IJC Heart & Vasculature 49 (2023) 101284

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Editorial

INOCA and epicardial adipose tissue: "Friends" or "foes"?

Myocardial ischemia with non-obstructed coronary arteries (INOCA) and myocardial infarction with non-obstructed coronary arteries (MINOCA) involve several different pathophysiological mechanisms, such as coronary plaque erosion or rupture, microvascular dysfunction, vasospasm, and supply demand mismatch (1).

A topic of great interest is the identification of cardiovascular (CV) imaging markers that might correlate with the risk of ischemia in non-obstructive coronary artery disease (CAD) [1].

The recent technological advances in coronary computed tomography angiography (CCTA) allow evaluation of anatomical markers beyond the degree of coronary artery stenosis, including atherosclerotic high-risk plaque (HRP) features as low attenuation, positive remodeling, napkin ring sign and spotty calcifications [2].

The epicardial adipose tissue (EAT), is a metabolic active fat depot enclosed by visceral pericardium and surrounding the coronary arteries [3].EAT has an important interplay with the heart [4], and an increased EAT volume associated with the release of pro-inflammatory cytokines seems to correlate with a higher risk of coronary atherosclerosis and microvascular dysfunction [5]. For these reasons, the pathological role of increased EAT volume is an intriguing current topic of research (Fig. 1). However, the association between increased EAT volume and myocardial ischemia remains unclear [6,7].

In the current issue of IJC Heart & Vasculature, Khan et al. evaluated the association between EAT volume and CV risk factors, inflammation, left ventricular mass index (LVMi), coronary calcium score, demand-induced myocardial ischemia, and coronary artery plaque volume and vulnerability [8].

They selected 125 patients (median age: 63 years, women: 58%) from the Micro CAD (Myocardial Ischemia in Non-obstructive coronary artery Disease) study which includes patients with symptomatic chronic coronary syndrome and non-obstructive CAD (<50% diameter stenosis).

All patients underwent non-contrast cardiac CT, CCTA, echocardiography and myocardial contrast dobutamine stress echocardiography. EAT volume was measured from non-contrast cardiac CT and the participants were clustered into two groups respectively with low (<125 ml, n = 82 patients) and high EAT volume (≥125 ml, n = 43 patients).

The main results of the study were the following: clustering of ≥ 3 CV risk factors, increased LVMi, inflammation and positive remodeling, were significantly more frequent among patients with high EAT volume and, in a multivariable analysis, LVMi and positive coronary remodeling remained independently associated with high EAT volume, although coronary calcium score, plaque burden and presence of demand myocardial ischemia were not statistically different between the groups.

These findings allow some important considerations.

First, the study confirms the association between high EAT volume and CV risk factors, increased LVMi and inflammation. These results reinforce the role of EAT as a prognostic and risk stratification factor for CV disease. In a *meta*-analysis of twenty-nine articles comprising 19,709 patients, increased EAT volume was associated with higher risks of cardiac death, myocardial infarction, coronary revascularization, and major cardiovascular events [9].

Second, Khan et al. demonstrated a significant association between increased EAT volume and positive plaque remodeling. It should be noted that in a recent *meta*-analysis of nine articles comprising 3772 patients, increased EAT volume was associated with the presence of HRP features [10], thus suggesting that EAT evaluation should integrate assessment of established CT coronary markers of HRP [2].

Furthermore, it is necessary to specify that the value of EAT volume measured by CT, although performed with the use of dedicated software, changes according to the attenuation thresholds chosen for recognition of the EAT (normally between −45 HU and −195 HU).

Moreover, the EAT attenuation can be decreased (more negative) in case of hypertrophic and hyperplastic fat deposits or on the contrary it can be increased (i.e. "less negative") in cases of fibrotic and inflamed fat deposits [2].

In addition, it would be useful consider the EAT volume indexed to the patients' body surface area or body mass index, in order to achieve more specific thresholds [2].

