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REVIEW

Obesity and left atrial function: state of the art

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Abstract

Obesity is an established risk factor for heart failure (HF), with every unit increase in body mass index, the risk of HF increases by 5-7%. Obesity can especially increase the risk for HF with preserved ejection fraction due to left atrial (LA) dysfunction caused by underlying systemic inflammation, chronic volume overload, and growth of epicardial adipose tissue. LA function can be assessed by measuring LA reservoir, conduit and booster, which correspond to physiological functions of LA filling during filling phase of cardiac cycle, LA pushing blood into left ventricle passively, and LA contraction to push the blood into left ventricle, respectively. Existing data show strong prognostic ability of LA strain reservoir for cardiovascular mortality and HF hospitalization. Several studies have also suggested that obesity in itself can cause reduction in LA strain and deterioration of LA function. Whether various weight loss interventions for patients with obesity can minimize and reverse LA remodeling and dysfunction remains unclear. In this review, we summarize the evidence regarding the impact of obesity on LA function, and discuss the impact of various weight reduction techniques on LA strain.

Key words: obesity, left atrial reservoir strain, left atrial conduit strain, left atrial booster strain, bariatric surgery.

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Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is a growing global health issue that accounts for about half of the patients diagnosed with HF.[1] Obesity is an established risk factor for HFpEF with over 80% of the patients with HFpEF reported to be either overweight or obese.[2,3] Obese individuals without documented cardiovascular illness frequently exhibit subclinical cardiac dysfunction and are more likely to develop HFpEF.[4]
Traditionally, HFpEF was linked to impaired left ventricular (LV) diastolic function. However, recently, left atrial (LA) dysfunction, measured by LA strain, has been recognized as an important factor in the pathogenesis of HFpEF.[3] LA function assessment has been a topic of investigation for numerous years in cardiology. The initial techniques employed to evaluate LA function were Doppler and volumetric methodologies. In contemporary times, speckle tracking echocardiography, which was originally devised for the purpose of evaluating LV function, has been utilized for the evaluation of LA deformation. The utilization of speckle tracking echocardiography to analyze LA performance, specifically LA strain, offers insight into all aspects of LA function, including reservoir, conduit, and booster pump phases. This method has demonstrated prognostic significance in various pathological conditions, including HFpEF, where impaired LA strain and worse cardiac outcomes have been reported.[5] Lower systolic LA strain is associated with higher HF hospitalization rates, decreased LV systolic function, higher LV mass and left atrial volume index (LAVi), suggesting the important role of LA dysfunction in the pathophysiology of HFpEF.[5] Speckle-tracking strain analysis of the LA is a stronger correlate of adverse outcomes than LV and RV longitudinal strain in patients with HFpEF.[6]
Obesity is prevalent in patients with HFpEF as it contributes to LA dysfunction by causing systemic inflammation, chronic volume overload, and growth of epicardial adipose tissue (EAT).[7-9] Visceral fat accumulation has a strong correlation with impaired LA strain.[10] In the CARDIOBESE (The CARdiac Dysfunction In Obesity: Early Signs Evaluation) study, an increase in BMI markedly reduced LA function parameters.[3] Moreover, patients with HFpEF and obesity (BMI=31 kg/m^2), with similar

New York Heart Association (NYHA) class symptoms may have higher uric acid levels, suggesting more severe systemic inflammation, hence, leading to more impairment in LA strain.[11] This review summarizes the evidence regarding association and impact of obesity on LA strain and its parameters, and its reliability as a diagnostic and prognostic parameter in these patients. We also discuss the impact of various weight reduction techniques on LA strain in patients with obesity. Lastly, we discuss the clinical implications, reliability and limitations of using LA strain in patients with obesity.

Obesity and left atrial strain

Left atrial strain components

The LA strain reservoir (LASr), conduit (LASc), and booster/pump (LASb) parameters are the three LA function components that contribute to the LV filling process and are quantified by LA strain (Figure 1). The LASr refers to the capacity of the LA to enlarge and stretch during the filling phase of the cardiac cycle. Throughout this phase, which corresponds to LV isovolumetric contraction, ejection, and relaxation, the LA is filled with blood from the pulmonary veins whereas the mitral valve remains closed. During early diastole, the LA enlarges in preparation for passive emptying, the ventricle receives blood from the atrium utilizing the atrium as a passive conduit, and the LA volume decreases. Towards the conclusion of diastole, the atrial muscle undergoes a phase of active contraction as it performs its function as a pump to load the ventricles to capacity. Hence, the role of the atrium as a reservoir is around 40%, as a passive channel is typically 35%, and as a pump is generally 25% in individuals without cardiovascular disease.[12] Since the atrium retains 40% of the systolic volume while the LV is contracting, the reservoir function of the LA is especially important.

