean heart rate, *bpm*	67 ± 13	67.2 ± 15.3	67.1 ± 8.0	1
Systolic blood pressure, *mmHg*	107 ± 18	110 ± 18	101 ± 17	0.008
Diastolic blood pressure, *mmHg*	67 ± 9	68 ± 9	64 ± 8	0.009
NYHA class, *n (%)*				0.06
NYHA class I	40 (27)	34 (33)	6 (10)	
NYHA class II	84 (55)	54 (53)	30 (60)	
NYHA class III	27 (18)	14 (14)	13 (26)	
NT-proBNP, *pmol/L*	141 (35 – 279)	71 (26 – 166)	303 (180 – 540)	<0.001
Features of HF, *n (%)*				
Ischemic heart disease	67 (44)	42 (41)	25 (50)	0.3
Hypertension	2 (1)	2 (2)	0 (0)	0.8
Cardiomyopathy	58 (38)	38 (37)	20 (40)	0.9
Secondary to valvular heart disease	4 (3)	2 (2)	1 (2)	1
Other etiology of HF	13 (8)	11 (11)	2 (1)	1
Unknown	9 (6)	8 (8)	1 (2)	0.3
Medical history, *n (%)*				
Myocardial Infarction	65 (43)	40 (39)	24 (48)	0.3
PCI	58 (38)	39 (38)	18 (38)	1
CABG	15 (10)	10 (10)	5 (10)	1
Atrial fibrillation	46 (30)	22 (21)	22 (46)	0.009
Diabetes Mellitus	37 (24)	23 (22)	13 (27)	0.8
Chronic renal failure	61 (40)	31 (30)	28 (58)	0.003
COPD	22 (14)	14 (14)	8 (1)	0.8
Medication use, *n (%)*				
Beta blockers	145 (95)	99 (96)	46 (92)	0.5
ACE inhibitors	106 (69)	75 (73)	33 (66)	0.4
Angiotensin II receptor blockers	43 (28)	27 (26)	14 (28)	0.9
Loop diuretics	143 (94)	93 (90)	50(100)	0.04
Aldosteron antagonists	110 (71)	69 (67)	41 (82)	0.06

PEP, primary endpoint; HF, heart failure; NYHA, new york heart association; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; ACE, angiotensine converting enzyme. Normally distributed data are presented as mean ± sd, non-normally distributed data are presented as median (25th – 75th percentile). P-values represent overall comparison between PEP and no PEP.

Table 2 Echocardiographic characteristics of first available echo in relation to the composite endpoint

	Overall	No PEP	PEP	p-value	Missing values
Left atrial strain					
LASr, %	20.9 ± 11.3	25.3 ± 10.5	11.7 ± 6.6	<0.001	13(3%)
LAScd, %	10.0 (7.2 - 15.5)	12.5 (8.8 - 17.4)	7.9 (3.75 - 9.22)	<0.001	13(3%)
LASct, %	9.3 (3.2 - 14.4)	12.0 (7.1 - 16.0)	2.8 (1.8 - 5.7)	<0.001	13(3%)
Systolic parameters					
LV GLS, %	-9.0 ± 3.7	-10.2 ± 3.6	-6.4 ± 2.4	<0.001	10(2%)
LVEF, %	29.1 ± 10.4	31.6 ± 9.8	23.2 ± 9.3	<0.001	10(2%)
Diastolic parameters					
LA volume index, *mL/m²*	39.1 ± 17.3	34.3 ± 14.3	49.3 ± 18.7	<0.001	15(4%)
E/A ratio	1.4 ± 1.0	1.2 ± 0.9	2.1 ± 1.1	<0.001	44(11%)
E/e' ratio	15.6[9.5 - 19.7]	12.8[7.9 - 19.2]	22.0[12.9 - 24.0]	<0.001	18(4%)
TR velocity, *m/s*	2.5 (2.1 - 2.9)	2.4 (2.1 - 2.7)	2.7 (2.2 - 3.1)	0.117	50(12%)
Mitral valve regurgitation, *n (%)*				0.001	11(3%)
None	50 (33)	44 (45)	6 (14)		
Mild	60 (39)	35 (36)	25 (58)		
Moderate	23 (15)	16 (17)	7 (16)		
Severe	7 (5)	2 (2)	5 (12)		

PEP, primary endpoint; LASr, left atrial reservoir strain; LAScd, left atrial conduit strain; LASct, left atrial contractile strain; LV GLS, left ventricular global longitudinal strain; LVEF, left ventricular ejection fraction; E/A ratio, the ratio of the peak early left ventricular filling velocity over the late filling velocity; E/e' ratio, E to early diastolic mitral annular tissue velocity; TR, tricuspid regurgitation. Normally distributed data are presented as mean ± sd, non-normally distributed data are presented as median (25th – 75th percentile). P-values represent overall comparison between PEP and no PEP.

evaluations performed, with 65% having at least 3 evaluations. An overview of the characteristics of the first available echocardiogram for each patient is presented in Table 2.

Mean left ventricular ejection fraction (LVEF) in the total study population was 29.1% ± 10.4%, and mean LASr was 20.9% ± 11.3%. Patients who reached the PEP had significantly worse LASr compared to patients who remained PEP-free (LASr 11.7% ± 6.6% vs. 25.3% ± 10.5%, p<0.001;. LVEF and GLS were also lower in patients who reached the PEP (resp. 23.2% ± 9.3% vs. 31.6% ± 9.8, p<0.001; -6.4% ± 2.4% vs. -10.2% ± 3.6%, p<0.001). LAVI, E/A ratio and E/e' were significantly higher in the PEP group (resp. 49.3 mL/m^2 ± 18.7 mL/m^2 vs. 34.3 mL/m^2 ± 14.3 mL/m^2, p<0.001; 2.13 ± 1.09 vs. 1.19 ± 0.92, p<0.001; 22.0 (12.9 - 24.0) vs. 12.8 (7.9 - 19.2), p<0.001).

There was an inverse correlation between LASr and GLS (r=-0.74, p<0.001), E/A ratio (r=-0.52, p<0.001), E/e' ratio (r=-0.5, p<0.001), LAVI (r=-0.55, p<0.001), and NT-proBNP (r=-0.61, p<0.001) (Figure 2).

Figure 2: Scatterplots for LASr and variables of interst. LA, left atrial. R= correlation coefficient. Regression lines are provided for the variables of interest. Each dot represents a single patient.

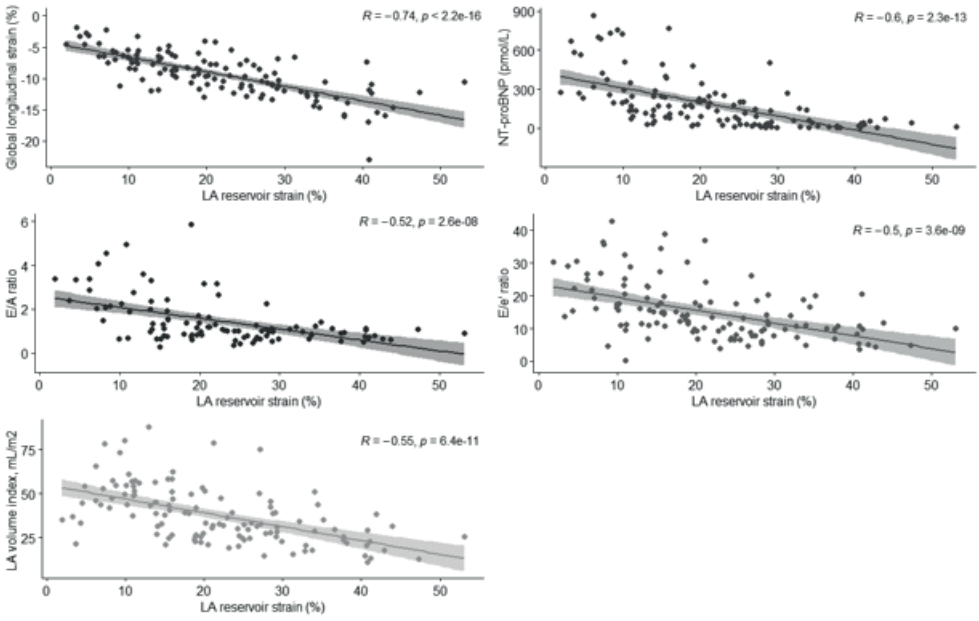
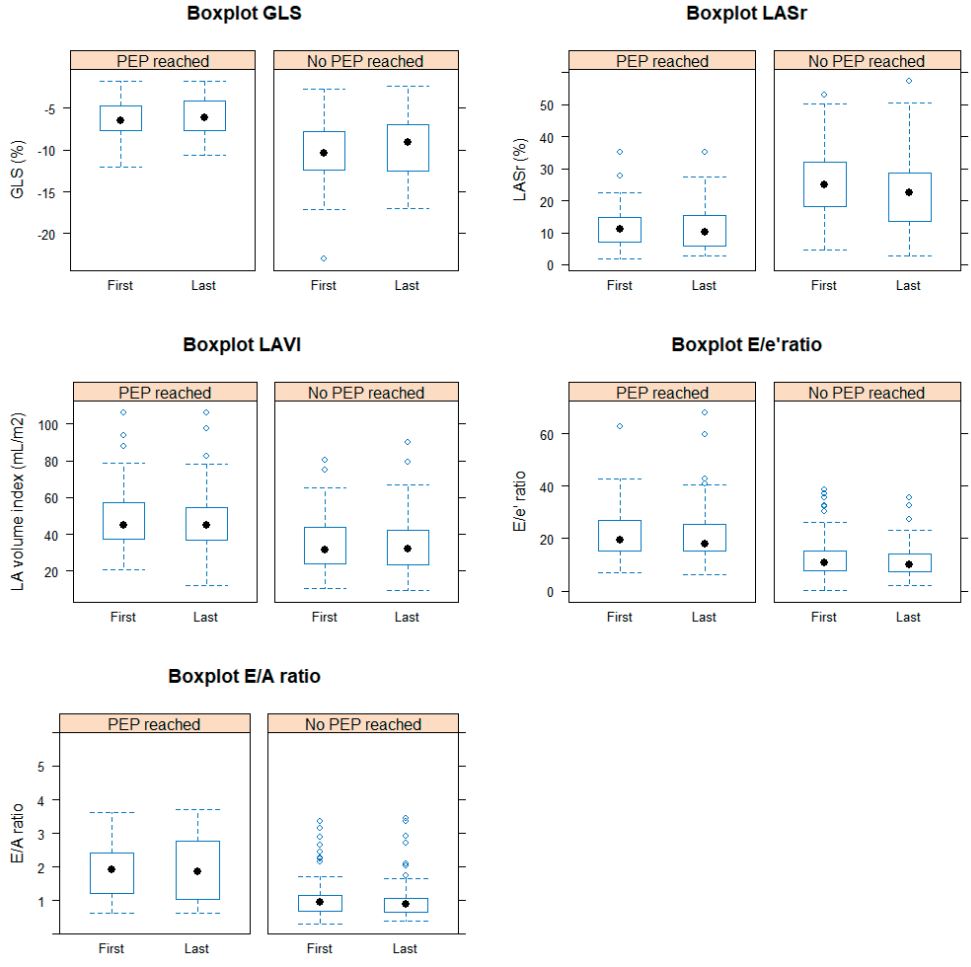


Figure 3 Medians of first and last available values of variables of interest, according to endpoint status. PE, primary endpoint; LA, left atrial; GLS, global longitudinal strain. The boxplots show the average LA reservoir strain, GLS, LAVI, E/e' ratio, and E/A ratio at the first and last available measurements. The average values of patients with the endpoint is shown in the left panel, whereas the average values in patients without the endpoint is shown in the right panel.



Baseline and repeatedly measured LASr in relation to the composite endpoint

When entered into separate models, baseline measurements of GLS, E/e' ratio, and LASr were significantly associated with the PEP, independent of age, sex, duration of HF, and NT-proBNP, with the largest effect per one unit increase for LASr (resp. HR 0.46, 95% CI, 0.28 – 0.72; 0.56 95% CI, 0.37 – 0.84; HR 0.20, 95% CI, 0.10 – 0.41) (Table 3). Longitudinally measured LASr was significantly associated with the PEP in all the fitted joint models (Table 3). In the first model, adjusted for age, sex, and duration of HF, the HR was 0.19 (95% 0.11 – 0.32). The association remained significant when NT-proBNP was added (HR 0.14, 95% CI 0.06 – 0.27). In model 3, GLS and LVEF were added as well (HR 0.21, 95% CI 0.12 – 0.33), and the association also remained significant in model 4, in which we adjusted for diastolic parameters (HR 0.13, 95% CI 0.10 – 0.29). The association between LASr and the PEP persisted in model 5 after adjusting for comorbidities (HR 0.19, 95% CI, 0.09 -0.25).

The results of the multivariable joint models, wherein repeatedly measured LASr, as well as the other repeatedly measured echocardiographic variables were entered, are shown in Table 3. The HR for repeatedly measured LASr remained significant when correcting for repeatedly measured GLS, LAVI, E/A ratio, E/e' ratio, and NT-proBNP (resp. HR 0.27, 95% CI 0.10 – 0.92; HR 0.47, 95% CI 0.25 – 0.79; HR 0.45, 95% CI 0.24 – 0.44; HR 0.56, 95% CI 0.31 – 0.95; HR 0.42, 95% CI 0.17 – 0.95).

Temporal evolution of LASr

In the total population, there was a decrease in LASr over time as the PEP or censoring approached (beta: -1.72, 95% CI -2.46 - -0.98) per LASr (%) change per year). Figure 3 and Figure 4 show the temporal evolution of patients who experienced the PEP and those who did not. Although, as described above, repeatedly measured LASr was associated with the occurrence of the PEP, and average LASr was lower in patients who experienced the PEP compared to those who did not, this difference remained stable over time. LASr did not diverge further between patients with vs. without the PEP, as the PEP or censoring approached.

DISCUSSION

We demonstrated that during a median follow-up of 2.5 years, repeated measurements of LASr were significantly associated with adverse cardiovascular events in HFrEF patients, independent of repeatedly measured GLS, LAVI, E/A ratio, E/e' ratio, and NT-proBNP. LASr was a stronger predictor than GLS, LAVI, E/A ratio, and E/e' ratio.

Although repeated measurements of LASr were associated with the primary outcome, the difference in LASr remained stable over time, and temporal LASr evolutions did not further diverge in patients with events versus those without events. Therefore, for clinical purposes, repeated measurements of LASr do not seem to provide additional value over single measurements over a time frame of 2.5 years. To our knowledge this is the first study that investigated the prognostic value of repeated LASr measurements in HFrEF.

Table 3 Associations of baseline and repeatedly measured LASr with the primary endpoint.

	HR (95%CI)	P value
Baseline measurements*		
LASr	0.20 (0.10 - 0.41)	<0.001
GLS	0.46 (0.28- 0.76)	0.003
LAVI	0.78 (0.58 - 1.05)	0.1
E/A ratio	0.66 (0.48- 0.90)	0.01
E/e' ratio	0.56 (0.37 - 0.84)	0.01
Repeated measurements of LASr		
Model 1	0.19 (0.11 - 0.32)	<0.001
Model 2	0.14 (0.06 - 0.27)	<0.001
Model 3	0.21 (0.12 - 0.33)	<0.001
Model 4	0.13 (0.10 - 0.29)	<0.001
Model 5	0.19 (0.09 - 0.25)	<0.001
Repeated measurements of LASr and GLS, LAVI or E/e' ratio †		
LASr and GLS		
LASr	0.27 (0.10 - 0.92)	0.038
GLS	0.53 (0.16 - 1.72)	0.3
LASr and LAVI		
LASr	0.47 (0.25 - 0.79)	0.004
LAVI	0.59 (0.46 - 1.45)	0.6
LASr and E/A ratio		
LASr	0.45 (0.24 - 0.44)	0.006
E/A ratio	0.93 (0.62 - 1.19)	0.8
LASr and E/e' ratio		
LASr	0.56 (0.31 - 0.95)	0.03
E/e' ratio	0.90 (0.62 - 1.43)	0.4
LASr and NT-proBNP		
LASr	0.42 (0.17 - 0.95)	0.04
NT-proBNP	0.47 (0.20 - 1.11)	0.4

*Corrected for age, sex, duration of HF, baseline NT-proBNP

†Multivariable Joint Models: Corrected for age, sex, duration of HF, atrial fibrillation, renal failure, systolic and diastolic blood pressure

Model 1: corrected for age, sex, duration of HF

Model 2: corrected for age, sex, duration of HF, NT-proBNP

Model 3: corrected for age, sex, duration of HF, NT-proBNP, GLS, LVEF

Model 4: corrected for age, sex, duration of HF, NT-proBNP, E/A ratio, E/e ratio, LAVI

Model 5: corrected for age, sex, duration of HF, atrial fibrillation, renal failure, systolic and diastolic blood pressure LASr, left atrial reservoir strain; GLS, global longitudinal strain; LAVI, left atrial volume indexed

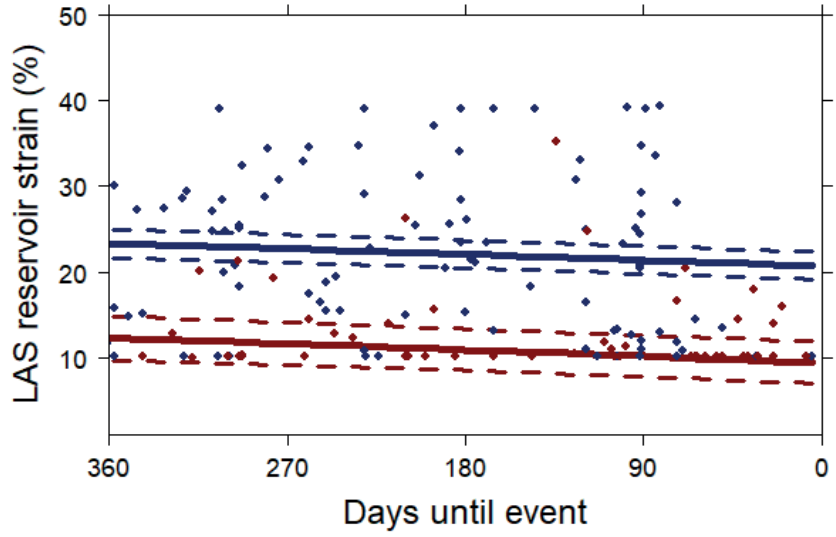
Echocardiographic determinants of survival in patients with HFrEF

Although significant improvements in HF therapy have been made in the last two decades, the mortality and morbidity due to HF remain substantial [21]. Numerous multivariable risk models have been proposed to identify patients with a poor prognosis, but the usefulness of these models in clinical practice has been limited [21]. Most of these risk scores incorporate parameters of systolic function. Yet, the assessment of diastolic function may be equally important, or even more important, as diastolic parameters provide a non-invasive estimation of LAP [5]. However, in a substantial part of HFrEF patients, guideline-based estimation of LAP is not possible, as crucial parameters are often affected by mitral regurgitation (MR) and/or atrial fibrillation (AF) [4,5]. In addition, some of the conventional parameters that are used for diastolic function in HFrEF have several limitations. For instance, LAVI, which is widely used as an indicator of LAP, does not always provide an accurate estimation of LAP, as LAVI can be increased in the presence of normal filling pressures (e.g. healthy athletes). A study by Benfari et. al. demonstrated that E/e' ratio outperformed other diastolic parameters as a prognosticator in HFrEF patients, but LA strain was not included in their study [22]. The use of LASr as a non-invasive estimate for LAP has recently gained more interest, as LASr has been shown to be correlated with invasively measured LV filling pressures and LASr showed better prognostic performance than LAVI and E/e' ratio [8,11-13]. Our results are in line with these previous studies, as we show that LASr is a strong predictor of adverse cardiovascular events; and a stronger predictor than other echocardiographic parameters, such as E/e'. In contrast, in our study LAVI was not associated with an increased risk of the PEP, which is similar to a study by Modin et al. [23]. This could in part be explained by the fact that LASr is a more sensitive parameter than a volumetric parameter such as LAVI, and that an impairment in LA function is detected earlier than changes in LA volume [24].

Our study confirms and extends previous evidence on the added prognostic value of LASr in HFrEF. A few previous studies have investigated the prognostic value of single measurements of LASr in HFrEF patients [11-13]. In a study consisting of 405 patients with a LVEF <40%, LASr strongly predicted adverse outcomes, independent of other clinical and echocardiographic predictors of prognosis [11]. A study by Malagoli et al. showed similar results; patients with lower LASr showed worse event-free survival than those with higher LASr [12]. In acute HF, LASr was also shown to be a significant prognosticator [13]. These studies only examined baseline measurements of LASr. Our study is the first to investigate the prognostic value of repeatedly measured LASr, and its added value over a single baseline LASr assessment, and over repeated measurements of other echocardiographic variables. We showed that repeated measurements of LASr were associated with the PEP, and the association persisted after consecutively adding repeated measurements of GLS, LAVI, E/A ratio, E/e' ratio, and NT-pro-BNP.

However, the difference in LASr between patients with events versus those without events remained stable over time, and temporal LASr evolutions did not further diverge as the PEP or censoring approached.

Figure 4 Mean temporal patterns of LA reservoir strain until occurrence of the primary endpoint or censoring. Continuous lines represent mean temporal patterns for patients with the PEP (red) and patients who remained PEP-free (blue), as extracted from the joint model. Time-point zero represents the occurrence of an event in the PEP patients and censoring in patients who remained PEP-free. Dotted lines represent 95% confidence intervals. Each dot represents a single measurement.



Results in the context of LA physiology and function in HFrEF

The LA plays a pivotal role in the filling of the LV and contributes to the cardiac output as the LA interacts with the LV and the pulmonary veins. The LA cycle is composed of three phases, which reflect the three main LA functions, reservoir, conduit, and contractile function [17]. A recent meta-analysis found a normal value of >39% for LASr in healthy individuals [25,26]. Mean LASr in our population of HFrEF patients was 20.9%. Therefore, profound LA dysfunction exists in our cohort of HFrEF patients, which is in line with previous literature [25].

In the cardiac cycle, LASr and GLS are tightly coupled, as maximal expansion of the LA takes place during LV systole. This is supported by the observation that LASr and GLS are significantly correlated in HFrEF [8]. Our results confirm this, as a more

advanced impairment of GLS was significantly correlated with an impairment in LASr. Previously, we have demonstrated that baseline and repeated measurements of GLS provide incremental prognostic value over LVEF [27]. In the current investigation, we observed that LASr outperforms GLS as a prognostic marker in chronic HFrEF patients. This finding is in line with previous studies that have shown that LASr was superior in predicting outcomes compared to GLS [28]. A potential explanation is that LASr might be affected by atrial inflammation and atrial fibrosis, which restricts atrial stretching, independent of LV longitudinal contraction and a subsequent impairment of GLS. Our study is the first to report that repeated measurements of LASr were associated with clinical outcomes, independent of repeated measurements of GLS. Our results extend and add to previous studies and underline that LASr has more value as a prognostic marker in clinical practice than GLS, as well as other known prognostic markers, in stable patients with chronic HFrEF.

Study limitations

Several limitations of our study should be noted. First, treating physicians were not blinded to the conventional parameters assessed by echocardiography and therefore echocardiographic characteristics might have influenced treatment. However, LASr values were not available for the treating physicians as these were assessed retrospectively. Secondly, the sample size of the study was modest and so was the number of endpoints, which limits statistical power. To prevent overfitting, we fitted multiple multivariable models containing different confounders, instead of one model containing all covariates. In addition, we adjusted for the duration of HF at baseline, to control for possible lead-time or length time bias. Furthermore, we could not assess the potential effect of sodium glucose transporter 2 (SGLT2) inhibitors on LASr, as they were not yet recommended by the guidelines at the time of this study. Lastly, our cohort consisted of patients who were relatively young and in NYHA class I and II. Our results can therefore not be extrapolated to older patients in a more advanced stage of HF.

CONCLUSION

Repeatedly measured LASr was significantly associated with adverse cardiovascular events in patients with HFrEF. However, although the temporal trajectories of LASr were different in patients who reached the PEP compared to those who did not, they did not diverge as the PEP or censoring approached, and therefore repeatedly measuring LASr does not seem to provide additional incremental prognostic information over a single baseline measurement over a median follow-up time of 2.5 years. A single measurement of LASr showed stronger prognostic value than conventional

echocardiographic parameters. Therefore, LASr should be considered for routine use in clinical practice in patients with HFrEF, for prognostication and potentially for guiding treatment.

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SUPPLEMENTARY CONTENT

Supplementary figure 1 Study design: first available and follow-up echocardiograms

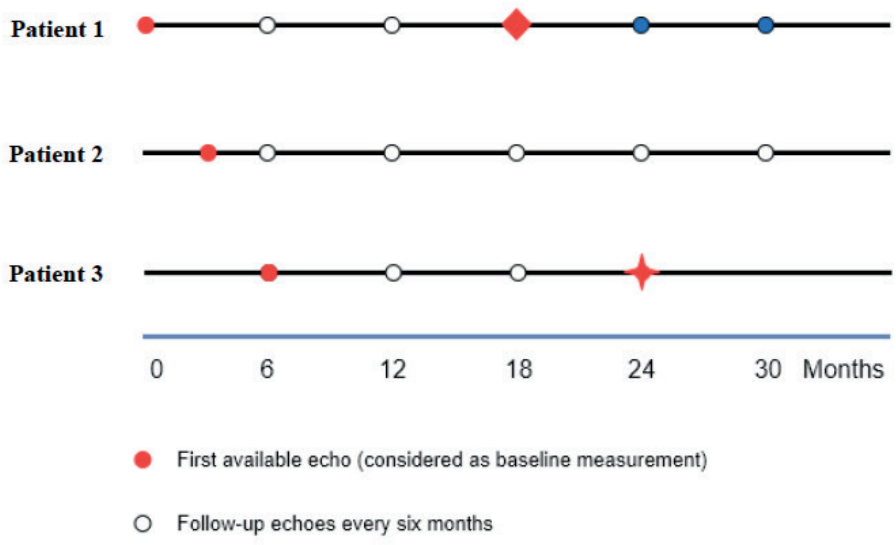

Figure provides 3 example patients to illustrate which echocardiograms were the first available echocardiograms, considered as 'baseline' in the analysis (red circles), and at which time-points follow-up echocardiograms were scheduled (white circles). 55% of the first available echocardiograms were performed at baseline (follow-up time zero), 12.8% were performed during the first study follow-up visit (target follow-up time 3 months) and 18% were performed during the second follow-up visit (target 6 months). Subsequently, echoes were performed every six months.

4

Chapter 4

Decreased left atrial function in obesity patients without known cardiac disease

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ABSTRACT

Purpose

Obesity is a risk factor for heart failure with preserved ejection fraction (HFpEF). We hypothesized that assessment of left atrial (LA) strain may be useful to reveal precursors of HFpEF in obesity patients.

Methods

Echocardiograms of obesity patients without known cardiovascular disease who underwent bariatric surgery, and echocardiograms of age- and gender matched controls were analyzed. The echocardiogram was repeated one year after bariatric surgery. LA reservoir strain (LASr), LA conduit strain (LAScd), and LA contractile strain (LASct) were measured.

Results

77 obesity patients were compared with 46 non-obese controls. Obesity patients showed a significantly decreased LA function compared with non-obese individuals (LASr 32.2% ± 8.8% vs. 39.6% ± 10.8%, p<0.001; LAScd 20.1% ± 7.5% vs. 24.9% ± 8.3%, p=0.001; LASct 12.1% ± 3.6% vs. 14.5% ± 5.5%, p=0.005). There was no difference in prevalence of diastolic dysfunction between the obesity group and controls (9.1% vs. 2.2%, p=0.139). One year after bariatric surgery, LASr improved (32.1% ± 8.9% vs. 34.2% ± 8.7%, p=0.048). In the multivariable linear regression analysis, BMI was associated with LASr, LAScd, and LASct (β = -0.34, CI -0.54 - -0.13; β = -0.22, CI -0.38 - -0.06; β = -0.10, CI -0.20 - -0.004).

Conclusion

Obesity patients without known cardiovascular disease have impairment in all phases of LA function. LA dysfunction in obesity may be an early sign of cardiac disease and may be a predictor for developing HFpEF. LASr improved one year after bariatric surgery, indicating potential reversibility of LA function in obesity.

INTRODUCTION

Obesity affects around 650 million adults worldwide and the prevalence is increasing (1). Obesity is a major risk factor for heart failure with preserved ejection fraction (HFpEF) (2, 3). A one-unit increase in body mass index (BMI) is associated with a 34% increased risk of future HFpEF, and more than 80% of HFpEF patients are either overweight or obese (4, 5). In the recent years, left atrial (LA) dysfunction has been increasingly recognized as an important parameter in HFpEF (6, 7). Obesity causes LA dysfunction due to systemic inflammation, expansion of epicardial adipose tissue, and chronic volume overload, all factors that can favor the development of diastolic dysfunction and HFpEF (8-10). Traditionally, the LA is evaluated by using LA volume indexed (LAVI) to body surface area (BSA), which is widely used and recommended in guidelines as a criterion for diastolic function and HFpEF (11). However, LAVI in obesity is unsuitable as indexing to BSA overcorrects LA volume and thus does not reflect a proper evaluation of the LA (12). Recent studies have shown that LA strain provides superior information over the use of LAVI and left ventricular global longitudinal strain (LV GLS), and has better correlation with invasive filling pressures than LAVI (13-17). Furthermore, LA strain independently predicts incident HFpEF and appears to be altered before traditional parameters of HFpEF can be detected (18-21). Considering the limited value of LAVI in obesity, we hypothesized that LA strain may be especially useful in these patients. Additionally, symptoms such as dyspnea and edema, findings at physical examination, and brain natriuretic peptides (BNP) might be less specific and/or sensitive for heart failure in patients with obesity (10, 22), another argument stressing the need for improvement of objective parameters of HFpEF in obesity. The aim of our study was to 1) determine whether LA function measured by LA strain in in obesity patients without known cardiovascular disease differs from non-obese individuals and 2) to determine whether LA function improves one year after bariatric surgery in obesity patients.

METHODS

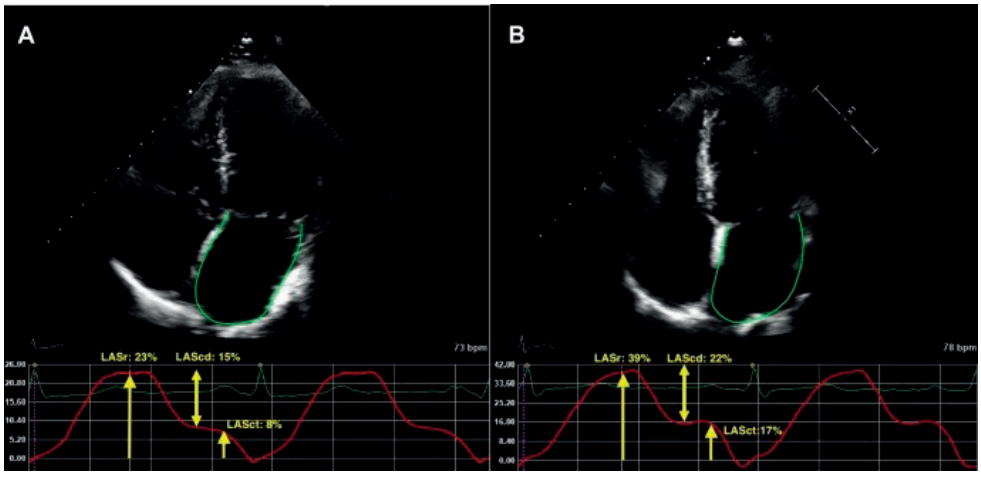
For this study, the CARDIOBESE (The CARdiac Dysfunction In Obesity – Early Signs Evaluation) database was used. The protocol of the CARDIOBESE study has been described before (23). Briefly, the CARDIOBESE study recruited a cohort of 100 patients with obesity aged 35 to 65 years, with a body mass index (BMI) ≥ 35 kg/m^2 who were referred for bariatric surgery at The Franciscus Gasthuis & Vlietland and Maasstad hospital, both in Rotterdam, the Netherlands. Patients with a suspicion of or known cardiovascular disease were excluded. Fifty age- and gender-matched non-obese (BMI ≤ 30 kg/m^2) controls without a suspicion of or known cardiovascular

disease were enrolled. The study protocol was approved by the ethics committee and participants provided written informed consent.

Echocardiography and strain analyses

Conventional and speckle tracking echocardiography was performed on all participants at baseline. In the obesity group echocardiography was repeated one year after bariatric surgery. Two-dimensional greyscale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system (EPIQ 7, Philips, the Netherlands), equipped with a broadband (1–5 MHz) X5-1 transducer. All acquisitions and measurements were performed according to the current guidelines (24, 25). LA strain was measured with speckle tracking and analyzed offline with dedicated software (TomTec-Arena, integrated in Sectra IDS7). LA strain measurements were performed by a single observer (D.K.) who was blinded to clinical data. The apical 4-chamber view was used preferably for the analysis. LA endocardial borders were automatically traced using end-diastole as reference. When tracking was suboptimal, fine-tuning was performed manually. If the 4-chamber view was of poor image quality, the 2-chamber view was used. Patients with images of insufficient quality to perform LA strain analysis were excluded. LA function was described according to the three phases of the LA cycle: LA reservoir strain (LASr) which starts at the end of ventricular diastole (mitral valve closure) and continues until mitral valve opening, LA conduit strain (LAScd) which occurs from the time of mitral valve opening through diastasis until the onset of LA contraction, and LA contractile strain (LASct) which occurs from the onset of LA contraction until the end of ventricular diastole (mitral valve closure). LASr, LAScd, and LASct were computed in all participants. All strain values are reported as absolute values for improved readability and data interpretation (26). An example of LAS measurement in a patient without obesity and with obesity is shown in Figure 1.

Figure 1: A: Example of LA strain curve in a patient with obesity. B: Example of LA strain curve in a control subject obesity. LASr: Left Atrial Reservoir Strain, LAScd: Left Atrial Conduit Strain, LASct: Left Atrial Contractile Strain.



Statistical analysis

Normally distributed data are presented as means and standard deviation, skewed data as medians and inter-quartile range, and categorical variables as percentages and frequencies. Continuous variables were compared between obesity patients and controls using the independent student T-test in case of normally distributed data and the Mann-Whitney U test for non-normally distributed data. For the comparison before and one year after bariatric surgery, the dependent T-test was used for normally distributed data and the Wilcoxon signed rank for non-normally distributed data. Categorical data was analyzed with the Chi-square test and the McNemar's test for respectively normally and non-normally distributed data. To determine whether BMI was associated with LASr, LAScd, and LASct, independent of potential confounders, univariable and multivariable linear regression analysis were performed. Variables were included in the model at a statistical level p-value of <0.05 and performed using the enter method in linear regression. In the multivariable model we included age, gender, diabetes mellitus, hypertension, obstructive sleep apnea syndrome (OSAS), because of the potential clinical relation with the outcome variable. For the linear regression we report coefficients, 95% confidence intervals (CI) and p-values. Analyses were performed using SPSS Statistical Package version 28.0.

RESULTS

A total of 100 patients with obesity and 50 controls were included in the CARDIOBESE study. Out of these, 77 patients with obesity and 46 controls had sufficient image quality to quantify LA strain and were thus included in the analysis. Of the patients with obesity, 72 underwent bariatric surgery, of whom 59 patients were included in the analysis. The remaining patients were excluded because of insufficient image quality to measure LA strain. Clinical characteristics of the study population are shown in Table 1.

Comparison between non-obese controls and obese patients

As presented in Table 1, patients with obesity showed several differences compared to non-obese controls. Obesity patients had a higher systolic blood pressure (141.2 mmHg ± 20.5 mmHg vs. 126.7 mmHg ± 10.4 mmHg, p<0.001), and comorbidities, such as diabetes mellitus, hypertension, and OSAS were more frequently present in the obesity group (22.1% vs. 0%, p<0.001; 29.9% vs. 6.5%, p<0.001; 11.7% vs. 2.2%, p=0.028 resp.). Obesity patients more often used Beta-Blockers, RAS-inhibitors, statins and diuretics.

Differences in echocardiographic parameters are shown in Table 2. There was no difference in LAVI between the two groups (26.1 ml/m^2 ± 6.1 ml/m^2 vs. 25.8 ml/m^2 ± 6.7 ml/m^2, p=0.809). As for parameters of left ventricular (LV) diastolic function, obese patients had lower E/A ratio (1.0 ± 0.25 vs. 1.2 ± 0.3, p<0.001) and lower lateral e' velocity (11.0 cm/s ± 3.2 cm/s vs. 13.4 cm/s ± 6.5 cm/s, p=0.007). There was no significant difference in the prevalence of diastolic dysfunction (2.2% vs. 9.1%, p=0.087).

Comparison between obese patients at baseline and one year after bariatric surgery

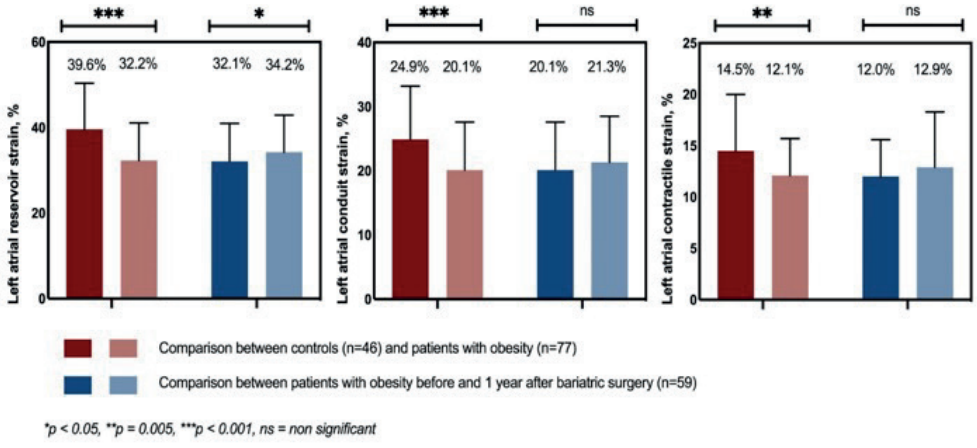
Table 1 shows the differences in clinical characteristics for patients with obesity from baseline to one year after bariatric surgery. Gastric bypass was the most common type of bariatric surgery in this group (54.2%), followed by gastric sleeve (35.6%) and mini bypass surgery (10.2%). There was a significant reduction in BMI (41.2 kg/m^2 (39.5 kg/m^2 – 46.1 kg/m^2) vs. 28.4 kg/m^2 (24.7 kg/m^2 – 31.2 kg/m^2), p<0.001) and improvement of systolic blood pressure one year after bariatric surgery (140.0 mmHg (129.0 mmHg - 157.0 mmHg) vs. 129.5 mmHg (116.5 mmHg - 143.3 mmHg), p=0.004). Furthermore, the rates of diabetes mellitus and OSAS improved significantly (22.0% vs. 8.5%, p=0.008; 10.2% vs. 3.4%, p=0.031). Also, there was less use of RAS-inhibitors and statins after bariatric surgery (22.0% vs. 8.5%, p=0.021; 23.7% vs. 11.9%, p=0.039). As for echocardiographic parameters (Table 2), E/A ratio and lateral e' velocity both showed a significant change (1.0 (0.9 - 1.1) vs. 1.1 (0.9 - 1.2),

p=0.047; 11.0 cm/s ± 3.4 cm/s vs. 12.1 cm/s ± 3.2 cm/s, p=0.003). Remarkably, LAVI increased one year after bariatric surgery (25.1 ml/m^2 ± 6.5 ml/m^2 vs. 28.5 ml/m^2 ± 7.3 ml/m^2, p<0.001). There was no difference in prevalence of diastolic function (10.2% vs. 6.8%, p=0.727).

LA function in obesity

Differences in LA function measured by LA strain are shown in Figure 2. Obesity patients had significantly reduced LA strain in all phases of the LA cycle compared with non-obese controls (LASr 32.2% vs. 39.6%, p<0.001; LAScd 20.1% vs. 24.9%, p<0.001; LASct 12.1% vs. 14.5%. p=0.005).

Figure 2: Left atrial stain in patients with obesity before and after bariatric surgery, and in non-obese controls.



In the obese bariatric surgery group, LASr improved significantly one year after bariatric surgery (32.1% vs. 34.2%, p=0.048) (Figure 2). LAScd and LASct showed a tendency towards improvement after bariatric surgery, but did not reach statistical significance. Figure 3 shows the changes in LASr, LAScd, and LASct at individual level for the obese bariatric surgery group.

Table 1: Clinical characteristics of the study population

	Comparison between controls and obesity patients			Comparison between patients with obesity before and one year after bariatric surgery		
	Controls (N = 46)	**Obesity patients (N = 77)**	**P-value**	**Baseline (N = 59)**	**One-year after bariatric surgery (N = 59)**	**P-value**
Age, years	49.5 ± 9.4	48.1 ± 7.1	0.379	48.1 ± 7.2	-	-
Female, n (%)	33 (71.7)	59 (76.6)	0.550	46 (78.0)	-	-
BMI, kg/m²	25.1 (22.0-27.5)	42.5 (41.6-43.4)	<0.001	41.2 (39.5 – 46.1)	28.4 (24.7 – 31.2)	<0.001
Systolic BP, mmHg	126.7 ± 10.4	141.2 ± 20.5	<0.001	140.0 (129.0 – 157.0)	129.5 (116.5 – 143.3)	0.004
Diastolic BP, mmHg	76.0 ± 8.6	79.6 ± 10.9	0.067	79.0 (73.0 – 88.0)	80.0 (74.0 – 86.0)	0.248
Diabetes mellitus, n (%)	0	17 (22.1)	<0.001	13 (22.0)	5 (8.5)	0.008
Hypertension, n (%)	3 (6.5)	23 (29.9)	<0.001	18 (30.5)	9 (15.3)	0.064
Hypercholesterolaemia, n (%)	5 (10.9)	16 (20.8)	0.134	12 (20.3)	6 (10.2)	0.146
OSAS, n (%)	1 (2.2)	9 (11.7)	0.028	6 (10.2)	2 (3.4)	0.031
Beta-blockers, n (%)	0	6 (7.8)	0.013	4 (6.8)	3 (5.1)	1.000
RAS-inhibitor, n (%)	2 (4.3)	18 (23.4)	0.001	13 (22.0)	5 (8.5)	0.021
Statins, n (%)	3 (6.5)	16 (20.8)	0.018	14 (23.7)	7 (11.9)	0.039
Diuretics, n (%)	1 (2.2)	14 (18.2)	0.002	11 (18.6)	5 (8.5)	0.070

BMI, Body Mass Index; BP, Blood Pressure; OSAS, Obstructive Sleep Apnea Syndrome; RAS, Renin-Angiotensin-System

Normally distributed data are presented as mean ± sd, non-normally distributed data are presented as median (25^{th} interquartile – 75^{th} interquartile), categorical data are presented as n (%).

Table 2: Echocardiographic parameters of the study population

	Comparison between controls and patients with obesity			Comparison between patients with obesity before and one year after bariatric surgery		
	Controls (N = 46)	**Patients with obesity (N = 77)**	**P-value**	**Baseline (N = 59)**	**One-year after bariatric surgery (N = 59)**	**P-value**
LVM, g	146.1 ± 40.9	190.0 ± 69.8	<0.001	184.3 ± 74.4	156.8 ± 66.3	0.004
LVM index, g/m²	74.3 ± 18.9	77.3 ± 24.5	0.470	75.1 ± 25.8	77.8 ± 24.7	0.41
LVEDD, mm	44.9 ± 5.1	49.7 ± 6.0	<0.001	49.3 ± 6.4	48.5 ± 5.4	0.33
E/A ratio	1.2 ± 0.3	1.0 ± 0.3	<0.001	1.0 (0.9 – 1.1)	1.1 (0.9 – 1.2)	0.047
Lateral e' velocity, cm/s	13.4 ± 6.5	11.0 ± 3.2	0.007	11.0 ± 3.4	12.1 ± 3.2	0.003
E/e' ratio	8.6 ± 2.1	9.1 ± 2.3	0.278	9.1 ± 2.4	8.7 ± 2.3	0.27
Deceleration time, s	0.2 ± 0.03	0.18 ± 0.04	0.578	0.19 ± 0.04	0.19 ± 0.05	0.87
TR velocity, cm/s	137.8 ± 69.8	123.7 ± 54.5	0.255	105.9 (89.6 – 140.5)	194.8 (108.3 ± 223.6)	<0.001
LA volume index, mL/m²	26.1 ± 6.1	25.8 ± 6.7	0.809	25.1 ± 6.5	28.5 ± 7.3	0.001
LV ejection fraction, %	65.3 ± 5.5	57.1 ± 6.7	<0.001	55.8 ± 6.5	57.3 ± 7.0	0.21
GLS, %	-20.1 ± 1.5	-16.7 ± 2.8	<0.001	-16.6 ± 2.7	-18.2 ± 3.1	0.003
Diastolic dysfunction, n (%)	1 (2.2)	7 (9.1)	0.139	6 (10.2)	4 (6.8)	0.73

LVM, Left Ventricular Mass; LVEDD, Left Ventricular End-Diastolic diameter; TR, Tricuspid Regurgitation; LA, Left Atrial; LV, Left Ventricular; GLS, Global Longitudinal Strain. Normally distributed data are presented as mean ± sd, non-normally distributed data are presented as median (25th interquartile – 75th interquartile), categorical data are presented as n (%).

