Canadian Journal of Cardiology 33 (2017) 1459–1461

Editorial

Is Reduction in Coronary Blood Flow the Mechanism by Which Epicardial Fat Produces Left Ventricular Diastolic Dysfunction?

Simon W. Rabkin, MD, FRCPC FCCS, FACC

Department of Medicine (Cardiology), University of British Columbia, Vancouver, British Columbia, Canada

See article by Nakanishi et al., pages 1489–1497 of this issue.

Interest in epicardial adipose tissue (EAT), the adipose tissue around the heart, has grown dramatically over the past decade as fascination with an organ that had been synonymous with sloth (fat) is juxtaposed to the most dynamic (hard working) organ in the body—the heart. The normal or physiologic functions of epicardial fat have been categorized and include acting as a buffer for coronary arteries against torsion, regulation of fatty acid metabolism for coronary arteries, thermogenesis, and protection of the cardiac autonomic ganglia and nerves.[1] The beneficial mechanical effects of epicardial fat on the coronary arteries are analogous to the benefit of applying material to the outside of pipes or flexible tubes transporting pulsatile fluid, to minimize deformations. Epicardial fat might reduce the twisting, bending, and stretching of coronary arteries that is produced by cardiac contraction and the tethering of the large coronary arteries to the epicardial surface of the heart.[2] In addition, epicardial fat might blunt fluid flow-induced arterial vibrations because these vibrations might damage parts of the arterial wall specifically its elastin content and endothelial cells.[2] Excessive epicardial fat is believed to play several 'pathologic' roles because epicardial fat has been associated with atherosclerotic coronary artery disease,[3] atrial fibrillation,[4] and diastolic dysfunction or abnormal relaxation properties of the heart.

In this issue of the *Canadian Journal of Cardiology*, Nakanishi and colleagues show that periventricular EAT is associated with the development of left ventricular diastolic dysfunction and that EAT is associated with reduced small coronary artery blood flow.[5] They further suggest that EAT operating through its impairment in small vessel blood flow is responsible for abnormal left ventricular diastolic function.[5] This proposition needs further analysis.

The association of increased epicardial fat with diastolic dysfunction has been recognized for a long time and has been consistently shown in different study populations using different approaches to characterize diastolic function. Several studies presented the correlations of EAT with indices of diastolic function, which permits a summary approach.[6-13] One of the basic, albeit simplistic, indicators of diastolic dysfunction is mitral valve E/A ratio, which has shown a significant correlation between epicardial fat and diastolic dysfunction (Fig. 1A). The correlation is also evident between epicardial fat and E/e′, another measure of diastolic dysfunction (Fig. 1B).

Studies have confirmed that the relationship between EAT and diastolic dysfunction is independent of other factors in multivariate analysis. In patients after myocardial infarction, impaired left ventricular diastolic function was associated with increased central adiposity.[14] Increasing EAT was independently associated with worse left ventricular diastolic function even after adjusting for age, sex, hypertension, and other indices of adiposity.[14] In patients with newly diagnosed diabetes mellitus, a multivariate analysis reported that EAT was significantly related to left ventricular wall compliance during late diastole after adjusting for fasting glucose, body mass index, and lipids.[15] Epicardial fat volume was independently associated with diastolic dysfunction after considering age, systolic blood pressure, Framingham risk score, and left ventricular mass.[16]

Nakanishi and colleagues showed that epicardial fat is related to the deterioration in diastolic function over time, which was independent of other factors such as age and diabetes mellitus.[5] The strength of their correlation between epicardial fat and subsequent deterioration in diastolic function was not high. The low-order magnitude of the correlation provides a caution when embracing their results. Although the relationship remained significant after their multivariate analysis, only a limited number of variables were included in that multivariate analysis. The strength of their data is the relatively large number of subjects and the long time frame of follow-up data. It is most important to appreciate is that epicardial fat is only one of many factors related to diastolic

Received for publication August 11, 2017. Accepted August 15, 2017.

Corresponding author: Dr Simon W. Rabkin, University of British Columbia, 9th Floor, 2775 Laurel St, Vancouver, British Columbia V5Z 1M9, Canada. Tel.: +1-604-875-5847; fax: +1-604-875-5849.

