Epicardial Fat Volume and Aortic Stiffness in Healthy Individuals: A Quantitative Cardiac Magnetic Resonance Study

Zusammenfassung

Ziel: Das Ziel war die Messung des epikardialen Fettvolumens sowie der aortalen Steifigkeit (bestimmt anhand der aortalen Pulswellengeschwindigkeit (PWV)) bei Gesunden, sowie die Untersuchung möglicher Zusammenhänge zwischen diesen Maßen, Body Mass Index (BMI) und Alter.

Material und Methoden: 58 gesunde Studienteilnehmer (29 Männer; mittleres Alter 44.7 ± 13.9 Jahre [J]) wurden mittels Kardio-MRT bei 1.5 Tesla untersucht. Die Berechnung der PWV erfolgte mittels 2D-Flussmessung. Das epikardiale Fettvolumen (EFV) wurde anhand einer 3D-mDixon-Sequenz ermittelt. Es folgte eine Gruppeneinteilung nach Alter in < 45 J (n = 30; 33.4 ± 6.6 J) und > 45 J (n = 28; 56.7 ± 8.4 J) sowie nach BMI in < 25 kg/m² (n = 28; BMI 21.9 ± 2.5 kg/m²) und > 25 kg/m² (n = 30; 28.7 ± 4.0 kg/m²). Die Gruppen wurden untereinander verglichen und Zusammenhänge wurden mittels Kovarianzanalysen untersucht.

Ergebnisse: Die Mittelwerte von PWV und EFV (bezogen auf die Körperoberfläche) waren 6.9 ± 1.9 m/s und 44.2 ± 25.0 ml/m². Die Gruppe der älteren Personen hatte signifikant höhere PWV- und EFV-Werte als die jüngere Gruppe (PWV = 7.9 ± 2.0 m/s vs. 6.0 ± 1.2 m/s; EFV = 54.7 ml/m² vs. 34.5 ml/m²; jeweils p < 0.01), ohne einen signifikanten Unterschied bezüglich BMI und Geschlecht. Übergewichtige Personen (BMI > 25 kg/m²) hatten signifikant höhere EFV-Werte als die Gruppe mit einem BMI < 25 kg/m² (EFV = 56.1 ± 27.1 ml/m² vs. 31.5 ± 14.6 ml/m²; p < 0.01), ohne signifikante Unterschiede in der PWV. Die Kovarianzanalyse zeigte eine signifikante Korrelation zwischen EFV und PWV, auch nach Adjustierung für das Alter (p = 0.025).

Schlussfolgerung: Das EFV und die PWV zeigen nicht nur einen Zusammenhang mit dem Alter, sondern auch untereinander, unabhängig vom Alter. Eine metabolische und pro-inflammatorische Aktivität bei erhöhtem epikardialem Fettvolumen.

Abstract

Purpose: To determine epicardial fat volume (EFV) and aortic stiffness (assessed by aortic pulse wave velocity (PWV)) in healthy individuals, and to investigate the relationship of these parameters, and their association with body mass index (BMI) and age.

Materials and Methods: 58 subjects (29 men, mean age 44.7 ± 13.9 years) underwent a CMR exam at 1.5 Tesla. A 2D velocity-encoded CMR scan was acquired to determine PWV. The EFV was measured based on a 3D-mDixon sequence. Group comparisons were made between younger (age <45y; n = 30; mean age 33.4 ± 6.6y) and older (≥45y; n = 28; 56.7 ± 8.4y) subjects and between subjects with a BMI < 25 kg/m² (n = 28; BMI 21.9 ± 2.5 kg/m²) and a BMI ≥ 25 kg/m² (n = 30; 28.7 ± 4.0 kg/m²).

Associations between the determined parameters were assessed by analyses of covariance (ANCOVAs).

Results: The mean values of PWV and EFV (normalized to body surface area) were 6.9 ± 1.9 m/s and 44.2 ± 25.0 ml/m², respectively. The PWV and EFV were significantly higher in the older group (PWV = 7.9 ± 2.0 m/s vs. 6.0 ± 1.2 m/s; EFV = 54.7 ml/m² vs. 34.5 ml/m²; p < 0.01, each), with no significant differences in BMI or sex. In the overweighted group the EFV was significantly higher than in subjects with a BMI < 25 kg/m² (EFV = 56.1 ± 27.1 ml/m² vs. 31.5 ± 14.6 ml/m²; p < 0.01) but without a significant difference in PWV. ANCOVA revealed a significant correlation between EFV and PWV, also after adjustment for age (p = 0.025).