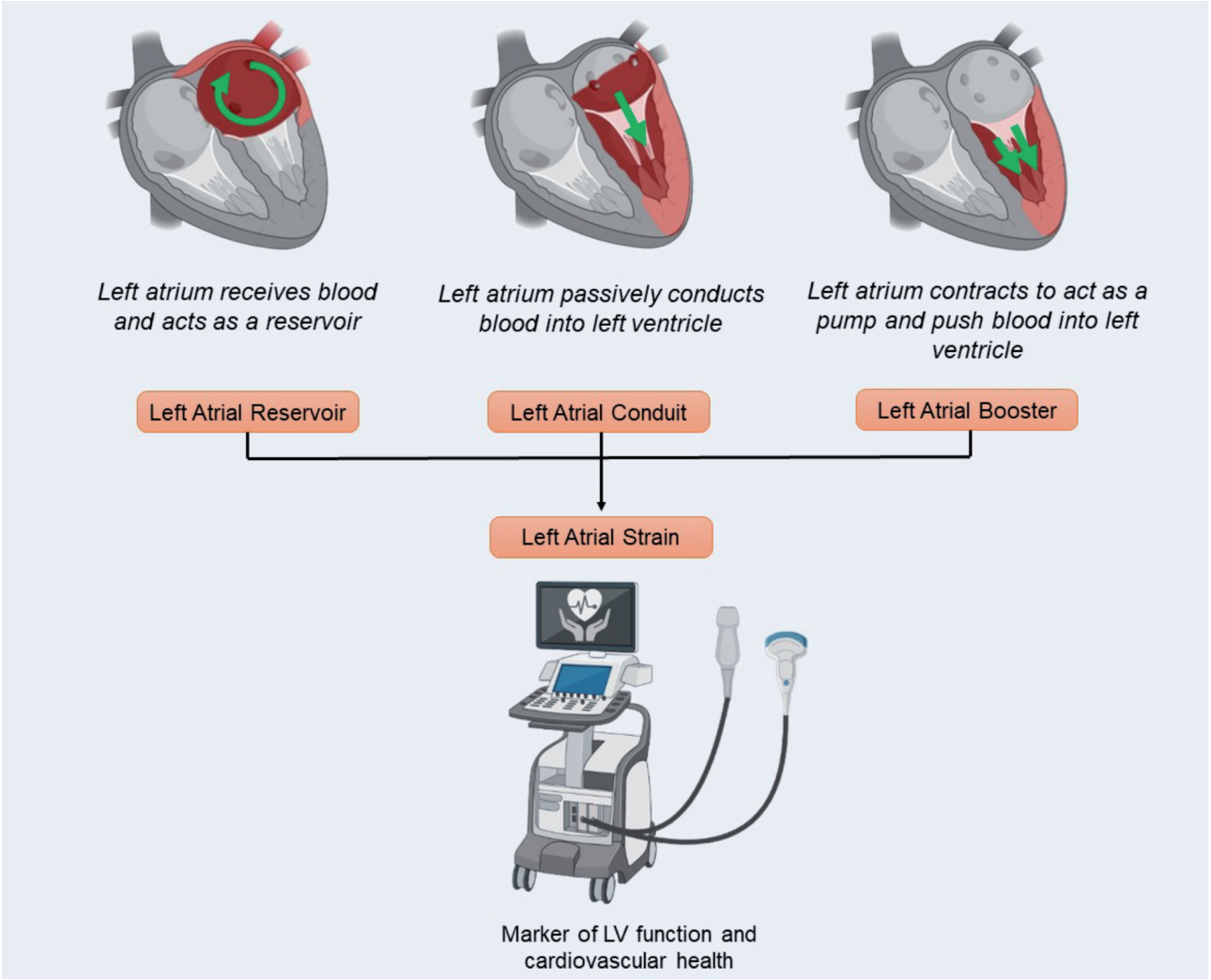

Figure 1. Parameters of left atrial strain analysis. LV, left ventricle.

Reservoir function is commonly assessed by echocardiography and is a marker of LV function and cardiovascular health; hence, an impaired LASr may be an early prognostic marker for cardiac dysfunction.[12] Moreover, its prognostic ability is further validated by a meta-analysis of 7787 patients with HF, where LASr predicted all-cause mortality and cardiovascular readmission independently.[13]

Impact of obesity on left atrial strain components

Obesity leads to a significant deterioration of LA function, measured in terms of LA strain, and is linked with poor clinical outcomes, as shown by studies conducted to assess LA strain in patients with obesity. Data from 77 patients with obesity (BMI=42.5 kg/m^2), without any significant cardiac disease, and 46 patients without obesity (BMI=25.1 kg/m^2), reported significant deterioration in LASr (32.2% *vs*. 39.6%, p<0.001), LASc (20.1% *vs*. 24.9%, p<0.001), and LASb (12.1% *vs*. 14.5%. p=0.005) in patients with obesity.[3] In extension to this, any additional increase in BMI was linked with further worsening of LA strain parameters. Further analysis consistently supported an association between obesity and poor health outcomes. For example, patients with obesity had significantly elevated systolic blood pressure (141.2 mmHg *vs*. 126.7 mmHg), and a higher risk of developing comorbidities, such as diabetes mellitus (DM) and hypertension (22.1% *vs*. 0%, p<0.001; and 29.9% *vs*. 6.5%, p<0.001), in comparison to non-obese patients.[3] However, these patients had no previous history of cardiovascular disease or other underlying comorbidities, hence indicating that existence of high BMI may alone increase risk of LA myopathy, dilation and dysfunction. These observations are consistent with findings in a study by Deal *et al.*, with 45 patients with obesity (BMI=39.2 kg/m^2), and observed significantly worse LASr in patients with obesity without any comorbidities (36.3% and 41.3%), compared to patients without obesity.[14] However, this study failed to establish any association between change in LA emptying fraction (LAEF) in patients without any comorbidities, implying that an association may exist between LAEF and more severe LA dysfunction seen in obese patients with comorbidities due to severe underlying pathophysiological impairments which further worsens cardiac health. However, obese individuals without any significant history of any cardiac disease, demonstrate signs of subclinical cardiac abnormalities,[15] and are predisposed to an elevated risk of progressing to HFpEF.[3,4] Conversely, limited small-scale data from 25 patients with obesity showed no significant differences in LAS parameters across BMI categories, highlighting heterogeneity likely due to small sample size and methodological differences.[16]

Table 1 summarizes the included studies on LAS. The included cohorts ranged in size from approximately 45 to 280 participants, with mean ages spanning the mid-40s to the late-60s. Mean BMI showed wide variation, ranging from approximately 22 to 39 kg/m^2 with normal-weight groups around 22 to 23.6 kg/m^2 and obese cohorts with mean BMIs of about 30 to 39.1 kg/m^2; several studies enrolled patients with BMI greater than or equal to 35 kg/m^2. The most commonly reported metrics were LASr and LASc. Most studies found larger LA volumes and reduced reservoir and conduit strain in obesity, and several linked visceral, epicardial, and pericardial fat to worse strain.