E-mail: simon.rabkin@ubc.ca

See page 1461 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2017.08.013

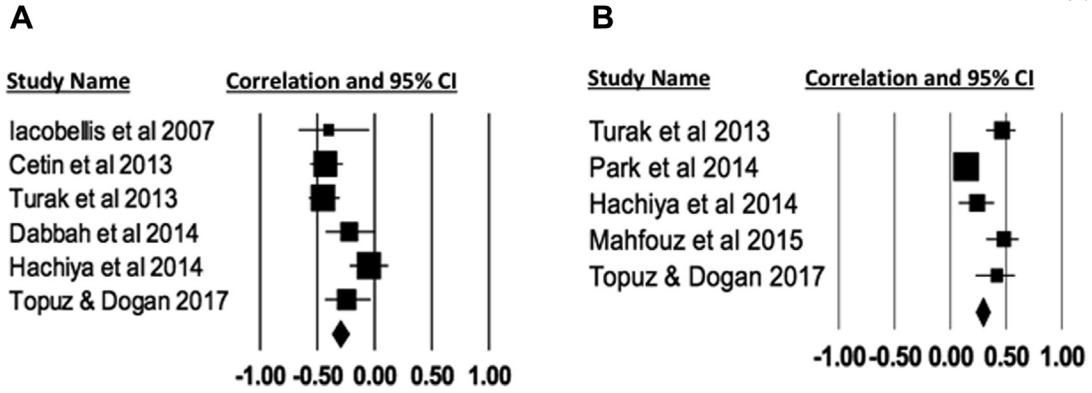

Figure 1. Correlation coefficients for the relationship between indices of the amount of epicardial fat and diastolic dysfunction measured according to the mitral (**A**) E/A ratio or (**B**) E/e′ ratio. CI, confidence interval.

dysfunction. There is a need for further research to identify all of the causative factors for diastolic dysfunction and to dissect out their interrelationships.

Stronger evidence that epicardial fat is linked to diastolic dysfunction comes from data that showed reductions in epicardial fat reduce diastolic dysfunction. Diet and exercise programs can reduce epicardial fat.[17] A 1-year weight reduction program with diet and lifestyle components showed that reduction of epicardial fat was predictive of an improvement in diastolic function in multivariate analysis considering other variables.[18] Of course a major issue is that weight loss strategies do not selectively reduce epicardial fat but rather reduce all adipose depots. A strategy that selectively reduced EAT would be of benefit to prove any linkage between EAT and diastolic dysfunction. Nevertheless from the perspective of clinical practice a strategy aimed at weight loss through diet and exercise can be recommended to improve diastolic function.[18]

Conceptually it is initially difficult to believe that fat, which has a relative low mass (compared with the heart), could have a meaningful effect to influence the relaxation stiffness of a muscular structure such as the left ventricle. However, adipose tissue is maintained in its location by a fibrous tissue scaffold, which can pack the fat onto the surface of the heart, adding mass to affect ventricular relaxation. This issue of the relatively smaller mass of adipose tissue compared with left ventricular muscle, however, has led investigators to search for other mechanisms by which epicardial fat might alter diastolic function.

The proposal that EAT might lead to diastolic dysfunction through impairment of coronary blood flow is not new. Sade et al. reported that "coronary microvascular dysfunction, as diagnosed by chest pain with impaired coronary flow reserve, in the absence of obstructive coronary lesions, is more closely associated with epicardial fat than any traditional risk factor of atherosclerosis."[19] They concluded that although epicardial fat correlates with insulin resistance, abdominal obesity, and hypertension, epicardial fat is more closely associated with impaired coronary blood flow than 'these metabolic abnormalities.'[19]

Cetin et al. suggested that increased EAT might produce a deterioration in diastolic function by decreasing coronary flow reserve by secreting mediators that affect "myocardial tissue and/or coronary arteries either by endocrine effect or by direct diffusion via vasa vasorum or by passive perivascular compressive and thermogenic effects even before clinically evident ischemia."[7] Nakanishi and colleagues sought to add data to 'prove' this hypothesis.[5] They measured small-vessel blood flow indirectly as the difference between resting flow and adenosine-induced increase in flow in the distal left anterior descending coronary artery (LAD). Coronary blood flow was measured using Doppler estimates from a modified foreshortened 2-chamber view, which was applied to determine blood flow in the distal portion of the LAD. Coronary blood flow velocity was estimated at baseline and after intravenous administration of adenosine. The challenges of this approach are apparent and include visualization using echo/Doppler of the blood in a vessel the size of the LAD using a transthoracic probe and ensuring that the location of the probe and its visualization of the same LAD segment is constant before and after adenosine infusion.

The possibility that coronary artery blood flow was compromised to some extent by the presence of atherosclerotic coronary artery disease cannot be totally excluded. EAT volume was greater, although not statistically different, between patients with compared with those without coronary artery disease (91.3 vs 82.7 mL) in the study by Nakanishi et al.[5] Overall meta-analysis data show an increased prevalence of coronary artery disease in patients with increased epicardial fat.[3]

The cause(s) of diastolic dysfunction is (are) complex and many of the causes are likely still unknown. Diastolic dysfunction has been ascribed to deficiencies or abnormalities in myocardial calcium reuptake, mitochondrial function, myocardial hypertrophy, myocardial fibrosis, and the relationship of cardiomyocytes to its matrix. Thus, proving the contribution of one factor such as coronary blood flow in patients who might have one or more known and unknown causes of diastolic dysfunction is a challenge.