Relation between BMI and LA function

Results of the linear regression are presented in Table 3. In simple linear regression, BMI was significantly associated with a LASr, LAScd, and LASct (b: -0.39, 95% CI -0.57; -0.20, p<0.001; b: -0.25, 95% CI -0.40; -0.10, p=0.001; b: -0.12, 95% CI -0.21; -0.04, p=0.005). In a multivariable model, including age, gender, BMI, diabetes mellitus, OSAS, hypertension, beta-blocker use, RAS-inhibitor use, diuretics use, and statin use, an increase in BMI remained significantly associated with a decrease in all three components of LA function (LASr b: -0.34, 95% CI -0.54; -0.13, p=0.002; LAScd b: -0.22, 95% CI -0.38; -0.06, p=0.008; LASct b: -0.10, 95% CI -0.20; -0.004, p=0.041).

Figure 3: LASr, LAScd, and LASct at individual level for the obesity bariatric surgery group at baseline and 1 year follow-u

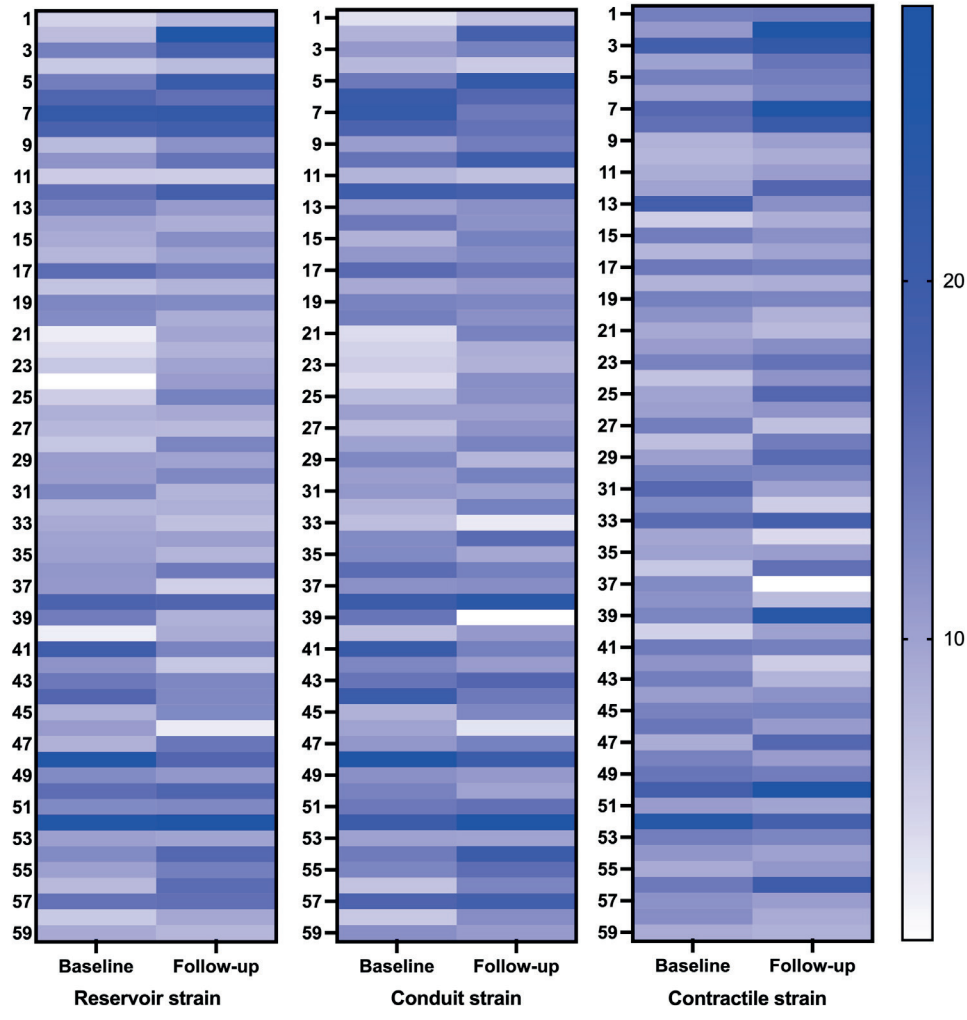


Table 3: Multivariable linear regression: association of body mass index with left atrial reservoir strain

	Univariable[a]			Multivariable[b]		
Dependent variable	**Coefficient**	**95% CI**	**P-value**	**Coefficient**	**95% CI**	**P-value**
LASr	-0.39	-0.57; -0.20	<0.001	-0.34	-0.54; -0.13	0.002
LAScd	-0.25	-0.40; -0.10	0.001	-0.22	-0.38; -0.06	0.008
LASct	-0.12	-0.21; -0.04	0.005	-0.10	-0.20; -0.004	0.041

Dependent variable: left atrial reservoir strain

aUnivariable analysis included BMI

bMultivariable analysis included: age, gender, BMI, diabetes mellitus, OSAS, hypertension, beta-blocker, RAS-inhibitor, diuretics, statin. CI, confidence interval; BMI, Body Mass Index; OSAS, Obstructive Sleep Apnea Syndrome; RAS, Renin-Angiotensin-System

DISCUSSION

In the present study we have demonstrated that obesity patients without known cardiovascular disease have significantly decreased LA function in all three LA functional components compared to non-obese controls. There was no difference in prevalence of diastolic dysfunction as assessed by the current guidelines, suggesting that LA dysfunction occurs before diastolic dysfunction may be recognized by conventional parameters in obesity patients. An increase in BMI was significantly associated with a decrease in all three components of LA function, confirming that obesity plays an important role in LA dysfunction. LA dysfunction measured with LA strain could be an important parameter of diastolic dysfunction and predictor of HFpEF in obesity. In addition, LASr improved one year after bariatric surgery, reflecting positive effects of weight reduction and associated metabolic improvements.

Identifying diastolic dysfunction and HFpEF in obesity

Obese individuals without known cardiovascular disease often have signs of subclinical cardiac dysfunction (27, 28) and are at greater risk for developing HFpEF (2, 3, 29). Obesity causes hemodynamic changes, inflammation, and expansion of epicardial adipose tissue that lead to LA myopathy and LA dysfunction which can form a substrate for HFpEF (8, 30, 31). LA dysfunction measured by strain could be an early marker of subclinical dysfunction and predictor for HFpEF in patients with obesity, but current guidelines do not recommend the use of LA strain in diagnosing HFpEF (11). In obesity, identifying and recognizing HFpEF is particularly challenging, as signs and symptoms of HFpEF are often attributed to the extra weight and/or other comorbidities that are common in obesity (10). Moreover, the use of BNP in obesity as diagnostic and prognostic biomarker is hampered, due to the inverse relationship

between BMI and BNP (22). All of this underlines the potential added value of LA strain in obesity.

The use of LAVI as a criterion for diastolic dysfunction and HFpEF in obesity is unsuitable because of the use of BSA as indexation. BSA is disproportionally driven by an increase in fat mass and the use of BSA leads to an overcorrection in obesity (12). The results of our study are consistent with this notion as is reflected by the observation that LAVI paradoxically increased after bariatric surgery. Furthermore, our results demonstrate that LA impairment is apparent in obesity and that this subclinical cardiac dysfunction would have remained largely unidentified with assessment of diastolic function according to the current guidelines, as is shown by the comparable proportion of obese and non-obese individuals with diastolic dysfunction. This observation emphasizes that LA strain could have beneficial diagnostic and prognostic value in obesity. In addition to the observation that patients with obesity have impairment in LA function, we also demonstrated that an increase in BMI was significantly associated with a decrease in all three components of LA function, after adjusting for confounders. However, it should be noted that various factors, such as hypertension, diabetes, and use of cardio-protective medication that ameliorate systemic inflammation, can also potentially influence LA function (32-35). Thus, it cannot be stated that BMI is the sole explanation for impairment in LA function. Nonetheless, after adjusting for these confounders in our study, LA strain remained significantly associated with BMI, which supports the notion that obesity is related to LA dysfunction.

LA function in obesity, comparison with other studies

In our analyses, we observed that LASr, LAScd and LASct were significantly reduced in patients with obesity compared to a non-obese control group. Few prior studies have assessed LA function in obesity with speckle tracking echocardiography (36-38). Findings comparable to our results were reported in a sample consisting of young adolescents with obesity (38). A study that compared LA function in diabetic patients with and without obesity, found a decreased LASr and LASct in patients with obesity with diabetes (37). In a larger sample size, Chirinos et al. found lower LASr and LAScd in patients with obesity, but a slightly higher LASct in the obesity group compared to normal weight subjects (36). A comparison between their study and ours shows that our population had a higher BMI (42.5 kg/m^2 vs. 32.7 kg/m^2), which could mirror a more progressive systemic inflammation and atrial myopathy that is reflected in reduced LASct. This is however speculative and further studies are needed for a definite explanation.

LA function and the effect of bariatric surgery

LASr significantly increased one year after bariatric surgery. We did not find significant improvement of LAScd and LASct. Strzelcyk et al. observed similar results and reported a significant increase in LASr and LAScd after bariatric surgery, and a decrease in LASct (39). The authors explained the decrease in LASct in their study mechanistically as an improvement of early LV diastolic filling that may lead to a relative decrease of the contribution of atrial contraction (39). Bariatric surgery leads to complex metabolic and hemodynamic changes. Studies have demonstrated that gastric bypass leads to more favorable outcomes when compared to gastric sleeve in terms of improvement of comorbidities, such as diabetes mellitus, and improvement of LV function (40, 41). In our study, the majority of patients underwent gastric bypass surgery, and we observed that LASr improved one year after bariatric surgery. It is uncertain how the type of surgery affects LA function and whether the type of surgery had a role in these improvements in our population. Nonetheless, the observation that LA function can improve after bariatric surgery is promising and might indicate reversibility of LA dysfunction.

Study limitations

The study has some limitations. First of all, LA strain analysis requires good image quality and not all our subjects had analyzable LA images, which may have affected the identified proportion of LA dysfunction. Secondly, our population consisted of patients who underwent bariatric surgery and contained a large number of women, which could have biased the results. However, around 80% of patients who undergo bariatric surgery are female (42), which explains the high percentage of females in our study. Lastly, our study included bariatric patients with a BMI ≥ 35 kg/m^2. It is undetermined whether our results also apply to patients with a BMI ≥ 30 kg/m^2 < 35 kg/m^2.

Conclusion

Obesity patients without known cardiovascular disease have impairment in all phases of LA function. Our findings suggest that LA dysfunction in obesity occurs before diastolic dysfunction, assessed by conventional echocardiographic parameters, may become apparent. Considering the difficult diagnosis of HFpEF in obesity patients due to the relatively limited value of history taking, physical examination, BNP and LAVI measurement, assessment of LA strain could have important added value in identifying these patients at higher risk at an early stage. Finally, our results indicate that LA function can improve after bariatric surgery, indicating potential reversibility of LA function in obesity.

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5

Chapter 5

Improved identification of left atrial enlargement in patients with obesity

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Submitted

ABSTRACT

Background

Accurate standardization of left atrium volume (LAV) in patients with obesity is challenging. The aim of this study was to investigate the value of LA volume indexed to height2 in patients with moderate to severe obesity, and to examine the relation between this parameter and left atrial function.

Methods

Echocardiograms of patients with moderate to severe obesity (body mass index (BMI) ≥ 35 kg/m2) without known cardiac disease were analyzed. LAV was indexed to body surface area (BSA) and height2, and patients were divided into those with or without left atrial enlargement (LAE) based on normalization using either BSA (LAEbsa) or height2 (LAEh2). Using speckle tracking echocardiography, LA reservoir strain (LASr), LA conduit strain (LAScd), and LA contractile strain (LASct) were assessed as a measure of LA function. LA dysfunction was defined as LASct <14%.

Results

A total of 142 patients were included in the analysis of whom 54.2% had LAEh2 and 18.3% LAEBSA. The LAEh2 group had significantly lower LASct (12.2% ± 3.2% vs. 13.6% ± 4.5%, p=0.019) as compared to the patients without LAEh2. Significantly more patients with LA dysfunction would be correctly identified by LAEh2 than by LAEBSA (41.5% vs. 15.0%, p<0.001).

Conclusion

In patients with moderate to severe obesity, the use of LAEh2 identified significantly more patients with decreased LA function. LAVh2 should be preferred over LAVBSA in patients with moderate to severe obesity.

INTRODUCTION

Left atrial enlargement (LAE) is well established as a prognostic marker in heart failure with preserved ejection fraction (HFpEF) and is used as one of the morphologic diagnostic criteria to diagnose HFpEF [1]. Current ESC guidelines recommend indexing LAV to body surface area (LAV_{BSA}) to determine LAE because of the widely available data [2]. However, since BSA is mainly driven by an increase in fat mass, indexing LAV to BSA can lead to overcorrection of LAV among patients with obesity and thereby has the potential of normalizing LA dilatation. Moreover, LAV indexed to BSA is an isometric measure that assumes a linear relationship between LAV and BSA, which is incorrect since heart and body size do not grow proportionally [3]. This is especially relevant since the majority of heart failure patients are either overweight or have obesity [4,5]. It has been suggested that a more appropriate measure to define LAE in patients with obesity could be to use allometric scaling by indexing LAV to height^2 (LAV_{h2}) [6]. Recent studies have demonstrated that indexing LAV to height^2 better predicts mortality in patients with severe obesity, whereas indexing to BSA has limited predictive value in these patients [7,8] . Another emerging parameter of the LA in obesity patients is LA strain (LAS) [9]. A previous study by our group demonstrated that patients with obesity have impairment in LA function before alterations in conventional echocardiographic parameters occur [10]. The potential value of LAV_{h2} may be underscored if this parameter would be related to LA function, which has not been investigated before. The purpose of our study was to investigate the prevalence of LAE as defined by either LAV_{BSA} or LAV_{h2}in subjects with moderate to severe obesity without known cardiac disease. In order to further establish the added value of LAV_{h2} as a parameter for LAE, the relation between LAV_{h2} and LAS will also be investigated.

METHODS

For this study, echocardiograms from the CARDIOBESE study and AF OBESE study were used. The CARDIOBESE and AF OBESE study are both multicenter prospective cross-sectional studies in which 192 patients with obesity were enrolled who were referred for bariatric surgery, in the period between 2016 and 2021, in the Franciscus Gasthuis & Vlietland and Maasstad Ziekenhuis, both in Rotterdam, the Netherlands 11,12. Patients were enrolled if they were between 35 and 65 years old. All patients had a BMI of ≥ 35 kg/m2. Patients with a history of cardiac disease were excluded. Height (in meters) and weight (in kilograms) were measured at the time of the echocardiogram. BMI was calculated as weight/height2. BSA was calculated by using the Du Bois formula (BSA [m2]) = 0.007184 x height [cm]0.725 x weight

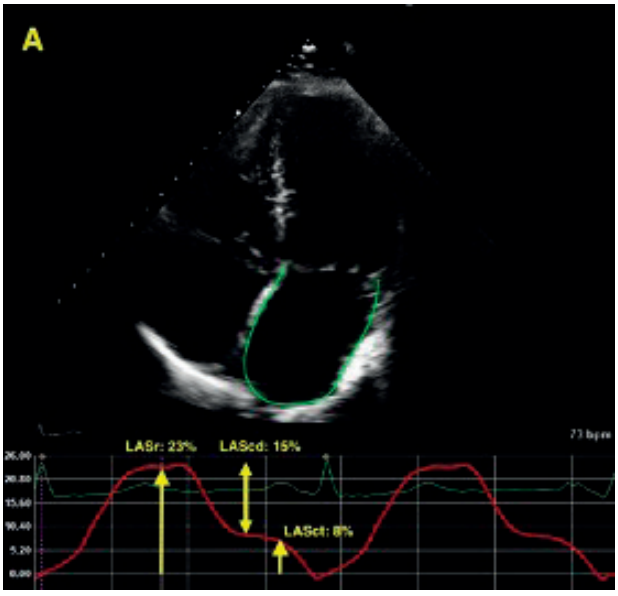
[kg]0.425. Study protocols were approved by the local ethics committee and participants provided written informed consent.

Transthoracic echocardiography

Two-dimensional greyscale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system (EPIQ 7, Philips, the Netherlands), equipped with a broadband (1–5 MHz) X5-1 transducer. All acquisitions and measurements were performed according to the current guidelines [2,13]. LAV was measured on the 4-chamber and 2-chamber view. LAV was then indexed to height^2 (LAV_{h2}) [6,7] and LAV_{BSA}. LAE_{h2} was defined according to the ESC/ESH hypertension guidelines (LAV_{h2} >18.5 ml/m^2 in males and LAV_{h2} >16.5 ml/m^2 in females) [14]. When BSA was used, LAE_{BSA} was defined as LAV_{BSA} > 34 ml/m^2 [2]. For a sub-analysis, the study population was split by obesity class according to the World Health Organization definition to check the difference in prevalence of LAE when using LAV_{h2} and LAV_{BSA} [15].

LA strain was measured with speckle tracking and analyzed offline with dedicated software (TomTec-Arena, integrated in Sectra IDS7). The apical 4-chamber view was used preferably for the analysis (REF). LA endocardial borders were automatically traced using end-diastole as reference. When tracking was suboptimal, fine-tuning was performed manually. If the 4-chamber view was of poor image quality, the 2-chamber view was used. Patients with images of insufficient quality to perform LA strain analysis were excluded. LA function was described according to the three phases of the LA cycle: LA reservoir strain (LASr) which starts at the end of ventricular diastole (mitral valve closure) and continues until mitral valve opening, LA conduit strain (LAScd) which occurs from the time of mitral valve opening through diastasis until the onset of LA contraction, and LA contractile strain (LASct) which occurs from the onset of LA contraction until the end of ventricular diastole (mitral valve closure). LASr, LAScd, and LASct were computed in all patients. An example of LAS measurement in a patient with obesity is shown in Figure 1. All strain values are reported as absolute values for improved readability and data interpretation [16]. LA dysfunction was defined as LASct <14% based on a previous study wherein a LASct>14% was associated with normal left ventricular filling pressures in patients with normal left ventricular ejection fraction (LVEF) [17,18]. We did not use LASr as measure of LA function, as a decreased LASr is mostly associated with increased left ventricular filling pressures in individuals with decreased LVEF [18], and our population consisted of patients with no history of cardiovascular disease.

Figure 1: Example of LA strain curve in a patient with obesity. LASr: Left Atrial Reservoir Strain, LAScd: Left Atrial Conduit Strain, LASct: Left Atrial Contractile Strain.



Statistical analysis

Normally distributed data are presented as means and standard deviation, skewed data as medians and inter-quartile range, and categorical variables as percentages and frequencies. Continuous variables were compared using the independent student T-test in case of normally distributed data and the Mann-Whitney U test for non-normally distributed data. Categorical data were analyzed with the Chi-square test and the McNemar's test for respectively normally and non-normally distributed data. Statistical significance was defined as a p value less than 0.05. Univariable binary logistic regression (with odds ratio (OR) as main analysis) was used to assess whether abnormal LASct was associated with parameters of diastolic function. Parameters of diastolic function were dichotomized according to defined normal values (2). Analyses were performed using SPSS Statistical Package version 28.0.

RESULTS

Image quality was insufficient to quantify LA strain in 50 patients, leaving 142 patients for the analysis. Clinical characteristics of the study population are shown in Table 1. 79.6% of the patients were female. Mean age and mean BMI were respectively 52.3 ± 7.3 years and 42.4 kg/m^2 ± 4.4 kg/m^2. As shown in Table 2, in the total study

population LAV_{BSA} was 25.6 ml/m^2 ± 7.5 ml/m^2 and LAV_{h2} was 18.4 ml/m^2 ± 5.3 ml/m^2, resulting in a total of 26 (18.3%) patients having LAE_{BSA}, and 77 (54.2%) patients having LAE_{h2}. In Figure 2, LAV_{BSA} and LAV_{h2} were plotted against BMI. As can be seen, LAV_{BSA} decreased with increasing BMI, whereas LAV_{h2} increased with increasing BMI. The prevalence of LAE_{h2} was significantly higher than LAE_{BSA} in both obesity class groups (obesity class 2: p<0.001; obesity class 3 p<0.001) (Figure 3). As for LA function, LASr was 30.0 ± 7.8%, LAScd 17.1 ± 6.4%, and LASct 12.8 ± 3.9% in the total study population.

Figure 2: Correlation between body mass index (BMI) and left atrial volume indexed to body surface area (LAVBSA), and BMI and left atrial volume indexed to height2 (LAVh2).

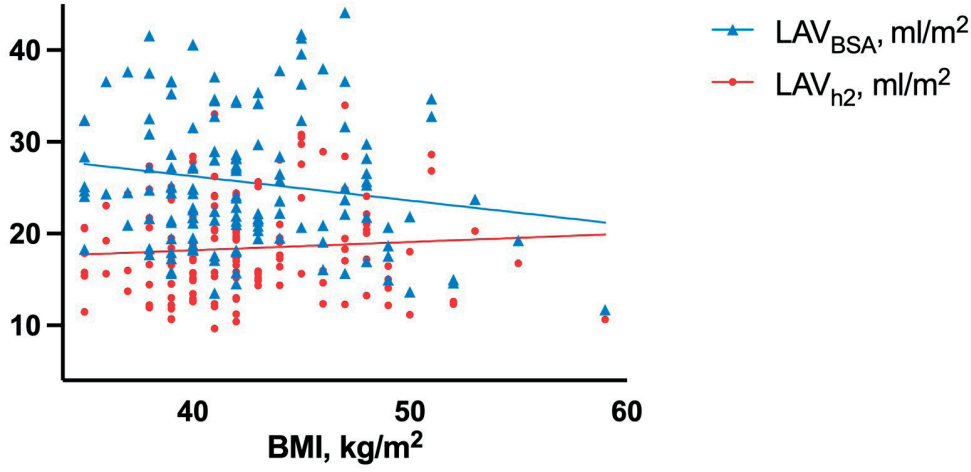


Table 1: Clinical characteristics of the study population

	Total (n=142)	LAE_{h2} (n=77)	No LAE_{h2} (n=65)	p-value
Age, *years*	52.3 ± 7.3	51.1 ± 7.9	53.7 ± 6.3	0.033
Female, *n (%)*	113 (79.6)	63 (81.8)	50 (76.9)	0.471
Weight, *kg*	121.0 ± 17.8	121.7 ± 16.9	120.1 ± 19.0	0.592
Height, *m*	1.69 ± 0.09	1.69 ± 0.1	1.68 ± 0.1	0.647
BMI, kg/m^2	42.4 ± 4.4	42.5 ± 4.2	42.2 ± 4.6	0.704
Systolic BP, *mmHg*	146.0 ± 21.4	147.7 ± 24.0	144.0 ± 17.8	0.317
Diastolic BP, *mmHg*	79.7 ± 11.0	79.6 ± 12.1	79.7 ± 10.1	0.971
Heartrate, *bpm*	79 ± 13	76 ± 12	82 ± 12	0.007
Diabetes mellitus, *n (%)*	26 (18.4)	14 (18.2)	12 (18.8)	0.931
Hypertension, *n (%)*	49 (34.5)	33 (42.9)	16 (24.6)	0.023
OSAS, *n (%)*	28 (19.7)	16 (20.8)	12 (18.5)	0.729
Beta-blocker, *n (%)*	16 (11.3)	11 (14.3)	5 (7.7)	0.216
ACE-inhibitor, *n (%)*	18 (12.7)	10 (13.0)	8 (12.3)	0.904
ARB, *n (%)*	18 (12.7)	12 (15.6)	6 (9.2)	0.257
Diuretics, *n (%)*	27 (19.0)	20 (26.0)	7 (10.8)	0.021

LAEh2, left atrial enlargement indexed to height2 ; BMI, body mass index; BP, blood pressure; bpm, beats per minute; OSAS, obstructive sleep apnea syndrome; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker. LAEh2 was defined as >16.5 ml/m2 for females and >18.5 ml/m2 for males. Normally distributed data are presented as mean ± sd, non-normally distributed data are presented as median (25th interquartile – 75th interquartile), categorical data are presented as n (%). P-value represents comparison between LAEh2 and No LAEh2.

Comparison between patients with and without LAE_{h2}

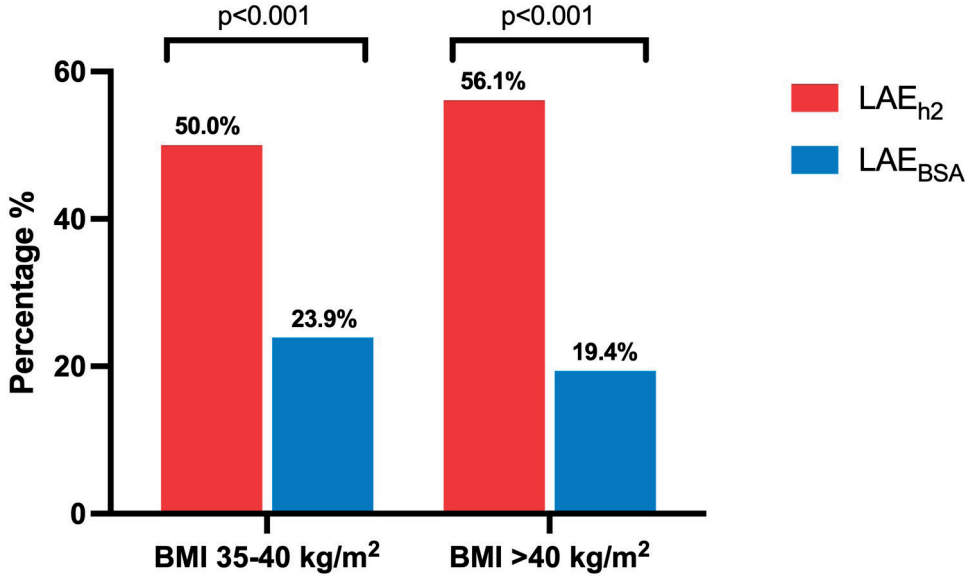
As presented in Table 1, there was a small but significant difference in age (51.1 years ± 7.9 years vs. 53.7 years ± 6.2 years, p=0.033) between the groups. Patients in the LAE_{h2} group more often had a history of hypertension and more often used diuretics (42.9% vs. 24.6%, p=0.023, and 26.0% vs. 10.8%, p=0.021, respectively). Echocardiographic parameters are shown in Table 2. Apart from an expected significant difference in LAV_{BSA} (30.8 ml/m^2 ± 6.0 ml/m^2 vs. 19.6 ml/m^2 ± 3.1 ml/m^2, p<0.001), there were no differences in other conventional diastolic echocardiographic parameters between the groups. As for LA function, the LAE_{h2} group had significantly lower LASct (12.2% ± 3.2% vs. 13.6% ± 4.5%, p=0.019). There was no difference in LASr and LAScd between groups.

Table 2: Echocardiographic parameters of the study population

	Total (n=142)	LAE_{h2} (n=77)	No LAE_{h2} (n=65)	p-value
LVEDD, *mm*	48.1 ± 6.1	49.4 ± 6.0	46.6 ± 5.9	0.004
E/A ratio	1.0 ± 0.3	1.0 ± 0.3	0.9 ± 0.2	0.241
E/e' ratio	9.6 ± 2.8	9.6 ± 3.0	9.6 ± 2.5	0.902
Septal e' velocity, *cm/s*	7.6 ± 1.9	7.8 ± 1.8	7.4 ± 1.9	0.254
TR velocity, *m/s*	1.14 (0.9 - 1.81)	1.13 (0.86 - 1.48)	1.29 (0.92 - 2.09)	0.112
LAV, *ml*	52.8 ± 17.8	63.9 ± 16.4	39.7 ± 7.3	<0.001
LAV_{BSA}, ml/m^2	25.6 ± 7.5	30.8 ± 6.0	19.6 ± 3.1	<0.001
LAV_{h2}, ml/m^2	18.4 ± 5.3	22.1 ± 4.3	13.9 ± 1.9	<0.001
LVEF, *%*	57.2 ± 5.6	57.7 ± 5.8	56.6 ± 5.4	0.274
LASr, *%*	30.0 ± 7.8	29.9 ± 6.9	30.0 ± 8.8	0.982
LAScd, *%*	17.1 ± 6.4	17.8 ± 6.1	16.4 ± 6.7	0.200
LASct, %	12.8 ± 3.9	12.2 ± 3.2	13.6 ± 4.5	0.019

LVEDD, left ventricular end-diastolic diameter; E/A ratio, peak early mitral inflow velocity / peak late mitral inflow velocity ratio; e', peak early diastolic mitral annular displacement velocity; TR, tricuspid regurgitation; LAV, left atrial volume; LAVBSA, left atrial volume indexed to BSA; LAVh2, left atrial volume indexed to height2; LASr, left atrial reservoir strain; LAScd, left atrial conduit strain; LASct, left atrial contractile strain. LAEh2 was defined as >16.5 ml/m2 for females and >18.5 ml/m2 for males. Normally distributed data are presented as mean ± sd, non-normally distributed data are presented as median (25th interquartile – 75th interquartile), categorical data are presented as n (%). P-value represents comparison between LAEh2 and No LAEh2.

Figure 3: Prevalence of left atrial enlargement according to BMI group. LAEBSA ,left atrial enlargement indexed to body surface area threshold (LAEBSA); LAEh2 , left atrial enlargement indexed to height2 ; BMI, body mass index.



LAE in relation to LASct

In Figure 4 the correlations between LAV_{h2}, LAV_{BSA}, and LASct are depicted. There was a significant, but weak, negative correlation for both LAV_{h2} and LASct (r=-0.22, p=0.009) and LAV_{BSA} and LASct (r=-0.21, p=0.015). Significantly more patients with LA dysfunction as defined by LASct <14% would have been correctly classified by LAE_{h2} as compared to LAE_{BSA} (41.5% vs. 15.0%, p<0.001) (Figure 4 and Figure 5). Table 3 shows the association of various LV diastolic parameters with LASct. In binary logistic regression LAE_{h2} was significantly associated with an abnormal LASct (OR 2.64, CI 1.29 – 5.42, p=0.008).

Table 3: Association of different left ventricular diastolic parameters with left atrial contractile strain

Dichotomous analysis	Abnormal LASct strain	
	OR (95% CI)	p value
Abnormal septal e' velocity *(<7 cm/s)*	0.52 (0.26 – 1.0)	0.067
Abnormal E/e' average *(>14)*	0.73 (0.19 – 2.70)	0.632
$LAE_{h2,}$ ml/m^2	2.64 (1.29 – 5.42)	0.008
$LAE_{BSA,}$ ml/m^2	2.38 (0.84 – 6.79)	0.104

LASct, left atrial contractile strain; e', peak early diastolic mitral annular displacement velocity; E, peak early mitral inflow velocity; LAEh2, left atrial enlargement indexed to height2; LAEBSA , left atrial enlargement indexed to body surface area; CI, confidence interval; OR, odds ratio. Abnormal LASct strain was defined as LASct strain <14%, LAEBSA >34 ml/m2, and LAEh2 as >16.5 ml/m2 for females and >18.5 ml/m2 for males.

Figure 4: A: Relation between left atrial volume indexed to body surface area (LAVBSA) and left atrial contractile strain (LASct). Horizontal red dashed line represents left atrial enlargement indexed to body surface area threshold. Vertical red dashed line represents left atrial strain contractile dysfunction. B: Relation between left atrial volume indexed to height2 (LAVh2) and LASct. Horizontal red dashed lines represent left atrial enlargement indexed to height2 thresholds (female and male respectively). Vertical red dashed line represents left atrial strain contractile dysfunction.

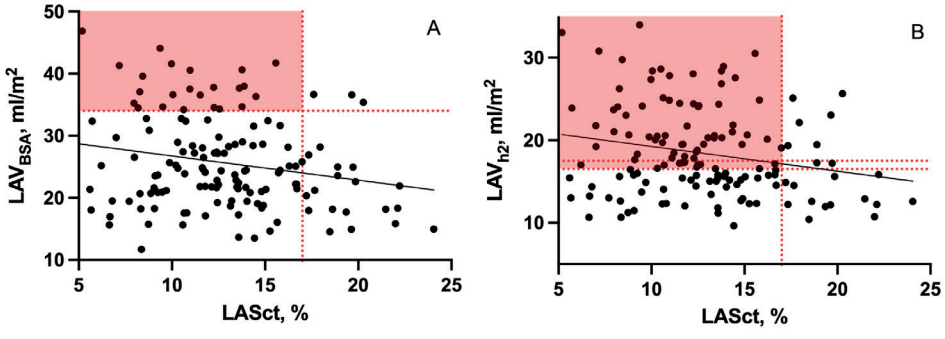
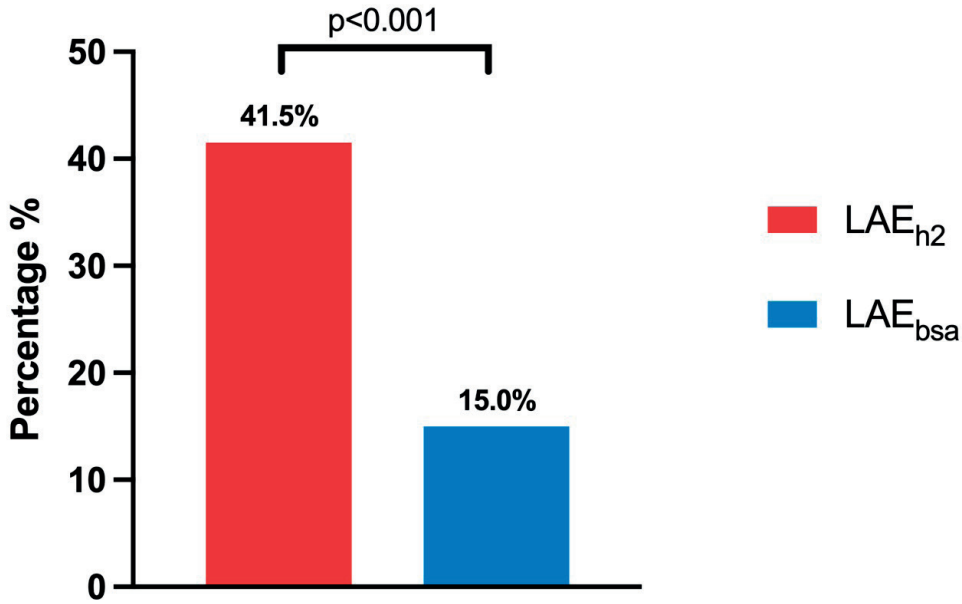


Figure 5: Prevalence of left atrial dysfunction and left atrial enlargement when left atrial volume was indexed to body surface area (LAEh2), and prevalence of left atrial dysfunction and left atrial enlargement when left atrial volume was indexed to height2 (LAEbsa).



DISCUSSION

We demonstrated that, in subjects with moderate and severe obesity without known cardiac disease, indexation of LAV to height^2 resulted in a higher prevalence of LAE compared to indexation of LAV to BSA in these subjects. Furthermore, LAE_{h2} was associated with an increased risk for LA dysfunction, in contrast to LAE_{BSA} and other traditional parameters of LV diastolic function. Considering the limitations of indexation to BSA in obesity and the importance of a reliable parameter of LAE for diagnosis and prognosis of a broad range of cardiac diseases,LAE_{h2} may be of added value in patients with obesity.

LAE in obesity

Obesity is an important risk factor for developing LAE [19], which is an essential parameter in identifying diastolic dysfunction and HFpEF [1,2]. In addition, both obesity and LAE are associated with an increased risk for developing atrial fibrillation (AF) [20-23]. There are several mechanisms by which obesity can lead to LAE. For example, obesity can induce hemodynamic changes that can alter cardiac structures, it can

cause atrial myopathy related to systemic inflammation, and promote paracrine effects from epicardial adipose tissue [24-26].

Normalization of heart chamber sizes is common and necessary, as it reduces the effect of dissimilarities in patients' proportions. Additionally, normalization allows inter- and intragroup comparisons of cardiac dimensions [27]. Normal values enable the possibility to define normal ranges, that can be used to predict, diagnose, and monitor disease. The use of BSA as indexation method in LA scaling dates back to the 1980s [28], and is still recommended in the current guidelines [2]. However, indexation of LAV to BSA is inaccurate for patients with obesity [6]. The reasons for this are several fold. First of all, indexing LAV to BSA assumes a linear relationship. However, data on the growth patterns of the human heart indicate that the growth relationship is exponential rather than linear [27,29,30]. This can be overcome by choosing allometric scaling instead, as allometric scaling assumes an exponential relationship [6]. A few previous studies have assessed different indexation methods in patients with obesity. First, Zong et al. found that allometric scaling was superior to conventional isometric indexation in a population of 717 patients with obesity with a mean BMI of 42.2 kg/m2 [31]. Second, in a paper by Carnavelini et al., a similar conclusion was drawn in 63 patients with mild , and 26 patients with moderate obesity [32]. Although both studies demonstrated that allometric scaling was superior to isometric scaling, potential supportive data regarding the relation of alternative indexing methods with LA function was not available.

The second concern with indexing LAV to BSA in obesity, is that cardiac size is driven by fat free mass (FFM) [27]. In normal weight subjects, BSA is a suitable surrogate for FFM and thus a suitable scaler to index LAV [33]. However, in patients with obesity, BSA is disproportional to FFM and therefore possibly overcorrects LAV [6]. Height appears to be a better estimate for FFM [6]. Our results are consistent with this notion, as can be seen in Figure 1 where LAV indexed to height^2 was related to increasing BMI as expected, in contrast to LAV indexed to BSA. In addition, we found that indexing LAV to height^2 resulted in a higher prevalence of LAE compared to indexing LAV to BSA. A recent study showed similar results, where as many as 55.4% of the severely obese patients were reclassified into LAE when height^2 was used for indexation instead of BSA [7]. Additionally, recent studies have demonstrated that indexation of LAV to height^2 has better predictive value concerning clinical outcomes in patients with obesity [7,8]. However, both studies did not investigate the relation between LAV_{h2} and LA function as measured with LAS.

Relation between LAV_{h2} and LA function in obesity

In theory, the larger number of obese subjects with LAE identified by LAV_{h2} as compared to LAV_{BSA}, could also be due to a larger number of false positive results and thereby to overdiagnosis of disease. In order to further investigate the potential added value of LAV_{h2}, our study was the first to relate LAV_{h2} and LAV_{BSA} to LA strain. Recently, LA strain has emerged as a parameter that has potential added value in identifying diastolic dysfunction. LASr and LASct are both associated with LV filling pressures [34-36]. Therefore, improved relation between a parameter of LAE and LA strain would underscore the usefulness of such a parameter of LAE. Patients with obesity with LAE_{h2} had significantly lower LASct compared to patients without LAE_{h2}. Also, more patients with abnormal LASct were identified by LAE_{h2} as compared to LAE_{BSA}. In addition, LAE_{h2} was associated with an increased risk (OR 2.64) for an abnormal LASct, in contrast to LAE_{BSA} and other traditional diastolic parameters. Our novel findings underscore the notion that LAV_{h2} is not only a more sensitive measure of LAE in patients with obesity, but indeed more sensitive for identification of LA dysfunction as well. With the rising prevalence of obesity worldwide, it is pivotal to have an early and accurate assessment of cardiac dysfunction in order to prevent further deterioration to heart failure. Early detection can lead to timely initiation of lifestyle modifications and treatment, and therefore reduce the associated risks and morbidity of obesity.

Study limitations

This study has some limitations that should be noted. First of all, LA strain analysis requires good image quality and not all our subjects (26%) had analyzable LA images, which may have affected the identified proportion of LA dysfunction. Secondly, a considerable proportion of the subjects had comorbidities, such as hypertension and diabetes, that can also affect LA function. Thirdly, our cohort mostly consisted of females which could have biased the results. Around 80% of patients who undergo bariatric surgery are female, which explains the high percentage of females in our study. Lastly, only LASct and not LASr and LAScd were different between patients with and without LAE_{h2}. Although most of the previous research has focused on LASr, added value of LASct has already been proven as well [16] and is therefore also considered as an important measure for LA function.

CONCLUSION

In conclusion, relatively easy assessment of LAV_{h2} could overcome inherent limitations of LAV_{BSA} in patients with obesity and thereby contribute to the detection of cardiac dysfunction in these patients. LAV_{h2} was more sensitive for detection of LAE and

better related to LA dysfunction as compared to the current standard of normalization of LAV for BSA in our population of patients with moderate to severe obesity without known cardiac disease.

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Part III

Early detection of cardiac dysfunction in obesity – the left ventricle

6

Chapter 6

Prognostic value of temporal patterns of global longitudinal strain in patients with chronic heart failure

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ABSTRACT

Background

We investigated whether repeatedly measured global longitudinal strain (GLS) has incremental prognostic value over repeatedly measured left ventricular ejection fraction (LVEF) and N-terminal pro B-type natriuretic peptide (NT-proBNP), and a single 'baseline' GLS value, in chronic heart failure (HF) patients.

Methods

In this prospective observational study, echocardiography was performed in 173 clinically stable chronic HF patients every six months during follow up. During a median follow-up of 2.7 years, a median of 3 (25^{th}-75^{th} percentile:2-4) echocardiograms were obtained per patient. The endpoint was a composite of HF hospitalization, left ventricular assist device, heart transplantation, cardiovascular death. We compared hazard ratios (HRs) for the endpoint from Cox models (used to analyze the first available GLS measurements) with HRs from joint models (which links repeated measurements to the time-to-event data).

Results

Mean age was 58±11 years, 76% were men, 81% were in New York Heart Association functional class I/II, and all had LVEF<50% (mean±SD:27±9%). The endpoint was reached by 53 patients. GLS was persistently decreased over time in patients with the endpoint. However, temporal GLS trajectories did not further diverge in patients with versus without the endpoint and remained stable during follow-up. Both single measurements and temporal trajectories of GLS were significantly associated with the endpoint (HR per SD change (95%CI): 2.15(1.34-3.46), 3.54 (2.01-6.20)). In a multivariable model, repeatedly measured GLS maintained its prognostic value while repeatedly measured LVEF did not (HR per SD change(95%CI): GLS:4.38(1.49-14.70), LVEF:1.14(0.41-3.23)). The association disappeared when correcting for repeatedly measured NT-proBNP.

Conclusions

Temporal evolution of GLS was associated with adverse events, independent of LVEF but not independent of NT-proBNP. Since GLS showed decreased but stable values in patients with adverse prognosis, single measurements of GLS provide sufficient information for determining prognosis in clinical practice compared to repeated measurements, and temporal GLS patterns do not add prognostic information to NT-proBNP.

INTRODUCTION

Left ventricular ejection fraction (LVEF) is the most commonly used parameter to evaluate LV systolic function in chronic heart failure (HF) patients. The use of LVEF in chronic HF patients carries several known limitations, such as high variability, geometric assumptions, load dependency, and a low reproducibility (1, 2). Furthermore, previous studies have shown that the predictive value of LVEF for cardiac events in HF patients leaves room for improvement (1, 3, 4). Global longitudinal strain (GLS) is independently associated with all-cause mortality, cardiovascular death and heart transplantation (2, 5, 6), and also predicts risk of HF hospitalization (4, 7). When compared to LVEF, GLS has incremental prognostic value (3, 8, 9), and carries potential to be used as a standard measurement for chronic HF (10). However, most of the studies on GLS in HF have focused on a single measurement of GLS, which only reflects a snapshot of the patient's physiological state. The prognostic value of repeated measurements of GLS in chronic HF patients has not been addressed and has never been compared with repeatedly measured LVEF. Therefore, we hypothesize that temporal patterns of GLS are associated with adverse clinical events in chronic HF patients, and that temporal patterns of GLS may provide incremental value to temporal patterns of LVEF and N-terminal pro-brain natriuretic peptide (NT-proBNP), since this is the blood biomarker most commonly used for prognostication in HF). To test this hypothesis, we repeatedly measured GLS, LVEF and NT-proBNP in 173 clinically stable patients with chronic HF. Moreover, we compared the prognostic value of repeatedly measured GLS with a single 'baseline' GLS value.

