

Original Article

Echocardiographic epicardial adipose tissue as a new indicator of cardiovascular risk: A review of article

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(Received: 25 December 2015; Revised: 7 May 2016; Accepted: 14 June 2016)

Abstract:

Background and Purpose: Epicardial fat is the true visceral fat located around the heart, particularly around sub-epicardial coronary arteries that may locally interact and modulate the coronary arteries and myocardium through paracrine or vasocrine secretion of anti-inflammatory and proatherogenic cytokines. Most previous studies have used echocardiography and reported controversial results, probably due to differences in measuring techniques and study population.

Materials and Methods: A review of literature was conducted using the PubMed and Google Scholar databases in addition to Google and Yahoo search engines. The purpose was to look for articles describing the association between echocardiographically measured EAT and the major related outcomes including coronary artery disease, left ventricular systolic, diastolic dysfunction, and atrial fibrillation. Finally, 34 articles were included in the results of the present review.

Result: The potential role of echocardiographic epicardial fat thickness as a marker and predictor of cardio metabolic risk has been suggested.

Conclusion: The potential role of echocardiographic epicardial fat thickness as a marker and predictor of cardio metabolic risk, metabolic syndrome, excess visceral fat accumulation, insulin resistance, subclinical atherosclerosis, and CAD has been documented in the present study.

Keywords: Atherosclerosis; Coronary Disease; Echocardiography; Epicardial Adipose Tissue; Epicardial Fat; Obesity

1. Introduction

Epicardial fat is the true visceral fat located around the heart, particularly around sub epicardial coronary arteries (1). Epicardial and intra-abdominal fat derive from brown adipose tissue within embryogenesis (2). Because of the close anatomical relationship to the heart, and the absence of fascial boundaries, epicardial adipose tissue (EAT) may locally interact and modulate the coronary arteries and myocardium through paracrine or vasocrine secretion of anti-inflammatory and proatherogenic cytokines (3).

It can secrete a number of bioactive molecules, such as adiponectin, resistin and inflammatory cytokines (4). Interestingly, inflammatory mediators originating outside the coronary artery can also induce reciprocal changes in the inner layer of intima by diffusion from outside to inside (5). Therefore, increased EAT might act as an inflammatory organ, which affects vascular function (6). More direct measurements of visceral fat, including magnetic resonance imaging (MRI) and/or CT, are certainly accurate, but they are expensive and unmanageable, especially if they are planned to be performed in clinical practice. At the same time, epicardial fat thickness can be measured in two-dimensional (2D) echocardiography; the first suggested by Iacobellis et al. as Standard parasternal long-axis view, and second, short-axis view from 2D images which enables the most precise measurement of epicardial fat thickness on the right ventricle, with ideal cursor beam direction in each view. Echocardiographically, epicardial fat is usually determined as the nearly echo-free space between the outer wall of the myocardium and the visceral layer of

pericardium; its thickness is measured perpendicularly on the free wall of the right ventricle at end-systole in 3 cardiac cycles. Epicardial fat thickness is also reduced during diastole. Therefore, it is preferable to measure its thickness at end-systole at the point on the free wall of the right ventricle with ultrasound beam aligned in a perpendicular style, and using the aortic annulus as an anatomic marker (7).

The literature on articles describing the association between echocardiographically measured EAT and the major related outcomes including coronary artery disease, left ventricular systolic and diastolic dysfunction and atrial fibrillation was reviewed. This survey was performed through using the data bases Pub Med, Google Scholar, as well as Google and Yahoo search engines. For this purpose and to find the title and summary of the article, the following key words were used: epicardial, pericardial, sub epicardial, fat, adipose.

A normal upper-limit value for epicardial fat thickness has not been accepted. Epicardial fat thickness changes from a minimum of 1 mm to a maximum value of almost 23 mm. Iacobellis et al. found its median thickness to be 7 mm in men and 6.5 mm in women in a large population of patients who underwent transthoracic echocardiography for standard clinical indications. Furthermore, they indicated that an epicardial fat thickness of 9.5 mm is associated with clinical signs of insulin resistance (2).

