Official Journal of
the Italian Society of Gerontology
and Geriatrics

03
2019
vol. LXVII - Supplement

JGG

JOURNAL OF GERONTOLOGY AND GERIATRICS

Indexed in Embase, Excerpta Medica Database, Scopus Elsevier Database and Emerging Sources Citation Index (ESCI), a new edition of Web of Science

Special Issue

Cardiac visceral fat and age-related cardiovascular diseases

Guest Editor
Dario Leosco

Reviews

PACINI EDITORE MEDICINA

Periodico trimestrale - marzo - Aut. Trib. di Firenze n. 705 del 29 gennaio 1953 - ISSN 2499-6564 (Online)

www.jgerontology-geriatrics.com

Official Journal of
the Italian Society of Gerontology
and Geriatrics

JGG
JOURNAL OF GERONTOLOGY AND GERIATRICS

Indexed in Embase, Excerpta Medica Database, Scopus Elsevier Database and Emerging Sources Citation Index (ESCI), a new edition of Web of Science

03 2019
vol. LXVII - Supplement

PACINI EDITORE MEDICINA

www.jgerontology-geriatrics.com

JGG
JOURNAL OF GERONTOLOGY AND GERIATRICS

Scientific secretariat
Valentina Bàrberi
Journal of Gerontology and Geriatrics
Pacini Editore Srl
Via Gherardesca - 56121 Pisa, Italy
Tel. +39 050 3130376 - Fax +39 050 3130300
secretary@jgerontology-geriatrics.com

Società Italiana di Gerontologia e Geriatria
Via G.C. Vanini 5, 50129 Firenze, Italy
Tel. +39 055 474330 - Fax +39 055 461217
E-mail: sigg@sigg.it - www.sigg.it

Managing Director
Raffaele Antonelli Incalzi

Publisher
Pacini Editore Srl
Via Gherardesca - 56121 Pisa, Italy
Tel. +39 050 313011 - Fax +39 050 3130300
info@pacinieditore.it

Published online by Pacini Editore Srl,
Pisa, October 2019
online: www.jgerontology-geriatrics.com

Authors Informations
www.jgerontology-geriatrics.com/category/authorsinformation/

Submission online
submission.jgerontology-geriatrics.com

Journal registered at "Registro pubblico degli Operatori della Comunicazione" (Pacini Editore srl registration n. 6269 - 29/8/2001).

CONTENTS

Journal of Gerontology and Geriatrics

Official Journal of
the Italian Society of Gerontology
and Geriatrics

03 2019
vol. LXVII - Supplement

Special Issue
Cardiac visceral fat and age-related cardiovascular diseases

Guest Editor
Dario Leosco

Reviews

JGG 2019;67(Suppl):195-204

Review

Proinflammatory phenotype of cardiac visceral fat in heart failure with preserved ejection fraction in the elderly

D. Leosco, L. Petraglia, F.V. Grieco, M. Conte, N. Ferrara, V. Parisi

Department of Translational Medical Science, University of Naples "Federico II", Naples, Italy

Nearly half of all patients with heart failure (HF) symptoms have HF with preserved ejection fraction (HFpEF) and the prevalence of this pathologic condition is rising being aging one of the most important risk factors. HFpEF is a very challenging syndrome vulnerable and frail affecting, in the most of cases, patients, with high health care costs due to high number of hospitalizations and medical cares.

More and more evidence are accumulating on the role of inflammation in the pathogenesis of HFpEF. The presence of multiple comorbidities in HFpEF may significantly contribute to a systemic pro-inflammatory state which negatively affects the myocardium.

Obesity promotes systemic inflammation and exacerbates the inflammatory burden imposed by many chronic extracardiac comorbidities. Importantly, the chronic systemic inflammation related to obesity is associated to a significant increase of the amount of epicardial adipose tissue (EAT), the cardiac visceral fat. The increase of EAT volume is associated to a pro-inflammatory state of this fat depot. Several observations support the hypothesis that the inflammation of EAT can act in a paracrine and vasocrine manner to influence the structure and function of the heart, thus contributing to the pathohenesis of HFpEF. Given the recognized role of EAT in the pathophysiology of HFpEF, it should be desirable to identify specific therapies targeting the cardiac visceral fat and able to modulate its pro-inflammatory profile and the negative effect of the inflammatory burden on the neighboring myocardium.

Key words: Epicardial adipose tissue, Heart failure, Elderly

INTRODUCTION

In the elders, heart failure (HF) shows clinical features that are substantially different to those observed in the adult population. In fact, in patients over 75 years, this syndrome predominantly affects women with isolated systolic hypertension, normal left ventricular ejection fraction, and several extracardiac comorbidities. In this regard, since 2000, Rich et al. identified the main characteristics of HF in the elderly population and paved the way for the nosographic identification of a new cardiovascular syndrome, to date known as heart failure with preserved ejection fraction (HFpEF) [1]. Nearly half of all patients with HF symptoms have HFpEF and the prevalence of this pathologic condition is rising being aging one of the most important risk factors. The clinical outcomes of HFpEF are similar to those with HFrEF. In fact, 30-day to 1-year mortality post hospital discharge is similar between HFpEF and HFrEF and patients with either HF syndrome show similar functional limitations and poor quality of life [2-10]. On the other hand, morbidity and cause of death are quite different between the two syndromes, being HFpEF predominantly associated with extracardiac comorbidities and deaths of non cardiac causes. The peculiarities of HFpEF imply many challenges for the researchers and the clinicians for several reasons: the population affected by HFpEF

Received: July 17, 2019 - Accepted: September 3, 2019

Correspondence: Dario Leosco, Department of Translational Medical Science, University of Naples "Federico II", via S. Pansini 5, 80130, Naples, Italy. E-mail: dleosco@unina.it

is very heterogeneous and its inclusion in clinical trials is particularly difficult, especially for the oldest-old; mechanistic hypothesis are still lacking due to limited access to biopsies from human heart tissues and the difficulties in obtaining adequate experimental models; the pathophysiological mechanisms accounting for this syndrome are often multifactorial, thus explaining why there is no evidence based therapy, to date, showing efficacy on the hard outcomes, such as morbidity and mortality [11-15].

Overall, HFpEF is a very challenging syndrome, affecting, in the most of cases, patients vulnerable and frail, with high health care costs due to high number of hospitalizations and medical cares. This review aims to report recent advances in the knowledge of the pathophysiology of HFpEF that can help for a better understanding of the mechanisms potentially involved in the onset and progression of such devastating cardiovascular disease.

EXTRACARDIAC COMORBIDITIES, SYSTEMIC INFLAMMATION AND HFPEF

More and more evidence are accumulating on the role of inflammation in the pathogenesis of HFpEF. Results from left ventricular (LV) endomyocardial biopsy [16] and analyses of inflammatory cell markers [17] indicate increased oxidative stress and depressed NO-signaling resulting in inflammation. Importantly, the presence of multiple comorbidities in HFpEF may significantly contribute to a systemic pro-inflammatory state which negatively affects the myocardium.

Chronic kidney disease (CKD) occurs in one third of HFpEF patients and is associated with poor prognosis [7 18 19]. Albuminuria, occurring in almost 30% of HFpEF patients, leads to activation of the RAAS system, and systemic inflammation. It has been hypothesized a bidirectional continuum between renal dysfunction and HFpEF. CKD may lead by itself to myocardial inflammation, fibrosis, and resultant HFpEF. On the other hand, HFpEF may cause renal dysfunction by triggering RAAS pathway activation and venous congestion. In this regard, there are several pathways that may link renal and cardiac disease such as transient receptor potential channel-6, a Gq-receptor and ROS activated nonselective cation channel that plays an important role in proteinuria and glomerular dysfunction [20] but that can also induce cardiac hypertrophy [21] and fibrosis [22].

Chronic inflammation is obviously associated to chronic obstructive pulmonary disease (COPD), which is a crucial determinant of HFpEF mortality [23]. Furthermore, sleep disordered breathing, often associated to COPD and HF, lead to systemic inflammation, other than adrenergic and oxidative activation [24].

Iron deficiency and anemia also contribute to immune responses, systemic inflammation and oxidative stress in HFpEF [25].

Diabetes mellitus (DM) is a common comorbidity in HFpEF and has a significant negative impact on prognosis. Insulin resistance in diabetes mellitus increases free fatty acid utilization by cardiomyocytes, thus leading to mitochondrial dysfunction, production of toxic lipid intermediates, and increased reactive oxygen species [26]. Increased visceral fat, frequently seen in the DM population, also results in the release of proinflammatory cytokines. Hyperglycemia-induced advanced glycation end-products impair microvascular function and decrease nitric oxide availability [26].

Sarcopenia is another common condition in HFpEF. Frail patients with HFpEF are frequently affected by sarcopenia, which is a major component of the pathophysiology of frailty [27]. Sarcopenia, given the impairment of limb and respiratory skeletal muscles leading to further functional decline, may contribute to cardiovascular remodelling and dysfunction and to the development of HFpEF through systemic inflammation and different metabolic and endocrine abnormalities [28].

The incidence of new-onset depression is high in HF (5.7-7.9%). The pathophysiology underlying the adverse effect of depression in HF patients has not been delineated. Potential factors linking depression with HF include activation of inflammatory cascades, dysregulation of neurohormonal axes, arrhythmias, and behavioural effects [29].

All these comorbidities induce a systemic proinflammatory state with elevated plasma levels of interleukin (IL)-6, tumor necrosis factor (TNF)-a, soluble ST2 (sST2), and pentraxin 3 [30]. Coronary microvascular endothelial cells reactively produce reactive oxygen species, vascular cell adhesion molecule (VCAM), and E-selectin. Production of ROS leads to formation of peroxynitrite and reduction of nitric oxide bioavailability with consequent lower soluble guanylate cyclase (sGC) activity in cardiomyocytes. Lower sGC activity decreases cyclic guanosine monophosphate concentration and protein kinase G (PKG) activity. This represents a prohypertrophic stimuli inducing cardiomyocyte hypertrophy. Endothelial expression of VCAM and E-selectin is associated to monocytes migration into the subendothelium which release transforming growth factor, thus stimulating conversion of fibroblasts to myofibroblasts, with consequent deposition of collagen in the interstitial space.

EPICARDIAL ADIPOSE TISSUE MEDIATES DELETERIOUS EFFECTS OF OBESITY AND INFLAMMATION ON THE MYOCARDIUM IN HFPEF

Obesity promotes systemic inflammation [31 32] and exacerbates the inflammatory burden imposed by many chronic extracardiac comorbidities. Importantly, the chronic systemic inflammation related to obesity is accompanied by a significant increase of epicardial adipose tissue (EAT) mass [33]. It is known that inflammation may lead to adipogenesis. This represents an adaptive mechanism preventing the deposition of proinflammatory fatty acids in cells [34]. Interestingly, EAT is more sensitive to lipogenesis than other types of visceral adipose tissue [35]. In fact, it contains plastic mesenchymal cells that are the source of progenitor cardiomyocytes during fetal development but, in adulthood, differentiate into adipocytes [36]). Systemic inflammation affects the biology of EAT [37-39], promoting its transition toward a proinflammatory phenotype [40]. Several observations support the hypothesis that the inflammation of EAT can act in a paracrine manner to influence the structure and function of neighboring tissues [41 42]. Furthermore, the release of proinflammatory adipocytokines from EAT into the general circulation may contribute to the systemic inflammatory state; systemic inflammation, in turn, can promote the accumulation of EAT, which induces local and systemic inflammation and end-organ dysfunction, thus creating a bidirectional continuum [43-48].

Therefore, obesity, such as other extracardiac comorbidities, promotes changes in the physiological characteristics of EAT which starts to produce and secrete proinflammatory factors. Of these, leptin, tumor necrosis factor-a, interleukin 1-β, interleukin-6, and resistin promote the infiltration of macrophages, destroy microvascular systems, and activate profibrotic pathways [49-52]. As regard to leptin, it is known that obesity is characterized by high circulating levels of aldosterone, secreted by adipocytes or directly released from the adrenal gland in response to leptin [53]. This is also exacerbated by a loss of the antialdosterone action of natriuretic peptides given the increased neprilysin activity in obesity. Visceral adiposity also leads to increased signaling through the leptin receptor, which causes sodium retention by a direct action on the renal tubules. EAT-derived leptin promotes cardiac inflammation, microcirculatory abnormalities, and fibrosis. The resulting interaction of aldosterone and leptin promotes plasma volume expansion and regional and systemic inflammation and fibrosis.

Another important mechanism by which EAT may exert an unfavourable activity for the myocardium and causes cardiac damage depends on the migration of EAT derived mesenchymal stem cells to the neighboring myocardium and differentiation of these cells into fibroblasts [54-56].

There are several experimental and clinical studies indicating a relationship between EAT volume and inflammatory profile and the degree of cardiac inflammation [43 50 57 58]. It is widely recognized that EAT, especially the periatrial fat, may represent an inflammatory substrate acting as a trigger for the development of atrial arrhythmias [59-64]. Interestingly, increased volume and proinflammatory abnormalities of EAT are close to myocardial areas of myocardium characterized by marked electrophysiological derangement [65 66]. In obese individuals, increased EAT volume is significantly associated with an impaired myocardial microcirculation, abnormalities of cardiac diastolic properties and increased vascular stiffness, and left atrial dilatation [67-70]. In these patients, structural and functional abnormalities of EAT often precedes clinical presentation of HFpEF [71-74]. Another important evidence supporting the role of EAT as transducer of inflammatory signals derives from the observation of the structural abnormalities of cardiac visceral fat in patients affected by chronic systemic inflammatory disorders. In this regard, patients with rheumatoid arthritis, human immunodeficiency, virus infection, psoriasis, show increased EAT mass that is also associated to alterations of cardiac microcirculation, myocardial fibrosis, and cardiac diastolic abnormalities, that are all typical of HFpEF [75-79]. This may explain the significant higher risk of developing HF in these clinical settings.

If it is true that extracardiac comorbidities contribute to the pathogenesis of HFpEF, it is also evident that EAT may play a role, through the release of proinflammatory adipocytokines, in exacerbating the dysfunction of visceral organs, other than the heart. In fact, increased EAT volume is associated to inflammation and fibrosis in the kidneys, lungs, liver, and brain, whose dysfunction participates to the clinical features of HFpEF [80-82].

EAT AND CARDIAC SYMPATHETIC DENERVATION IN HF

Cardiac sympathetic nervous system (SNS) hyperactivity is associated to HF [1-6] and represents a compensatory mechanism to the loss of cardiac contractility aiming at increasing myocardial inotropism to preserve cardiac output. However, in the long term, this mechanism is associated to unfavourable cardiac remodeling and increased mortality [83-88]. In the failing heart, a defect of neuronal norepinephrine reuptake caused by post-transcriptional downregulation of the cardiac norepinephrine transporter [89-93] leads to an increase

in norepinephrine concentration in the sympathetic synapses. This is responsible for impaired myocardial β-adrenergic receptor system and functional and anatomic sympathetic denervation of the heart [94 95].

Although SNS hyperactivity in HF is mainly mediated by norepinephrine-releasing neurons and by circulating norepinephrine and epinephrine, other mechanisms may contribute to sympathetic derangement. For example, the adipose tissue, particularly the visceral fat depots, may stimulate central SNS activity through dysregulated adipokines production and secretion [96 97]. In addition, experimental studies have recently demonstrated that adipocytes produce and secrete both norepinephrine and epinephrine [98], thus indicating that the sympathetic fibers within adipose tissue are not the only source of catecholamines. In a recent study, Parisi et al have demonstrated, in HF patients, that EAT represents an important source of norepinephrine, whose levels are 2-fold higher than those found in plasma [99]. Because of the EAT proximity to the myocardium, the increase in catecholamine content in this tissue could result in a negative feedback on cardiac sympathetic nerves, which are associated with the ventricular myocardium, thus inducing a functional and anatomic denervation of the heart. Therefore, in the context of a widespread SNS hyperactivity in HF, EAT seems to play an additive role in generating the final net effect of cardiac sympathetic denervation. In this study, the EAT thickness, assessed by echocardiography, was an independent predictor of 123I-MIBG planar and SPECT scintigraphic parameters (indexes of cardiac sympathetic innervation) and provided additional predictive information on cardiac adrenergic nerve activity respect to important demographic, clinical, and left ventricular function parameters. Therefore, assessing EAT thickness in patients with HF may provide surrogate information on the status of cardiac adrenergic derangement that is strongly correlated with worse prognosis in HF.

In another study, Parisi et al. also explored the relationship between the presence of sleep disordered breathing and EAT thickness in patients with HF [100]. They found a significant correlation between the EAT increase and the presence and the severity of sleep apneas and a significant increase of circulating norepinephrine in patients with central sleep apnea (CSAs). These data confirm the results of previous study exploring SNS activation in HF patients with prevalent obstructive or central sleep apneas (CSAs). According to results of Parisi et al, all these studies indicate that CSAs are associated with a greater SNS activation [101-103]).

Overall these evidence indicate EAT as a possible contributor to SNS activation in HF, thus reinforcing the negative activity of cardiac visceral fat in the pathogenesis and progression of HF.

EAT AS A POTENTIAL THERAPEUTIC TARGET IN HF

Given the recognized role of EAT in the pathophysiology of HFpEF, it should be desirable to identify specific therapies targeting the cardiac visceral fat and able to modulate its pro-inflammatory profile and the negative effect of the inflammatory burden on the neighboring myocardium. The discovery of new drugs for HFpEF is dramatically needed since the lack, to date, of evidence based therapy able to ameliorate the outcomes of this syndrome. In this rewiew, we report the results of recent studies focusing on this topic.

Statins have been shown to reduce both EAT accumulation and inflammatory status in HF patients [104 105]. In a recent study, Parisi et al. [106-108] explored, in a population of elderly patients with calcific aortic stenosis, a clinical model of HFpEF, whether statin therapy might affect EAT accumulation and inflammatory profile. Major findings of this study was that statin therapy was significantly associated to a reduced EAT thickness. Furthermore, the association between statin therapy and reduction of EAT accumulation was paralleled by an attenuation of EAT inflammatory profile. Finally, in vitro studies conducted on the EAT secretomes, obtained from patients with aortic stenosis, indicated that statin had a direct and selective anti-inflammatory effect on EAT.

These evidence may explain why statins, independently from their antihyperlipidemic effect, reduce the development of ventricular diastolic abnormalities, myocardial microcirculatory alterations, and cardiac fibrosis [109-111]. Furthermore, the use of statins in patients with HFpEF is associated with a reduced risk of death in several observational studies [112 113].

Patients with type 2 diabetes show a marked increase in the amount of EAT and a high incidence of HFpEF has been reported in this population [114]. Importantly, many antidiabetic drugs cause weight gain, thus inducing a further increase of adipogenesis and of EAT. In this regard, insulin increases the volume of EAT [39 73]; this may explain, at least in part, why its use is associated with an increased risk of heart failure [115]. Sulfonylureas promote the insulin activity on adipocytes and enhance the secretion of proinflammatory adipokines [116-118]. Thiazolidinediones reduce EAT volume and inflammation and the secretion of proinflammatory adipocytokines [119-122].

Newer antihyperglycemic medications, such as glucagon-like peptide 1 receptor antagonists are typically associated with weight loss and may reduce the accumulation of EAT [123], although they do not revert its pro-inflammatory phenotype [124 125]. This may explain why these drugs do not affect the HF outcome in clinical trials [126 127]. Although other antidiabetic drugs, such as dipeptidyl peptidase-4 inhibitors are able to reduce

the volume of EAT [128], they may exacerbate its inflammatory state and lead to cardiac fibrosis [129-131]. This finding explains why dipeptidyl peptidase-4 inhibitors negatively affect cardiac remodeling and increase the risk of HF in patients with type 2 diabetes [132].

It has been recently demonstrated that sodium-glucose cotransporter 2 inhibitors not only reduce the amount of EAT, but also ameliorate its inflammation and its secretion of pro-atherosclerotic and pro-fibrotic cytokines [133 134]. This may explain why these drugs reduce myocardial fibrosis and improve ventricular diastolic properties [135-137] and reduce the risk of several HF outcomes in observational studies and randomized controlled trials [138-141].

Given the ability of mineralocorticoid receptor antagonists, such as eplerenone to revert inflammation in visceral adipose tissue of obese individuals [142], further studies are desiderable to confirm this effect also in EAT. Preliminary data on these drugs indicate a favourable activity to reduce cardiovascular events in patients with HFpEF [143].

Recent encouraging evidence indicate a positive activity of neprilysin inhibition in HFpEF [144]. This drug could counteract the breakdown of natriuretic peptides that is known to be accelerated in HFpEF.

Finally, the prominent role of inflammation in HFpEF represents an important motivation for the current research to explore the efficacy of drugs targeting circulating and local inflammatory mediators. The results of the recent CANTOS trial have demonstrated that inhibition of Interleukin 1β has potent effect on cardiovascular morbidity and mortality in patients with previous myocardial infarction [145]. Future studies are needed the potential role of immune therapy also in HFpEF.

CONCLUSIONS

Accumulating evidence strongly support the role of structural and functional changes of EAT in the pathogenesis of HFpEF. Many inflammatory factors produced by cardiac visceral fat may penetrate the myocardium and coronary vessels in a paracrine and vasocrine manner and express their toxicity in the neighboring tissue. This promotes profound cardiac alterations such as fibrosis, alterations of left ventricular filling, derangement of electrophysiological properties, and sympathetic denervation that are all crucial factors for the development of HFpEF. Although it is widely recognized the multifactorial nature of HFpEF, EAT represents an intriguing target for future therapeutic strategies since its tight interconnection with the heart and its prominent role in enhance local and systemic inflammation. The epidemiological explosion of HFpEF and the lack of efficacious therapy strengthen the need to explore novel mechanisms and innovative therapeutic approaches to face the dramatic increase of cardiovascular deaths that are expected in the next decades.

Conflict of interest

The Authors declare to have no conflict of interest.

References

1 Rich MW, Kitzman DW; PRICE-III Organizing Committee; PRICE-III Investigators. *Third pivotal research in cardiology in the elderly (PRICE-III) symposium: heart failure in the elderly: mechanisms and management*. Am J Geriatr Cardiol 2005;14:250-61.

2 Steinberg BA, Zhao X, Heidenreich PA, et al. *Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes*. Circulation 2012;126:65-75.

3 Owan TE, Hodge DO, Herges RM, et al. *Trends in prevalence and outcome of heart failure with preserved ejection fraction*. N Engl J Med 2006;355:251-9.

4 Bhatia RS, Tu JV, Lee DS, et al. *Outcome of heart failurewith preserved ejection fraction in a population-based study*. N Engl J Med 2006;355:260-9.

5 Liao L, Jollis JG, Anstrom KJ, et al. *Costs for heart failure with normal vs reduced ejection fraction*. Arch Intern Med 2006;166:112-8.

6 Fonarow GC, Stough WG, Abraham WT, et al. *Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the optimize-hf registry.* J Am Coll Cardiol 2007;50:768-77.

