Abdominal and Pericoronary Adipose Tissue Quantification with Computed Tomography and Their Relationship to Cardiovascular Risk Factors and Inflammatory Markers

Ph.D. Thesis

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Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the industrialized countries. Improvements in CVD risk factor profiles have led to significant reductions in death from CVD over the past 50 years, but recent data suggest that the increasing prevalence of obesity may have slowed this rate of decline.

The Abdominal Adipose Tissue Compartment

Several metabolic studies demonstrated that central type of obesity pose a greater risk for developing obesity-related disorders than obesity defined by BMI alone. In particular, the visceral adipose tissue (VAT) compartment seems to act as a unique pathogenic fat depot. Visceral adipose tissue has been termed an endocrine organ, in part because it secretes adipocytokines and other vasoactive substances that can influence the risk of developing metabolic disorders. Furthermore, it became clear that chronic low-grade inflammation is encountered in individuals with an excess of visceral fat. Thus, in terms of its proinflammatory and metabolic features, visceral adiposity is an emergent powerful but modifiable risk factor for CVD. Therefore, the precise and reproducible quantification of abdominal fat depots is important in order to further characterize the role of adipose tissue in the development of cardiovascular disorders. Current imaging studies evaluating abdominal fat depots are limited to small, referral-based samples often enriched for adiposity-related traits. Furthermore, no data is available in a community-based sample of women and men free of CVD across the

spectrum of BMI whether the volume of subcutaneous adipose tissue (SAT) and VAT are associated with metabolic risk factors and markers of inflammation cross-sectionally.

The Pericoronary Adipose Tissue Compartment

Epicardial adipose tissue (EAT) covers 70-100% of the cardiac circumference as a layer of adipose tissue between the myocardium and the visceral pericardium. It has been suggested that adipocytokines produced by fat surrounding the coronary arteries might amplify vascular inflammation and generate a pro-atherogenic milieu. The portions of EAT which directly surround the coronary arteries is termed the pericoronary adipose tissue (PCAT) compartment.

The precise and reproducible quantification of this rather small fat compartment is crucial for the understanding of its role in the pathophysiology of coronary artery disease. The most commonly used techniques for PCAT quantification in CT datasets are based on thickness and area measurements on a limited number of axial image slices. These 2-dimensional quantification techniques do not reflect the inhomogeneous distribution of PCAT along the atrioventricular and interventricular grooves.

Aims

Planimetric and volumetric adipose tissue quantification methods

We sought to assess the intra- and inter-observer reproducibility of MDCT based volumetric quantification of subcutaneous and visceral abdominal adipose tissue. Furthermore, our aim was to investigate the differences

between the relative amounts of visceral and subcutaneous abdominal tissue quantity as assessed by volumetric and planimetric methods.

Abdominal adipose tissue volumes and metabolic risk factors

We aimed to assess whether the volume of SAT and VAT are associated with metabolic risk factors in a community-based sample free of CVD. Furthermore, we sought to determine whether sophisticated volumetric imaging methods of SAT and VAT provide information about metabolic risk other than that offered by classic anthropometric measures such as BMI and waist length (WL).

Abdominal adipose tissue volumes and markers of inflammation and oxidative stress

We aimed to investigate the association of abdominal fat compartment volumes with a panel of systemic inflammatory markers. Furthermore, we sought to assess whether volumetric measurements of SAT and VAT explained additional interindividual variability in biomarker concentrations above that accounted for by the simple clinical anthropometric measures of obesity (BMI and WL).

Novel volumetric pericoronary adipose tissue quantification

We aimed to assess the feasibility and reproducibility of a novel threshold-based method of PCAT volume quantification using cardiac CT, furthermore to determine the relationship of PCAT volume with the presence of coronary atherosclerotic plaque on patient, vessel and subsegment basis.

Methods

Study population

Participants for abdominal adipose tissue assessment were drawn from the Framingham Heart Study Multidetector Computed Tomography Study, a population-based substudy of the community-based Framingham Heart Study Offspring and Third-Generation Study cohorts. Between June 2002 and April 2005, 3529 participants (2111 third generation, 1418 offspring participants) underwent chest and abdominal MDCT scan. Men had to be ≥35 years of age; women had to be ≥40 years of age and not pregnant (1,2).
The biomarkers and inflammatory substances were assessed in the offspring participants with technically interpretable CT scans (n=1377), attendance at the seventh examination cycle (1998-2001; n=1355), complete covariate information (n=1253), and measurement of at least one inflammatory marker, resulting in a total sample size of 1250 participants.
Participants for pericoronary adipose tissue assessment were drawn from the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. From the 368 ROMICAT patients, we included 51 patients in this age- and gender-matched 1:1:1 case-control design. Patients were stratified into 3 groups based on presence of coronary atherosclerosis and hs-CRP levels. Group 1 included patients with presence of coronary plaque and hs-CRP >2.0 mg/L; intermediate group (Group 2) included patients with no plaque and hs-CRP >2.0 mg/L, Group 3 included patients with no plaque and hs-CRP <1.0 mg/L.