If epicardial fat produces diastolic dysfunction though reductions in coronary blood flow, one would anticipate that interventions that increase coronary blood flow should improve diastolic dysfunction. It is disappointing for this concept that known coronary vasodilators such as nitrates do not improve diastolic dysfunction that exists as part of heart failure with preserved ejection fraction.[20] In addition, other agents that should reduce the effect of the vasoconstrictor angiotensin also do not alter the outcome of patients with

heart failure with preserved ejection fraction.[21] Epicardial fat possesses a large array of genes involved in production of factors that might affect coronary blood flow.[22] It is noteworthy that EAT is increased and coronary blood flow reduced in in patients with nonalcoholic liver disease.[23] Furthermore, in that population, multivariate regression analysis showed that elevated levels of serum vaspin were an independent predictor of coronary blood flow.[23] Further research should be conducted to identify factors originating from epicardial fat that are responsible for the reduction in coronary blood flow. These factors might be targeted to improve coronary blood flow, not only in patients with increased epicardial fat but also in patients with heart failure with preserved ejection fraction, and as an adjunct to current medications and coronary interventions to improve coronary blood flow.

Disclosures

The author has no conflicts of interest to disclose.

References

1. Rabkin SW. Epicardial fat: properties, function and relationship to obesity. Obes Rev 2007;8:253-61.
2. Rabkin SW. Role of epicardial fat to buffer deformation and vibration in coronary arteries. Clin Med Rev Vasc Health 2017;9: 1179256617690147.
3. Xu Y, Cheng X, Hong K, Huang C, Wan L. How to interpret epicardial adipose tissue as a cause of coronary artery disease: a meta-analysis. Coron Artery Dis 2012;23:227-33.
4. Zhu W, Zhang H, Guo L, Hong K. Relationship between epicardial adipose tissue volume and atrial fibrillation: a systematic review and meta-analysis. Herz 2016;41:421-7.
5. 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.
6. Iacobellis G, Leonetti F, Singh N, M Sharma A. Relationship of epicardial adipose tissue with atrial dimensions and diastolic function in morbidly obese subjects. Int J Cardiol 2007;115:272-3.
7. Cetin M, Kocaman SA, Durakoglugil 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.
8. Mahfouz RA, Alzaiat A, Yousry A. Relationship of epicardial fat thickness with endothelial and cardiac functions in children with family history of type 2 diabetes mellitus. Echocardiography 2015;32:28-33.
9. Hachiya K, Fukuta H, Wakami K, et al. Relation of epicardial fat to central aortic pressure and left ventricular diastolic function in patients with known or suspected coronary artery disease. Int J Cardiovasc Imaging 2014;30:1393-8.
10. Dabbah S, Komarov H, Marmor A, Assy N. 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.
11. Park HE, Choi SY, Kim M. Association of epicardial fat with left ventricular diastolic function in subjects with metabolic syndrome: assessment using 2-dimensional echocardiography. BMC Cardiovasc Disord 2014;14:3.
12. Turak O, Ozcan F, Canpolat U, et al. Increased echocardiographic epicardial fat thickness and high-sensitivity CRP level indicate diastolic dysfunction in patients with newly diagnosed essential hypertension. Blood Press Monit 2013;18:259-64.
13. Topuz M, Dogan A. The effect of epicardial adipose tissue thickness on left ventricular diastolic functions in patients with normal coronary arteries. Kardiol Pol 2017;75:196-203.
14. Fontes-Carvalho R, Fontes-Oliveira M, Sampaio F, et al. Influence of epicardial and visceral fat on left ventricular diastolic and systolic functions in patients after myocardial infarction. Am J Cardiol 2014;114: 1663-9.
15. Kazlauskaite R, Doukky R, Evans A, et al. Predictors of diastolic dysfunction among minority patients with newly diagnosed type 2 diabetes. Diabetes Res Clin Pract 2010;88:189-95.
16. Cavalcante JL, Tamarappoo BK, Hachamovitch R, et al. Association of epicardial fat, hypertension, subclinical coronary artery disease, and metabolic syndrome with left ventricular diastolic dysfunction. Am J Cardiol 2012;110:1793-8.
17. Rabkin SW, Campbell H. Comparison of reducing epicardial fat by exercise, diet or bariatric surgery weight loss strategies: a systematic review and meta-analysis. Obes Rev 2015;16:406-15.
18. Fenk S, Fischer M, Strack C, et al. Successful weight reduction improves left ventricular diastolic function and physical performance in severe obesity. Int Heart J 2015;56:196-202.
19. Sade LE, Eroglu S, Bozbas H, et al. Relation between epicardial fat thickness and coronary flow reserve in women with chest pain and angiographically normal coronary arteries. Atherosclerosis 2009;204:580-5.
20. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. N Engl J Med 2015;373: 2314-24.
21. Zheng S, Chan F, Nabeebaccus A, et al. Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis [e-pub ahead of print]. Heart doi:10.1136/heartjnl-2017-311652, accessed September 16, 2017.
22. Yim J, Rabkin SW. Differences in gene expression and gene associations in epicardial fat compared to subcutaneous fat. Horm Metab Res 2017;49:327-37.
23. Yilmaz Y, Kurt R, Gurdal A, et al. Circulating vaspin levels and epicardial adipose tissue thickness are associated with impaired coronary flow reserve in patients with nonalcoholic fatty liver disease. Atherosclerosis 2011;217:125-9.