7 Yancy CW, Lopatin M, Stevenson LW, et al. *Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the acute decompensated heart failure national registry (adhere) database.* J Am Coll Cardiol 2006;47:76-84.

8 Cacciatore F, Abete P, de Santis D, et al. *Mortality and blood pressure in elderly people with and without cognitive impairment.* Gerontology 2005;51:53-61.

9 Ungar A, Galizia G, Morrione A, et al. *Two-year morbidity and mortality in elderly patients with syncope*. Age Ageing 2011;40:696-702.

10 Cacciatore F, Abete P, Mazzella F, et al. *Six-minute walking test but not ejection fraction predicts mortality in elderly patients undergoing cardiac rehabilitation following coronary artery bypass grafting*. Eur J Prev Cardiol 2012;19:1401-9.

11 Ather S, Chan W, Bozkurt B, et al. *Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction.* J Am Coll Cardiol 2012;59:998-1005.

12 Yusuf S, Pfeffer MA, Swedberg K, et al. *Effects of candesartan in patients with chronic heart failure and preserved left ventricular ejection fraction: the charm-preserved trial.* Lancet 2003;362:777-81.

[13] Ahmed A, Rich MW, Fleg JL, et al. *Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary digitalis investigation group trial.* Circulation 2006;114:397-403.

[14] Chan MM, Lam CS. *How do patients with heart failure with preserved ejection fraction die?* Eur J Heart Fail 2013;15:604-13.

[15] Mangla A, Kane J, Beaty E, et al. *Comparison of predictors of heart failure-related hospitalization or death in patients with versus without preserved left ventricular ejection fraction*. Am J Cardiol 2013;112:1907-12.

[16] van Heerebeek L, Hamdani N, Falcao-Pires I, et al. *Low myocardial protein kinase g activity in heart failure with preserved ejection fraction*. Circulation 2012;126:830-9.

[17] Westermann D, Lindner D, Kasner M, et al. *Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction*. Circ Heart Fail 2011;4:44-52.

[18] Shah SJ, Heitner JF, Sweitzer NK, et al. *Baseline characteristics of patients in the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial*. Circ Heart Fail 2013;6:184-92.

[19] Rusinaru D, Buiciuc O, Houpe D, et al. *Renal function and long-term survival after hospital discharge in heart failure with preserved ejection fraction.* Int J Cardiol 2011;147:278-82.

[20] Dryer SE, Reiser J. *Trpc6 channels and their binding partners in podocytes: role in glomerular filtration and pathophysiology.* Am J Physiol Renal Physiol 2010;299:F689-701.

[21] Eder P, Molkentin JD. *Trpc channels as effectors of cardiac hypertrophy*. Circ Res 2011;108:265-72.

[22] Davis J, Burr AR, Davis GF, et al. *A trpc6-dependent pathway for myofibroblast transdifferentiation and wound healing in vivo*. Developmental cell 2012;23:705-15.

[23] Ather S, Chan W, Bozkurt B, et al. *Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction.* J Am Coll Cardiol 2012;59:998-1005.

[24] Triposkiadis F, Giamouzis G, Parissis J, et al. *Reframing the association and significance of co-morbidities in heart failure.* Eur J of Heart Failure 2016;18:744-58.

[25] Macdougall IC, Canaud B, de Francisco AL, et al. *Beyond the cardiorenal anaemia syndrome: recognizing the role of iron deficiency*. Eur J Heart Fail 2012;14:882-6.

[26] McHugh K, DeVore AD, Wu J, et al. *Heart failure with preserved ejection fraction and diabetes.* J Am Coll Cardiol 2019;73:602-11.

[27] Martone AM, Bianchi L, Abete P, et al. *The incidence of sarcopenia among hospitalized older patients: results from the Glisten study*. J Cachexia Sarcopenia Muscle 2017;8:907-14.

[28] Kinugasa Y, Yamamoto K. *The challenge of frailty and sarcopenia in heart failure with preserved ejection fraction*. Heart 2017;103:184-9.

[29] Luijendijk HJ, Tiemeier H, van den Berg JF, et al. *Heart failure and incident late-life depression*. J Am Geriatr Soc 2010;58:1441-8.

[30] Paulus WJ, Tschöpe C. *A novel paradigm for heart failure with preserved ejection fraction*. J Am Coll Cardiol 2013;62:263-71.

[31] Ghigliotti G, Barisione C, Garibaldi S, et al. *Adipose tissue immune response: novel triggers and consequences for chronic inflammatory conditions.* Inflammation 2014;37:1337-53.

[32] Berg AH, Scherer PE. *Adipose tissue, inflammation, and cardiovascular disease.* Circ Res 2005;96:939-49.

[33] Packer M. *Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium.* J Am Coll Cardiol 2018;71:2360-72.

[34] Wernstedt Asterholm I, Tao C, Morley TS, et al. *Adipocyte inflammation is essential for healthy adipose tissue expansion and remodeling*. Cell Metab 2014;20:103-18.

[35] Marchington JM, Pond CM. *Site-specific properties of pericardial and epicardial adipose tissue: the effects of insulin and high-fat feeding on lipogenesis and the incorporation of fatty acids in vitro.* Int J Obes 1990;14:1013-22.

[36] von Gise A, Pu WT. *Endocardial and epicardial epithelial to mesenchymal transitions in heart development and disease.* Circ Res 2012;110:1628-45.

[37] Thalmann S, Meier CA. *Local adipose tissue depots as cardiovascular risk factors.* Cardiovasc Res 2007;75:690-701.

[38] Mach L, Bedanova H, Soucek M, et al. *Impact of cardiopulmonary bypass surgery on cytokines in epicardial adipose tissue: comparison with subcutaneous fat*. Perfusion 2017;32:279-84.

[39] Hirata Y, Kurobe H, Akaike M, et al. *Enhanced inflammation in epicardial fat in patients with coronary artery disease.* Int Heart J 2011;52:139-42.

[40] Shibasaki I, Nishikimi T, Mochizuki Y, et al. *Greater expression of inflammatory cytokines, adrenomedullin, and natriuretic peptide receptor-C in epicardial adipose tissue in coronary artery disease.* Regul Pept 2010;165:210-7.

[41] Verhagen SN, Visseren FL. *Perivascular adipose tissue as a cause of atherosclerosis.* Atherosclerosis 2011;214:3-10.

[42] Aghamohammadzadeh R, Unwin RD, Greenstein AS, et al. *Effects of obesity on perivascular adipose tissue vasorelaxant function: nitric oxide, inflammation and elevated systemic blood pressure*. J Vasc Res 2015;52:299-305.

[43] Lai YH, Yun CH, Yang FS, et al. *Epicardial adipose tissue relating to anthropometrics, metabolic derangements and fatty liver disease independently contributes to serum high-sensitivity C-reactive protein beyond body fat composition: a study validated with computed tomography.* J Am Soc Echocardiogr 2012;25:234-41.

[44] Nakanishi K, Fukuda S, Tanaka A, et al. *Epicardial adipose tissue accumulation is associated with renal dysfunction and coronary plaque morphology on multidetector computed tomography.* Circ J 2016;80:196-201.

[45] Cheng KH, Chu CS, Lee KT, et al. *Adipocytokines and proinflammatory mediators from abdominal and epicardial adipose tissue in patients with coronary artery disease.* Int J Obes (Lond) 2008;32:268-74.

[46] Kotulák T, Drápalová J, Kopecký P, et al. *Increased circulating and epicardial adipose tissue mRNA expression of*

fibroblast growth factor-21 after cardiac surgery: possible role in postoperative inflammatory response and insulin resistance. Physiol Res 2011;60:757-67.

47 Aydin H, Toprak A, Deyneli O, et al. *Epicardial fat tissue thickness correlates with endothelial dysfunction and other cardiovascular risk factors in patients with metabolic syndrome.* Metab Syndr Relat Disord 2010;8:229-34.

48 Christensen RH, von Scholten BJ, Hansen CS, et al. *Epicardial, pericardial and total cardiac fat and cardiovascular disease in type 2 diabetic patients with elevated urinary albumin excretion rate.* Eur J Prev Cardiol 2017;24:1517-24.

49 Gruzdeva OV, Akbasheva OE, Dyleva YA, et al. *Adipokine and cytokine profiles of epicardial and subcutaneous adipose tissue in patients with coronary heart disease*. Bull Exp Biol Med 2017;163:608-11.

50 Patel VB, Basu R, Oudit GY. *ACE2/Ang 1-7 axis: a critical regulator of epicardial adipose tissue inflammation and cardiac dysfunction in obesity.* Adipocyte 2016;5:306-11.

51 Company JM, Booth FW, Laughlin MH, et al. *Epicardial fat gene expression after aerobic exercise training in pigs with coronary atherosclerosis: relationship to visceral and subcutaneous fat.* J Appl Physiol (1985) 2010;109:1904-12.

52 Bambace C, Sepe A, Zoico E, et al. *Inflammatory profile in subcutaneous and epicardial adipose tissue in men with and without diabetes.* Heart Vessels 2014;29:42-8.

53 Packer M. *Leptin-aldosterone-neprilysin axis. Identification of its distinctive role in the pathogenesis of the three phenotypes of heart failure in people with obesity.* Circulation 2018;137:1614-31.

54 Naftali-Shani N, Itzhaki-Alfia A, Landa-Rouben N, et al. *The origin of human mesenchymal stromal cells dictates their reparative properties.* J Am Heart Assoc 2013;2:e000253.

55 Naftali-Shani N, Levin-Kotler LP, Palevski D, et al. *Left ventricular dysfunction switches mesenchymal stromal cells toward an inflammatory phenotype and impairs their reparative properties via toll-like receptor-4.* Circulation 2017;135:2271-87.

56 Ruiz-Villalba A, Simón AM, Pogontke C, et al. *Interacting resident epicardium-derived fibroblasts and recruited bone marrow cells form myocardial infarction scar.* J Am Coll Cardiol 2015;65:2057-66.

57 Patel VB, Mori J, McLean BA, et al. *ACE2 deficiency worsens epicardial adipose tissue inflammation and cardiac dysfunction in response to diet-induced obesity.* Diabetes 2016;65:85-95.

58 Wu CK, Tsai HY, Su MM, et al. *Evolutional change in epicardial fat and its correlation with myocardial diffuse fibrosis in heart failure patients.* J Clin Lipidol 2017;11:1421-31.

59 Lin YK, Chen YC, Chang SL, et al. *Heart failure epicardial fat increases atrial arrhythmogenesis*. Int J Cardiol 2013;167:1979-83.

60 Hatem SN, Sanders P. *Epicardial adipose tissue and atrial fibrillation.* Cardiovasc Res 2014;102:205-13.

61 Yorgun H, Canpolat U, Aytemir K, et al. *Association of epicardial and peri-atrial adiposity with the presence and severity of non-valvular atrial fibrillation.* Int J Cardiovasc Imaging 2015;31:649-57.

62 Kusayama T, Furusho H, Kashiwagi H, et al. *Inflammation of left atrial epicardial adipose tissue is associated with paroxysmal atrial fibrillation.* J Cardiol 2016;68:406-11.

63 Mahajan R, Lau DH, Brooks AG, et al. *Electrophysiological electroanatomical, and structural remodeling of the atria as consequences of sustained obesity.* J Am Coll Cardiol 2015;66:1-11.

64 Venteclef N, Guglielmi V, Balse E, et al. *Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokines.* Eur Heart J 2015;36:795-805.

65 Nagashima K, Okumura Y, Watanabe I, et al. *Does location of epicardial adipose tissue correspond to endocardial high dominant frequency or complex fractionated atrial electrogram sites during atrial fibrillation?* Circ Arrhythm Electrophysiol 2012;5:676-83.

66 Zghaib T, Ipek EG, Zahid S, et al. *Association of left atrial epicardial adipose tissue with electrogram bipolar voltage and fractionation: electrophysiologic substrates for atrial fibrillation.* Heart Rhythm 2016;13:2333-9.

67 Nakanishi K, Fukuda S, Tanaka A, et al. *Relationships between periventricular epicardial adipose tissue accumulation, coronary microcirculation, and left ventricular diastolic dysfunction.* Can J Cardiol 2017;33:1489-97.

68 Natale F, Tedesco MA, Mocerino R, et al. *Visceral adiposity and arterial stiffness: echocardiographic epicardial fat thickness reflects, better than waist circumference, carotid arterial stiffness in a large population of hypertensives*. Eur J Echocardiogr 2009;10:549-55.

69 Iacobellis G, Leonetti F, Singh N, et al. *Relationship of epicardial adipose tissue with atrial dimensions and diastolic function in morbidly obese subjects.* Int J Cardiol 2007;115:272-3.

70 Ozturk C, Balta S, Demirkol S, et al. *Epicardial adipose tissue thickness may be related diastolic dysfunction in obese adolescents.* Eur Rev Med Pharmacol Sci 2014;18:1109.

71 Hage C, Michaëlsson E, Linde C, et al. *Inflammatory biomarkers predict heart failure severity and prognosis in patients with heart failure with preserved ejection fraction: a holistic proteomic approach*. Circ Cardiovasc Genet 2017;10:e001633.

72 Chan MM, Santhanakrishnan R, Chong JP, et al. *Growth differentiation factor 15 in heart failure with preserved vs reduced ejection fraction*. Eur J Heart Fail 2016;18:81-8.

73 Glezeva N, Voon V, Watson C, et al. *Exaggerated inflammation and monocytosis associate with diastolic dysfunction in heart failure with preserved ejection fraction: evidence of M2 macrophage activation in disease pathogenesis*. J Card Fail 2015;21:167-77.

74 Lam CS, Lyass A, Kraigher-Krainer E, et al. *Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community.* Circulation 2011;124:24-30.

75 Mavrogeni S, Karabela G, Stavropoulos E, et al. *Imaging patterns of heart failure in rheumatoid arthritis evaluated by cardiovascular magnetic resonance.* Int J Cardiol 2013;168:4333-5.

[76] Holloway CJ, Ntusi N, Suttie J, et al. *Comprehensive cardiac magnetic resonance imaging and spectroscopy reveal a high burden of myocardial disease in HIV patients.* Circulation 2013;128:814-22.

[77] Davis JM 3rd, Lin G, Oh JK, et al. *Five-year changes in cardiac structure and function in patients with rheumatoid arthritis compared with the general population*. Int J Cardiol 2017;240:379-85.

[78] Fontes-Carvalho R, Mancio J, Marcos A, et al. *HIV patients have impaired diastolic function that is not aggravated by anti-retroviral treatment.* Cardiovasc Drugs Ther 2015;29:31-9.

[79] Ozden HK, Polat M, Ozturk S, et al. *Assessment of subclinical cardiac damage in chronic plaque psoriasis patients: a case control study.* Arch Med Sci Atheroscler Dis 2016;1:e126-32.

[80] Ozturk MT, Ebinç FA, Okyay GU, et al. *Epicardial adiposity is associated with microalbuminuria in patients with essential hypertension*. Acta Cardiol Sin 2017;33:74-80.

[81] Kiraz K, Gökdeniz T, Kalaycıoglu E, et al. *Epicardial fat thickness is associated with severity of disease in patients with chronic obstructive pulmonary disease.* Eur Rev Med Pharmacol Sci 2016;20:4508-15.

[82] Akıl E, Akıl MA, Varol S, et al. *Echocardiographic epicardial fat thickness and neutrophil to lymphocyte ratio are novel inflammatory predictors of cerebral ischemic stroke*. J Stroke Cerebrovasc Dis 2014;23:2328-34.

[83] Lymperopoulos A, Rengo G, Koch WJ. *Adrenergic nervous system iheart failure: pathophysiology and therapy.* Circ Res 2013;113:739-53.

[84] Rengo G, Lymperopoulos A, Koch WJ. *Future G protein-coupled receptor targets for treatment of heart failure*. Curr Treat Options Cardiovasc Med 2009;11:328-38.

[85] Triposkiadis F, Karayannis G, Giamouzis G, et al. *The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications.* J Am Coll Cardiol 2009;54:1747-62.

[86] Iaccarino G, Barbato E, Cipolletta E, et al. *Elevated myocardial and lymphocyte GRK2 expression and activity in human heart failure.* Eur Heart J 2005;26:1752-8.

[87] Rengo G, Perrone-Filardi P, Femminella GD, et al. *Targeting the β-adrenergic receptor system through G-protein-coupled receptor kinase2: a new paradigm for therapy and prognostic evaluation in heart failure: from bench to bedside.* Circ Heart Fail 2012;5:385-91.

[88] Rengo G., Lymperopoulos A, Leosco D, et al. *GRK2 as a novel gene therapy target in heart failure.* J Mol Cell Cardiol 2011;50:785-92.

[89] Böhm M, La Rosée K, Schwinger RH, et al. *Evidence for reduction of norepinephrine uptake sites in the failing human heart.* J Am Coll Cardiol 1995;25:146-53.

[90] Ungerer M, Hartmann F, Karoglan M, et al. *Regional in vivo and in vitro characterization of autonomic innervation in cardiomyopathic human heart*. Circulation 1998;97:174-80.

[91] Backs J, Haunstetter A, Gerber SH, et al. *The neuronal norepinephrine transporter in experimental heart failure: evidence for a posttranscriptional downregulation.* J Mol Cell Cardiol 2001;33:461-72.

[92] Paolillo S, Rengo G, Pagano G, et al. *Impact of diabetes on cardiac sympathetic innervation in patients with heart failure: a 123I metaiodobenzylguanidine (123I MIBG) scintigraphic study.* Diabetes Care 2013;36:2395-401.

[93] Jacobson AF, Senior R, Cerqueira MD, et al.; ADMIRE-HF Investigators. *Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure. Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study*. J Am Coll Cardiol 2010;55:2212-21.

[94] Mardon K, Montagne O, Elbaz N, et al. *Uptake-1 carrier downregulates in parallel with the beta-adrenergic receptor desensitization in rat hearts chronically exposed to high levels of circulating norepinephrine: implications for cardiac neuroimaging in human cardiomyopathies.* J Nucl Med 2003;44:1459-66.

[95] Bristow MR, Ginsburg R, Minobe W, et al. *Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts*. N Engl J Med 1982;307:205-11.

[96] Maffei M, Halaas J, Ravussin E, et al. *Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects*. Nat Med 1995;1:1155-61.

[97] Considine RV, Sinha MK, Heiman ML, et al. *Serum immunoreactive-leptin concentrations in normal-weight and obese humans.* N Engl J Med 1996;334:292-5.

[98] Vargovic P, Ukropec J, Laukova M, et al. *Adipocytes as a new source of catecholamine production*. FEBS Lett 2011;585:2279-84.

[99] Parisi V, Rengo G, Perrone-Filardi P, et al. *Increased epicardial adipose tissue volume correlates with cardiac sympathetic denervation in patients with heart failure*. Circ Res 2016;118:1244-53.

[100] Parisi V, Paolillo S, Rengo G, et al. *Sleep-disordered breathing and epicardial adipose tissue in patients with heart failure.* Nutr Metab Cardiovasc Dis 2018;28:126-32.

[101] Naughton MT, Benard DC, Liu PP, et al. *Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea.* Am J Respir Crit Care Med 1995;152:e473-9.

[102] Solin P, Kaye DM, Little PJ, et al. *Impact of sleep apnea on sympathetic nervous system activity in heart failure*. Chest 2003;123:e1119-26.

[103] Mansfield D, Kaye DM, La Rocca BH, et al. *Raised sympathetic nerve activity in heart failure and central sleep apnea is due to heart failure severity.* Circulation 2003;107:e1396-400.

[104] Soucek F, Covassin N, Singh P, et al. *Effects of atorvastatin (80 mg) therapy on quantity of epicardial adipose tissue in patients undergoing pulmonary vein isolation for atrial fibrillation*. Am J Cardiol 2015;116:1443-6.

[105] Cho KI, Kim BJ, Cha TJ, et al. *Impact of duration and dosage of statin treatment and epicardial fat thickness on the recurrence of atrial fibrillation after electrical cardioversion.* Heart Vessels 2015;30:490-7.

[106] Parisi V, Petraglia L, D'Esposito V, et al. *Statin therapy modulates thickness and inflammatory profile of human epicardial adipose tissue*. Int J Cardiol 2019;274:326-30.

[107] Parisi V, Rengo G, Pagano G, et al. *Epicardial adipose tissue has an increased thickness and is a source of inflammatory mediators in patients with calcific aortic stenosis*. Int J Cardiol 2015;186:167-9.

[108] Parisi V, Leosco D, Ferro G, et al. *The lipid theory in the pathogenesis of calcific aortic stenosis*. Nutr Metabob Cardiovasc Dis 2015;25:519-25.

[109] Wu CK, Yeh CF, Chiang JY, et al. *Effects of atorvastatin treatment on left ventricular diastolic function in peritoneal dialysis patients-the ALEVENT clinical trial*. J Clin Lipidol 2017;11:657-66.

[110] Beck AL, Otto ME, D'Avila LB, et al. *Diastolic function parameters are improved by the addition of simvastatin to enalapril-based treatment in hypertensive individuals*. Atherosclerosis 2012;222:444-8.

[111] Akahori H, Tsujino T, Naito Y, et al. *Atorvastatin ameliorates cardiac fibrosis and improves left ventricular diastolic function in hypertensive diastolic heart failure model rats.* J Hypertens 2014;32:1534-41.

[112] Fukuta H, Goto T, Wakami K, et al. *The effect of statins on mortality in heart failure with preserved ejection fraction: a meta-analysis of propensity score analyses*. Int J Cardiol 2016;214:301-6.

[113] Liu G, Zheng XX, Xu YL, et al. *Meta-analysis of the effect of statins on mortality in patients with preserved ejection fraction.* Am J Cardiol 2014;113:1198-204.

[114] Altara R, Giordano M, Nordén ES, et al. *Targeting obesity and diabetes to treat heart failure with preserved ejection fraction*. Front Endocrinol (Lausanne) 2017;8:160.

[115] Ferrara N, Abete P, Corbi G, et al. *Insulin-induced changes in beta-adrenergic response: an experimental study in the isolated rat papillary muscle.* Am J Hypertens 2005;18:348-53.

[116] Nichols GA, Koro CE, Gullion CM, et al. *The incidence of congestive heart failure associated with antidiabetic therapies.* Diabetes Metab Res Rev 2005;21:51-7.

[117] Shi H, Moustaid-Moussa N, Wilkison WO, et al. *Role of the sulfonylurea receptor in regulating human adipocyte metabolism*. FASEB J1999;13:1833-8.

[118] Haffner SM, Hanefeld M, Fischer S, et al. *Glibenclamide, but not acarbose, increases leptin concentrations parallel to changes in insulin in subjects with NIDDM.* Diabetes Care 1997;20:1430-4.

[119] Grosso AF, de Oliveira SF, Higuchi Mde L, et al. *Synergistic antiinflammatory effect: simvastatin and pioglitazone reduce inflammatory markers of plasma and epicardial adipose tissue of coronary patients with metabolic syndrome*. Diabetol Metab Syndr 2014;6:47.