Abdominal Adipose Tissue Assessment

All subjects underwent CT scanning using an eight-slice MDCT (LightSpeed Ultra, General Electric, Milwaukee, WI, USA). Twenty-five contiguous 5 mm thick slices were acquired covering 125 mm above the level of S1. The raw data were reconstructed using a 55 cm field of view. The effective radiation exposure was 2.7 mSv (1).

We measured the subcutaneous and visceral adipose tissue areas (SAA and VAA) and volumes (SAV and VAV) as well as the waistline (WL) and sagital diameter (SD) using a dedicated offline workstation (Aquarius 3D Workstation, TeraRecon Inc., San Mateo, CA, USA). The SAA and VAA as well the WL and SD were measured using a single slice (5mm thickness) at the umbilical level, whereas the SAV and VAV were assessed using the whole imaging volume (1).

The reproducibility study sample represents a random subset of 100 subjects (age range: 37 – 83 years; 49% female). Two observers performed an independent analysis of all datasets in random order to assess for inter-observer variability. One reader repeated the analysis one week later to assess for intra-observer variability (1).

Risk factors and biomarkers were measured at the regular Framingham Study examinations.

Pericoronary Adipose Tissue Assessment

Contrast-enhanced gated CT imaging was performed using a standard coronary artery 64-slice MDCT (Sensation 64, Siemens Medical Solutions, Forchheim, Germany) imaging protocol.

We started the PCAT quantification at the ostium of the left main (LM)/left anterior descending coronary artery (LAD), left circumflex artery (LCx), and

right coronary artery (RCA). The method of threshold-based volumetric PCAT assessment is based on a modified application of software for volumetric assessment of coronary atherosclerotic plaques (Vitrea 2, Version 3.9.0.1, Vital Images Inc, Plymouth, MN and SUREPlaque, Toshiba Medical Systems, Tustin, CA). We recorded PCAT volumes in 5 mm increments, and summed PCAT along the measured vessel lengths. Two independent readers who were blinded to the coronary plaque and hs-CRP results performed the PCAT measurements. Observer 1 performed measurements around the proximal 40 mm of the coronaries in all 51 patients once. For inter-observer and intra-observer reproducibility, observer 2 performed the measurements in 20 randomly selected patients, and Observer 1 repeated this process in the same 20 patients 1 month later. A total of 153 vessels and 1224 coronary artery subsegments were evaluated across the three patient groups.

Results

The reproducibility study

The mean SAV was 2929.8±1260.0 cm^3 (range of 501.0 - 6695.0) and the mean VAV was 2031.6±1013.7 cm^3 (range of 288.0 - 4731.0). The mean SAA was 543.5±252.4 cm^2 and the mean VAA was 325.9 ± 162.3 cm^2. The mean WL was 100.0±12.3 cm (range of 74.9 - 131.3) and the mean SD was 24.2±4.0 cm (range of 15.9 - 35.9).

The intra-observer reproducibility was excellent for VAV and SAV (ICC=0.99). The mean absolute intra-observer differences were small and non-significant for both measurements (SAV: -0.6±6.1 cm^3, p=0.29; VAV: 0.7±6.0 cm^3; p=0.26).

The mean absolute difference was 0.1±0.6 cm (p=0.09) for WL measurements and -0.01±0.2 cm (p=0.68) for SD measurements. Both WL and SD measurements were highly correlated (ICC: 0.99).

The mean absolute inter-observer differences were extremely small and both measurements were highly correlated (SAV: -9.1±12.0 cm^3, ICC=0.99, and VAV: 9.9±14.8 cm^3; ICC=0.99). The relative difference between observers was small and non-significant -0.34%±0.52% for SAV and 0.59%±0.93% for VAV (p=n.s.).