Third, in the present study a correlation between EAT volume and inducible myocardial ischemia was not found, possibly because of small sample size and lack of comprehensive assessment of INOCA endotypes. In fact, the diagnostic pathway of INOCA and MINOCA patients should include invasive coronary function testing, in order to identify the INOCA endotype (i.e. microvascular dysfunction, vasospasm) and to provide tailored therapy [1,2]. Recent articles showed the correlation between increased vascular-specific EAT volume and the *peri*-coronary adipose tissue volume (which represent a part of the larger EAT depot) with coronary artery spasm and significant coronary ischemia detected respectively by provocative challenge and fractional flow reserve testing [6,11,12]. Thus, Coronary spasm represents another possible presentation of inflammation-mediated coronary artery disease [12] but it could be missed on standard stress testing, and, if suspected, it should be ruled-out by invasive intracoronary pharmacological challenge [13]. These findings could be biologically plausible because the EAT near to the coronary artery may exert a paracrine effect, emphasizing the possible role of inflammation and vasoreactivity also in the absence of

DOI of original article: https://doi.org/10.1016/j.ijcha.2023.101240.

https://doi.org/10.1016/j.ijcha.2023.101284
Received 26 September 2023; Received in revised form 11 October 2023; Accepted 15 October 2023
Available online 20 October 2023