[120] Sacks HS, Fain JN, Cheema P, et al. *Inflammatory genes in epicardial fat contiguous with coronary atherosclerosis in the metabolic syndrome and type 2 diabetes: changes associated with pioglitazone.* Diabetes Care 2011;34:730-3.

[121] Distel E, Penot G, Cadoudal T, et al.. *Early induction of a brown-like phenotype by rosiglitazone in the epicardial adipose tissue of fatty Zucker rats*. Biochimie 2012;94:1660-7.

[122] Della-Morte D, Palmirotta R, Rehni AK, et al. *Pharmacogenomics and pharmacogenetics of thiazolidinediones: role in diabetes and cardiovascular risk factors.* Pharmacogenomics 2014;15:2063-82.

[123] Dutour A, Abdesselam I, Ancel P, et al. *Exenatide decreases liver fat content and epicardial adipose tissue in patients with obesity and type 2 diabetes: a prospective randomized clinical trial using magnetic resonance imaging and spectroscopy.* Diabetes Obes Metab 2016;18:882-91.

[124] Pastel E, McCulloch LJ, Ward R, et al. *GLP-1 analogue-induced weight loss does not improve obesity-induced AT dysfunction.* Clin Sci (London) 2017;131:343-53.

[125] Al-Barazanji KA, Arch JR, Buckingham RE, et al. *Central exendin-4 infusion reduces body weight without altering plasma leptin in (fa/fa) Zucker rats*. Obes Res 2000;8:317-23.

[126] Marso SP, Daniels GH, Brown-Frandsen K, et al. *Liraglutide and cardiovascular outcomes in type 2 diabetes*. N Engl J Med 2016;375:311-22.

[127] Marso SP, Bain SC, Consoli A, et al. *Semaglutide and cardiovascular outcomes in patients with type 2 diabetes*. N Engl J Med 2016;375:1834-44.

[128] Lima-Martínez MM, Paoli M, Rodney M, et al. *Effect of sitagliptin on epicardial fat thickness in subjects with type 2 diabetes and obesity: a pilot study.* Endocrine 2016;51:448-55.

[129] Mulvihill EE, Varin EM, Ussher JR, et al. *Inhibition of dipeptidyl peptidase-4 impairs ventricular function and promotes cardiac fibrosis in high fat-fed diabetic mice.* Diabetes 2016;65:742-54.

[130] Jackson EK, Zhang Y, Gillespie DD, et al. *SDF-1a (stromal cell-derived factor 1a) induces cardiac fibroblasts, renal microvascular smooth muscle cells, and glomerular mesangial cells to proliferate, cause hypertrophy, and produce collagen*. J Am Heart Assoc 2017;6:e007253.

[131] Chu PY, Zatta A, Kiriazis H, et al. *CXCR4 antagonism attenuates the cardiorenal consequences of mineralocorticoid excess.* Circ Heart Fail 2011;4:651-8.

[132] McMurray JJV, Ponikowski P, Bolli GB, et al. *Effects of vildagliptin on ventricular function in patients with type 2 diabetes mellitus and heart failure: a randomized placebo-controlled trial.* J Am Coll Cardiol HF 2018;6:8-17.

[133] Bouchi R, Terashima M, Sasahara Y, et al. *Luseogliflozin reduces epicardial fat accumulation in patients with type 2 diabetes: a pilot study.* Cardiovasc Diabetol 2017;16:32.

[134] Fukuda T, Bouchi R, Terashima M, et al. *Ipragliflozin reduces epicardial fat accumulation in non-obese type 2 diabetic patients with visceral obesity: a pilot study.* Diabetes Ther 2017;8:851-61.

[135] Hammoudi N, Jeong D, Singh R, et al. *Empagliflozin improves left ventricular diastolic dysfunction in a genetic model of type 2 diabetes.* Cardiovasc Drugs Ther 2017;31:233-46.

[136] Habibi J, Aroor AR, Sowers JR, et al. *Sodium glucose transporter 2 (SGLT2) inhibition with empagliflozin improves*

cardiac diastolic function in a female rodent model of diabetes. Cardiovasc Diabetol 2017;16:9.

[137] Kusaka H, Koibuchi N, Hasegawa Y, et al. *Empagliflozin lessened cardiac injury and reduced visceral adipocyte hypertrophy in prediabetic rats with metabolic syndrome*. Cardiovasc Diabetol 2016;15:157.

[138] Joubert M, Jagu B, Montaigne D, et al. *The sodium-glucose cotransporter 2 inhibitor dapagliflozin prevents cardiomyopathy in a diabetic lipodystrophic mouse model*. Diabetes 2017;66:1030-40.

[139] Eurich DT, Weir DL, Majumdar SR, et al. *Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients.* Circ Heart Fail 2013;6:395-402.

[140] Zinman B, Wanner C, Lachin JM, et al. *Empagliflozin, cardiovascular out-comes, and mortality in type 2 diabetes*. N Engl J Med 2015;373:2117-28.

[141] Neal B, Perkovic V, Mahaffey KW, et al. *Canagliflozin and cardiovascular and renal events in type 2 diabetes*. N Engl J Med 2017;377:644-57.

[142] Guo C, Ricchiuti V, Lian BQ, et al. *Mineralocorticoid receptor blockade reverses obesity related changes in expression of adiponectin, peroxisome proliferator-activated receptorgamma, and proinflammatory adipokines*. Circulation 2008;117:2253-61.

[143] Anand IS, Claggett B, Liu J, et al. *Interaction between spironolactone and natriuretic peptides in patients with heart failure and preserved ejection fraction: from the TOPCAT trial.* J Am Coll Cardiol HF 2017;5:241-52.

[144] Solomon SD, Zile M, Pieske B, et al. *The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial.* Lancet 2012;380:1387-95.

[145] Ridker PM, Everett BM, Thuren T, et al. *Antiinflammatory therapy with canakinumab for atherosclerotic disease*. N Engl J Med 2017;377:1119-31.

How to cite this article: Leosco D, Petraglia L, Grieco FV, et al. *Proinflammatory phenotype of cardiac visceral fat in heart failure with preserved ejection fraction in the elderly*. Journal of Gerontology and Geriatrics 2019;67(Suppl):195-204.

JGG 2019;67(Suppl):205-212

Review

Epicardial adipose tissue in the pathogenesis and progression of coronary artery disease

L. Petraglia, M. Conte, F.V. Grieco, L. Ferrante, C. Russo, V. Parisi

Department of Translational Medical Science, University of Naples "Federico II", Naples, Italy

Coronary artery disease (CAD) represents one of the most important causes of morbility, hospitalization and death, and its incidence greatly increases in the elderly population. In the last decades, several pieces of evidence have suggested a pathogenetic role of systemic and visceral fat inflammation in the development and progression of CAD. The epicardial adipose tissue (EAT), the visceral fat depot of heart, produces and secretes numerous pro-inflammatory mediators that could be involved in the pathogenesis of coronary atherosclerosis. Furthermore, age-related low-grade inflammation leads to the accumulation and inflammation of EAT. Therefore, this review aims to explore the potential implication of EAT in the pathogenesis of CAD, the link between systemic inflammation and an EAT pro-inflammatory phenotype, and, finally the perspectives for novel therapeutic strategies targeting the cardiac visceral fat.

Key words: Epicardial adipose tissue, Coronary artery disease, Elderly

INTRODUCTION

Coronary artery disease (CAD) represents one of the most important causes of morbility, hospitalization and death worldwide. In the elders, the incidence of cardiovascular disease is greatly increased. In particular, advanced age is associated with higher incidence of myocardial infarction, cardiovascular and extracardiac comorbidities [1-5]. Furthermore, elderly subjects form the largest and fastest growing part of the population, accounting for one-third of hospitalization for acute cardiovascular events and for most of all cardiac deaths [6-8]. Age has been reported as an important risk predictor in patients admitted in hospital with non-ST elevation myocardial infarction (NSTE-ACS) [9] and some studies have shown poor outcomes and high age-related mortality rates, after primary percutaneous coronary interventions in the elderly [10 11].

The causes of cardiovascular diseases are complex, but increasing evidence suggests a pathogenetic role of inflammation in the development and progression of CAD. The epicardial adipose tissue (EAT), the visceral fat depot of heart, produces and secretes numerous inflammatory mediators that could be involved in the pathogenesis of coronary atherosclerosis.

Inflammation and CAD

A correlation between inflammation and CAD has been initially hypothesized since autopsy studies, conducted in patients died for acute coronary syndrome, showed the presence of rich inflammatory infiltrates, consisting of lymphocytes, monocytes, and macrophages, in the adventitia of coronary arteries. In these studies, the degree of coronary narrowing correlated with the number of inflammatory cells in the coronary adventitia [12].

In the last decades, several pieces of evidence have supported the association between inflammation and CAD, identifying many inflammatory mediators involved in the atherosclerotic process. In particular, it has been demonstrated that, following an atherogenic stimulus, vascular cells adhesion molecule-1 binds monocytes and T lymphocytes [13]. Once adherent to

Received: July 31, 2019 - Accepted: October 1, 2019

Correspondence: Laura Petraglia, Department of Translational Medical Science, University of Naples "Federico II", via S. Pansini 5, 80130, Naples, Italy. E-mail: laura_petraglia@virgilio.it

the endothelium, the leukocytes penetrate the intima. Some chemoattractant molecules, such as monocyte chemoattractant protein-1 (MCP-1), are responsible for this transmigration at sites of lesion formation [14 15]. The recruited macrophages ingest lipids and become foam cells [16]. Afterwards, blood-derived inflammatory cells trigger and perpetuate a local inflammatory response, also through the release of numerous inflammatory and fibrogenic mediators, as tumor necrosis factor-α (TNF-α) and interleukins (IL) [17]. Interestingly, in the atherosclerotic plaque, activated macrophages and T cells can release hydrolytic enzymes, cytokines, chemokines and growth factors, leading to a focal necrosis of the fibrous cap, that becomes thin, weak, and susceptible to rupture [18 19]. Macrophages also produce tissue factor, the major procoagulant mediator, triggering thrombosis found in the plaques [20]. Thus, inflammation is responsible for the onset and progression of atherosclerotic process and plaques rupture.

The pathogenetic role of inflammation in the atherosclerotic process is also confirmed by high circulating levels of acute phase proteins. In clinical studies, elevated serum levels of C-reactive protein (CRP), IL-6 and TNF-α represent an important prognostic factor of atherosclerosis development both in patients with known CAD and in healthy population [21 22]. There is also a direct correlation between the level of CRP in the serum and the severity of atherosclerosis in patients with stable CAD [23]. In apparently healthy men, elevated levels of IL-6 are associated with increased risk of future myocardial infarction [24].

Of note, aging is characterized by the presence of chronic low-grade inflammation. This condition can contribute to the recruitment of inflammatory cells, damage and impairment of endothelial function, migration and proliferation of smooth muscle cells to the site of injury, resulting in the formation of early atherosclerotic lesions and higher susceptibility to CAD [19].

VISCERAL ADIPOSE TISSUE AND CAD

In the literature, visceral adipose tissue (VAT) is usually defined as an intra-abdominal accumulation of adiposity, predominantly localized at the omental and mesenteric level. The adipose tissue is composed of 50% of adipocytes and 50% of other cells, such as stromal vasculature fraction of fibroblasts, endothelial cells, macrophages and preadipocytes [25]. It has been demonstrated that persistent positive caloric balance, as occurs in obesity, induces excessive fat cell enlargement with consequent adipocyte metabolic and immune dysfunction [26-29]. These alterations lead to the activation of lipolysis, increased formation of free fatty acids (FFA), oxidative stress, hypoxia, and increased apoptosis of adipocytes [30]. Moreover, infiltrated monocytes generate M1 macrophages, increasing the total secretion of pro-inflammatory cytokines, such as TNF-a, IL-1β, and IL-6. Through these mediators, the increase of VAT mass can also contribute to systemic inflammation [31 32]. Several studies have confirmed the central role of this pro-inflammatory state in endothelial dysfunction and cardiovascular disease [33-35]. Of note, clinical data initially suggested the association between VAT and CAD. In one of the first observations, non-obese men with CAD showed larger VAT deposits than age- and BMI-matched controls [36]. The association with CAD remained significant even after adjustment for risk factors [37]. In a small study population with known CAD, it has been reported that increased VAT volume correlates with the presence of multivessel rather than single vessel disease [38]. In a recent study, VAT was associated with the risk of progression of non-calcified coronary artery plaques in patients with CAD [39]. Interestingly, in obese people, cardiovascular risk is predominantly associated with visceral than with subcutaneous adiposity [40 41].

EPICARDIAL ADIPOSE TISSUE AND CORONARY ARTERY DISEASE (FIG. 1)

EAT is the visceral fat depot of the heart, principally distributed in atrio-ventricular and interventricular grooves, between the myocardium and the visceral layer of pericardium. The absence of fascial boundaries permits a direct influence of EAT on surrounding tissues and coronary arterial vessels [42 43]. The increase of EAT mass is associated to production of several pro-inflammatory and pro-atherogenic mediators [44-47]. Interestingly, subjects with angiographically significant CAD show higher EAT thickness than patients without CAD. EAT thickness increases as the number of vessels with > 50% stenosis increase. On multiple logistic analysis including various CAD risk factors, EAT results an independent predictor of CAD [48 49]. A prospective study, exploring the metabolic activity of EAT measured by positron emission tomography (PET)/CT, has demonstrated that patients with NSTE-ACS show maximum fludeoxyglucose uptake (SUV) in fat surrounding coronary arteries. Additionally, the inflammatory activity of EAT was greater than in subcutaneous, visceral or thoracic adipose tissue, and correlated with plaque burden and with the necrotic core component, assessed by virtual histology intravascular ultrasound [50 51]. These clinical observations have been also supported by a positive correlation between density of macrophage infiltrates and SUV, in an experimental model of atherosclerosis [52].

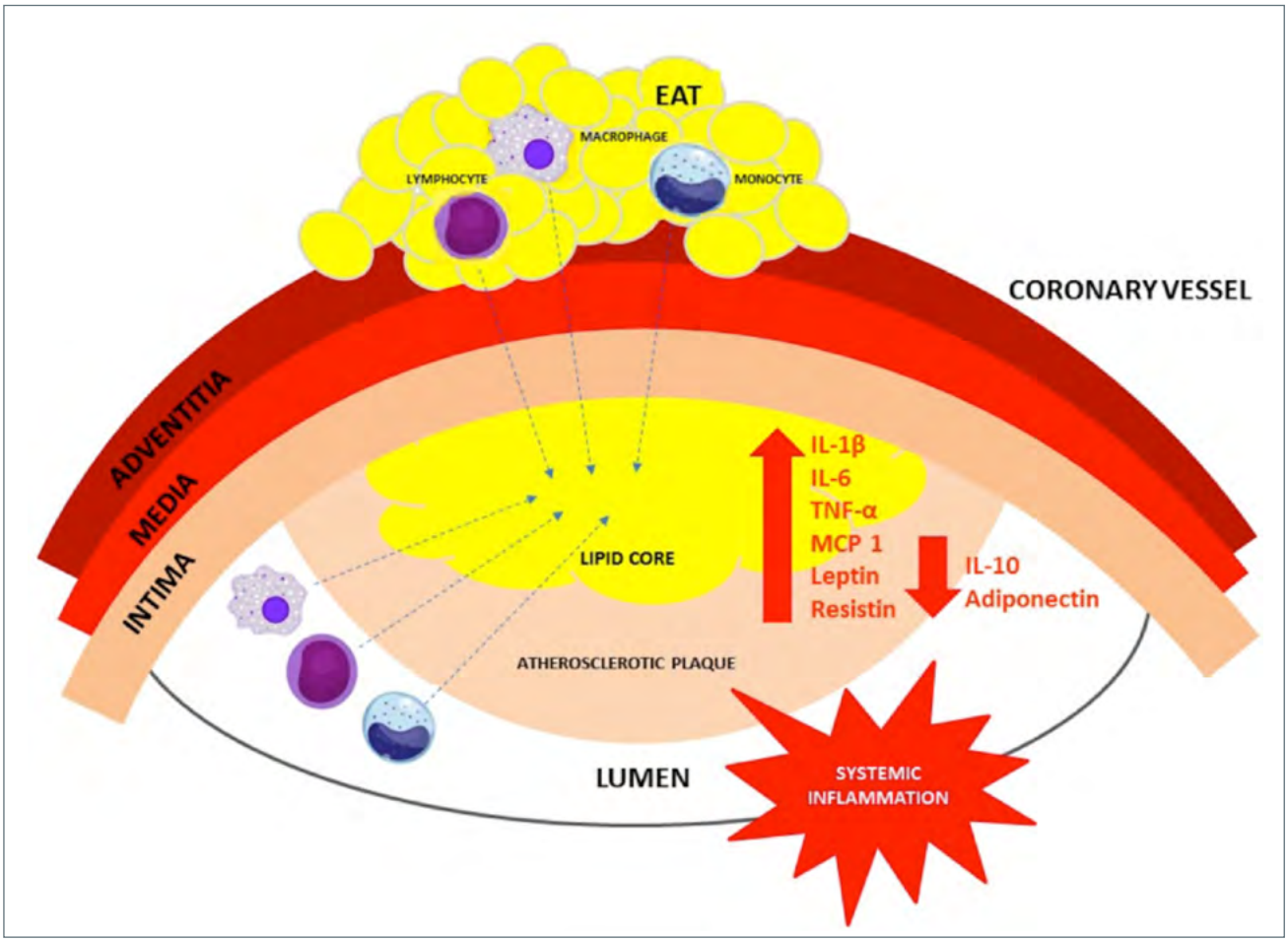

Figure 1. Involvement of epicardial adipose tissue in the pathogenesis of atherosclerotic plaque. The figure illustrates the intercorrelation between Epicardial Adipose Tissue (EAT) and systemic inflammation through a bidirectional continuum. Inflammatory cells from systemic circulation and from EAT penetrate the lipid core of the atherosclerotic plaque. The imbalance between production of pro-inflammatory and anti-inflammatory molecules promotes plaque progression and contributes to plaque instability and rupture.

Other studies, conducted in patients with established CAD, have demonstrated a pathological increase of EAT-derived inflammatory mediators and their messenger RNA, with a dense infiltration of inflammatory cells observed in EAT but not in the subcutaneous adipose tissue [45]. The inflammatory proatherogenic stimulus results more evident in patients with acute coronary syndromes than in patients with stable CAD [53].

In patients undergoing coronary artery bypass graft (CABG) surgery, it has been reported an increased EAT expression of interleukin (IL)-1β, IL-6, TNF-α, and MCP-1 compared to that observed in the subcutaneous adipose tissue [45 46]. In order to investigate the underlying mechanism of pro-inflammatory cytokines levels in EAT of CAD patients, Bourlier et al., performed immunohistochemistry against CD68, marker for all types of macrophages, CD11c, marker for inflammatory M1 macrophages, and CD206, marker for anti-inflammatory M2 macrophage. CD68 positive macrophages were significantly increased in the EAT of the CAD group. The ratio of CD11c/CD68-positive cells was significantly increased, while the ratio of CD206/CD68-positive cells was significantly decreased in the EAT of the CAD group [54]. This result demonstrates a relative increase of M1 macrophages and a relative decrease of M2 macrophages in the EAT of the CAD group. Furthermore, the ratio of M1/M2 macrophages showed a positive correlation with the severity of CAD. Overall, these results suggest that the macrophage polarization in EAT would play a central pathological role in the coronary atherosclerotic process [55-57].

Other studies have demonstrated that patients with acute coronary syndrome present with a higher expression and secretion of resistin in the EAT, compared to patients with stable CAD or subjects without CAD [58]. The exact role of resistin is currently unclear. It is

probably involved in the processes of inflammation and atherogenesis through increasing expression of adhesion molecules on endothelial cells and impairing vasodilation [59 60]. Resistin has been recently linked to the incidence of acute coronary syndromes and stroke [61]. In humans, resistin is produced by macrophages [62] and correlates with markers of inflammation, as well as with coronary atherosclerosis [63]. Plasma resistin levels have been also recently shown to be predictive of mortality in patients with acute myocardial infarction [64]. Similar clinical evidence has been reported for Leptin [65].

Several studies have identified adiponectin as the principal antiatherogenic protein detected in EAT in physiologic conditions. Adiponectin inhibits the expression of IL-8 by endothelial cells, increases the production of anti-inflammatory IL-10 and tissue inhibitor of metalloproteinase-1 in macrophages. Finally, this cytokine exerts vasodilatory properties on small arteries [66]. The observation of lower levels of adiponectin in the EAT of CAD patients [67] suggests that the pro-atherogenic properties of EAT in CAD are determined by both an increase of pro-inflammatory mediators and a decrease of anti-inflammatory cytokines.

Of note, the definitive demonstration of the causative role of EAT in the development and progression of CAD derives from animal studies. In fact, surgical resection of EAT depot in pigs arrests coronary atherogenesis [68-70].

As regards the intercorrelation between EAT and systemic inflammation, it is plausible to hypothesize a bidirectional continuum. The release of proinflammatory adipocytokines from EAT into the blood may contribute to the systemic inflammatory state; systemic inflammation in turn promotes the accumulation of EAT, which induces local and systemic inflammation and end-organ dysfunction [70-72].

PREVENTION AND THERAPEUTIC INTERVENTIONS

Given the recognized role of EAT in the development and progression of CAD, this adipose depot could represent a novel therapeutic target. First of all, dietary and lifestyle changes can affect the EAT volume and its inflammatory profile. Some studies have demonstrated that a marked wheight loss can lead to a reduction or stabilization of EAT volume [73 74]. Furthermore, in obese patients, Kim et al. [75] have shown that aerobic exercise is associated with lowering EAT mass. However, these data remain controversial and are only partially confirmed by studies conducted on patients underwent bariatric surgery, showing a greater decrease in VAT compared to EAT [76 77]. Interestingly, in experimental animals, Walker et al. [78] have tested EAT fatty acid composition and inflammatory gene expression after exposure to two different dietary patterns, containing respectively high levels of saturated or polyunsaturated fatty acids. High saturated fatty acids diet modulates EAT composition, increasing percentage of saturated fatty acid, and results positively associated with the expression of pro-inflammatory genes, providing a link between diet and EAT inflammation. Thus, changes in dietary quality could represent a nutritional strategy to reduce EAT inflammation and development of CAD.

As regards pharmacological interventions, new interesting perspectives could result from oral statin therapy. As known, this class of drug, in addition to lipid levels control, exerts relevant pleiotropic effects, such as modulation of cell signalling, differentiation and proliferation [79]. A recent study has reported a statin-induced decrease in EAT attenuation on computed tomography, independent of low-density lipoprotein cholesterol lowering, thus demonstrating a decrement in the metabolic activity of EAT by reduction in cellularity, vascularity and inflammation [80]. As reported by Parisi et al., the EAT thickness correlates with its inflammatory profile, thus the EAT volume reduction corresponds to a lower secretion of pro-inflammatory cytokines [44 81 82].

