Early Access
Case Report

Chest Disease Reports

eISSN 2039-4772

https://www.pagepressjournals.org/index.php/chest/index

Chest Disease Reports 2024 [online ahead of print]

To cite this article:

Fulvio Cacciapuoti, Ciro Mauro, Davide D'Andrea, et al. Epicardial Adipose Tissue and cardiovascular disease: unmasking the hidden culprit. Chest Disease Reports. 2024;12:12044. doi:10.4081/cdr.2024.12044

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Epicardial Adipose Tissue and cardiovascular disease: unmasking the hidden culprit

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Key words: Epicardial Adipose Tissue, residual cardiovascular risk, GLP-1 receptor agonists, atherosclerosis, case report.

Authors' contributions: Fu. C. and Fe. C. conception and drafting of the manuscript; CM and DDA. performed the angiogram; Fu. C. provided echocardiographical measurements; CL provided CT measurements; Fu. C., VC and Fe. C. verified the analytical methods. All authors discussed the

results, have read and approved the final version of the manuscript, and agreed to be held accountable for all aspects of the work.

Conflict of interest: Fu. C. has been a speaker and advisory board member for Novo Nordisk.

Funding: VC was supported by the CardioPath PhD Program.

Consent to participate: written informed consent was obtained from the patient for publication of this case report, including accompanying images.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Abstract

The role of Epicardial Adipose Tissue (EAT) has evolved in the latest years from a passive energy repository to a dynamic contributor in cardiovascular health. This case discusses the role of EAT in residual cardiovascular risk and the potential benefits of GLP-1 receptor agonist liraglutide in mitigating its effects.

We describe the case of a 62-year-old male patient, obese, hypertensive, and with a history of ischemic heart disease, was admitted to the emergency room complaining palpitations and shortness of breath. The ECG showed atrial fibrillation with rapid ventricular response with evidence of a new-onset left bundle branch block. The echocardiogram revealed heart-rate dependent regional dyskinesias, while both echocardiogram and CT scan evidenced the presence of EAT. Intrastent restenosis in the left anterior descending artery was found and treated with percutaneous revascularization. The patient was initiated on liraglutide to address residual cardiovascular risk. Follow-up showed reduced Low-Density Lipoprotein Cholesterol (LDL-c) and High-Sensitivity C-Reactive Protein (hs-CRP) levels, as well as decreased EAT thickness and Body Mass Index (BMI).

EAT's contribution to residual cardiovascular risk underscores the need for targeted interventions and treatments. Glucagon-Like Peptide-1 Receptor Agonists (GLP-1-RA) like liraglutide offer promise in addressing this risk, representing a potential venue for therapeutic exploration.

Introduction

Epicardial Adipose Tissue (EAT), once regarded as a passive energy depot, has recently emerged as a pivotal player in the intricate landscape of cardiovascular health.[1] Positioned between the heart's outer layer and the underlying myocardium, the significance of EAT extends far beyond its adipose composition. Research has unveiled its multifaceted role, encompassing both metabolic and inflammatory functions, making it a critical determinant of cardiovascular risk.[2,3]

We present the case of a 62-year-old patient with a history of coronary artery disease who was admitted to the emergency room due to sudden palpitations and dyspnea. After undergoing coronary revascularization, the patient was treated with a multidisciplinary approach, including medication and lifestyle modification, aimed to reduce EAT thickness.

Case Report

A 62-year-old patient was admitted to the emergency room due to the sudden onset of palpitations and dyspnea that started about 20 minutes earlier. The patient was an obese (Body Mass Index, BMI, of 32), hypertensive with good pharmacological control, suffering from chronic coronary syndrome and Obstructive Sleep Apnea syndrome (OSA) treated with nighttime Continuous Positive Airway Pressure (CPAP). He had previously undergone percutaneous coronary revascularization on the left anterior descending artery with the implantation of a drug-eluting stent four years earlier. The patient was on home therapy with bisoprolol 2.5 mg, ramipril 5 mg, ASA 100 mg, ezetimibe 10 mg and rosuvastatin 10 mg. Upon admission, the patient was symptomatic for palpitations and shortness of