When other cardio metabolic variables are separately evaluated, epicardial fat could also be independently related to blood pressure (8), low-density lipoprotein cholesterol (8), fasting

glucose (9), and inflammatory markers (10, 11). Echocardiographic epicardial fat thickness is particularly higher in persons with impaired fasting glucose, a prediabetes condition, than in norm glycemic individuals, suggesting its potential role as an additional tool for diabetes-related cardiac risk stratification (9). According to the previous research, the majority of population-based clinical studies have described excellent inter-observer and intra-observer agreement for epicardial fat thickness measurement (3, 7, 12). Intra-class correlation coefficients have ranged from 0.90 to 0.98 and from 0.93 to 0.98, respectively, indicating good reproducibility and reliability. Concordance of long-axis and short-axis average epicardial fat thickness measurement was also excellent at 0.98 (95% confidence interval, 0.97-0.98) (3). Hence, the aim of present study was a review on the value of echocardiographic assessment of EAT in the prediction of CAD severity and its potential role as a marker and predictor of cardio-metabolic risk.

2. Materials and methods

A review of literature was conducted using PubMed and Google Scholar databases as well as Google and Yahoo search engines. The main purpose was to describe the association between echocardiographically measured EAT and major related outcomes including coronary artery disease, left ventricular systolic, and diastolic dysfunction and atrial fibrillation. Accordingly, 34 articles were included in the results of the present review.

In 2007, Ahn et al. measured epicardial fat thickness in 527 patients undergoing their first coronary angiography. They found that

epicardial fat was thicker in subjects with CAD than in those without it. Ahn et al. also found that the patients with unstable angina had thicker epicardial fat measurements than those with stable angina or atypical chest pain (11). In 2008, Eroglu et al. assessed the association between epicardial fat thickness and coronary atherosclerosis in 150 patients (100 patients with CAD and 50 patients with normal coronary arteries evaluated by coronary angiography). Epicardial fat thickness was measured by echocardiography at end-diastole. Epicardial fat thickness was documented to be significantly higher in patients with CAD as compared with those with normal coronary arteries. Furthermore, thickness increased with the severity of CAD, and the Gensini score was significantly correlated with epicardial thickness (13).

In 2013, Nabati et al. conducted a historical cohort study on 143 patients, 40 to 87 years old, admitted for coronary angiography. The patients underwent transthoracic echocardiography and measurement of epicardial fat thickness in parasternal long-axis view at end-systole for 3 cardiac cycles. The findings showed that epicardial fat thickness was significantly correlated with the existence and severity of coronary artery disease ($P < 0.001$). There was also a trend toward lower plasma high-density lipoprotein in males with thicker epicardial fat. Furthermore, Nabati et al. concluded that an epicardial fat thickness equal to or more than 7 mm may identify an individual with higher probability of having coronary atherosclerosis (14).

Influence of epicardial fat on LV (left ventricular) mass and diastolic function:

Echo Doppler studies have reported that patients with asymptomatic LV diastolic dysfunction have a higher incidence rate of all-cause mortality. Mild diastolic dysfunction and moderate-to-severe dysfunction were associated with 8.3-fold and 10.2-fold increased risks of mortality, respectively. The overall mortality rates of symptomatic patients with diastolic or systolic heart failure are very similar (15). On the other hand, increased LV mass and LV hypertrophy are independent cardiovascular risk factors. Increased epicardial fat thickness has been associated with changes in LV mass and diastolic function, as detected by echocardiography (16, 17). Echocardiographic LV mass is also significantly correlated with the amount of epicardial fat thickness in persons with a wide spectrum of adiposity, independent of body mass index and age (16). An increase in epicardial fat thickness is also significantly correlated with enlarged atria and impaired right ventricular and LV diastolic filling in morbidly obese individuals (18). The primary abnormality of myocardial relaxation is characterized by a decrease in the trans-mitral peak early velocity (E wave), an increase in the trans-mitral peak late velocity (A-wave), and a decrease in the E/A ratio. Additionally, a decrease in the early diastolic mitral annular motion (e') is observed to be related to a decrease in LV elastic recoil, which is noted as an early sign of ischemia and impaired relaxation. Using the E/ e' ratio, a ratio < 8 is usually associated with normal LV filling pressures, whereas a ratio > 15 is associated with increased filling pressures. When the E/ e'