Furthermore, in the obese and diabetic populations, some studies have demonstrated that the use of glucagon-like-protein-1 receptor agonists (GLP-1R), in particular of liraglutide, induces a significant reduction of EAT (13%) after 12 weeks of treatment [83-85]. Moreover, liraglutide, but not metformin, reduces EAT by 29% and 36% at 3 and 6 months, respectively [84]. In an animal model, liraglutide also promotes browning and thermogenesis independently of nutrient intake [86].

Accordingly, sitagliptin, a DPP-4 inhibitor that prevents GLP-1 degradation, reduces EAT (15%) and VAT in diabetic individuals [87]. The thiazolidinediones, acting mainly through the PPAR-γ, regulate the expression of numerous factors secreted from adipose tissue that greatly influence insulin sensitivity [88].

Finally, novel opportunities could result from genetic manipulation using oligonucleotide inhibitors or microRNA mimics. MicroRNAs are short noncoding RNA molecules, that permit the fine-tuning of protein expression *in vivo* [89] and the modulation of important biological pathways, such as vascular proliferation (miR-21), remodeling (miR-143/miR145), and atherosclerosis (miR-126) [90]. It has been demonstrated that some microRNAs, involved in regulation of adiponectin, glucose and fatty acids, are upregulated in abdominal adipose tissue of obese patients [91 92]. Further studies are needed to demonstrate the same effect in EAT.

Unfortunately, outcome studies reporting the predictive value of diet and/or drug related EAT reduction in CAD patients are not yet available. These studies are

dramatically needed given the emergent role of EAT in the pathogenesis of several cardiovascular diseases.

CONCLUSIONS

Several studies have demonstrated the participating role of pro-inflammatory mediators in the atherogenic process. Because of the intimacy with myocardium and coronary vessels, the EAT seems to be the main source of pro-atherogenic molecules, involved in the development and progression of CAD. Realistically, the causative role of EAT in CAD is determined by both an increase of pro-inflammatory mediators and a decrease of anti-inflammatory molecules. Furthermore, chronic inflammatory disorders and age-related low-grade inflammation lead to the accumulation and inflammation of EAT, promoting in turn local and systemic inflammation with unavoidable implications in the pathogenesis of CAD. Finally, dietary/life-style changes and/or drug therapies can modify volume and secretory profile of EAT, thus suggesting that cardial visceral fat might represent, in the next future, a novel therapeutic target for CAD patients.

Conflict of interest

The Authors declare to have no conflict of interest.

References

1 Forman DE, Chen AY, Wiviott SD, et al. *Comparison of outcomes in patients aged < 75, 75 to 84, and ≥ 85 years with ST-elevation myocardial infarction (from the ACTION Registry-GWTG)*. Am J Cardiol 2010;106:e1382-8.

2 Lye M, Donnellan C. *Heart disease in the elderly.* Heart 2000;84:e560-6.

3 Ungar A, Galizia G, Morrione A, et al. *Two-year morbidity and mortality in elderly patients with syncope*. Age Ageing 2011;40:696-702. Doi: 10.1093/ageing/afr109.

4 Cacciatore F, Abete P, de Santis D, et al. *Mortality and blood pressure in elderly people with and without cognitive impairment*. Gerontology 2005;51:53-61.

5 Ungar A, Mussi C, Ceccofiglio A, et al. *Etiology of syncope and unexplained falls in elderly adults with dementia: Syncope and Dementia (SYD) study.* J Am Geriatr Soc 2016;64:1567-73.

6 Goldberg RJ, Yarzebski J, Lessard D, et al. *A two-decades (1975 to 1995) long experience in the incidence, in-hospital and long-term case-fatality rates of acute myocardial infarction: a community-wide perspective.* J Am Coll Cardiol 1999;33:1533-9.

7 Cacciatore F, Abete P, Mazzella F, et al. *Six-minute walking test but not ejection fraction predicts mortality in elderly patients undergoing cardiac rehabilitation following coronary artery bypass grafting.* Eur J Prev Cardiol 2012;19:1401-9. Doi: 10.1177/1741826711422991.

8 Martone AM, Bianchi L, Abete P, et al. *The incidence of sarcopenia among hospitalized older patients: results from the Glisten study.* J Cachexia Sarcopenia Muscle 2017;8:907-14.

9 Fox KAA, Dabbous OH, Goldberg RJ, et al. *Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE)*. BMJ 2006;333:1091. Doi:10.1136/ bmj.38985.646481.55

10 Wang TY, Gutierrez A, Peterson ED. *Percutaneous coronary intervention in the elderly.* Nat Rev Cardiol 2011;8:e79-90.

11 McKellar SH, Brown ML, Frye RL, et al. *Comparison of coronary revascularization procedures in octogenarians: a systematic review and meta-analysis.* Nat Clin Pract Cardiovasc Med 2008;5:e738-46.

12 Kohchi K, Takebayashi S, Hiroki T, et al. *Significance of adventitial inflammation of the coronary artery in patients with unstable angina: results of autopsy.* Circulation 1985;71:709-16.

13 Li H, Cybulsky MI, Gimbrone MA Jr, et al. *An atherogenic diet rapidly induces VCAM-1, a cytokine regulatable mononuclear leukocyte adhesion molecule, in rabbit endothelium.* Arterioscler Thromb 1993;13:197-204.

14 Gu L, Okada Y, Clinton S, et al. *Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low-density lipoprotein-deficient mice.* Mol Cell 1998;2:275-81, 8.

15 Boring L, Gosling J, Cleary M, et al. *Decreased lesion formation in CCR -/- mice reveals a role for chemokines in the initiation of atherosclerosis.* Nature 1998;394:894-7.

16 Smith JD, Trogan E, Ginsberg M, et al. *Decreased atherosclerosis in mice deficient in both macrophage colony-stimulating factor (op) and apolipoprotein E.* Proc Natl Acad Sci USA 1995;92:8264-8.

17 Hansson G, Libby P. *The role of the lymphocyte*. In: Fuster V, Ross R, Topol E, Eds. *Atherosclerosis and CAD.* New York, NY: Lippincott-Raven 1996, pp. 557-68.

18 Virmani R, Burke AP, Farb A, et al. *Pathology of vulnerable plaque*. JACC 2006;47:C13-8.

19 Libby P. *Current concepts of the pathogenesis of the acute coronary syndromes*. Circulation 2001;104:365-72.

20 Libby P, Simon DI. *Inflammation and thrombosis: the clot thickens.* Circulation 2001;103:1718-20.

21 Tommasi S, Carluccio E, Bentivoglio M, et al. *C-reactive-protein as a marker for cardiac ischemic events in the year after a first, uncomplicated myocardial infarction*. Am J Cardiol 1999;83:1595-9.

22 Curcio F, Ferro G, Basile C, et al. *Biomarkers in sarcopenia: a multifactorial approach*. Exp Gerontol 2016;85:1-8.

23 Liuzzo G, Biasucci LM, Gallimore JR, et al. *The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina.* N Engl J Med 1994;331:417-23.

24 Ridker PM, Rifai N, Stampfer MJ, et al. *Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men.* Circulation 2000;101:1767-72.

25 Bays HE, González-Campoy JM, Bray GA, et al. *Pathogenic*

potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. Expert Rev Cardiovasc Ther 2008;6:343-68. Doi: 10.1586/14779072.6.3.343.

26 Bays H, Blonde L, Rosenson R. *Adiposopathy: how do diet, exercise, weight loss and drug therapies improve metabolic disease?* Expert Rev Cardiovasc Ther 2006;4:871-95.

27 Ailhaud G. *Adipose tissue as a secretory organ: from adipogenesis to the metabolic syndrome*. CR Biol 2006;329:570-7.

28 Salans LB, Bray GA, Cushman SW, et al. *Glucose metabolism and the response to insulin by human adipose tissue in spontaneous and experimental obesity*. *Effects of dietary composition and adipose cell size*. J Clin Invest 1974;53:848-56.

29 Bray GA, Glennon JA, Salans LB, et al. *Spontaneous and experimental human obesity: effects of diet and adipose cell size on lipolysis and lipogenesis*. Metabolism 1977;26:739-47.

30 Alkhouri N, Gornicka A, Berk MP, et al. *Adipocyte apoptosis, a link between obesity, insulin resistance, and hepatic steatosis*. J Biol Chem 2010;285:e3428-38.

31 Guarner V, Rubio-Ruiz ME. *Low-grade systemic inflammation connects aging,metabolic syndrome and cardiovascular disease.* Interdiscip Top Gerontol 2015;40:99-106. Doi: 10.1159/000364934.

32 Frigolet ME, Torres N, Tovar AR. *White adipose tissue as endocrine organ and its role in obesity*. Arch Med Res 2008;39:715-28.

33 Mathieu P, Poirier P, Pibarot P, et al. *Visceral obesity: the link among inflammation, hypertension, and cardiovascular disease.* Hypertension 2009;53:577-84. Doi: 10.1161/HYPERTENSIONAHA.108.110320

34 Neeland IJ, Ayers CR, Rohatgi AK, et al. *Associations of visceral and abdominal subcutaneous adipose tissue with markers of cardiac and metabolic risk in obese adults*. Obesity 2013;21:e439-47. Doi: 10.1002/oby.20135

35 Britton KA, Massaro JM, Murabito JM, et al. *Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality.* J Am Coll Cardiol 2013;62:921-5.

36 Nakamura T, Tokunaga K, Shimomura I, et al. *Contribution of visceral fat accumulation to the development of CAD in non-obese men.* Atherosclerosis 1994;107:e239-46.

37 Marques MD, Santos RD, Parga JR, et al. *Relation between visceral fat and CAD evaluated by multidetector computed tomography.* Atherosclerosis 2010;209:e481-6.

38 Lee YH, Lee SH, Jung ES, et al. *Visceral adiposity and the severity of CAD in middle-aged subjects with normal waist circumference and its relation with lipocalin-2 and MCP-1*. Atherosclerosis 2010;213:e592-7.

39 Imai A, Komatsu S, Ohara T, et al. *Visceral abdominal fat accumulation predicts the progression of noncalcified coronary plaque.* Atherosclerosis 2012;222:e524-9.

40 Fox CS, Massaro JM, Hoffmann U, et al. *Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart study*. Circulation 2007;116:e39-48.

41 De Fronzo RA. I*nsulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009*. Diabetologia 2010;53;e1270-87.

42 Sacks HS, Fain JN. *Human epicardial adipose tissue: a review.* Am Heart J 2007;153:907-17.

43 Rabkin RW. *Epicardial fat: properties, function and relationship to obesity*. Obes Rev 2007;8:253-61.

44 Parisi V, Petraglia L, D'Esposito V, et al. *Statin therapy modulates thickness and inflammatory profile of human epicardial adipose tissue.* Int J Cardiol 2019;274:326-30. Doi: 10.1016/j.ijcard.2018.06.106

45 Mazurek T, Zhang L, Zalweski A, et al. *Human epicardial adipose tissue is a source of inflammatory mediators*. Circulation 2003;108:2460-6.

46 Parisi V, Rengo G, Perrone-Filardi P, et al. *Increased epicardial adipose tissue volume correlates with cardiac sympathetic denervation in patients with heart failure*. Circ Res 2016;118:1244-53. Doi: 10.1161/CIRCRESAHA.115.307765

47 Parisi V, Paolillo S, Rengo G, et al. *Sleep-disordered breathing and epicardial adipose tissue in patients with heart failure.* Nutr Metab Cardiovasc Dis 2018;28:126-32. Doi: 10.1016/j.numecd.2017.09.012

48 Ahn SG, Lim HS, Joe DY, et al. *Relationship of epicardial adipose tissue by echocardiography to CAD.* Heart 2008;94:e7.

49 Picard FA, Gueret P, Laissy JP, et al. *Epicardial adipose tissue thickness correlates with the presence and severity of angiographic CAD in stable patients with chest pain*. PloS One 2014;Oct 21. Doi: 10.1371/journal.pone.0110005

50 Mazurek T, Opolski G. *Pericoronary adipose tissue: a novel therapeutic target in obesity-related coronary atherosclerosis.* J Am Coll Nutr 2015;34:244-54. Doi: 10.1080/07315724.2014.933685

51 Mazurek T, Kochman J, Kobylecka M, et al. *Inflammatory activity of pericoronary adipose tissue may affect plaque composition in patients with acute coronary syndrome without persistent ST-segment elevation: preliminary results*. Kardiol Pol 2013;72:410-6.

52 Ogawa M, Magata Y, Kato T, et al. *Application of 18-F-FDG PET for monitoring the therapeutic effect of antiinflammatory drugs on stabilization of vulnerable atherosclerotic plaques.* J Nucl Med 2007;47:1845-50.

53 Nakanishi K, Fukuda S, Tanaka A, et al. *Epicardial adipose tissue accumulation is associated with renal dysfunction and coronary plaque morphology on multidetector computed tomography*. Circ J 2016;80:196-201.

54 Bourlier V, Zakaroff-Girard A, Miranville A, et al. *Remodeling phenotype of human subcutaneous adipose tissue macrophages*. Circulation 2008;117:806-15. Doi: 10.1161/CIRCULATIONAHA.107.724096

55 Lumeng CN, Bodzin JL, Saltiel AR. *Obesity induces a phenotypic switch in adipose tissue macrophage polarization.* J Clin Invest 2007;117:175-84.

56 Hirata Y, Tabata M, Kurobe H, et al. *Coronary atherosclerosis is associated with macrophage polarization in epicardial adipose tissue.* J Am Coll Cardiol 2011;58:248-55.

[57] Margaritis M, Antonopoulos AS, Digby J, et al. *Interactions between vascular wall and perivascular adipose tissue reveal novel roles for adiponectin in the regulation of endothelial nitric oxide synthase function in human vessels*. Circulation 2013;127:2209-21.

[58] Cheng KH, Chu CS, Lee KT, et al. *Adipocytokines and proinflammatory mediators from abdominal and epicardial adipose tissue in patients with CAD*. Int J Obes (Lond) 2008;32:268-74.

[59] Verma S, Li SH, Wang CH, et al. *Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction*. Circulation 2003;108:736-40.

[60] Gentile MT, Vecchione C, Marino G, et al. *Resistin impairs insulin-evoked vasodilation.* Diabetes 2008;57:577-83.

[61] Weikert C, Westphal S, Berger K, et al. *Plasma resistin levels and risk of myocardial infarction and ischemic stroke.* J Clin Endocrinol Metab 2008;93:2647-53.

[62] Fain JN, Cheema PS, Bahouth SW, et al. *Resistin release by human adipose tissue explants in primary culture*. Biochem Biophys Res Commun 2003;300:674-8.

[63] Reilly MP, Lehrke M, Wolfe ML, et al. *Resistin is an inflammatory marker of atherosclerosis in humans.* Circulation 2005;111:932-9.

[64] Lee SH, Ha JW, Kim JS, et al. *Plasma adiponectin and resistin levels as predictors of mortality in patients with acute myocardial infarction: data from infarction prognosis study registry*. Coron Artery Dis 2009;20:33-9.

[65] Payne GA, Borbouse L, Kumar S, et al. *Epicardial perivascular adipose-derived leptin exacerbates coronary endothelial dysfunction in metabolic syndrome via a protein kinase C-beta pathway.* Arterioscler Thromb Vasc Biol 2010;30:1711-7.

[66] Kumada M, Kihara S, Ouchi N, et al. *Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages*. Circulation 2004;109:2046-9.

[67] Pischon T, Girman CJ, Hotamisligil GS, et al. *Plasma adiponectin levels and risk of myocardial infarction in men.* JAMA 2004;291:1730-7.

[68] McKenney-Drake ML, Rodenbeck SD, Bruning RS, et al. *Epicardial adipose tissue removal potentiates outward remodeling and arrests coronary atherogenesis.* Ann Thorac Surg 2017;103:1622-30.

[69] McKenney ML, Schultz KA, Boyd JH, et al. *Epicardial adipose excision slows the progression of porcine coronary atherosclerosis.* J Cardiothorac Surg 2014;9:2.

[70] Packer M. *Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium.* J Am Coll Cardiol 2018;71:2360-72. Doi: 10.1016/j.jacc.2018.03.509

[71] Patel VB, Shah S, Verma S, et al. *Epicardial adipose tissue as a metabolic transducer: role in heart failure and coronary artery disease.* Heart Fail Rev 2017;22:889-902.

[72] Baghdadi LR, Woodman RJ, Shanahan EM, et al. *The impact of traditional cardiovascular risk factors on cardiovascular outcomes in patients with rheumatoid arthritis: a systematic review and meta-analysis.* PLoS One 2015;10:e0117952.

[73] Nakazato R, Rajani R, Cheng VY, et al. *Weight change modulates epicardial fat burden: a 4-year serial study with non-contrast computed tomography.* Atherosclerosis 2012;220:139-44.

[74] Fu CP, Sheu WH, Lee IT, et al. *Effects of weight loss on epicardial adipose tissue thickness and its relationship between serum soluble CD40 ligand levels in obese men*. Clin Chim Acta 2013;421:98-103.

[75] Kim MK, Tomita T, Kim MJ, et al. *Aerobic exercise training reduces epicardial fat in obese men*. J Appl Physiol 2009;106:5-11.

[76] Foppa M, Pond KK, Jones DB, et al. *Subcutaneous fat thickness, but not epicardial fat thickness, parallels weight reduction three months after bariatric surgery: a cardiac magnetic resonance study*. Int J Cardiol 2013;168:4532-3. Doi: 10.1016/j.ijcard.2013.06.099

[77] Wu FZ, Huang YL, Wu CC, et al. *Differential effects of bariatric surgery versus exercise on excessive visceral fat deposits.* Medicine 2016;95:e2616.

[78] Walker ME, Matthan NR, Goldbaum A, et al. *Dietary patterns influence epicardial adipose tissue fatty acid composition and inflammatory gene expression in the Ossabaw pig*. J Nutr Biochem 2019;70:138-46. Doi: 10.1016/j.jnutbio.2019.04.013

[79] Corsini A. Bellosta S, Baetta R, et al. *New insights into the pharmacodynamic and pharmacokinetic properties of statins.* Pharmacol Ther 1999;84:413-28.

[80] Raggi P, Gadiyaram V, Zhang C, et al. *Statins reduce epicardial adipose tissue attenuation independent of lipid lowering: a potential pleiotropic effect*. J Am Heart Assoc 2019;8:e013104. Doi: 10.1161/JAHA.119.013104

[81] Parisi V, Rengo G, Pagano G, et al. *Epicardial adipose tissue has an increased thickness and is a source of inflammatory mediators in patients with calcific aortic stenosis*. Int J Cardiol 2015;186:167-9. Doi: 10.1016/j.ijcard.2015.03.201

[82] Parisi V, Leosco D, Ferro G, et al. *The lipid theory in the pathogenesis of calcific aortic stenosis.* Nutr Metab Cardiovasc Dis 2015;25:519-25. Doi: 10.1016/j.numecd.2015.02.001

[83] Morano S, Romagnoli E, Filardi T, et al. *Short-term effects of glucagon-like peptide 1 (GLP-1) receptor agonists on fat distribution in patients with type 2 diabetes mellitus: an ultrasonography study.* Acta Diabetol 2015;52:727-32.

[84] Iacobellis G, Mohseni M, Bianco SD, et al. *Liraglutide causes large and rapid epicardial fat reduction.* Obesity 2017;25:311-6.

[85] Ferrara N, Abete P, Corbi G, et al. *Insulin-induced changes in beta-adrenergic response: an experimental study in the isolated rat papillary muscle.* Am J Hypertens 2005;18:348-53.

[86] Beiroa D, Imbernon M, Gallego R, et al. *GLP-1 agonism stimulates brown adipose tissue thermogenesis and browning through hypothalamic AMPK*. Diabetes 2014;63:3346-58.

[87] Lima-Martínez MM, Paoli M, Rodney M, et al. *Effect of sitagliptin on epicardial fat thickness in subjects with*

type 2 diabetes and obesity: a pilot study. Endocrine 2016;51:448-55.

88 Della-Morte D, Palmirotta R, Rehni AK, et al. *Pharmacogenomics and pharmacogenetics of thiazolidinediones: role in diabetes and cardiovascular risk factors.* Pharmacogenomics 2014;15:2063-82. Doi: 10.2217/pgs.14.162

89 Gallagher IJ, Scheele C, Keller P, et al. *Integration of microRNA changes in vivo identifies novel molecular features of muscle insulin resistance in type 2 diabetes.* Genome Med 2010;2:9.

90 Small EM, Olson EN. *Pervasiveroles of microRNAs in cardiovascular biology.* Nature 2011;469:336-42.

91 Keller P, Gburcik V, Petrovic N, et al. *Gene-chip studies of adipogenesis-regulated microRNAs in mouse primary adipocytes and human obesity.* BMC Endocr Disord 2011;11:7.

92 Xie H, Lim B, Lodish HF. *MicroRNAs induced during adipogenesis that accelerate fat cell development are downregulated in obesity.* Diabetes 2009;58:1050-7.

How to cite this article: Petraglia L, Conte M, Grieco FV, et al. *Epicardial adipose tissue in the pathogenesis and progression of coronary artery disease*. Journal of Gerontology and Geriatrics 2019;67(Suppl):205-12.

JGG 2019;67(Suppl):213-218

Review

Cardiac visceral fat as anatomic substrate and functional trigger for the development of atrial fibrillation

F.V. Grieco, L. Petraglia, M. Conte, C. Russo, S. Provenzano, L. Ferrante, N. Ferrara, V. Parisi

Department of Translational Medical Science, University of Naples "Federico II", Naples, Italy

Atrial Fibrillation (AF) is the most frequent sustained cardiac arrhythmia. It is well known that several risk factors are associated with AF, such as hypertension, diabetes mellitus and metabolic syndrome, smoking, alcohol, coronary artery disease (CAD), obstructive sleep apnea, myocardial infarction (MI), heart failure (HF) and obesity. Furthermore, several pieces of evidence suggest the implication of epicardial adipose tissue (EAT) in the onset of AF. EAT is the visceral fat depot of the heart, located between the visceral pericardium and the myocardium. In physiologic conditions, EAT represents a source of antiatherogenic and anti-inflammatory adipokines, shows thermogenic properties, provides energy, and acts as an immune barrier.

However, in pathologic conditions, EAT may contribute to the anatomical cardiac substrate for the development of AF. In fact, EAT can produce and secrete pro-inflammatory cytokines, activin A, matrix metalloproteinases-MMPs, and reactive oxygen species, that are all factors potentially contributing to atrial collagen deposition, fibrosis, and scar formation. Furthermore, EAT may penetrate the myocardium and generate atrial fatty infiltrates that in turn may alter the atrial electrophysiological properties.

This review aims to analyze the main mechanisms underlying the role of EAT in the pathogenesis of AF, and the potential therapeutic strategies targeting the cardiac visceral fat.

Key words: Epicardial adipose tissue, Atrial fibrillation, Elderly

PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION IN PATIENTS WITH AND WITHOUT HEART DISEASE

Atrial Fibrillation (AF) is the most frequent sustained cardiac arrhythmia affecting 2.5% of the population worldwide; its prevalence increases with age: 2.3% in people above 40 years, 5.9% after 65 years, and 10% in people above 80 years [1].