breath in the absence of chest pain. The initial electrocardiogram showed atrial fibrillation with an average heart rate of 131 bpm and left bundle branch block that was not present in the last check-up. The echocardiogram, during high ventricular response atrial fibrillation, showed akinesia of the apex and apical segment of the left ventricular anterior wall, accompanied by a significant reduction in ejection fraction (35% evaluated using the Simpson's method). Moreover, a hypoechoic zone between the ventricular wall and the visceral pericardium with a thickness of 1.21 cm was also evident (Figure 1; Video 1), which was recognized as EAT. The presence of adipose tissue was confirmed in the pericoronary region upon subsequent CT scan examination (Figure 2) that reported an EAT volume of 165 mL. The blood pressure was 145/70 mmHg and the oxygen saturation (SpO2) on room air was 97%. After restoring sinus rhythm through intravenous administration of amiodarone, the patient was admitted to the cardiology department. A new echocardiogram, performed after the restoration of sinus rhythm and with a heart rate of 65 bpm, showed global and segmental contractility within normal limits, with a left ventricular systolic function of 55% (calculated using the biplane Simpson's method). Laboratory tests on admission showed: troponin I 0.1 ng/mL (N.V.<0.3); creatinine 0.8 mg/dL (N.V. 0.7-1.2); glucose 92 mg/dL (N.V. 70-110); Low-Density Lipoprotein cholesterol (LDL-c) 62 mg/dL (N.V. 25-50 for risk profile); High-Sensitivity C-Reactive Protein (hs-CRP) 3.7 mg/L (N.V.<3.0 mg/L). The detection of a new onset left bundle branch block during paroxysmal atrial fibrillation could be indicative of either ischemic heart disease or an intrinsic pathology of the conduction system. Suspecting a progression of coronary artery disease due to dyspnea, QRS widening, and regional wall motion abnormalities during high ventricular response atrial fibrillation, a coronary angiography study was scheduled. The angiogram revealed a significant intrastent

restenosis in the left anterior descending artery with disease progression to the middle segment (Figure 3A; Video 2), and it was treated with percutaneous revascularization (Figure 3B; Video 3). Furthermore, to reduce residual cardiovascular risk, the patient was started on the Glucagon-Like Peptide-1 Receptor Agonist (GLP-1-RA) liraglutide, titrated up to a dose of 2.4 mg per day, and entrusted to a weight control and lifestyle correction program. The patient was discharged on the sixth day in good hemodynamic condition, on dual antiplatelet therapy, and continuing treatment with rosuvastatin 10 mg and ezetimibe 10 mg.

Outpatient follow-up showed a progressive reduction in LDL-c levels to 46 mg/dL and hs-CRP levels to 0.8 mg/L within the first six months. No further episodes of arrhythmia or dyspnea were reported in the next 12 months. Additionally, after one year of therapy, both Computed Tomography (CT) and echocardiographic control showed a significant reduction in EAT thickness (138 mL and 0.799 cm respectively) (Figure 2, Figure 4, Video 4), while the BMI decreased to a value of 26. Specifically, the echocardiographic quantification of EAT was performed using a long-axis parasternal approach, while the CT parameter was measured using a universal imaging software for 2D, 3D and 4D reading and advanced visualization (Syngo.via, Siemens Healthineers, Germany). Furthermore, along with weight reduction, nighttime apnea events have also decreased with a reduction in the Apnea-Hypopnea Index (AHI), no longer requiring nighttime CPAP therapy and further contributing to the reduction of residual cardiovascular risk.

Discussion

This case prompts extensive contemplation concerning the management and mitigation of residual cardiovascular risk in patients with ischemic heart disease undergoing revascularization, with a specific focus on the role of epicardial adipose tissue in atherogenesis. The reduction of residual cardiovascular risk is one of the key therapeutic aspects in the management of patients with chronic coronary syndrome undergoing revascularization.[4] In this regard, obesity control has been associated with a decrease in the incidence of heart failure, ischemic heart disease, myocardial infarction, and cerebrovascular event. Despite advances in the management of ischemic heart disease and its major risk factors, the recurrence of coronary events and the progression of atherosclerotic disease indicate that the control of residual cardiovascular risk is not always optimal. In particular, data from the EUROASPIRE IV and V surveys have shown that, among patients hospitalized for ischemic heart disease, 34.9% of patients were obese, and 46% were overweight.[5] Furthermore, over 80% of these patients failed to achieve their target weight. In recent years, research has focused on the role of EAT as a factor that can contribute to maintaining high cardiovascular risk in general, and coronary risk in particular.[6] The accumulation of lipid tissue between the outer layer of the heart and the underlying myocardium has long been considered a "passive" energy reserve, devoid of metabolic activity. On the contrary, an increasing number of evidence have demonstrated its active role as an endocrine organ capable of secreting numerous molecules, including cytokines, adipokines, and free fatty acids, which can influence nearby cardiac structures and promote both the development and progression of atherosclerosis. Several studies have shown a direct correlation between the presence of EAT and the incidence and severity of coronary atherosclerotic disease. Obesity, especially visceral obesity, is one of the main cardiovascular risk factors, contributing to the pathogenesis of conditions such as