value is between 8 and 15, other echocardiographic indices should be used (19). In 2013, Lin et al. conducted a cross-sectional study on 149 patients with preserved left ventricular systolic function who were undergoing peritoneal dialysis. LV diastolic dysfunction was diagnosed (according to the European Society of Cardiology guidelines) and epicardial fat thickness was measured by echocardiography. The patients without LV diastolic dysfunction were used as controls. The persons with LV diastolic dysfunction had higher levels of hs CRP, more visceral and peritoneal fat, and thicker epicardial fat than controls. Visceral adipose tissue, hs CRP, and epicardial fat all significantly correlated with LV diastolic dysfunction. The Multivariate regression analysis showed that the relationship between visceral adipose tissue and LV diastolic dysfunction was insignificant, whereas epicardial fat was the most powerful determinant of LV diastolic dysfunction. Epicardial fat thickness also correlated significantly with the ratio of trans-mitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (20).

Correlation with coronary microvascular dysfunction (CMVD):

Epicardial coronary artery stenosis is usually responsible for myocardial ischemia. In the past 30 years, studies have shown that abnormalities in coronary microcirculation may also cause myocardial ischemia (21). Coronary microvascular dysfunction is often suggested in patients with typical chest pain and abnormal stress test results indicative of myocardial ischemia, in whom also coronary angiography

fails to show fixed stenosis in epicardial coronary arteries (22).

Several mechanisms have been proposed for its pathophysiology, including smooth muscle cell hypertrophy, impairment of smooth muscle cell relaxation, and enhanced vasoconstrictor activity in coronary microcirculation (21). In patients with non-ST-elevation myocardial infarction, acute coronary syndrome and normal coronary arteries, a one-year rate of death from myocardial infarction was 1.2%, and a recurrence of unstable angina was 8.4% (23).

Another case-controlled study was conducted on 124 patients, aged 40 to 91 years. A matched set of 62 symptomatic and 62 asymptomatic patients underwent an exercise electrocardiogram and transthoracic echocardiography. Coronary angiography was performed in the patients with abnormal exercise test results. The participants of the study were patients without coronary artery disease. EFT was measured by transthoracic echocardiography in all patients. It was documented that the epicardial fat thickness was significantly higher in patients with positive exercise test results (but normal epicardial coronary arteries) as compared with patients with negative exercise test results. They concluded that the patients with increased epicardial fat thickness are at an increased risk of developing angina, recurrent hospitalisation, and adverse outcomes, even with normal epicardial coronary arteries (24).

In another study, Sade Le et al. assessed the association between epicardial fat tissue and coronary flow reserve on 68 women who underwent coronary angiography and had no objective CAD. It was found that menopause,

hypertension, and abnormal stress tests were significantly more prevalent. Insulin resistance and epicardial fat thickness were also found to be significantly increased in women with microvascular dysfunction as compared with those without it (12).

Epicardial fat in atrial fibrillation (AF):

AF is the most common arrhythmia found in clinical practice (25). It also accounts for 1/3 of hospital admissions for cardiac rhythm disturbances that are associated with significant morbidity and mortality (26). Obesity represents an important risk factor for new-onset AF. Epidemiological studies have reported an association between epicardial fat and AF (27-32). At the same time, epicardial fat has usually been associated with increased expression of numerous inflammatory markers, which plays a hazardous role in AF pathogenesis (33-35). Cytokines have also been shown to activate fibroblasts, with the extracellular matrix deposition and fibrosis producing electro anatomical remodeling (36). In 2014, Iacobellis et al. conducted a cross-sectional study in 84 consecutive subjects with clinical and ECG-documented history of permanent (AF) or paroxysmal AF (PAF) who underwent echocardiographic epicardial fat thickness measurement. 64 subjects had AF and 20 showed PAF. AF subjects had also higher prevalence of heart failure (HF), defined by ejection fraction (EF) < 50 %. Furthermore, subjects with AF had a larger amount of epicardial fat thickness than PAF subjects (37).