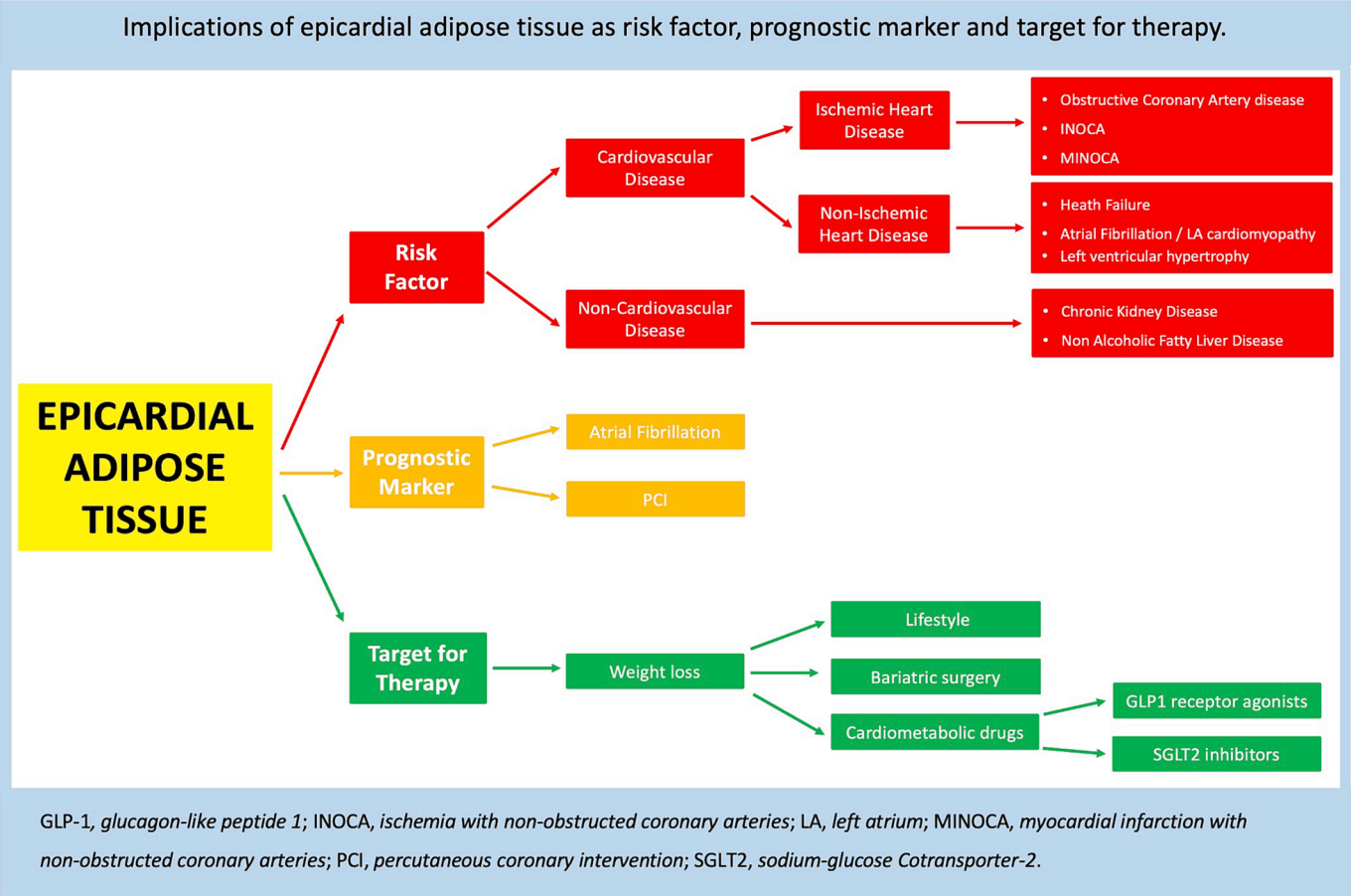

Fig. 1.

obstructive coronary atherosclerosis [14] and in stable coronary artery disease [15].

Lastly, it should be noted that the EAT volume can be assessed routinely by non-contrast cardiac CT examination [3]. This finding is not trivial. With a single prospective cardio-synchronized CT scan without the use of contrast medium and with a very low radiation dose, could be evaluated the coronary calcium score and, in addition, the EAT volume improving the CV risk stratification of the patient, thus allowing a more accurate cardiovascular risk stratification [4]. Moreover, a main limitation could be represented by the absence of standardized EAT volume normal values, since definitions and cut-offs significantly vary across different studies [9].

However, studies like this by Khan et al. should stimulate research in this field, in order to promote a "CCTA mindset" approach which should aspire to a more comprehensive assessment beyond the solely evaluation of the degree of coronary stenosis.

In conclusion, CT assessment of EAT volume could represent a "friend" in the evaluation of cardiovascular risk and in the assessment of challenging conditions such as INOCA and MINOCA, but could be a "foe" if it is not considered in the context of other clinical and imaging features. The contribution of EAT in the occurrence of demand-type myocardial ischemia remains to be elucidated.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] G. Ciliberti, P. Compagnucci, A. Urbinati, F. Bianco, G. Stronati, S. Lattanzi, A. D. Russo, F. Guerra, Myocardial infarction without obstructive coronary artery disease (MINOCA): a practical guide for clinicians, Curr. Probl. Cardiol. 46 (3) (2021), 100761.
[2] H.R. Reynolds, A. Diaz, D.D. Cyr, L.J. Shaw, G.B.J. Mancini, J. Leipsic, M.J. Budoff, J.K. Min, C.J. Hague, D.S. Berman, B.R. Chaitman, M.H. Picard, S.W. Hayes, M. Scherrer-Crosbie, R.Y. Kwong, R.D. Lopes, R. Senior, S.K. Dwivedi, T.D. Miller, B.J.W. Chow, R. de Silva, G.W. Stone, W.E. Boden, S. Bangalore, S.M. O'Brien, J. S. Hochman, D.J. Maron, ISCHEMIA Research Group, Ischemia With Non-obstructive Coronary Arteries: Insights From the ISCHEMIA Trial, JACC Cardiovasc. Imaging. 16 (2023) 63–74.
[3] M. Goeller, S. Achenbach, H. Duncker, D. Dey, M. Marwan, Imaging of the Pericoronary Adipose Tissue (PCAT) Using Cardiac Computed Tomography: Modern Clinical Implications, J. Thorac. Imaging. 36 (2021) 149–161.
[4] G. Iacobellis, Epicardial adipose tissue in contemporary cardiology, Nat. Rev. Cardiol. 19 (2022) 593–606.
[5] Q. Wang, J. Chi, C. Wang, Y. Yang, R. Tian, X. Chen, Epicardial adipose tissue in patients with coronary artery disease: A meta-analysis, J. Cardiovasc. Dev. Dis. 9 (2022) 253.
[6] D. Shan, X. Wang, G. Dou, W. Zhang, J. Jing, B. He, Y. Li, Y. Chen, J. Yang, Vascular-specific epicardial adipose tissue in predicting functional myocardial ischemia for patients with stable chest pain, J. Thromb Thrombolysis 51 (2021) 915–923.
[7] J. Mancio, D. Azevedo, F. Saraiva, A.I. Azevedo, G. Pires-Morais, A. Leite-Moreira, I. Falcao-Pires, N. Lunet, N. Bettencourt, Epicardial adipose tissue volume assessed by computed tomography and coronary artery disease: a systematic review and meta-analysis, Eur. Heart J. Cardiovasc. Imaging 19 (2018) 490–497.
[8] I. Khan, C.A. Berge, I. Eskerud, T.H. Larsen, E.R. Pedersen, M.T. Lønnebakken, Epicardial adipose tissue volume, plaque vulnerability and myocardial ischemia in non-obstructive coronary artery disease, IJC Heart Vasc. 13 (2023), 101240.
[9] B. Chong, J. Jayabaskaran, J. Ruban, R. Goh, Y.H. Chin, G. Kong, C.H. Ng, C. Lin, S. Loong, M.D. Muthiah, C.M. Khoo, E. Shariff, M.Y. Chan, F. Lajeunesse-Trempe, A. Tchernof, P. Chevli, A. Mehta, M.A. Mamas, G.K. Dimitriadis, N.W.S. Chew, Epicardial Adipose Tissue Assessed by Computed Tomography and Echocardiography Are Associated With Adverse Cardiovascular Outcomes: A Systematic Review and Meta-Analysis, Circ. Cardiovasc. Imaging. 16 (2023) e015159.