The most common symptoms are dyspnea, fatigue, palpitations and angina but, especially in the elderly population, AF can be asymptomatic and diagnosed only for the occurrence of thromboembolic complications [2 3].

Several risk factors are associated with AF: 1) *hypertension*: the relationship between blood pressure has already been widely demonstrated in the Framingham Heart Study, in which patients with a systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg were more prone to develop AF [4 5]; 2) *diabetes mellitus and metabolic syndrome*: it is known that diabetic cardiomyopathy is associated with changes in sympathetic tone which, in turn, predispose to AF [4 6]; 3) *smoking*: smoke-linked mechanisms, such as oxidative stress and myocardial fibrosis are the direct culprits of AF [4]; 4) *alcohol*: alcohol-related cardiac structural changes, such as dilated cardiomyopathy and electromechanical delay predispose to AF [7]; 5) *coronary artery disease* (CAD): patients with CAD have concomitant conditions predisposing to AF, such as diabetes, hypertension [8]; 6) *obstructive sleep apnea*: changes in intrathoracic pressure

Received: July 31, 2019 - Accepted: October 1, 2019

Correspondence: Fabrizio Vincenzo Grieco, Department of Translational Medical Science, University of Naples "Federico II", via S. Pansini 5, 80130, Naples, Italy. E-mail: fvgrieco@gmail.com

cause alterations of cardiac transmural pressure which, in turn, predisposes to AF [9]; 7) *myocardial infarction* (MI): possible mechanisms of post-MI AF include ischemia of the atrial myocardium or the sinus node, myocardial remodeling [10]; 8) *heart failure* (HF): HF related mechanisms predisposing to AF are diastolic dysfunction, electromechanical remodeling of the left atrium, hydrosaline retention and increased sympathetic tone [11-18].

Another very important risk factor for the development of AF is obesity. It is known that obesity is a chronic metabolic disease associated with several conditions such as cardiovascular diseases and type 2 diabetes. Body fat mass is distributed in several depots, localized into two main compartments: subcutaneous (SAT) and visceral (VAT) adipose tissue. The aforementioned deposits predominantly contain white adipose tissue (WAT). WAT is involved in the process of energy production (white adipocytes store excess lipids in the form of triglycerides (TG) and release free fatty acids (FFA) in periods of body energy demand), it synthesizes and releases adipokines which regulate metabolic homeostasis. Moreover, WAT is involved in hormone and cytokines secretion, insulin resistance and vascular diseases.

Brown adipose tissue (BAT) is located in cervical-supraclavicular, perirenal, paravertebral regions and around the major vessels such as aorta. It is involved in the process of energy dissipation by thermogenesis, which occurs through the uncoupling protein-1 (UCP-1), present in the inner membrane of mitochondria, acting through the uncoupled respiration.

Numerous studies have reported the association between obesity and AF, and several hypotheses have been formulated to explain this correlation: patients with increased BMI present with increased left atrial size [19]; obesity is associated to a chronic low-grade systemic inflammation contributing to AF development [19], as well as to other pathological conditions potentially associated to cardiovascular complications [20]; in obese patients, shorter refractory periods in both left atrial and pulmonary veins have been identified; obesity is associated with atrial inflammation and atrial contractile dysfunction which, in turn, lead to structural remodeling and electrophysiological abnormalities, thus contributing to an arrhythmogenic atrial substrate [21].

ASSOCIATION BETWEEN EPICARDIAL ADIPOSE TISSUE (EAT) AND AF (FIG. 1)

There is accumulating evidence linking EAT to AF. EAT, the visceral fat depot of the heart, is located between the visceral pericardium and the myocardium with absence of fascial boundaries. Cardiac visceral fat is more represented in the atrio-ventricular, inter-ventricular furrows and on the lateral wall of the right ventricle. Therefore, this tissue is anatomically different from the pericardial fat (located inside the parietal pericardium) and from the paracardial fat (located outside the parietal pericardium) [22]. From an embryological point of view, EAT derives from the splanchno-pleural mesoderm, while the paracardial fat from the primitive thoracic mesenchyme; their vascularization is also different: EAT is served by the coronary arteries, while the paracardial fat by the branches of the internal mammary artery.

EAT has several functions: it provides mechanical support to coronary arteries, protecting them from tensions and twists. In physiologic conditions, it represents a source of antiatherogenic and anti-inflammatory adipokines, has thermogenic properties, provides energy, acts as an immune barrier and is a source of fatty acids [22].

The quantification of EAT occurs through different imaging methods, such as echocardiography, computerized tomography, magnetic resonance [23]. The visualization of EAT by ultrasonography takes place in parasternal long-axis view at the level of the fold of Rindfleish, between the free wall of the right ventricle and the anterior surface of the ascending aorta. There are several pieces of evidence showing a correlation between increased EAT thickness and AF.

Several pathogenetic mechanisms have been proposed on the implication of EAT in the onset of AF: since the proximity of EAT to the underlying myocardium, it can infiltrate the myocardium, thus creating circuits that alter the propagation of the depolarizing wave and generating the return phenomena [24]; EAT produces several adipokines that promote myocardial fibrosis: *activin A* (a member of TGF-β superfamily) and *matrix metalloproteinases-MMPs* (such as MMP1, MMP2, MMP7, MMP8, MMP9 more abundantly represented than in subcutaneus adipose tissue). Activin A induces synthesis of collagen types I, III and VI, thus promoting a fibrotic effect on atrial myocardium; EAT secretes several inflammatory factors (PCR, IL-6, IL-8, IL-1b, TFN-a) [25] that have local pro-inflammatory effects on atrial myocardium and promote arrythmogenesis [22 26]. EAT is a source of reactive oxygen species (ROS) and their production is greater in human EAT than in SAT. In animal models, atrial remodeling is attenuated by inhibition of ROS [22]. Ganglionated plexuses have been identified in EAT. In this regard, it is known that the autonomic nervous system is implicated in the initiation of AF and the activation of ganglionated plexuses can cause both parasympathetic and sympathetic stimulation, resulting in shortening of action potential duration that, in turn, plays an important role in the genesis of AF [22]. EAT influences triggers, which are areas located near the pulmonary veins having spontaneous, rapid and repetitive electrical activity that can promote AF [22]. Inflammatory

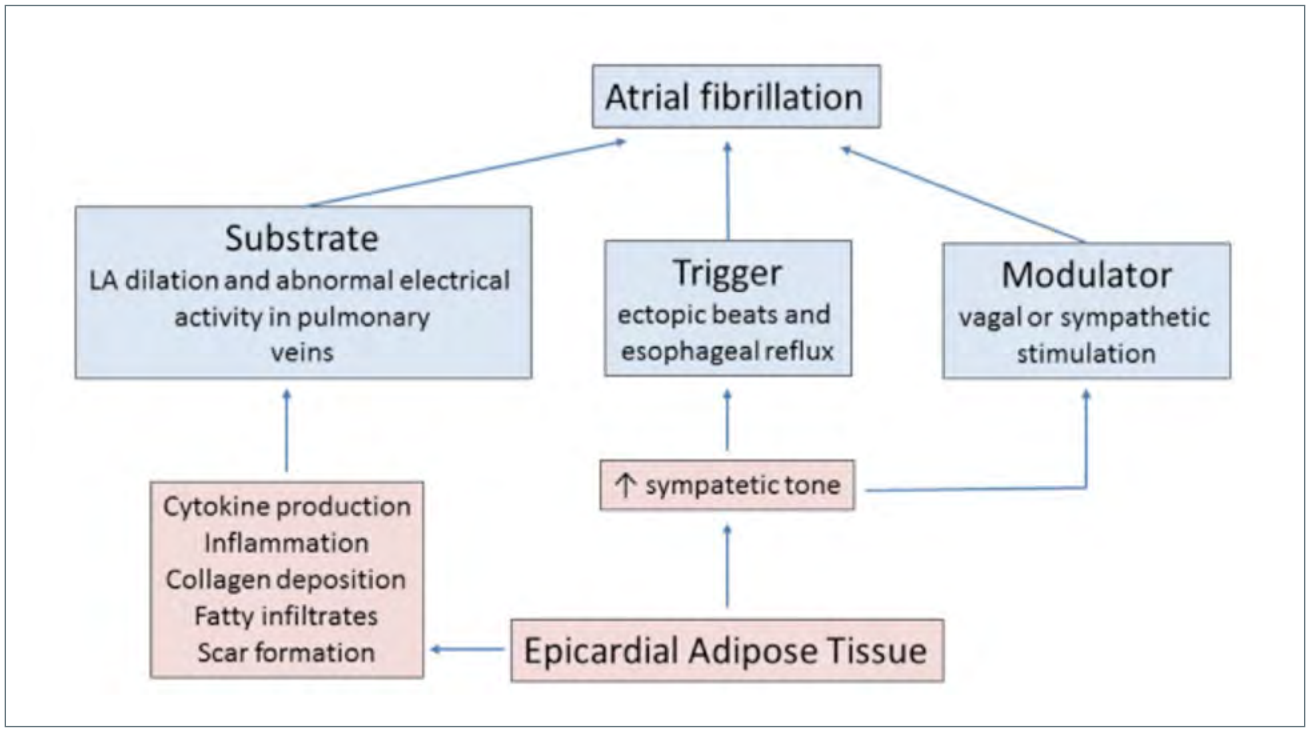

Figure 1. Role of epicardial adipose tissue in the pathogenesis of atrial fibrillation. Epicardial adipose tissue (EAT) may contribute to the anatomical substrate for the development of atrial fibrillation. In fact, EAT produces and secretes pro-inflammatory cytokines, activin A, matrix metalloproteinases-MMPs, and reactive oxygen species, that are all factors potentially contributing to atrial collagen deposition, fibrosis, and scar formation. Furthermore, EAT may penetrate the myocardium and generate atrial fatty infiltrates that may alter the atrial electrophysiological properties. EAT contains ganglionated plexus and sympathetic fibers. Furthermore, it is a source of endogenous catecholamines. All these factors may contribute to an increased sympathetic tone and to a sympatho-vagal imbalance, thus promoting atrial arrhythmias.

cells, like macrophages, have been found in EAT: these cells produce cytokines, like connective tissue growth factor (cTGF) that, in turn, stimulate myocardial fibroblasts to produce type I and II collagen [27]. Aromatase is an enzymatic protein whose function is to convert androgens into estrogens. It is abundantly expressed in subcutaneous and visceral adipose tissue. Aromatase is also expressed in the myocardium and in EAT, thus indicating the ability of these tissues to synthesize locally estrogens which, in turn, play an important role in modulating electromechanical properties, with consequent susceptibility to atrial arrhythmias. In experimental models, EAT levels of aromatase have been shown to be higher in aged than in young animals [28 29].

ASSOCIATION BETWEEN EAT AND FORMS OF AF

The association between the presence of AF and the amount of EAT is well recognized [30]. Recent studies have also identified a stronger relationship between the amount of EAT and the persistence of arrhythmia: from a recent meta-analysis, it is possible to establish that the EAT amount is greater in patients with paroxysmal AF and persistent AF than in healthy subjects. Therefore, these results not only demonstrate the association between EAT amount and AF, but also indicate a correlation with AF severity. The greatest amount of EAT has been found in patients with persistent AF. This finding is in line with the pathophysiological hypothesis, since it reflects the reduced role of EAT in patients with self-limiting AF in whom the triggers (vagal hypertone, gastroesophageal reflux) play an important role compared to the EAT modulator activity [23 31].

ATRIAL FIBRILLATION RECURRENCE AFTER ABLATION: RELATIONSHIP WITH EAT AMOUNT

Ablation is one of the procedures used for the treatment of symptomatic and drug-resistant AF. It consists of the introduction of a catheter in the blood vessels that is pushed up to the heart, canceling the anomalous electrical paths; more precisely this procedure prevents

the departure of unwanted electrical currents from the pulmonary veins and their arrival at the atria.
Several scientific pieces of evidence have shown the correlation between EAT and recurrence of atrial fibrillation post ablation. Maeda et al studied fibrillating patients subjected to ablation and stratified the population according to the EAT volume; it was found that recurrent post-ablation AF is more frequent in the group of patients with higher EAT amount, thus demonstrating how EAT volume is an independent predictor of recurrent AF post ablation [32].
In another study, the relationship between EAT volume and early and late post-ablation AF was examined; even in this study, EAT volume resulted as an independent predictor of early but not late post-ablation AF [33].
According to the findings of a recent meta-analysis, the EAT measurement, both volume and thickness measurements, seemed to be acceptable strategies for risk stratification of AF recurrence. This meta-analysis showed that total and left atrial-EAT volumes, as well as EAT thickness, were higher in patients with AF recurrence compared to those without AF recurrence after ablation [34].
Overall, these pieces of evidence indicate that the EAT volume can be used as a new imaging marker for the prediction of AF recurrence, together with the already established predictive factors: older age, female gender, classical cardiovascular risk factors, non-paroxysmal AF, left ventricular disfunction, myocardial fibrosis, atrial enlargement.

THERAPEUTIC PERSPECTIVES

Given the recognized pathogenetic role of EAT on AF occurrence, it is plausible to hypothesize different therapeutic strategies for AF acting on EAT volume and modulating EAT pro-inflammatory profile in the future.
In an AF rabbit model associated with heart failure, eicosapentaenoic acid has been shown to increase adiponectin and decrease proinflammatory adipokines, such as TNF-α, in the atrium and EAT [35 36].
Botulinum toxin suppresses AF inducibility when injected into EAT in experimental models [37]. Accordingly, in patients with paroxysmal AF, botulinum toxin injection into EAT during coronary artery bypass grafting provided atrial tachyarrhythmia suppression both early, as well as at 1-year follow-up [38]. Interestingly, the use of statins, such as atorvastatin, is able to reduce the EAT volume and blunt inflammation [39]. A recent meta-analysis reported that, in patients with sinus rhythm undergoing cardiac surgeries, perioperative statin therapy was associated with a decrease in the development of postoperative AF [40]. Finally, the use of anti-activin antibodies is able to neutralize the EAT pro-fibrotic effect in animal models, thus avoiding negative atrial remodeling [41].

CONCLUSIONS

Current epidemiological and clinical studies demonstrate a strong association between EAT and AF. However, many pathophysiological mechanisms are still unexplored and further studies, especially in humans, are required to clarify the causative mechanisms of this association. Additional evidence is also needed regarding the specific roles of different sub-depots of EAT for AF development. Finally, it will be important to define whether EAT quantification may contribute to risk stratification and therapeutic management of AF patients.

Conflict of interest

The Authors declare to have no conflict of interest.

References

1 Karamichalakis N, Letsas KP, Vlachos K, et al. *Managing atrial fibrillation in the very alderly patient: challenges and solutions.* Vasc Health Risk Manag 2015;11:555-62. Doi: 10.2147/VHRM.S83664

2 Pulignano G, Del Sindaco D, Tinti MD, et al. *Atrial fibrillation management in older heart failure patients: a complex clinical problem*. Heart Int 2016;11:e41-9 (2016). Doi: 10.5301/heartint.5000230

3 Kirchhof P, Benussi S, Kotecha D, et al. *2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS*. Eur J Cardio-Thoracic Surg 2016;50:e1-e88. Doi: 10.1093/europace/euw295

4 Pauchal G, Mahmood M, Lip G. *Revisiting the risks of incident atrial fibrillation: a narrative review. Part 1*. Kardiol Pol 2019;77:430-6. Doi: 10.33963/KP.14806

5 Cacciatore F, Abete P, de Santis D, et al. *Mortality and blood pressure in elderly people with and without cognitive impairment*. Gerontology 2005;51:53-61. Doi: 10.1159/000081436

6 Della-Morte D, Palmirotta R, Rehni AK, et al. *Pharmacogenomics and pharmacogenetics of thiazolidinediones: role in diabetes and cardiovascular risk factors.* Pharmacogenomics 2014;15:2063-82. Doi: 10.2217/pgs.14.162

7 Pauchal G, Mahmood M, Lip G. *Revisiting the risks of incident atrial fibrillation: a narrative review. Part 2*. Kardiol Pol 2019;77:515-24. Doi: 10.33963/KP.14846

8 Parisi V, Leosco D, Ferro G, et al. *The lipid theory in the pathogenesis of calcific aortic stenosis*. Nutr Metab Cardiovasc Dis 2015;25:519-25. Doi: 10.1016/j.numecd.2015.02.001

9 Parisi V, Paolillo S, Rengo G, et al. *Sleep-disordered breathing and epicardial adipose tissue in patients with heart failure*. Nutr Metab Cardiovasc Dis 2018;28:126-32. Doi: 10.1016/j.numecd.2017.09.012

[10] Romanov A, Martinek M, Purefellner H, et al. *Incidence of atrial fibrillation detected by continuous rhythm monitoring after acute myocardial infarction in patients with preserved left ventricular ejection fraction: results of the ARREST study*. Europeace 2018;20:263-70. Doi: 10.1093/europeace/euw344

[11] Selthofer-Relatic K, Bosnjak I. *Myocardial fat as a part of cardiac visceral adipose tissue: physiological and pathophysiological view.* J Endocrinol Invest 2015;38:933-9. Doi: 10.1007/540618-015-0258-y

[12] Parisi V, Rengo G, Perrone-Filardi P, et al. *Increased epicardial adipose tissue volume correlates with cardiac sympathetic denervation in patients with heart failure*. Circ Res 2016;118:1244-53. Doi: 10.1161/CIRCRESAHA.115.307765

[13] Ferrara N, Abete P, Corbi G, et al. *Insulin-induced changes in beta-adrenergic response: an experimental study in the isolated rat papillary muscle.* Am J Hypertens 2005;18:348-53. Doi: 10.1016/j.amjhyper.2004.10.006

[14] Cacciatore F, Abete P, Mazzella F, et al. *Six-minute walking test but not ejection fraction predicts mortality in elderly patients undergoing cardiac rehabilitation following coronary artery bypass grafting.* Eur J Prev Cardiol 2012;19:1401-9. Doi: 10.1177/1741826711422991

[15] Ungar A, Galizia G, Morrione A, et al. *Two-year morbidity and mortality in elderly patients with syncope.* Age Ageing 2011;40:696-702. Doi: 10.1093/ageing/afr109

[16] Ungar A, Mussi C, Ceccofiglio A, et al. *Etiology of syncope and unexplained falls in elderly adults with dementia: syncope and dementia (SYD) study*. J Am Geriatr Soc 2016;64:1567-73. Doi: 10.1111/jgs.14225

[17] Curcio F, Ferro G, Basile C, et al. *Biomarkers in sarcopenia: multifactorial approach.* Exp Gerontol 2016;85:1-8. Doi: 10.1016/j.exger.2016.09.007

[18] Martone AM, Bianchi L, Abete P, et al. *The incidence of sarcopenia among hospitalized older patients: results from the Glisten study.* J Cachexia Sarcopenia Muscle 2017;8:907-14. Doi: 10.1002/jcsm.12224

[19] Aronis KN, Wang N, Phillips CL, et al. *Associations of obesity and body fat distribution with incident atrial fibrillation in the biracial health aging and body composition cohort of older adults*. Am Heart J 2015;170:498-505.e2. Doi: 10.1016/j.ahj.2015.06.007

[20] Ungar A, Galizia G, Morrione A, et al. *Two-year morbidity and mortality in elderly patients with syncope*. Age Ageing 2011;40:696-702. Doi: 10.1093/ageing/afr109

[21] Wong CX, Sun MT, Odutayo A, et al. *Associations of epicardial, abdominal, and overall adiposity with atrial fibrillation*. Circ Arrhythm Electrophysiol 2016;9:1-15. Doi: 10.1161/CIRCEP.116.004378

[22] Wong CX, Ganesan AN, Selvanayagam JB. *Epicardial fat and atrial fibrillation: current evidence, potential mechanisms, clinical implications, and future directions*. Eur Heart J 2017;38:1294-302. Doi: 10.1093/eurheartj/ehw045

[23] Gaeta M, Bandera F, Tassinari F. *Is epicardial fat depot associated with atrial fibrillation? A systematic review and meta-analysis*. Europace 2017;19:747-52. Doi: 10.1093/europeace/euw398

[24] Goudis CA, Vasileiadis IE, Liu T. *Epicardial adipose tissue and atrial fibrillation: pathophysiological mechanisms, clinical implications and potential therapies*. Curr Med Res Opin 2018;34:1933-43. Doi: 10.1080/03007995.2018.146278

[25] Parisi V, Rengo G, Pagano G, et al. *Epicardial adipose tissue has an increased thickness and is a source of inflammatory mediators in patients with calcific aortic stenosis*. Int J Cardiol 2015;186:167-9. Doi: 10.1016/j.ijcard.2015.03.201

[26] Iacobellis G, Barbaro G. *The double role of epicardial adipose tissue as pro- and anti-inflammatory organ*. Horm Metab Res 2008;40:442-5. Doi: 10.1055/s-2008-1062724

[27] Wang Q, Xi W, Yin L, et al. *Human epicardial adipose tissue cTGF expression is an independent risk factor for atrial fibrillation and highly associated with atrial fibrosis*. Sci Rep 2018;8:3585. Doi: 10.1038/s41598-018-21911-y

[28] Bernasochi GB, Boon WC, Curl CL. *Pericardial adipose and aromatase: a new translational target for aging, obesity and arrhythmogenesis?* J Mol Cell Cardiol 2017;111:96-101. Doi: 10.1016/j.yjmcc.2017.08.006

[29] Silaghi A, Piercecchi-Marti, Grino M, et al. *Epicardial adipose tissue extent: relationship with age, body fat distribution, and coronaropathy.* Obesity (Silver Spring) 2008;16:2424-30. Doi: 10.1038/oby.2008.379

[30] Hatem SN, Redheuil A, Gandjbakhch E. *Cardiac adipose tissue and atrial fibrillation: the perils of adiposity*. Cardiovasc Res 2016;109:502-9. Doi: 10.1093/cvr/cvw001

[31] Schotten U, Verheule S, Kirchof P, et al. *Pathophysiological mechanisms of atrial fibrillation: a translational appraisal*. Physiol Rev 2011;91:265-325. Doi: 10.1152/physrev.00031.2009

[32] Maeda M, Oba K, Yamaguchi S, et al. *Usefulness of epicardial adipose tissue volume to predict recurrent atrial fibrillation after radiofrequency catheter ablation*. Am J Cardiol 2018;122:1694-700. Doi: 10.1016/j.amjcard.2018.08.005

[33] Masuda M, Mizuno H, Enchi Y, et al. *Abundant epicardial adipose tissue surrounding the left atrium predicts early rather than late recurrence of atrial fibrillation after catheter ablation.* J Interv Card Electrophysiol 2015;44:31-7. Doi: 10.1007/s10840-015-0031-3

[34] Sepehri Shamloo A, Dagres N, Dinov B, et al. *Is epicardial fat tissue associated with atrial fibrillation recurrence after ablation? A systematic review and meta-analysis*. Int J Cardiol Heart Vasc 2019;22:132-8. Doi: 10.1016/j.ijcha.2019.01.003

[35] Kitamura K, Shibata R, Tsuji Y, et al. *Eicosapentaenoic acid prevents atrial fibrillation associated with heart failure in a rabbit model.* Am J Physiol Heart Circ Physiol 2011;300:H1814-21. Doi: 10.1152/ajpheart.00771.2010

[36] Walker ME, Matthan NR, Goldbaum A. *Dietary patterns influence epicardial adipose tissue fatty acid composition and inflammatory gene expression in the Ossabaw pig*. J Nutr Biochem 2019;70:138-46. Doi: 10.1016/j.jnutbio.2019.04.013

[37] Oh S, Choi EK, Zhang Y, et al. *Botulinum toxin injection*

in epicardial autonomic ganglia temporarily suppresses vagally mediated atrial fibrillation. Circ Arrhythm Electrophysiol 2011;4:560-5. Doi: 10.1161/CIRCEP.111.961854

38 Pokushalov E, Kozlov B, Romanov A, et al. *Long-term suppression of atrial fibrillation by botulinum toxin injection into epicardial fat pads in patients undergoing cardiac surgery: one-year follow-up of a randomized pilot study*. Circ Arrhythm Electrophysiol 2015;8:1334-41. Doi: 10.1161/CIRCEP.115.003199

39 Parisi V, Petraglia L, D'Esposito V, et al. *Statin therapy modulates thickness and inflammatory profile of human epicardial adipose tissue.* Int J Cardiol 2019;274:326-30. Doi: 10.1016/j.ijcard.2018.06.106

40 Rezaei Y, Gholami-Fesharaki M, Dehghani MR, et al. *Statin antiarrhythmic effect on atrial fibrillation in statin-naive patients undergoing cardiac surgery: a meta-analysis of randomized controlled trials.* J Cardiovasc Pharmacol Ther 2016;21:167-76. Doi: 10.1177/1074248415602557

41 Venteclef N, Guglielmi V, Balse E, et al. *Human epicardial adipose tissue induces fibrosis of the atrial myocardium through the secretion of adipo-fibrokines*. Eur Heart J 2015;36:795-805. Doi: 10.1093/eurheartj/eht099

How to cite this article: Grieco FV, Petraglia L, Conte M, et al. *Cardiac visceral fat as anatomic substrate and functional trigger for the development of atrial fibrillation*. Journal of Gerontology and Geriatrics 2019;67(Suppl):213-18.