3. Discussion

According to the findings of the present study, central obesity (visceral adipose tissue) has a powerful correlation with the appearance of metabolic syndrome and coronary artery disease (38). It has been documented that echocardiographic epicardial fat is a measure of visceral fat, as measured by gold-standard techniques. For the most part, echocardiographic epicardial fat highly represents the intra-abdominal mass of visceral fat as measured on MRI and does much better than waist circumference. Therefore, echocardiographic epicardial fat thickness is an independent predictor of visceral adiposity and poorly represents the degree of obesity as measured by body mass index. Persons with higher waist circumferences usually have higher epicardial fat thickness. Until recently, magnetic resonance imaging (MRI) had been accepted as the gold standard for measuring epicardial fat thickness. In 2003, Iacobellis et al. reported the echocardiographical measurement of epicardial fat for the first time (7). They showed an excellent correlation among echocardiographical epicardial fat thickness, MRI abdominal fat, and epicardial fat measurements. Echocardiographically measured epicardial fat may provide a highly reliable index of true visceral fat content, avoiding the possible confounding effect of increased subcutaneous abdominal fat (39). Whether echocardiographic epicardial fat can be associated with intramyocardial and intrahepatic fat accumulation is still unknown. The potential role of echocardiographic epicardial fat thickness as an index and predictor of cardiometabolic risk has been

evaluated. Furthermore, echocardiographic epicardial fat has been associated with CAD. Epicardial fat thickness > 7 mm has also been associated with subclinical atherosclerosis and CAD. However, different and lower epicardial fat thickness cut-off values (>4.5 mm) have shown a good sensitivity and specificity to detect low coronary flow reserve in women. Epicardial fat thickness seemed to be higher in patients with CAD and in those with unstable angina than in persons without CAD and in those with stable angina or atypical chest pain. Also, epicardial fat thickness was significantly correlated with the extent and severity of CAD, as assessed by the Gensini score. At the same time, echocardiographic epicardial fat thickness has been shown to predict coronary flow reserve in women with angiographically normal coronary arteries. The relationship between epicardial fat and atherosclerosis was also found to be significant. Carotid intima-media thickness (C-IMT), as measured by ultrasound, is a well-recognized clinical predictor of subclinical atherosclerosis. Echocardiographic epicardial fat thickness was the best independent predictor of C-IMT in persons involved in the human immunodeficiency virus with associated metabolic syndrome. Indeed, echocardiographic epicardial fat thickness may be an independent predictor of subclinical atherosclerosis in persons with excess visceral adiposity. Similar results have recently been published in a more general high-risk population, which showed interestingly, epicardial fat thickness was correlated with C-IMT and arterial stiffness better than waist circumference in hypertensive subjects (2).

4. Conclusion

The potential role of echocardiographic epicardial fat thickness has been documented as a marker and predictor of cardio metabolic risk, metabolic syndrome, excess visceral fat accumulation, insulin resistance, subclinical atherosclerosis, and CAD. The potential limitations of echocardiography also included problems in differentiating between epicardial fat thickness and pericardial and changes in the velocity of sound in adipose tissue. Although there has been no current study on how the latter might involve the accuracy of epicardial fat thickness measurement by echocardiography, it would be important to know if it is necessary to correct this confounding factor when determining the amount of epicardial fat (2).

Conflict of Interest

The authors declare no conflict of interest.