METHODS

Study design

Details on the design of the Serial Biomarker Measurements and New Echocardiographic Techniques in Chronic Heart Failure Patients Result in Tailored Prediction of Prognosis (Bio-SHiFT) study have been published previously (11). In short, Bio-SHiFT is a prospective, observational cohort of stable patients with chronic HF, conducted in the Erasmus MC, Rotterdam, and Northwest clinics, Alkmaar, The Netherlands. Patients were recruited during their regular outpatient visits while in clinically stable condition (i.e., they had not been hospitalized for HF in the 3 months prior to inclusion). The main inclusion criteria were diagnosis of HF 3 or more months before inclusion according to the then prevailing guidelines of the European Society of Cardiology (12), and age ≥18 years. Patients were followed for a maximum of 30 months, during which study follow-up visits were scheduled every 3 months. At each visit, a short medical evaluation was performed, and blood samples were

drawn. During the study, the routine outpatient follow-up by the treating physician continued for all patients, independently of the study visits. The study was approved by the medical ethics committees, conducted in accordance with the Declaration of Helsinki, and registered in ClinicalTrials.gov (NCT01851538). All patients signed informed consent for the study. A total of 398 patients were included in Bio-SHiFT. All patients included at Erasmus MC were eligible for the repeated echo substudy. This substudy included a total of 175 patients in whom echocardiography was performed every 6 months during follow-up (13). Two patients had insufficient image quality. The remaining 173 patients were included in the analysis.

Echocardiography Measurements and Evaluation

Two-dimensional gray-scale harmonic images were obtained in the left lateral decubitus position. Standard apical four-, three-, and two-chamber views were recorded. A commercially available ultrasound system was used (iE33, Philips, Best, The Netherlands), equipped with a broadband (1-5 MHz) S5-1 transducer (frequency transmitted 1.7 MHz, received 3.4 MHz). Images were stored in the echo core lab of Erasmus MC (13). Using specialized software (2D Cardiac Performance Analysis version 4.5; TomTec Imaging Systems, Unterschleissheim, Germany), LVEF, end-diastolic and end-systolic LV diameter, and end-systolic left atrial diameter were measured. The vena cava inferior diameter, the tricuspid regurgitation (TR) velocity, and the function of the mitral, and tricuspid valves were also assessed. The diastolic parameters were evaluated using Philips Excellera version R4.1 (Philips Medical Systems, The Netherlands) or TomTec Imaging Systems. To assess diastolic function, the peak early filling velocity (E)/late filling velocity (A) ratio and the ratio of the E and early diastolic mitral annular velocity (e') were calculated. For the e', we used the mean of the lateral and medial e' when available; however, if only one of the two was available, this value was used (14). All echocardiographic measurements were performed blinded to biomarker and clinical event data.

Strain analysis based on speckle tracking echocardiography was also performed using TomTec Imaging Systems. A frame rate above 30 f/s is sufficient for accurate GLS assessment (15), and all the echoes had a frame rate of 30 f/s or higher; with the majority of the echoes having a frame rate of 50 f/s, and a part of the echoes performed in the beginning of the study having a rate of 30 f/s. The images were analysed retrospectively after completion of follow-up by a single operator, who was blinded to other echocardiographic parameters and the patients' characteristics. The GLS assessment of the left ventricle was performed in 18 LV segments on the standard apical four-, three-, and two-chamber views, where the endocardial border was traced manually at end systole. We only obtained GLS if tracking was sufficient in ≥5 of the 6 segments per view. Extremely low values of GLS (<-5%) were verified by a second

observer. If a patient had AF during the echocardiography, the index beat method was used. This is a validated method to measure echocardiographic parameters during AF (16). The mean GLS from the three apical views was considered the LV GLS. By convention, GLS results were interpreted as absolute values (17). In other words, a change of GLS from for example -18% to -15% will be reported as a decrease of GLS. Intra-observer reproducibility was assessed by re-measuring GLS in 20 echoes and calculating the intraclass correlation coefficient.

NT-proBNP Measurement

During each study visit (every 3 months), blood samples were drawn to measure a set of biomarkers, including NT-proBNP. Blood samples were processed and stored at–80°C within 2 hours after collection. To determine NT-proBNP levels, a batch analysis was performed using an electrochemiluminescence immunoassay (Elecsys 2010; Roche Diagnostics, Indianapolis, IN). Accordingly, results of the biomarker assays were not available to treating physicians at the time of the outpatient visits and did not interfere with usual care.

Clinical Study Endpoints

The primary endpoint comprised the composite of hospitalization for the management of acute or worsened HF, left ventricular assist device (LVAD) implantation, cardiac transplantation, and cardiovascular death, whichever occurred first in time. All events were adjudicated by a clinical event committee blinded to the echocardiographic assessments and biomarker measurements, after reviewing corresponding hospital records and discharge letters.

Statistical Analyses

Distributions of continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed continuous variables are presented as mean±standard deviation (SD), and nonnormally distributed variables as median and interquartile range (25^{th}-75^{th} percentile). Categorical variables are presented as numbers and percentages. Differences in baseline characteristics between patients who experienced the endpoint and those who did not were tested using the t-test and Mann-Whitney test, according to variable distributions, for continuous variables, and χ^2-tests and Fisher's exact tests, when appropriate, for categorical variables. We evaluated the association of baseline clinical and echocardiographic characteristics with baseline GLS using linear regression, with GLS being the dependent variable. Moreover the Pearson correlation coefficient was calculated to examine the correlation between the variables of interest. Then we used linear mixed models to examine the associations of baseline clinical characteristics with repeatedly measured GLS, as well as the associations of repeatedly measured echocardiographic parameters and repeatedly measured GLS. Random ef-

fects were used to account for the presence of multiple echocardiograms per patient. Hereafter, we assessed the value of repeated echocardiographic measurements for prediction of the endpoint, as well as their incremental value to sole, baseline measurements. We used the framework of joint models for longitudinal and survival data. (18) In these joint models, a linear mixed effects (longitudinal) model provided estimates of the individual temporal trajectories of the echo parameters. These estimated trajectories were combined with a relative risk model, to study their association with the risk of the study endpoint. The individual trajectories were adjusted for all variables that showed statistically significant differences between patients with and without the endpoint ($P<0.05$; age, sex, duration of HF, systolic blood pressure, diastolic blood pressure, renal failure, and atrial fibrillation). The associations between the temporal evolutions of GLS and the endpoint, resulting from the relative risk model, were first only adjusted for age and sex. Thereafter, baseline LVEF and baseline NT-proBNP levels were added consecutively. Lastly, all variables with significant differences between those with and without the endpoint were added. To investigate the incremental value of repeatedly measured GLS to repeatedly measured LVEF and NT-proBNP, we combined the repeated measurements of each of these variables in multivariable joint models. To enable comparisons of effect sizes of different variables, prior to the analyses, all investigated echo parameters, and the NT-proBNP measurements, were first log transformed to achieve a normal distribution, after which the corresponding Z-scores were calculated. For GLS no transformation was needed. The first echoes were selected and entered into Cox models to obtain the hazard ratios (HRs) entailed by the first echoes only. To obtain the HRs entailed by the repeatedly measured echoes, joint models were used. Thus, the results of the regression analyses of the Cox and joint models can be directly compared and are presented as HRs, which represent risk per SD increase/decrease of the standardized variable, along with the corresponding 95% confidence interval (CI). As described above, one of our aims was to investigate whether repeatedly measured GLS carries incremental predictive value to repeatedly measured LVEF and NT-proBNP. We chose to present our results solely as adjusted HRs and not to combine them with C-statistics. Pepe et al. (19) have demonstrated that testing for improvement in prediction performance is not necessary if a variable has already been shown to be an independent risk factor, and that standard testing procedures for C-indices are very conservative and thus insensitive to improvements in prediction performance. Missing values in GLS and the other echo parameters were, except for the A wave, always due to poor image quality and were as such missing completely at random. Accordingly, we chose to perform a complete case analysis. Missing values for the A wave were mostly due to atrial fibrillation during the echo or due to mitral valve replacement or clipping. In this specific patient group imputation of missing values is inappropriate, as the A wave can never be measured. Thus, we again chose for a complete case analysis here. The results of this analysis should not

be extrapolated to patients excluded from the analysis. All analyses were performed with R Statistical Software using packages nlme (20) and JMbayes. (18) All tests were two-tailed, and P values < .05 were considered statistically significant.

RESULTS

Baseline Characteristics and Clinical Endpoints

From October 2011 to January 2018, 173 patients were included. All patients had EF <50%, with a mean±SD LVEF of 27±9%. In 150 patients, EF was below 40% (HFrEF). The remaining 23 patients had an EF between 40% and 49% (HFmrEF) (21). Mean age was 58±11 years, 76% were men, and mean BMI was 27.6± 4.7 kg/m^2. The median time between diagnosis of HF and inclusion in the study was 6.8(6.3-7.3) years. The highest proportion of the patients was in NYHA class II (55%) and 41% had HF due to ischemic heart disease. There was no significant difference in proportions of males and females between the patients who reached the endpoint and remained endpoint free (Table 1).

Table 1: Baseline patient characteristics in relation to the composite endpoint.

	Overall	Endpoint- free	Endpoint	p-value
N	173	120	53	
Demographics				
Males, n (%)	132(76)	92(76)	40(75)	1
Age, years (mean(SD))	58.0(11.2)	57.3(11.4)	59.6(10.8)	0.2
Clinical characteristics				
Duration of HF, years (mean(SD))	6.8(6.3-7.3)	6.5(5.9-7.1)	8.1(7.0-9.2)	<0.001
Body mass index, kg/m² (mean(SD))	27.5(4.7)	27.6(4.7)	27.2(4.5)	0.5
Heart rate, bpm (mean(SD))	67(12.9)	67(14.5)	67(8.5)	0.8
Systolic blood pressure, mmHg (mean(SD))	108(18.3)	110(18.4)	102(17.1)	0.008
Diastolic blood pressure, mmHg (mean(SD))	67(9.8)	68(9.8)	65(9.3)	0.03
NYHA class (%)				0.009
I	45(26.3)	39(33)	6(12)	
II	94(55)	62(52)	32(62)	
III	32(19)	18(15)	14(27)	
NT-proBNP, pmol/L (median[25th-75th percentile])	118[31,223]	73[25,175]	235[140,410]	<0.001
Features of HF				
Ischemic heart disease (%)	71(41)	44(37)	27(51)	0.1
Hypertension (%)	2(1)	2(2)	0(0)	0.9
Cardiomyopathy (%)	73(42)	52(43)	21(40)	0.8
Secondary to valvular heart disease (%)	4(2)	2(2)	2(4)	0.8
Other etiology of HF (%)	16(28)	14(17)	2(1)	0.8
Unknown (%)	9(5)	8(7)	1(2)	0.4
Medical history				
Myocardial Infarction (%)	69(40)	43(36)	26(50)	0.1
PCI (%)	62(36)	43(36)	19(36)	1
CABG (%)	16(9)	10(8)	6(11)	0.7
Atrial fibrillation (%)	53(31)	28(23)	25(47)	0.003
Diabetes Mellitus (%)	40(23)	26(22)	14(26)	0.6
Chronic renal failure (%)	69(40)	38(32)	31(59)	0.002
COPD (%)	24(14)	15(13)	9(17)	0.6
Medication use				
Beta blockers (%)	165(95)	116(97)	49(93)	0.4
ACE inhibitors (%)	120(69)	84(70)	36(68)	0.9
Angiotensin II receptor blockers (%)	48(28)	34(28)	14(26)	0.9
Loop diuretics (%)	161(93)	108(90)	53(100)	0.039
Aldosteron antagonists (%)	128(74)	84(70)	44(83)	0.1

HF, heart failure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; ACE, angiotensin converting enzyme.

In total, the composite endpoint was reached by 53 patients, and first occurrence of any of the components was as follows; 40 patients were re-hospitalized for acute or worsened HF, six patients received a heart transplantation, four patients received an LVAD implantation, and three patients died from cardiovascular causes. Patients who reached the composite endpoint had a significantly lower LVEF, longer duration of HF at study inclusion, lower systolic and diastolic blood pressure and higher NT-proBNP levels (Table 1).

Echocardiography

During a median (25^{th}-75^{th} percentile) follow-up time of 2.7 (2.5–2.8) years, 505 echocardiograms were performed with a median (25^{th}-75^{th} percentile) of 3 (2–4) echoes per patient. Patients had up to eight consecutive echocardiographic evaluations performed with 65% of patients having at least three evaluations. Missing echocardiograms mostly occurred due to logistic circumstances (e.g., the unavailability of an ultrasound technician during the study visit). GLS was successfully measured in 96% of the total of 505 echocardiograms. Missing values were due to insufficient image quality (90% of these missing values of these missing values) or the absence of one of the apical views (10% of these missing values). The intraclass correlation coefficients for intra-observer reproducibility were 0.91 and 0.85 for GLS and LVEF, respectively.

First Available Echocardiogram

The characteristics of the first available echocardiogram for each patient are presented in Table 2. Due to logistic reasons, 55% of these first available echoes were performed at baseline (follow-up time zero), 12.8% of the first available echoes were performed during the first follow-up visit (target follow-up time 3 months), 18% during the second follow-up visit (target 6 months), and the remaining 14.2% thereafter. The date of the first available echocardiogram was considered as the start of follow-up. After the first available echoes, subsequent echocardiograms were performed every six months during follow-up (Supplementary figure 1)._Patients who reached the composite endpoint had a significantly decreased GLS with a mean difference of 3.7% (95%CI:2.6-4.7) and a lower LVEF with a mean difference of -9% (95%CI:-12.00,-5.88) compared to patients who remained endpoint-free (Table 2). The dimensions of the left ventricle, left atrium, and inferior vena cava were significantly larger than those of patients who did not reach the endpoint. Moreover, patients who reached the endpoint had higher E/A ratio, E/e' ratio and TR velocities (Table 2).

Table 2: Echocardiographic characteristics from first available echo in relation to the composite endpoint.

	Endpoint- free	Endpoint	p-value	Missing values
Systolic parameters				
LV GLS, % (mean (SD))	-10.1(3.6)	-6.4(2.3)	<0.001	13(8%)
LVEF, % (mean (SD))	31.1(9.8)	22.9(9.2)	<0.001	10(6%)
Systolic LV diameter, mm (median[25th-75th percentile])	53.00[46.3,62.0]	60.00 [54.0, 70.5]	<0.001	16 (9%)
Systolic LA diameter, mm (mean(SD))	40.3(7.6)	48.3(7.5)	<0.001	18(10%)
TR velocity, m/s (median[25th-75th percentile])	2.40[2.03,2.65]	2.62[2.29,3.03]	0.04	56(32%)
Diastolic parameters				
Left atrial volume index, mL/m2 (mean(SD))	34.5(5.3)	49.2(5.8)	<0.001	18(10%)
E/A ratio (mean(SD))	1.17(0.88)	2.19(1.05)	<0.001	44(25%)*
E/e' ratio (mean(SD))	12.9(7.3)	21.4(10.2)	<0.001	20(12%)
Diastolic LV diameter, mm (median[25th-75th percentile])	63.0[57.0,70.0]	67.0[63.0,77.0]	0.003	14(8%)
Vena Cava				
Inferior vena cava, mm(median[25th-75th percentile])	14.70[12.00,17.50]	20.00[16.00,23.55]	<0.001	39(23%)
VCI sniff test: No (%)	4(4)	14(35)	<0.001	43(25%)
Mitral valve regurgitation (%)			<0.001	13(8%)
None	47(42)	6(13)		
Mild	43(38)	29(60)		
Moderate	20(18)	7(15)		
Severe	2(2)	6(13)		
Tricuspid valve regurgitation (%)			<0.001	16(9%)
None	68(61)	16(35)		
Mild	36(32)	18(39)		
Moderate	6(5)	6(13)		
Severe	1(1)	6(13)		
Aortic valve stenosis (%)			0.1	16(9%)
None	109(99)	44(94)		
Mild	1(1)	2(4)		
Moderate	0(0)	1(2)		
Aortic valve regurgitation (%)			0.01	16(9%)
None	101(92)	36(77)		
Mild	8(7)	7(15)		
Moderate	1(1)	4(9)		

LV GLS, left ventricular global longitudinal strain; LVEF, left ventricular ejection fraction; LV, left ventricular; LA, left atrium; TR, tricuspid regurgitation; VCI, vena cava inferior.

Associations of baseline and serially measured GLS with clinical and echocardiographic characteristics

Supplementary Tables 1 and 2 display the associations of baseline GLS with clinical and echocardiographic characteristics. GLS showed the strongest association with LVEF and was significantly decreased in patients in a higher NYHA class and patients with other comorbidities, indicating worse LV function. Although GLS was decreased in men compared with women, this did not translate into a higher incidence of PEP in men (Table 1). GLS was also significantly different between patients with and without ischemic HF, with a mean(95%CI) of -7.7%(-8.5%- -6.9%) and -9.9%(-10.6%- -9.1%) respectively. Baseline GLS and LVEF showed a moderate to strong correlation (r= -0.68, p <0.001), which was stronger than the correlation between GLS and NT-proBNP (r=0.54,p<0.001). Scatterplots are depicted in figure 2. Associations remained essentially the same when examined for longitudinally measured GLS (Figure 1 and Supplementary Table 3). GLS showed significant associations with almost all examined echocardiographic parameters. The strongest association was found with the E/A ratio and TR velocities. Repeatedly measured echocardiographic parameters also remained strongly associated with repeatedly measured GLS (Supplementary Figure 3 and Supplementary Table 4).

Figure 1: Association of baseline clinical characteristics with serially measured GLS. Betas depict the change in GLS (in %) when the explanatory variable is increased by 1 unit. 95%CI: 95% confidence interval.

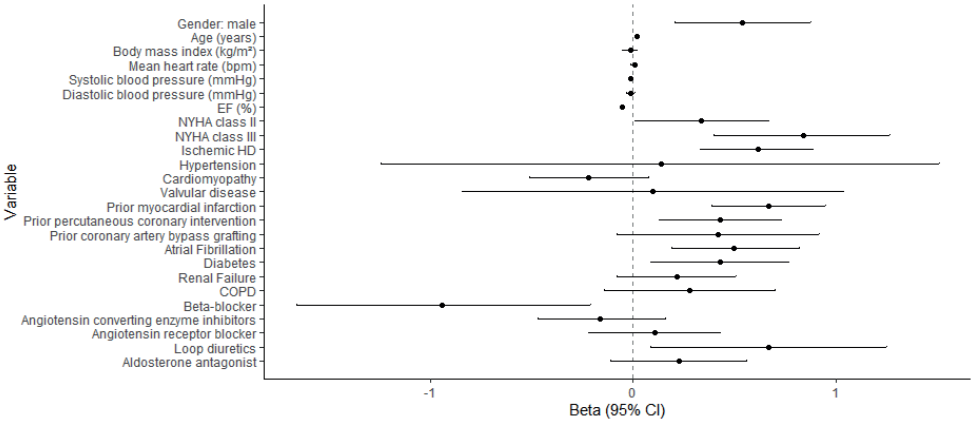


Table 3: Associations of the baseline and repeatedly measured GLS with the primary endpoint

	HR (95%CI)	P value
Baseline measurements		
GLS*	2.15(1.34-3.46)	<0.001
LVEF*	1.41(1.01-2.13)	0.04
GLS and LVEF*		
GLS	2.76(1.66-4.58)	<0.001
LVEF	1.11(0.71-1.75)	0.6
GLS and NT-proBNP**		
GLS	2.15(1.34-3.46)	0.002
NT-proBNP	1.82(1.07-3.09)	0.03
Repeated measurements of GLS		
Model 1	3.33(1.95-6.09)	<0.001
Model 2	3.54(2.01- 6.20)	<0.001
Model 3	3.50(2.18-5.89)	<0.001
Model 4	1.75(1.30-2.85)	<0.001
Model 5	4.04(2.34-7.40)	<0.001
Repeated measurements of GLS and LVEF or NT-proBNP		
Model 6		
GLS	4.38(1.49-14.70)	0.008
LVEF	1.14(0.41-3.23)	0.8
Model 7		
GLS	0.79(0.47-1.30)	0.4
NT-proBNP	2.90(1.59-5.55)	<0.001

*Corrected for age, sex, baseline NT-proBNP and HF duration

**Corrected for age, sex, HF duration

Model 1:corrected for age, sex, HF duration, baseline LVEF

Model 2:corrected for age, sex, HF duration, baseline NT-proBNP

Model 3:corrected for age, sex, HF duration, baseline LVEF and NT-proBNP

Model 4:corrected for age, sex, HF duration, baseline LVEF, E/A ratio, LAVI

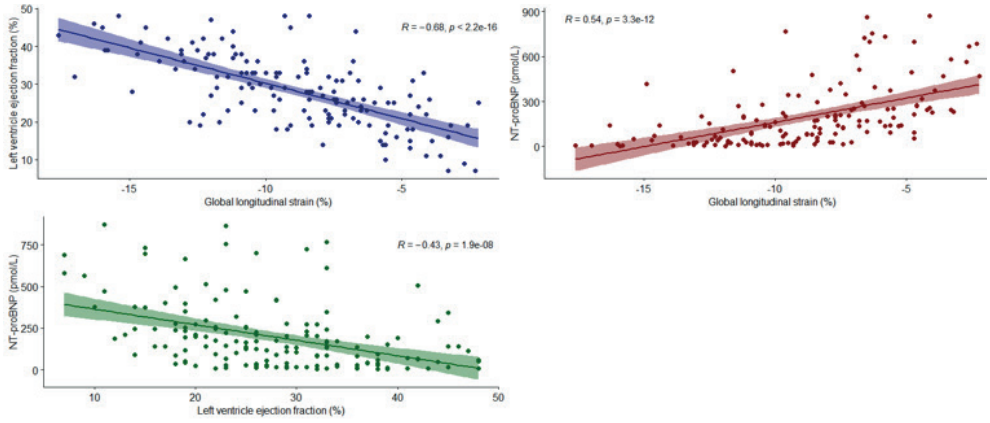
Model 5:corrected for age, sex, HF duration, New York Heart Association(dichotomized as NYHA class I-II versus NYHA class III-IV), atrial fibrillation, renal failure, systolic and diastolic blood pressure

Model 6 and 7:Multivariable Joint Models: Corrected for age, sex, HF duration, New York Heart Association(dichotomized as NYHA class I-II versus NYHA class III-IV), atrial fibrillation, renal failure, systolic and diastolic blood pressure

Baseline and repeatedly measured GLS in relation to the composite endpoint

When entered into separate models, baseline GLS and LVEF were both significantly associated with the endpoint, independently of age, sex, baseline NT-proBNP and the duration of HF (Table 3), with HRs(95%CI) per SD change of 2.15(1.34–3.46) and 1.41(1.01-2.13), respectively. When entered into one model corrected for the same covariates, the association of baseline GLS with the endpoint remained (HR(95%CI: 2.76(1.66-4.58)), while that of LVEF disappeared (HR(95%CI: 1.11(0.71-1.75)). GLS was also significantly associated with the endpoint after adjustment for the most important systolic and diastolic echocardiographic parameters, namely EF, E/A ratio, E/e' and LAVI (HR(95%CI: 1.75(1.30-2.85)). In the total population, there was a slight decrease in GLS over time as the endpoint or censoring approached (Beta[95%CI]: 0.71[0.47-0.94] per SD change of GLS per year), p<0.001). Figure 3 and Supplementary figure 3 show the temporal evolution of GLS in patients who experienced the endpoint and those who did not. At 12 months before the endpoint or censoring occurred, GLS was already decreased in patients that later experienced the endpoint compared to those who did not; and it remained decreased as the endpoint approached. However, the curves were parallel for patients with and without the endpoint, with no significant difference in slope, similar to the temporal evolution of LVEF (Figure 3 and Supplementary figure 3 and 5). The temporal evolution of E/A and E/e' (Supplementary figure 4) also showed similar patterns. When we calculated, from the mixed models, the mean relative change in GLS and LVEF compared to baseline values of GLS and LVEF in the patients with the endpoint, on average, for GLS, these patients had a relative decrease of 5% compared to baseline at day 185. This was 255 days earlier than the relative decrease of LVEF of 5% at day 440. Accordingly, longitudinally measured GLS was significantly associated with the endpoint in all the fitted joint models (Table 3). In the first model, adjusted for age, sex and duration of HF, the HR was 2.11 (95%CI:1.37-3.31). When baseline LVEF was added to the model, the HR was 3.33 (95%CI:1.95-3.31). After adding baseline NT-proBNP to the models, the association still persisted (3.50(95%CI:2.18-5.89)). The results of the multivariable joint models into which the repeatedly measured GLS, as well as repeatedly measured LVEF and NT-proBNP, were entered, are shown in Table 3. GLS showed a HR(95%CI) of 4.38(1.49-14.70) for the endpoint when correcting for repeatedly measured LVEF. However, the HR(95%CI) became 0.79(0.47–1.30) when correcting for repeatedly measured NT-proBNP.

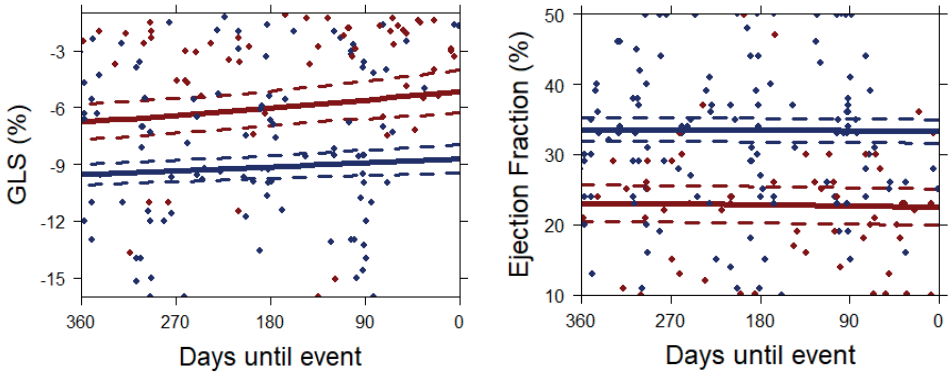
Figure 2: Scatterplots for GLS, LVEF and NT-proBNP. The regression lines represent the correlation between the variables of interest. Each dot represents a single patient.



DISCUSSION

In this study consisting of 173 chronic HF patients with reduced EF, that had limited symptoms at baseline, firstly, temporal evolution of GLS was significantly associated with adverse cardiovascular events during a median follow-up of 2.7 years, independent of both baseline and repeated LVEF and baseline NT-proBNP measurements. However, the association disappeared after adjustment for repeated NT-proBNP measurements. Secondly, while GLS was decreased in patients that later experienced the endpoint as compared to those who did not, and remained decreased as the endpoint approached, the temporal trajectories of GLS did not further diverge in patients with versus without the endpoint and remained stable over this 2.7-year time frame. For this reason, we infer that repeatedly measuring GLS over a short time frame does not provide additional incremental prognostic information over a single measurement, and a single baseline measurement of GLS provides sufficient information for prognostication in clinical practice. Previously, we have examined the prognostic value of repeated measurements of LVEF, as well as repeated measurements of established diastolic echo parameters, in the context of the Bio-SHiFT study (13). Similar to GLS, the temporal trajectories of LVEF and the diastolic parameters did not diverge between patients with and without the endpoint. However, to our knowledge, the prognostic value of repeatedly measured GLS, and its added value over a single 'baseline' GLS assessment, and over repeatedly measured LVEF, has not yet been examined in patients with HF. Herewith, this study confirms and increases previous evidence on the added prognostic value of GLS over LVEF.

Figure 3: Mean temporal patterns of GLS and LVEF until occurrence of the primary endpoint or censoring. Continuous lines represent mean temporal patterns for patients with the endpoint (red) and patients who remained endpoint-free (blue), as extracted from the joint model. Time-point zero represents the occurrence of an event in the endpoint patients and censoring in patients who remained endpoint-free. Dotted lines represent 95% confidence intervals. Each dot represents a single measurement.



Several studies have shown that 'baseline' GLS carries prognostic value over LVEF (1, 3, 5, 7). A meta-analysis by Kamal et al. (3) showed that baseline GLS was more strongly associated with mortality than LVEF. In a study by Bertini et al. (22) in 1060 HF patients, baseline GLS showed incremental value over LVEF as well. These studies only examined baseline measurements of GLS, whereas our study contained multiple GLS measurements per patient. Baseline GLS can be considered low in this cohort (mean[95%CI]:-9.2%[-9.5%- -8.8%]) compared to healthy populations. However, this is inherent to the study population, and studies in other HFrEF cohorts have shown similarly low GLS values (10). While in our study the association of repeatedly measured GLS with the endpoint persisted when correcting for repeatedly measured LVEF, it disappeared when correcting for repeatedly measured NT-proBNP. In advanced stages of HF, further reduction in already low values of GLS and LVEF is unlikely, whereas NT-proBNP may further increase in advanced HF stages. This may have contributed to the finding that the incremental value of GLS disappeared after correcting for repeatedly measured NT-proBNP. Furthermore, GLS and EF provide no information about the detrimental impact of LV dysfunction on the right ventricle, whereas NT-proBNP does. In addition, the presence of mitral regurgitation (MR) could negatively affect the validity of LVEF (23). In contrast, NT-proBNP has been shown to be a reliable biomarker in MR and is an independent predictor in this group (24). Previous studies have already shown that NT-proBNP carries strong prognostic value in HF (25, 26). Our study demonstrates that the prognostic value of

NT-proBNP is independent of repeated GLS measurements, but not vice versa. Herewith, and in combination with the availability and ease of implementation of simple laboratory tests, our study further supports the use of NT-proBNP for prognostication in HF. It should be noted though, that NT-proBNP levels could be impacted due to the presence of AF, and that the NT-proBNP to BNP ratio varies according to heart rhythm (27). This should be taken into account when interpreting NT-proBNP levels in patients with AF. Prevalence of AF was higher among patients who reached the endpoint. To account for potential confounding, we adjusted the models for AF. The use of GLS in clinical practice is currently limited due to inter-vendor variability, poor predictive ability in images with low quality and load-dependency (3, 28). Nevertheless, in 2015 a EACVI/ASE/Industry Task Force consensus document was published to standardize deformation imaging (29). Furthermore, GLS is known to have better intra-observer and inter-observer variability than LVEF (3). Also, several studies have shown the prognostic incremental value of GLS over LVEF when EF was normal. A meta-analysis which included 5721 patients demonstrated that impaired GLS was present in patients with normal LVEF, and predicted cardiac events (3), which is also shown in another study (9). These studies show that LVEF also carries potential limitations regarding diagnosis and prognostication of HF and illustrate the potential incremental value of GLS over LVEF for prognostication in clinical practice.

Several limitations of our study warrant consideration. First, treating physicians were not blinded to the echocardiograms. However, GLS values were measured retrospectively and were not available for the physicians. Second, the number of endpoints in the study was limited, and consequently so was the number of variables that could be entered into the models. To prevent overfitting, we fitted multiple multivariable models containing different confounders, instead of one model containing all covariates. Although residual confounding might be present, all these models were corrected for NT-proBNP. In addition, we also corrected for the duration of HF, to control for possible lead time or length time bias. Furthermore, multicollinearity (highly correlated variables) could be present when GLS and LVEF are entered in the model (r=-0.68), so results should be interpreted with caution. Nevertheless, examining the prognostic value of GLS over LVEF warranted inclusion of both variables in the model. Finally, the patients in this echo substudy were relatively young and there was a high proportion of patients in NYHA classes I and II. Older patients with worse condition may have been less likely to participate in the substudy. However, prognosis of patients in advanced stages of HF is already known to be poor, while in a population like ours, differentiating between patients who reach an event and patients who remain event free remains more difficult. Therefore, parameters with high prognostic value are essential in this group particularly.

Altogether, in a population of chronic HF patients, temporal evolution of GLS was significantly associated with adverse cardiovascular events during a median follow-up of 2.7 years, independent of both baseline and repeated LVEF, and baseline NT-proBNP measurements. After correction for repeated NT-proBNP in a multivariable model, the association disappeared. We conclude that repeatedly measuring GLS over a short time frame does not seem to provide additional incremental prognostic information over a single measurement in clinical practice. The incremental prognostic value of repeatedly measured NT-proBNP over GLS, supports the use of NT-proBNP for prognostication in clinical practice. Further studies in larger and more diverse cohorts are needed to confirm our findings; moreover, use of temporal trajectories of GLS for other purposes, such as assessment of response to therapy, warrants further research.

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SUPPLEMENTARY MATERIAL

Supplementary table 1: Association baseline GLS with clinical characteristics*

	β (95% CI)	P value
Demographics		
Gender: male	0.44 (0.07 – 0.81)	0.02
Age (years)	0.01 (-0.58 – 0.06)	0.09
Clinical characteristics		
Body mass index (kg/m²)	-0.03 (-0.07 – 0.01)	0.1
Mean heart rate (bpm)	0.01 (-0.01 – 0.02)	0.2
Systolic blood pressure (mmHg)	-0.02 (-0.03 – -0.01)	<0.001
Diastolic blood pressure (mmHg)	-0.02 (-0.03 – -0.01)	0.03
NYHA class I (reference group)		
NYHA class II	0.38 (0.02 – 0.74)	0.04
NYHA class III	0.91 (0.44 – 1.39)	<0.001
Features of HF		
Ischemic HD	0.56 (0.25 – 0.87)	<0.001
Hypertension	-0.04 (-1.45 – 1.40)	1
Cardiomyopathy	-0.26 (-0.58 – 0.06)	0.1
Valvular disease	-0.19 (-1.19 – 0.82)	0.7
Medical history		
Prior myocardial infarction	0.60 (0.30 – 0.91)	<0.001
Prior percutaneous coronary intervention	0.37 (0.05 – 0.70)	0.03
Prior coronary artery bypass grafting	0.35 (-0.17 – 0.87)	0.2
Atrial Fibrillation	0.35 (0.01 – 0.69)	0.04
Diabetes	0.34 (-0.35 – 0.71)	0.08
Renal Failure	0.19 (-0.14 – 0.51)	0.3
COPD	0.23 (-0.21 – 0.67)	0.3
Medication use		
Beta-blocker	-0.97 (-1.71 – -0.22)	0.01
Angiotensin converting enzyme inhibitors	-0.19 (-0.53 – 0.16)	0.3
Angiotensin receptor blocker	0.14 (-0.22 – 0.49)	0.5
Loop diuretics	0.81 (0.19 – 1.41)	0.01
Aldosterone antagonist	0.39 (0.04 – 0.74)	0.03

*The betas represent the mean change in GLS (in %) when the explanatory variable is increased by one unit, or the mean difference between two groups when the explanatory variable is categorical.

Supplementary table 2: Association baseline GLS with echocardiographic parameters*

	β (95% CI)	P value
Systolic parameters		
Ejection fraction (%)	-0.07 (-0.08 - -0.05)	<0.001
Diastolic LV diameter (mm)	0.01 (-0.01 – 0.02)	0.5
Systolic LV diameter (mm)	0.05 (0.03 – 0.06)	<0.001
Systolic Left Atrial diameter (mm)	0.05 (0.03 – 0.06)	<0.001
Diastolic parameters		
E/A ratio	0.33 (0.17 – 0.48)	<0.001
E/e ratio	0.05 (0.04 – 0.07)	<0.001
TR velocity	0.38 (0.11 – 0.66)	0.006
Vena Cava		
Vena Cava Inferior	0.06 (0.03 – 0.09)	<0.001
Vena cava Sniff: No	0.88 (0.38 – 1.38)	<0.001
Mitral valve regurgitation		
Mild	0.62 (0.27 – 0.96)	<0.001
Moderate	0.69 (0.26 – 1.13)	0.002
Severe	0.95 (0.25 – 1.65)	0.008
Tricuspid valve regurgitation		
Mild	0.33 (-0.01 – 0.66)	0.05
Moderate	1.22 (0.66 – 1.79)	<0.001
Severe	0.80 (0.08 – 1.52)	0.03

*The betas represent the mean change in GLS (in %) when the explanatory variable is increased by one unit, or the mean difference between two groups when the explanatory variable is categorical.

Supplementary table 3: Association serially measured GLS with clinical characteristics

	β (95% CI)	P value
Demographics		
Gender: male	0.54 (0.21 – 0.88)	0.002
Age (years)	0.02 (0.01 – 0.03)	0.006
Clinical characteristics		
Body mass index (kg/m²)	-0.01 (-0.05 – 0.02)	0.5
Mean heart rate (bpm)	0.01 (-0.01 – 0.02)	0.2
Systolic blood pressure (mmHg)	-0.01 (-0.02 – 0.01)	0.009
Diastolic blood pressure (mmHg)	-0.01 (-0.03 – 0.01)	0.1
NYHA class I (reference group)		
NYHA class II	0.34 (0.01 – 0.67)	0.04
NYHA class III	0.84 (0.40 – 1.27)	<0.001
Features of HF		
Ischemic HD	0.62 (0.33 – 0.89)	<0.001
Hypertension	0.14 (-1.24 – 1.51)	0.8
Cardiomyopathy	-0.22 (-0.51 – 0.08)	0.1
Valvular disease	0.10 (-0.84 – 1.04)	0.8
Medical history		
Prior myocardial infarction	0.67 (0.39 – 0.95)	<0.001
Prior percutaneous coronary intervention	0.43 (0.13 – 0.73)	0.005
Prior coronary artery bypass grafting	0.42 (-0.08 – 0.92)	0.1
Atrial Fibrillation	0.50 (0.19 – 0.82)	0.002
Diabetes	0.43 (0.09 – 0.77)	0.01
Renal Failure	0.22 (-0.08 – 0.51)	0.2
COPD	0.28 (-0.14 – 0.70)	0.2
Medication use		
Beta-blocker	-0.94 (-1.66 – -0.21)	0.01
Angiotensin converting enzyme inhibitors	-0.16 (-0.47 – 0.16)	0.3
Angiotensin receptor blocker	0.11 (-0.22 – 0.43)	0.5
Loop diuretics	0.67 (0.09 – 1.25)	0.02
Aldosterone antagonist	0.23 (-0.11 – 0.56)	0.2

*The betas represent the mean change in GLS (in %) when the explanatory variable is increased by one unit, or the mean difference between two groups when the explanatory variable is categorical.

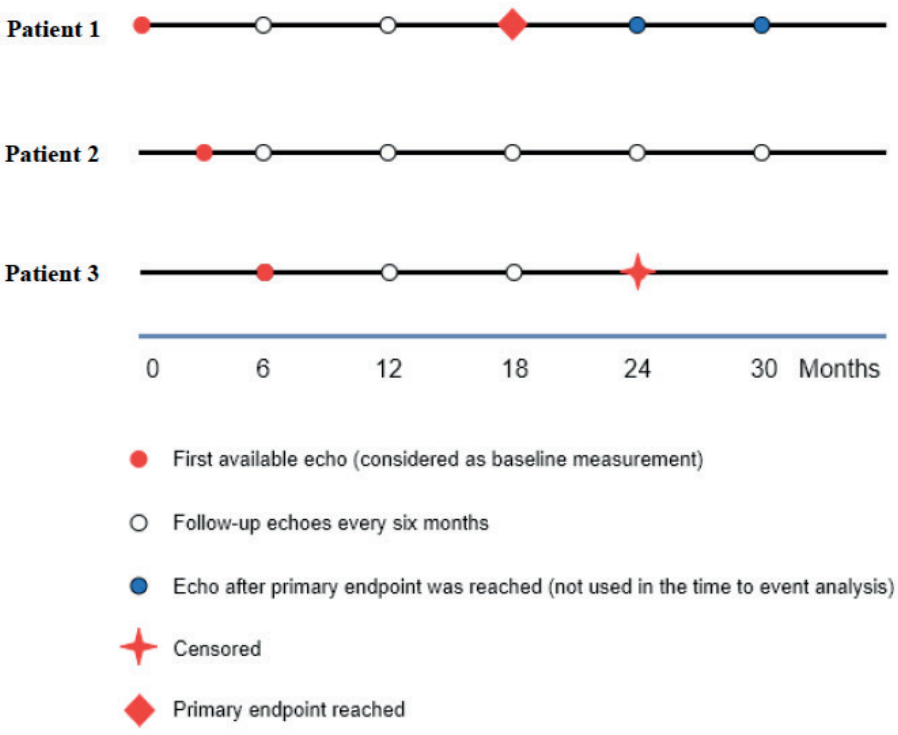
Supplementary table 4: Association serially measured GLS with serially measured echocardiographic parameters

	β (95% CI)	P value
Systolic parameters		
Ejection fraction (%)	-0.05 (-0.06 – -0.04)	<0.001
Diastolic LV diameter (mm)	0.01 (-0.09 – 0.01)	0.5
Systolic LV diameter (mm)	0.03 (0.02 – 0.04)	<0.001
Systolic Left Atrial diameter (mm)	0.03 (0.02 – 0.04	<0.001
Diastolic parameters		
E/A ratio	0.07 (0.01 - 0.13)	0.02
E/e ratio	0.02 (0.01 - 0.03)	<0.001
TR velocity	0.18 (0.06 - 0.29)	0.004
Vena Cava		
Vena cava inferior	0.02 (0.01 - 0.04)	0.008
Vena cava Sniff: No	0.31 (0.07 - 0.55)	0.01
Mitral valve regurgitation		
Mild	0.13 (-0.02 – 0.28)	0.08
Moderate	0.35 (0.11 – 0.58)	0.004
Severe	0.62 (0.26 – 0.97)	0.008
Tricuspid valve regurgitation		
Mild	0.24 (0.11 – 0.37)	<0.001
Moderate	0.59 (0.32 – 0.86)	<0.001
Severe	0.20 (-0.23 – 0.64)	0.4

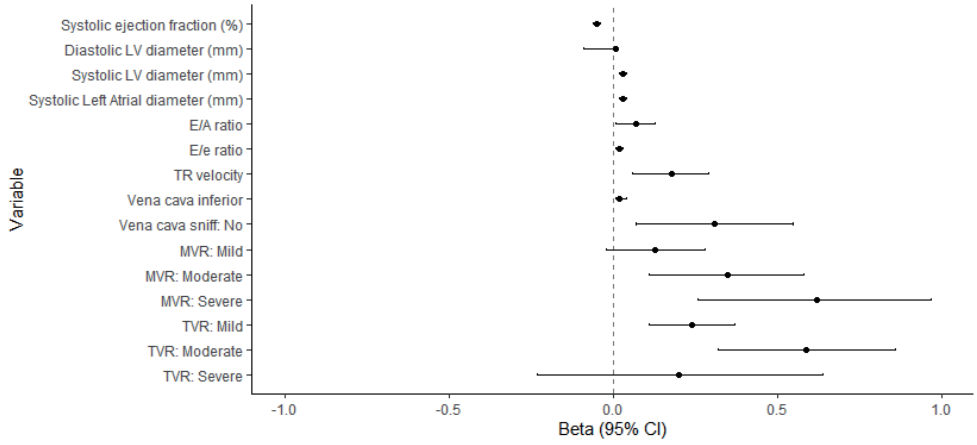
*The betas represent the mean change in GLS (in %) when the explanatory variable is increased by one unit, or the difference between two groups when the explanatory variable is categorical.

SUPPLEMENTARY MATERIAL

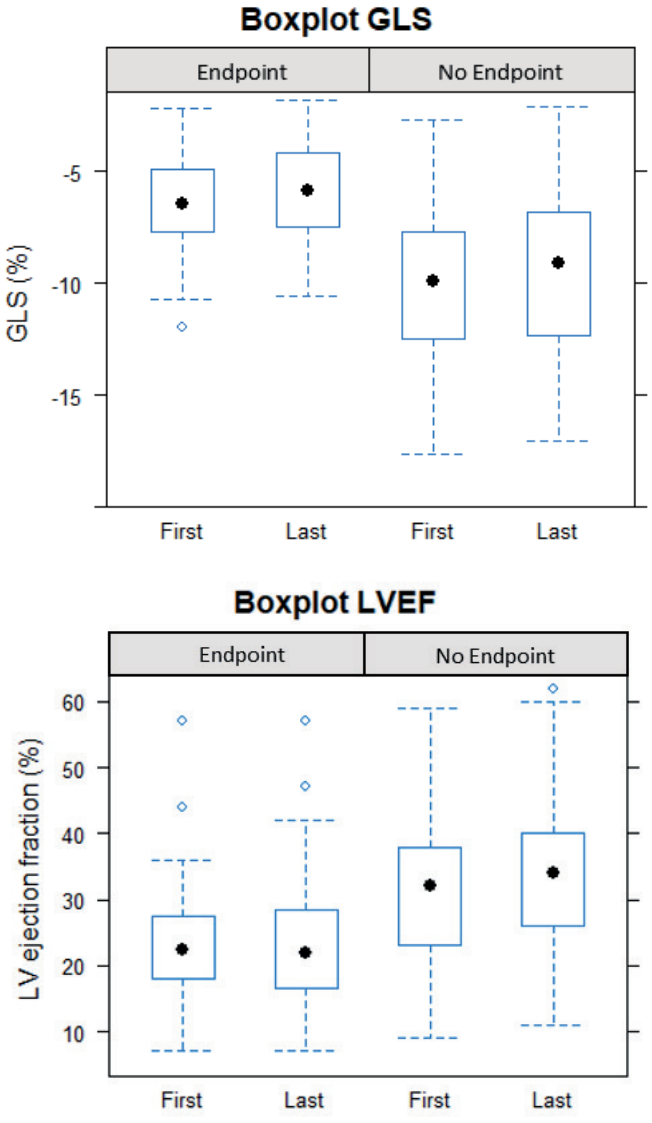
Supplementary figure 1: Study design: first available and follow-up echocardiograms
The figure provides 3 example patients to illustrate which echocardiograms were the first available echocardiograms, considered as 'baseline' in the analysis (red circles), and at which time-points follow-up echocardiograms were scheduled. 55% of the first available echocardiograms were performed at baseline (follow-up time zero), 12.8% were performed during the first study follow-up visit (target follow-up time 3 months) and 18% were performed during the second follow-up visit (target 6 months). Subsequently, echoes were performed every six months.