JGG 2019;67(Suppl):219-225

Review

Potential role of epicardial adipose tissue in the pathogenesis of calcific aortic stenosis

M. Conte, L. Petraglia, F.V. Grieco, C. Russo, S. Provenzano, P. Campana, V. Parisi

Department of Translational Medical Science, University of Naples "Federico II", Naples, Italy

Aortic stenosis (AS) is the most common valvular heart disease in industrialized countries, with a prevalence that increases with age, and represents an important cause of morbidity, hospitalization and death in the elderly population.
It is widely recognized that AS is a progressive and active process that leads to calcific degeneration of the aortic valve, involving complex and multifactorial pathological mechanisms, and including triggering factors which lead to inflammation. In the last decades, several pieces of evidence have suggested a pathogenetic role of the epicardial adipose tissue (EAT), the cardiac visceral fat depot, in the development and progression of AS. EAT contributes to the inflammatory burden of AS through the secretion of numerous pro-inflammatory and pro-atherogenic cytokines. Therefore, this review aims to explore the potential role of EAT in the pathogenesis of AS and the potential therapeutic perspectives to slower AS progression.

Key words: Epicardial adipose tissue, Aortic stenosis, Elderly

CALCIFIC AORTIC STENOSIS IN THE ELDERLY

Aortic stenosis (AS) is the most common valvular heart disease in industrialized countries, with a prevalence that increases with age. Therefore, a significant increase in prevalence is expected considering aging of the global population, thus making this disease a huge health and socio-economic burden [1-3].
Given the demographic changes leading to an increase of older people in industrialized countries, the number of patients affected by degenerative AS will dramatically rise in the next decades. In this regard, it has been estimated that, in the European countries, the number of subjects with symptomatic severe AS will increase from 1.3 million in 2025 to 2.1 million in 2050. AS is associated with frequent hospitalizations, functional decline even in the absence of reduction of myocardial contractility [4], and severe prognosis (average survival rate after symptom onset 50% at two years and 20% at five years) [5-9].

ACTIVE PATHOPHYSIOLOGICAL MECHANISMS INVOLVED IN AS (FIG. 1)

In adults, especially in patients over 70 years, calcific degeneration represents the main mechanism involved in the development of AS. Several pieces of evidence support the concept that the pathophysiology of AS shares many features with vascular atherosclerosis and is associated with traditional atherosclerotic risk factors such as age, hypercholesterolemia, smoking, hypertension, diabetes and obesity [10 11]. For decades, valve calcification has been considered as an inevitable consequence of ageing; nowadays, it is widely recognized that AS is a progressive and active process, involving multifactorial pathological mechanisms, ranging from an initial calcification and focal thickening leaflet with preserved valvular function, to valvular aortic sclerosis up to the end-stage with obstruction of the left ventricular outflow due to severe calcification and immobilization of the valvular leaflets.

Received: July 31, 2019 - Accepted: October 1, 2019
Correspondence: Maddalena Conte, Department of Translational Medical Science, University of Naples "Federico II", via S. Pansini 5, 80130, Naples, Italy. E-mail: maddalena-conte@libero.it

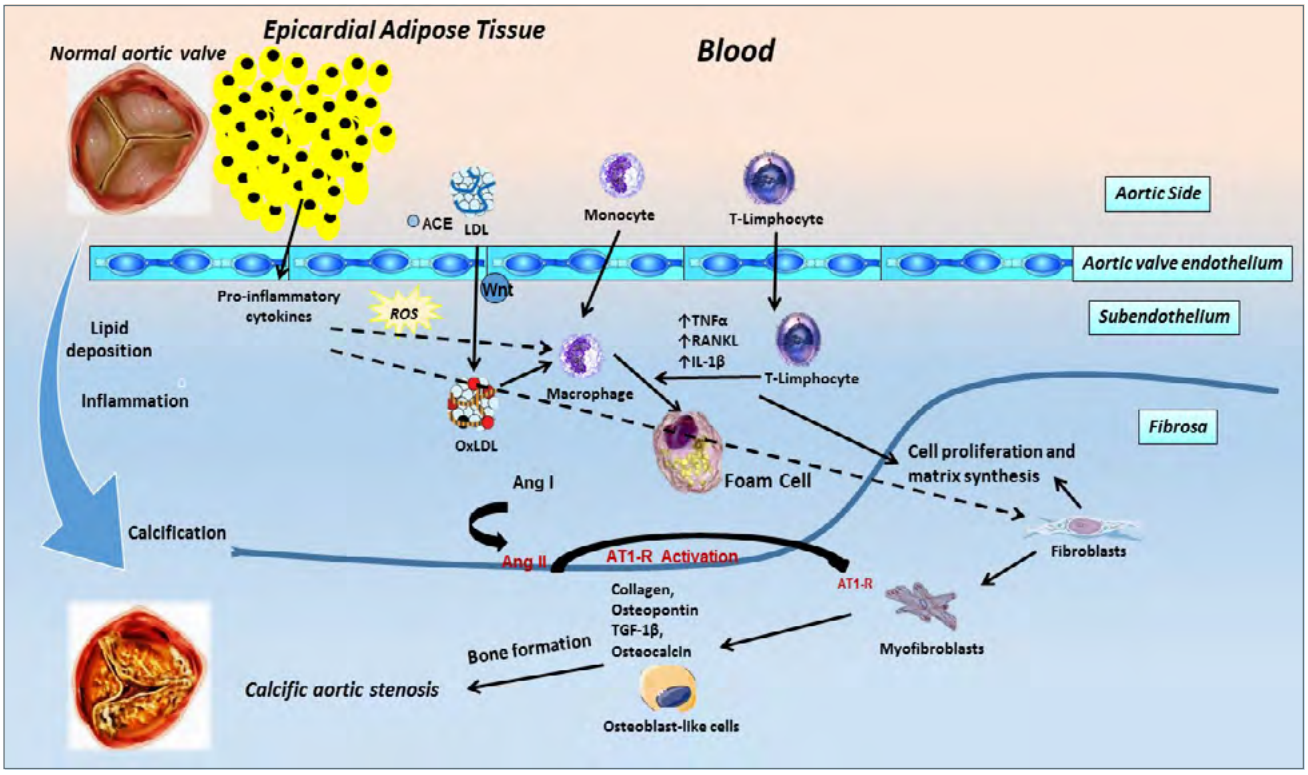

Figure 1. Mechanisms involved in the pathogenesis of calcific aortic stenosis. Differentiation of resident valvular interstitial cells to an osteoblast-like phenotype is mediated by proinflammatory cytokines such as interleukin 1β (IL-1β), IL-6, IL-8, insulin- like growth factor 1, tumor necrosis factor (TNF-a), transforming growth factor β (TGF-β), mainly secreted by circulating macrophages and activated T lymphocytes penetrating the endothelium of aortic valve leaftlets. EAT could contribute to this mechanism through the secretion of pro-inflammatory cytokines reaching the aortic valve interstitium via paracrine and vasocrine pathways.

The active mechanisms involved in the calcific degeneration of the aortic valve are particularly complex and include triggering factors which lead to inflammation. In this regard, mechanical stresses affecting the aortic valve during the cardiac cycle may play an important role in damaging the integrity of the leaflet tissue and promoting valve calcification. As with atherosclerosis, increased mechanical stress and reduced shear stress result in damage and dysfunction of the valvular endothelial cells that lose the barrier function against mechanical, metabolic and inflammatory insults.

Endothelial injury allows infiltration of lipid and inflammatory cells into the interstitial valvular tissue. In early aortic valve lesions, there is the presence of low-density lipoprotein (LDLs) and lipoprotein A, also implicated in atherogenesis, which undergo oxidative modifications becoming highly cytotoxic and promoting inflammatory activity and mineralization by secretion of proinflammatory and profibrotic cytokines. Oxidized LDLs stimulate the activation of valve fibroblasts and consequently the formation of a core for calcium deposition.

In stenotic valve, an important increase in oxidative stress due to reduction in expression and activity of antioxidant enzymes was described, associated to a high production of free radicals, such as superoxide and oxygen peroxide, which play an important role in the pathogenesis and progression of AS, promoting the activation of profibrotic and pro-osteogenic signals [12].

Increased endothelial expression of adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), may allow monocytes and T lymphocytes to penetrate the valvular endothelium and accumulate in areas of inflammation, where monocytes differentiate toward macrophages, and activated T cells release cytokines and growth factors capable of inducing fibrosis and progression of calcification.

Changes in the renin-angiotensin-aldosterone system occurring in AS generate high levels of Angiotensin II, which contributes to the pathogenesis of disease increasing LDL uptake, inflammation, and profibrotic state via the angiotensin II type 1 (AT1) receptor [13]. Moreover, the inflammatory infiltrate, through the release of mediators, favors the process of angiogenesis with an increase in growth factors and endothelial changes able to promote the progression of fibrosis and calcification.

As the disease progresses, a remodeling of the extracellular matrix promoted by the activation of metalloproteinases and cathepsins occurs, which stimulates the degradation of elastin and the proliferation of fibroblasts with consequent fibrosis, thickening and valvular stiffness up to stenosis. In the most advanced stages of the disease, the presence of cells with osteoblast-like activity and proteins normally present in the bone, such as osteonectin, osteopontin, and osteocalcin has been demonstrated in the valve, suggesting that the calcification process occurs in a similar way to that observed in the bone. The formation of bone tissue at the valvular level would be the consequence of the activation of multiple signaling pathways that lead to the differentiation of fibroblasts into myofibroblasts and osteoblast-like cells, with consequent formation of calcification nodules [14].

The formation of skeletal bone occurs through the initial deposition of collagen matrix, which provides a basis for progressive calcification. A similar process has been described in the aortic valve.

Several data suggest that inflammation, lipoprotein infiltration, oxidative stress and extracellular matrix remodeling are the main triggers and promoters of the osteogenic processes observed in aortic valve degeneration [15].

In stenotic aortic valves, an hyperactivation of bone morphogenetic protein (BMP) signaling is observed, with secretion of high levels of bone-forming proteins 2 and 4 from the valvular endothelium, that are implicated in the mechanism of bone mineralization. This process increases further as the impairment of the valve opening progresses [16].

Several studies demonstrated the presence of osteoblast-like cells and an increase in the gene expression of different osteoblast-specific proteins commonly associated with skeletal bone formation such as osteopontin and bone sialoprotein in the valve [17].

Concerning the origin of osteoblast-like cells, the most accredited hypothesis calls into question the myofibroblasts present in the valve interstitium, whose osteoblastic differentiation is modulated by numerous molecules and very complex signaling pathways.

Some data suggest that differentiation of resident valvular interstitial cells toward an osteoblast-like phenotype would be mediated by proinflammatory cytokines such as interleukin 1β (IL-1β), IL-6, IL-8, insulin-like growth factor 1, tumor necrosis factor (TNF), transforming growth factor-β (TGF-β), mainly secreted by macrophages. However, in the later stages of the disease, this differentiation seems to be modulated by complex calcified pathways, including the Notch, Wnt/β-catenin, and receptor activator of nuclear factor kappa B/receptor activator of nuclear factor kappa B ligand/osteoprotegerin pathways (RANK/RANKL/OPG) [18-20].

RANKL is a member of the TNF cytokine family; RANK is a transmembrane protein expressed on osteoclast precursors but also on valvular interstitial cells. In the bone tissue, binding of RANKL to RANK promotes osteoclastic differentiation and maturation, inducing the process of bone resorption and demineralization. By contrast, in the aortic valve, RANKL binds to RANK in valvular interstitial cells, acting as a strong inducer of osteogenic differentiation with subsequent calcium deposition and formation of calcific nodules [21].

This pathway is inhibited by osteoprotegerin, a soluble receptor that binds RANKL and prevents its linking to RANK, contrasting both the bone demineralization process and the calcium deposition at the valve level. RANKL acts with pro-osteoblastic effects even against vascular smooth muscle cells through the upregulation of BMP-2 [22].

VISCERAL FAT AND OBESITY AS RISK FACTORS FOR AS

It is now recognized that the process of calcific aortic valve degeneration shares many mechanisms with atherosclerosis including risk factors, such as obesity. Importantly, the increase in visceral fat is associated with the incidence of cardiovascular events both in general and in AS populations [23].

In recent decades, a significant increase in the prevalence of overweight or obese subjects, often with type 2 diabetes or with metabolic alterations associated with insulin resistance has been observed: we are talking about “the metabolic syndrome”. In this regard, the visceral abdominal fat, through the production of inflammatory cytokines, is strongly associated with the development of insulin resistance [24] and diabetes mellitus, and with an increased risk of cardiovascular outcomes. Pathogenetic factors underlying the complications related to visceral obesity include a pro-atherogenic alteration of the lipid profile with a reduction of high-density lipoproteins and an increase in small, low-density lipoprotein particles. Moreover, another important characteristic is represented by the chronic inflammatory state with large production of pro-inflammatory cytokines [25].

Therefore, central obesity contributes to the definition of the metabolic syndrome, which is an important cardiovascular risk factor associated with the progression of coronary artery disease, but it is also highly related to the development and progression of calcific aortic degeneration. Indeed, several studies have shown the importance of abdominal visceral adipose tissue in the development of aortic valve calcification.

The Multi-Ethnic Study of Atherosclerosis (MESA) showed a significant association between the metabolic syndrome and the incidence of aortic valve calcification [26].

Oikawa et al. highlighted the relationship between the abdominal visceral adiposity and the presence of aortic valve calcification, thus supporting the role of visceral adipose tissue as an independent risk factor for this valve disease [27].

The ASTRONOMER (Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin) study showed a significant association between the metabolic syndrome and the progression of aortic valve calcification [28].

There is a growing body of evidence that the involvement of visceral adipose tissue in the pathogenesis of AS implies inflammatory and oxidative stress processes, through the production of inflammatory cytokines and reactive oxygen species (ROS). Reis et al. described an increased expression of TNF-α, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and plasminogen activator inhibitor-1 in the adipose tissue of obese mice. Similarly, they reported an increase in oxidative stress with greater ROS production and increase in NADPH oxidase activity in obese humans [29].

Other Authors evaluated the association between global (estimated with the Body Max Index) and regional adiposity and valve calcification and mortality for all cardiovascular causes in a cohort of symptomatic elderly patients with severe AS, referred to transcatheter aortic valve replacement (TAVR). Paradoxically, in this population a low BMI was associated with aortic valve calcification and higher incidence of death. Accordingly, the amount of visceral adipose tissue was inversely associated with the aortic valve calcification mass score.

This paradox would be, at least in part, explained by the progressive reduction of the fat mass observed with aging, that must be ascribed to the increase of catabolic processes up to the development of sarcopenia and cachexia [30 31]. Therefore, in elderly obese patients with heart disease, the favorable prognosis could be linked to the greater metabolic reserve that allows to better tolerate the catabolic stress with respect to non-obese patients [32].

ASSOCIATION BETWEEN CARDIAC VISCERAL FAT AND AS

Several studies explored whether the epicardial adipose tissue (EAT), the cardiac visceral fat depot, could contribute to the inflammatory burden of AS.

Parisi et al. enrolled 95 patients with severe calcific AS, who underwent cardiac surgery for aortic valve replacement. In these patients, EAT thickness was assessed by echocardiography, and systemic and local inflammatory profiles were analyzed measuring the levels of 27 cytokines both in plasma and in the EAT secretome. EAT thickness was significantly higher in patients with AS than in the control group. Plasma levels of inflammatory mediators were almost similar in AS patients and controls. Noteworthy, the EAT secretome of patients with increased EAT thickness showed higher levels of inflammatory mediators. Furthermore, the thickness of EAT significantly correlated with the levels of different pro-inflammatory and pro-atherogenic cytokines, such as IL-6, TNF-α, MCP-1, IL-1β, so that the greater the thickness of EAT, the greater the secretion of these mediators. These data support the hypothesis of a pro-inflammatory activation of EAT in patients with AS, and of EAT involvement in aortic valve calcific degeneration [33].

Other studies investigated and confirmed the association between EAT and AS development. A retrospective study determined the EAT thickness in 400 patients with and without AS, concluding that the EAT thickness was significantly associated with severe AS, independently of traditional risk factors [34].

A recent study evaluated the prognostic value of EAT volume (assessed by pre-procedural multi-detector computed tomography) in 503 patients with severe AS undergoing TAVR. The volume of EAT was significantly correlated with mortality after TAVR, resulting independently associated with all-cause mortality at 1, 2 and 3 years. Therefore, the pre-interventional assessment of EAT volume was proposed by these authors as an important prognostic factor for risk stratification of TAVR candidate patients [35].

Importantly, EAT could also contribute to unfavorable cardiac remodeling in response to the presence of aortic valve disease. AS determines an increase in postload and leads to a chronic pressure overload of the left ventricle, resulting in concentric hypertrophy. This response is initially an adaptive phenomenon that allows the heart to overcome the obstacle represented by valve stenosis while maintaining adequate cardiac output even under stress. However, as for other compensatory mechanisms, it becomes a maladaptive phenomenon over time and evolves towards diastolic dysfunction, finally leading to heart failure [36]. Numerous pieces of evidence support the role of EAT in promoting myocardial hypertrophy [37]. The presence of increased EAT mass in AS could enhance the hypertrophic stimuli induced by chronic pressure overload and contribute to negative cardiac remodeling.

Coisne et al. recently analyzed the specific association between EAT and ventricular remodeling assessed by a comprehensive transthoracic echocardiography (TTE) in patients suffering from severe AS and normal left ventricular ejection fraction. In these patients, the Authors showed that the EAT thickness was significantly and independently associated with the hypertrophic response estimated by indexed left ventricular mass and with a more pathological remodeling pattern. The intense

metabolic and pro-inflammatory activity of EAT could account for this association. The causative mechanism explaining the association between EAT pro-inflammatory activity and cardiac damage was demonstrated in rodent models and in vitro cardiomyocyte cultures [38].
Overall, these data confirm, at least in part, the previous hypothesis of Iacobellis et al. and of other Authors, who analyzed the relationship between EAT and left ventricle morphology in healthy subjects with different degrees of obesity, and established an association between increased EAT volume and increased left ventricular mass [37], and heart failure [39 40].

THERAPEUTIC PERSPECTIVES

AS is the result of a very complex active process that involves several cell lines, in particular myofibroblasts and valvular interstitial cells, which undergo osteoblastic transformation and promote the formation of calcification nodules and bone deposition at the valve level. These events involve different signaling pathways which could be considered as potential therapeutic targets to control the development and progression of the disease.
Considering the pathophysiological similarities with atherosclerosis, especially in the early stages of the disease, it was hypothesized that statins might be beneficial to slow the progression of AS.
Studies in hypercholesterolemic animal models showed that atorvastatin is able to counteract the deposition of lipids and the oxidative stress that is observed in the early stages of degenerative calcified aortic disease [41].
A prospective open label study by Moura et al., showed a positive effect of statin therapy, proving that rosuvastatin treatment in AS patients, by lowering serum LDL, slowed the hemodynamic progression of disease [42].
The possible beneficial effects of this drug class would not be exclusively ascribed to the reduction of cholesterol biosynthesis and therefore of C-LDL levels, but also to pleiotropic effects. In fact, several activities of statin therapy have been described: wall effect on endothelial cells and vascular smooth muscle cells, inhibitory effect on migration and proliferation of these cells, with consequent anti-inflammatory and antithrombotic properties [43].
Anti-inflammatory effects of statins were also reported on visceral fat depots, and starting from this assumption, recent studies have been conducted to evaluate their potential effects also on EAT, which represents a potential new target for drugs, given its significant involvement in the development and progression of heart disease [44].
A recent study conducted by Parisi et al. has explored, in vivo and in vitro, the effects of statin therapy on EAT accumulation and inflammatory activity, enrolling 193 patients with severe calcific AS taking and not taking statins. In order to evaluate the association between statin therapy and EAT inflammation, EAT biopsies were performed and the corresponding secretomes were analyzed to explore the concentration of different cytokines. In addition, ithe EAT and subcutaneous adipose tissue (SCAT) biopsies from patients not assuming statins were treated *in vitro* with atorvastatin to verify whether this statin might directly affect EAT inflammatory profile. The results of this study showed a significant association between statin therapy, EAT thickness and levels of cytokines secreted from this tissue. In fact, statin therapy was associated with a reduction of EAT thickness and a parallel attenuation of its inflammatory profile. Furthermore, the in vitro studies showed a direct and selective anti-inflammatory effect of atorvastatin on EAT but not on SCAT. These results support the unique role of EAT in cardiac diseases and suggest EAT as a potential new therapeutic target for statin therapy [45].
If it is true that EAT might be involved in the pathogenesis of AS through its pro-inflammatory activities, we should expect that therapies able to modulate the EAT inflammatory profile, such as statin therapy, could positively affect the progression of AS. In contrast to the preliminary results reported by the open label study of Moura et al, three randomized controlled trials, SALTIRE, ASTRONOMER, and SEAS trials, utilizing atorvastatin, rosuvastatin, and simvastatin plus ezetimibe respectively in patients with mild to moderate AS, failed to demonstrate a beneficial effect of statin therapy in halting or slowing AS progression despite the significant reduction in serum LDL cholesterol concentrations [46-48]. A plausible explanation for this failure could be referred to the timing of therapy, which probably should be started in the early stages of the disease in order to significantly affect its progression. In fact, whether in the initial phase of the disease, inflammation and lipid deposition are the predominant pathophysiological mechanisms, in later stages, the propagation phase of the disease is characterized by self-perpetuating the process of formation, and the deposition of calcium and valve degeneration that cannot be affected by statins. Future long-term controlled trials conducted on patients with less advanced AS are needed to examine and establish the effect of statin therapy in this disease and explore whether this effect could be reconducted to an influence on EAT activity.
As for statin therapy, other therapeutic strategies were proven in AS patients targeting several signaling pathways potentially contributing to the inflammatory activity described in the valve in the early stage of the disease. In this regard, renin-angiotensin system, oxidative stress, RANK-RANK ligand pathway and peroxisome proliferator-activated receptors were all recognized as potentially

involved in the pathological processes leading to AS. Intriguingly, the same pathways were shown to contribute to the shift of EAT toward a pro-inflammatory and pro-atherogenic phenotype. Unfortunately, studies exploring these pathways as potential therapeutic targets in AS failed to demonstrate a favorable effect [49].