References:

1. Jeong J-W, Jeong MH, Yun KH, Oh SK, Park EM, Kim YK, et al. Echocardiographic epicardial fat thickness and coronary artery disease. *Circulation Journal*. 2007;71(4):536-9.
2. Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. *Journal of the American Society of Echocardiography*. 2009;22(12):1311-9.
3. Iacobellis G, Willens HJ, Barbaro G, Sharma AM. Threshold Values of High-risk Echocardiographic Epicardial Fat Thickness. *Obesity*. 2008;16(4):887-92.
4. Mousavi S, Ghaderi F, Eshraghi A. Epicardial adipose tissue and coronary artery disease: an article review. *Reviews in Clinical Medicine*. 2014;2(1):49-51.
5. Baker AR, Da Silva NF, Quinn DW, Harte AL, Pagano D, Bonser RS, et al. Human epicardial adipose tissue expresses a pathogenic profile of adipocytokines in patients with cardiovascular disease. *Cardiovascular diabetology*. 2006;5(1):1.
6. Bachar GN, Dicker D, Kornowski R, Atar E. Epicardial adipose tissue as a predictor of coronary artery disease in asymptomatic subjects. *The American journal of cardiology*. 2012;110(4):534-8.
7. Iacobellis G, Assael F, Ribaldo MC, Zappaterreno A, Alessi G, Mario U, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. *Obesity research*. 2003; 11(2): 304-10.
8. Iacobellis G, Ribaldo MC, Assael F, Vecchi E, Tiberti C, Zappaterreno A, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. *The Journal of Clinical Endocrinology & Metabolism*. 2003;88(11):5163-8.
9. Iacobellis G, Barbaro G, Gerstein HC. Relationship of epicardial fat thickness and fasting glucose. *International journal of cardiology*. 2008;128(3):424-6.
10. Malavazos AE, Ermetici F, Cereda E, Coman C, Locati M, Morricone L, et al. Epicardial fat thickness: relationship with plasma visfatin and plasminogen activator inhibitor-1 levels in visceral obesity. *Nutrition, Metabolism and Cardiovascular Diseases*. 2008;18(8):523-30.
11. Ahn S-G, Lim H-S, Joe D-Y, Kang S-J, Choi B-J, Choi S-Y, et al. Relationship of epicardial adipose tissue by echocardiography to coronary artery disease. *Heart*. 2008;94(3):e7-e.
12. Sade LE, Eroglu S, Bozbaş H, Özbiçer S, Hayran M, Haberal A, et al. Relation between epicardial fat thickness and coronary flow reserve in women with chest pain and angiographically normal coronary arteries. *Atherosclerosis*. 2009;204(2):580-5.
13. Eroglu S, Sade LE, Yildirim A, Bal U, Ozbicer S, Ozgul AS, et al. Epicardial adipose tissue thickness by echocardiography is a marker for the presence and severity of coronary artery disease. *Nutrition, Metabolism and Cardiovascular Diseases*. 2009;19(3):211-7.