[10] N. Nerlekar, A.J. Brown, R.G. Muthalaly, A. Talman, T. Hettige, J.D. Cameron, D.T. L. Wong, Association of Epicardial Adipose Tissue and High-Risk Plaque Characteristics: A Systematic Review and Meta-Analysis, J. Am. Heart Assoc. 6 (2017) e006379.
[11] R. Ma, R. Fari, P. van der Harst, C. N De Cecco, A. E Stillman, R. Vliegenthart, M. van Assen, Evaluation of pericoronary adipose tissue attenuation on CT, Br. J. Radiol. 96 (2023) 20220885.
[12] G. Ciliberti, F. Guerra, A. Capucci, Coronary Spasm and Inflammation: Can We Kill 2 Birds With 1 Stone? J. Am. Coll. Cardiol. 71 (23) (2018) 2707–2708.
[13] G. Ciliberti, S.R. Seshasai, G. Ambrosio, J.C. Kaski, Safety of intracoronary provocative testing for the diagnosis of coronary artery spasm, Int. J. Cardiol. 1 (244) (2017) 77–83.
[14] G. Ciliberti, S. Coiro, I. Tritto, M. Benedetti, F. Guerra, M. Del Pinto, G. Finocchiaro, C. Cavallini, A. Capucci, J.C. Kaski, G. Ambrosio, Predictors of poor clinical outcomes in patients with acute myocardial infarction and non-obstructed coronary arteries (MINOCA), Int. J. Cardiol. 15 (267) (2018) 41–45.
[15] G. Ciliberti, F. Guerra, S. Coiro, A. Capucci, Is there an 'atherosclerotic continuum'from angina with unobstructed coronary arteries to MINOCA? Eur. Heart J. 40 (24) (2019) 1987.

Giuseppe Ciliberti*
Cardiology and Arrhythmology Clinic, Marche University Hospital, Ancona, Italy

Nicolò Schicchi
Cardiovascular Radiological Diagnostics, Department of Radiological Sciences, University Hospital of Marche, Ancona, Italy

Giuseppe Ambrosio
Division of Cardiology, University of Perugia, School of Medicine, Perugia, Italy

Antonio Dello Russo
Cardiology and Arrhythmology Clinic, Marche University Hospital, Ancona, Italy

Marco Fogante
Maternal-Child-Senological-Cardiological Radiology and Outpatient Ultrasound, Department of Radiological Sciences, University Hospital of Marche, Ancona, Italy

* Corresponding author at: Cardiology Department, Marche University Hospital, Via Conca 71, 60126 Ancona, AN, Italy.
E-mail address: giuseppe.ciliberti@ospedaliriuniti.marche.it (G. Ciliberti).