Conclusion: An association was found between age and EFV as well as PWV. EFV and PWV were related to each other also after adjustment for age. The metabolic and pro-inflammatory activity found with increased epicardial fat volume may promote the development of atherosclerosis and aortic stiffness. CMR may be valuable for future studies investigating the relationship between
Introduction

Subclinical aortic vascular damage with consecutive aortic stiffness can be assessed by the determination of the aortic pulse wave velocity (PWV), which is regarded as an important predictor of cardiovascular adverse events [1]. The pulse wave is generated by the systolic contraction of the left ventricle (LV) and travels through the aorta with a certain velocity depending on the constitution of the aortic wall. The aorta distends and stores the ejected blood and the elasticity of the aorta dampens the generation of the pulse wave ("Windkessel" function) [2]. A reduced aortic elasticity (higher aortic stiffness), as occurs with aging, leads to a higher PWV and unfavorable effects on the heart and other organs. Aortic stiffness also increases earlier in life in the presence of cardiovascular risk factors and metabolic diseases [1, 2]. Another parameter that has been associated with increased cardiovascular risk is the amount of epicardial fat, which is the fat surrounding the heart and covered by the pericardium [3]. A metabolic and inflammatory role of this adipose tissue is discussed, and the amount of epicardial fat has also been related to age and obesity [4–6]. However, it is unclear if aortic PWV and the amount of epicardial fat are related with each other.

Cardiac magnetic resonance (CMR) allows the accurate assessment of these two parameters in a single examination. Aortic PWV can be determined by velocity-encoded CMR and the amount of epicardial fat can be accurately measured by a volumetric approach using a 3D-mDixon pulse sequence [7, 8]. The rationale of this quantitative cardiac magnetic resonance (CMR) study was to investigate a possible association between epicardial fat volume (EFV) and aortic PWV in healthy individuals within a single examination, and also to relate the results to body mass index (BMI) and age.

Materials and Methods

The study protocol was approved by the local ethics committee. All scans were performed on a 1.5 Tesla (T) MR system (Ingenia, Philips Healthcare, Best, The Netherlands) with a maximum gradient strength of 45mT/m and a maximum slew rate of 120mT/m/s. A 32-channel torso coil with digital interface was used for signal reception. 58 consecutive healthy subjects with a wide BMI and age range but without known medical conditions, without history of cardiac disease and without chronic medications were examined. All participants had blood pressure within the normal range. Written informed consent was obtained from all study participants prior to CMR. Exclusion criteria included contraindications for CMR and any evidence of cardiovascular pathologies.

Key Points:

- EFV and PWV can be assessed in a single CMR exam.
- EFV and aortic stiffness are both associated with cardiovascular risk.
- EFV correlates with aortic stiffness, possibly due to similar pro-inflammatory mechanisms.

Citation Format:

Image Analysis

Cardiac parameters

The left ventricular end systolic and end diastolic volume (LVESV, LVEDV), LV function and LV myocardial mass as well as the peak filling rate were determined offline by manual tracing of the endocardial borders. Papillary muscles were included in the left ventricular cavity volume. Left ventricular function was assessed in all subjects by computation of the ejection fraction (LVEF) using the formula (LVEDV – LVESV)/LVEDV × 100. The peak filling rate was also adjusted for LVEDV by dividing it by the LVEDV resulting in a normalized peak filling rate (nPFR) [9, 10]. Left ventricular volumes and mass were additionally normalized to the body surface area (BSA), yielding the LVESV index, LVEDV index and LV mass index (LVESVi, LVEDVi, LVMi).

Aortic PWV

PWV quantification was performed using a tool implemented in the software Segment (Segment, version 1.9, R3918; http://segment.heilberg.se) [11]. First, the path length of the aortic arch (aortic length [AL]), i.e. the distance between the section through the AA and through the proximal AD, was measured between the center of the cross-sections of the AA and proximal AD. The time interval between the arrival of the velocity waveform at the section of the AA and at the section of the proximal AD is called the transit time (TT) and was determined by contour drawing in the aortic velocity maps. The TT is measured as the time between the intercept of the two calculated tangents with the time axis. The PWV was finally calculated by PWV = AL / TT [7]. The post-processing time for the determination of the aortic PWV was about 5 minutes.