Conflict of interest

The Authors declare to have no conflict of interest.

References

1 Osnabrugge RL, Mylotte D, Head SJ, et al. *Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study*. J Am Coll Cardiol 2013;62:1002-12. Doi: 10.1016/j.jacc.2013.05.015

2 Nkomo VT, Gardin JM, Skelton TN, et al. *Burden of valvular heart diseases: a population-based study*. Lancet 2006;368:1005-11.

3 Iung B, Butchart EG, Delahaye F, et al. *A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on valvular heart disease*. Eur Heart J 2003;24:1231-43.

4 Cacciatore F, Abete P, Mazzella F, et al. *Six-minute walking test but not ejection fraction predicts mortality in elderly patients undergoing cardiac rehabilitation following coronary artery bypass grafting.* Eur J Prev Cardiol 2012;19:1401-9. Doi: 10.1177/1741826711422991

5 Thaden JJ, Nkomo VT, Enriquez-Sarano M. *The global burden of aortic stenosis*. 2014;56:565-71. Doi: 10.1016/j.pcad.2014.02.006

6 Otto CM. *Timing of aortic valve surgery*. Heart 2000;84:211-8. Doi:10.1136/heart.84.2.211

7 Cacciatore F, Abete P, de Santis D, et al. *Mortality and blood pressure in elderly people with and without cognitive impairment.* Gerontology 2005;51:53-61.

8 Ungar A, Galizia G, Morrione A, et al. *Two-year morbidity and mortality in elderly patients with syncope*. Age Ageing 2011;40:696-702. Doi: 10.1093/ageing/afr109

9 Ungar A, Mussi C, Ceccofiglio A, et al. *Etiology of syncope and unexplained falls in elderly adults with dementia: Syncope and Dementia (SYD) study*. J Am Geriatr Soc 2016;64:1567-73.

10 Cho KI, Sakuma I, Sohn IS, et al. *Inflammatory and metabolic mechanisms underlying the calcific aortic valve disease.* Atherosclerosis 2018;277:60-5. Doi: 10.1016/j.atherosclerosis.2018.08.029

11 Della-Morte D, Palmirotta R, Rehni AK, et al. *Pharmacogenomics and pharmacogenetics of thiazolidinediones: role in diabetes and cardiovascular risk factors*. Pharmacogenomics 2014;15:2063-82. Doi: 10.2217/pgs.14.162

12 Rajamannan NM, Evans FJ, Aikawa E, et al. *Calcific aortic valve disease: not simply a degenerative process: a review and agenda for research from the National Heart and Lung and Blood Institute Aortic Stenosis Working Group. Executive summary: calcific aortic valve disease-2011 update*. Circulation 2011;124:1783-91. Doi: 10.1161/CIRCULATIONAHA.110.006767

13 Helske S, Lindstedt KA, Laine M, et al. *Induction of local angiotensin II-producing systems in stenotic aortic valves*. J Am Coll Cardiol 2004;44:1859-66.

14 Izquierdo-Gómez MM, Hernández-Betancor I, García-Niebla J, et al. *Valve calcification in aortic stenosis: etiology and diagnostic imaging techniques*. Biomed Res Int 2017;2017:5178631. Doi: 10.1155/2017/5178631

15 Parisi V, Leosco D, Ferro G, et al. *The lipid theory in the pathogenesis of calcific aortic stenosis*. Nutr Metab Cardiovasc Dis 2015;25:519-25. Doi: 10.1016/j.numecd.2015.02.001

16 Wirrig EE, Hinton RB, Yutzey KE. *Differential expression of cartilage and bone-related proteins in pediatric and adult diseased aortic valves*. J Mol Cell Cardiol 2011;50:561-9. Doi: 10.1016/j.yjmcc.2010.12.005

17 Alfieri CM, Cheek J, Chakraborty S, et al. *Wnt signaling in heart valve development and osteogenic gene induction.* Dev Biol 2010;338:127-35. Doi: 10.1016/j.ydbio.2009.11.030

18 Nigam V, Srivastava D. *Notch1 represses osteogenic pathways in aortic valve cells*. J Mol Cell Cardiol 2009;47:828-34. Doi: 10.1016/j.yjmcc.2009.08.008

19 Wirrig EE, Hinton RB, Yutzey KE. *Differential expression of cartilage and bone-related proteins in pediatric and adult diseased aortic valves.* J Mol Cell Cardiol 201;50:561-9. Doi: 10.1016/j.yjmcc.2010.12.005

20 Pfister R, Michels G, Sharp SJ, et al. *Inverse association between bone mineral density and risk of Aortic Stenosis in men and women in EPIC-Norfolk prospective study.* Int J Cardiol 2015;178:29-30. Doi: 10.1016/j.ijcard.2014.10.065

21 Kaden JJ, Bickelhaupt S, Grobholz R, et al. *Receptor activator of nuclear factor kappaB ligand and osteoprotegerin regulate aortic valve calcification.* J Mol Cell Cardiol 2004;36:57-66.

22 Bucay N, Sarosi I, Dunstan CR, et al. *Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification.* Genes Dev 1998;12:1260-8.

23 Calle EE, Thun MJ, Petrelli JM, et al. *Body-mass index and mortality in a prospective cohort of U.S. adults*. N Engl J Med 1999;341:1097-105.

24 Ferrara N, Abete P, Corbi G, et al. *Insulin-induced changes in beta-adrenergic response: an experimental study in the isolated rat papillary muscle.* Am J Hypertens 2005;18:348-53.

25 Despres JP. *Body fat distribution and risk of cardiovascular disease: an update.* Circulation 2012;126:1301-13. Doi: 10.1161/CIRCULATIONAHA.111.067264

26 Katz R, Budoff MJ, Takasu J, et al. *Relationship of metabolic syndrome with incident aortic valve calcium and aortic valve calcium progression: the Multi-Ethnic Study of Atherosclerosis (MESA).* Diabetes 2009;58:813-9. Doi: 10.2337/db08-1515

27 Oikawa M, Owada T, Yamauchi H, et al. *Predominance of abdominal visceral adipose tissue reflects the*

presence of aortic valve calcification. Biomed Res Int 2016;2016:2174657. Doi: 10.1155/2016/2174657

28 Pagé A, Dumesnil JG, Clavel MA, et al. *Metabolic syndrome is associated with more pronounced impairment of left ventricle geometry and function in patients with calcific aortic stenosis: a substudy of the ASTRONOMER (Aortic Stenosis Progression Observation Measuring Effects of Rosuvastatin).* J Am Coll Cardiol 2010;55:1867-74. Doi: 10.1016/j.jacc.2009.11.083

29 Reis JP, Macera CA, Araneta MR, et al. *Comparison of overall obesity and body fat distribution in predicting risk of mortality.* Obesity 2009;17:1232-9. Doi: 10.1038/oby.2008.664

30 Martone AM, Bianchi L, Abete P, et al. T*he incidence of sarcopenia among hospitalized older patients: results from the Glisten study.* J Cachexia Sarcopenia Muscle 2017;8:907-14.

31 Curcio F, Ferro G, Basile C, et al. *Biomarkers in sarcopenia: a multifactorial approach.* Exp Gerontol 2016;85:1-8.

32 Mancio J, Fonseca P, Figueiredo B, et al. A*ssociation of body mass index and visceral fat with aortic valve calcification and mortality after transcatheter aortic valve replacement: the obesity paradox in severe aortic stenosis*. Diabetol Metab Syndr 2017;19;9:86. Doi: 10.1186/s13098-017-0285-2

33 Parisi V, Rengo G, Pagano G, et al. *Epicardial adipose tissue has an increased thickness and is a source of inflammatory mediators in patients with calcific Aortic Stenosis.* Int J Cardiol 2015;186:167-9. Doi: 10.1016/j.ijcard.2015.03.201

34 Mahabadi AA, Kahlert HA, Dykun I, et al. *Epicardial adipose tissue thickness independently predicts severe aortic valve stenosis*. J Heart Valve Dis 2017;26:262-7.

35 Eberhard M, Stocker D, Meyer M, et al. *Epicardial adipose tissue volume is associated with adverse outcomes after transcatheter aortic valve replacement.* Int J Cardiol 2019;286:29-35. Doi: 10.1016/j.ijcard.2019.01.068

36 Hill JA, Olson EN. *Cardiac plasticity*. N Engl J Med 2008;358:1370-80. Doi: 10.1056/NEJMra072139

37 Iacobellis G, Ribaudo MC, Zappaterreno A, et al. *Relation between epicardial adipose tissue and left ventricular mass.* Am J Cardiol 2004;94:1084-7.

38 Coisne A, Ninni S, Ortmans S, et al. *Epicardial fat amount is associated with the magnitude of left ventricular remodeling in aortic stenosis*. Int J Cardiovasc Imaging 2019;35:267-73. Doi: 10.1007/s10554-018-1477-z

39 Parisi V, Paolillo S, Rengo G, et al. *Sleep-disordered breathing and epicardial adipose tissue in patients with heart failure.* Nutr Metab Cardiovasc Dis 2018;28:126-32. Doi: 10.1016/j.numecd.2017.09.012

40 Parisi V, Rengo G, Perrone-Filardi P, et al. *Increased epicardial adipose tissue volume correlates with cardiac sympathetic denervation in patients with heart failure*. Circ Res 2016;118:1244-53. Doi: 10.1161/CIRCRESAHA.115.307765

41 Rajamannan NM, Subramaniam M, Springett M, et al. *Atorvastatin inhibits hypercholesterolemia-induced cellular proliferation and bone matrix production in the rabbit aortic valve.* Circulation 2002;105:2660-5.

42 Moura LM, Ramos SF, Zamorano JL, et al. *Rosuvastatin affecting aortic valve endothelium to slow the progression of aortic stenosis*. J Am Coll Cardiol 2007;49:554-61.

43 Corsini A, Bellosta S, Baetta R, et al. *New insights into the pharmacodynamic and pharmacokinetic properties of statins.* Pharmacol Ther 1999;84:413-28.

44 Saito S, Fujiwara T, Matsunaga T, et al. *Increased adiponectin synthesis in the visceral adipose tissue in men with coronary artery disease treated with pravastatin: a role of the attenuation of oxidative stress.* Atherosclerosis 2008;199:378-83. Doi: 10.1016/j.atherosclerosis.2007.11.010

45 Parisi V, Petraglia L, D'Esposito V, et al. *Statin therapy modulates thickness and inflammatory profile of human epicardial adipose tissue.* Int J Cardiol 2019;274:326-30. Doi: 10.1016/j.ijcard.2018.06.106

46 Cowell SJ, Newby DE, Prescott RJ, et al. *A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis.* N Engl J Med 2005;352:2389-97.

47 Chan KL, Teo K, Dumesnil JG, et al. *Effect of lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial.* Circulation 2010;121:306-14. Doi: 10.1161/CIRCULATIONAHA.109.900027

48 Rosseb AB, Pedersen TR, Boman K, et al. *Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis*. Engl J Med 2008;359:1343-56. Doi: 10.1056/NEJMoa0804602

49 Rosenhek R, Rader F, Loho N, et al. *Statins but not angiotensin-converting enzyme inhibitors delay progression of aortic stenosis*. Circulation 2004;110:1291-5.

How to cite this article: Conte M, Petraglia L, Grieco FV, et al. *Potential role of epicardial adipose tissue in the pathogenesis of calcific aortic stenosis*. Journal of Gerontology and Geriatrics 2019;67(Suppl):219-25.

JGG 2019;67(Suppl):226-232

Review

Cardiac visceral fat and cardiometabolic risk in the elderly

A. Lo Buglio, F. Bellanti, G. Vendemiale

Centre for Aging Research, Department of Medical and Surgical Sciences, University of Foggia, Italy

Aging is characterized by several changes in body mass composition with loss of muscle mass and increase in fat mass, particularly visceral fat. Visceral fat is represented mainly by abdominal and cardiac depots and it is directly related to chronic low-grade inflammation, insulin-resistance and metabolic syndrome. Unfavourable outcomes as cardiovascular death are also associated with the amount of visceral fat depots. In this scenario, the cardiac visceral fat seems to play an important role in increasing the cardiometabolic risk. This review aims to provide a literature revision about the role of cardiac visceral fat on cardiometabolic risk in elderly.

Key words: Cardiac adipose tissue, Visceral fat, Cardiometabolic risk, Elderly

INTRODUCTION

The relationship between body fat and the risk of morbidity and mortality changes with changing age. Indeed, overweight or obese middle-aged adults present with an increased risk of morbidity and mortality, while a body mass index (BMI) included between 25 and 30 kg/m^2 shows a potential protective effect in aged people [1]. Body fat redistribution associated with age may be the underlying factor of the "obesity paradox", according to which overweight is associated with an increased risk – but decreased mortality – for cardiovascular disease (CD) [2]. Several mechanisms have been proposed to explain the protective role of increased body fat and BMI in older people, such as a greater metabolic reserve, a different cytokine profile secerned by fat, a lower activation of the sympathetic nervous system, and a reduced concentration of plasmatic natriuretic peptides [2]. Aging is associated with progressive changes in body composition characterized by a loss of fat free mass and an increase in fat mass, particularly referred as visceral fat (VF) [3]. The increase in VF, a key factor for the development of insulin-resistance, is a hallmark of metabolic syndrome (MetS) [4-6]. MetS is a clinical condition characterized by several abnormalities in lipid and glucose metabolism [7]. In aged subjects, MetS associates with a higher risk for acute coronary events, myocardial infarction, heart failure, and cardiovascular mortality [8]. MetS includes several cardiovascular risk factors such as increased fasting glucose, low HDL cholesterol, hypertriglyceridemia and hypertension [9]. In sight of this, body fat distribution rather than BMI is suggested to be a better predictor factor of morbidity and mortality in older people [1].

For many years, intra-abdominal fat has been considered the main representative of visceral fat. However, in recent times cardiac visceral fat (CVF) has been shown to play an important role in cardiometabolic risk [10].

Cardiac visceral fat is closely associated with the body mass index (BMI), since it increases during weight gain, and it decreases after weight loss [11].

This review aims to present the current evidence related to the clinical importance of cardiac visceral fat as marker of metabolic dysfunction and cardiovascular disease risk in old people. Since most studies were not specifically performed on aged patients (and other investigations excluded old subjects, focusing on adults), we will try to summarize the available data in the geriatric population.

Received: July 31, 2019 - Accepted: September 5, 2019

Correspondence: Aurelio Lo Buglio, Department of Medical and Surgical Sciences, University of Foggia, viale Pinto 1, 71122, Foggia, Italy. Tel. +39 0881 732671. E-mail: aurelio.lobuglio@unifg.it

THE DIFFERENT DEPOTS OF ADIPOSE TISSUE IN THE HEART

The nomenclature used to differentiate cardiac visceral fat depots is often misleading, with several discrepancies and ambiguities among different Authors [12]. Cardiac visceral fat includes both intra- and extra-pericardial fat. Intra-pericardial fat is represented by depots situated between the myocardium and the visceral pericardium, in direct contact with the surface of myocardium and coronary vessels. This fat layer has been referred as epicardial fat (EF) [13] (Fig. 1). Fat depots localized between the visceral and the parietal pericardium, or just external but attached to the parietal pericardium, are named pericardial fat (PF) [13]. The fat layer surrounding arteries and arterioles is defined as perivascular fat (PVF). Extra-pericardial fat (EPF) (or intrathoracic or paracardial fat) is referred to thoracic adipose tissue external to the parietal pericardium [13-15]. In this review we will refer to this nomenclature.

Another classification of cardiac visceral fat identifies three types of depot: the EF, located within the pericardial sac; the PF, located between the external surface of the parietal pericardium and medial face of mediastinum; the pericoronary fat (PCF), represented by the adipose tissue surrounding the coronary arteries within the visceral epicardium [16].

EF and PF can be assessed by cardiac CT, MRI and echocardiography. Ultrasonography is a very safe and reliable technique to identify EF and PF. EF is visualized as echo-free space between the myocardium surface and the visceral layer of pericardium, whereas PF appear as a hypoechoic space anterior to the EF and the parietal pericardium [17].

Particularly, several recent studies have been currently focusing on EF [18]. Nevertheless, in many studies EF and PF are used indifferently [16]. For instance, reports from the Framingham Heart Study did not differentiate between EF and PF, since the biomolecular properties of these two fat depots were supposed to be similar [19 20]. Nevertheless, the inappropriate use of EF and PF is misleading and is incorrect according to the main literature [21].

On the contrary, studies on the association between extra-pericardial fat and cardiovascular risk are lacking. Chen et al. found an association between EPF and MetS, even though this study is characterized by a reduced number of the sample and a short follow-up time [22].

EPICARDIAL FAT AND CARDIOMETABOLIC RISK

EF origins from the splanchnic-pleural mesoderm associated with the gut, similarly to the mesenteric and omental fat [14]. EF is mainly localized on the right ventricle surface and anterior wall of the left ventricle as well as on atrioventricular grooves and great coronary vessels, reaching the main thickness at the anterior and lateral walls of the right atrium. Normally, about 80% of the heart surface is covered by the epicardial adipose tissue, EF contributing for the 20% to the whole heart mass [15].

Two-dimensional echocardiography can be used to visualize and measure EF. Parasternal long-axis and short-axis views allow the most accurate measurement of EF thickness overlying the right ventricle. EF thickness ranges from 1 to 23 mm [23].

EF and myocardium are not divided by muscle fascia, sharing the same microcirculation [24]. Taking into account that fat accumulation in the epicardial space is limited - especially in obese individuals - the largest ectopic depots as body weight increases are located in the visceral abdominal area and in the extra-pericardial area [10].

EF is characterized by a wide individual variability which is dependent on the instrumental methodology but also on different clinical and demographic features such as age, obesity, gender, and ethnicity [25]. Indeed, EF tends to increase with age [25 26]. No consensus exists about the impact of gender on the EF thickness. The amount of EF increases with the increase of total body fat [27] and seems to be related to male gender and high body mass index (BMI) [26]. On the other hand, a recent study showed that in old age EF thickness was greater in women than in men [28].

Based on data from the Framingham study, some Authors described a higher association between EF and female gender, but this observation was not confirmed by other studies [20 25 29 30]. Postmenopausal women with

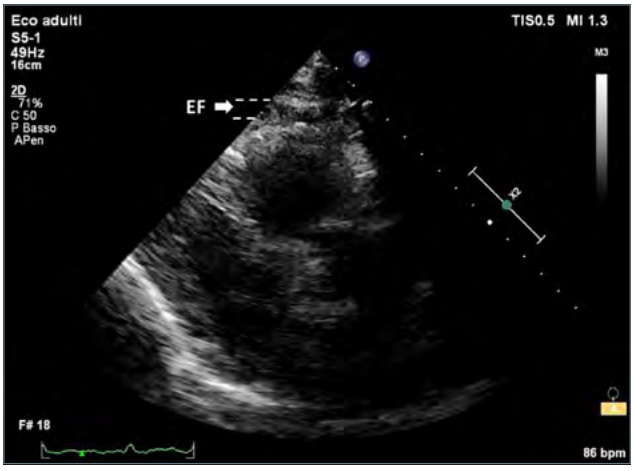

Figure 1. Transthoracic echocardiographic measurement of epicardial adipose tissue (white arrow), that appears as an echo-free space. EF: epicardial fat.

MetS showed a greater amount of EF with respect to those without MetS [31]. Concerning ethnicity, African-American men present with less EF depots than non-Hispanic white men, but these data may be also related to the high frequency of central obesity reported in the first group [25 32].

Patients with Mets present with higher EF thickness compared to patients without Mets, and the presence of MetS is an independent predictor of increased EF [33]. Iacobellis et al. described that values of EF of 9.5 mm in men and 7.5 mm in women may predict accurately the presence of Mets [34]. However, this study enrolled subjects aged 40.8 ± 11.5 years old.

Another study showed how in old patients EF, but not intra-abdominal fat, was associated with MetS, while both were closely related with hepatic steatosis [35].

Normally, epicardial adipocytes exert several physiological function for the myocardium at metabolic, thermogenic, mechanic and textural level [36]. However, this positive role is lost in particular conditions associated with an augmented amount of EF, such as obesity [37].

EF presents with the most intensive metabolic activity as compared to pericardial and other visceral fat [14 24]. In fact, EF produces higher levels of free fatty acids (FFA), with increased release of FFA after catecholamine stimulation; moreover, high lipolysis activity in EF could be associated with lower insulin sensitivity and a larger number of β3-adrenoreceptors [38].

EF is also associated to the pro-inflammatory state, and it is characterized by unique physiological and metabolic profile. Indeed, with respect to visceral fat in other body sites, EF presents with small adipocyte size, characterized by low reduction during weight loss, and several metabolic features such as different fatty acid composition, high protein content and fatty acid synthesis, reduced glucose utilization, and high level of adipokine secretion [26]. Moreover, compared to the sub-cutaneous, the epicardial adipose tissue is able to produce higher level of chemokines and inflammatory cytokines such as interleukin 1β (IL-1β), interleukin 6 (IL-6), and tumor necrosis factor (TNF-α), interacting with numerous cardiovascular pathways via vasocrine and paracrine signalling [39 40]. Increased EF deposits are associated with higher serum level of C-reactive protein (PCR) and low-grade systemic inflammation [33]. These proinflammatory properties are independent of clinical conditions such as the presence of diabetes or obesity [39]. Nevertheless, EF may produce anti-inflammatory and antiatherogenic adipokines, but the regulation of this balance is still unknown [23]. Adiponectin and adrenomedullin represent the most important adipokines secerned by EF, particularly in the coronary circulation. Adiponectin plays a role in the modulation of insulin sensitivity, and it exerts anti-inflammatory and antiatherogenic effects, whereas adrenomedullin acts as vasodilator, anti-inflammatory and anti-vasogenic [23]. Moreover, EF presents with the highest percentage of lipogenesis and free fatty acid metabolism as compared to other visceral fat depots [41].