Impact of comorbidities in obesity on left atrial strain

Impairment in cardiac function has been observed consistently in patients with obesity and underlying comorbidities, such as in patients with obesity and comorbid type 2 DM where consistently lower LAEF were observed compared to healthier control group.[17] Comorbidities in patients with obesity can develop due to existing metabolic derangements in the body. Visceral fat plays a major role in metabolic disturbances, such as insulin resistance, inflammation, and oxidative stress, which can increase LA diameter and results in LA dysfunction, particularly in LASr and LASc.[10] In addition, type 2 DM related to insulin resistance is a prevalent comorbidity in obese patients and is associated with poor LA strain metrics. Evidence from 331 young adult patients with obesity and DM demonstrated lower LASr (45.1 *vs*. 46.6 *vs*. 52.2), LASc (32.8 *vs*. 33.1 *vs*. 36.8) and LASb (12.3 *vs*. 13.1 *vs*. 16.6) as compared to normal weight individuals.[18] Similar impairments in LA function have been observed in patients with metabolic syndrome.[19] Impairments in insulin sensitivity and signaling due to obesity-associated insulin resistance predisposes the patient to microvascular dysfunction.[20] This can occur by increased oxidative stress which leads to damage to blood vessels at a cellular level and leads to endothelial dysfunction. In healthy patients, perivascular adipose tissue (PVAT) generates vasodilatory mediators such as nitric oxide (NO).[20] However, in patients with obesity, NO secretion is reduced due to hypertrophy and hyperplasia in adipose tissue, leading to pro-inflammatory cytokines in blood which lead to low-grade inflammation and supplements the oxidative harm occurring in the patient.

HFpEF is also a common comorbidity in patients with obesity, and leads to impaired LA strain. Additionally, obesity in patients with HFpEF is also linked to higher levels of serum uric acid, indicating more severe systemic inflammation, and lower N-terminal pro brain natriuretic peptide (NT-proBNP), which is associated to elevated adipose tissue and greater plasma volume levels.[11,21,22] Obesity with HFpEF can also lead to impairment in quality of life and poor cardiac outcomes, such as poor LV filling pressures, along with LA strain. Data from a small-scale study in 75 elderly patients with obesity (BMI=38.5 kg/m^2) and comorbid HFpEF suggested a link between obesity and significantly lower functional status, measured in terms of 6-minute walk distance (6MWD), and a significantly higher LA stiffness index (0.86 *vs.* 0.53; p<0.001), as compared to normal weight group.[23] Subsequent analysis demonstrated worsening LASr (16.4% *vs* 18.2; p=0.018) and LASc (7.7% *vs* 9.1 %; p=0.028) parameters in patients with obesity.

Table 1. Summary of included studies for left atrial strain.

Study	Mean age years	BMI kg/m^2	Follow-up	Sample	Comorbidities	Measurement of left atrial strain	Left atrial strain parameters reported	Changes in LA strain parameters
Mishima *et al.*, 2022	62±10	Obese: ≥30 Overweight: 25 to <30 Normal weight: <25	-	Low CRF: 81 High CRF: 73	Hypertension, Type 2 diabetes, hyperlipidemia, coronary artery disease, obstructive sleep apnea	Transthoracic echocardiography	LAVI, LAVmax, LAVmin, LAEF, LASr and LASb, LAS-cd, LA stiffness index, LA ejection fraction	Obesity is associated with LA dilatation but preserved LA mechanical function. Obesity was associated with increased LA volumes with relatively preserved LA mechanical function.
Aga *et al.*, 2022	Control: 49.5±9.4 Obese patients: 48.1±7.1	≥35	1 year	Patients with obesity: 77 Healthy patients: 46	Diabetes Mellitus, hypertension, obstructive sleep apnea syndrome	Conventional and speckle tracking echocardiography was performed on all participants at baseline	LASr, LAS-cd, and LASct	LASr, LAScd and LASct were significantly reduced in patients with obesity compared to a non-obese control group. LASr improved 1 year after bariatric surgery.
Deal *et al.*, 2022	45±11	39.1±6.7	373 days	Patients with obesity: 45 Healthy patients: 27		Steady-state free precession MRI cine in the 2-chamber and 4-chamber orientation	LAVmax, LAEF, LA longitudinal strain	Obesity was also associated with a higher LAV max and a significantly reduced LA reservoir function. Patients with obesity had normal global LA function and normal LASb function when compared with controls. LA function improves linearly with the reduction in visceral fat.
Sawada *et al.*, 2021	57±10	23.6	-	Obese population: 67	Diabetes Mellitus, hyperlipidemia and hypertension	Speckle-tracking echocardiography	LA reservoir, conduit and pump strain	VFA accumulation was independently associated with worse LAS-cd. A significant association was observed between visceral fat accumulation and LA dysfunction
Steele *et al.*, 2020	22.1	Normal: 22.5 Obese: 36.6 T2DM: 35.8		Normal weight: 101 Obese: 114 T2DM: 116	Hypertension and T2DM	Spectral and tissue Doppler and 2-D speckle tracking measurements of diastolic function were obtained	LASr, LA conduit, and LASb	Obese and T2DM had significantly lower LASr, conduit and LASb compared to normal subjects
He *et al.*, 2022	Patients with HFpEF and obesity: 46±14 Patients with HFpEF and normal weight: 64±10 Patients with obesity: 45±11 Controls: 44±10	Patients with HFpEF and obesity: 31±2 Patients with HFpEF and normal weight: 22±2 Patients with obesity: 31±3 Controls: 22±1	-	Total: 280 Patients with HFpEF and obesity: 108 Patients with HFpEF and normal weight: 50 Patients with obesity: 72 Healthy controls: 50	HFpEF	Echocardiography with conventional and tissue Doppler imaging and CMR imaging	LAVmax, LAVi	Patients with HFpEF and obesity had lower LAVi, when compared with patients with HFpEF and normal weight. In comparison to patients with obesity and controls, patients with HFpEF and obesity had higher LAVi
Singleton *et al.*, 2021	HFpEF and obesity group: 67±5 Healthy group: 69±7	30		Patients with obesity and HFpEF: 75 Healthy controls: 53	HFpEF, Diabetes Mellitus, hypertension	Magnetic resonance imaging using feature tracking	LA stiffness index, LASb strain, LAS-cd, LASr	LA stiffness is independently associated with impaired exercise tolerance and quality of life. Participants with obesity and HFpEF had significantly lower LASr and strain rate, lower LAS-cd and strain rate, and higher LA stiffness index. LASr and LAScd were decreased in patients with obesity and HFpEF compared with . controls. LASr significantly decreased in patients with obesity

BMI, Body Mass Index; CRF, Cardiorespiratory Fitness; HFpEF, Heart Failure with Preserved Ejection Fraction; LA, Left Atrium; LAEF, Left Atrial Emptying Fraction; LASb, Left Atrial Strain booster; LAScd, Left Atrial Strain conduit; LASct, Left Atrial Strain contractile; LASr, Left Atrial Strain reservoir; LAVi, Left Atrial Volume Index; T2DM, Type 2 Diabetes Mellitus.