Epicardial fat volume

Dixon images were analyzed offline on a personal computer using dedicated software written in MATLAB (The MathWorks, Inc., Natick, MA) with an analysis time of about 7–10 minutes per subject. The epicardial fat volume was measured between the bifurcation of the pulmonary artery and the most inferior transverse slice of the myocardium [3]. A 3D region of interest (ROI) was defined by manually contouring the epicardial border in each slice. Fat-fraction maps were computed based on fat- and water-only images with an appropriate noise threshold and correction for relaxation effects to identify voxels predominantly containing fat. The epicardial fat volume was finally determined by multiplying the number of fat voxels inside the three-dimensional ROIs by the voxel size and was normalized to the BSA [8].

Statistical Analysis

Statistical analyses were performed in SPSS (IBM SPSS Statistics 22.0, Armonk, New York). Study participant characteristics are presented as mean ± standard deviation or as absolute frequency. Group comparisons were made between younger (age < 45y) and older subjects (age ≥ 45y) and between subjects with a BMI < 25 kg/m² and overweight subjects (BMI > 25 kg/m²). Possible associations between the determined parameters were further assessed by analyses of covariance (ANCOVAs). A value of p < 0.05 was considered statistically significant.

Results

A total of 58 subjects (29 men, 29 women) were enrolled in this study. The mean age was 44.7 ± 13.9y (range: 21 to 78y) and the mean BMI was 25.5 kg/m² (range: 13.9 to 42.2 kg/m²). The detailed characteristics of the study participants and CMR-derived parameters are summarized in Table 1. The mean values of the aortic PWV and EFV were 6.9 ± 1.9 m/s and 44.2 ± 25.0 ml/m². Examples of the measurements are shown in Fig. 1, 2.

Group comparisons according to age (cut-off 45y) revealed that older subjects (mean age: 56.7 ± 8.4y, n = 28) had significantly higher aortic PWV and EFV values than younger individuals (mean age: 33.4 ± 6.6y, n = 30) with PWV= 7.9 ± 2.0 m/s vs. 6.0 ± 1.2 m/s and EFV = 54.7 ml/m² ± 27.1 vs. 34.5 ml/m² ± 18.6 (p < 0.01, each). There were no significant differences in BMI or sex between the two groups (p = 0.83 and p = 0.30). By splitting the individuals into two groups according to BMI (cut-off 25 kg/m²), over-
weighted individuals (n = 30) had significantly higher EFV values than non-overweighted subjects (mean BMI 21.9 ± 2.5 kg/m², n = 28) with EFV = 56.1 ± 27.1 ml/m² vs. 31.5 ± 14.6 ml/m² (p < 0.01). No significant difference in PWV was observed between the two BMI groups (p = 0.20). The complete results of the two group comparisons including all determined cardiac parameters are summarized in Table 1.

Analyses of covariance with PWV and EFV as dependent variables and BMI and age as independent variables confirmed an association between EFV and BMI (p < 0.001), and that PWV and EFV were both significantly associated with age (p < 0.001, each). PWV was higher in subjects with an increased epicardial fat volume. This association was statistically significant, also after adjustment for age effects (p = 0.025).

**Discussion**

CMR is not widely used for the evaluation of cardiovascular risk parameters such as aortic stiffness and the amount of epicardial fat, even though CMR has several advantages. With the 3D-Dixon technique, for instance, it is possible to measure the whole epicardial fat volume without the use of ionizing radiation (in contrast to CT). In echocardiography only the thickness of the epicardial fat is determined as a diameter at a specific location [3, 8]. Additionally, with CMR the PWV can be assessed in particular aortic segments, whereas tonometric devices measure a more general arterial stiffness, as this includes different superficial locations such as between the carotid or brachial artery and the femoral artery. These arteries, however, are also muscular vessels and involve muscular stiffening with a consecutively greater variance of the measured PWV. Also the real path length of the pulse wave can only be estimated [1, 7, 12, 13].

The MR sequences on which the above named measurements are based (3D-Dixon and velocity-encoded CMR) can easily be integrated into the routine workflow of a CMR study. This is a clear advantage of CMR, as all measurements can be performed in a single examination, in contrast to other approaches which necessitate the application of different modalities [1, 3, 7].
In the present study, the aortic PWV and the epicardial fat volume were determined in healthy individuals. A statistically significant association was found not only between aortic PWV and age, and between epicardial fat volume and age and BMI, but also between epicardial fat volume and aortic PWV.