The mean WL was 100.0±12.3 cm (range of 74.9-131.3) with a mean absolute difference of -0.1±0.8 cm and a mean relative difference of -0.08% ±0.84% between the two observers (ICC=0.99). The mean SD was 24.2±4.0 cm (range of 15.9 - 35.9) with a mean absolute difference of -0.2 ±0.4 cm and a mean relative difference of -0.73%±1.82% (ICC=0.99).

The mean SAA/VAA ratio (2.0±1.2; range: 0.5 - 6.7) was significantly greater than the mean SAV/VAV ratio (1.7 ± 0.9; range: 0.4 - 5.3); (p<0.001) (1).

The abdominal adipose tissue depots and metabolic risk factors

Overall, 1452 women and 1549 men were available for analysis. The mean age was 50 years; approximately one quarter of the sample was hypertensive, 5% had diabetes, and approximately one third had metabolic syndrome (MetS). Approximately half of the women were postmenopausal. The mean SAT volume among the offspring and the third gen participants was 3071±1444 cm^3 in women and 2603±1187 cm^3 in men. The mean VAT volume in women was 1306±807 cm^3 and in men was 2159±967 cm^3.

SAV was positively correlated with age in women (r=0.13, P<0.001) but not men, and VAV was positively correlated with age in both sexes (r=0.36 in

women and men, P<0.001). SAV and VAV were highly correlated, with an age-adjusted correlation coefficient between SAV and VAV of 0.71 (P<0.0001) in women and 0.58 (P<0.0001) in men. Both BMI and WL were strongly correlated with SAV and VAV after adjustment for age. All risk factors were highly correlated with both SAV and VAV, except for serum total cholesterol with SAV in men and physical activity index with VAV in men.

In women and men, the association of both SAV and VAV with continuous measures of metabolic risk factors was highly significant. For fasting plasma glucose, the effect of VAV was stronger than that of SAV (P<0.0001 for difference in women, P=0.001 in men). Strong and significant results for log triglycerides and HDL cholesterol followed similar patterns.

Highly significant associations with SAV and VAV also were noted for dichotomous risk factor variables. Among women and men, both SAV and VAV were associated with an increased odds of hypertension. In women, the odds ratio of hypertension per 1-SD increase in VAV (odds ratio, 2.1) was stronger than that for SAV (odds ratio, 1.7; P=0.001 for difference between SAV and VAV); similar differences were noted for men. Similar highly significant differences also were noted for impaired fasting glucose, diabetes, and MetS.

The magnitude of association between VAV and all risk factors examined was consistently greater for women than for men. Weaker sex differences were observed for SAV (2).

Abdominal Adipose Tissue Depots and the Markers of Inflammation and Oxidative Stress

The mean age of the 1250 individuals (52% women) was 60±9 years. Mean SAV was 3023±1329 cm^3, and mean VAV was 2126±1112 cm^3. SAV and VAV were positively and similarly correlated with most circulating inflammatory biomarkers. CD40 ligand, lipoprotein-associated phospholipase A2 (Lp-PLA2), osteoprotegerin, and tumor necrosis factor (TNF)-α were not correlated with either SAV or VAV.

In multivariable models, CRP, fibrinogen, intercellular adhesion molecule-1 (ICAM-1), IL-6, isoprostanes, monocyte chemoattractant-1 (MCP-1), P-selectin, and TNF receptor-2 remained associated with both SAV and VAV. For most markers, the estimated increase in concentrations per 1 SD of SAV was comparable to and not statistically significantly different from that of VAV, with 2 exceptions. For isoprostanes, the magnitude of the estimated association with VAV was almost double that of SAV (p=0.002 for difference in effect between SAV versus VAV). Although less striking, we also observed differences in the magnitude of the SAV versus VAV association with MCP-1 (p=0.04 for SAV versus VAV comparison) (3).

Pericoronary Adipose Tissue Quantification

The average PCAT volume was 26.98±13.33 cm^3 (range: 5.45 – 60.54 cm^3). The reproducibility of PCAT volume measurement was excellent with intra-observer and inter-observer ICC >0.94 overall and >0.87 on a per-vessel basis. The Bland-Altman analysis of the individual reads by Observer 1 and 2 for PCAT volume on a per patient basis with good concordance and slight systematic bias at greater PCAT volumes.