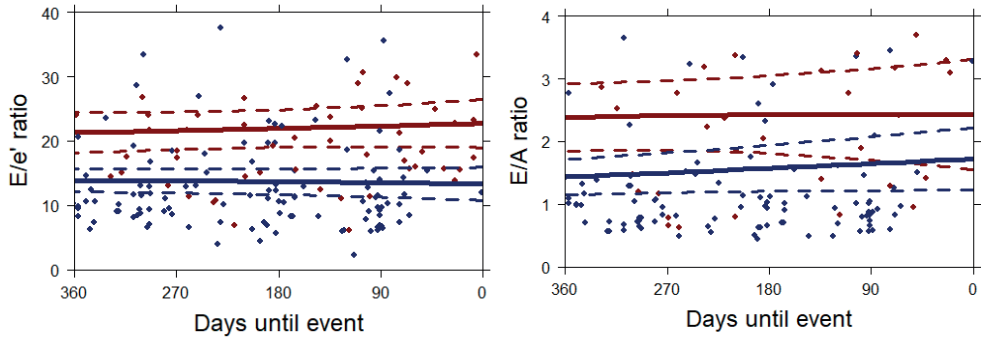
Supplementary figure 2: Associations of serially measured echocardiographic parameters with serially measured GLS.
Betas depict change in GLS (in %) when the explanatory variable is increased by 1 unit. 95%CI: 95% confidence interval. MVR: Mitral valve regurgitation. TVR: Tricuspid valve regurgitation)



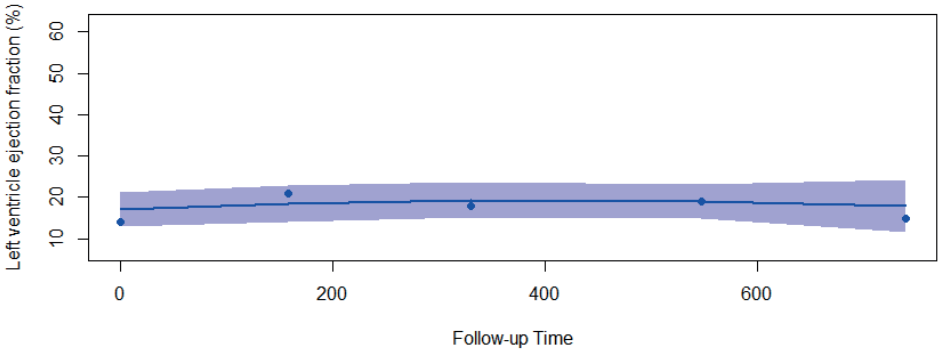
Supplementary figure 3: First and last GLS and LVEF values according to endpoint status. The boxplots show the average GLS and LVEF at the first and last available measurements. The averages of GLS and LVEF in patients with the endpoint is shown in the left panel, whereas the average GLS in patients without the endpoint is shown in the right panel.

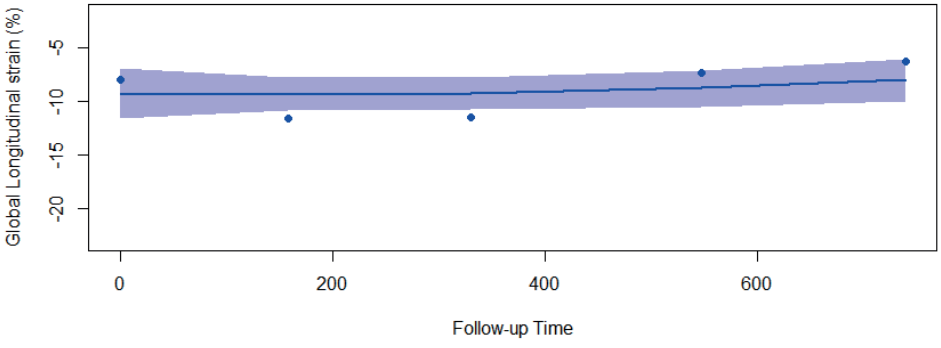


Supplementary Figure 4: Mean temporal patterns of E/e' and E/A ratio until occurrence of the primary endpoint or censoring.
Continuous lines represent mean temporal patterns for patients with the PEP (red) and patients who remained PEP-free (blue), as extracted from the joint model. Time-point zero represents the occurrence of an event in the PEP patients and censoring in patients who remained PEP-free. Dotted lines represent 95% confidence intervals. Each dot represents a single measurement.



Supplementary Figure 5: Temporal evolution LVEF and GLS for one example patient.





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Chapter 7

Cardiac function normalizes 1 year after bariatric surgery in half of the obesity patients with subclinical cardiac dysfunction

Sanne Snelder, Yaar Aga, Lotte de Groot-de Laat, Ulas Biter, Manuel Castro Cabezas, Nadine Pouw, Bianca Boxma-de Klerk, René Klaassen, Felix Zijlstra, Bas van Dalen

Obesity Surgery 2021

INTRODUCTION

Obesity has reached epidemic proportions globally and the prevalence is still increasing. Subclinical cardiac dysfunction is common in obesity patients and obesity is associated with an increased risk of heart failure (1). Clinically significant weight loss is difficult to achieve with lifestyle interventions and the results are often temporary. In contrast, bariatric surgery is an effective and safe treatment option resulting in large long-term weight loss (2). However, little is known about potential improvement of subclinical cardiac dysfunction after bariatric surgery. The CARdiac Dysfunction In Obesity – Early Signs Evaluation (CARDIOBESE) study is a prospective study that was designed to investigate this, using a combination of (speckle tracking) echocardiography, blood tests, and Holter monitoring to simultaneously investigate different possible expressions of subclinical cardiac dysfunction. The protocol of the CARDIOBESE study has been described before (3). In this research letter we briefly describe the main results. Additional analyses of the data will be performed in the near future to provide further insight in the pathophysiological background of the findings.

METHODS

We enrolled 100 obesity patients who were referred for bariatric surgery in this longitudinal study. Inclusion criteria were age 35-65 years and BMI ≥35 kg/m^2. Patients with a suspicion of or known cardiovascular disease were excluded. Bariatric surgery was performed by either a gastric sleeve, a gastric bypass, or a mini bypass operation. Conventional and speckle tracking echocardiography, Holter monitoring, and blood tests were performed. Patients were seen pre- and one-year post-bariatric surgery. Subclinical (in other words, not previously diagnosed) cardiac dysfunction was based on the diagnostics used in CARDIOBESE and defined as either a reduced left ventricular (LV) ejection fraction (4), decreased GLS (<17%), diastolic dysfunction (5), (supra) ventricular arrhythmia or an increased BNP (>30 pmol/L) or hs Troponin I (≥34 ng/L for male and ≥16 ng/L for female subjects). The study protocol was approved by the ethics committee and written informed consent was obtained from all participants. Baseline characteristics of the studied population have been described before (6). Subclinical cardiac dysfunction was present in 59 patients, mainly uncovered by decreased GLS (6).

STATISTICAL ANALYSIS

Patients who completed the follow-up were included in the analysis. The normality of the data was checked by the Shapiro-Wilk test. Continuous values with normal distributions were expressed as mean ± standard deviation, with skewed distributions as median and interquartile range and categorical values as percentages. The paired Student's t-test was used for continuous variables with normal distributions, the nonparametric Wilcoxon signed-rank test for variables with skewed distributions, and the McNemar test for categorical variables was used to compare parameters pre-and post-surgery.

RESULTS

A total of 85 patients underwent bariatric surgery and 72 patients completed the one-year follow-up. Patients did not undergo bariatric surgery because of various reasons, but mostly because of disapproval by a psychologist or because they had withdrawn themselves from surgery. There was a significant reduction in weight and BMI one year after bariatric surgery (Table 1). Prevalence of comorbidities decreased and medication use was reduced. Blood tests showed a decrease of CRP, HbA1c, ALAT, total cholesterol, LDL-C, and triglycerides. Moreover, HDL-C, folic acid, vitamin B6, and vitamin D significantly increased. The echocardiogram revealed a decrease in LV mass and Holter monitoring a decreased heart rate one year after bariatric surgery.

Regarding changes in parameters of cardiac function after bariatric surgery (Table 1), there was a mild increase in BNP. Levels of hs troponin I were comparable. Echocardiography showed an improvement of GLS. The prevalence of diastolic dysfunction and the LV ejection fraction did not change. There were no arrhythmias and the frequency of extrasystoles did not change.

Fifty of the 59 patients with subclinical cardiac dysfunction at baseline underwent bariatric surgery and 40 completed the follow-up. Of these patients, 20 (50%) had normalized cardiac function (in other words, no remaining signs of cardiac dysfunction as defined in this study) after bariatric surgery. Of the 20 patients with persistent cardiac dysfunction, 17 (43%) still had decreased GLS, one patient had an elevated hs troponin I level, and two patients had diastolic dysfunction.

DISCUSSION

Although in previous studies changes in cardiac morphology and function after bariatric surgery have been investigated (7), CARDIOBESE is the first study in which the focus was specifically on *subclinical* cardiac dysfunction, also with an innovative approach using several diagnostic modalities to concurrently investigate different possible expressions of this.

This methodology allowed us to show for the first time that bariatric surgery not only was associated with a reduction in BMI and comorbidities, but also with a decrease in LV mass and improvement of LV function, resulting in normalized cardiac function in half of the patients with subclinical cardiac dysfunction before surgery. An impressive result, bearing in mind that in large studies in which the effect of for example ACE inhibitors on LV function were studied in high-risk patient groups, results were clearly less pronounced (8, 9). However, these studies noticeably did show improvement in hard clinical endpoints that are not available in the current study and obviously focused on other patient categories. Nevertheless, our findings emphasize the relatively marked positive effect bariatric surgery may have on cardiac function.

Table 1: Clinical characteristics and parameters of cardiac function

	Pre-surgery (n = 72)	1-year post-surgery (n = 72)	p value
General characteristics			
Age (years)	48 [43–54]		
Female (n, %)	54 (75%)		
Weight (kg)	122 [113–133]	83 [74–91	< 0.001
BMI (kg/m2)	41 [39–46	28 [25–31]	< 0.001
Comorbidity			
Diabetes mellitus (n, %)	16 (22%)	6 (8%)	0.002
Hypertension (n, %)	24 (33%)	12 (17%)	0.035
Medication			
ACE inhibitors/ARBs (n, %)	11 (15%)	8 (11%)	0.012
Statins (n, %)	16 (22%)	9 (13%)	0.039
Oral anti-diabetics (n, %)	10 (14%)	4 (6%)	0.031
Blood tests			
CRP (mg/L)	6 [3–9]	0 [0–2]	< 0.001
HbA1c (mmol/mol)	45 ± 15	38 ± 8	< 0.001
Creatinine (umol/L)	73 ± 10	67 ± 9	< 0.001
ALAT (U/L)	30 [20–37]	19 [15–26]	0.004
Total cholesterol (mmol/L)	5.3 ± 0.9	4.6 ± 0.8	< 0.001
LDL cholesterol (mmol/L)	3.2 ± 0.8	2.6 ± 0.7	< 0.001
HDL cholesterol (mmol/L)	1.2 ± 0.3	1.4 ± 0.3	< 0.001
Triglycerides (mmol/L)	2.06 ± 1.8	1.20 ± 0.8	< 0.001
Folic acid (nmol/L)	13 [9–16]	27 [16–36]	< 0.001
Vitamin D (nmol/L)	49 ± 25	78 ± 26	< 0.001
Echocardiography parameters			
Left ventricular mass (g)	186 ± 72	156 ± 62	< 0.001
Holter monitoring			
Average heart rate (bpm)	83 ± 10	73 ± 8	< 0.001
Minimal heart rate (bpm)	53 [47–57]	46 [4–51]	< 0.001
Maximum heart rate (bpm)	137 [128–150]	130 [120–142]	0.005
Parameters of cardiac function			
BNP (pmol/L	5 [3–8]	8 [6–10]	0.029
hs troponin I positive (n, %)	1 (1%)	5 (7%)	0.06
Diastolic dysfunction (n, %)	7 (10%)	3 (4%)	0.28
LV ejection fraction (%)	58 ± 8	57 ± 7	0.25
Global longitudinal strain (%)	– 15.6 ± 3.1	– 18.1 ± 3.3	0.001
Total PAC per 24 h (n)	9 [2–38]	20 [8–68]	0.07
Total PVC per 24 h (n)	3 [0–22]	5 [2–58]	0.29
Supraventricular arrhythmia (n, %)	1 (1%)	0	0.53

Values represent mean ± SD, median [Q1-Q3] or n (%). BMI body mass index, ACE angiotensin-converting enzyme, ARBs angiotensin II receptor blockers, CRP Creactive protein, HbA1c glycated haemoglobin, ALAT alanine transaminase, LDL low-density lipoprotein, HDL high-density lipoprotein, BNP brain natriuretic peptide, hs troponin I high sensitive troponin I, LV left ventricular, PAC premature atrial complex, PVC premature ventricular complex *Significant at $p < 0.05$

CONCLUSION

Cardiac function improves significantly in obesity patients one year after bariatric surgery, resulting in normalized cardiac function in half of the patients with subclinical cardiac dysfunction before bariatric surgery.

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Chapter 8

Normalization of cardiac function after bariatric surgery is related to autonomic function and Vitamin D

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Obesity Surgery 2023

ABSTRACT

Purpose

Subclinical cardiac dysfunction is common in patients with obesity. Bariatric surgery is associated with normalization of subclinical cardiac function in 50% of the patients with obesity. The aim of this study was to identify predictors for a lack of improvement of subclinical cardiac dysfunction one-year post-bariatric surgery.

Methods

Patients who were referred for bariatric surgery were enrolled in a longitudinal study. Inclusion criteria were age 35-65 years and BMI ≥35 kg/m^2. Patients with a suspicion of or known cardiovascular disease were excluded. Conventional and advanced echocardiography, Holter monitoring, and blood tests were performed pre- and one-year post-bariatric surgery. Subclinical cardiac dysfunction was defined as either a reduced left ventricular ejection fraction, decreased global longitudinal strain (GLS), diastolic dysfunction, arrhythmia or an increased BNP or hs Troponin I.

Results

A total of 99 patients were included of whom 59 patients had cardiac dysfunction at baseline. Seventy-two patients completed the one year follow-up after bariatric surgery. There was a significant reduction in weight and cardiovascular risk factors. Parameters of cardiac function, such as GLS, improved. However, in 20 patients cardiac dysfunction persisted. Multivariate analysis identified a decreased heart rate variability (which is a measure of autonomic function), and a decreased vitamin D pre-surgery as predictors for subclinical cardiac dysfunction after bariatric surgery.

Conclusion:

Although there was an overall improvement of cardiac function one year post-bariatric surgery, autonomic dysfunction and a decreased vitamin D pre-bariatric surgery were predictors for a lack of improvement of subclinical cardiac dysfunction.

INTRODUCTION

Obesity has reached epidemic proportions globally and the prevalence is still increasing (1). Subclinical cardiac dysfunction is common in patients with obesity (2), and obesity is associated with an increased risk of heart failure (3). Heart failure is characterized by an impaired quality of life, frequent hospitalizations, and poor outcome (4). Considering that prevention and treatment of heart failure have enormous medical and socioeconomic implications, a deeper understanding of risk factors for heart failure such as obesity is imperative. Clinically significant weight loss is difficult to achieve with lifestyle interventions and the results are often temporary. In contrast, bariatric surgery is an effective and safe treatment option resulting in large long-term weight loss (5). Several studies suggest that weight loss achieved by bariatric surgery has a positive impact on heart morphology, even in patients with obesity without heart failure (6). We recently demonstrated that subclinical cardiac dysfunction normalized in half of the patients with obesity one-year after bariatric surgery (7). Also, bariatric surgery is associated with a 35% reduced incidence of new-onset heart failure during long term follow-up (8). However, little is known about the pathophysiology of cardiac dysfunction in obesity patients and the factors determining the evolution of cardiac function after bariatric surgery are unknown. We have previously shown that subclinical cardiac dysfunction is related to autonomic dysfunction in obesity patients (2). but it is unknown whether autonomic dysfunction may be related to a lack of recovery of cardiac dysfunction after bariatric surgery as well. The CARdiac Dysfunction In Obesity – Early Signs Evaluation (CARDIOBESE) study was the first study in which (speckle tracking) echocardiography, blood tests, and Holter monitoring were combined to simultaneously investigate different aspects that may all play a role in the pathophysiology of subclinical cardiac dysfunction in obesity patients. The aim of this study was to identify predictors for persistent cardiac dysfunction one-year post-bariatric surgery.

METHODS

Study design and study group

The protocol of the CARDIOBESE study has been described before. (9) In short, the CARDIOBESE study is a longitudinal study in which we prospectively enrolled 100 patients with obesity who were referred for bariatric surgery to the Franciscus Gasthuis & Vlietland (75 patients) and Maasstad Ziekenhuis (25 patients), both in Rotterdam, the Netherlands. Patients were included if they were between 35 and 65 years old and had a BMI of ≥35 kg/m^2. Patients with a suspicion of or known cardiovascular disease were excluded. Bariatric surgery was performed by either a gastric sleeve, a

gastric bypass or one anastomosis gastric bypass (OAGB)operation. Patients were seen pre- and one-year post-bariatric surgery to study the intra-personal impact of obesity and bariatric surgery-related changes on cardiac function. The study protocol was approved by the ethics committee and written informed consent was obtained from all participants (9).

The presence or absence of subclinical cardiac dysfunction in the 100 patients with obesity of the CARDIOBESE-study has been described in detail before (2). In short, cardiac dysfunction was defined as either a reduced LV ejection fraction, (10) a decreased global longitudinal strain (GLS) (<17%), diastolic dysfunction, (11) ventricular arrhythmia or an increased BNP (>30 pmol/L) or hs Troponin I(≥34 ng/L for male and > 16 ng/L for female subjects). Of the predefined studied parameters, a decreased GLS (<17%) was by far the most abundant, in 57 patients; one had diastolic dysfunction without an available GLS, one had a normal GLS but an increased BNP (49 pmol/L, normal value <30 pmol/L), and one had a positive hs Troponin I. One patient with cardiac dysfunction was diagnosed with acromegaly after inclusion and was excluded from further analysis, leaving 59 patients with versus 40 without subclinical cardiac dysfunction**.**

Transthoracic echocardiography

Two-dimensional grayscale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system (EPIQ 7, Philips, Best, the Netherlands), equipped with a broadband (1-5MHz) X5-1 transducer. All acquisitions and measurements were performed according to current guidelines (10, 11).

Interventricular septal thickness (IVSd), posterior wall thickness (PWd), and left ventricular dimension (LVEDD) were all measured at end-diastole. The left ventricular mass (LVM) was calculated according to the Deveraux formula using these measurements: LVM (g) = 0.80 × {1.04[(IVSd +LVEDD + PWd)3-(LVEDD)3]} + 0.6. LVM-index (LVMI) was calculated by dividing LVM by body surface area.

To optimize speckle tracking echocardiography, apical images were obtained at a frame rate of 60 to 80 frames/s. Three consecutive cardiac cycles were acquired from all apical views. Subsequently, these cycles were transferred to a QLAB workstation (version 10.2, Philips, Best, the Netherlands) for off-line speckle tracking analysis. Peak regional longitudinal strain was measured in 17 myocardial regions and a weighted mean was used to derive GLS.

Blood tests

Non-fasting blood samples were taken both for the study and as part of regular care. Routine laboratory measurements included; glucose, glycosylated haemoglobin (HbA1C), creatinine, estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALAT), Apolipoprotein B, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, ferritin, active vitamin B12, folic acid, vitamin B1, vitamin B6, albumin, magnesium, vitamin D, and haemoglobin were determined by standard clinical procedures as described (12). In addition to the regular patient care path blood tests, high sensitive troponin I (hs troponin I), C reactive protein (CRP) and brain natriuretic peptide (BNP) were determined specifically for this study.

Holter monitoring

Heart rhythm was recorded for 24 consecutive hours using a portable digital recorder (GE HEER Light, USA). The digital recorder was connected using stickers that were placed on the chest. Average heart rate, minimal heart rate, maximum heart rate, total premature atrial contractions (PAC), total premature ventricular contractions (PVC), the standard deviation of all NN (often also referred to as RR) intervals (SDNN) and SDNN-index were measured. 24-hour recording of the SDNN reveals the sympathetic nervous system contribution to heart rate variability (13). The SDNN-index estimates the variability due to the factors affecting heart rate variability (HRV) within a 5 minute period. It is calculated by first dividing the 24 hours record into 288 5-minute-segments and then calculating the standard deviation of all NN intervals contained within each segment (14).

Statistical analysis

Patients who completed the follow-up were included in the analysis. The normality of the data was checked by the Shapiro-Wilk test. Continuous values with normal distributions were expressed as mean ± standard deviation, with skewed distributions as median and interquartile range and categorical values as percentages. The paired Student's t-test was used for continuous variables with normal distributions, the nonparametric Wilcoxon signed-rank test for variables with skewed distributions, and the McNemar test for categorical variables was used to compare parameters pre- and post-surgery. The unpaired Student's t-test for continuous variables was used to compare the pre- and post-surgery values of patients with versus without cardiac dysfunction post-surgery, the non-parametric Mann-Whitney U test for continuous parameters with skewed distributions, and the $\chi 2$ test for categorical variables. Pre-surgery parameters that significantly differed between patients with post-surgery normal cardiac function and patients with post-surgery cardiac dysfunction in the univariate analyses were added to multivariate logistic regression analysis (method:

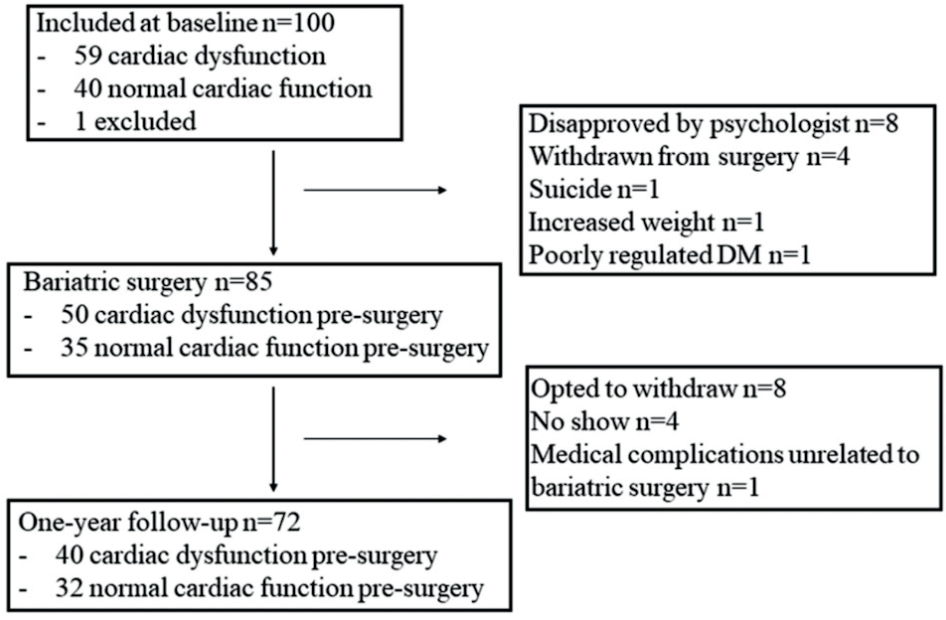
backward stepwise analysis). The discriminative ability of the resulting model was investigated by calculating the area under the receiver operating curve (AUC). Odds ratios and 95% confidence intervals were calculated. A two-tailed p-value of <0.05 was considered statistically significant. Statistical analyses were performed with SPSS version 26.0 or higher (SPSS Inc., Chicago, USA).

RESULTS

Changes in features of obesity from pre- to one-year post-bariatric surgery

A total of 100 patients with obesity were included, 85 patients underwent bariatric surgery and 72 patients completed the one-year follow-up (Figure 1). Fifteen patients did not undergo bariatric surgery because of various reasons, but mostly because of disapproval by the psychologist or because they withdrew from surgery for personal reasons. In Table 1 it is shown that weight loss and decreased BMI were significant one-year post-bariatric surgery. Systolic blood pressure and heart rate decreased significantly as well. Also, the prevalence of comorbidities such as diabetes mellitus, hypertension, and obstructive sleep apnoea syndrome decreased significantly. Medication use was reduced post-surgery, with a significant reduction in use of ACE inhibitors/angiotensin receptor blockers, statins, and oral anti-diabetics.

Figure 1: Flow-chart of patients with completion of or loss to follow-up. DM: diabetes mellitus



Blood tests showed a significant decrease in CRP, HbA1c, creatinine, ALAT, Apolipoprotein B, total cholesterol, LDL-C, and triglycerides post-bariatric surgery. HDL-C, folic acid, vitamin B6, and vitamin D increased significantly. The echocardiogram showed a decrease in LVM, but when corrected for the body surface area (LVM-index), there was no significant decrease. Holter monitoring showed a decreased mean, minimal and maximum heart rate one-year post-surgery, whereas the SDNN and the SDNN-index increased.

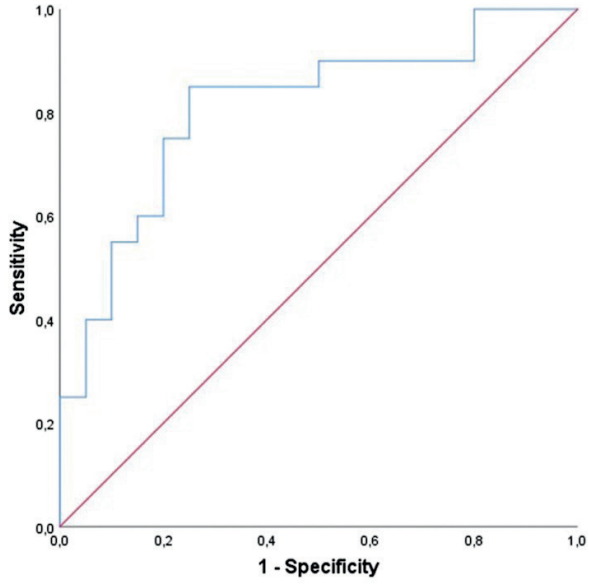
Changes of parameters of cardiac dysfunction from pre- to one-year post-bariatric surgery

There was a mild but statistically significant increase in BNP one-year post-bariatric surgery (Table 2). Levels of hs troponin I were comparable. Echocardiography showed a significant improvement of GLS. The prevalence of diastolic dysfunction and the LV ejection fraction did not change. Also, the frequency of extrasystoles did not change from pre- to one-year post-bariatric surgery.

Comparison of patients with versus without normalization of cardiac function after bariatric surgery

Of the patients with complete follow-up, 40 (56%) had subclinical cardiac dysfunction pre-surgery. In 50% of these patients cardiac function had normalized one-year post-surgery (Table 3). In the 20 patients in whom subclinical cardiac dysfunction persisted, 17 (43%) had a decreased GLS, one patient had an elevated hs troponin I level, and two patients had diastolic dysfunction. When comparing patients with versus without normalization of cardiac function after bariatric surgery, most pre-surgery parameters were comparable, except for albumin, vitamin D and SDNN. Post-surgery only albumin was mildly decreased in patients without normalization. Multivariate analysis was applied including the parameters which were different pre-surgery, identifying a decreased SDNN and a decreased vitamin D pre-surgery as significant predictors for maintaining cardiac dysfunction after bariatric surgery (Table 4). The multivariate model including these two parameters to identify patients who maintained cardiac dysfunction post-surgery, had an AUC of 0.81 (95% CI: 0.67-0.95, p=0.001), with a sensitivity of 70% (95%CI: 66%-87%) and a specificity of 80% (95%CI: 56%-93%) (Figure 2).

Figure 2: ROC-curve for the prediction model for cardiac dysfunction post-surgery. Model; combination of SDNN and vitamin D pre-surgery. Area under the curve = 0.81 (95% CI: 0.67–0.95, p = 0.001), sensitivity of 70%, and a specificity of 80%.



DISCUSSION

The main finding of the current study is that persistence of cardiac dysfunction in patients with obesity one year after bariatric surgery was related to autonomic dysfunction and a decreased vitamin D pre-surgery.

Although in previous studies changes of cardiac morphology and function after bariatric surgery have been investigated (6, 8), CARDIOBESE is the first study in which the focus was specifically on *subclinical* cardiac dysfunction. Furthermore, analysis with the combination of speckle tracking echocardiography, blood tests, and Holter monitoring was used for the first time to simultaneously investigate different aspects of cardiac dysfunction and the underlying pathophysiology. As expected, and in-line with previous findings, (6, 8) many cardiovascular risk factors and parameters of cardiac function improved post-surgery. Prevalence of comorbidities decreased, lipid levels and HbA1c improved, and CRP decreased. Also, there was a mild but statistically significant increase of BNP one-year post-surgery. BNP is known to be decreased in patients with obesity, both with and without heart failure (15). Although the reason

for this remains incompletely understood, it is most likely due to lower release in these patients, rather than increase in their clearance (16).

Improvement of LV function following bariatric surgery has been described before in small studies (17-20). However, CARDIOBESE is the largest study in which speckle tracking echocardiography was used to investigate improvement of LV function after bariatric surgery. As we recently reported, there was an overall improvement of GLS one-year post-surgery, resulting in normalization of subclinical cardiac dysfunction in 50% of the patients with obesity (7).

While it was already known that autonomic dysfunction as expressed by a decreased HRV may be related to either cardiac dysfunction (21) or to obesity (22), previously reported baseline data of the patients included in the CARDIOBESE study (2) for the first time showed that autonomic dysfunction appears to have a prominent role in the pathophysiology of cardiac dysfunction in obesity. However, so far it was unknown whether autonomic dysfunction may play a role in *persistence* of cardiac dysfunction after bariatric surgery as well. In the current study it was shown that a decreased SDNN pre-surgery was a predictor for persistent subclinical cardiac dysfunction one-year post-bariatric surgery. The SDNN represents the beat-to-beat variation during Holter monitoring by measuring the standard deviation of NN intervals (22). The SDNN is a parameter of autonomic function through the sympathetic nervous system contribution to HRV (13). A balanced autonomic function is crucial for normal cardiac function (21). On the other hand, a depressed HRV is related to morbidity and mortality (23, 24). Oher studies already described a favourable effect of bariatric surgery on HRV (25). Yet, by combining findings from Holter monitoring and echocardiography, our study is the first to relate the severity of autonomic dysfunction in obesity to the potential of recovery of cardiac dysfunction after bariatric surgery.
In the patients in our study, there was a significant increase in SDNN one-year post-surgery, indicative of improvement of autonomic function, both in patients with improvement of LV function and in patients with persistent LV dysfunction. It can therefore be hypothesized that more severe autonomic dysfunction in obesity as expressed by decreased SDNN pre-surgery, may lead to either a permanent or delayed lack of improvement of LV function after bariatric surgery. Longer follow-up of obesity patients post-bariatric surgery may elucidate whether LV function will improve after all, in-line with improvement of autonomic function.

While, as described above, a role of autonomic dysfunction was somewhat anticipated, the finding that a decreased vitamin D before bariatric surgery was also independently related to persistent subclinical cardiac dysfunction one year post-surgery was less expected. Nevertheless, vitamin D has been suggested to be involved in multiple patho-

physiological pathways related to heart failure, such as inflammation, atherosclerosis, endothelial dysfunction, and thrombosis (26). Furthermore, vitamin D deficiency is a predictor of reduced survival in patients with heart failure (27). Also, vitamin D is known to be decreased in patients with obesity (28), and in patients with known cardiovascular disease (29), suggesting that vitamin D may have a role in the increased risk of cardiac dysfunction in obesity. However, previous studies from our group failed to show significant effects of vitamin D supplementation on inflammatory changes in females with overweight, making this mechanism less likely (30). Although the underlying mechanism remains to be elucidated, by combining findings from blood tests and echocardiography in our study, it was shown for the first time that a relative decreased vitamin D level pre-bariatric surgery is related to a lack of improvement of cardiac function after bariatric surgery.

Limitations

A relatively large number (32%) of the patients with cardiac dysfunction did not complete the follow-up: 15% because they did not undergo bariatric surgery, and 17% dropped out because of various other reasons. Meanwhile, 20% of the patients with a normal cardiac function was lost to follow-up. The reason for this difference is unknown, but probably it was just coincidence. Furthermore, follow-up after bariatric surgery was one year and it may be hypothesized that a longer follow-up would have shown improvement of cardiac function in a larger proportion of patients.

CONCLUSIONS

Autonomic dysfunction at baseline was related to a lack of normalization of cardiac function in patients with obesity one year after bariatric surgery. This result is in-line with previous findings of our group (2), confirming an important role of autonomic dysfunction in the pathophysiology of cardiac dysfunction in obesity. Decreased vitamin D before bariatric surgery was also independently related to persistent subclinical cardiac dysfunction one year post-surgery. Since this finding was less expected, we consider this less affirmative and more hypothesis-generating. Nevertheless, signs of either autonomic dysfunction or a decreased vitamin D pre-bariatric surgery may be indicative of a need for cardiologic follow-up after bariatric surgery.

Table 1: Clinical characteristics of the study population. Differences between obesity patients from pre- to 1-year post-bariatric surgery.

	Pre-surgery (n=72)	One-year post-surgery (n=72)	p-value
General characteristics			
Age (years)	48 (43-54)		
Female (n, %)	54 (75%)		
Physical examination			
Weight (kg)	122 [113-133]	83 [74-91]	<0.001
BMI (kg/m^2)	41 [39-46]	28 [25-31]	<0.001
Systolic BP (mmHg)	146 ± 21	133 ± 20	0.003
Diastolic BP (mmHg)	79 [73-88]	80 [75-86]	0.18
Heart rate (bpm)	80 [73-86]	65 [57-71]	<0.001
Comorbidity			
Diabetes Mellitus (n,%)	16 (22%)	6 (8%)	0.002
Hypertension (n,%)	24 (33%)	12 (17%)	0.035
Hypercholesterolemia (n,%)	15 (21%)	8 (11%)	0.09
Current smoking (n,%)	11 (15%)	3 (6%)	0.18
COPD (n,%)	4 (6%)	0	0.13
OSAS (n,%)	8 (11%)	0	0.008
Medication			
Beta-blockers (n,%)	5 (7%)	3 (4%)	0.63
ACE inhibitors / ARBs (n,%)	11 (15%)	8 (11%)	0.012
Calcium channel blockers (n,%)	6 (8%)	5 (7%)	0.66
Statins (n,%)	16 (22%)	9 (13%)	0.039
Diuretics (n,%)	13 (18%)	8 (11%)	0.18
Insulin (n,%)	5 (7%)	4 (6%)	0.56
Oral anti-diabetics (n,%)	10 (14%)	4 (6%)	0.031
Blood tests			
CRP (mg/L)	6 [3-9]	0 [0-2]	<0.001
Glucose (mmol/L)	5.4 [4.8-6.4]	5.0 [4.6-5.6]	0.051
HbA1c (mmol/mol)	39 [35-48]	36 [33-39]	<0.001
Creatinine (umol/L)	70 [65-78]	67 [62-71]	<0.001
eGFR (ml/min/1.73m^2)	83 ± 9	87 ± 5	<0.001
ALAT (U/L)	30 [20-37]	19 [15-26]	0.004
Apolipoprotein B (g/L)	1.04 [0.88-1.25]	0.84 [0.73-1.05]	<0.001
Total cholesterol (mmol/L)	5.3 ± 0.9	4.6 ± 0.8	<0.001
LDL cholesterol (mmol/L)	3.2 ± 0.8	2.6 ± 0.7	<0.001
HDL cholesterol (mmol/L)	1.2 [1.0-1.4]	1.4 [1.2-1.6]	<0.001
Triglycerides (mmol/L)	1.7 [1.3-2.3]	1.0 [0.8-1.4]	<0.001
Ferritin (ug/L)	83 [53-177]	97 [49-171]	0.60
Active Vitamin B12 (pmol/L)	101 [71-132]	104 [66-128]	0.24
Folic acid (nmol/L)	13 [9-16]	27 [16-36]	<0.001
Vitamin B1 (nmol/L)	140 ± 28	131 ± 40	0.17
Vitamin B6 (nmol/L)	67 [52-81]	98 [61-128]	0.009
Albumin (g/L)	42 [39-44]	41 [40-43]	0.033
Magnesium (mmol/L)	0.82 [0.76-0.87]	0.82 [0.78-0.86]	0.38
Vitamin D (nmol/L)	39 [27-66]	75 [61-98]	<0.001
Haemoglobin (mmol/L)	8.8 [8.1-9.1]	8.5 [8.0-9.1]	0.012

Table 1: continue

	Pre-surgery (n=72)	One-year post-surgery (n=72)	p-value
Echocardiography parameters			
Left ventricular mass (g)	177 [138-214]	150 [121-182]	<0.001
LVM-index (g/m^2)	72 [59-87]	77 [64-87]	0.49
Holter monitoring			
Ventricular arrhythmia (n, %)	0	0	
Average heart rate (bpm)	83 ± 10	73 ± 8	<0.001
Minimal heart rate (bpm)	53 [47-57]	46 [44-51]	<0.001
Maximum heart rate (bpm)	137 [128-150]	130 [120-142]	0.005
SDNN (ms)	106 ± 46	124 ± 47	<0.001
SDNN-index (ms)	46 [38-57]	59 [49-69]	<0.001

Values represent mean ± SD, median (Q1–Q3), or n (%). BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnoea syndrome; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; CRP, C-reactive protein; HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate; ALAT, alanine transaminase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; LVM index, left ventricular mass index; SDNN, standard deviation of NN intervals; SDNN index, mean of the standard deviations of all the NN intervals for each 5-min segment of a 24-h heart rate variability recording

Table 2: Parameters of cardiac function. Differences between obesity patients from pre- to one-year post bariatric surgery.

	Pre-surgery (n=72)	One year post-surgery (n=72)	p-value
Blood tests			
BNP (pmol/L)	5 [3-8]	8 [6-10]	0.029
hs troponin I positive (n, %)	1 (1%)	5 (7%)	0.06
Echocardiography parameters			
Mitral inflow E-wave (cm/s)	66 ± 16	69 ± 14	0.45
Mitral inflow A-wave (cm/s)	71 ± 14	65 ± 12	<0.001
E/A-ratio	0.98 [0.9-1.1]	1.1 [0.9-1.2]	0.008
Septal e' velocity (cm/s)	7.8 ± 2.1	8.3 ± 1.7	0.56
Lateral e' velocity (cm/s)	9.6 ± 3.1	12.2 ± 3.1	<0.001
E/e'-ratio	8.7 [7.5-9.9]	8.3 [7-.0-9.6]	0.07
Deceleration time (s)	0.18 [0.17-0.21]	0.18 [0.15-0.21]	0.51
LA volume index (ml/m2)	24 [20-31]	27 [23-34]	0.07
TR velocity (cm/s)	106 [91-139]	191 [106-218]	<0.001
Diastolic dysfunction (n, %)	7 (10%)	3 (4%)	0.28
LV ejection fraction (%)	58 ± 8	57 ± 7	0.25
Global longitudinal strain (%)	-15.6 ± 3.1	-18.1 ± 3.3	0.001
Holter monitoring			
Total PAC per 24 hours (n)	9 [2-38]	20 [8-68]	0.07
Total PVC per 24 hours (n)	3 [0-22]	5 [2-58]	0.29
Supraventricular arrhythmia (n, %)	1 (1%)	0	0.53
Ventricular arrhythmia (n, %)	0	0	

Values represent mean ± SD, median (Q1-Q3) or n (%). BNP= brain natriuretic peptide, hs troponin I= high sensitive troponin I, E-wave= early diastolic transmitralflow velocity, A-wave= late diastolic transmitralflow velocity, e'= early diastolic mitral annular velocity, LA-volume index= left atrial volume index, TR velocity= tricuspid regurgitation, LV= left ventricular, PAC= premature atrial contraction, PVC= premature ventricular contraction.

Table 3: Comparison of characteristics of patients with pre-existent cardiac dysfunction subdivided into those who showed normalization of cardiac function after bariatric surgery compared to those with persistent cardiac dysfunction.

	Post-surgery normal cardiac function (n=20)		Post-surgery cardiac dysfunction (n=20)		p-value pre	p-value post
	Pre-surgery	Post-surgery	Pre-surgery	Post-surgery		
General characteristics						
Age (years)	48±7		51±8		0.19	
Female (n, %)	13 (65%)		12 (60%)		0.74	
Physical examination						
Weight (kg)	121 [113-132]	83 [75-90]	125 [111-144]	84 [76-98]	0.37	0.62
BMI (kg/m^2)	41 [40-46]	28 [26-31]	42 [39-46]	28 [26-30]	0.83	0.76
Systolic BP (mmHg)	140 [130-159]	138 [116-148]	147 [137-160]	128 [121-134]	0.34	0.48
Diastolic BP (mmHg)	80±13	78±10	86±14	81±7	0.23	0.54
Heart rate (bpm)	80 [78-93]	67 [59-73]	80 [77-88]	63 [53-73]	0.41	0.40
Comorbidity						
Diabetes Mellitus (n,%)	6 (30%)	2 (10%)	4 (20%)	2 (10%)	0.46	1
Hypertension (n,%)	9 (45%)	3 (15%)	7 (35%)	4 (20%)	0.52	0.62
Hypercholesterolemia (n,%)	7 (35%)	3 (15%)	3 (15%)	4 (20%)	0.14	0.62
Current smoking (n,%)	1 (5%)	2 (10%)	3 (15%)	1 (5%)	0.29	0.74
COPD (n,%)	1 (5%)	0	0	0	0.31	
OSAS (n,%)	3 (15%)	0	3 (15%)	0	1	
Medication						
Beta-blockers (n,%)	3 (15%)	2 (10%)	0	1 (5%)	0.07	0.72
ACE inhibitors / ARBs (n,%)	5 (25%)	2 (10%)	5 (25%)	3 (15%)	1	0.54
Calcium channel blockers (n,%)	3 (15%)	1 (5%)	2 (10%)	2 (10%)	0.63	0.49
Statins (n,%)	8 (40%)	3 (15%)	4 (20%)	5 (25%)	0.17	0.34
Diuretics (n,%)	5 (25%)	2 (10%)	3 (15%)	33 (15%)	0.43	0.54
Insulin (n,%)	3 (15%)	2 (10%)	1 (5%)	1 (5%)	0.29	0.62
Oral anti-diabetics (n,%)	4 (20%)	1 (5%)	2 (10%)	1 (5%)	0.38	0.94
Blood tests						
BNP (pmol/L)	5 [3-6]	7 [4-11]	3 [3-7]	8 [6-11]	0.72	0.83
hs Troponin I positive (n)	0	0	0	2 (10%)		0.15
CRP (mg/L)	5 [4-9]	1 [0-3]	6 [4-9]	0 [0-1]	0.64	0.38
Glucose (mmol/L)	6.4±2.2	5.6±1.6	7.2±3.3	6.5±2.2	0.37	0.23
HbA1c (mmol/mol)	51±18	40±9	44±12	38±3	0.13	0.41
Creatinine(umol/L)	71 [65-78]	68 [60-71]	71 [63-77]	66 [64-73]	0.94	0.74
eGFR (ml/min/1.73m^2)	85±8	87±5	85±9	89±3	0.93	0.60
ALAT (U/L)	31 [21-51]	19 [16-29]	31 [27-37]	18 [14-26]	0.91	0.39
Apolipoprotein B (g/L)	0.98±0.26	0.92±0.22	1.1±0.28	0.89±0.22	0.22	0.84
Total cholesterol (mmol/L)	5.0±1.0	4.6±0.7	5.2±0.9	4.6±0.8	0.53	0.89
LDL cholesterol (mmol/L)	2.8±0.6	2.7±0.7	3.0±0.8	2.6±0.9	0.59	0.62
HDL cholesterol (mmol/L)	1.1 [1.0-1.3]	1.3 [1.1-1.4]	1.1 [1.0-1.3]	1.4 [1.2-1.7]	0.98	0.24
Triglycerides (mmol/L)	2.2±1.4	1.3±0.7	2.3±1.1	1.5±0.9	0.74	0.56
Ferritin (ug/L)	150±142	128±90	134±70	153±139	0.66	0.53
Active Vitamin B12 (pmol/L)	82 [70-114]	95 [62-128]	97 [60-108]	128 [74-303]	0.83	0.06
Folic acid (nmol/L)	13 [11-17]	28 [16-35]	13 [9-17]	25 [10-45]	0.60	0.79

Table 3: Comparison of characteristics of patients with pre-existent cardiac dysfunction subdivided into those who showed normalization of cardiac function after bariatric surgery compared to those with persistent cardiac dysfunction.