Pathophysiology of obesity and left atrial strain

Hypertension and obesity are key determinants of LA dilation, as shown by long-term analysis of 10-year MONICA/KORA (monitoring of trends and determinations in cardiovascular disease/cooperative research in the region of Augsburg).[24] Furthermore, obesity has a stronger association with LA enlargement than hypertension.[24] Obesity increases total and central blood volumes and stroke volume, producing chronic volume overload and higher cardiac output. This promotes LV hypertrophy and diastolic dysfunction, raises LV end-diastolic pressure and LA afterload, and eventually causes LA enlargement and impaired LA strain.[24-26] Therefore, key mechanisms in obesity include the rise in cardiac output and the LV eccentric or concentric hypertrophy, along with LV diastolic dysfunction.[27] Hypertension is also a serious concern in obese individuals, developing in approximately half of the patients with obesity, and over 60% of patients with morbid obesity.[28] In the second Nurses' Health Study, 82,882 adult women were prospectively followed for 14 years, and BMI emerged as the strongest risk factor for developing hypertension, with women with obesity having almost 5-fold higher hypertension incidence than those with BMI less than 23.0 kg/m^2.[29] The underlying mechanisms linking obesity with hypertension are complex. They include activation of sympathetic nervous system and renin angiotensin aldosterone system (RAAS), which leads to increased heart rate and cardiac output. Obesity also promotes renal tubular sodium re-absorption, which causes sodium and water retention, activating the sympathetic nervous system.[30,31] Visceral fat may also compress renal vessels and reduce renal blood flow, further worsening volume and pressure load. Moreover, insulin resistance in obesity results in loss of vasodilator effect of the hormone and elevated glucose levels.[30,31] Hypertension also increases the after-load of the LV and thus increases the workload of the myocardium which results in LV hypertrophy, and LV diastolic filling, which are linked to LA enlargement.[32]

Poor LA strain in patients with obesity also occurs due to greater LA stretch and inadequate LA outflow, which has been documented previously.[33] Obesity has been linked to elevated inflammatory markers, adipocytokines and metabolic factors, such as transforming growth factor ß1, platelet-derived growth factor, LA fibrosis, LA inflammatory infiltrates, and lipidosis in the LA tissue.[34] These factors altogether contribute to LA remodeling and dilation, hence, leading to dysfunction in the chamber. Additionally, increased pericardial and EAT deposition leads to an increased risk of HFpEF in patients with obesity. These observations support data from 6785 participants of MESA (Multi-Ethnic Study of Atherosclerosis), where analysis based on BMI indicated obesity as a leading factor for increased pericardial fat volume (55% *vs*. 10%), in comparison to normal weight patients, and also further lead to an elevated risk of HFpEF.[35] Increased pericardial fat leads a greater deposit of visceral fat, which has been previously linked to a deterioration in LA function.[33] Both pericardial and epicardial fat secrete metabolic and inflammatory factors and adipocytokines, and leads to reactions inducing atrial fibrosis, continuous fatty infiltrates in the LA myocardium, and fibrotic modification of the adipose layer in the atria.[27] Hence, all these changes culminate as LA enlargement and lead to an elevated risk of atrial fibrillation, HFpEF, stroke, and cardiovascular mortality.[36] A summary of pathophysiology is illustrated in Figure 2.

Weight loss and left atrial strain

Lifestyle

Lifestyle adjustments such as restricting caloric intake and exercise are commonly used for weight loss. Lifestyle adjustments have been shown to improve blood pressure and reduce the risk of developing incident cardiovascular disease.[17,37] In the secondary analysis of DIASTOLIC (Diabetes Interventional Assessment of Slimming or Training to Lessen Inconspicuous Cardiovascular Dysfunction) trial, patients with moderate obesity (BMI=36.1 kg/m^2) and type 2 diabetes mellitus were stratified according to routine care (n=28), aerobic exercise intervention (n=22), or low energy (≈810 kcal/day) dietary replacement (n=23) to evaluate the impact on LA strain at 12-weeks of follow-up.[17] Patients in the low energy meal replacement group had a significant reduction in BMI, fasting glucose levels, and systolic blood pressure, while there were no significant improvements in the exercise group. Moreover, patients in the low energy meal replacement had improved LASr function by +2.4% and LASb function by +2.6%, in comparison to standard care.[17] The standard care arm had no significant improvements in LA strain, while exercise training demonstrated a trend towards improvements in LASb function (1.8%) but no improvement in LASr.[17,38]

Bariatric surgery

Bariatric surgeries such as Roux-en-Y gastric bypass, sleeve gastrectomy and surgical adjustable gastric band are also commonly used for weight loss. Data from 114 patients with morbid obesity (average BMI of 48.8 kg/m^2) showed superiority of bariatric surgery, where morbidly obese patients had an insignificant change in LA volume from baseline, compared with patients who did not undergo bariatric surgery and had a rise in LA volume by 15±28 mL from baseline, at 3.6 years of follow-up.[39] These findings also corroborate with data from 65 patients with morbidly severe obesity (43.72 kg/m^2) which evaluated changes in LA function by assessing longitudinal strain in LASr, LASc and LASb parameters.[40] In this cohort of patients with severe obesity undergoing bariatric surgery, improvement in LA function was observed, where a significant increase in LASr (+3.25%) and LASc (+4.8%), however, LASb function (-2.0%) was reduced at 12.2 months of follow-up, compared to baseline.[40] The decrease in LA booster may be attributed to the enhancement of LV diastolic filling, which

minimizes the demand for LA contraction. However, in particular, Roux-en-Y gastric bypass has shown superiority over other types of bariatric surgeries in patients with morbid obesity. In a study of 37 patients with morbid obesity who underwent gastric bypass (BMI=47.9 kg/m^2) and sleeve gastrectomy (BMI=51.6 kg/m^2), gastric bypass had significantly higher reduction in epicardial fat (1.38 mm *vs*. 1.50mm) at 6 months, compared with sleeve gastrectomy.[41] Furthermore, consistently beneficial results were observed, with substantially greater reduction in LA diameter (-2.50mm *vs*. -1.78mm) and BMI (34.5 *vs*. 38.3) at 6 months with gastric bypass, compared to sleeve gastrectomy.[41]

