Nutrition, Metabolism & Cardiovascular Diseases (2014) 24, 286–293

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Determinants of intrathoracic adipose tissue volume and associations with cardiovascular disease risk factors in Amish

X. Liu [a,*], W.S. Post [b], J. McLenithan [c], M. Terrin [a], L. Magder [a], I. Zeb [d], M. Budoff [d], B.D. Mitchell [a,c]

[a] Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD, USA
[b] Department of Medicine and Epidemiology, Johns Hopkins University School of Medicine and Bloomberg School of Public Health, Baltimore, MD, USA
[c] Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA
[d] Los Angeles Biomedical Research Institute, Harbor UCLA Med Center, Torrance, CA, USA

Received 22 April 2013; received in revised form 18 September 2013; accepted 23 September 2013
Available online 1 November 2013

KEYWORDS
Ectopic fat;
Intrathoracic fat;
Epicardial fat;
Obesity;
Coronary artery calcification;
Cardiovascular diseases

Abstract *Background and aim:* Hypothesizing that intrathoracic fat might exert local effects on the coronary vasculature, we assessed the association of intrathoracic fat volume and its two subcomponents with coronary artery calcification (CAC) in 909 relatively healthy Amish adults.
Methods and results: Intrathoracic fat, which is comprised of fat between the surface of the heart and the visceral epicardium (epicardial fat) and fat around the heart but outside of the fibrous pericardium (pericardial fat), was measured from electron beam CT scans. We examined the association between intrathoracic fat volume and cardiovascular disease risk factors in multivariate regression model. Fat volume in the epicardial and pericardial compartments were highly correlated with each other and with body mass index. Neither CAC extent nor CAC presence (Agatston score > 0) was associated with increased intrathoracic fat volume in sex-stratified models adjusting for age ($p > 0.10$). Intrathoracic fat volume was significantly correlated with higher systolic/diastolic blood pressure, pulse pressure, fasting glucose, insulin, triglyceride and lower high-density lipoprotein cholesterol in sex-stratified models adjusting for age ($p < 0.05$). However, associations were attenuated after further adjustment for body mass index.
Conclusions: These data do not provide support for a significant role for intrathoracic fat in the development of CAC.

Introduction

Obesity is associated with numerous cardiovascular and metabolic risk factors and predicts the development of cardiovascular disease and diabetes. It is widely appreciated that cardiometabolic risk is influenced not only by the absolute quantity of adipose tissue accumulation but also by where it is distributed. For example, fat tissue in the abdominal visceral compartments may pose particular risk for metabolic diseases because these tissues actively secrete adipocytokines and inflammatory factors and are in close proximity to the abdominal internal organs [1–6].

Intrathoracic adipose tissue is an extra-abdominal visceral fat depot located around the heart in the thoracic cavity. Similar to abdominal fat, intrathoracic fat also expresses and secretes high concentrations of proinflammatory adipokines [6–11]. Intrathoracic fat consists of two compartments: epicardial fat (within the pericardial sac) and pericardial fat (outside the pericardial sac). Because there is no separating fascia between epicardial fat and the myocardium, some have hypothesized that intrathoracic fat, and more specifically, epicardial fat,

* Corresponding author. 220 Arch Street, 12th Floor Room 308, Baltimore, MD 21202, USA. Tel.: +1 4109005003.
E-mail address: xliu@rx.umaryland.edu (X. Liu).

0939-4753/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.numecd.2013.09.015

might exert local paracrine effects on the cardiac vasculature that influences the development of coronary artery disease [7,11–21].

In recent years the volume of intrathoracic fat has been associated with both prevalent [13] and incident [21] cardiovascular disease (CVD). Moreover, evidence for a local effect of intrathoracic fat on the coronary vasculature was suggested by the Framingham Heart Study, which showed that coronary artery calcification (CAC) was independently associated with epicardial fat volume, after adjustment for body mass index and visceral adipose tissue [20]. In observational studies of smaller samples of individuals, intrathoracic fat has also been associated with other subclinical measures of atherosclerosis, including severity of angiographic coronary disease and carotid artery wall thickness [22]. In summary, studies have suggested that intrathoracic fat could have a local effect to the anatomical structures by the virtue of proximity and such hypothesis has been supported by epidemiological evidences showing independent effect of intrathoracic fat on top of other obesity measurements.