	Post-surgery normal cardiac function (n=20)		Post-surgery cardiac dysfunction (n=20)		p-value pre	p-value post
	Pre-surgery	Post-surgery	Pre-surgery	Post-surgery		
Vitamin B1 (nmol/L)	150±24	147±55	149±21	133±34	0.93	0.52
Vitamin B6 (nmol/L)	95±88	112±39	69±17	82±26	0.39	0.06
Albumin (g/L)	43±3	42±3	39±3	40±3	0.002	0.008
Magnesium (mmol/L)	0.83±0.05	0.84±0.05	0.81±0.05	0.82±0.04	0.43	0.45
Vitamin D (nmol/L)	54 [30-80]	80 [67-98]	33 [25-54]	62 [42-104]	0.04	0.12
Haemoglobin (mmol/L)	8.9±0.5	8.8±0.6	8.7±0.8	8.8±1.0	0.42	0.91
Echocardiography parameters						
Mitral inflow E-wave (cm/s)	68.8±10.6	69.5±16.3	64.1±8.7	62.8±12.0	0.14	0.15
Mitral inflow A-wave (cm/s)	69.1±12.0	66.2±12.0	72.8±15.1	63.7±10.0	0.45	0.48
E/A-ratio	0.97 [0.92-1.00]	0.94 [0.80-1.35]	0.88 [0.76-1.01]	1.05 [0.85-1.10]	0.29	0.98
Septal e' velocity (cm/s)	8.1±1.6	8.3±2.1	7.8±1.9	7.9±1.4	0.64	0.54
Lateral e' velocity (cm/s)	10.5±2.3	12.2±3.6	9.8±3.0	10.9±2.4	0.45	0.20
E/e'-ratio	8.7 [7.6-9.7]	8.5 [7.6-9.7]	8.0 [6.8-9.9]	7.9 [6.6-9.3]	0.45	0.42
Deceleration time (s)	0.19±0.03	0.20±0.05	0.19±0.04	0.19±0.05	0.60	0.49
LA volume index (ml/m2)	24.7±7.6	28.7±8.3	26.4±9.7	27.7±6.3	0.56	0.70
TR velocity (cm/s)	92 [90-169]	180 [101-214]	97 [82-112]	189 [111-214]	0.81	0.42
Left ventricular mass (g)	179 [140-226]	157 [132-196]	202 [140-235]	151 [128-200]	0.43	0.70
LVM-index (g/m^2)	72 [61-89]	81 [69-97]	78 [62-92]	76 [65-90]	0.53	0.27
Holter monitoring						
Total PAC per 24 hours (n)	7 [2-41]	24 [9-107]	15 [2-56]	19 [9-90]	0.44	0.63
Total PVC per 24 hours (n)	3 [0-18]	4 [2-30]	4 [0-32]	4 [1-89]	0.51	0.86
Average heart rate (bpm)	86±8	75±7	82±11	74±7	0.21	0.68
Minimal heart rate (bpm)	57±13	48±5	51±7	45±10	0.08	0.18
Maximum heart rate (bpm)	136±15	135±18	138±14	125±33	0.58	0.26
SDNN (ms)	107 [77-136]	145 [117-155]	77 [46-98]	84 [65-160]	**0.011**	0.09
SDNN-index (ms)	45±15	58±15	42±6	59±22	0.64	0.98

Values represent mean ± SD, median (Q1-Q3) or n (%). BMI= body mass index, BP= blood pressure, COPD= chronic obstructive pulmonary disease, OSAS= obstructive sleep apnoea syndrome, ACE= angiotensin-converting enzyme, ARBs= angiotensin II receptor blockers, BNP= brain natriuretic peptide, hs troponin I= high sensitive troponin I, CRP= C-reactive protein, HbA1c= glycated haemoglobin, eGFR= estimated glomerular filtration rate, ALAT= alanine transaminase, LDL= low-density lipoprotein, HDL= high-density lipoprotein, E-wave= early diastolic transmitralflow velocity, A-wave= late diastolic transmitralflow velocity, e'= early diastolic mitral annular velocity, LA-volume index= left atrial volume index, TR velocity= tricuspid regurgitation, LVM-index= left ventricular mass-index, PAC= premature atrial contraction, PVC= premature ventricular contraction, SDNN= standard deviation of NN intervals, SDNN-index= mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h heart rate variability recording

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Part IV

Early detection of cardiac dysfunction in obesity – biomarkers

9

Chapter 9

Biomarkers profiles in obesity patients and their relation to cardiac dysfunction

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ABSTRACT:

Background

Current knowledge on the role of obesity in causing cardiac dysfunction is insufficient. Several biomarkers reflecting biological processes that may play a role in the occurrence of cardiac dysfunction in obesity patients are available.

Purpose

To compare cardiovascular biomarker profiles between obesity patients and non-obese controls, and between obesity patients with and without cardiac dysfunction, in order to better understand the underlying pathophysiology of cardiac dysfunction in obesity patients.

Methods

Blood samples were obtained from 100 obesity patients (BMI ≥35 kg/m2) without known cardiovascular disease, and from 50 age- and gender-matched non-obese controls (BMI ≤30 kg/m2). The cardiovascular panel III of the Olink Multiplex platform was used for the measurement of 92 biomarkers.

Results

The majority (53%) of biomarkers were increased in obesity patients compared to non-obese controls. Only 5% of the biomarkers were elevated in obesity patients with cardiac dysfunction compared to those without. Biomarkers discriminating cardiac dysfunction from no cardiac dysfunction in obesity patients differed from those discriminating obese from non-obese patients. An elastic net model for the prediction of cardiac dysfunction in obesity patients had a high AUC of 0.87 (95% CI:0.79-0.94, p< 0.001). The sensitivity of this model was 84% and the specificity was 79%.

Conclusion

A multiplex immunoassay was used for the first time in obesity patients without known cardiovascular disease. These patients have cardiovascular biomarker profiles that are clearly different from non-obese controls. Comparison of obesity patients with and without cardiac dysfunction suggested an important role for inflammation, atherosclerosis, and insulin resistance in the underlying pathophysiology of cardiac dysfunction in obesity patients.

INTRODUCTION

Obesity is a growing worldwide problem. If the current trends continue, global obesity prevalence will reach 18% in men and surpass 21% in women by 2025 (1). Obesity is associated with an increased risk of all-cause mortality and cardiovascular disease (2). A body mass index (BMI) ≥30 kg/m^2 doubles the lifetime risk of developing heart failure (3). With the rising prevalence of obesity worldwide, cardiac dysfunction in obesity patients is a growing problem (4, 5), which warrants efficient screening to identify those at highest cardiovascular risk (6). Current knowledge on factors contributing to cardiac dysfunction in obesity patients is insufficient to optimally develop such strategies for these patients (2).

Nowadays, biomarkers play a major role in the diagnosis and management of heart failure (7). Natriuretic peptides are the gold standard biomarkers for the diagnosis and prognosis of heart failure (8). However, natriuretic peptides are decreased in obesity patients and are therefore of less use than in non-obese patients (9). In addition, heart failure in obesity patients appears to result not only from cardiac overload or injury but also from factors specifically related to the abundant fat tissue (10). As such, natriuretic peptides might not be the only biomarkers relevant in cardiac dysfunction in obesity patients. Currently, a variety of biomarkers are described, reflecting several biological processes that have been hypothesized to play an important role in the occurrence of cardiac dysfunction (11, 12). The hypothesized processes are inflammation (reflected by biomarkers such as SELE, SELP, and RARRES2) (13-16), insulin resistance (IGFBP-1 and IGFBP-2) (17), coagulation, oxidative stress, myocardial stretch, matrix remodeling, and atherosclerosis (CHIT1 (18), OPG (19), and t-PA(20)). Investigating such biomarkers, using a multiplex immunoassay to determine a broad spectrum of blood biomarkers related to processes such as inflammation, atherosclerosis and insulin resistance, may help to better understand the underlying pathophysiology of cardiac dysfunction in obesity patients. Therefore, we examined cardiovascular biomarker profiles in obesity patients versus non-obese controls, and the relationship between these profiles and subclinical cardiac dysfunction in obesity.

METHODS

Study group

Blood samples from patients included in the CARdiac Dysfunction In Obesity – Early Signs Evaluation study (CARDIOBESE) were used. The protocol of the CARDIOBESE study has been described in detail (21). CARDIOBESE is a multicenter, prospective study including 100 obesity patients referred for bariatric surgery, designed to identify novel risk factors associated with cardiovascular disease in this

cohort. Patients were included if they were between 35 and 65 years old and had a BMI of ≥35 kg/m^2. Patients with a suspicion of or known cardiovascular disease were excluded. Fifty age- and gender-matched non-obese (BMI<30 kg/m^2) controls were enrolled as controls.
The presence or absence of subclinical cardiac dysfunction in the 100 obesity patients of the CARDIOBESE study has been described in detail before (22). In short, cardiac dysfunction was defined as either a reduced LV ejection fraction, a decreased GLS, diastolic dysfunction, ventricular arrhythmia or an increased BNP or hs Troponin I. As previously shown, cardiac dysfunction was present in 60 patients. However, one patient with cardiac dysfunction was diagnosed with acromegaly after inclusion and was excluded from further analysis, leaving 59 obesity patients with versus 40 without subclinical cardiac dysfunction.
The study protocol was approved by the medical ethics committee Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. (TWOR). Written informed consent was obtained from all participants (21). The present study was carried out in accordance with the Declaration of Helsinki. All participants underwent a transthoracic echocardiogram, Holter registration, and laboratory tests.

Laboratory procedures

Non-fasting blood samples were collected at the outpatient clinic at the moment of screening for bariatric surgery. High sensitive (hs) Troponin I and brain natriuretic peptide (BNP) were determined immediately according to local procedures of the laboratory for clinical chemistry of our hospital. The other blood samples were processed and stored at -80°C within 2 hours after collection. Serum aliquots were thawed and randomly divided over three microwell plates. Internal controls were added to each plate. Plates were frozen at -80°C and shipped on dry ice to Olink Proteomics AB, Uppsala, Sweden. The cardiovascular panel III of the Olink Multiplex platform for biomarkers was used for analysis. This panel was chosen, because it contains known human cardiovascular and inflammatory markers as well as some exploratory human proteins with potential as new cardiovascular markers. The kits are based on the proximity extension assay technology, where 92 oligonucleotide-labelled antibody probe pairs are allowed to bind to their respective target present in the sample. The proximity extension assay technique shows exceptionally high specificity and sensitivity (23, 24). The biomarkers are delivered in normalized protein expression units (NPX), which are relative units. Therefore, NPX values for 2 different analyses/proteins are not directly comparable. They are expressed on a log2 scale where 1 unit higher NPX value represents a doubling of the measured protein concentration. For statistical analysis, NPX were converted back to a linear scale: 2^{NPX}= linear NPX. All biomarkers and abbreviations are shown in Supplementary Table 1.

Transthoracic echocardiography

Two-dimensional grayscale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system (EPIQ 7, Philips, the Netherlands), equipped with a broadband (1-5MHz) X5-1 transducer. All acquisitions and measurements were performed according to the current guidelines (25, 26). Off-line speckle tracking was performed using a QLAB workstation (version 10.2, Philips, the Netherlands). Peak regional longitudinal strain was measured in 17 myocardial regions and a weighted mean was used to derive Global Longitudinal Strain (GLS) (25) .

Sample size calculation

A conservative estimate would be that cardiac dysfunction based on conventional echocardiography is present in 20% of obesity patients and 2.5% of age-matched and gender-matched non-obese controls.(27) Given these estimates, to be able to reject the null hypothesis of the CARDIOBESE study that cardiac dysfunction rates are equal between patients and controls, at least 97 obesity patients and 49 non-obese controls have to be included in the analysis (alpha: 0.05 (two sided), power: 0.80, 2:1 ratio of patients:controls). The use of more sensitive techniques may increase the proportion of non-obese controls with an early sign of cardiac dysfunction. Nevertheless, the proportion of obesity patients with an early sign of cardiac dysfunction is expected to increase even more, assuring that the previous sample size calculation will still suffice.

Statistical analysis

The normality of the data was checked by the Shapiro–Wilk test. Normally distributed data are presented as means and standard deviations, skewed data as medians and interquartile ranges, and categorical variables as counts and percentages.

Differences in clinical characteristics, parameters of cardiac function, and biomarkers between obesity patients and matched non-obese controls were estimated by using generalized linear mixed models with obesity as the independent variable, and the aforementioned variables entered consecutively as the dependent variable. Random intercepts were used to account for the matched pairs. Missing variables were omitted. For dependent variables with complete separation, Bayesian generalized linear mixed models were used. The Benjamini–Hochberg procedure, with a 5% false discovery rate, was used to correct for the multiple testing (28).

Linear regression was used to compare biomarker levels between obesity patients with cardiac dysfunction to those without. For the biomarkers, results were displayed as the beta-coefficients of each biomarker from the generalized linear mixed model and the linear regression, which signifies the difference in biomarker level (in NPX units) according to the presence of obesity or cardiac dysfunction. Again, the Benjamini-Hochberg procedure was used to correct for multiple testing.

Subsequently, a multiple biomarker model was constructed to optimally identify patients with cardiac dysfunction. In order to select the subset of biomarkers that carries the best predictive value for cardiac dysfunction and, at the same time, to reduce the risk of overfitting (which is especially important in the setting where the number of events is low relative to the number of predictors), elastic net logistic regression was used. This method combines two established shrinkage-methods: Ridge regression and Lasso regression (29). Patient characteristics and all available biomarkers were used as input for this model. The discriminative ability of the resulting model was investigated by calculating the area under the receiver operating curve (AUC). Odd's ratios of the Z-scores were reported. All statistical tests were 2-sided and a p-value of 0.05 was considered statistically significant unless otherwise stated. The analyses were performed with R 3.0.3 (glmnet and nlme packages were used) and SPSS version 25.

RESULTS

Patient characteristics

A total of 100 obesity patients and 50 non-obese controls were studied, both without a suspicion of or known cardiovascular disease. The characteristics of the participants are shown in Table 1. Physical examination showed an increased weight, BMI, systolic blood pressure, waist circumference and heart rate in obesity patients. Obesity patients had more often comorbidities such as diabetes mellitus and hypertension and used more often medication than non-obese controls. Echocardiography showed that obesity patients had an increased left ventricular mass (LVM), a higher prevalence of diastolic dysfunction, and a decreased GLS and LV ejection fraction.
Comparison betwween obesity patients with and without cardiac dysfunction revealed that patients with cardiac dysfunction were more often male and had an increased heart rate. The prevalence of comorbidities and medication use were comparable between these two groups.

Cardiovascular biomarkers in obesity patients compared to non-obese controls

The differences in biomarker levels between the obesity patients and the non-obese controls are presented in Figure 1a, where the bars represent the beta coefficients of the biomarkers (difference in NPX units between those with and without obesity). The majority (49 out of 92, 53%) of biomarkers were significantly increased in obesity patients. The most strongly increased biomarkers in obesity patients were: E-selectin (SELE) with beta=1581 (95% CI:592 – 2571), p=0.002 (SELE was 1581 NPX higher in the obesity patients than in the non-obese controls), Retinoic acid receptor responder protein 2 (RARRES2), beta=976 (95%CI: 695 – 1257), p<0.001,

and P-selectin (SELP), beta=687 (95%CI: 224 – 1149), p=0.004. The most strongly decreased biomarkers in obesity patients were: Insulin-like growth factor-binding protein 2 (IGFBP-2) with a beta= –109 (95%CI: –147, –71), p<0.001, Paraoxonase (PON3), beta= –77 (95%CI: –95, –59), p<0.001, and Insulin-like growth factor-binding protein 1 (IGFBP-1), beta= –27 (95%CI: –39, –15), p<0.001.

Cardiovascular biomarkers in obesity patients with cardiac dysfunction compared to those without

Figure 1b shows that 5 out of 92 (5%) biomarkers were significantly increased in obesity patients with cardiac dysfunction compared to those without cardiac dysfunction. The most strongly increased biomarkers in the obesity patients with cardiac dysfunction were: SELE with a beta=2492 (95%CI: 1228 – 3755), p<0.001, and Tumor necrosis factor receptor superfamily member 6 (FAS), beta=13 (95%CI: 5 – 21), p=0.002. None of the biomarkers were significantly decreased in patients with cardiac dysfunction.

Table 1: Characteristics of the obesity patients compared to non-obese controls, and comparison between obesity patients with or without cardiac dysfunction.

	Non-obese controls (n=50)	Obesity patients (n=100)	p-value	Obesity patient without cardiac dysfunction (n=59)	Obesity patient with cardiac dysfunction (n=40)	p-value
General characteristics						
Age (years)	50 (40-59)	48 (42-50)	**0.02***	47 (42-52)	49 (42-56)	0.53
Female (%)	35 (70%)	70 (70%)	>0.99	35 (87.5%)	35 (59.3%)	**0.004***
Physical examination						
Length (m)	1.74 ± 0.1	1.71 ± 0.1	0.08	1.69 ± 0.1	1.73 ± 0.1	**0.045**
Weight (kg)	76 (64-82)	123 (115-135)	**<0.001***	123 (115-132)	124 (114-138)	0.28
BMI (kg/m^2)	25 (22-28)	42 (40-46)	**<0.001***	43 (40-46)	42 (40-45)	0.56
Systolic BP (mmHg)	127 (118-136)	140 (127-157)	**<0.001***	139 ± 21	144 ± 20	0.08
Diastolic BP (mmHg)	78 (71-82)	79 (72-88)	0.11	75 (70-84)	80 (73-89)	0.06
Waist circumference (cm)	79 (74-89)	131 (125-140)	**<0.001***	128 (122-134)	137 (127-141)	**0.048**
Heart rate (bpm)	64 ± 9	80 ± 13	**<0.001***	76 ± 11	83 ± 14	**0.019***
Comorbidity						
Diabetes Mellitus	0	22 (22%)	**0.007***	8 (20%)	13 (22%)	0.81
Hypertension	4 (8%)	32 (32%)	**0.003***	11 (27.5%)	20 (33.9%)	0.27
Hypercholesterolemia	5 (10%)	18 (18%)	0.21	8 (20%)	10 (16.9%)	0.89
Current smoking	7 (14%)	17 (17%)	0.63	7 (17.5%)	9 (15.3%)	0.77
COPD	1 (2%)	5 (5%)	0.39	3 (7.5%)	2 (3.4%)	0.37
OSAS	1 (2%)	12 (12%)	0.07	3 (7.5%)	8 (13.5%)	0.35
Medication						
Beta-blockers	0	8 (8%)	**0.03**	3 (8.1%)	5 (8.8%)	0.36
ACE inhibitors / ARBs	2 (4%)	24 (24%)	**0.008***	10 (27%)	13 (22.8%)	0.53
Calcium channel blockers	0	12 (12%)	**0.04**	3 (8.1%)	7 (12.3%)	0.13
Statins	3 (6%)	20 (20%)	**0.03**	5 (13.5%)	14 (24.6%)	0.12
Diuretics	1 (2%)	18 (18%)	**0.02***	6 (16.2%)	11 (19.3%)	0.13
Insulin	0	7 (7%)	**0.04**	2 (5.4%)	5 (8.8%)	0.51
Oral anti-diabetics	0	15 (15%)	**0.02***	5 (13.5%)	9 (15.8%)	0.70
Blood tests						
BNP	6 (3-9)	5 (3-8)	0.59	6 (4-11)	4 (3-6)	0.29
hs Troponin I	0	1 (1%)	0.37	0	0	
Echocardiography						
LVM (g)	148 (117-175)	194 (149-231)	**<0.001***	169 (140-215)	203 (156-241)	0.10
LVM-index (g/m2)	79 (62-88)	76 (64-92)	0.16	72 (59-88)	81 (67-94)	0.16
Diastolic dysfunction (%)	1 (2%)	11 (11%)	0.09	0	10 (17%)	**<0.001***
Global Longitudinal Strain (%)	-20 (-21 - -19)	-16 (-18 - -14)	**<0.001***	-19.2 ± 1.3	-14.4 ± 2.1	**<0.001***
LV ejection fraction (%)	65 ± 5	57 ± 7	**<0.001***	62 ± 6	54 ± 7	**<0.001***

Values represent mean ± SD, median (Q1-Q3) or n (%). P-values displayed for obesity patients versus matched non-obese controls were analyzed by using generalized linear mixed models, and p-values for obesity patients with cardiac dysfunction versus normal cardiac function were analyzed by univariable logistic regression. * significant after Benjamini–Hochberg correction. BMI= body mass index, BP=blood pressure, COPD= chronic obstructive pulmonary disease, OSAS= obstructive sleep apnea syndrome, ACE= angiotensin-converting enzyme, ARBs= angiotensin II receptor blockers, BNP= brain natriuretic peptide, hs Troponin I= high sensitive Troponin I, LV= left ventricular, LVM= left ventricular mass.

The biomarkers discriminating cardiac dysfunction from no cardiac dysfunction in obesity patients differed from those discriminating obesity patients from non-obese controls (as shown by Figure 1b compared to 1a).

Model for identification of cardiac dysfunction in obesity patients

The elastic net regression analysis selected the following biomarkers for inclusion in the multivariable model for identification of cardiac dysfunction in obesity patients: the biomarkers Cathepsin D (CTSD), Chitotriosidase-1 (CHIT1), SELE, Osteopontin (OPN), Osteoprotegerin (OPG), Tartrate-resistant acid phosphatase type 5 (TR-AP), Tissue-type plasminogen activator (t-PA), and FAS. Patient characteristics that were selected by this model were male gender, waist circumference, systolic blood pressure, heart rate, and LVM. Table 2 shows the odd's ratios of Z-scores of the variables selected by the elastic net regression. Figure 2 shows the ROC-curve for this model. The ability of this model to discriminate between obesity patients with and without cardiac dysfunction had an AUC of 0.87 (95% CI;0.79-0.94, p<0.001). The sensitivity of this model was 84%, the specificity was 79%, the positive predictive value 82%, and the negative predictive value 81%.

Table 2: Odd's ratios of the Z-scores of the variables selected by the elastic net regression.

Variable	Odd's ratio
CTSD	1.43
CHIT1	0.34
SELE	2.05
OPN	1.19
OPG	1.41
TR-AP	1.37
t-PA	1.27
FAS	1.16
Male gender	1.58
Waist circumference	0.84
Systolic blood pressure	1.66
Heart rate	1.48
Left ventricular mass	1.41

CTSD= Cathepsin D, **CHIT1=** Chitotriosidase-1, **SELE=** E-selectin, **OPN=** Osteopontin, **OPG=** Osteoprotegrin, **TR-AP=** Tartrate-resistant acid phosphatase type 5, **t-PA=** Tissue-type plasminogen activator, **FAS=** Tumor necrosis factor receptor superfamily member 6

DISCUSSION

The main findings of the current study are that the cardiovascular biomarker profile of obesity patients without known cardiovascular disease is overtly different from that of non-obese controls, and that obesity patients with subclinical cardiac dysfunction have a different cardiovascular biomarker profile than obesity patients with normal cardiac function. To our knowledge, this is the first publication describing cardiovascular biomarkers in relation to subclinical cardiovascular dysfunction in obesity patients.

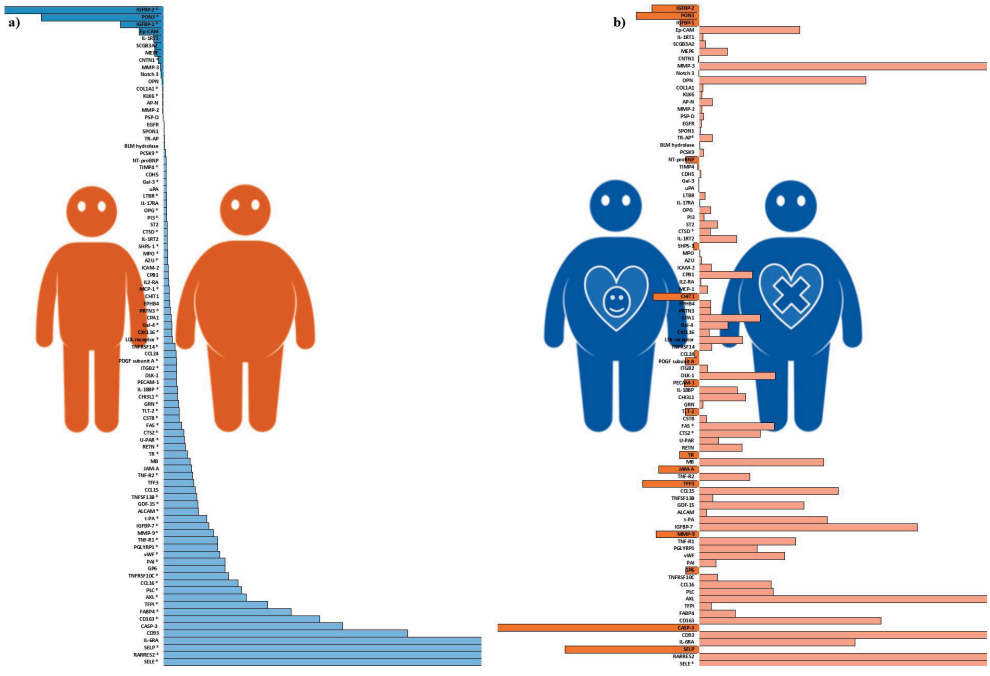
While there is strong evidence from epidemiological studies on the detrimental effects of obesity on health outcomes, the underlying biological mechanisms are not completely understood (30). The use of multiplex immunoassays that determine a broad spectrum of blood biomarkers to increase insights in pathophysiological aspects of diseases is gaining interest in medical science (11). In our study, such a multiplex immunoassay was used for the first time to compare obesity patients and non-obese controls. Even in obesity patients without known cardiovascular disease, the cardiovascular biomarker profile was very different from non-obese controls. Since the studied biomarkers covered several processes potentially involved in the pathophysiology of cardiovascular disease in obesity, such as inflammation, insulin resistance, coagulation, oxidative stress, myocardial stretch, matrix remodeling, and atherosclerosis, our findings support the hypothesis of a multifactorial origin of cardiovascular disease in obesity patients. Nevertheless, there remains uncertainty on the precise extent of the mechanisms involved. In our analysis, the most strongly elevated biomarkers in obesity patients (SELE, SELP, and RARRES2) were biomarkers known to be linked to inflammation (13-16). It has been hypothesized before, that inflammation has an important role in the increased risk of cardiovascular disease in obesity (31). However,

the most strongly decreased biomarkers in obesity patients (IGFBP-1, IGFBP-2, and PON-3), are not related to inflammation. Both IGFBP-1 and IGFBP-2 levels are known to be decreased in obesity patients (32), which mainly has been related to insulin resistance (17). PON-3 has been suggested to play an important role in protection against the detrimental effects of obesity (33), and is involved in the metabolism of lipids as well as protection against atherosclerosis (34).
In a recent paper, we described a high prevalence (61%) of subclinical cardiac dysfunction in obesity patients (22). In the current study, we compared cardiovascular biomarkers between obesity patients with and without cardiac dysfunction to further investigate the underlying pathophysiology. While one may expect that the dissimilarities in cardiovascular biomarker profile between obesity patients and non-obese controls may be comparable and even exaggerated between obesity patients with and without cardiac dysfunction, the opposite was found (as shown by Figure 1a compared to 1b). Herewith, these findings suggest that obesity patients with cardiac dysfunction

do not just have a more extensive presence of abnormal underlying pathophysiological processes that play a role in obesity patients in general. On the contrary, our results suggest that processes reflected by the 5 biomarkers that were increased in obesity patients with versus without cardiac dysfunction may be relatively important factors.

Characteristics of these 5 biomarkers are mainly related to inflammation, atherosclerosis and insulin resistance. SELE (13, 35) and TR-AP (36, 37) are related to all three processes, while FAS (38, 39) and CTSD (40, 41) are linked to both inflammation and atherosclerosis. CTSZ is only related to inflammation (42). Of these 5 biomarkers increased in obesity

Figure 1: Graphical representation of the betas from the generalized linear mixed model for all 92 biomarkers in obesity patients (n=100) versus non-obese controls (n=50) (a) and the linear regression for the obesity patients with cardiac dysfunction (n=59) versus obesity patients with normal cardiac function (n=40) (b). * Significant by p<0.05 by generalized linear mixed model (a) or linear regression (b).

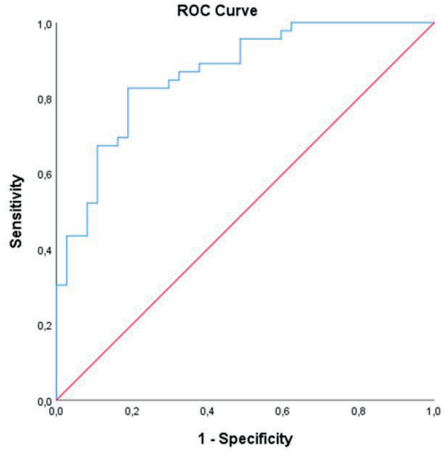


patients with cardiac dysfunction, TR-AP stood out because, contrary to the other 4, it did not differ between the obesity patients and the non-obese controls. In other words, while our findings suggest that processes reflected by SELE, FAS, CTSD and CTSZ play a role in obesity patients in general and also in obesity patients with cardiac dysfunction, TR-AP appeared to be linked most specifically to obesity patients

with cardiac dysfunction. TR-AP has been proposed before as a useful marker for screening and assessment of cardiovascular disease risk (43). Our findings suggest that there may be such a role for this biomarker in obesity patients as well. Nevertheless, further research would be required to confirm this notion.

Finally, a multivariable model was developed to predict the presence of subclinical cardiac dysfunction in obesity patients. This elastic net model selected several biomarkers and clinical characteristics as the optimal set of predictors and had a very good AUC of 0.87 (95% CI:0.79-0.94, p< 0.001). While there was overlap with findings from the univariate analysis discussed above (SELE, FAS, TR-AP, and CTSD were identified by the univariate analysis too), other biomarkers were selected by the model as well. This selection of biomarkers further supported the hypothesis of an important role for the combination of inflammation, atherosclerosis and insulin resistance in the pathophysiology of cardiac dysfunction in obesity patients. OPN is a biomarker related to inflammation and insulin resistance (44), whereas the other biomarkers have been associated with atherosclerosis (CHIT1 (18), OPG (19), and t-PA(20)). Assessment of a well-chosen combination of biomarkers may be used to identify obese patients at relatively high risk of having subclinical cardiac dysfunction.

Figure 2: ROC-curve for the elastic net model (n=99). Variables included were CTSD, CHIT1, SELE, OPN, OPG, TR-AP, t-PA, FAS, male gender, waist circumference, systolic blood pressure, heart rate, and left ventricular mass. AUC= 0.87 (95% CI: 0.79-0.94), p<0.001.



A broad range of processes potentially involved in the pathophysiology of cardiovascular disease in obesity has been described before (45, 46), a relatively important role for the combination of inflammation, atherosclerosis and insulin resistance therefore seems plausible. Previous studies already have shown a relation between these three processes and cardiac dysfunction in general patient populations (not specifically obese). The pivotal role of inflammation in the initiation and progression of cardiovascular disease has been extensively studied and is widely accepted (47), Endothelial inflammation may cause coronary dysfunction and thereby myocardial fibrosis (48). Atherosclerosis can lead to ischemia, which in its turn can lead to heart failure (49). Insulin resistance is an independent risk factor for the development of cardiac dysfunction (50). On the other hand, next to being linked to cardiac dysfunction, these three processes are also known to be independently related to obesity (51, 52). However, our study is the first in which the importance of inflammation, atherosclerosis and insulin resistance was shown in obesity patients with subclinical cardiac dysfunction.

Limitations

The assay we used to determine the biomarkers is designed as a biomarker discovery tool rather than being an approved clinical test. The clinical significance of the biomarker profiles needs to be elucidated. Our cohort predominantly consisted of female patients (70%). Moreover, although obesity is usually defined as a BMI ≥30 kg/m^2 all patients in our study had a BMI ≥35kg/m^2 because they were included at the outpatient clinic for screening for bariatric surgery (BMI ≥35kg/m^2 is a condition to qualify for bariatric surgery). Therefore, the conclusions may only be applied to morbidly obese patients and not to obesity patients in general. Also, although we selected patients without known cardiovascular disease, a relatively large proportion of patients did have cardiovascular risk factors such as diabetes and hypertension, which may also partly explain some of the biomarker differences between obesity patients and non-obese controls. Nevertheless, these risk factors were not different between the obesity patients with and without cardiac dysfunction, limiting the influence on differences in biomarker profiles between these patients. Finally, the sample size was relatively small. However, as mentioned before, the current study was the first to create a risk model for cardiac dysfunction in obesity patients without known cardiovascular disease with this cardiovascular biomarker panel consisting of 92 biomarkers, and we accounted for potential overfitting by applying the elastic net model.

CONCLUSIONS

In the current study, a multiplex immunoassay was used for the first time in obesity patients without known cardiovascular disease. This multiplex allowed assessment of

92 biomarkers covering a broad spectrum of processes potentially involved in cardiac dysfunction in obesity patients. Obesity patients without known cardiovascular disease have cardiovascular biomarker profiles that are clearly different from non-obese controls. Comparison of obesity patients with and without cardiac dysfunction suggested an important role for inflammation, atherosclerosis and insulin resistance in the underlying pathophysiology of cardiac dysfunction in obesity patients.

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10

Chapter 10

Cardiovascular biomarker profiles in obesity and relation to normalization of subclinical cardiac dysfunction after bariatric surgery

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ABSTRACT

Aims

We aimed to gain insight into the underlying pathophysiology of cardiac dysfunction in obesity patients and the improvement of cardiac function after weight loss.

Methods

This is a longitudinal study in which 92 cardiovascular biomarkers were measured by multiplex immunoassays in obesity patients without known cardiovascular disease before and one year after bariatric surgery.

Results

Out of 100 eligible patients, 72 patients completed the follow-up. A total of 72 (78%) biomarkers changed significantly. The biomarkers with the highest relative changes represented mainly processes linked to insulin resistance and inflammation. In the patients with persisted subclinical cardiac dysfunction, baseline values of 10 biomarkers were different from values in patients with normalization of cardiac function. Most of these biomarkers were linked to inflammation or atherosclerosis. Finally, a model was developed to investigate the relation between changes of the biomarkers and persistent subclinical cardiac dysfunction. Seven biomarkers, were retained in this model, mainly linked to inflammation, atherosclerosis, and hypercoagulability.

Conclusion

The majority (78%) of cardiovascular biomarkers changed, pointing mainly at modulation of insulin resistance and inflammation. Baseline levels of 10 biomarkers, as well as pre- to post-bariatric surgery changes in 7 biomarkers, were related to persistent subclinical cardiac dysfunction after bariatric surgery.

INTRODUCTION

Obesity has reached epidemic proportions globally and the prevalence will continue to increase (1, 2). The risk of heart failure is known to be increased in obesity patients (3), and subclinical cardiac dysfunction is present even in 60% of obesity patients without known cardiovascular disease (4). Bariatric surgery has proven to be an effective and safe treatment option resulting in large long-term weight loss (5, 6). Weight loss and associated metabolic improvement achieved by bariatric surgery have a positive impact on heart morphology even in obesity patients without heart failure (7), and subclinical cardiac dysfunction normalizes in 50% of the patients one-year post-bariatric surgery (8). However, little is known about the pathophysiology behind this improvement, and it remains unknown why in some patients cardiac function does not normalize.

Currently, an extensive body of evidence is available on the role of circulating proteins in cardiovascular disease. These proteins reflect several biological processes, such as inflammation, atherosclerosis, insulin resistance and hypercoagulation that also have been hypothesized to play an important role in cardiac dysfunction in obesity patients (9, 10). Moreover, the use of multiplex immunoassays that determine a broad spectrum of biomarkers is gaining momentum in medical science (11). In the current study, we investigate changes in cardiovascular biomarker profiles one year after bariatric surgery. Herewith we aim to gain insight into the underlying pathophysiology of cardiac dysfunction in obesity patients and the improvement of cardiac function after weight loss.

METHODS

Study design and study group

The protocol of the CARDIOBESE study has been described before (12). In short, this study is a multicentre, prospective study in which 100 obesity patients who were referred for bariatric surgery were enrolled. Patients were included if they were between 35 and 65 years old with a body mass index (BMI) of ≥35 kg/m^2. Patients with a suspicion of or known cardiovascular disease were excluded. Bariatric surgery included either a gastric sleeve, gastric bypass, or a mini-gastric bypass. Patients were seen before and one year after bariatric-surgery. The study protocol was approved by the ethics committee and written informed consent was obtained from all participants (12). All participants underwent a transthoracic echocardiogram and laboratory tests. The presence or absence of subclinical cardiac dysfunction in the 100 obesity patients of the CARDIOBESE-study has been described in detail before (4). In short, cardiac dysfunction was defined as either a reduced left ventricular (LV) ejection fraction

(13), a decreased global longitudinal strain (GLS), diastolic dysfunction (14), ventricular arrhythmia or an increased BNP or hs Troponin I. Of the predefined studied parameters, a decreased GLS (<17%) was by far the most abundant, in 57 patients; one had diastolic dysfunction without an available GLS, one had a normal GLS but an increased BNP (49 pmol/L, normal value <30 pmol/L), and one had a positive hs Troponin I. One patient with cardiac dysfunction was diagnosed with acromegaly after inclusion and was excluded from further analysis, leaving 59 obesity patients with versus 40 without subclinical cardiac dysfunction. Of these, 40 patients with and 32 patients without subclinical cardiac dysfunction underwent bariatric surgery and completed the one-year follow-up (Figure 1). These patients were included in the current study.
In order to gain insight in the pathophysiology of cardiac dysfunction in obesity, a broad range of biomarkers was determined before and after bariatric surgery in patients with and without subclinical cardiac dysfunction before surgery.

Laboratory procedures

Non-fasting blood samples were collected before- and one-year after bariatric-surgery. Blood samples were processed and stored at -80°C within two hours after collection. Biomarker measurements were subsequently performed in one batch. Serum aliquots were thawed and randomly divided over three microwell plates. Internal controls were added to each plate. Plates were frozen at -80°C and shipped on dry ice to Olink Proteomics AB, Uppsala, Sweden. The cardiovascular panel III of the Olink Multiplex platform for biomarkers was used for analysis. The kits are based on the proximity extension assay technology, where 92 oligonucleotide-labelled antibody probe pairs are allowed to bind to their respective target in the sample. The proximity extension assay technique shows exceptionally high specificity and sensitivity. (15, 16) The biomarkers are delivered in normalized protein expression units (NPX), which are relative units. Therefore, NPX values for 2 different analyses/proteins are not directly comparable. They are expressed on a log2 scale where 1 unit higher NPX value represents a doubling of the measured protein concentrations. NPX were converted into a linear scale: 2^{NPX}= linear NPX. Abbreviations of all 92 biomarkers are listed in Supplementary Table 1.

Transthoracic echocardiography

Two-dimensional grayscale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system (EPIQ 7, Philips, Best, the Netherlands), equipped with a broadband (1-5MHz) X5-1 transducer. All acquisitions and measurements were performed according to current guidelines (13, 14). To optimize speckle tracking echocardiography, apical images were obtained at a frame rate of 60 to 80 frames/s. Three consecutive cardiac cycles were acquired from all

apical views. Subsequently, these cycles were transferred to a QLAB workstation (version 10.2, Philips, Best, the Netherlands) for off-line speckle tracking analysis. Peak regional longitudinal strain was measured in 17 myocardial regions and a weighted mean was used to derive global longitudinal strain (GLS).

Statistical analysis

Patients who completed the one year follow-up were included in the analysis. The distributions of the variables were tested for normality by the ShapiroχWilk test. Continuous variables with normal distributions were expressed as mean ± standard deviation, those with skewed distributions as median and interquartile range, and categorical variables as counts and percentages. Missing values were omitted (between 0-2%, none of the biomarkers were missing). To compare variables pre- and one-year post-surgery, paired t-tests were used for continuous variables with normal distributions, the nonparametric Wilcoxon signed-rank test for variables with non-normal distributions, and the McNemar test for categorical variables.

Relative changes of all biomarkers from pre- to one year post-bariatric surgery were calculated by subtracting the median value of biomarkers pre-surgery from the value of the biomarkers post-surgery, and dividing the obtained difference by the median value of the biomarkers pre-surgery. In addition to aforementioned exploration, change between pre- and post-surgery was analysed by univariable linear mixed modelling for each of the biomarkers, with moment of measurement (baseline and follow-up) as the independent variable, and all of the biomarkers entered consecutively as the dependent variable. Random intercepts and slopes were used to account for presence of two biomarker measurements per patient. The Benjamini–Hochberg procedure, with a 5% false discovery rate, was used to correct for multiple testing (17).

In the subset of obesity patients with pre-surgery cardiac dysfunction, baseline biomarker levels in those with normalization of cardiac function were compared to levels in those with persisting cardiac dysfunction post-surgery with the Mann-Whitney U test. Again, the Benjamini-Hochberg procedure was used to correct for multiple testing. A multiple biomarker model was than constructed to investigate the relation between changes in biomarkers and persistent cardiac dysfunction post-surgery. In order to select the subset of biomarkers that carries the best predictive value for cardiac dysfunction and, at the same time, to reduce the risk of overfitting (which is especially important in the setting where the number of events is low relative to the number of predictors), elastic net logistic regression was used. An alpha of 0.3 was used and lambda was selected by cross-validation in the "glmnet" package for the optimization of different model arguments. This method combines two established shrinkage-methods: Ridge regression and Lasso regression. (18) Delta's (value post-surgery minus value pre-surgery) of all individual biomarkers were used simultaneously as input for this model. The discriminative ability of the resulting model was

investigated by calculating the area under the receiver operating curve (AUC). Odds ratios of the Z-scores were reported. In addition to the elastic net logistic regression model, we performed a spls-DA analysis with the "mixomics" package in R. A two-tailed p-value of <0.05 was considered statistically significant unless otherwise reported. Statistical analyses were performed with SPSS version 25.0 or higher (SPSS Inc., Chicago, USA) or R 3.0.3 (glmnet R package).

RESULTS

Changes in clinical characteristics from before to one year after bariatric-surgery

There was a significant decrease in weight, BMI, systolic blood pressure, and heart rate post-bariatric surgery (Table 1). Also, the prevalence of comorbidities such as diabetes mellitus, hypertension, obstructive sleep apnoea syndrome, and use of medication decreased.

Table 1: Clinical characteristics of the study population. Changes in obesity patients from pre- to post-bariatric surgery.

	Pre-surgery (n=72)	1-yr post-surgery (n=72)	p-value
General characteristics			
Age (years)	48 (43-54)		
Female (%)	54 (75%)		
Physical examination			
Weight (kg)	122 [113-133]	83 [74-91]	<0.001
BMI (kg/m^2)	41 [39-46]	28 [25-31]	<0.001
Systolic BP (mmHg)	146 ± 21	133 ± 20	0.003
Diastolic BP (mmHg)	79 [73-88]	80 [75-86]	0.18
Heart rate (bpm)	80 [73-86]	65 [57-71]	<0.001
Comorbidity			
Diabetes Mellitus (%)	16 (22%)	6 (8%)	0.002
Hypertension (%)	24 (33%)	12 (17%)	0.035
Hypercholesterolemia (%)	15 (21%)	8 (11%)	0.09
Current smoking (%)	11 (15%)	3 (6%)	0.18
COPD (%)	4 (6%)	0	0.13
OSAS (%)	8 (11%)	0	0.008
Medication			
Beta-blockers (%)	5 (7%)	3 (4%)	0.63
ACE inhibitors / ARBs (%)	11 (15%)	8 (11%)	0.012
Calcium channel blockers (%)	6 (8%)	5 (7%)	0.66
Statins (%)	16 (22%)	9 (13%)	0.039
Diuretics (%)	13 (18%)	8 (11%)	0.18
Insulin (%)	5 (7%)	4 (6%)	0.56
Oral anti-diabetics (%)	10 (14%)	4 (6%)	0.031

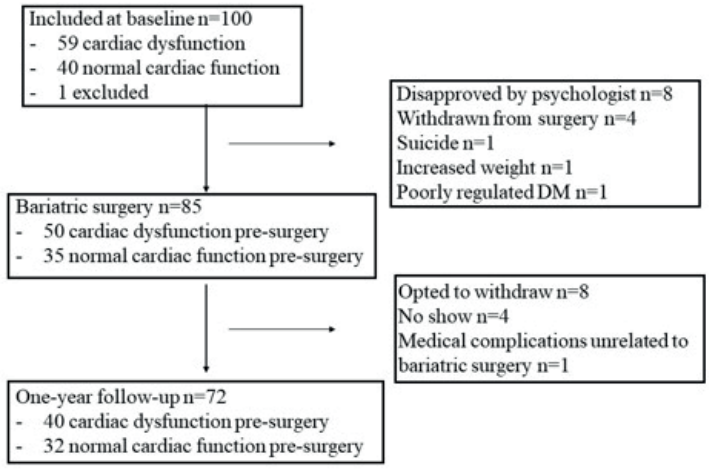
Values represent mean ± SD, median [Q1-Q3] or n (%). BMI= body mass index, BP= blood pressure, COPD= chronic obstructive pulmonary disease, OSAS= obstructive sleep apnoea syndrome, ACE= angiotensin-converting enzyme, ARBs= angiotensin II receptor blockers

Changes in cardiovascular biomarker levels from before to one year after bariatric surgery

The relative changes of all 92 biomarkers from before to one year after bariatric surgery are displayed in Figure 2 and Supplementary Table 2. A total of 72 (78%) biomarkers were significantly different: 52 (56%) biomarkers decreased, and 20 (22%) increased after bariatric surgery. The biomarkers with the highest relative changes were Insulin-like growth factor-binding protein 1 (IGFBP-1) (increase of 175%, p<0.001), Integrin beta-2 (ITGBP2) (increase of 139%, p<0.001), Epithelial cell adhesion molecule (Ep-CAM) (increase of 90%, p<0.001), Osteopontin (OPN) (increase of 59%, p<0.001), N-terminal prohormone brain natriuretic peptide (NT-

proBNP) (increase of 58%, p=0.01), and Insulin-like growth factor-binding protein 2 (IGFBP-2) (decrease of -58%, p<0.001).