As previously cited, EF is closely related to MetS as well as its main several components such as endothelial dysfunction, blood pressure, insulin-resistance, high fasting glucose, presence of diabetes or hypertension, high serum levels of LDL-cholesterol and triglycerides, and increased risk of cardiovascular disease [23 42 43]. The study by Yorgun et al. demonstrated that EF and pericoronary fat thickness are associated with the presence of MetS [5]. Particularly, the Authors found that subjects presenting with MetS were older than those without, highlighting a progressive relationship between the growing number of MetS components and EF thickness [5]. Of note, in this study age was reported as an independent risk factor associated with mean EF thickness [5].

With respect to visceral abdominal fat (VAT), EF is also associated with coronary atherosclerosis, probably mediated by paracrine pathways which induce the progression of coronary vessel inflammation and atherosclerosis [5 16]. In this context, EF measurement may be useful to evaluate coronary artery disease (CAD) risk and to predict the extent and activity of CAD [7 44].

Another evidence from the Framingham Heart Study identified how fat deposits around the heart are an independent predictor of CVD risk 29. Mahabadi et al. demonstrated the role of EF as an independent predictive factor of future major adverse cardiac events (MACE) beyond traditional cardiovascular risk factors in the general population [45 46]. Of note, the statistical models used in this study were all adjusted for age.

Even though cardiac visceral fat has been recently proposed as a new marker of cardiometabolic risk [10], in a recent observational study on 113 subjects, some Authors did not find any independent association between EF and metabolic components such as blood pressure, plasma triglycerides, and insulin resistance [10]. The evidence of this study suggests how the isolated increase of EF is not necessarily associated with higher metabolic or CV risk [10]. Nevertheless, people enrolled in this investigation were from 18 to 74 years old, but data were not stratified for age classes.

In the last years, several pieces of evidence have been highlighted about the association between EF and hypertension. Cardiac fat has been found expanded in patients with hypertension compared to healthy controls [47]. Dicker et al. found a higher EF thickness in hypertensive patients rather than patient without hypertension, as well as in hypertensive patients with non-dipper profile [48-50]. Of note, in this study hypertensive

patients were older than controls, and EF thickness was associated with age [48]. A positive correlation was also found between EF thickness and blood pressure among prehypertensive patients (even though no older subjects were enrolled) [51-53]. In untreated adult patients, high values of EF thickness may be independently associated with diastolic dysfunction and atrial dilatation; EF thickness results as a stronger predictive factor than abdominal obesity [54].

Data about the relationship between EF and serum triglyceride levels are discordant through studies, showing a large degree of variability. Some studies did not show any association between serum triglycerides and EF thickness, while other Authors highlighted a low degree of correlation [5 55-58]. This heterogeneity could be linked to the difference in age, weight and morbidity of the different study populations.

Recently, Calabuig et al. have shown how EF thickness was independently associated with high-density lipoprotein cholesterol and high level of serum triglycerides [59]. This study also demonstrated that EF thickness increases with age even in subjects without MetS [59].

Both EF and extra-pericardial fat are associated with insulin resistance. Particularly, a positive association was found between EF and insulin-resistance or glucose tolerance in patients without diabetes and normal cardiac function [11 60]. Insulin resistance, age and blood glucose level after 2 hours of oral tolerance test were found independent predictor factors of high EF thickness in non-diabetic patients [61]. Similarly, Narumi et al. highlighted that increased values of EF thickness were independently associated with IR in non-obese and non-diabetic patients [62]. Furthermore, patients with morbid obesity showed higher EF thickness values associated with insulin resistance, inappropriate high left ventricular mass, and left ventricular dysfunction [63]. In addition, Iacobellis et al. found a significant association between EF thickness and obesity-related insulin resistance [64].

Despite the associative results, the exact pathogenesis between EF and insulin resistance is not yet clear [65].

Diabetes is an important perturbing factor in the normal homeostasis of glucose metabolism in the heart. In fact, diabetic patients show that peripheral insulin resistance and low insulin stimulated myocardial glucose uptake with a range of reduction up to 40% [11]. In a study performed on a geriatric population, diabetic patients showed higher EF thickness compared to non-diabetic subjects [66]. Recently, Yagi et al. have confirmed that the amount of EF is greater in patients with diabetes, regardless of type 1 or 2 diabetes mellitus and of EF measured method used, suggesting that an augmented EF could be an independent predictor of newly-diagnosed diabetes mellitus [67]. A strong correlation between fasting plasma glucose and EF measured with echocardiography and CT has also been lately highlighted [68].

Recent investigations suggest that EF may represent a more reliable measure of visceral adiposity. In fact, although visceral fat correlates with the waist circumference, this can be modified by numerous factors such as the amount of subcutaneous fat, especially in older people [7 18 69].

EF measured by ultrasonography is associated with anthropometric and clinical parameters of MetS (as body mass index, BMI) so that EF may be a useful index of MetS 5. Echocardiographic measure of EF is more and more often considered as a new parameter to evaluate cardiac and visceral obesity [7].

PERICARDIAL FAT AND CARDIOMETABOLIC RISK

Pericardial fat originates from the division of primitive thoracic mesenchyme, which gives rise to the parietal pericardium and the external thoracic wall [23].

Data from the Framingham Heart Study Offspring and Third Generation showed that, as compared with other ectopic fat depots (including abdominal subcutaneous adipose tissue, abdominal visceral adipose tissue, intramuscular fat, intrathoracic fat, thoracic periaortic fat, intrahepatic fat, and renal sinus fat), pericardial fat presented with the great magnitude of correlation with intrathoracic and abdominal visceral fat [26 70]. However, the metabolic activity of EF and PF is different [21]. Unlike EF, PF has not yet shown an association with metabolic syndrome, visceral adiposity, heart morphology, insulin resistance, and other features [21]. Moreover, the term “pericardial” used in several studies is referred to fat in the pericardium without any distinction between EF and PF [20 71 72]. Recent pieces of evidence – even though on adult subjects – indicate that PF appears strongly associated with obesity and hypertension [17 47]. Sicari et al. studied EF and PF separately and found how PF – rather than EF – is related to parameters of metabolic syndrome, such as serum triglyceride and glucose concentrations, blood pressure, insulin sensitivity, and BMI [73]. Notably, in this study the PF thickness detected by echocardiography, but not that detected by MRI, was correlated with age [73]. Another correlation between PF and cardiovascular risk was found considering the 10-year CHD Framingham risk score [73]. Dabbah et al. investigated the association between EF and PF, and diastolic filling, finding a low correlation among PF and diastolic indices [74]. Definitely, despite several studies suggesting that PF could play an active role as a cardiovascular risk factor, its role still needs to be studied [75].

CONCLUSIONS

Among the cardiac visceral fat depots, the EF presents with peculiar metabolic features. Indeed, the EF is characterized by differences in fatty acid composition, higher protein content and dissimilar metabolic profile, such as higher production of FFA, high levels of lipolysis activity, and reduced glucose utilization. Moreover, the EF shows active endocrinal properties as compared to the PF, and a close association with a low-grade pro-inflammatory state favoured by sharing the microcirculation with the myocardium. While a few studies on the association between the PF and cardiometabolic risk are available, there is strong evidence supporting the close association between the EF and cardiometabolic risk. Beyond the CV risk factors, EF is also an independent predictor factor of MACE. However, the available literature on cardiac visceral fat and cardiovascular risk includes only a small number of studies specifically targeting the old population. Future investigations are needed to address many questions in the geriatric field of research.

Conflict of interest

The Authors declare to have no conflict of interest.

References

1 Chang S-H, Beason TS, Hunleth JM, et al. *A systematic review of body fat distribution and mortality in older people.* Maturitas 2012;72:175-91.

2 Chapman IM. *Obesity paradox during aging.* In: *Body composition and aging*. Basel: KARGER 2010;37:20-36.

3 Lo Buglio A, Bellanti F, Capurso C, et al. *Adherence to Mediterranean diet, malnutrition, length of stay and mortality in elderly patients hospitalized in internal medicine wards.* Nutrients 2019;11:790.

4 Mottillo S, Filion KB, Genest J, et al. *The metabolic syndrome and cardiovascular risk.* J Am Coll Cardiol 2010;56:1113-32.

5 Yorgun H, Canpolat U, Hazırolan T, et al. *Increased epicardial fat tissue is a marker of metabolic syndrome in adult patients.* Int J Cardiol 2013;165:308-13.

6 Phillips CM, Tierney AC, Perez-Martinez P, et al. *Obesity and body fat classification in the metabolic syndrome: Impact on cardiometabolic risk metabotype.* Obesity 2013;21:e154-61.

7 Veronica G, Esther R-RM. *Aging, metabolic syndrome and the heart*. Aging Dis 2012;3:269-79.

8 Butler J, Rodondi N, Zhu Y, et al. *Metabolic syndrome and the risk of cardiovascular disease in older adults.* J Am Coll Cardiol 2006;47:1595-602.

9 Saad MAN, Cardoso GP, Martins W de A, et al. *Prevalence of metabolic syndrome in elderly and agreement among four diagnostic criteria.* Arq Bras Cardiol 2014;102:263-9.

10 Sironi AM, Petz R, De Marchi D, et al. *Impact of increased visceral and cardiac fat on cardiometabolic risk and disease.* Diabet Med 2012;29:622-7.

11 Gastaldelli A, Morales MA, Marraccini P, et al. *The role of cardiac fat in insulin resistance.* Curr Opin Clin Nutr Metab Care 2012;15:523-8.

12 Guglielmi V, Sbraccia P. *Epicardial adipose tissue: at the heart of the obesity complications*. Acta Diabetol 2017;54:805-12.

13 Iozzo P. *Myocardial, perivascular, and epicardial fat.* Diabetes Care 2011;34(Suppl 2):S371-9.

14 Sacks HS, Fain JN. *Human epicardial adipose tissue: a review.* Am Heart J 2007;153:907-17.

15 Ansaldo AM, Montecucco F, Sahebkar A, et al. *Epicardial adipose tissue and cardiovascular diseases*. Int J Cardiol 2019;278:254-60.

16 Lim S, Meigs JB. *Ectopic fat and cardiometabolic and vascular risk.* Int J Cardiol 2013;169:166-76.

17 Iacobellis G, Assael F, Ribaudo MC, et al. *Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction*. Obes Res 2003;11:304-10.

18 CENGEL A. *Epicardial adipose tissue, metabolic syndrome, inflammation, and cardiovascular risk.* Turk Kardiyol Dern Arsivi-Archives Turkish Soc Cardiol 2012;40:696-8.

19 Fox CS, Gona P, Hoffmann U, et al. *Pericardial fat, intrathoracic fat, and measures of left ventricular structure and function: the Framingham heart study*. Circulation 2009;119:1586-91.

20 Rosito GA, Massaro JM, Hoffmann U, et al. *Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample.* Circulation 2008;117:605-13.

21 Iacobellis G. *Epicardial and pericardial fat: close, but very different*. Obesity 2009;17:625.

22 Chen O, Sharma A, Ahmad I, et al. *Correlation between pericardial, mediastinal, and intrathoracic fat volumes with the presence and severity of coronary artery disease, metabolic syndrome, and cardiac risk factors.* Eur Heart J Cardiovasc Imaging 2015;16:37-46.

23 Iacobellis G, Willens HJ. *Echocardiographic epicardial fat: a review of research and clinical applications.* J Am Soc Echocardiogr 2009;22:1311-9.

24 Iacobellis G, Corradi D, Sharma AM. *Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart.* Nat Clin Pract Cardiovasc Med 2005;2:536-43.

25 Bertaso AG, Bertol D, Duncan BB, et al. *Epicardial fat: definition, measurements and systematic review of main outcomes*. Arq Bras Cardiol 2013;101:e18-28.

26 Mazzoccoli G, Dagostino MP, Greco A. *Age-related changes of epicardial fat thickness*. Biomed Prev Nutr 2012;2:38-41.

27 Womack HC. T*he relationship between human body weight, subcutaneous fat, heart weight, and epicardial fat.* Hum Biol 1983;55:667-76.

28 Kim S-A, Kim M-N, Shim W-J, et al. *Epicardial adipose*

tissue is related to cardiac function in elderly women, but not in men. Nutr Metab Cardiovasc Dis 2017;27:41-7.

29 Mahabadi AA, Massaro JM, et al. *Association of pericardial fat, intrathoracic fat, and visceral abdominal fat with cardiovascular disease burden: the Framingham heart study*. Eur Heart J 2008;30:850-6.

30 Shmilovich H, Dey D, Cheng VY, et al. *Threshold for the upper normal limit of indexed epicardial fat volume: derivation in a healthy population and validation in an outcome-based study*. Am J Cardiol 2011;108:1680-5.

31 Fernández Muñoz MJ, Basurto Acevedo L, Córdova Pérez N, et al. *Epicardial adipose tissue is associated with visceral fat, metabolic syndrome, and insulin resistance in menopausal women*. Rev Española Cardiol (English Ed) 2014;67:436-41.

32 Willens HJ, Gómez-Marín O, Chirinos JA, et al. *Comparison of epicardial and pericardial fat thickness assessed by echocardiography in African American and non-Hispanic white men: a pilot study*. Ethn Dis 2008;18:311-6.

33 Tok D, Kadife I, Turak O, et al. *Increased epicardial fat thickness is associated with low grade systemic inflammation in metabolic syndrome*. Turk Kardiyol Dern Ars 2012;40:690-5.

34 Iacobellis G, Willens HJ, Barbaro G, et al. *Threshold values of high-risk echocardiographic epicardial fat thickness*. Obesity 2008;16:887-92.

35 Stramaglia G, Greco A, Guglielmi G, et al. *Echocardiography and dual-energy x-ray absorptiometry in the elderly patients with metabolic syndrome: a comparison of two different tecniques to evaluate visceral fat distribution*. J Nutr Health Aging 2010;14:6-10.

36 Fitzmaurice DA, Accetta G, Haas S, et al. *Comparison of international normalized ratio audit parameters in patients enrolled in GARFIELD-AF and treated with vitamin K antagonists.* Br J Haematol 2016;174:610-23.

37 Yamaguchi Y, Cavallero S, Patterson M, et al. *Adipogenesis and epicardial adipose tissue: a novel fate of the epicardium induced by mesenchymal transformation and PPARγ activation*. Proc Natl Acad Sci 2015;112:2070-5.

38 Gruzdeva O, Borodkina D, Uchasova E, et al. *Localization of fat depots and cardiovascular risk.* Lipids Health Dis 2018;17:218.

39 Mazurek T, Zhang L, Zalewski A, et al. *Human epicardial adipose tissue is a source of inflammatory mediators.* Circulation 2003;108:2460-6.

40 Xourgia E, Papazafiropoulou A, et al. *Effects of antidiabetic drugs on epicardial fat.* World J Diabetes 2018;9:141-8.

41 Marchington JM, Pond CM. *Site-specific properties of pericardial and epicardial adipose tissue: the effects of insulin and high-fat feeding on lipogenesis and the incorporation of fatty acids in vitro.* Int J Obes 1990;14:1013-22.

42 Nelson MR, Mookadam F, Thota V, et al. *Epicardial fat: an additional measurement for subclinical atherosclerosis and cardiovascular risk stratification?* J Am Soc Echocardiogr 2011;24:339-45.

43 Roever L, Resende ES, Diniz ALD, et al. *Epicardial adipose tissue and metabolic syndrome: an update protocol for systematic review and meta-analysis*. Medicine (Baltimore) 2018;97:e0387.

44 Bronas UG, Dengel DR. *Influence of vascular oxidative stress and inflammation on the development and progression of atherosclerosis.* Am J Lifestyle Med 2010;4:521-34.

45 Mahabadi AA, Berg MH, Lehmann N, et al. *Association of epicardial fat with cardiovascular risk factors and incident myocardial infarction in the general population*. J Am Coll Cardiol 2013;61:1388-95.

46 Possner M, Liga R, Gaisl T, et al. *Quantification of epicardial and intrathoracic fat volume does not provide an added prognostic value as an adjunct to coronary artery calcium score and myocardial perfusion single-photon emission computed tomography.* Eur Hear J Cardiovasc Imaging 2016;17:885-91.

47 Sironi AM, Gastaldelli A, Mari A, et al. *Visceral fat in hypertension.* Hypertension 2004;44:127-33.

48 Dicker D, Atar E, Kornowski R, et al. *Increased epicardial adipose tissue thickness as a predictor for hypertension: a cross-sectional observational study*. J Clin Hypertens 2013;15:893-8.

49 Sengul C, Cevik C, Ozveren O, et al. *Epicardial fat thickness is associated with non-dipper blood pressure pattern in patients with essential hypertension*. Clin Exp Hypertens 2012;34:165-70.

50 Ertas F, Kaya H, Acet H, et al. *Increased echocardiographic epicardial fat thickness is related to impaired diurnal blood pressure profiles.* Blood Press 2012;21:202-8.

51 Sironi AM, Pingitore A, Ghione S, et al. *Early hypertension is associated with reduced regional cardiac function, insulin resistance, epicardial, and visceral fat*. Hypertens (Dallas, Tex. 1979) 2008;51:282-8.

52 Eroğlu S, Sade LE, Yıldırır A, et al. *Association of epicardial adipose tissue thickness by echocardiography and hypertension.* Turk Kardiyol Dern Arsivi-Archives Turkish Soc Cardiol 2013;41:115-22.

53 Turak O. *Relation between epicardial adipose tissue thickness and blood pressure levels in prehypertension.* Turk Kardiyol Dern Arsivi-Archives Turkish Soc Cardiol 2014;42:358-64.

54 Çetin M, Kocaman SA, Durakoğlugil ME, et al. *Effect of epicardial adipose tissue on diastolic functions and left atrial dimension in untreated hypertensive patients with normal systolic function.* J Cardiol 2013;61:359-64.

55 Cha S-A, Park Y-M, Yun J-S, et al. *A comparison of effects of DPP-4 inhibitor and SGLT2 inhibitor on lipid profile in patients with type 2 diabetes*. Lipids Health Dis 2017;16:58.

56 Konishi M, Sugiyama S, Sugamura K, et al. *Association of pericardial fat accumulation rather than abdominal obesity with coronary atherosclerotic plaque formation in patients with suspected coronary artery disease.* Atherosclerosis 2010;209:573-8.

57 Jang H-C, Lee H-K, Lee H, et al. *Analyzing correlation between epicardial fat area and metabolic syndrome risk factor by using low-dose Lung CT*. Pakistan J Med Sci 2015;31:1207-12.

58 Goel R, Alharthi M, Jiamsripong P, et al. *Epicardial fat and*

its association with cardiovascular risk: a cross-sectional observational study. Hear Views 2010;11:103.

59 Calabuig Á, Barba J, Guembe MJ, et al. *Epicardial adipose tissue in the general middle-aged population and its association with metabolic syndrome.* Rev Española Cardiol 2017;70:254-60.

60 Tan-Ramos KC, Allyn-Sy R, Choa V. *Echocardiographic epicardial adipose tissue thickness as a marker of insulin resistance.* J. ASEAN Fed Endocr Soc 2014;29:129-34.

61 Altin C, Sade LE, Gezmis E, et al. *Assessment of epicardial adipose tissue and carotid/femoral intima media thickness in insulin resistance.* J Cardiol 2017;69:843-50.

62 Narumi T, Watanabe T, Iwayama T, et al. *Increased epicardial adipose tissue volume predicts insulin resistance and coronary artery disease in non-obese subjects without metabolic syndrome.* IJC Metab Endocr 2014;3:14-9.

63 Pucci G, Battista F, de Vuono S, et al. *Pericardial fat, insulin resistance, and left ventricular structure and function in morbid obesity.* Nutr Metab Cardiovasc Dis 2014;24:440-6.

64 Iacobellis G, Leonetti F. *Epicardial adipose tissue and insulin resistance in obese subjects*. J Clin Endocrinol Metab 2005;90:6300-2.

65 Canpolat U, Bahadir N, Coteli C. *Chicken or egg causality paradox between insulin resistance and epicardial fat*. Angiology 2016;67:970-1.

66 Baldasseroni S, Pratesi A, Orso F, et al. *Epicardial adipose tissue and insulin resistance in patients with coronary artery disease with or without left ventricular dysfunction*. Monaldi Arch Chest Dis 2013;80:170-6.

67 Li Y, Liu B, Li Y, et al. *Epicardial fat tissue in patients with diabetes mellitus: a systematic review and meta-analysis.* Cardiovasc Diabetol 2019;18:3.

68 Wang T-D, Lee W-J, Shih F-Y, et al. *Relations of epicardial adipose tissue measured by multidetector computed tomography to components of the metabolic syndrome are region-specific and independent of anthropometric indexes and intraabdominal visceral fat*. J Clin Endocrinol Metab 2009;94:662-9.

69 Snijder M, Visser M, Dekker J, et al. *The prediction of visceral fat by dual-energy X-ray absorptiometry in the elderly: a comparison with computed tomography and anthropometry.* Int J Obes 2002;26:984-93.

70 Lee JJ, Pedley A, Hoffmann U, et al. *Visceral and intrahepatic fat are associated with cardiometabolic risk factors above other ectopic fat depots: the Framingham heart study*. Am J Med 2018;131:684-92.e12.

71 Yamada H, Sata M. *Role of pericardial fat: the good, the bad and the ugly*. J Cardiol 2015;65:2-4.

72 Okura K, Maeno K, Okura S, et al. *Pericardial fat volume is an independent risk factor for the severity of coronary artery disease in patients with preserved ejection fraction*. J Cardiol 2015;65:37-41.

73 Sicari R, Sironi AM, Petz R, et al. *Pericardial rather than epicardial fat is a cardiometabolic risk marker: an MRI vs echo study.* J Am Soc Echocardiogr 2011;24:1156-62.

74 Dabbah S, Komarov H, Marmor A, et al. *Epicardial fat, rather than pericardial fat, is independently associated with diastolic filling in subjects without apparent heart disease*. Nutr Metab Cardiovasc Dis 2014;24:877-82.

75 Hirata Y, Yamada H, Sata M. *Epicardial fat and pericardial fat surrounding the heart have different characteristics*. Circ J 2018;82:2475-6.

How to cite this article: Lo Buglio A, Bellanti F, Vendemiale G. *Cardiac visceral fat and cardiometabolic risk in the elderly*. Journal of Gerontology and Geriatrics 2019;67(Suppl):226-32.