Bariatric surgery has also shown long-term benefits in patients with obesity. In a study of 59 patients with obesity (BMI>35 kg/m^2) undergoing bariatric surgery, results 1 year after bariatric surgery demonstrated that patients, in comparison to baseline, had a significantly lower LASr (32.1% *vs*. 34.2%).[3] Consistent results were observed in long-term data

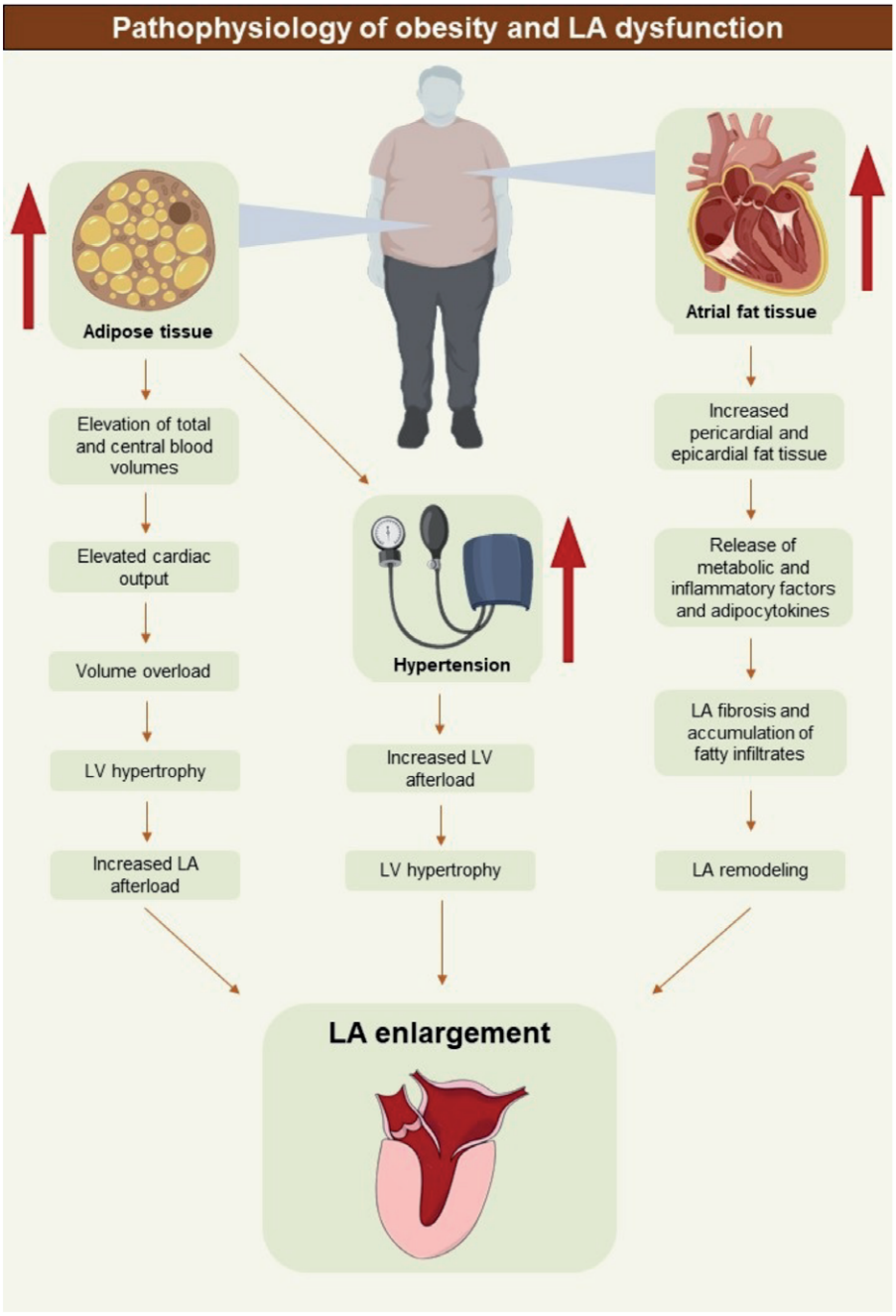

Figure 2. Summary of pathophysiology of obesity and left atrial dysfunction. LA, left atrium; LV, left ventricle.

from 52 patients with severe obesity (BMI=45 kg/m^2) undergoing abdominal ultrasound. It was observed that both visceral and subcutaneous fat regions significantly reduced by 30% and 29%, respectively, from baseline to 5 years after bariatric surgery. Conversely, the EAT significantly decreased by 14% in patients who underwent bariatric surgery.[42] A significant change in LA strain was also observed with a reduction by -1.8% after 5 years of bariatric surgery.[42] Bariatric surgery has also demonstrated superior efficacy over diet modifications. Comparative analysis in patients with obesity (BMI=39.1kg/m^2) undergoing bariatric surgery (n=17) or low glycemic diet (n=28) reported greater degree of weight loss (50.6% *vs*. 30.4%) with bariatric surgery, compared to low glycemic diet.[14] Moreover, consistently substantial improvements in LASr (+8.4% *vs*. 0.1%) and LASc (4.3% *vs*. 1.6%) functions was observed in patients achieving greater degree of weight loss with bariatric surgery, compared to patients achieving a lower degree of weight loss.[14] Hence, bariatric surgery may have led to a trend towards improvement in diastolic function, yet, differences between bariatric surgery and low-glycemic diet were not significant for LASb (3.6% *vs*. 0.3%) and LA emptying fraction (2.0 *vs* 2.0).[14]