Figure 1: Overview of the study population. DM: diabetes mellitus.



Comparison of baseline values of biomarkers in patients with versus without normalization of cardiac function after bariatric surgery

Further analysis was performed in the 40 patients with subclinical cardiac dysfunction pre-surgery. Of these 40 patients, one year after bariatric surgery 20 (50%) had normal cardiac function, and 20 (50%) still had cardiac dysfunction. Table 2 shows that baseline values of 10 biomarkers were significantly decreased in patients with persisting cardiac dysfunction post-bariatric surgery as compared to patients with normalization of cardiac function: Bleomycin hydrolase (BLM hydrolase), Caspase-3 (CASP-3), Junctional adhesion molecule A (JAM-A), P-selectin (SELP), Platelet endothelial cell adhesion molecule (PECAM-1), Platelet glycoprotein VI (GP6), Platelet-derived growth factor subunit A (PDGF subunit A), Retinoic acid receptor responder protein 2 (RARRES2), Trem-like transcript 2 protein (TLT-2), and Tumor necrosis factor receptor superfamily member 14 (TNFRSF14).

Association of changes in biomarker levels with presence of cardiac dysfunction post-bariatric surgery

The elastic net regression model selected the delta of the following set of biomarkers to optimally predict the presence of cardiac dysfunction post-surgery: Carboxypeptidase B (CPB1), CASP-3, SELP, GP6, PDGF subunit A, TLT-2, and von Willebrand factor

(vWF) (Table 3). Figure 3 shows the ROC-curve for this model. The ability of this model to identify patients with cardiac dysfunction post-surgery was high, as shown by the AUC of 0.91 (95% CI: 0.82-0.99, $p<0.001$). The sensitivity of this model was 90%, specificity 80%, positive predictive value 82%, and negative predictive value 89%. A spls-DA analysis was performed in addition to the elastic net regression model. This model largely corresponds to the elastic net model (supplementary Table 3).

Table 2: Comparison of baseline biomarker values in obesity patients with cardiac dysfunction pre-surgery and normalization of cardiac function one-year post-bariatric surgery vs. persisting cardiac dysfunction.

Abbreviation	Post-surgery normal cardiac function (n=20)	Post-surgery cardiac dysfunction (n=20)	p-value
AP-N	37.6 [34.2-41.5]	36.5 [32.6-40.1]	0.81
AZU	7.8 [6.4-10.4]	6.4 [5.3-7.8]	0.61
BLM hydrolase	9.9 [8.2-10.8]	7.4 [6.3-8.6]	**0.004***
CCL15	126 [108-178]	126 [110-183]	0.37
CCL16	155 [114-163]	150 [104-172]	0.97
CCL24	41 [28-68]	43 [23-60]	0.90
CXCL16	51 [40-59]	51 [48-61]	0.15
CDH5	26 [23-28]	26 [19-32]	0.95
CPA1	67 [52-99]	70 [49-98]	0.30
CPB1	61 [46-85]	67 [44-95]	0.31
CASP-3	750 [564-903]	295 [155-551]	**<0.001***
CTSD	8.3 [6.4-11.6]	7.9 [5.9-10.5]	0.67
CTSZ	59.5 [54.5-68.5]	60.1 [43.2-70.6]	0.67
ALCAM	232 [209-284]	222 [197-244]	0.91
CHI3L1	21.1 [17.6-30.0]	18.9 [13.5-27.2]	0.96
CHIT1	26.2 [20.0-38.1]	36.2 [14.9-48.5]	0.84
COL1A1	8.2 [7.3-9.7]	9.1 [8.0-10.8]	0.42
CD93	2200 [2002-2592]	2572 [2058-2955]	0.22
CNTN1	29.1 [24.3-33.5]	27.0 [24.7-32.0]	0.95
CSTB	26.8 [19.9-33.3]	21.5 [17.5-26.5]	**0.012**
SELE	7543 [5486-9772]	7098 [5587-10785]	0.38
PI3	5.7 [5.0-7.8]	5.8 [5.0-7.5]	0.41
EPHB4	49.6 [44.8-58.5]	51.4 [46.3-60.4]	0.57
EGFR	11.9 [11.1-13.3]	11.1 [10.1-12.7]	0.22
Ep-CAM	49.6 [33.5-75.1]	51.8 [26.3-126.9]	0.91
FABP4	109.2 [88.9-169.3]	104.2 [85.1-142.8]	0.59
Gal-3	11.5 [10.6-13.1]	11.0 [10.4-12.4]	0.96
Gal-4	19.7 [13.7-23.8]	18.0 [14.8-21.5]	0.72
GRN	60.1 [46.6-75.5]	59.8 [53.6-70.0]	0.42
GDF-15	72.0 [46.6-96.8]	54.4 [48.1-59.4]	0.85
IGFBP-1	10.6 [6.4-18.8]	9.5 [6.2-13.3]	0.63
IGFBP-2	159 [127-200]	170 [133-226]	0.22
IGFBP-7	296 [243-323]	275 [247-322]	0.22
ITGB2	58.4 [49.1-66.6]	54.6 [46.3-65.3]	0.37
ICAM-2	57.3 [48.3-66.9]	53.1 [44.0-69.8]	0.96
IL-1RT1	91.3 [78.1-104.4]	81.9 [74.8-101.4]	0.64
IL-1RT2	57.2 [45.5-62.8]	50.9 [40.9-54.3]	0.91
IL-17RA	24.2 [19.3-33.6]	20.4 [15.8-26.1]	0.06
IL-18BP	72.2 [65.5-80.9]	68.0 [64.6-86.3]	0.65
IL2-RA	15.3 [14.1-17.8]	12.4 [10.2-17.8]	**0.033**
IL-6RA	5523 [4150-6345]	4812 [3881-6379]	0.96
JAM-A	160 [116-205]	64 [29-103]	**<0.001***
KLK6	5.8 [5.1-7.3]	5.4 [4.6-6.0]	0.26

Table 2: Continue

Abbreviation	Post-surgery normal cardiac function (n=20)	Post-surgery cardiac dysfunction (n=20)	p-value
LDL receptor	27.4 [19.9-40.3]	25.2 [21.6-31.2]	0.82
LTBR	17.9 [15.5-19.4]	17.3 [14.5-19.0]	0.31
MEPE	74.8 [64.0-89.3]	65.7 [62.4-80.6]	0.58
MMP-2	16.6 [14.8-19.6]	18.8 [15.4-20.2]	**0.014**
MMP-3	183 [137-241]	210 [168-266]	**0.018**
MMP-9	68.7 [50.8-123.1]	60.5 [36.9-86.8]	0.06
TIMP4	12.3 [11.4-14.7]	14.2 [11.8-15.5]	0.62
MCP-1	20.2 [17.8-24.6]	17.5 [13.9-19.9]	0.33
PRTN3	19.6 [15.7-25.4]	17.4 [14.2-24.9]	0.92
MPO	12.0 [9.8-14.9]	12.0 [9.3-15.0]	0.57
MB	205 [170-267]	226 [193-286]	**0.014**
NT-proBNP	11.6 [7.2-15.2]	7.7 [4.4-16.6]	0.41
Notch 3	50.2 [41.6-54.4]	53.3 [42.0-63.4]	**0.018**
OPN	224 [196-271]	218 [165-275]	0.71
OPG	18.0 [14.4-22.6]	16.7 [14.0-19.7]	0.66
SELP	3845 [2941-4907]	2152 [1093-2368]	**<0.001***
PON3	70.7 [61.2-105.7]	91.4 [75.1-106.8]	0.10
PGLYRP1	205 [175-255]	177 [159-211]	0.23
PLC	308 [284-336]	315 [290-348]	0.40
PAI	95 [74-202]	73 [52-97]	0.05
PECAM-1	89 [77-116]	56 [31-63]	**<0.001***
GP6	23 [18-27]	12 [7-16]	**<0.001***
PDGF subunit A	36 [26-48]	19 [13-28]	**<0.001***
PCSK9	9.1 [7.5-11.8]	9.5 [7.7-10.4]	0.57
DLK-1	79 [60-105]	94 [70-105]	0.65
PSP-D	6.4 [5.4-9.9]	8.6 [5.6-10.8]	0.52
RETN	87 [76-108]	81 [71-98]	0.73
RARRES2	4849 [4614-5629]	4256 [4044-4862]	**0.003***
CD163	381 [305-455]	367 [251-407]	0.45
SCGB3A2	5.1 [4.3-6.5]	3.8[3.0-5.2]	0.08
SPON1	4.9 [4.4-5.3]	4.4 [4.0-5.9]	0.73
ST2	33.3 [22.3-40.1]	23.3 [15.3-27.8]	**0.047**
TR-AP	15.8 [14.4-22.0]	15.8 [13.5-18.3]	0.93
TFPI	792 [688-850]	742 [646-877]	0.50
t-PA	134 [97-167]	144 [96-170]	0.58
TR	65 [39-87]	62 [42-75]	0.70
TFF3	39 [33-46]	38 [28-45]	0.73
TLT-2	73 [64-88]	51 [42-62]	**<0.001***
TNFSF13B	170 [152-184]	174 [143-205]	0.54
TNF-R1	139 [128-155]	141 [128-174]	0.37
TNF-R2	68 [62-78]	65 [61-79]	0.67
TNFRSF10C	192 [132-253]	161 [98-199]	0.45
TNFRSF14	40 [37-46]	33 [29-36]	**0.004***
FAS	79 [73-94]	83 [75-89]	0.17
AXL	650 [547-763]	623 [544-809]	0.29

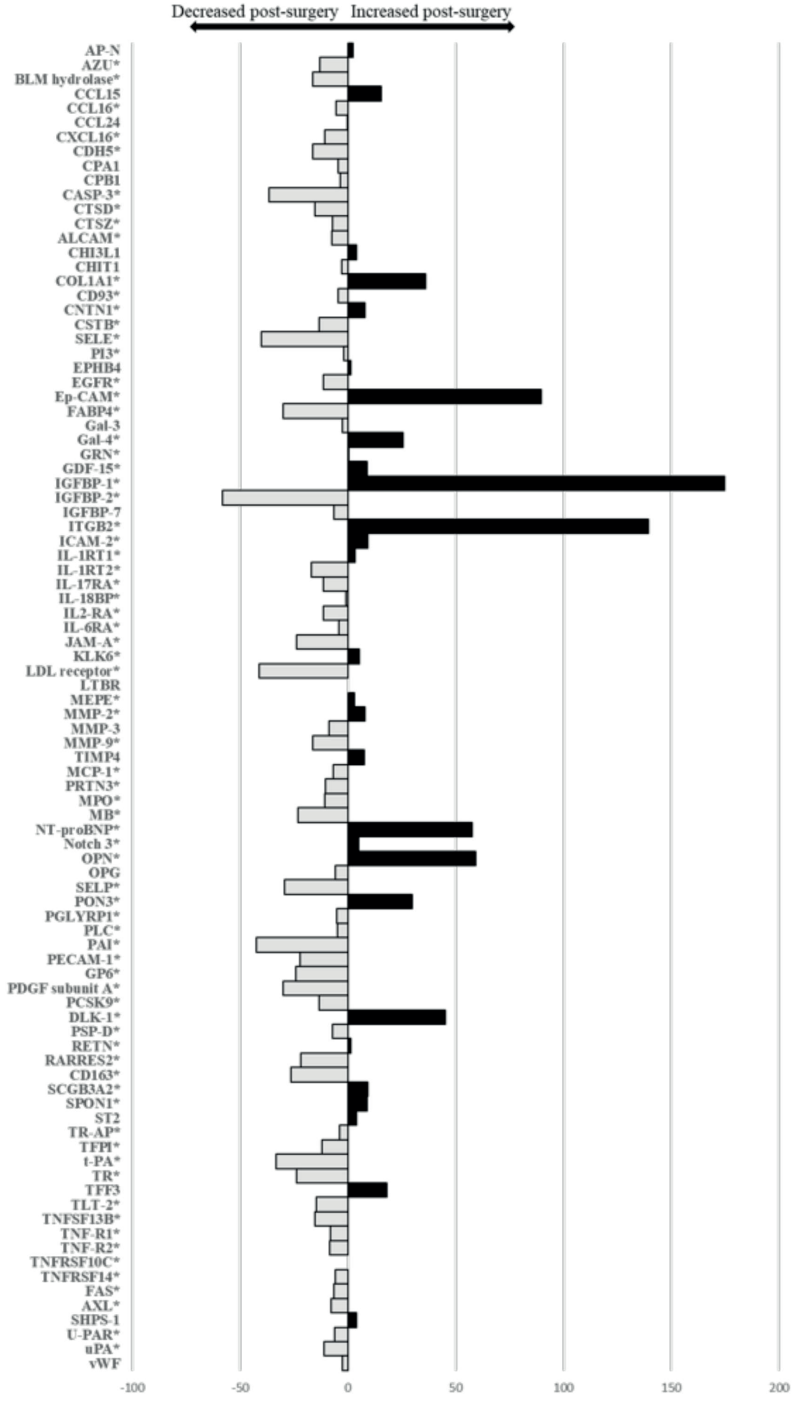
Table 2: Continue

Abbreviation	Post-surgery normal cardiac function (n=20)	Post-surgery cardiac dysfunction (n=20)	p-value
SHPS-1	16.3 [13.6-20.4]	13.6 [11.5-17.5]	0.62
U-PAR	54.4 [45.6-63.7]	48.8 [39.5-60.7]	0.53
uPA	31.0 [25.9-38.3]	30.7 [25.0-34.3]	0.36
vWF	211 [151-313]	176 [108-239]	0.85

Values represent median [Q1-Q3] of pre-surgery biomarker levels, all units are NPX.

P-values displayed were obtained with the Mann-Whitney U test.* Significant after Benjamini–Hochberg correction

Figure 2: Graphical representation of the relative changes of all 92 biomarkers, pre- and post-bariatric surgery.* significant after Benjamini–Hochberg correction



DISCUSSION

A multiplex immunoassay was used for the first time to investigate changes of a broad spectrum of cardiovascular biomarkers in obesity patients from pre- to one-year post-bariatric surgery. The main findings are that the majority (78%) of the cardiovascular biomarkers changed, and reduced levels of 10 biomarkers pre-surgery were related to persistent subclinical cardiac dysfunction post-surgery. Furthermore, a multivariable model showed that changes in 7 biomarkers were associated with a lack of improvement of cardiac function.

A total of 72 biomarkers significantly changed from pre- to post-surgery, indicating alterations in a wide range of processes related to metabolic status and cardiovascular function. However, the biomarkers with the highest relative changes mainly represented processes linked to insulin resistance and inflammation. For example, IGFBP-1 is known to be lower in patients with impaired glucose tolerance (19). IGFBP-1 increased after bariatric surgery, suggesting improved glucose tolerance. Also, circulating IGFBP-2 levels are associated with reduced insulin sensitivity in obesity patients (20), and the decrease in IGFBP-2 post-surgery indicates an increase in insulin sensitivity. ITGBP2 is of crucial importance for leukocyte trafficking and immune cell activation, but interestingly plays a role in immune suppression as well. Consequently, dysfunctional or absent ITGPB-2 is linked not only to immune deficiency disease but also to inflammatory disease, thereby contributing to both ends of the spectrum of immune-related diseases (21). The increase of ITGBP2 post-bariatric surgery may indicate a change of balance towards a decrease of inflammation, however further research is needed to explore this finding.
OPN showed a relatively large increase post-bariatric surgery. At first sight, a surprising finding since OPN has been suggested to play a key role in linking obesity to the development of insulin resistance by promoting inflammation (22, 23). Nevertheless, our result is in line with findings from other studies (24, 25). Changes in bone metabolism have been suggested as a potential source of enhanced OPN concentrations post-bariatric surgery, and not inflammation or insulin resistance (24). Again, further research will be needed to explore this relation.
NT-proBNP also strongly increased post-bariatric surgery. NT-proBNP is known to be decreased in obesity patients, both with and without heart failure. (26) Although the reason for this remains incompletely understood, it is most likely due to lower release in obesity patients, rather than an increase in clearance. (27)

A distinctive aspect of the CARDIOBESE study is that different diagnostic techniques were used in parallel to simultaneously investigate a variety of cardiac and metabolic changes after bariatric surgery. This design allowed us to correlate changes

in cardiovascular biomarkers with (a lack of) improvement of cardiac function after bariatric surgery.

Baseline values of 10 biomarkers were related to persistent cardiac dysfunction post-surgery. Most of these biomarkers are known to be linked to inflammation and/or atherosclerosis. JAM-A plays an important role in leukocyte transmigration and is upregulated on the early atherosclerotic endothelium (28). PECAM-1 is upregulated in inflammatory conditions (29), and is particularly evident in atherosclerotic lesions (30), TNFRSF14 is a mediator of atherosclerosis by inducing inflammation (31). TLT-2 is known to regulate inflammation through the integration of inflammatory signals (32). RARRES2 has been associated with inflammation, obesity, and the metabolic syndrome (33). SELP is expressed at the surface of platelets in activated endothelium and mediates atherosclerotic plaque progression (34). Also, GP6 has been described to mediate platelet adhesion on atherosclerotic plaque tissues (35), and PDGF subunit A is expressed by macrophages within atherosclerotic lesions (36). The remaining 2 biomarkers do not have a clear relationship with either inflammation or atherosclerosis. CASP-3 is activated in the apoptotic cell and is known to be elevated after myocyte injury (37). The normal physiological role of BLM hydrolase is unknown (38), however, it has been suggested that BLM hydrolase may play a part in inflammation by regulating the secretion of chemokines (39).

Table 3: Odds ratios of the Z-scores of the biomarkers selected by the elastic net regression

Biomarker	Odds ratio
CPB1	0.94
CASP3	1.06
SELP	1.01
GP6	1.12
PDGFsubunitA	1.03
TLT-2	1.22
vWF	1.03

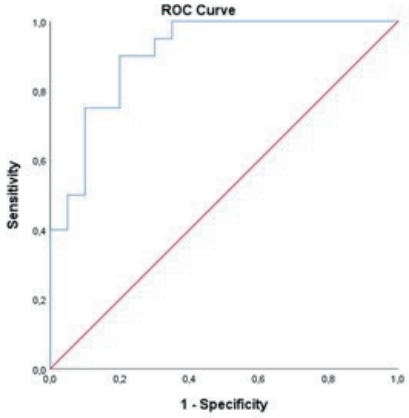
Afterward, a model was developed to investigate the relation between *changes* of the biomarkers from pre- to one-year post-surgery and the presence of subclinical cardiac dysfunction post-surgery. The change in 7 biomarkers selected by the multivariable model for the persistence of cardiac dysfunction post-surgery suggests that there is an important role for the combination of inflammatory status (reflected by CPB1 (40), TLT-2 (41), and vWF (42)), markers of atherosclerosis (reflected by SELP, (34) PDGF subunit A (36), GP6 (35), CASP-3 (37)) and hypercoagulability (reflected by CPB1 (40), SELP (34), GP6 (35), and vWF (42)).

The relation between a relative lack of improvement of inflammatory status and persistence of cardiac dysfunction after bariatric surgery is in line with our previously mentioned finding that pre-bariatric surgery values of biomarkers related to inflammation were associated with persistence of cardiac dysfunction. Inflammation is known to be increased in obesity patients, and is has been suggested that heart failure with preserved ejection fraction in these patients is typically the result of systemic inflammation (43). The increased size of adipocytes plays a decisive role in inflammation, because, to the extent that it increases in the adipose tissue, the production of adipocytokines increases, and this triggers a series of inflammation-related pathophysiological processes (44).

Our study suggests that both increased baseline levels of markers of atherosclerosis and an increase of these levels over time may play a part in the persistence of cardiac dysfunction post-surgery. Obesity is a well-known major risk factor for atherosclerotic vascular disease. The exact mechanism behind this remains to be elucidated, but probably there is an important role for increased inflammation (45). When atherosclerosis causes myocardial ischemia, it can lead to cardiac dysfunction (46).

Hypercoagulability was related to the persistence of cardiac dysfunction in obesity patients after bariatric surgery as well. Hypercoagulability has previously been described in obese patients (47). Possible explanations for this are the actions of adipocytokines from adipose tissue, increased activity of the coagulation factors, decreased activity of the fibrinolytic system, increased inflammation, increased oxidative stress, endothelial dysfunction, and disturbances of lipids and glucose tolerance in association with the metabolic syndrome (47). Also, the presence of platelet activation and hypercoagulability in heart failure has been well documented (48), suggesting that indeed there may be a relation between hypercoagulability and cardiac dysfunction in obesity patients as found in our study.

Figure 3: ROC-curve for the elastic net model. Biomarkers included are CPB1, CASP3, SELP, GP6, PDGF-subunit A, TLT2, and vWF. AUC 0.91 (95% CI: 0.82-0.99, p<0.001)



Limitations

Some patients included in the CARDIOBESE did not undergo bariatric surgery because of various reasons, but mostly because of disapproval by the psychologist or because they withdrew themselves from surgery. Incomplete follow-up was mainly because of withdrawal from follow-up. Although the definition of cardiac dysfunction used in the CARDIOBESE study is unconventional, combining parameters assessed by echocardiography, Holter registration and blood tests, this was chosen to highlight different potential effects of obesity on cardiac function. The assay that was used to determine the biomarkers is designed as a biomarker discovery tool rather than being an approved clinical test. Therefore, the 7 biomarkers related to persistent subclinical cardiac dysfunction after bariatric surgery can currently not be used to predict this in daily clinical practice. Furthermore, while for some of the investigated biomarkers extensive evidence on involvement in biological processes is available, this is lacking for other biomarkers. Finally, the findings of the current study should considered to be exploratory. Although there were clear associations between echocardiography and laboratory findings, it was not possible to establish a cause-effect relationship.

CONCLUSIONS

The present study provides novel data on 92 cardiovascular biomarkers measured in obesity patients before and one year after bariatric surgery. The vast majority of these biomarkers changed one-year after bariatric-surgery, indicating alterations in a wide range of processes related to metabolic status and cardiovascular function. However,

the biomarkers with the highest relative changes mainly represent processes linked to insulin resistance and inflammation.

This design of the study allowed correlation of changes in cardiovascular biomarkers with a (lack of) improvement of cardiac function after bariatric surgery. Most of the biomarkers with baseline levels associated with persistence of cardiac dysfunction are known to be linked to inflammation, while there also appeared to be a relatively important role for subclinical atherosclerosis. The relation between changes of certain biomarkers and the persistence of subclinical cardiac dysfunction post-surgery again highlighted the importance of inflammation and atherosclerosis, with a potential role for hypercoagulability as well. Inflammatory status is known to have an important role in the induction of both atherosclerosis and hypercoagulability (49, 50). Thus, although cardiac dysfunction in obesity seems to be a heterogeneous disorder, inflammation plays a central part (43, 51).

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Part V

Obesity and heart failure in clinical practice

II

Chapter II

The role of obesity in atrial fibrillation in patients with heart failure with preserved ejection fraction

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Submitted

ABSTRACT

Introduction

Obesity is an important risk factor for atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF). The purpose of this study was to investigate the association between obesity and AF in a large real-world contemporary cohort of HFpEF patients.

Methods

Patients with chronic HFpEF were selected from the CHECK-HF registry. Patients were divided into those with BMI $\geq$30 kg/m^2 and those with BMI <30 kg/m^2. A multivariable regression analysis was performed to investigate differences in the AF prevalence between BMI groups in relation to clinical risk factors.

Results

A total of 2094 HFpEF patients were included, of whom 691 (33%) were obese. Obese patients were younger (72.7 $\pm$ 10.8 vs. 74.7 $\pm$ 12.9 years, p<0.001),more often female (58.6% vs. 51.6%, p=0.02) and more often suffered from comorbidities. Obese HFpEF patients had a significantly higher prevalence of AF compared to non-obese HFpEF patients (39.7% vs. 34.4%, p=0.018). Furthermore, in the multivariable regression analysis obesity was significantly associated with AF (OR 1.45, CI 1.16 – 1.81).

Conclusion

In this large cohort of HFpEF patients, the prevalence of AF was higher among patients with obesity. In addition, obesity was significantly associated with AF even after adjusting for multiple confounders. This result suggests that obesity and development of AF in HFpEF patients are closely associated.

INTRODUCTION

Obesity is a global epidemic affecting around 650 million persons worldwide (1). The prevalence of obesity has doubled in more than 70 countries since 1980 and it is expected that the prevalence of obesity will continue to rise without any signs of waning (1, 2). Obesity is an important contributor in the development of atrial fibrillation (AF) and heart failure with preserved ejection fraction (HFpEF) (3, 4). The obesity-related HFpEF phenotype is prevalent, especially in individuals with metabolic disorders (5). In the general population, individuals with obesity have a 50% increased risk for AF compared to individuals without obesity (6). Identifying AF in HFpEF is important, as AF is associated with worse clinical outcomes (7-9) . Obesity has an important role in both the onset of HFpEF and AF, as it leads to systemic inflammation, expansion of epicardial adipose tissue (EAT), and chronic volume overload that can influence the onset of AF and HFpEF (10-12). In addition, obesity is associated with comorbidities, such as hypertension and insulin resistance, that are associated with an increased risk for both conditions (11). The role of obesity in the onset of HFpEF and AF, in combination with the increasing prevalence of obesity, requires an in-depth exploration of AF in patients with HFpEF and obesity from a clinical perspective. A detailed analysis on the association between obesity and AF in a large HFpEF cohort is currently lacking. Therefore, the purpose of this study was to investigate the association between obesity and AF in a large real-world contemporary cohort of HFpEF patients.

METHODS

For this study, data was used from the CHECK – HF (Chronisch Hartfalen ESC – richtlijn Cardiologische praktijk Kwaliteitsproject HartFalen) registry. The design and methods of the CHECK-HF registry have been published in detail before (13). Briefly, the CHECK-HF registry consists of 10,910 patients with chronic HF from a total of 34 participating Dutch centers, contributing in the inclusion for this cross-sectional observational cohort. Between 2013 and 2016, all centers included patients diagnosed with HF according to 2012 ESC guidelines on HF, based on symptoms and echo parameters, who were seen at the outpatient HF clinic (96%) or general cardiology outpatient clinic (4%) if no specific HF clinic was present. HFpEF was classified as left ventricular function (LVEF) ≥50% with no previously known reduced LVEF. AF was defined as a documented history of AF, which included permanent, persistent, paroxysmal AF, and AF of unknown type, or AF diagnosed by 12-lead electrocardiogram, performed during the most recent outpatient clinic visit. Detailed information on patient characteristics, demographics, comorbidities and guideline-

recommended HF drug prescription and dosages was recorded. Patients were divided based on their BMI into those with BMI ≥30 kg/m^{2}and those with BMI <30 kg/m^2 (14). Patients with no information on their BMI were excluded. In the CHECK-HF registry 2153 patients had HFpEF. BMI was available in 2094 HFpEF patients. The study was conducted according to the Declaration of Helsinki. Ethical approval was provided for anonymously analyzing existing patient data by the Ethical Committee of the Maastricht University Medical Center, The Netherlands.

Statistical analysis

Continuous data are presented as mean value ± SD or median and interquartile range, depending on the distribution of the data. Comparisons were performed using the independent T-test or Mann-Whitney U test. Categorical data are expressed as counts and percentages and compared with the Chi-square test. A 2-sided *P* of 0.05 was considered statistically significant. In order to investigate whether the observed differences in AF between BMI groups were independent of potential confounders, multivariable logistic regression were used. The results of these regression analyses are expressed as odds ratios (OR) and 95% confidence intervals (CI). In model 1, we adjusted for age, gender, and BMI group. In model 2, we further adjusted for New York Heart Association (NYHA) classification. In model 3, we further included hypertension, diabetes mellitus, and OSAS, as these comorbidities were clinically related to the outcome variable. In a separate analysis, BMI was added to the models as a continuous variable. All variables were included at a statistical level p-value <0.05 in the logistic regression model. Analyses were performed using SPSS Statistical Package version 25.0

RESULTS

A total of 2094 HFpEF patients were included, of whom 691 (33%) had a BMI ^{3} 30 kg/m^2. The baseline characteristics are shown in Table 1. Mean age of the study population was 74.1 $\pm$ 12.3 years and 53.8% were female. Mean BMI was 28.3 $\pm$ 5.9 kg/m^2. A diagnosis of AF was present in 36.1% of the study population, out of which 11.2% was paroxysmal AF, 17.6% persistent AF, 44.7% permanent AF, and in 26.1% AF was of unknown type. Median LVEF was 58% and most patients were in NYHA class II (48.3%). Hypertension was diagnosed in over half of the patients (53.1%) and as many as 28.0% patients suffered from diabetes mellitus type 2 (DM2). As for medication use, diuretics and beta-blocker were most commonly used, respectively in 74.5% and 73.5% of the patients.

Comparison of HFpEF patients with obesity and HFpEF patients without obesity

As presented in Table 1, HFpEF patients with obesity had a number of differences compared to HFpEF patients without obesity. Patients with a BMI ^{3} 30 kg/m^2 were significantly younger (72.7 $\pm$ 10.8 vs. 74.7 $\pm$ 12.9 years, p<0.001) and were more often female (58.6% vs. 51.6%, p=0.02). HF symptoms were more severe in patients with obesity, indicated by worse NYHA class. Furthermore, patients with obesity more often had hypertension (63.7% vs. 47.9%, p<0.001), DM2 (41.3% vs. 21.4%, p<0.001), and obstructive sleep apnea syndrome (OSAS) (17.3% vs. 3.0%, p<0.001). Patients with obesity were significantly more often treated with diuretics, RAS-inhibitors, beta-blockers and MRAs (Table 1).

Prevalence of AF in HFpEF in relation with obesity

As shown in Figure 1, a significantly higher proportion of HFpEF patients with obesity had AF compared to patients without obesity (39.6% vs. 34.4%, p=0.019). A one unit increase in BMI was significantly associated with a higher likelihood of AF (OR 1.02, CI 1.01 – 1.04)

Table 1: Patient characteristics of HFpEF patients according to obesity.

	Overall population (*n=2094)*	BMI < 30 kg/m^2 (*n=1403*)	BMI ³ 30 kg/m^2 (*n=691*)	*p* value
Age, *years*	74.1 ± 12.3	74.7 ± 12.9	72.7 ± 10.8	<0.001
BMI, *kg/m^2*	28.3 ± 5.9	25.0 ± 3.0	35.0 ± 4.5	<0.001
LVEF, *%*	58.0 (53.0 – 62.0)	58.0 (52.8 -62.0)	59.0 (54.0 – 62.0)	0.263
Systolic BP, *mmHg*	134.0 (120.0 – 150.0)	132 (120 – 149)	135 (120 – 152)	0.024
Diastolic BP, *mmHg*	72.0 (65.0 – 80.0)	70.0 (64.0 – 80.0)	75.0 (65.0 – 81.0)	<0.001
Heart rate, *bpm*	72 ± 15	72 ± 15	73 ± 15	0.072
LBBB, *n (%)*	156 (7.4)	115 (8.2)	41 (5.9)	0.062
QRS, *ms*	98.0 (87.0 – 116.0)	98.0 (88.0 – 118.)	96.0 (86.0 – 114.0)	0.076
Female, *n (%)*	1126 (53.8)	722 (51.6)	404 (58.6)	0.002
NYHA , *n (%)*				<0.001
I	461 (22.2)	364 (26.1)	97 (14.3)	
II	1001 (48.3)	676 (48.5)	325 (47.9)	
III	577 (27.8)	334 (24.0)	243 (35.8)	
IV	33 (1.6)	19 (1.4)	14 (2.1)	
Comorbidity				
Hypertension, *n (%)*	1039 (53.1)	624 (47.9)	415 (63.7)	<0.001
Anemia, *n (%)*	135 (6.4)	101 (7.8)	34 (5.2)	0.037
Diabetes mellitus, *n (%)*	548 (28.0)	279 (21.4)	269 (41.3)	<0.001
OSAS, *n (%)*	152 (7.8)	39 (3.0)	113 (17.3)	<0.001
COPD, *n (%)*	386 (19.7)	244 (18.7)	142 (21.8)	0.110
Peripheral arterial disease, *n (%)*	58 (3.0)	43 (3.3)	15 (2.3)	0.219
Atrial fibrillation, *n (%)*	756 (36.1)	482 (34.4)	274 (39.6)	0.019
Medication				
Diuretics, *n (%)*	1561 (74.5)	987 (70.4)	574 (82.9)	<0.001
RAS-inhibitor, *n (%)*	1321 (63.1)	851 (60.7)	470 (67.9)	0.001
Beta-blocker, *n (%)*	1540 (73.5)	998 (71.2)	542 (78.3)	<0.001
MRA, *n (%)*	751 (35.9)	477 (34.0)	274 (39.6)	0.012
Digoxin, *n (%)*	355 (17.0)	232 (16.5)	123 (17.8)	0.482
Amiodaron, *n (%)*	83 (4.0)	54 (3.9)	29 (4.2)	0.708

BMI, Body Mass Index; LVEF, Left Ventricular Ejection Fraction; BP, Blood Pressure; LBBB, Left Bundle Branch Block; NYHA, New York Heart Association classification; OSAS, Obstructive Sleep Apnea Syndrome; COPD, Chronic Obstructive Pulmonary Syndrome: RAS, Renin-Angiotensin-System; MRA, Mineralocorticoid Receptor Antagonists.

Table 2: Multivariable analysis: association of obesity with AF in patients with HFpEF, BMI as a continuous variable

Univariable		Multivariable					
		Model 1		Model 2		Model 3	
OR	p-value	OR	p-value	OR	p-value	OR	p-value
1.01 [0.99 – 1.02]	0.275	1.03 [1.01 – 1.05]	<0.001	1.03 [1.01 – 1.05]	0.002	1.02 [1.01 – 1.04]	0.012

Model 1 included age, gender, per one unit BMI kg/m2

Model 2 included age, gender, per one unit BMI kg/m2, NYHA

Model 3 included age, gender, per one unit BMI kg/m2, NYHA, hypertension, diabetes mellitus, OSAS

AF, Atrial Fibrillation; BMI, Body Mass Index; HFpEF, Heart Failure with preserved Ejection Fraction; NYHA, New York Heart Association classification; OSAS,

Obstructive Sleep Apnea Syndrome.

Table 3: Multivariable analysis: association of obesity with AF in patients with HFpEF, BMI as a dichotomous variable <30 and >=30

Univariable		Multivariable					
		Model 1		Model 2		Model 3	
OR	p-value	OR	p-value	OR	p-value	OR	p-value
1.25 [1.04 – 1.51]	0.20	1.57 [1.28 – 1.92]	<0.001	1.50 [1.22 – 1.84]	<0.001	1.45 [1.16 – 1.81]	0.001

Model1 included age, gender, BMI group <30/≥30

Model 2 included age, gender, BMI group <30/≥30, NYHA

Model 3 included age, gender, BMI group <30/≥30, NYHA, hypertension, diabetes mellitus, OSAS

AF, Atrial Fibrillation; BMI, Body Mass Index; HFpEF, Heart Failure with preserved Ejection Fraction; NYHA, New York Heart Association classification; OSAS, Obstructive Sleep Apnea Syndrome.

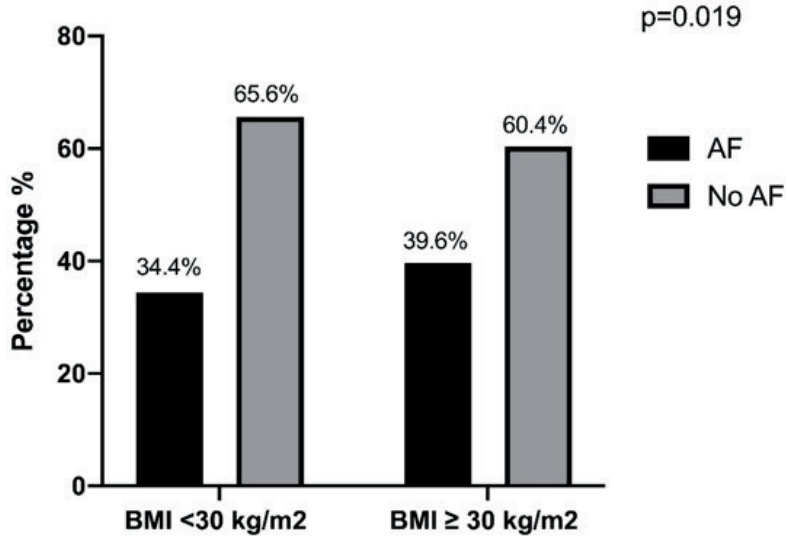
(Table 2). In the binary logistic regression analysis, after adjusting for multiple potential confounders, obesity was significantly associated with a higher probability of AF (OR 1.45, CI 1.16 – 1.81) (Table 3).

DISCUSSION

In this large real-world cohort of HFpEF patients, we demonstrated that AF was more prevalent in patients with obesity compared to patients without obesity. Furthermore, in multivariable logistic regression obesity was independently associated with AF in HFpEF patients, even after adjusting for confounders and common comorbidities that are associated with an increased risk for AF. Our results provide evidence that in a large HFpEF cohort, AF is more prevalent in patients with obesity and that BMI is strongly related with AF, despite other common risk-factors for AF.

To the best of our knowledge, our study is the largest cohort of HFpEF patients with obesity with an extensive and detailed analysis of the association between obesity and AF. In contrast to our results, previous studies documented a higher percentage of AF in HFpEF patients without obesity (3, 15, 16). In these studies, the sample size was smaller (n=195, n=151, and n=89). In addition, in two studies patients with obesity class 1 (BMI 30-35 kg/m2) were excluded from the analysis (3, 15). In HFpEF, obesity class 1 is prevalent, and it is therefore of value and clinical importance to include this group in the analysis (17). Our results extend prior work as our cohort consisted of 2094 HFpEF patients and we included all patients with obesity starting from a of BMI 30kg/m2. In addition, we demonstrated that obesity was significantly associated with AF even after adjusting for other common risk factors, such as age, gender, hypertension, diabetes mellitus, and OSAS, which reflects an important role of obesity in patients with HFpEF.

Figure 1: AF prevalence in obese and non-obese HFpEF patients.



In the recent years, attention on obesity as a risk factor for both AF and HFpEF has been increasing (3, 4, 6). Obesity is the second highest population attributable risk factor for AF (18). In the Framingham Heart study, every one unit increase in BMI, was associated with a 4% increase in risk of AF (19). In HFpEF, more than 80% of patients are either overweight or obese (20). Several studies have described the obesity-related HFpEF phenotype and it is considered a clinically relevant phenotype that may require a specific treatment (3, 5). Apart from obesity, AF in itself is associated with incident HFpEF and HFpEF is associated with incident AF (21, 22). Some studies have shown a higher prevalence of AF in HFpEF than in HFrEF (22-24). In addition, the presence of AF in HFpEF is associated with worse clinical outcomes (8, 9). The interactions between AF, HFpEF, and obesity suggest a shared pathophysiological mechanism wherein obesity has an important role. There are several possible explanations regarding how obesity can lead to both HFpEF and AF. First of all, obesity is associated with several comorbidities, such as hypertension and DM, that are also known risk factors for both HFpEF and AF (25). Besides that, obesity causes hemodynamic changes that can alter cardiac structure and function potentially leading to HFpEF and AF (26, 27). Obesity causes activation of the sympathetic nervous system as well as the renin-angiotensin-aldosteron-system (RAAS) which alters autonomic tone and increases the risk for abnormal conduction (28). In addition, obesity is related to systemic inflammation and expansion of EAT (11, 12). Both have gained more attention in the recent years and are important contributors in the pathophysiology of both HFpEF and AF. Expansion of EAT promotes inflammation and stimulates the release of inflammatory cytokines and pro-fibrotic markers which affect the myocardium and cause atrial fibrosis and ventricular stiffening and can lead to AF and HFpEF (29). In our cohort, we did not have data on inflammation, but the notion that obesity promotes systemic inflammation has been established before. A study by Sabbah et al. distinguished three different obesity-inflammation cluster in HFpEF and demonstrated that obese HFpEF patients that exhibited the highest circulating levels of inflammatory mediators and fibrosis (pan-inflammatory phenotype), had the highest prevalence of AF (30). This highlights the significant role of inflammation in obesity, AF, and HFpEF.

The results of our study are relevant, as they heighten the awareness that patients with obesity and HFpEF are at increased risk for AF. We found a relatively high prevalence of AF (39.6%) in patients with HFpEF and obesity. Currently, recognizing and diagnosing AF in patients with HFpEF and obesity in clinical practice is challenging. Signs and symptoms of AF are easily missed and frequently attributed to other comorbidities that are common in patients with obesity. In addition, AF is difficult to capture due to the often silent and paroxysmal nature of the arrhythmia. Besides the challenge in diagnosing AF, HFpEF patients with obesity and AF might require

a different treatment approach that focuses on ameliorating systemic inflammation and expansion of EAT (29). However, most importantly to consider in treatment is that obesity is not only a major risk factor, but also a modifiable risk factor, as shown by numerous studies that have found that weight loss reduces the burden of AF, restores sinus rhythm, improves cardiac function, and improves symptoms of HFpEF (31-33). This suggests that the effects of obesity on cardiac structures are reversible and underlines the importance of heightening the awareness of the relation between obesity, AF and HFpEF.

Study limitations

The study has some limitations that should be noted. First of all, due to the cross-sectional design of the study, is was not possible to draw causal inference or to study longitudinal patient outcomes. Secondly, in some cases BMI was based on estimated height and weight provided by patients, which could have led to slightly less accurate BMI values. Thirdly, additional echocardiographic data was not available, therefore we could not investigate whether echocardiographic features might mediate the relationship between obesity and AF. Lastly, AF was defined as a documented history of AF or AF diagnosed by 12-lead electrocardiogram, performed during the most recent outpatient clinic visit. History of AF was based on hospital record and tests, but paroxysmal AF patients could have been missed as in comparable studies. Nevertheless, the CHECK-HF registry is the first large-scale-real-world registry incorporating a great number of HFpEF patients with detailed information on clinical characteristics and drug treatment, and therefore provides a unique view on the interplay between obesity and AF in HFpEF.

CONCLUSION

In this contemporary registry including a large number of HFpEF patients, we demonstrated that AF is more prevalent in patients with obesity than in HFpEF patients without obesity. This suggests that obesity is associated with AF in HFpEF patients, even after adjusting for potential confounders. Future research is needed to further clarify the underlying pathophysiological pathways in order to recommended a specific treatment for AF in HFpEF patients with obesity.

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12

Chapter 12

Heart failure treatment in patients with and without obesity with an ejection fration below 50%

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ABSTRACT

Background

The aim of this study was to assess heart failure (HF) treatment in patients with and without obesity in a large contemporary real-world Western European cohort.

Methods

Patients with chronic HF with a left ventricular ejection fraction (LVEF) <50% and available information on body mass index (BMI) were included and divided into BMI categories. Differences in HF medical treatment were analyzed and multivariable logistic regression analysis (dichotomized as BMI < 30 kg/m^2 and ≥ 30 kg/m^2) was performed.