dyslipidemia, type 2 diabetes, hypertension, heart failure, and ischemic heart disease. Advances in imaging techniques have allowed for a more detailed characterization of adipose tissue, enabling the accurate study of visceral fat deposits, including EAT, which is now universally recognized as an independent indicator of cardiovascular risk. Currently, echocardiography is the quickest and most repeatable method for recognizing EAT, although it is less precise compared to techniques such as CT that is more reliable method in estimating volume, characteristic and distribution of EAT. Numerous studies have shown that the presence of EAT, especially if distributed in the pericoronary region (PCAT), is associated with a more frequent and early development of coronary atherosclerosis, regardless of BMI.[7] Therefore, the recognition and estimation of EAT volume is becoming a new therapeutic target both in primary and secondary cardiovascular prevention. An explanation for this phenomenon lies in the nature of EAT itself, which is present from birth and undergoes continuous changes over time, with different characteristics from other visceral fat deposits. During early life, EAT is rich in brown adipocytes, which have thermogenic and cardioprotective functions. As years go by, the proportion of brown adipocytes progressively decreases, making way for macrophages with pro-inflammatory and profibrotic activity, factors that promote the development of various cardiovascular conditions, including atrial fibrillation, heart failure, and ischemic heart disease, depending on the regional distribution. The presence of PCAT not only leads to lipid infiltration of the coronary wall and volumetric enlargement of atherosclerotic lesions but also promotes the development of a pro-inflammatory state due to increased synthesis of cytokines (IL-6, TNF) and adipokines (resistin, chemerin, serglycin, *etc*.).[8] This condition, when combined with hyperglycemia, is burdened by increased oxidative stress, resulting in endothelial damage and the destabilization of

coronary plaques. Previous studies on experimental animals have demonstrated that surgical removal of EAT, although not reducing plaque volume, slows the progression of atherogenesis[9] while, after acute coronary syndrome, reduces the expression of TNF-α and interleukin-1 beta, slowing down lipolysis and weakening the inflammatory response. Due to these characteristics, researchers are increasingly interested in the presence of EAT, considering it as a new therapeutic target for reducing residual cardiovascular risk in patients with ischemic heart disease. Various molecules have shown efficacy in reducing EAT volume, including statins, Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i), and GLP-1-RA. Among them, liraglutide, a synthetic GLP-1 analogue, has been found to effectively and safely reduce visceral adipose tissue, including epicardial adipose tissue, reducing its harmful effects on the cardiometabolic aspect in both diabetic and non-diabetic patients.[10,11] The mechanisms of action of liraglutide on EAT are not yet fully understood, but one of the possible dynamics involved could be the presence of GLP-1 receptors in visceral adipose tissue.[12] Furthermore, the favorable effects that the use of liraglutide would exert on the inflammatory component of the coronary plaque should be mentioned. In fact, myocardial PET studies have shown a significant reduction in the uptake of the radiotracer [64Cu]Cu-DOTATATE after 26 weeks of treatment with the GLP-1 receptor agonist, probably due to its effects on macrophages and modulation of pro-inflammatory signaling.[13]

In our case, the decision to introduce liraglutide was driven by the need to influence weight reduction and the lipid content within the epicardium, regardless of glycemic status. Furthermore, the beneficial effect of weight reduction on obstructive sleep apnea syndrome should also be emphasized, as it

significantly contributes to defining residual cardiovascular risk, especially in heart failure with preserved ejection fraction.[14]

Further studies will be essential to fully understand the effects of liraglutide on EAT. Great expectations are placed on the results of the SELECT study (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity), currently underway, which aims to evaluate the cardiovascular effects of another GLP-1-RA, semaglutide, on overweight and obese non-diabetic patients with previous history of cardiovascular disease.[15]

In conclusion, visceral obesity is an important cardiovascular risk factor that should be identified and promptly treated. For this reason, the echocardiographic estimation of EAT should be included in the standards for assessing residual cardiovascular risk, particularly in patients with known ischemic heart disease. In patients with cardiometabolic syndrome (ischemic heart disease, diabetes, hypertension, obesity, dyslipidemia), especially those who have already undergone coronary revascularization interventions, GLP-1 receptor agonists should be considered to enhance the effectiveness of the therapeutic arsenal for reducing EAT, with the aim of controlling residual cardiovascular risk.