Establishing that intrathoracic fat predicts cardiovascular outcomes or atherosclerosis independently of overall body mass index has important implications not only because it could provide further insights into mechanisms through which obesity promotes cardiometabolic risk, but also because it would offer ways to more precisely identify individuals at higher cardiometabolic risk and could invite discussion about new approaches for prevention. With this in mind, we sought to replicate the previously reported association between intrathoracic fat and coronary artery calcification [20] in a different population characterized by a rural lifestyle and low prescription medication usage, and to determine if the association would be independent of overall adiposity. We sought further to assess the associations of intrathoracic fat, as well as epicardial fat and pericardial fat, with a panel of cardiovascular and metabolic risk factors.

Methods

Study population

This report is based on our ongoing epidemiologic and genetic studies of adults from the Old Order Amish (OOA) community in Lancaster County, Pennsylvania [23–25]. Subjects included in this substudy were relatively healthy individuals who volunteered to participate in a study of cardiovascular health, including assessment of coronary artery calcification, between the years of 2002 and 2008. Participants included many sets of related individuals, and indeed all OOA in Lancaster County are more than third degree cousins by virtue of their social insularity.

Intrathoracic fat volume measurement

Non-contrast electron beam computed tomography (EBCT) scans were obtained on an Imatron scanner (Imatron Inc., San Francisco, CA) in 3-mm thick contiguous slices with pixel size of 0.7813 × 0.7813 mm. The scans cover the full length of the heart from the great vessels to the apex of the heart. Scans were initially obtained for measurement of coronary artery calcification (see below), but were re-analyzed for this substudy for assessment of intrathoracic fat volume.

In this paper, epicardial adipose tissue is defined as adipose tissue between the surface of the heart and the visceral epicardium (within the intrathoracic sac). Pericardial adipose tissue is defined as pericardial adipose tissue around the heart but outside of the fibrous pericardium. Intrathoracic adipose tissue refers to the combination of the epicardial (within the pericardial sac) and pericardial adipose tissue (in the thorax but outside of pericardial sac) from the right pulmonary artery to the diaphragm and the anterior chest wall to the vertebral column. Manual segmentation of the epicardial and pericardial adipose tissue was performed by drawing regions-of-interest (ROIs) on every selected slice from the lower boundary of right pulmonary artery as it crosses the mid−sagittal plane to diaphragm. A threshold of −190 to −30 Hounsfield units was applied to identify adipose tissue voxels. Volumes (cm^3) of intrathoracic, epicardial, and pericardial adipose tissue were measured without knowledge of the participant's coronary calcification score. Sample images showing the ROIs are shown in Fig. 1 for the upper (Fig. 1a), middle (Fig. 1b), and lower (Fig. 1c) heart.

Both inter-observer and intra-observer reproducibility of the fat volume measurement were evaluated. Two observers (authors X.L. and I.Z.) reviewed and measured epicardial and pericardial fat volume on 12 representative scans using the manual segmentation protocol described above. The correlation in measurements between the two observers was 0.93 ($p < 0.001$) and in no case did we find a between-observer difference more than 10%. X.L. also evaluated intra-observer reproducibility by re-measuring 100 randomly chosen scans one month after the initial measurement without knowledge of the initial measure. The correlation in repeat measurements of the same scan was 0.97 ($p < 0.001$). Using Bland-Altman analysis, we observed high agreement between the two observers for both intrathoracic (9.7 cm^3; 95% CI 1.1−18.4) and epicardial (−0.4 cm^3; 95% CI -4.2 to 3.3) fat volume. Moreover, differences between the two observers reading the same scan were relatively constant across the range of intrathoracic and epicardial fat volume (data not shown). There was very high intra-observer agreement between measurements for both intrathoracic (mean difference = 6.5 cm^3, 95% CI: 1.6−11.3) and epicardial (−4.6 cm^3; 95% CI: −7.7 to −1.4) fat volume. Similarly high measures of inter- and intra-observer agreement were found for epicardial and pericardial fat volume measurements.

Cardiovascular disease risk factor measurement

All participants underwent a detailed clinical examination at the Amish Research Clinic in Strasburg (PA) that included assessment of CVD risk factors and a medical