Results

7671 patients were included, 1284 (16.7%) had a BMI ≥30 kg/m^2, and 618 (8.1%) had a BMI ≥35 kg/m^2. Median BMI was 26.4 kg/m^2. Prescription rates of guideline-directed-medical therapy (GDMT) increased significantly with BMI. The differences were most pronounced for mineralocorticoid receptor antagonists (MRAs) and diuretics. Patients with obesity more often received the guideline-recommended target dose. In multivariable logistic regression, obesity was significantly associated with a higher likelihood of receiving ≥100% of the guideline-recommended target dose of beta-blockers (OR 1.34, 95% CI 1.10-1.63), renin-angiotensine-system (RAS)-inhibitors (OR 1.34, 95% CI 1.14-1.56) and MRAs (OR 1.41, 95% CI 1.05-1.89)

Conclusions

Guideline recommended HF drugs are more frequently prescribed and at higher dose in patients with obesity as compared to HF patients without obesity.

INTRODUCTION

The rising number of people with obesity worldwide is considered to be an important contributor to the increasing incidence of heart failure (HF) (1, 2). Individuals with obesity have a double life-time risk of heart failure, and the risk increases with every unit increase in body mass index (BMI) (3). Furthermore, obesity is associated with comorbidities such as hypertension, atrial fibrillation, and diabetes mellitus (4). As a result, individuals with obesity are rarely naïve to cardioprotective medication at their time of HF diagnosis which may lead to differences in HF drug treatment and dosage in patients with and without obesity. The difference in HF treatment in patients with obesity has been postulated as a reason for the obesity paradox, the phenomenon that refers to lower mortality in HF patients with mild overweight and obesity compared to their leaner counterparts (5-7) .

Unfortunately, there is a considerable gap of knowledge with regard to HF treatment in patients with obesity and a left ventricular ejection fraction (LVEF) <50%. As obesity and HF often co-exist, better understanding of HF drug treatment, including doses, in obesity is important to further improve the pharmacological HF management of this high-risk population. Therefore, the aim of this study was to investigate whether differences in HF treatment exist between patients with and without obesity with an LVEF <50% in a large real-world Western European setting.

METHODS

For this study, data was used from the CHECK-HF (Chronisch Hartfalen ESC – richtlijn Cardiologische praktijk Kwaliteitsproject HartFalen) registry. The design and methods of the CHECK-HF registry have been published in detail before (8). Briefly, a total of 10,910 patients with chronic HF from 34 participating Dutch centres between 2013 and 2016 were included in this cross-sectional observational cohort. All included patients were diagnosed with HF according to the 2012 European Society of Cardiology (ESC) HF guidelines, and almost all were seen at a dedicated outpatient HF clinic (96%) (9). Detailed information on patient characteristics, comorbidities, and guideline recommended HF drug prescription and dosages was recorded. An overview of guideline recommended prescription rates and dosages is provided in Supplementary Table 1. Comorbidities were noted as recorded in medical history (diabetes mellitus, hypertension, hypercholesterolaemia, renal insufficiency (estimated glomerular filtration rate <60 ml/min/1.73m2), anaemia (haemoglobin below age dependent threshold), chronic obstructive pulmonary disease (COPD), or obstructive sleep apnoea, and (8). The study was conducted according to the Declaration of

Helsinki. Ethical approval was provided for anonymously analysing existing patient data by the Ethical Committee of the Maastricht University Medical Center, the Netherlands, approval number MUMC-METC-18-4-282.

In the CHECK-HF registry, patients were classified based on LVEF or visual assessment of the left ventricle (LV) into HF with an LVEF <50% (n=8,360) or HF with an LVEF ≥50% (n=2,267) and were treated according to the 2012 ESC HF guidelines (9). For the current analysis, patients with an LVEF ≥50% were excluded as the focus of this study was on guideline-recommended therapy in patients with systolic dysfunction. Furthermore, in 283 patients, recording of LV function was insufficient to classify these patients into HF type and they were excluded from this analysis as well. Additionally, patients with missing data on BMI (N=689) were excluded, leaving a total of 7671 patients to be included in this analysis. For a subanalysis according to the later 2016 ESC HF guidelines, patients with an LVEF <50% were categorized into HF with reduced ejection fraction (HFrEF, LVEF <40%, n=5276) and HF with mid-range ejection fraction (HFmrEF, LVEF 40-49%, n=1462). Patients without an exactly specified ejection fraction, but in whom reduced LV function was visually assessed, were presented separately as a semi-quantitative group (n=933).

For the current analysis, patients were divided into five BMI (body mass index) categories according to the World Health Organization classification: underweight (BMI <18.5 kg/m2), normal weight (BMI 18.5 to 24.99 kg/m2), overweight (BMI 25 to 29.99 kg/m2), obesity class I (BMI 30 to 34.99 kg/m2), and obesity class II (BMI 35 to 39.99 kg/m2) (10). Prescription rates and prescribed doses of guideline-recommended HF therapy were compared between the BMI groups. Reporting of the study conforms to broad EQUATOR guidelines (11).

STATISTICAL ANALYSIS

Continuous data are expressed as mean or median with standard deviation or interquartile range, depending on the distribution of the data. Comparisons were performed using the Student's t-test or Kruskal-Wallis test. Categorical data are expressed as counts and percentages, and were compared with Pearson's chi-squared test, or the Fisher's exact test as appropriate. A two-sided p-value ≤ 0.05 was considered statistically significant. In order to investigate whether treatment differences between patients with and without obesity were independent of potential confounders, we dichotomized patients into those with a BMI <30 kg/m2 and BMI ≥30 kg/m2 and univariable and multivariable logistic regression analyses were used. The results of these regression analyses are expressed as odds ratios (OR) with corresponding 95%

confidence intervals (CIs). We adjusted for age and gender, New York Heart Association (NYHA) classification, hypertension, obstructive sleep apnea syndrome (OSAS), atrial fibrillation, diabetes mellitus, renal insufficiency (defined as estimated glomerular filtration rate <60/ml/min/1.73m2 or a history of renal insufficiency), chronic obstructive pulmonary disease (COPD) and QRS duration, as we hypothesized that these variables and comorbidities would be clinically relevant for the association between obesity and treatment, which was also based upon earlier research (12-18). Analyses were performed using SPSS Statistical Package version 25.0.

RESULTS

Of the 7671 patients included, 1284 (16.7%) had a BMI ≥30 kg/m2, and 618 (8.1%) had a BMI ≥35 kg/m2. The baseline characteristics of the study population overall and in the five groups based on BMI are shown in Table 1. Median age of the study population was 74 years, 35.9% were female, and median LVEF was 30%. Median BMI was 26.4 kg/m2 and most patients were in NYHA class II (57.5%). Hypertension was diagnosed in 40.3% of the patients and as many as 28.8% patients suffered from diabetes mellitus. Almost half of the patients had renal insufficiency (47.5%).

Several baseline characteristics differed significantly between the BMI groups. Patients in obesity class I and II were younger and more often severely symptomatic (NYHA class III) compared to patients in lower BMI groups. As for comorbidities, patients in obesity class I and II had higher rates of hypertension, diabetes mellitus, and OSAS. Patients in the underweight group were most often female, had lower diastolic and systolic blood pressure and were most often in NYHA class I-II.

Table 1: Baseline characteristics of the study population

	Total population (n = 7671)	BMI <18.5 (n=123)	BMI ≥ 18.5 & < 25 (n=2668)	BMI ≥ 25 & < 30 (n = 2978)	BMI ≥ 30 & < 35 (n = 1284)	BMI ≥35 (n = 618)	*p value*
Age, years ***(n=7664)***	74 (16)	76 (20)	77 (14)	74 (15)	72 (15)	67 (18)	<0.001
Female ***(n=7638)***	2745 (35.9)	77 (62.6)	1029 (38.8)	909 (30.7)	454 (35.5)	340 (44.8)	<0.001
Weight, kg ***(n=7671)***	80 (21)	49 (6)	68 (15)	81 (13)	94 (14)	112 (24)	<0.001
Height, cm ***(n=7671)***	172 (13)	167 (10)	173 (14)	173 (12)	171 (13)	171 (16)	<0.001
BMI, kg/m^2 ***(n=7671)***	26.4 (6.4)	17.4 (1.4)	22.9 (2.5)	27.1 (2.7)	31.8 (2.2)	37.4 (4.1)	<0.001
Systolic BP, mmHg ***(n=7631)***	120 (23)	115 (28)	120 (20)	120 (23)	125 (27)	125 (28)	<0.001
Diastolic BP, mmHg ***(n=7636)***	70 (18)	65 (15)	70 (15)	70 (20)	72 (15)	67 (18)	<0.001
LVEF, % ***(n=5693)***	30 (15)	30 (18)	30 (15)	30 (15)	30 (14)	33 (15)	0.021
Heart rate, bpm ***(n=7590)***	69 (16)	79 (17)	70 (17)	68 (17)	70 (14)	70 (17)	<0.001
QRS ≥130ms ***(n=6505)***	2598 (39.9)	31 (30.1)	926 (40.6)	1005 (39.9)	446 (41.1)	190 (36.7)	0.11
eGFR ***(n=5472)***	57 (34)	51 (39)	54 (33)	58 (33)	58 (33)	60 (38)	0.007
NT-proBNP, pg/ml ***(n=2793)***	908 (2375)	1059 (10061)	1375 (3419)	747 (1860)	576 (1511)	694 (1796)	<0.001
NYHA class ***(n=7604)***							<0.001
I	1194 (15.7)	21 (17.2)	435 (16.5)	496 (16.8)	184 (14.4)	158 (9.5)	
II	4376 (57.5)	67 (54.9)	1507 (57.2)	1759 (59.4)	695 (54.5)	348 (56.9)	
III	1900 (25.0)	30 (24.6)	646 (24.5)	648 (21.9)	381 (29.9)	195 (31.9)	
IV	134 (1.7)	4 (3.3)	46 (1.7)	58 (2.0)	15 (1.2)	11 (1.8)	
Cause of HF ***(n=7449)***							
Ischaemic	3842 (51.6)	52 (43.3)	1305 (50.3)	1575 (54.6)	651 (51.8)	259 (43.5)	<0.001
Non-ischaemic	3607 (48.4)	68 (56.7)	1290 (49.7)	1307 (45.4)	606 (48.2)	336 (56.5)	

Table I: Continue

	Total population (n = 7671)	BMI <18.5 (n=123)	BMI ≥ 18.5 & < 25 (n=2668)	BMI ≥ 25 & < 30 (n = 2978)	BMI ≥ 30 & < 35 (n = 1284)	BMI ≥35 (n = 618)	*p value*
Comorbidities							
Hypertension *(n=6980)*	2814 (40.3)	32 (28.6)	882 (36.5)	1071 (39.7)	552 (46.5)	277 (48.7)	<0.001
Diabetes mellitus *(n=6980)*	2009 (28.8)	19 (17)	459 (19)	761 (28.2)	497 (41.9)	273 (48.0)	<0.001
OSAS *(n=6980)*	460 (6.6)	1 (0.9)	57 (2.4)	152 (5.6)	139 (11.7)	111 (19.5)	<0.001
COPD *(n=6980)*	1289 (18.5)	35 (31.3)	459 (19.0)	463 (17.2)	234 (19.7)	98 (17.2)	0.002
Hypercholesterolemia *(n=6980)*	937 (13.4)	10 (8.9)	309 (12.8)	363 (13.5)	167 (14.1)	88 (15.5)	0.26
Atrial fibrillation *(n=7599)*	1918 (25.2)	31 (25.6)	696 (26.3)	722 (24.5)	316 (24.9)	458 (25.0)	0.66
Anemia *(n=6980)*	374 (4.9)	5 (4.5)	150 (6.2)	141 (5.2)	49 (4.1)	29 (5.1)	0.12
Kidney insufficiency, *(n=6459)*	3645 (47.5)	44 (45.8)	1285 (58.0)	1414 (56.1)	621 (56.7)	250 (52.9)	0.05

Continuous data were non-normally distributed and were therefore presented as median with interquartile range.

BMI, body mass index; BP, blood pressure; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; NYHA, new York heart association; OSAS, obstructive sleep apnea syndrome; COPD, chronic obstructive pulmonary disease.

Table 2: Multivariable analysis: the likelihood (displayed as odds ratio) of receiving guideline-recommended therapy for patients with obesity compared to patients without obesity

	Univariable model		Multivariable model	
Prescription of drug	OR	p-value	OR	p-value
Beta-blocker	1.26	0.001	1.20	0.05
RAS inhibitor	1.33	<0.001	1.31	0.006
MRA	1.24	<0.001	1.16	0.047
Diuretics	1.61	<0.001	1.70	<0.001
Prescription of guideline-recommended target dose	OR	p-value	OR	p-value
Beta-blocker	1.57	<0.001	1.34	0.003
RAS inhibitor	1.53	<0.001	1.34	<0.001
MRA	1.65	<0.001	1.40	0.026

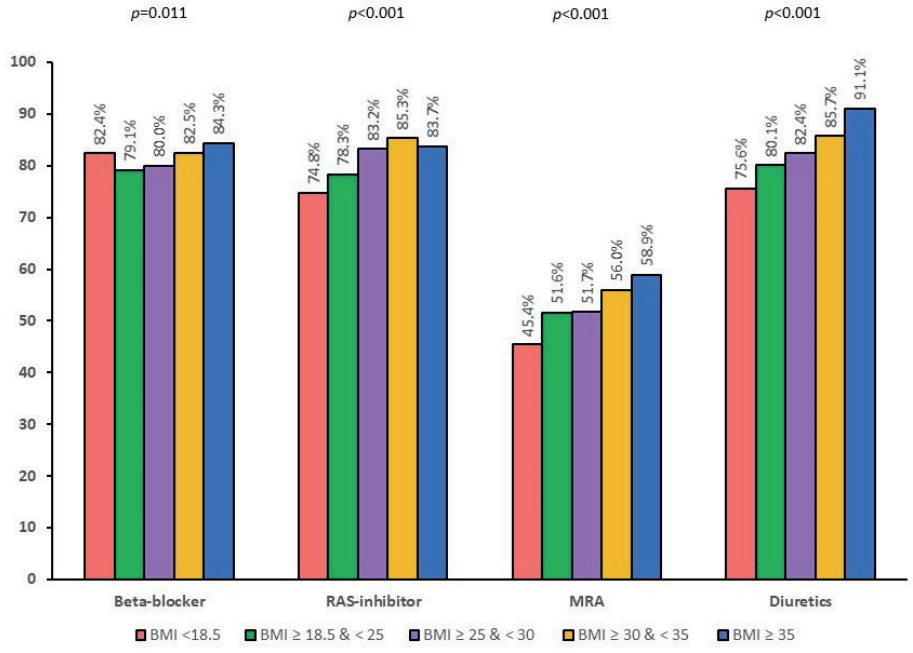
MRA, mineralocorticoid receptor antagonist; RAS, renin-angiotensin system; OR, odds ratio

The multivariable model included: age, gender, NYHA classification, hypertension, diabetes mellitus, obstructive sleep apnea syndrome, atrial fibrillation, renal insufficiency (defined as estimated glomerular filtration rate <60/ml/min/1.73m2 or a history of renal insufficiency) , chronic obstructive pulmonary disease, and QRS duration.

Pharmacological treatment

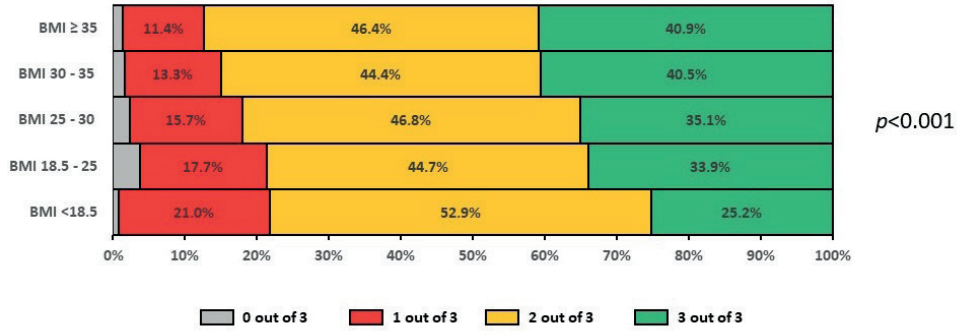
The pharmacological HF treatment of patients according to the BMI groups is shown in **Figure 1**. In short, patients in obesity class I and II significantly more often received renin–angiotensin system (RAS) inhibitors, mineralocorticoid receptor antagonists (MRAs) and diuretics. Overall, the proportion of patients who were prescribed guideline-recommended drugs appeared to increase with BMI with the exception of beta-blockers. In multivariable logistic regression, obesity (BMI ≥30kg/m^2) was associated with higher prescription rates of RAS inhibitors (OR 1.31, 95% CI 1.08-1.59), MRAs (OR 1.16, 95% CI 1.00-1.33), diuretics (OR 1.70, 95% CI 1.36-2.12) and beta-blockers (OR 1.20, 95% CI 1.00-1.44).

Figure 1: Prescription rates of guideline-recommended heart failure drugs according to BMI group. BMI, body mass index; RAS-inhibitor, renin-angiotensin-system; MRA, mineralocorticoid receptor antagonist.



Patients with obesity class I and II significantly more frequently received triple therapy (Figure 2). Furthermore, the proportion of patients who received ≥100% of the guideline-recommended target dose for beta-blockers, RAS-inhibitors and MRAs was significantly higher in patients with a BMI ≥35 kg/m2. In general, patients with a BMI ≥30 kg/m2 more often received the guideline-recommended target dose compared to those without obesity (Figure 3). Interestingly, patients in the normal BMI group (18.5 kg/m2 ≤ BMI <25 kg/m2) less frequently received the guideline-recommended dose than the average patient. In multivariable logistic regression, obesity (BMI ≥30 kg/m2) was significantly associated with a higher likelihood of receiving ≥100% of the guideline-recommended target dose of beta-blockers (OR 1.34, 95% CI 1.10-1.62), RAS-inhibitors (OR 1.34, 95% CI 1.15-1.57) and MRAs (OR 1.40, 95% CI 1.04-1.87) (Table 2).

Figure 2: Proportion of patients receiving triple therapy across different BMI groups. BMI, body mass index.



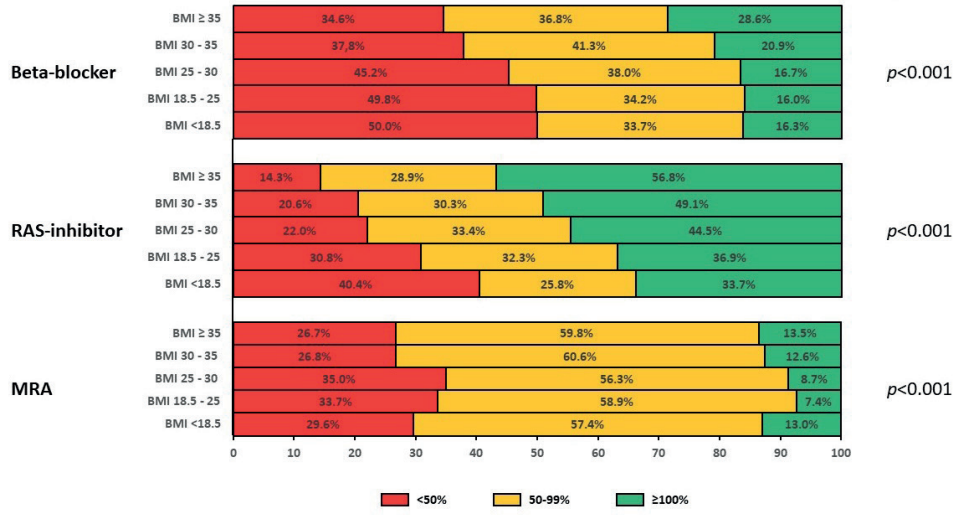
Medical therapy in patients with HFrEF and HFmrEF according to the 2016 European Society of Cardiology HF guidelines

Prescription rates of GDMT according to BMI group in patients with HFrEF, HFmrEF and those with a semi-quantitative recording of LV function are shown in Supplementary Figure 1. In the HFrEF group, inferences were similar to the main analysis. In the HFmrEF group, patients with a BMI <18.5 kg/m2 had higher and patients with BMI ≥18.5 kg/m2 lower prescription rates of RAS inhibitors and MRAs as compared to the main analysis, and differences between BMI groups were therefore less pronounced. In the semi-quantitative group, patients with a BMI <18.5 kg/m2 had strikingly low rates of RAS inhibitor and MRA use, and differences between groups in beta-blocker and diuretic use were less pronounced and non-significant.

DISCUSSION

In this large registry of chronic HF patients, guideline recommended HF drugs were more frequently prescribed in patients with obesity class I and class II as compared to patients without obesity, and patients with obesity more often received triple therapy. Additionally, patients with obesity more often received the guideline-recommended dose of HF drugs. Overall, HF patients with obesity had a higher level of GDMT than HF patients without obesity.

Figure 3: Percentage of the guideline-recommended target dose prescribed according to BMI group. BMI, body mass index; RAS-inhibitor, renin-angiotensin-system; MRA, mineralocorticoid receptor antagonist.



The global prevalence of obesity and HF is increasing which places a large burden on healthcare resources (19, 20). In our cohort, obesity was present in 16.7% of the HFrEF population, highlighting the fact that obesity constitutes an important proportion of the HFrEF population. For this reason, it is important to study the treatment of patients with obesity and HF. Only a few studies have reported prescription rates of HF drugs specifically in patients with obesity, but this was not the primary aim of these studies. In a recent analysis from Marcks et. al in which the investigators aimed to address the obesity paradox in HF, prescription rates of BB and RAS inhibitors appeared to increase with BMI, but this was not the case for MRAs. Interestingly, the prescription rates were different from our study (21). Beta-blockers and MRAs were prescribed in 46.5% and 16.4% of the total study population, which is markedly lower than in our study. Prescription rates of ACE inhibitors/ARB on the other hand, were comparable to our study. Several characteristics of the study by Marcks. need to be discussed in this context. First, the included studies in their meta-analysis were randomized clinical trials, and were therefore comprised of selected populations, whereas our study is a reflection of real-world practice. Furthermore, not all studies reported on drug use, and this may have resulted in lower prescription rates. Lastly, there were some differences with regard to patient characteristics: patient in our study were on average older (74 vs. 64.9 years) and suffered from atrial fibrillation more often (25.2% vs. 15.4%), whereas patients in the study by Marcks et al. were more often in NYHA class III/IV (39.2% vs. 26.7%, respectively). Limited data exist on

the prescription of target doses in patients with obesity. In the U.S. CHAMP-HF registry, patients who were prescribed target doses of ACE inhibitor/ARB/ARNI, BB, and MRA were more likely to have a BMI ≥30kg/m^2 (22). In addition, HF patients with obesity were more likely to receive the target dose of beta-blocker in multivariable regression analysis, and obesity was associated with a higher likelihood of receiving treatment with MRA (23). These findings are in line with our results, but the main strength of our study is that our analysis specifically focused on treatment differences between BMI groups in a real-world chronic HF population, both with regard to prescription rates as well as daily dose. We found that patients with obesity significantly more often received ≥100% of the guideline-recommended dose of beta-blockers, RAS-inhibitors, and MRAs. In our sub-analysis, where HFrEF was defined according to the 2016 ESC guidelines (24), the inferences of prescription rates were similar to the main analysis; further strengthening our finding that HFrEF patients with obesity more often receive GDMT. Our findings are important, as target doses of ACE-inhibitors, ARBs, and beta-blockers have been associated with a significant reduction in all-cause mortality (22). In addition, we demonstrated that BMI ≥30kg/m^2 was associated with a higher likelihood to receive target doses, even after adjusting for potential confounders. This is important as accompanying comorbidities such as hypertension and diabetes were more prevalent among those with obesity. The multivariable regression analyses suggest that obesity is independently associated with prescription of guideline-recommended doses.

Many factors may play a role in the prescription of higher doses of HF drugs in patients with obesity. Due to their higher body weight, patients with obesity often develop hypertension and symptoms such as dyspnea and edema at a younger age and are therefore rarely naïve to HF treatment. In our cohort, 16.7% of the patients were in the obesity group, they were on average younger, more often in NYHA class III, and more often suffered from comorbidities such as hypertension, diabetes, and OSAS. The higher doses of GDMT in patients with obesity may partially be attributed to a higher prevalence of hypertension and the higher average blood pressure. Low blood pressure and orthostatic hypotension are common reasons for suboptimal doses of RAS inhibitors in clinical practice, especially in older patients (12, 16). Obesity can lead to drug resistant hypertension, and can cause alterations of the RAAS system, which may explain why HF patients with obesity require higher doses of antihypertensive drugs (25). The higher proportion of patients in NYHA class III-IV amongst those with obesity may partially explain the higher prescription rates of diuretics.

Our findings are important as they indicate that patients with HF and obesity are better treated in comparison to those without obesity, but that there is still ample room for improvement of medical therapy, also in HF patients without obesity. Data

on the role of lifestyle interventions in established HF are scarce (26). A few studies have shown that bariatric surgery leads to an improvement in LVEF in patients with HF (27). A recent meta-analysis demonstrated that intentional weight loss leads to favourable cardiac remodelling in patients with obesity, but it remains unclear whether intentional weight loss results in improved clinical outcomes in HF patients with obesity (28). Drug optimization according to guideline recommendations is therefore as important in HF patients with obesity as in HF patients without obesity.

Numerous studies have demonstrated that obesity is associated with a reduced mortality risk in established HF, a phenomenon known as the obesity paradox (7). Remarkably, the paradox mainly exists in patients who are mildly overweight or in class I obesity, whereas underweight patients have worse prognosis (7). Interestingly, the obesity paradox is less pronounced in severe obesity (BMI ≥35kg/m^2) (28). There has been debate on whether this paradox is valid or mainly the result of methodological shortcomings (29). Several mechanisms of action have been postulated to explain the obesity paradox in HF, such as greater metabolic reserve, attenuation of harmful inflammatory processes, and the use of more cardioprotective medications at higher doses (5, 30). In the 2014 meta-analysis from the MAGGIC (Meta-analysis Global Group in Chronic Heart Failure) investigators, mortality in HFrEF patients was U-shaped with a nadir at BMI levels 30.0 – 34.9 kg/m^2, confirming the obesity paradox (29). Similar findings were found in a recent meta-analysis in which overweight and class I obesity were associated with lower all-cause mortality, and underweight with higher mortality all-cause mortality (28). However, the multivariable models in these studies were not adjusted for medication use, leaving it unclear whether potential differences in medical treatment may have mediated the observed mortality differences between those with and without obesity. Yet, a recent study by Gelini et. al. included medication use in the multivariable model, and confirmed the presence of the obesity paradox by demonstrating lower mortality in the overweight and class I obesity groups (31).

In our cohort, we observed that the presence of obesity was associated with a higher likelihood to receive GDMT. As target doses of the guideline-recommended HF drugs have been proven superior to lower doses in terms of survival (22, 32), the obesity paradox may be explained at least in part by the treatment differences that we found to favor those with a BMI 30.0 – 34.99 kg/m^2. However, it should be noted that guideline implementation was also better in the more severe obesity group, while the favourable outcomes in mortality are less pronounced in this BMI group. The titration process of HF drugs may also deviate from HF patients without obesity and may require a different approach due to differences in tolerability and side effects. Our results show that there is an important difference in HF treatment between patients

with and without obesity. Given the expanding population incidence of obesity and HF, future studies that focus specifically on medication use and outcomes in patients with obesity are required to further optimize treatment in this high-risk population.

Strengths and limitations

The CHECK-HF registry is a large-scale real world registry consisting of chronic heart failure patients in a Western European setting with detailed information on patient characteristics and medication use. It is therefore well suited to study guideline implementation in patients with HF and obesity compared to those without obesity. Unfortunately, due to the cross-sectional design of the study, there are no data on longitudinal patients outcomes. Furthermore, data on sodium glucose transporter 2 (SGLT2) inhibitors and angiotensin-receptor neprilysin inhibitors (33) were unavailable, as they were not yet recommended by the guidelines at the time of this study. Finally, BMI does not take into account body composition, whereas relative fat mass and waist circumference are less influenced by muscle mass and may have a stronger association with outcomes. However, the WHO still recommends the use of BMI to categorize the severity of obesity, and BMI is still frequently used in daily clinical practice.

CONCLUSION

In this large real-world registry of chronic HF patients with an LVEF <50%, guideline-recommended drugs were more frequently prescribed and at higher dose in patients with obesity as compared to HF patients without obesity. Better pharmacological treatment of patients with obesity may contribute to the obesity paradox. Additional research is required to further identify therapy trends in HF patients with obesity and to assess reasons for treatment differences between HF patients with and without obesity.

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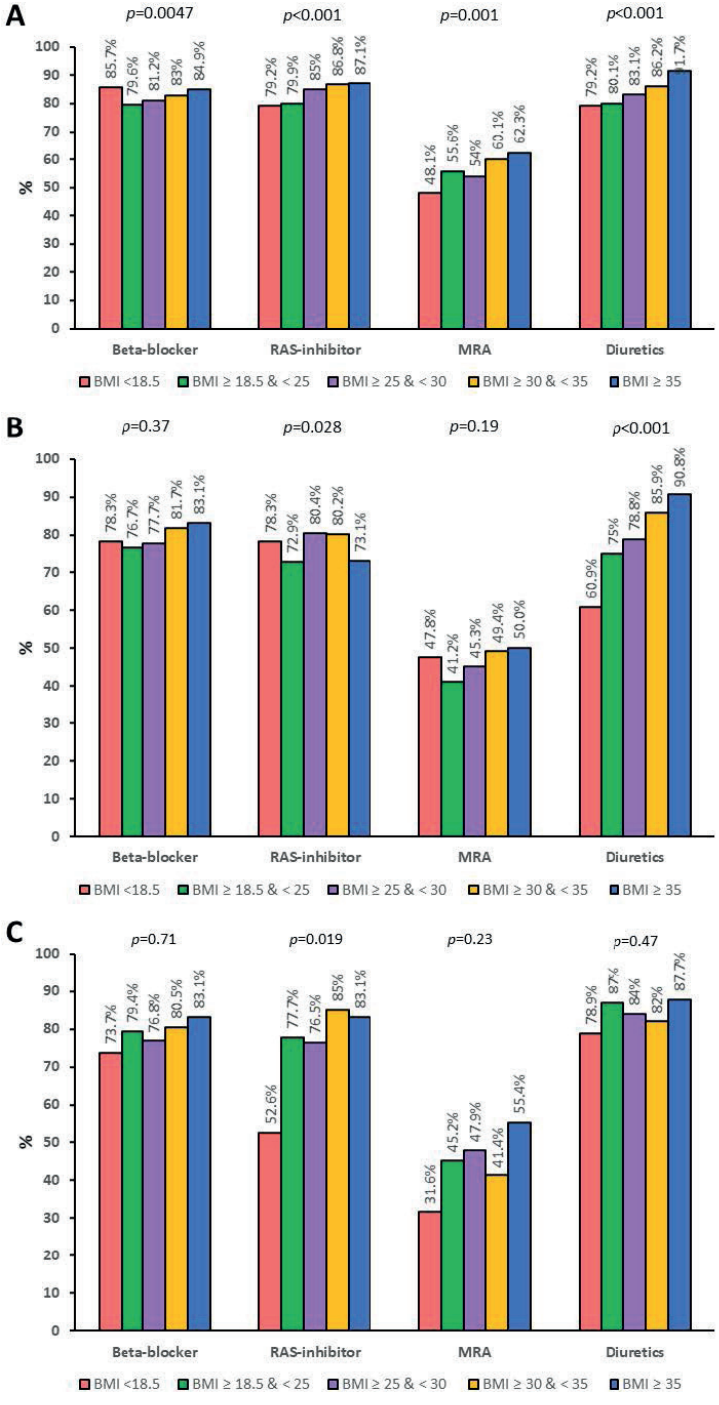
SUPPLEMENTARY MATERIAL

Supplementary Table 1: Target dosages for heart failure treatment according to the ESC guidelines 2012. ACE, angiotensine converting enzyme; ARB, angiotensine receptor blocker; MRA, mineralocorticoid receptor antagonist.

	Starting dose (mg)	Target dose (mg)
ACE-inhibitor		
Captopril	6.25 t.i.d.	50 t.i.d.
Enalapril	2.5 b.i.d.	10-20 b.i.d.
Lisinopril	2.5 – 5.0 o.d.	20 – 35 o.d.
Ramipril	2.5 o.d.	5 b.i.d.
Trandalopril	0.5. o.d.	4 o.d.
Beta-blocker		
Bisoprolol	1.25 o.d.	10 o.d.
Carvedilol	3.125 b.i.d.	25-50 b.i.d.
Metoprolol succinate	12.5/25 o.d.	200 o.d.
Nebivolol	1.25 o.d.	10 o.d.
ARB		
Candesartan	4 or 8 o.d.	32 o.d.
Valsartan	40 b.i.d.	160 b.i.d.
Losartan	50 o.d.	150 o.d.
MRA		
Eplenerone	25 o.d.	50 o.d.
Spironolactone	25 o.d.	25 – 50 o.d.

Supplementary figure 1: Prescription rates of HF drugs according to BMI group in A) HFrEF patients (LVEF <40%) (n=5276), B) HFmrEF patients (LVEF 40-49%) (n=1462), and C) semi quantitative patients (n=1075) according to the 2016 HF guidelines



Part VI

General discussion, future perspectives and summary

13

Chapter 13

General discussion and future perspectives

GENERAL DISCUSSION

In this thesis, we investigated obesity in heart failure with a specific focus on early detection of cardiac dysfunction. We assessed the role of early detection of cardiac dysfunction with the use of novel echocardiographic techniques, such as speckle tracking echocardiography, and the role of biomarkers in obesity patients. The research topic and the main findings in this thesis are highly relevant, given the projected increase in the prevalence of obesity and subsequent increase in risk of heart failure. In this chapter, the findings of this thesis will be discussed and future perspectives will be considered.

Signs of cardiac dysfunction in obesity

Obesity has become a global pandemic, affecting around 650 million people worldwide (1). It is projected that the global prevalence of obesity in 2025 will reach 18% in men, and more than 21% in women (2). These numbers are concerning, as obesity poses a serious healthcare risk, in part due to the concomitant diseases that are caused by obesity, such as diabetes mellitus type 2, hypertension, and cardiovascular disease (3-6). In the recent decades, in has become evident that obesity is a major risk factor for the development of heart failure (7, 8). Numerous epidemiological studies have confirmed this, and have demonstrated that the risk for heart failure rises with increasing BMI (8). The projected increase in prevalence of obesity and subsequent increase in risk of heart failure, necessitate accurate diagnostic methods in order to early identify signs of cardiac dysfunction in patients with obesity. This is especially important, so that early treatment can be initiated in this population and potential deterioration of heart failure may be diverted.

Currently, the detection of cardiac dysfunction in patients with obesity is challenging and the diagnosis is often missed due to several reasons. First of all, the signs and symptoms that patients with obesity present themselves with, such as dyspnea and edema, are often attributed to the extra weight or to other comorbidities. As for additional examination, such as the use of biomarkers and echocardiography in patients with obesity, a number of limitations also exists. These will be thoroughly discussed in the next two paragraphs.

Biomarkers in patients with obesity

For the diagnosis of heart failure and identification of cardiac dysfunction, guidelines recommend the use of BNP as a marker (9). The use BNP is patients with obesity is however hampered, due to the inverse relationship between BNP and BMI in patients with obesity (10). This essential biomarker is therefore not useful in this important population that is at increased risk for developing cardiac dysfunction. In

Chapter 9 we investigated 92 biomarkers in patients with and without obesity, and in obesity patients with and without cardiac dysfunction. In the obesity population, the most strongly elevated biomarkers were linked to inflammation (SELE, SELP, and RARRES2). Interestingly, biomarkers related to insulin resistance (IGFBP-1 and IGFBP-2), and PON-3, a biomarker involved in the protection against the detrimental effects of obesity and protection against atherosclerosis, were decreased in patients with obesity. The level of these biomarkers differed significantly compared to the normal weight control group. When we compared the biomarker profile between obesity patients with and without cardiac function, we found five biomarkers that were increased in obesity patients with cardiac dysfunction (SELE, TR-AP, FAS, CTSD, and CTSZ). These five biomarkers are related to atherosclerosis, inflammation, and insulin resistance, which underlines that a more extensive presence of an abnormal underlying metabolic pathophysiological process exists in obesity patients with cardiac dysfunction. In a multivariable model, the biomarkers CTSD, CHIT1, SELE, OPN, OPG, TR-AP, t-PA, and FAS were selected as predictors for identifying cardiac dysfunction. In addition, patient characteristics, such as male gender, waist circumference, systolic blood pressure, heart rate, and left ventricular mass were also selected by the model. The selection of the biomarkers by the model are also markers that are related to inflammation, atherosclerosis, and insulin resistance. Interestingly, the multivariable biomarker model also selected male gender as a predictor to identify cardiac dysfunction, this while the risk of developing heart failure in obesity is higher in women than in men (8). However, another study found that obesity as a risk factor among men had larger deleterious associations with changes in left ventricular cardiac function than in women, which might partly explain the finding of male gender in our model (11).

Only a few studies have investigated novel biomarkers in obesity. A study consisting of 56 healthy middle-aged overweight subjects, found similar results, as proteins linked to inflammation were strongly associated with BMI (12). Another study confirmed these findings, by showing that novel markers of inflammation, as well as markers of fibrosis and angiopoietins were among the protein biomarkers with the strongest associations with obesity (13). **Chapter 9** of this thesis, corroborates and extends these results, as we demonstrated that markers of inflammation, atherosclerosis and insulin resistance are related to obesity. The novel finding of our study is that we showed that specific biomarkers are more present in patients with obesity and established cardiac dysfunction, a result from which we can cautiously speculate that these specific biomarkers could be of clinical use in order to detect cardiac dysfunction in patients with obesity at risk. We can however not draw this conclusion from our data, and further studies that specifically focus on the prognostic value of these biomarkers in patients with obesity and cardiac dysfunction are needed.

Echocardiography

Echocardiography is the first-line, cornerstone imaging modality for the assessment of cardiac structure and function. The origins of clinical echocardiography date back to the 1950s, and there have been many important and innovative developments in the field of cardiac ultrasound since then (14). Left ventricular ejection fraction (LVEF) is the most commonly used parameter in echocardiography to assess cardiac function. However, in the recent decade the use speckle tracking echocardiography has emerged, and studies have shown that strain parameters are more sensitive for the detection of early myocardial dysfunction than LVEF (15). Therefore, the use of speckle tracking echocardiography for the assessment of the left ventricle function is now recommended by the most recent heart failure guidelines (9). Strain imaging represents myocardial deformation that occurs during the cardiac cycle. It automatically tracks the motion trajectory of the myocardium frame by frame throughout the cardiac cycle by identifying the motion of speckles.

The left ventricle

For the left ventricle, the assessment of global longitudinal strain is (GLS) recommended (16). Studies have shown that GLS is impaired in patients with chronic heart failure, and that it is independently associated with all-cause mortality, cardiovascular death, heart transplantation, and predicts risk of heart failure hospitalization (17-21). Interestingly, GLS seems to have more prognostic value than LVEF (22-24). In order to gain more insight into the prognostic value of GLS in chronic heart failure patients, we studied in **Chapter 6** whether repeated measurements of GLS have incremental prognostic value over repeated measurements of LVEF. Our study was the first study to investigate this, and we found that repeated measurements of GLS were associated with adverse cardiac events in a chronic, stable heart failure population. This association was independent of repeated LVEF measurements. However, significance was lost when we adjusted for repeated NT-proBNP measurements. Another interesting finding was that, although GLS was decreased in the patients who experienced an adverse cardiac event, the temporal trajectories did not further diverge in patients who did versus who did not experience an adverse cardiac event. The findings in **Chapter 6** help us to further understand, and appreciate, that GLS is a sensitive marker of cardiac dysfunction. The population that we studied in **Chapter 6** consisted of a chronic, stable heart failure population. These patients did not have obesity, but the study population was overweight with a mean BMI 27.5 kg/m^2. The finding that repeated measurement of GLS lost its prognostic value when adding repeated measurements of NT-proBNP is interesting, as we can carefully hypothesize that the release of biomarkers, that indicate cardiac dysfunction or predict an adverse event, are more sensitive than the use of traditional echocardiographic parameters. Nevertheless, it is evident that GLS is a sensitive marker for cardiac dysfunction and

is able to predict adverse events in this chronic heart failure population. The question that arises from the knowledge we gained from **Chapter 6**, is whether GLS is useful as a marker for cardiac dysfunction in patients with obesity.

GLS in obesity

In **Chapter 7** we found that patients with obesity, without cardiovascular disease, had a mean GLS of -15.6%, while mean LVEF was 58%. This reflects that there is indeed cardiac dysfunction in patients with obesity when assessing GLS, which is not captured by measuring LVEF. In addition, this finding confirms that also in this population, GLS is a more sensitive marker than LVEF. This finding is very important, as we have seen so far, that history taking and BNP are of limited help in identifying signs of cardiac dysfunction in this very important high-risk population.

The left atrium

The left atrium has a crucial role in the filling of the left ventricle, as it serves as a reservoir which collects blood from the pulmonary veins during left ventricular systole, and ejects the volume in diastole into the left ventricle. Physiologically, the cycle of the left atrium consists of three phases, which reflect the three main left atrial functions: the reservoir, conduit, and contractile function (25). The reservoir strain starts at the end of ventricular diastole (mitral valve closure) and continues until mitral valve opening. The conduit phase occurs from the time of mitral valve opening through diastasis until the onset of left atrial contraction. This phase is considered the passive emptying phase of the left atrium into the left ventricle. The last part, the contractile phase, starts from the onset of left atrial contraction until the end of diastole; it is the active emptying from the left atrium into the left ventricle.

In the recent years, assessment of left atrial strain by speckle tracking echocardiography has gained more interest (26, 27). Studies have shown that left atrial strain may be used for assessment of left ventricular filling pressures and subsequent left atrial pressure (26-28). It can also be used to predict prognosis, and it appears to provide superior information to LAVI (27-29). In addition, left atrial strain seems to have stronger correlation with LV filling pressure than LAVI (28). A study demonstrated that the optimal cut-off value to differentiate between normal and elevated left ventricular filling pressure was 18% for left atrial reservoir strain when defining PCWP >12 mmHg as elevated and 16% when using PCWP ≥ 15 mmHg (28). Values below <19-23% of left atrial reservoir strain are considered abnormally low (30, 31). For left atrial contractile strain 14% seemed to be an excellent marker of normal filling pressure (28).

Left atrial function in heart failure

In patients with HFrEF, left atrial strain is significantly impaired and it is significantly associated with prognosis. In **Chapter 2** and **Chapter 3**, we investigated the potential prognostic role of left atrial strain in patients with HFrEF. Assessment of left atrial function in HFrEF is mainly done in order to gain information on left atrial pressure, which is important to guide prognosis and treatment (32, 33). Cardiac catheterization is the gold standard for assessing left atrial pressure, but is less attractive because its invasive nature carries a non-negligible risk and adds significant costs (34). Using echocardiography, a rough estimation of LAP can be made with the use of the criteria for diastolic function as proposed by the guidelines (35). An important and widely used echocardiographic parameter for left atrial function is the ratio between peak early mitral velocity (E) and A, the A reflects the contractile function (35). However, in a large proportion of HFrEF patients the E/A ratio is not useable, as comorbidities such as atrial fibrillation and mitral valve disease might affect the E/A ratio (35). An accurate estimation of left atrial pressure can therefore not be made in this patient group. In **Chapter 2**, we examined whether left atrial reservoir strain can be used in patients with missing E/A ratio. We found that left atrial reservoir strain provides clinical and significant prognostic information in the group of HFrEF patients with missing E/A. An important finding, since there is often insufficient information and no accurate marker of prognosis in this group. We further investigated the potential role of left atrial reservoir strain in HFrEF patients in **Chapter 3**, where we examined whether repeated measurements of left atrial reservoir strain have incremental prognostic value over a single baseline measurement, and whether repeated measurements of left atrial reservoir strain provide more prognostic information than other echocardiographic markers in patients with HFrEF. Since categorization of heart failure is mainly focused on systolic function, there is less attention on diastolic determinants for prognosis in HFrEF. This while diastolic determinants can provide essential information on left atrial pressure. A study demonstrated that E/e' ratio outperformed other diastolic parameters as a prognosticator in HFrEF patients, they did however not include left atrial reservoir strain in their study (36). A few studies have shown that a single measurement of left atrial reservoir strain has strong prognostic value, independent of other clinical and echocardiographic parameters (29, 37, 38). The results in **Chapter 3** confirm and extend previous evidence. We showed that a single baseline measurement of left atrial reservoir strain is a stronger predictor for adverse cardiac events that other echocardiographic parameters, such as E/e' ratio. In addition, we found that repeatedly measured left atrial reservoir strain was significantly associated with the primary endpoint, but, similar as in **Chapter 6** with GLS, although the temporal trajectories of left atrial reservoir strain were different in patients who experienced an adverse event compared to those who did not, they did not diverge as the event approached. Another interesting finding in this chapter is that left atrial reservoir

strain outperformed GLS as a prognostic marker in this chronic HFrEF population. In the cardiac cycle, GLS and left atrial reservoir strain are tightly coupled, as maximal expansion of the left atrium takes places during left ventricular systole, which is supported by the observation that left atrial reservoir strain and GLS are significantly correlated. A precise explanation for the observation that left atrial reservoir strain is a better prognostic marker than GLS remains unknown, but it could be speculated that left atrial reservoir strain might be affected by atrial inflammation and atrial fibrosis, which restricts atrial stretching, independent of left ventricular longitudinal contraction. Another important finding of this chapter was that LAVI was not associated with the risk of an adverse event. A potential explanation for this is that left atrial reservoir strain may be a more sensitive parameter than a volumetric parameter such as LAVI, and that an impairment in left atrial function is detected earlier than changes in left atrial volume.