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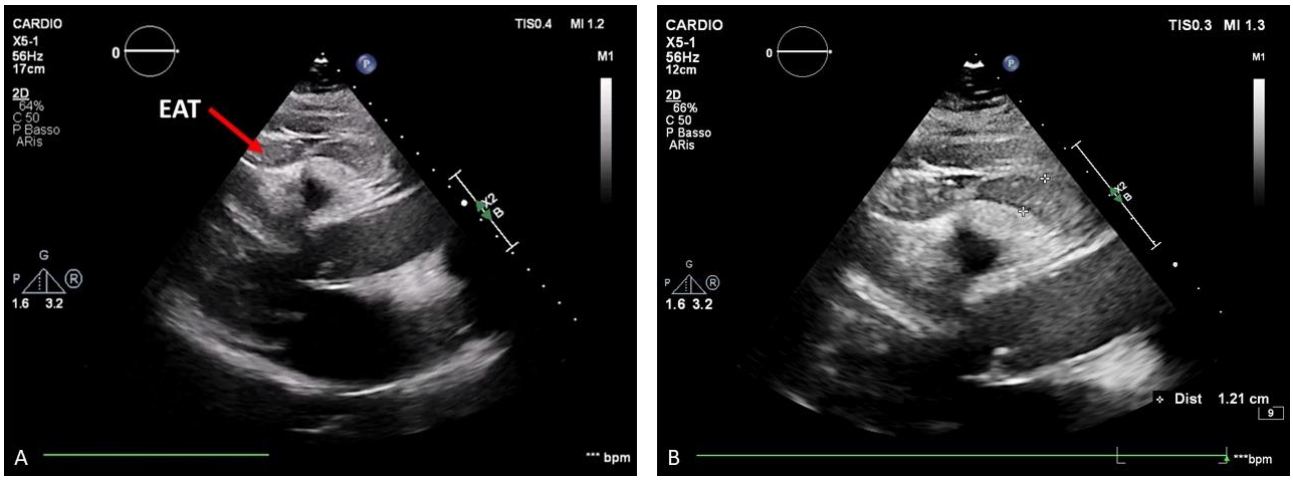

Figure 1. Two-dimensional echocardiography in parasternal long-axis view. Evidence of epicardial adipose tissue (arrow) (A); measurement of EAT thickness (B).