Pharmacological therapies

Therapeutic management for patients with obesity and LA dysfunction should be focused on reducing inflammation in EAT and mitigating consequences of LA myopathy. Although there is inadequate evidence for therapy specifically targeting LA myopathy in obese patients, there are various treatments that need more exploration. The aim of reducing the variables that contribute to LA epicardial adipose tissue inflammation and expansion has gained significant attention. This is because LA epicardial fat serves as a crucial connection between LA myopathy, obesity and AF, and in the formation of LA fibrosis, where inflammation emerges as a pivotal player.[43]

Statins

The use of statins has been suggested as a potential therapeutic approach for the treatment of LA myopathy in patients with AF and HFpEF. In a meta-analysis of 23,577 patients with AF, statins significantly reduced occurrence or recurrence of AF by 51%, and showed a reduction by 76% in secondary prevention of AF.[44] Furthermore, evidence from 79 patients with AF demonstrated a reduction in mean EAT mass (5.4 cm^3 *vs*. 0.6 cm^3) after statin initiation, in comparison to placebo.[45] The anti-inflammatory effect exerted on the epicardial layer may elucidate the mechanisms underlying the mitigating impact of statins on the progression of structural and functional anomalies inherent to atrial myopathy, both in experimental models of cardiac stress and within the clinical context of AF.[46] It has also demonstrated consistent efficacy in diminishing the occurrence of both initial-onset and recurrent AF in rigorously conducted randomized control trials.[44]

Thiazolidinediones

PPAR-γ agonism exerts a modulating influence on inflammation, oxidative stress, and hypertrophy across a spectrum of tissues, encompassing both adipocytes and cardiomyocytes. Conditions precipitating adipose tissue inflammation disrupt PPAR-γ expression, yet pharmacological activation of PPAR-γ reinstates the functional integrity of epicardial fat. Notably, thiazolidinedione agents, including pioglitazone and rosiglitazone, function as PPAR-γ agonists and, consequently, mitigate inflammation in the EAT, even in presence of augmented epicardial adipogenesis.[43,47] Clinical evidence from 72 patients with multivessel coronary artery disease supports use of pioglitazone in reducing inflammatory markers.[48] Similarly, in patients with type 2 DM and metabolic syndrome, pioglitazone significantly reduced inflammation in EAT.[49] In extension to this, these agents have also exhibited potential in ameliorating cardiac inflammation and systemic inflammation markers, independently of their glycemic effects.[50]

Metformin

Metformin's capacity to activate AMP-activated protein kinase facilitates a direct anti-inflammatory response, manifested through the inhibition of nuclear factor κB. Hence, leading to reduction in epicardial fat inflammation. In the secondary analysis of PIRAMID (Pioglitazone Influence on tRiglyceride Accumulation in the Myocardium in Diabetes) study including 78 patients with type 2 DM and an average BMI of 29.3 kg/m^2, metformin initiation led to a significant reduction in activin-A levels (293 to 261 pg/mL *vs*. 293 to 302 pg/mL), in comparison to pioglitazone.[51] These findings support the use of metformin in patients with obesity and EAT inflammation, as reduction in activin-A levels is linked to reduced inflammation and risk of LA fibrosis.[43]

Sodium-glucose cotransporter 2 inhibitors

Sodium-glucose cotransporter 2 (SGLT2) inhibitors efficiently restrict the functioning of the Nlrp3 inflammasome across several organs, hence reducing the secretion of proinflammatory cytokines.[43] Furthermore, SGLT2 inhibitors exhibit the capacity to improve adipocyte hypertrophy and mitigate inflammation, consequently promoting the restoration of adipose tissue to a healthier state. In tandem with this effect, these agents also diminish cardiac hypertrophy and fibrotic changes. Importantly, in experimental models characterized by HFpEF, SGLT2 inhibitors have demonstrated the ability to thwart the progression of heart failure, underscoring their potential therapeutic relevance in ameliorating both adipose tissue and cardiac health.[52,53] In patients with type 2 DM, canagliflozin significantly reduced EAT thickness from 9.3 mm to 7.3 mm, hence, suggesting potential to lower risk of LA dysfunction.[54] Corroborating observations in patients with DM, with coexistent coronary artery disease, demonstrated significant reduction in EAT volume (-16.4 *vs*. 4.7 cm^3) after dapagliflozin, in comparison to conventional therapy.[55]

Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) receptor agonists have shown to ameliorate inflammation in cardiac tissue and coronary arteries via interrupting proinflammatory pathways which can occur in patients with obesity.[43] In patients with DM and obesity with a mean BMI of 36.1 kg/m^2, exenatide demonstrated significant reduction in EAT (-8.8 *vs* -1.2%), as compared to reference treatment under French guidelines.[56] The suppression of proliferation, reduction of inflammation, and promotion of a nutritious state are potential mechanisms by which signaling through the GLP-1 receptor in adipocytes may contribute to the reduction of EAT mass in individuals diagnosed with type 2 DM.[43] These beneficial observations in context of EAT surpass the efficacy of other therapeutic agents employed within this particular cohort. In patients with type 2 DM and BMI ≥27 kg/m^2, liraglutide reduced EAT by 36% (9.6 to 6.2 mm), with no result observed in metformin group.[57] Furthermore, it is worth highlighting that GLP-1 receptor agonists have also exhibited a higher degree of efficacy and conferred more substantial therapeutic benefits when contrasted with SGLT2 inhibitors and statins. In a meta-analysis of 1064 patients, GLP-1 receptor agonist demonstrated a greater reduction in EAT (-1.005 *vs*. -0.552 *vs*. -0.195), in comparison to SGLT2 inhibitors and statins.[58] Further subgroup analysis yielded a higher benefit from GLP-1 receptor agonist in young patients with high BMI.[58]

Ongoing therapeutic trials

The impact of EAT on the metabolic, inflammatory, and fibrotic mechanisms of the cardiovascular system have significant implications for the cardiovascular function and LA strain for patients with obesity. Therefore, due to the wide array of pathways and the distinct microenvironment of EAT, a comprehensive and innovative therapeutic approach is warranted, which particularly targets EAT. This holds significant promise in addressing the complex relationship between cardiac adiposity and LA strain, to enhance clinical results and promote better outcomes among patients with obesity. Hence, a phase 1 trial comparing ertugliflozin to glipizide is underway to observe cardioprotective effects of ertugliflozin on epicardial fat in patients with type 2 DM and insulin resistance (NCT04167761).