Left atrial function in obesity

Left atrial enlargement (LAE) measured with LAVI is a well-established prognostic marker in heart failure, and also a predictor for hospitalisation and mortality (9, 39). In addition, LAE is associated with an increased risk for developing atrial fibrillation (40). Besides this, LAVI is also one of the morphologic diagnostic criteria in the diastolic dysfunction guidelines for patients with and without systolic dysfunction (9). In the ESC heart failure guidelines, LAVI is incorporated in the algorithm to diagnose HFpEF (9). There is, however, a major issue with the use of LAVI in patients with obesity. We describe this in **Chapter 5**. The calculation of LAVI is based on indexing on body surface area (BSA), but this is incorrect for patients with obesity. BSA is mainly driven by an increase in fat mass, meaning that indexing LAV to BSA may lead to an overcorrection of LAV among patients with obesity and thus potentially normalizing pathological left atrial enlargement (41). Since obesity is strongly associated with diastolic dysfunction and HFpEF, it is of crucial importance to have an accurate diagnostic marker to detect LAE. Studies have proposed that it would be more appropriate to index LAV to height^2 (42). An argument that supports the use of height^2, is that indexing LAV to height^2 assumes an exponential relationship, rather than a linear relationship when indexing to BSA, which is incorrect as body size and organs do not grow proportionally (41). In **Chapter 4,** we investigated left atrial function measured with left atrial strain in patients with obesity without known cardiovascular disease. We showed that left atrial strain may be a useful alternative, as we found that patients with obesity without known cardiovascular disease have significantly decreased left atrial function compared to non-obese controls. We did not find a difference in the proportion of diastolic dysfunction, further stressing that left atrial dysfunction occurs before diastolic dysfunction might be recognized. In the multivariable linear regression model, an increase in BMI was significantly associated with a decrease in

left atrial function, confirming that obesity has important role in left atrial function. These results underscore that left atrial strain could have important added value in identifying patients with obesity at an early stage. In **Chapter 5**, we investigated the relationship between LAV indexed to height^2 and left atrial function. Furthermore, we investigated whether LAV indexation to height^2 lead to better detection of left atrial enlargement. We found that in our population with a BMI ≥ 30 kg/m^2, the use of height^2 as an indexation method, lead to a significantly higher prevalence of LAE compared to indexing to BSA. More importantly, we found that indexing LAV to height^2 was associated with an increased risk for left atrial dysfunction. Considering the limitation of indexing LAV to BSA in obesity, our results are of added value in clinical practice. Our study confirms the results of a previous study, where as many as 55.4% of patients with severe obesity were reclassified into LAE when height^2 was used as an indexation method instead of BSA. More importantly, recent studies have found that indexing LAV to height^2 is better at predicting outcomes in patients with obesity (43). Our study was the first to explore the relationship between LAV indexed to height^2 and left atrial function.

The effect of weight loss on cardiac function

The positive effect of weight loss are significant, and include, among other effects, a decrease in blood pressure, improvement of insulin resistance, reduction in the risk of stroke and cardiovascular disease, and an improvement in quality of life (44). Weight loss can be achieved through various methods. Lifestyle interventions programs that provide a holistic approach that focus on a healthy diet, physical activity, and psychological health, are increasingly used with positive effects for patients with overweight and obesity. However, in a substantial proportion of patients the results of lifestyle interventions are often temporary and do not provide a sustainable, long-term solution for weight loss and health benefits. For these patients, bariatric surgery is an effective and safe treatment option that may result in long-term weight loss. In addition, bariatric surgery is associated with metabolic improvements and has favorable hemodynamic effects in patients without heart failure (45). We extensively studied the effects of bariatric surgery on cardiac function in this thesis, as we followed patients with obesity one year after bariatric surgery.

In **Chapter 7**, we found that 56% of the patients had subclinical cardiac dysfunction before surgery. In 50% of these patients, cardiac function normalised one year after bariatric surgery. However, in 43% a decreased GLS persisted This persistence of lower GLS was related to autonomic dysfunction and a decreased vitamin D pre-surgery. These findings suggest that autonomic dysfunction has a role in the development of cardiac dysfunction, but also contributes to the persistence of cardiac dysfunction after bariatric surgery. Vitamin D is involved in multiple pathophysiological pathways

related to heart failure, such as inflammation, atherosclerosis, endothelial dysfunction, and thrombosis (46). Our findings support that vitamin D may have a role in cardiac dysfunction in patients with obesity. In **Chapter 10** we found that 78% of the investigated biomarkers significantly change after bariatric surgery. The biomarkers with the highest relative change are related to insulin resistance and inflammation. Furthermore, we developed a biomarker model to predict the persistence of cardiac dysfunction post-bariatric surgery. The biomarkers in this model also represent processes linked to insulin resistance and inflammation. These results further stress the important and significant role of inflammation. As for the left atrium, in **Chapter 4** we found that left atrial reservoir strain significantly improved one year after bariatric surgery. This while there was no significant improvement in traditional diastolic parameters, suggesting that left atrial reservoir strain may be a more sensitive marker for the left atrium.

Bariatric surgery leads to complex metabolic and hemodynamic changes. Studies have demonstrated that gastric bypass surgery leads to more favourable outcomes than gastric sleeve in terms of improvement of comorbidities and improvement of left ventricular function (47, 48). In this thesis, the majority of patients underwent gastric bypass surgery. It is uncertain how the type of surgery might have affected the improvements in cardiac function that we observed in this thesis. Although a proportion of patients had persistent cardiac dysfunction after bariatric surgery, the observation that GLS as well as left atrial reservoir strain can improve after bariatric surgery is promising and indicates reversibility of cardiac dysfunction in patients with obesity without known cardiovascular disease.

Obesity and heart failure in clinical practice

In **Part V**, we explored the role of obesity in patients with clinically overt heart failure in a large registry of patients with chronic heart failure. In **Chapter 11**, we found that BMI is strongly related with atrial fibrillation in patients with HFpEF. The prevalence of atrial fibrillation was significantly higher in patients with obesity and HFpEF. This association supports the theory that HFpEF and atrial fibrillation share a common pathophysiological pathway that includes inflammation and fibrosis, through expansion of EAT (49, 50), and can lead to atrial myopathy, which in turn van cause HFpEF and/or atrial fibrillation.

Interestingly, HF patients with overweight and obesity have lower mortality compared to their leaner counterparts, a phenomenon commonly known as the obesity paradox (51-53). The obesity paradox has been described in HFpEF as well as HFrEF patients. There has been debate whether this paradox is valid or the result of methodological shortcomings. A potential explanation that has been postulated for the obesity para-

dox, is that patients with obesity use more cardioprotective medication. In **Chapter 12** we investigated HF treatment differences in patients with and without obesity and we found that guideline-recommended drugs were more frequently prescribed and at higher dose in patients with obesity as compared to HF patients without obesity. Better pharmacological treatment of patients with obesity may contribute to the obesity paradox. Evidence for the role of lifestyle interventions in established HF for patients with obesity is limited (9). Bariatric surgery has shown to lead to an improvement in LVEF in patients with HF (44), but it remains unclear whether intentional weight loss results in improved clinical outcomes in HF patients with obesity. Guideline recommended drug therapy is therefore an important pillar of therapy in HF patients with obesity. In clinical practice, it is important to consider that the titration process HF treatment in patients with obesity may require a different approach due to differences in tolerability and side effects.

CONCLUSION

The findings in this thesis indicate that cardiovascular dysfunction is present in patients with obesity without known cardiac disease, and that this cardiac dysfunction would have remained largely undiscovered with the use of conventional diagnostic criteria. Speckle tracking echocardiography was able to detect early signs of cardiac dysfunction in the left ventricle, as well as in the left atrium. Therefore, speckle tracking echocardiography could be a valuable tool in clinical practice to detect patients with obesity who are at high risk for developing clinically overt heart failure. Biomarker profiles in patients with obesity confirmed that processes of inflammation and fibrosis have a very important role in the pathophysiology that leads to cardiac dysfunction. In a large proportion of patients with obesity, GLS, as well as left atrial reservoir strain improved after bariatric surgery, indicating potential reversibility of cardiac dysfunction after major weight loss surgery. In clinically overt heart failure, the combination of HFpEF and atrial fibrillation in patients with obesity is prevalent, possibly due to the common inflammatory pathophysiological pathway induced by processes related to obesity. Patients with obesity and systolic heart failure, receive a different amount of guideline recommended drugs for heart failure, indicating that patients with obesity might require a different approach to heart failure drugs. Altogether, these findings demonstrate that signs of heart failure in obesity occur at an early stage, and that early detection of signs of cardiac dysfunction may help to divert further progress into clinically overt heart failure.

FUTURE PERSPECTIVES

In this thesis, we have demonstrated that patients with obesity have early signs of cardiac dysfunction, and that speckle tracking echocardiography has a role in the early detection of signs of heart failure in patients with obesity. Early detection may result in prompter initiation of treatment for heart failure, but it is unclear whether early detection would lead to less heart failure diagnoses, fewer hospitalizations, and lower mortality rates. It would be interesting to study the effect of early detection on clinical endpoints, and cost-effectiveness in a large, prospective study. Early detection is a form of prevention of heart failure, and prevention is crucial to counter the enormous threat that obesity poses on modern day medicine. A fundamental change is needed in the way we perceive and practice medicine, with a change of focus towards prevention of disease; as Desiderius Erasmus already stated in the year 1500: "prevention is better than cure".

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Chapter 14.1

Summary

PART I – INTRODUCTION

Obesity is a major risk factor for heart failure. The prevalence of obesity is increasing worldwide, with no sign of waning. The expected increase in the numbers of people with obesity will subsequently lead to a rise in heart failure diagnoses. The type of heart failure may vary based on left ventricular ejection fraction. It can be roughly divided into heart failure with reduced ejection fraction (HFrEF), and heart failure with preserved ejection fraction (HFpEF). HFpEF is the most prevalent type of heart failure in obesity. The pathogenesis of obesity that leads to heart failure is not completely understood, but in recent years it has become evident that systemic inflammation plays a key role in the pathophysiology. Early identification of patients with the highest risk of developing heart failure is important so that prompt treatment can be initiated at an early stage and further deterioration of cardiac function may be diverted. However, early detection of cardiac dysfunction in patients with obesity is challenging due to several reasons. First of all, signs and symptoms of heart failure are often attributed to the extra weight and other comorbidities that are related to obesity. Moreover, the common diagnostics tools for heart failure, such as echocardiography and the use of the biomarker BNP, are not always reliable in patients with obesity. Novel biomarkers in obesity that are related to inflammation and fibrosis may serve as more precise markers for cardiac function. As for echocardiography, the emergence of speckle tracking echocardiography potentially provides a more sensitive marker for cardiac dysfunction in individuals with obesity. The overall aim of this thesis is to investigate cardiac dysfunction in obesity, and the explore the role of biomarkers and speckle tracking echocardiography in the early detection of cardiac dysfunction.

PART II – EARLY DETECTION OF CARDIAC DYSFUNCTION IN OBESITY – THE LEFT ATRIUM

Currently, left atrial function is measured with echocardiography and expressed as left atrial volume indexed to body surface are (BSA) (LAVI). LAVI is a well-established prognostic marker in heart failure, and an important morphologic criterium in the diastolic dysfunction guidelines for patients with and without systolic dysfunction. In recent years assessment of left atrial strain by speckle tracking echocardiography has gained more interest as a new marker of left atrial function. Left atrial strain is able to predict prognosis and has a stronger correlation with left ventricular filling pressures than LAVI. Estimation of left ventricular pressures is important, as it estimates left atrial pressure, which in turn can be used to guide prognosis and treatment. In **Chapter** 2, we investigated the role of left atrial strain in a group of patients with HFrEF who have concomitant mitral valve regurgitation or atrial fibrillation. Estimation of

left atrial pressure with the use of conventional echocardiographic parameters is often limited in this group of patients, due to missing echocardiographic variables (e.g. E/A ratio). We found that left atrial strain provides important prognostic information in this group of patients in whom otherwise an estimation of left atrial pressure would not be possible. In **Chapter 3**, we examined whether repeated measurements of left atrial reservoir strain in patient with HFrEF have incremental prognostic value over a single baseline measurement and whether repeated measurements of left atrial reservoir strain provide more prognostic information than other echocardiographic parameters. We found that a baseline measurement of left atrial reservoir strain is a better predictor for adverse cardiac events than other echocardiographic parameters, such as E/e' ratio, LAVI, and global longitudinal strain (GLS). Repeatedly measured left atrial reservoir strain was associated with the primary endpoint, but the temporal trajectories of patients who experienced an adverse event compared to those who did not, did not diverge as the event approached. Therefore, repeatedly measured left atrial reservoir strain has, as yet, no additional value in clinical practice. A single measurement does not only provide sufficient prognostic information, but also seems to be a stronger prognosticator compared to conventional echocardiographic parameters.

In **Chapter 4** we examined left atrial function measured with left atrial strain in patients with obesity without known cardiovascular disease. We found that patients with obesity have significantly decreased left atrial function compared to a non-obese control group. Interestingly, we did not find a difference in the proportion of diastolic function between patients with obesity and non-obese controls. This observation underscores that left atrial dysfunction might occur before signs of diastolic dysfunction, with the use of conventional echocardiographic parameters may be recognized. In a multivariable linear regression model, an increase in BMI was significantly associated with a decrease in left atrial function; further stressing that obesity plays an important role is left atrial dysfunction. Furthermore, we demonstrated that left atrial reservoir strain significantly improved one year after bariatric surgery. This indicates that reversibility of left atrial function is possible after weight loss surgery. Information on left atrial function in patients with obesity is important as the use of LAVI as measure of left atrial function in these individuals is not useful. Indexing left atrial volume to BSA leads to an overcorrection of left atrial volume and potential normalization of pathological left atrial enlargement. In **Chapter 5** we investigated whether indexing left atrial volume to squared height (height^2) is more appropriate in patients with obesity, and whether this leads to better detection of left atrial dysfunction as measured with left atrial strain. We found that indexing left atrial volume to height^2 leads to a significantly higher prevalence of left atrial enlargement compared to indexing to BSA. More importantly, we found that indexing left atrial volume to height^2 was associated with an increased risk for left atrial dysfunction as measured with left atrial

contractile strain. The use of indexing left atrial volume to height^2 leads to better, and earlier detection of cardiac dysfunction, and is therefore clinically relevant.

PART III – EARLY DETECTION OF CARDIAC DYSFUNCTION IN OBESITY – THE LEFT VENTRICLE

For the left ventricle, the assessment of GLS with the use of speckle tracking echocardiography is recommended. GLS is impaired in patients with chronic heart failure, and GLS seems to have more prognostic value than left ventricular ejection fraction (LVEF); the most common used marker for systolic function. In **Chapter 6** we found that repeated measurements of GLS were associated with adverse cardiac events in a chronic heart failure population. This association was independent of repeated LVEF measurements. However, significance was lost after adjusting for repeated NT-proBNP measurements. Moreover, the temporal trajectories of GLS did not diverge in patients who experienced an adverse event compared to patients who did not experience an adverse event. Hence, there is no clinical additional value in repeated measurement of GLS, and a baseline measurement of GLS provides sufficient prognostic information. In **Chapter 7,** with the use of GLS we found a high prevalence of subclinical cardiac dysfunction in patients with obesity without cardiovascular disease. In 50% of these patients, cardiac function normalised one year after bariatric surgery. However, in 43% an impairment in GLS persisted one year after bariatric surgery. In **Chapter 8** we found that this persistence was related to autonomic dysfunction and a decreased vitamin D pre-surgery. Patients with signs of autonomic dysfunctions and/or a decreased vitamin D pre-bariatric surgery may require follow-up by a cardiologist after bariatric surgery.

PART IV – EARLY DETECTION OF CARDIAC DYSFUNCTION IN OBESITY – BIOMARKERS

In **Chapter 9**, we evaluated 92 cardiovascular biomarkers in patients with and without obesity, and in obesity patients with and without cardiac dysfunction. We found that patients with obesity without cardiovascular disease have a different biomarker profile compared to individuals without obesity. In patients with obesity, the levels of biomarkers related to inflammation and insulin resistance were significantly higher, supporting the theory that inflammation plays an important role in the pathophysiology. When we compared the biomarker profiles of patients with obesity without cardiac dysfunction to patients with obesity with cardiac dysfunction, we found a higher level of biomarkers related to atherosclerosis, inflammation, and insulin resistance in

the latter group. In a multivariable model, biomarkers related to insulin resistance, inflammation, and atherosclerosis were selected as predictors for identifying cardiac dysfunction in patients with obesity. These biomarkers may be a better marker for early detection of cardiac dysfunction in patients with obesity.
In **Chapter 10** we investigated the change in biomarker profiles in patient who underwent bariatric surgery. We found that 78% of the investigated biomarkers significantly changed one year after bariatric surgery. The biomarkers with the highest relative change were markers associated with processes of inflammation and insulin resistance. Furthermore, we developed a biomarker model to predict the persistence of cardiac dysfunction post-bariatric surgery. Again, biomarkers related to inflammation and insulin resistance were selected by the model. These results further stress the important role of inflammation in the pathophysiology of cardiac dysfunction in patients with obesity.

PART V – OBESITY AND HEART FAILURE IN CLINICAL PRACTICE

In **Chapter 11** we demonstrated that the prevalence of atrial fibrillation was significantly higher among HFpEF patients with obesity compared to HFpEF patients without obesity. In multivariable logistic regression model, we found that BMI was strongly related with atrial fibrillation in patients with HFpEF. These results support the theory of a common inflammatory pathophysiological pathway that is induced by obesity, that can lead to an expansion of epicardial adipose tissue and subsequent atrial myopathy that can manifest as HFpEF and/or atrial fibrillation.
Obesity patients with heart failure have lower mortality compared to heart failure patients without obesity, a phenomenon known as the obesity paradox. One of the proposed reasons for the obesity paradox is that heart failure patients with obesity use more cardioprotective medication than heart failure patients without obesity. In **Chapter 12** we investigated medical treatment differences in patients with chronic heart failure with and without obesity. We found that patients with obesity received guideline recommended heart failure therapy significantly more often and at a higher dosage. Better pharmacological treatment in heart failure patients with obesity may contribute to the obesity paradox, but further studies are required to investigate the effect of treatment differences on the obesity paradox.

PART VI – DISCUSSION

Chapter 13 provides the general discussion of this thesis. The results and interpretation of the findings are thoroughly discussed in relation to the aim of this thesis. Overall, the findings demonstrate that signs of heart failure in obesity occur at an early stage and that the current diagnostics methods fall short to identify signs of cardiac dysfunction. Speckle tracking echocardiography detects signs of cardiac dysfunction and therefore speckle tracking echocardiography is a valuable tool in clinical practice to identify obesity patients who are at high risk for developing clinically overt heart failure. An extensive panel of cardiovascular biomarkers demonstrated that inflammation plays a key role in the pathophysiology that leads to cardiac dysfunction. Obesity induced cardiac dysfunction is reversible after batriatric surgery, however cardiac dysfunction persists in a proportion of patients. This seems to be relatedto inflammation, autonomic dysfunction, and low levels of vitamin D pre-surgery. In clinically overt heart failure, clinicians should be aware of the high prevalence of atrial fibrillation in obesity patients with HFpEF. Patients with obesity and systolic heart failure receive higher dosage of guideline recommended heart failure therapy, which might affect their clinical outcomes. For future studies it would be interesting to investigate whether early detection of cardiac dysfunction translates into clinical outcomes, such as fewer hospitalizations and lower mortality rates.. These future perspectives are discussed in **Chapter 14**.

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Chapter 14.2

Nederlandse samenvatting

DEEL I – INTRODUCTIE

Obesitas is geassocieerd met een verhoogd risico op hartfalen. De prevalentie van obesitas stijgt wereldwijd en zal de komende jaren verder toenemen. Deze verwachte toename zal uiteindelijk leiden tot een stijging van het aantal patiënten met de diagnose hartfalen. Hartfalen wordt grofweg onderscheiden in twee typen: hartfalen met een verminderde ejectiefractie (HFrEF) en hartfalen met een behouden ejectiefractie (HFpEF). Het type HFpEF is de meest prevalente vorm van hartfalen bij mensen met obesitas. De pathogenese bij obesitas die leidt tot het ontstaan van hartfalen is complex en nog niet volledig opgehelderd. In het laatste decennium is het steeds duidelijker geworden dat systemische inflammatie, geïnduceerd door obesitas, een zeer belangrijke rol speelt in de pathogenese van obesitas en hartfalen. Het vroegtijdig detecteren en herkennen van tekenen van cardiale dysfunctie bij mensen met obesitas is van groot belang, zodat een eventuele behandeling vroegtijdig kan worden gestart en verdere ziekteprogressie tot hartfalen kan worden afgeremd dan wel teruggedraaid. Met de huidige diagnostische technieken is het momenteel lastig om tekenen van cardiale dysfunctie te herkennen bij mensen met obesitas. Ten eerste worden klachten en symptomen van hartfalen vaak toegeschreven aan het overgewicht en andere comorbiditeiten die soortgelijke klachten kunnen veroorzaken. Ten tweede, zijn de aanbevolen diagnostische meetinstrumenten voor hartfalen, zoals het gebruik van echocardiografie en de biomarker BNP, niet altijd betrouwbaar bij mensen met obesitas. Nieuwe biomarkers die gerelateerd zijn aan inflammatie en fibrose zijn mogelijk betere markers voor vroege tekenen van cardiale dysfunctie in deze patiëntenpopulatie. Wat echocardiografie betreft, biedt de opkomst van speckle tracking echocardiografie mogelijk een sensitievere methode om cardiale dysfunctie op te sporen bij mensen met obesitas. Het overkoepelende doel van dit proefschrift is om tekenen van vroegtijdige cardiale dysfunctie bij mensen met obesitas te bestuderen, en om te onderzoeken wat de potentiële rol is van speckle tracking echocardiografie en biomarkers in het vroegtijdig detecteren van cardiale dysfunctie bij mensen met obesitas.

DEEL II – VROEGTIJDIGE DETECTIE VAN CARDIALE DYSFUNCTIE IN OBESITAS – HET LINKER ATRIUM

De functie van het linker atrium wordt momenteel afgeleid van het linker atrium volume (LAV), wat wordt gemeten middels echocardiografie. De richtlijnen bevelen aan om het LAV te indexeren op de *body surface area* (BSA), en dit wordt afgekort als LAVI. Vele studies hebben aangetoond dat LAVI een belangrijke prognostische marker is voor hartfalen, en LAVI is ook een belangrijk morfologisch diagnostisch criterium om diastolische dysfunctie vast te stellen, bij zowel HFrEF als HFpEF.

De afgelopen jaren is er een grotere belangstelling ontstaan voor het meten van de linker atrium strain als maat voor de linker atrium functie met behulp van speckle tracking echocardiografie. Het is gebleken dat de linker atrium strain een belangrijke prognostische marker is, en de linker atrium strain blijkt een betere correlatie te hebben met invasief gemeten linkerventrikel vullingsdrukken in vergelijking met LAVI. Het niet-invasief kunnen schatten van linkerventrikel vullingsdrukken is van belang, aangezien dit een afgeleide schatting geeft van de druk in het linker atrium. Deze informatie is belangrijk om een inschatting te maken van de prognose bij hartfalen, en om de behandeling te kunnen begeleiden. In **hoofdstuk 2** hebben wij onderzocht of de linker atrium strain prognostische waarde heeft in een groep HFrEF patiënten, die naast HFrEF ook mitralisklepinsufficiëntie of atriumfibrilleren hebben. Normaliter is het niet-invasief schatten van de druk in het linker atrium in deze specifieke patiëntengroep niet mogelijk, aangezien belangrijke echocardiografische parameters niet beschikbaar zijn (bijv. E/A ratio) door de mitralisklepinsufficiëntie of het atriumfibrilleren. Wij hebben gevonden dat het meten van de linker atrium strain middels speckle tracking echocardiografie belangrijke prognostische informatie geeft voor deze patiëntengroep. Dit resultaat is van belang, gezien er voorheen voor deze groep geen specifieke prognostische marker beschikbaar was.

In **hoofdstuk 3** hebben wij in een groep van chronische hartfalen patiënten bestudeerd of het herhaaldelijk meten van de linker atrium reservoir strain aanvullende prognostische waarde heeft ten opzichte van het eenmalig meten van de linker atrium reservoir strain. Verder hebben wij in dit hoofdstuk onderzocht of het herhaaldelijk meten van de linker atrium reservoir strain beter is in het voorspellen van een nadelige klinische uitkomst vergeleken met het herhaaldelijk meten van andere echocardiografische parameters. Uit onze resultaten is gebleken dat een eenmalige meting van de linker atrium reservoir strain een betere voorspeller is voor nadelige klinische uitkomsten vergeleken met een eenmalige meting van andere echocardiografische parameters, zoals LAVI, E/e' ratio en globale longitudinale strain (GLS). Het herhaaldelijk meten van de linker atrium reservoir strain was significant geassocieerd met het eindpunt, maar de trajecten van de linker atrium strain liepen niet uiteen naarmate het eindpunt naderde tussen de groep die het eindpunt ervaarde versus de groep die het eindpunt niet ervaarde. Het herhaaldelijk meten van de linker atrium strain geeft derhalve geen additionele prognostische waarde. Het eenmalig meten van de linker atrium reservoir strain geeft voldoende prognostische informatie en is mogelijk ook een betere voorspeller dan andere echocardiografische parameters.

In **hoofdstuk 4** onderzochten wij de linker atrium functie met behulp van linker atrium strain in een groep mensen met obesitas zonder een cardiovasculaire voorgeschiedenis. Uit dit onderzoek zijn een aantal interessante resultaten gekomen. Ten eerste hebben wij gevonden dat mensen met obesitas zonder cardiovasculaire voorgeschiedenis een significant lagere waarde van de linker atrium strain hebben vergeleken

met een controlegroep van mensen zonder obesitas. Dit terwijl er tussen beide groepen geen verschil was in de proportie van diastolische dysfunctie. Deze observatie benadrukt dat linker atrium dysfunctie kan bestaan zonder dat er hier aanwijzingen voor zijn wanneer wij de conventionele echocardiografische parameters voor diastolische dysfunctie gebruiken. Verder hebben wij in een multivariabel lineair regressie model gevonden dat een toename in body mass index (BMI) significant is geassocieerd met een afname van linker atrium functie gemeten met de linker atrium reservoir strain. Deze observatie onderstreept de notie dat obesitas een belangrijke rol speelt bij het ontstaan van linker atrium dysfunctie. In **hoofdstuk 4** hebben wij ook bestudeerd wat het effect is van bariatrische chirurgie op de functie van het linker atrium. Één jaar na bariatrische chirurgie is er sprake van een significante verbetering van de linker atrium reservoir strain. Dit resultaat laat zien dat reversibiliteit van de functie van het linker atrium mogelijk is na significante gewichtsreductie door bariatrische chirurgie. Het verschaffen van informatie over de functie van het linker atrium bij obesitas is van belang, aangezien LAVI niet bruikbaar is bij mensen met obesitas. Het indexeren van het LAV op BSA leidt namelijk tot een over correctie van het LAV bij mensen met obesitas, en zo wordt mogelijk een pathologisch vergroot linker atrium gemist. In **hoofdstuk 5** onderzochten wij of het indexeren op lengte in het kwadraat (lengte^2) meer geschikt is om linker atrium vergroting en linker atrium dysfunctie op te sporen bij mensen met obesitas. Uit onze resultaten blijkt dat indexeren op lengte^2 leidt tot een hogere prevalentie van linker atrium vergroting vergeleken met indexeren op BSA, en dat indexeren op lengte^2 is geassocieerd met een verhoogd risico op linker atrium dysfunctie gemeten met de linker atrium contractiele strain. Het gebruik van indexeren van LAV op lengte^2 is klinisch relevant, gezien dit leidt tot een betere, en eerdere, detectie van linker atrium dysfunctie en dit kan mogelijk een voorloper zijn van hartfalen. Deze belangrijke informatie wordt momenteel gemist door het gebruik van indexeren op BSA.

DEEL II – VROEGTIJDIGE DETECTIE VAN CARDIALE DYSFUNCTIE IN OBESITAS – DE LINKERVENTRIKEL

Voor de linkerventrikel wordt het aanbevolen om GLS te bepalen met behulp van speckle tracking echocardiografie. GLS is verminderd in patiënten met chronisch hartfalen, en GLS lijkt een betere prognostische marker te zijn dan de linkerventrikel ejectiefractie (LVEF). In **hoofdstuk 6** hebben wij aangetoond dat het herhaaldelijk meten van GLS bij patiënten met chronisch hartfalen een significante marker is voor het voorspellen van klinische eindpunten. Deze associatie was onafhankelijk van het herhaaldelijk meten van de LVEF. Echter, deze associatie verloor statistische significantie wanneer het herhaaldelijk meten van NT-proBNP werd toegevoegd aan het

model. De trajecten van GLS liepen niet uiteen naarmate het eindpunt naderde tussen de groep die het eindpunt ervaarde versus de groep die het eindpunt niet ervaarde. Een eenmalige meting van GLS is derhalve voldoende om de prognose te voorspellen, en het herhaaldelijk meten van GLS lijkt geen meerwaarde te hebben.
In **hoofdstuk 7** hebben wij met behulp van GLS ontdekt dat er sprake is van een hoge prevalentie van cardiale dysfunctie bij mensen met obesitas zonder cardiovasculaire voorgeschiedenis. Bij 50% van de mensen met cardiale dysfunctie normaliseert de cardiale functie 1 jaar na bariatrische chirurgie. Echter, bij 43% van de patiënten persisteert de cardiale dysfunctie 1 jaar na bariatrische chirurgie. In **hoofdstuk 8** hebben wij gevonden dat het persisteren van cardiale dysfunctie gerelateerd blijkt te zijn aan autonome dysfunctie en een verlaagd vitamine D voor bariatrie. Cardiologische follow-up na bariatrie is eventueel geïndiceerd bij obesitas patiënten die autonome dysfunctie en/of een verlaagd vitamine D hebben pre-bariatrie.

DEEL IV – VROEGTIJDIGE DETECTIE VAN CARDIALE DYSFUNCTIE IN OBESITAS – BIOMARKERS

In **hoofdstuk 9** hebben wij 92 cardiovasculaire biomarkers vergeleken tussen mensen met obesitas en een controlegroep zonder obesitas, en tussen mensen met obesitas met cardiale dysfunctie en mensen met obesitas zonder cardiale dysfunctie. Er blijkt een verschil te bestaan in de biomarkerprofielen, waarbij mensen met obesitas hogere waarden van biomarkers hebben die gerelateerd zijn aan processen van inflammatie en insuline resistentie vergeleken met de controlegroep zonder obesitas. Wanneer wij kijken naar de verschillen tussen obesitas patiënten met en zonder cardiale dysfunctie, dan zien wij dat de waarden van biomarkers die gerelateerd zijn aan inflammatie, insuline resistentie en atherosclerose hoger zijn in de groep obesitas mensen met cardiale dysfunctie.
In **hoofdstuk 10** hebben wij de verandering in biomarkers onderzocht bij obesitas patiënten die bariatrie hebben ondergaan. In 78% van de onderzochte biomarkers was er 1 jaar na bariatrie sprake van een significante verandering. De biomarkers met de relatief grootste verandering waren markers die geassocieerd zijn met processen van inflammatie en insuline resistentie. Vervolgens, hebben wij getracht een model te ontwikkelen welke persisterende cardiale dysfunctie post bariatrie kan voorspellen. Ook in dit model bleken biomarkers die gerelateerd zijn aan processen van inflammatie en insuline resistentie belangrijke voorspellers te zijn. Deze resultaten onderstrepen nogmaals de belangrijke rol van inflammatie bij obesitas en cardiale dysfunctie. Mogelijk kunnen biomarkers die processen van inflammatie beschrijven een klinische waarde hebben bij het detecteren van cardiale dysfunctie bij mensen met obesitas.

DEEL V – OBESITAS EN HARTFALEN IN DE KLINISCHE PRAKTIJK

In **hoofdstuk 11** hebben wij aangetoond dat de prevalentie van atriumfibrilleren significant hoger is bij HFpEF patiënten met obesitas vergeleken met HFpEF patiënten zonder obesitas. Tevens hebben wij in een grote populatie HFpEF patiënten in een multivariabel logistisch regressiemodel gevonden dat BMI significant is geassocieerd met atriumfibrilleren. Deze resultaten ondersteunen het idee van een door obesitas geïnduceerd gemeenschappelijk, inflammatoir pathofysiologisch mechanisme wat leidt tot een toename van het epicardiale vetvolume, en zowel HFpEF als atriumfibrilleren kan veroorzaken.
Hartfalen patiënten met obesitas hebben een lagere mortaliteit vergeleken met hartfalen patiënten zonder obesitas, een fenomeen dat bekend staat als de obesitas paradox. Een mogelijke verklaring voor de obesitas paradox is de theorie dat hartfalen patiënten met obesitas meer cardioprotectieve medicatie gebruiken. In **hoofdstuk 12** hebben wij medicatie verschillen onderzocht in chronisch hartfalen patiënten met en zonder obesitas. Hartfalen medicatie wordt significant vaker voorgeschreven, en in een hogere dosering, aan hartfalen patiënten met obesitas. Bovendien, ontvangen hartfalen patiënten met obesitas ook significant vaker de richtlijn gedefinieerde targetdosering van hartfalen medicatie. Mogelijk speelt de betere medicamenteuze behandeling van hartfalen een rol bij de obesitas paradox. Hier is echter momenteel geen data over, en toekomstige studies zijn nodig om het effect van medicatie verschillen te onderzoeken in relatie tot de obesitas paradox.

DEEL VI – DISCUSSIE

In **hoofdstuk 13** worden de bevindingen en interpretatie van de resultaten uitvoerig besproken. De algehele bevindingen van dit proefschrift laten zien dat tekenen van cardiale dysfunctie al vroegtijdig ontstaan bij mensen met obesitas zonder cardiovasculaire voorgeschiedenis, en dat de huidige diagnostische middelen om hartfalen op te sporen tekortschieten in het detecteren van cardiale dysfunctie bij mensen met obesitas. Speckle tracking echocardiografie is een accurate methode om vroegtijdige tekenen van cardiale dysfunctie te detecteren, dit geldt voor zowel het linker atrium als de linkerventrikel. In een uitgebreid panel van cardiovasculaire biomarkers is gebleken dat inflammatoire processen een belangrijke rol spelen in de pathofysiologie bij obesitas. Obesitas geïnduceerde cardiale dysfunctie lijkt reversibel te zijn na bariatrie. In een proportie van patiënten persisteert echter de cardiale dysfunctie wat gerelateerd lijkt te zijn aan inflammatie, autonome dysfunctie en een verlaagd vitamine D. In HFpEF patiënten met obesitas is er een hoge prevalentie van atriumfibrilleren. Het

is belangrijk om in de klinische praktijk alert te zijn op de relatie tussen HFpEF en atriumfibrilleren bij mensen met obesitas. Chronisch hartfalen patiënten met obesitas ontvangen hogere doseringen van hartfalen medicatie, wat mogelijk een effect kan hebben op hun prognose. In de toekomst zou het interessant zijn om te onderzoeken of vroegtijdige detectie van cardiale dysfunctie zich vertaalt in een vermindering van hartfalen diagnoses, verminderde hospitalisaties en een verminderde mortaliteit. De mogelijkheden voor verder toekomstig onderzoek worden beschreven in **hoofdstuk 14**.

Part VII

Appendices

LIST OF PUBLICATIONS

1. **Aga YS**, Kroon D, Snelder SM, Biter LU, de Groot-de Laat LE, Zijlstra F, Brugts JJ, van Dalen BM. Decreased left atrial function in obesity patients without known cardiovascular disease. Int J Cardiovasc Imaging. 2023

2. **Aga YS*,** Radhoe SP*, Aydin D, Linssen GCM, Rademaker PC, Geerlings PR, van Gent MWF, Aksoy I, Oosterom L, Brunner-La Rocca HP, van Dalen BM, Brugts JJ. Heart failure treatment in patients with and without obesity with an ejection fraction below 50. Eur J Clin Invest. 2023

3. **Aga YS*,** Abou Kamar S, de Bakker M, van den Berg V, Strachinaru M, Bowen D, Frowijn R, Akkerhuis KM, Brugts JJ, Manintveld O, Umans V, de Boer RA, Boersma E, Kardys I, van Dalen BM. Prognostic value of temporal patterns of left atrial reservoir strain in patients with heart failure with reduced ejection fraction. ESC Heart Failure 2023

4. Abou Kamar S, **Aga YS**, de Bakker M, van den Berg VJ, Strachinaru M, Bowen D, Frowijn R, Akkerhuis KM, Brugts J, Manintveld O, Umans V, Geleijnse ML, Boersma E, van Dalen BM, Kardys I. Prognostic value of temporal patterns of global longitudinal strain in patients with chronic heart failure. Front Cardiovasc Med. 2023

5. Snelder SM, Pouw N, **Aga YS**, Castro Cabezas M, Biter LU, Zijlstra F, Kardys I, van Dalen BM. Cardiovascular Biomarker Profiles in Obesity and Relation to Normalization of Subclinical Cardiac Dysfunction after Bariatric Surgery. Cells. 2022

6. Snelder SM, Pouw N, **Aga YS**, Cabezas MC, Zijlstra F, Kardys I, van Dalen BM. Biomarker profiles in obesity patients and their relation to cardiac dysfunction. Biomark Med. 2021

7. Snelder SM, **Aga YS**, de Groot-de Laat LE, Biter LU, Castro Cabezas M, Pouw N, Boxma-de Klerk BM, Klaassen RA, Zijlstra F, van Dalen BM. Cardiac Function Normalizes 1 Year After Bariatric Surgery in Half of the Obesity Patients with Subclinical Cardiac Dysfunction. Obes Surg. 2021

8. Snelder SM, **Aga Y**, de Groot-de Laat LE, Biter LU, Cabezas MC, Pouw N, Birnie E, Boxma-de Klerk B, Klaassen RA, Zijlstra F, van Dalen BM. Normalization of Cardiac Function After Bariatric Surgery Is Related to Autonomic Function and Vitamin D. Obes Surg. 2023

SUBMITTED:

1. **Aga YS*,** Abou Kamar S*, Chin JF, van den Berg VJ, Strachinaru M, Bowen D, Frowijn R, Akkerhuis KM, Constantinescu AA, Umans V, Geleijnse ML, Boersma E, Brugts JJ, Kardys I, van Dalen BM. Potential role of left atrial strain in assessment of left ventricular filling pressures in heart failure with reduced ejection fraction. Submitted

2. **Aga YS*,** Acardag Y, Chin JF, Kroon D, Snelder SM, De Groot-de Laat L, Biter, U, Zijlstra F, Brugts JJ, van Dalen BM. Improved identification of left atrial enlargement in patients with obesity. Submitted

3. **Aga YS**, Radhoe SP, Linssen G, Brunner-la Rocca HP, Grosfeld MJW, Viergever EP, Takens LH, Pisters R, Hemels M, Zijlstra F, van Dalen BM, Brugts JJ. The role of ovesity in atrial fibrillation and heart failure with preserved ejection fraction: The CHECK-HF Registry. Submitted

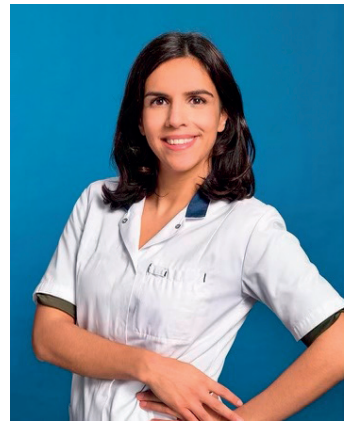
* both authors contributed equally

Portfolio

PhD training	Year	ECTS
Courses		
- Good Clinical Practice	2020	1.5
- Research Integrity	2021	0.3
- Biomedical English writing course	2020	1.5
- COEUR: Heart Failure	2021	0.5
- COEUR: Atrial Fibrillation	2021	0.5
- Biostatistics	2020	0.5
- Hou houd jij zin in zorg?	2022	1
Posters		
- Decreased left atrial function in morbid obese patients without known cardiac disease. Wetenschapsdag Franciscus, Rotterdam, the Netherlands	2021	1
- Decreased left atrial function in morbid obese patients without known cardiac disease. ESC, London, UK	2021	1
- Rationale and study design of the MINDfulness in Cardiac Obesity Rehabilitation using E-Health: the MINDCORE pilot study, Cardiovasculaire Preventie & Hartrevalidatie, Ede, the Netherlands	2022	1
- Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation, The Role of Obesity: Data From the CHECK-HF Registry, ESC, Madrid, Spain	2022	1
- Differences in chronic heart failure treatment between patients with and without obesity in a large real-world heart failure population, ESC, Barcelona, Spain	2022	1
- Rationale and study design of the MINDfulness in Cardiac Obesity Rehabilitation using E-Health: the MINDCORE pilot study, Landelijk Mindfulness Symposium, Nijmegen	2022	1
Presentations		
- The role of obesity in atrial fibrillation and heart failure. Wetenschapsdag Franciscus, Rotterdam, the Netherlands	2021	1
- Bruikbaarheid van wearables in de setting van hartrevalidatie. Capri, Rotterdam, the Netherlands	2021	0.5
- Decreased left atrial function in morbid obese patients without known cardiac disease. NVVC, Papendal, the Netherlands	2021	1
- Wetenschap van mindfulness bij hartrevalidatie, Capri, Rotterdam, the Netherlands	2022	0.5
- Improved identification of left atrial enlargement in patients with obesity. NVVC, Papendal, the Netherlands	2022	1
International conferences		
- ESC, London, United Kingdom	2021	1
- NVVC najaarscongres, Papendal, the Netherlands	2021	1
- Cardiovasculaire Preventie & Hartrevalidatie, Ede, the Netherlands	2022	1
- ESC Heart Failure, Madrid, Spain	2022	1
- ESC, Barcelona, Spain	2022	1
- NVVC najaarscongres, Papendal, the Netherlands	2022	1

Other tasks		
- Supervision of master student	2021	4
- Teamcaptain of "Zin in Zorg" team in Franciscus Gasthuis & Vlietland, Rotterdam	2021	2
- Member of "Arts Assistenten Vereniging" in Franciscus Gasthuis & Vlietland, Rotterdam	2021	2
- Peer-supporter for junior residents in Franciscus Gasthuis & Vlietland	2021	2
- Presentatie CASH3F (landelijk chirurgen AIOS onderwijs), De generatie inspirerende artsen, Noordwijkerhout, the Netherlands	2021	1
- Podcast host "Beyond The White Coat"	2022	2
- Organization of Wetenschapslunch in Franciscus Gasthuis & Vlietland	2022	2
- Deelname aan jonge dokters debat, Rode Hoed Congres, Amsterdam, the Netherlands	2022	
- Presentatie CASH3F (landelijk chirurgen AIOS onderwijs), Het imposter syndroom: een vloek of een super power?, Noordwijkerhout, the Netherlands	2022	1
Total		**38.8**

ABOUT THE AUTHOR



Yaar Aga was born and raised in the Netherlands. After finishing secondary school in Leidschendam in 2010 she started medical school at the Erasmus University in Rotterdam. During her studies she spent 7 months at the cardiology research department of the University of Miami in the USA. After obtaining her medical degree in 2017 she started working as a resident (ANIOS) at the department of internal medicine of the Albert Schweitzer Hospital in Dordrecht. In January 2018 she started as a resident (ANIOS) at the department of cardiology at Erasmus Medical Center in Rotterdam, and subsequently in August 2018 she started working as a cardiologist in training (AIOS) at the department of internal medicine at the Franciscus Gasthuis & Vlietland hospital in Rotterdam. After she finished the first part of her cardiology training she decided to pursue her PhD degree in May 2020. She conducted her PhD research under the supervision of dr. Bas van Dalen, dr. Jasper Brugts, prof. dr. Felix Zijlstra and prof. dr. Rudolf de Boer at the departments of cardiology in Franciscus Gasthuis & Vlietland and the Erasmuc Medical Center. As of June 1st 2023, Yaar will continue her cardiology training at the Maasstad hospital in Rotterdam. In her spare time Yaar enjoys reading and long-distance running. She also practices mindfulness and yoga.

DANKWOORD

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