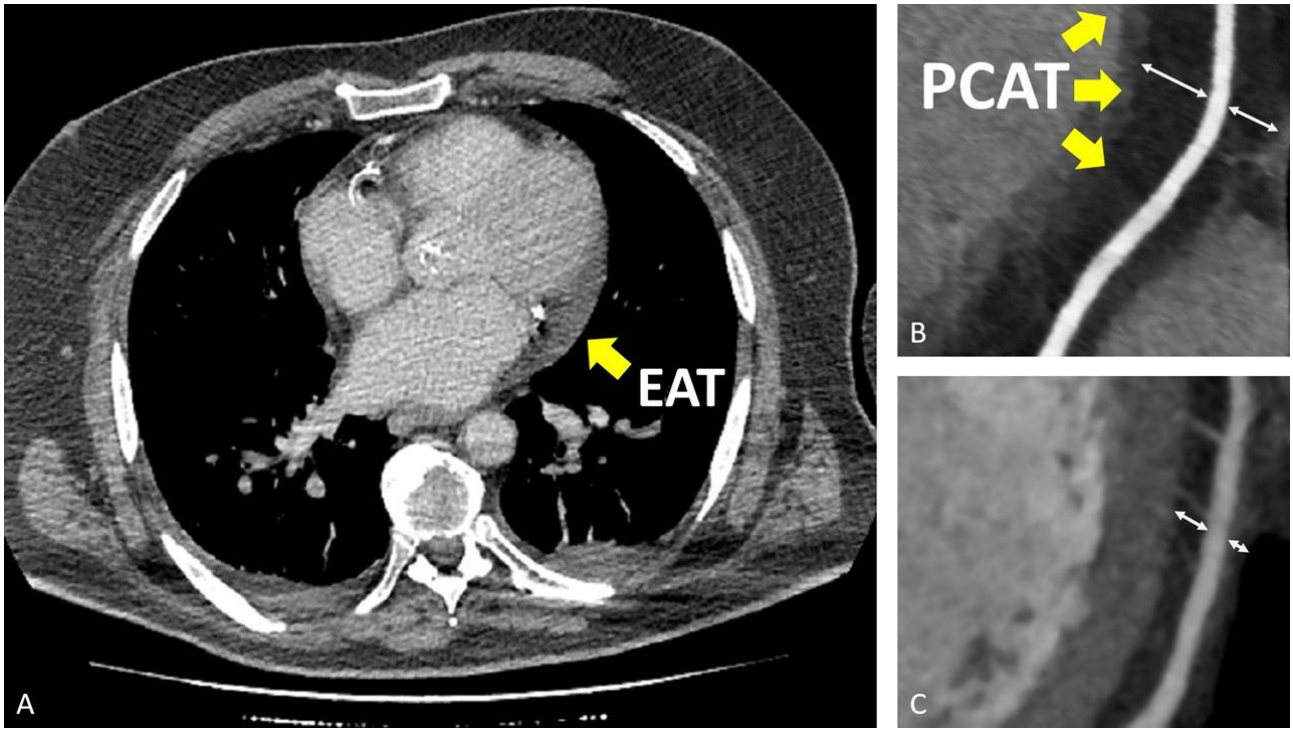

Figure 2: Thoracic Computed Tomography (CT) showing evidence of epicardial adipose tissue (A); detailed coronary CT showing evidence of pericoronary adipose tissue (B); detailed coronary CT at follow-up showing reduction of pericoronary adipose tissue thickness (C).

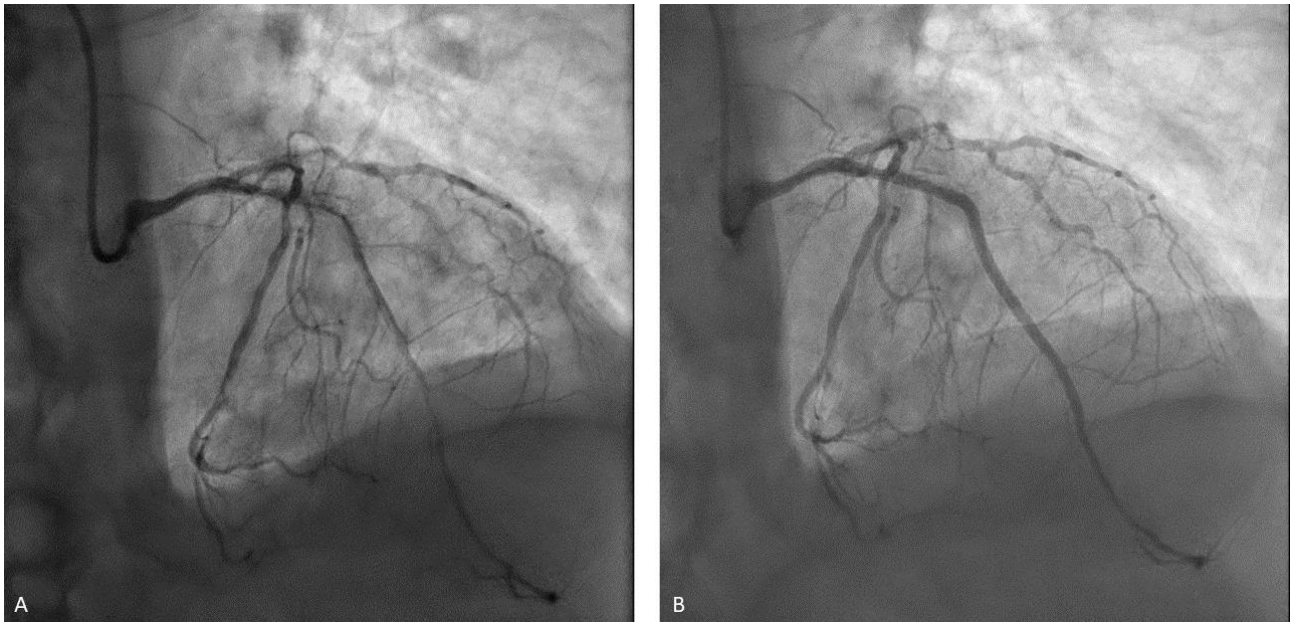

Figure 3: Coronary angiography showing evidence of intrastent restenosis on the left anterior descending artery and disease progression (A); post-revascularization examination (B).