Clinical implications of left atrial strain in obesity

Due to the higher risk of LA myopathy in obese individuals with impaired LA strain, clinicians may want to include screening for reduced LA strain in their regular cardiovascular investigations for obese patients. This may involve evaluating LA function by LA strain using echocardiography, along with other clinical assessments, to detect initial signs of LA myopathy. In obese individuals, LA strain could provide more evidence for risk classification, as incorporation of LA strain parameters into current risk prediction frameworks or scores may aid in risk stratification and clinical decision-making. Furthermore, timely identification of patients with obesity with a risk of cardiovascular complications can help in initiation of therapy to mitigate any risk of adverse cardiovascular outcomes. LA myopathy is linked with development of AF, and a subsequently elevated risk of stroke, HF and associated mortality.[27] Risk is greater when obese patients have comorbid diabetes and hypertension.[59] As a result, early diagnosis of LA myopathy may prompt additional assessment and considerations for treatment options to avoid or treat related cardiovascular complications, such as AF or HF. In patients with obesity, impaired cardiac function can alter pharmacokinetics and pharmacodynamics, and can lower effectiveness or have more severe adverse effects of certain drugs commonly used to treat AF, HF, and stroke.[60] Therefore, regular monitoring of LA function by LA strain may be considered in obese individuals to provide insights for effectiveness of therapy and assist clinicians' decision-making for modification of treatment strategies and dose-adjustment of medications. Longitudinal assessment of LA function may also assist in recording changes in LA mechanics which can guide appropriate interventions in obese individuals. Hence, this enables lifestyle intervention and therapeutic management in patients with obesity to be modified into individualized healthcare plans that can be followed and have long-term effectiveness. These modifications aim to improve LA function and underlying pathophysiology of LA strain, including pericardial fat accumulation, fibrosis, or inflammation. Moreover, individualized treatment approach for obesity enables patients act as active partners and may yield more favorable outcomes in terms of satisfaction and adherence to therapy.

The left atrium is a promising *biomarker* for patients with HFpEF. From a practical perspective, it is important to measure LA strain correctly and to be aware of the pitfalls and limitations when measuring LA strain in patients with obesity. LA strain should be measured from apical four and two chamber views with a narrow angle in order to increase frame rate. The image acquisition should include 3-5 consecutive beats. For the analysis of LA strain there are two options: to use the tool on the machine or to use vendor-independent software tools. In the echo reports the reservoir, conduit and (in case of sinus rhythm) contractile function should be mentioned.[61,62] However, in clinical practice, the LA reservoir strain is the most widely used and best evaluated parameter. In case of low image quality in patients with obesity, LA strain should not be obtained from inadequate loops. Another easy-to-measure parameter for assessing LA function is left atrial volume (LAVI). This should be part of every transthoracic echo exam and is a robust *biomarker* of left atrial and diastolic LV dysfunction.[63]

Reliability of left atrial strain as a prognostic tool

Existing evidence of LA strain analysis in patients with obesity demonstrates the significance of LAS measurements as a reliable prognostic tool for evaluation of LA function, which sur-

passes the conventionally used markers, including current guideline recommended parameters such as LA volume indexed to body surface area.[64] LAS has been recommended as potential imaging marker by Task Force from American Society of Echocardiography and European Association of Cardiovascular Imaging.[65] Conventionally used parameters of diastolic dysfunction lack in ability to take into account several abnormalities identified in obese patients, such as variations in cardiac adipose tissue and the occurrence of systemic inflammation. Previous literature comparing patients with and without obesity employed LA strain and diastolic dysfunction to assess LA function deterioration.[3] However, changes in diastolic dysfunction between the groups were not significantly different, hence indicating its poor diagnostic ability. Additionally, LA volume may not be an accurate measure of diastolic dysfunction. This has been observed in young adult patients with obesity and comorbid type 2 DM, where control patients with normal health had a significantly greater LV volume, mainly due to larger body proportions.[18] Therefore, unlike volumetric measures of LA function, such as LA volume or LA ejection fraction, LA strain may not be influenced by changes in LV filling pressures, making it a more robust indicator of LA contractile function in patients with obesity. Hence, incorporating LA strain into the assessment of LV diastolic dysfunction offers practitioners a more extensive comprehension of their patient's cardiac status, which is crucial to make informed healthcare decisions and improve patient outcomes for patients with AF, or HF.[17,66] Moreover, in patients with HF, LA strain, particularly the reservoir function, has shown to deteriorate much earlier than occurrence of LA dilation.[18] Furthermore, a reduction in LA strain, irrespective of LA dilation, is an important prognosticator of NYHA class II-IV symptoms.[18,67-69]