14. Nabati M, Saffar N, Yazdani J, Parsaee MS. Relationship between Epicardial Fat Measured by Echocardiography and Coronary Atherosclerosis: A Single-Blind Historical Cohort Study. *Echocardiography*. 2013; 30(5): 505-11.
15. Parsaee MS, Nabati M, Saffar N, Taghavi M. Effects of Everolimus-Eluting Stents on the Left Ventricular Systolic and Diastolic Functions. *The Journal of Tehran University Heart Center*. 2015;10(2):93-7.
16. Iacobellis G, Ribaudo MC, Zappaterreno A, Iannucci CV, Leonetti F. Relation between epicardial adipose tissue and left ventricular mass. *The American journal of cardiology*. 2004;94(8):1084-7.
17. Iacobellis G, Pond CM, Sharma AM. Different "weight" of cardiac and general adiposity in predicting left ventricle morphology. *Obesity*. 2006;14(10):1679-84.
18. Iacobellis G, Leonetti F, Singh N, Sharma AM. Relationship of epicardial adipose tissue with atrial dimensions and diastolic function in morbidly obese subjects. *International journal of cardiology*. 2007;115(2):272-3.
19. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. ecommendations for the evaluation of left ventricular diastolic function by echocardiography. *Journal of the American Society of Echocardiography*. 2009;22(2):107-33.
20. Lin H-H, Lee J-K, Yang C-Y, Lien Y-C, Huang J-W, Wu C-K. Accumulation of epicardial fat rather than visceral fat is an independent risk factor for left ventricular diastolic dysfunction in patients undergoing peritoneal dialysis. *Cardiovasc Diabetol*. 2013;12(127):1475-28.
21. Lanza GA, Crea F. Primary coronary microvascular dysfunction clinical presentation, pathophysiology, and management. *Circulation*. 2010; 121(21): 2317-25.
22. Lanza GA. Cardiac syndrome X: a critical overview and future perspectives. *Heart*. 2007; 93(2):159-66.
23. Bugiardini R, Manfrini O, De Ferrari GM. Unanswered questions for management of acute coronary syndrome: risk stratification of patients with minimal disease or normal findings on coronary angiography. *Archives of Internal Medicine*. 2006;166(13):1391-5.
24. Parsaei MS, Nabati M, Yazdani J, Bagheri B, Ghaemian A, Saffar N. Relationship between epicardial fat and coronary microvascular dysfunction. *Kardiologia polska*. 2013; 72(5): 417-24.
25. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *Jama*. 2001; 285(18):2370-5.
26. Friberg L, Hammar N, Pettersson H, Rosenqvist M. Increased mortality in paroxysmal atrial fibrillation: report from the Stockholm Cohort-Study of Atrial Fibrillation (SCAF). *European heart journal*. 2007.
27. Khawaja T, Greer C, Chokshi A, Chavarria N, Thadani S, Jones M, et al. Epicardial fat volume in patients with left ventricular systolic dysfunction. *The American journal of cardiology*. 2011;108(3):397-401.
28. Al Chekatie MO, Welles CC, Metoyer R, Ibrahim A, Shapira AR, Cytron J, et al. Pericardial fat is independently associated with human atrial fibrillation. *Journal of the American College of Cardiology*. 2010; 56 (10): 784-8.
29. Nagashima K, Okumura Y, Watanabe I, Nakai T, Ohkubo K, Kofune T, et al. Association between epicardial adipose tissue volumes on 3-dimensional reconstructed CT images and recurrence of atrial fibrillation after catheter ablation. *Circulation Journal*. 2011; 75(11): 2559-65.
30. Thanassoulis G, Massaro JM, O'Donnell CJ, Hoffmann U, Levy D, Ellinor PT, et al. Pericardial Fat Is Associated With Prevalent Atrial Fibrillation The Framingham Heart Study. *Circulation: Arrhythmia and Electrophysiology*. 2010;3(4):345-50.
31. Tsao H-M, Hu W-C, Wu M-H, Tai C-T, Lin Y-J, Chang S-L, et al. Quantitative analysis of quantity and distribution of epicardial adipose tissue surrounding the left atrium in patients with atrial fibrillation and effect of recurrence

- after ablation. *The American journal of cardiology*. 2011;107(10):1498-503.
32. Wong CX, Abed HS, Molaee P, Nelson AJ, Brooks AG, Sharma G, et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. *Journal of the American College of Cardiology*. 2011; 57 (17):1745-51.
 33. Issac TT, Dokainish H, Lakkis NM. Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data. *Journal of the American College of Cardiology*. 2007;50(21):2021-8.
 34. Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, et al. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation*. 2003;108(20):2460-6.
 35. Marcus GM, Smith LM, Ordovas K, Scheinman MM, Kim AM, Badhwar N, et al. Intracardiac and extracardiac markers of inflammation during atrial fibrillation. *Heart Rhythm*. 2010;7(2):149-54.
 36. Nguyen BL, Fishbein MC, Chen LS, Chen P-S, Masroor S. Histopathological substrate for chronic atrial fibrillation in humans. *Heart Rhythm*. 2009;6(4):454-60.
 37. Iacobellis G, Zaki M, Garcia D, Willens H. Epicardial fat in atrial fibrillation and heart failure. *Horm Metab Res*. 2014;46:587-90.
 38. Park J-S, Ahn S-G, Hwang J-W, Lim H-S, Choi B-J, Choi S-Y, et al. Original investigation Impact of Body Mass Index on the relationship of epicardial adipose tissue to metabolic syndrome and coronary artery disease in an Asian population. *imaging (MRI)*. 2010;2:3.
 39. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. *Nature clinical practice Cardiovascular medicine*. 2005; 2(10): 536-43.