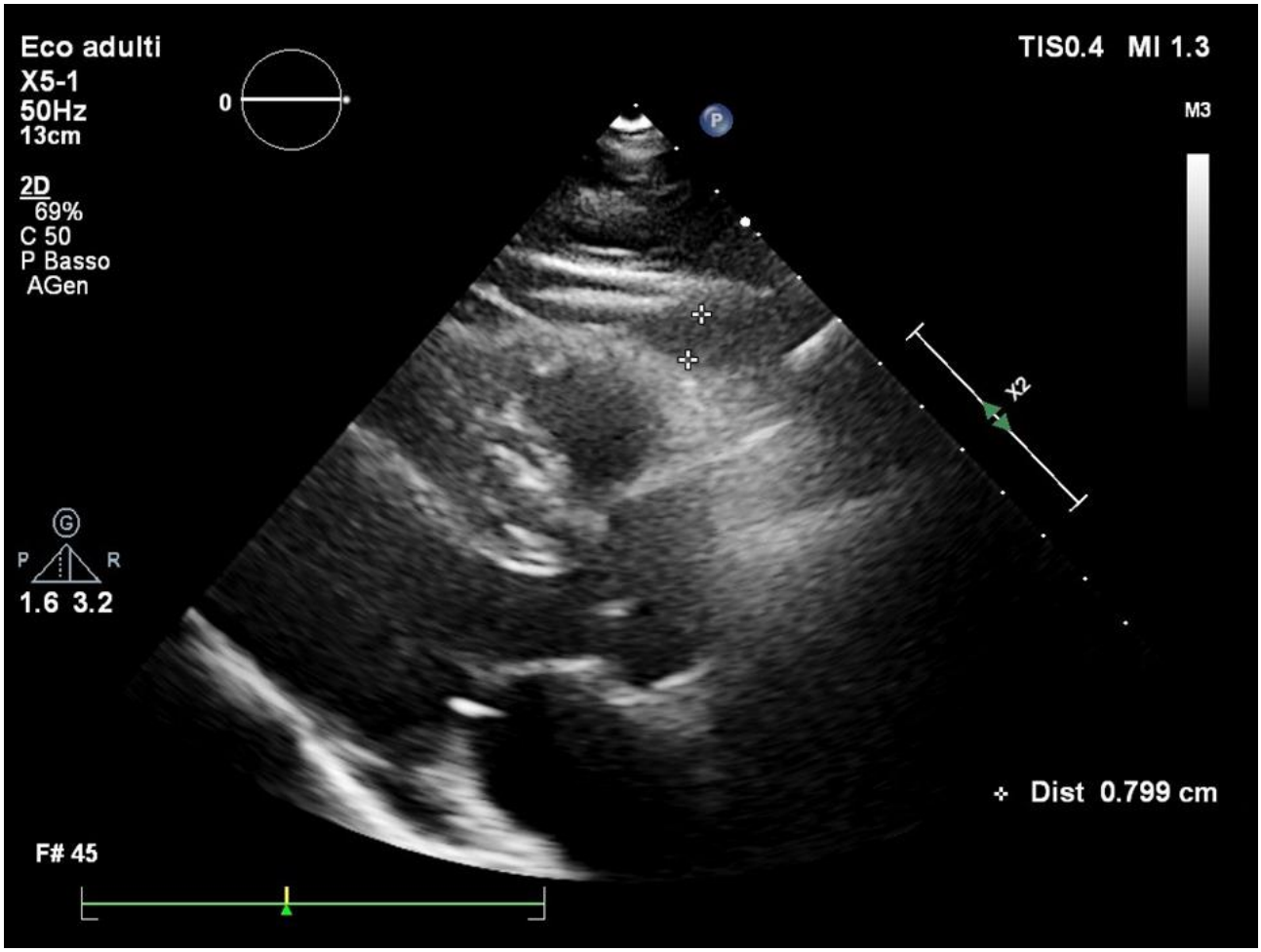

Figure 4. Follow-up two-dimensional echocardiography in long-axis parasternal view. Reduction of EAT thickness.