Limitations of left atrial strain in obese patients

The recent American and European guidelines underscore the value of LAS, and highlighted its efficacy in providing additional insight about LA dysfunction and identifying patients at a greater likelihood for serious adverse health outcomes. However, LAS has certain limitations in obese patients. First, the lack of a general consensus regarding the characterization of LAS results in variations in quantifications across different studies.[65] Specifically, studies vary in echocardiography vendor/software, speckle-tracking algorithms, frame rates, cardiac-cycle reference points, and whether strain values are indexed to body size. All of these factors contribute to inter-study variability and inconsistent cut-off values. In addition, it should be noted that there is a lack of uniformity in the assessment of obesity, thereby potentially impeding the accurate analysis of findings. Furthermore, LAS measures in patients with obesity can vary between patients with various comorbidities, such as co-existence of hypertension, obstructive sleep apnea, and DM. This complicates the process of establishing any changes in LAS solely to obesity. Second, there is limited data regarding relation between obesity and its underlying pathophysiological mechanisms, such as myocardial fat accumulation and inflammation, and their impact on LA function which can potentially alter LAS analysis. Third, optimal echocardiographic imaging and interpretation in obese patients also presents unique challenges. The optimal modification for body dimensions in these patients is challenging. Therefore, guidelines for cardiac imaging routinely advocate adjusting LA dimension, LV mass, and valvular hemodynamics for the individuals body measurement.[70] Lastly, concerns regarding LAS as load-dependent exist.[71] Hence, assessing LA function in obese patients can be influenced by factors such as preload, after-load, and LV function. LAS parameters of reservoir, conduit, and booster depend on blood being pumped by LV contraction, as any change in contractility influences LAS of obese patients. In extension to this, discrepancies in impairment of LASr with respect to variations in LV parameters of longitudinal strain has been observed which limits the usability of LASr.[72,73]

Knowledge gaps

Methodological inconsistencies currently restrict the clinical application of LA strain in patients with obesity. Measurement heterogeneity, driven by disparate vendor software, tracking algorithms, and cardiac-cycle reference points, impedes comparison across studies.[74] Although meta-analyses provide normative values, these data rarely stratify reference ranges by BMI, and variability related to heart rate and body size persists.[75,76] Furthermore, inconsistent implementation of acquisition guidelines, such as the European Association of Cardiovascular Imaging/American Society of Echocardiography/Industry Task Force, prevents the establishment of universal diagnostic thresholds.[74] The distinct clinical role of phasic strain components also remains undefined. While LASr shows the strongest prognostic signal robustly, the pathophysiologic significance of LASc and LASb regarding atrial function requires further investigation in obese cohorts.[77] Finally, reliance on small, cross-sectional datasets limits current evidence. Validating LA strain requires large longitudinal studies using standardized protocols to link mechanics to hard clinical outcomes.

Future directions

Further evaluation is warranted to explore potential disparities in LA strain measures in patients with obesity and with or without any underlying comorbidities. Although several studies report that obesity may worsen LA function, contrasting data has been reported in a small-scale study which demonstrated no change in LAS parameters in patients with obesity.[16] However, data supporting obesity and worsening LAS comes from

studies with cross-sectional designs, as there is a lack of longitudinal studies. Due to methodological limitations, such studies fail to adequately capture the correlation between obesity and impaired LA function, or to discern long-term temporal association between changes in obesity and LA function. Longitudinal studies are better powered to demonstrate such trends in terms of disparities in gender, age, ethnicity, comorbidities and quality of life. Additionally, these studies have higher predictability to assess if patients with obesity with LA dysfunction had a greater likelihood of worsening cardiac outcomes. Long-term studies can also assess the impact of various weight reducing interventions and their duration in order to achieve greater improvements in LA function. These studies may also assess the impact of impaired LA function on cardio-kidney-metabolic health.[78] Therefore, longitudinal studies are warranted for more conclusive evaluation of LAS and obesity, and can better inform clinical practice and public health regulations.[78] However, as LAS is a load-dependent measure, its dependence on LV function should also be taken into consideration in future clinical studies. As highlighted earlier, LAS does not have a consistent definition.[62] Future investigators should focus on developing consensus on uniform cut-off values and classifications of LAS, in order to allow it to be incorporated into, and improve prognostic ability of existing risk stratification models, hence, improving likelihood of identifying patients at high-risk of cardiovascular complications who may require urgent therapy.[62] Since LAS is also impaired in patients with HFpEF and obesity, therefore, optimal cut-off values can also help distinguish patients with subclinical diastolic function and can further help in characterization of HFpEF.[62] Lastly, future investigators should focus on using LAS conduit, instead of LAS reservoir, due to discrepancies and controversy associated with LASr.[62,79]

Conclusions

Obesity is a major risk factor for complications such as HFpEF, atrial fibrillation and LA enlargement. Moreover, hemodynamic stress and hypertension which accompany obesity increase the risk of LV hypertrophy and subsequent LA enlargement, which increases LA dysfunction and leads to poor filling of LV. LA strain analysis is a preferred prognostic tool for patients with obesity, due to its results being independent of LV filling pressures and other volumetric determinants. Existing evidence reports that LA strain parameters, particularly LASr, are more important in predicting mortality and hospitalizations in patients with obesity. Such prognostic ability is necessary for these patients, as obesity has demonstrated impaired quality of life and poor clinical outcomes in these patients, and a high risk of progression into worse clinical conditions such as HFpEF, hence, making it imperative to tackle obesity primarily to reduce the burden of its complications. Weight loss techniques such as meal replacement plans have demonstrated beneficial results over exercise regiments, however, bariatric surgery has demonstrated higher efficacy than meal replacement weight lost programs in morbidly obese patients, with long-term improvements in these patients.

Contributions

All the authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work. SDA and FK contributed as senior authors.

Conflict of interest

MSK has participated in a data safety monitoring board or advisory board for Bayer, and reports consulting fees from Bayer, Novartis, and Boehringer Ingelheim. SDA reported receiving grants from Abbott Laboratories; receiving personal fees from Actimed Therapeutics, Alleviant, AstraZeneca, Bayer, Berlin Heals, BioVentrix, Boehringer Ingelheim, Brahms, Cardiac Dimensions, Cardior Pharmaceuticals GmbH, Cordio, CSL Vifor, CVRx, Cytokinetics, Edwards Lifesciences, Farraday Pharmaceuticals, GSK, HeartKinetics, Impulse Dynamics, Lilly, Mankind Pharma, Medtronic, Novartis, Novo Nordisk, Occlutech, Pfizer, Regeneron, Relaxera, Repairon GmbH, SCIRENT Clinical Research and Science, Sensible Medical, Servier, Vectorious Medical Technologies, Vivus, and V-Wave; and being a named co-inventor of 2 patent applications regarding midregional proatrial natriuretic peptide, but does not benefit personally from the related issued patents. All other authors have no conflict of interests.

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