Increased aortic stiffness (and aortic PWV) occurs physiologically with aging and begins first at the level of the aorta ascendens and the aortic arch. The mechanisms are partly explained by intima media hypertrophy, sclerosis and changes of the extracellular matrix with replacement of elastin by collagen. Metabolic and general inflammatory mechanisms also play a role by leading to impaired arterial function and atherosclerosis [1, 2, 14]. These changes have unfavorable effects on the heart. As a consequence of the higher aortic stiffness, the afterload increases thus reducing the diastolic blood pressure and the coronary blood flow. This is further complicated when LV hypertrophy or coronary artery disease is also present. An increased PWV also occurs earlier in life in the presence of cardiovascular risk factors and metabolic diseases. PWV is one of the most important predictors of cardiovascular adverse events and an important diagnostic step in evaluating cardiovascular risk [1, 13]. Concerning BMI, previous studies observed inconsistent results [1, 15–17]. Although our CMR-based results demonstrated a strong association between aortic PWV and age, there was no significant relationship between aortic PWV and BMI. The lack of an association may be explained by the fact that all persons were healthy and a higher BMI does not necessarily lead to changes in the vasculature and higher arterial stiffness. It rather reflects the co-occurrence of other cardiovascular risk factors, which is more prevalent in obese persons [18, 19]. This may also explain why left ventricular mass index and nPFR – as a measure of diastolic function – did not differ significantly between the two BMI groups. None of the overweighted subjects had additional cardiovascular risk factors. Age was associated with a reduced nPFR. However, a somewhat reduced diastolic dysfunction may be regarded as a physiologic process in aging due to age-related structural and functional cardiac changes [9].

We observed that aging was also associated with an increase in epicardial fat volume which may be due to a loss of lean body mass with an increase in fat mass and redistribution to the trunk and viscera which occurs with aging [20]. In contrast to the aortic PWV, the epicardial fat volume was significantly associated with BMI which is in concordance with previous studies [21, 22]. We also observed a significant relationship between the epicardial fat volume and the aortic PWV. The mechanisms behind this relationship, however, are unclear. Possible mechanisms may be metabolic and inflammatory [23, 24]. Under normal circumstances, epicardial adipose tissue serves as a physiologic energy source and has beneficial effects through adipokines which are regarded as being anti-atherogenic and anti-inflammatory [4, 25]. With a substantial increase, these effects can unfavorably change its metabolic activity. Increased insulin resistance has been observed with an increased amount of epicardial fat and also with increased visceral fat in general [26, 27]. This increased insulin resistance is associated with vascular smooth muscle cell growth, glycation of the proteins in the arterial wall with consecutive organ damage and atherosclerosis, inhibition of the ability of insulin to elicit endothelium-dependent vasodilation. Consequently, the possibility for injury to the vessel wall and vessel wall stiffening is increased [16, 17, 28, 29]. Furthermore, the hypertrophied epicardial fat becomes hypoxic and dysfunctional, it reduces its secretion of anti-atherosclerotic adipokines, such as adiponectin, and additionally becomes invaded by inflammatory factors such as by an increased number of macrophages, fibroblasts, mast cells, lymphocytes and proinflammatory cytokines (such as TNF-α, MCP-1, IL-1β, IL-6). This increased inflammatory activity may contribute to aortic atherosclerosis, atherosclerosis and aortic stiffness by inflammation in the vascular wall [4, 25, 30]. However, a local metabolic and inflammatory activity of the epicardial adipose tissue through the same mechanisms may also play a role, as epicardial fat has direct contact with the coronary arteries, the aorta and the myocardium and also shares the same blood supply with the myocardium [22, 30]. All together, these metabolic and inflammatory mechanisms may explain the observed association between the amount of epicardial fat and the aortic PWV as a measure for aortic stiffness.

Limitations

In our study we only investigated healthy persons and future studies have to concentrate on patients with increased cardiovascular risk, such as hypertension or diabetes mellitus, in order to reveal relationships concerning aortic stiffness and epicardial fat in the presence of such risk factors. The low number of subjects examined in this study is also a limitation. However, the inclusion of healthy subjects with a wide BMI and age range made it possible to study associations with the obtained measures.

Conclusion

Epicardial fat volume and aortic stiffness are both associated with age, but also with each other, independent of age. Metabolic and inflammatory mechanisms found with increased epicardial fat may promote the development of atherosclerosis and aortic stiffness. A combined measurement of aortic PWV and epicardial fat volume as parameters of cardiovascular risk is feasible. Future studies should concentrate on these relationships in patients with increased cardiovascular risk and disease and with regard to the prediction of cardiovascular events. CMR provides a valuable tool for such studies.

Clinical relevance

- Epicardial fat and aortic stiffness are associated with each other, independent of age.
- With CMR, epicardial fat volume and aortic stiffness can be determined in a single exam.
- A combined measurement of PWV and EFV can easily be integrated in a routine CMR.
- A CMR-based assessment of PWV and EFV may in the future be helpful in cardiovascular risk stratification.

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