In a patient-based analysis, PCAT volume differed significantly across the

three groups ($p<0.0001$), and was greater in patients with coronary plaque (Group 1) than no plaque irrespective of hs-CRP levels (Group 2: high hs-CRP, $p<0.0001$; Group 3: low hs-CRP, $p<0.0001$). Moreover, in patients without plaque, no difference in PCAT volume was seen between patients with high and low hs-CRP levels ($p=1.0$). The difference in PCAT volumes remained significant across the three patient groups after adjustment for BMI, hypertension, and hyperlipidemia ($p=0.0002$). To determine the relationship of local adipose tissue volume and coronary plaque distribution, a subsegment-based analysis was performed in 5 mm increments to assess PCAT quantity adjacent to 1224 vessel subsegments with and without plaque. No atherosclerotic plaque was detected in 1005 subsegments while 219 subsegments contained plaque. The median fat volume surrounding 5 mm vessel subsegments with plaque was higher compared to subsegments without plaque ($p<0.0001$).

Conclusions

We demonstrated an excellent intra- and inter-observer reproducibility of MDCT based volumetric quantification of subcutaneous and visceral abdominal adipose tissue. We also demonstrated significant differences of the relative amounts of visceral and subcutaneous abdominal tissue between volumetric and planimetric measurements. Although both SAV and VAV correlated with metabolic risk factors, VAV remained more strongly associated with an adverse metabolic risk profile even after accounting for standard anthropometric indexes. Our findings are consistent with the hypothesized role of visceral fat as a unique, pathogenic fat depot. Furthermore, we found an association between both SAV and VAV with

inflammation and oxidative stress. The data suggest that the contribution of visceral fat to inflammation may not be completely accounted for by clinical measures of obesity (body mass index and waist circumference).

Measurement of VAV and SAV may provide a more complete understanding of metabolic and cardiovascular risk, and further studies are warranted to prospectively assess the impact of VAV and SAV lowering on the incidence of MetS and CVD.

Furthermore, we demonstrated the feasibility and excellent reproducibility of a novel threshold-based method for PCAT volume assessment. The local amount of PCAT volume was increased in the presence of plaque at the patient, vessel, and subsegmental level. In patients without plaque, PCAT volume did not differ based on hs-CRP level, highlighting the potential role of local PCAT depots in the process of atherogenesis in addition to systemic inflammatory processes. Further studies are needed to validate our findings and elucidate the role of local adipocytokines on atherosclerosis.

Publications closely related to the present thesis

1. **Maurovich-Horvat P**, Massaro JM, Fox CS, Moselewski F, O'Donnell CJ, Hoffmann U: Comparison of Anthropometric, Area and Volume based Assessment of Abdominal Subcutaneous and Visceral Adipose Tissue Volumes using Multi Detector Computed Tomography. Int J Obes 2007,31: 500-6. **IF: 3.56**

2. Fox CS, Massaro JM, Hoffmann U, Pou KM, **Maurovich-Horvat P**, Vasan RS, Murabito JM, Meigs JB, Cupples LA, D'Agostino Sr RB, O'Donnell CJ: Abdominal Visceral and Subcutaneous Adipose Tissue Compartments and Association with Metabolic Risk Factors: The Framingham Heart Study. Circulation 2007,116: 39-48. **IF: 12.755**

3. Pou KM, Massaro JM, Hoffmann U, Vasan RS, **Maurovich-Horvat P**, Larson MG, Keaney JF Jr., Meigs JB, Lipinska I, Murabito JM, O'Donnell CJ, Benjamin EJ, Fox CS: Visceral and Subcutaneous Adipose Tissue Volumes are Cross-Sectionally Related to Markers of Inflammation and Oxidative Stress: the Framingham Heart Study. Circulation 2007,116: 1234-41. **IF: 12.755**

4. **Maurovich-Horvat P,** Kallianos K, Engel LC, Fox CS, Hoffmann U, Truong QA: Influence of Pericoronary Adipose Tissue on Local Coronary Atherosclerosis as Assessed by a Novel MDCT Volumetric Method. Atherosclerosis. 2011 Jul 6. [Epub ahead of print] **IF: 4.086**

Publications not related to the present thesis

1. **Maurovich-Horvat P**, Alkadhi H, Kriegel M, Schlett C, Nakano M, Stolzmann P, Scheffel H, Vorpahl M, Tanaka A, Warger W, Maehara A, Ma S, Kaple RM, Mintz GS, Tearney GJ, Virmani R, Hoffmann U: Differentiation of early and advanced coronary atherosclerotic lesions: A systematic comparison of computed tomography, intravascular ultrasound and optical frequency domain imaging with histopathology in ex vivo human hearts. [submitted 2011].

2. **Maurovich-Horvat P**, Schlett C, Alkadhi H, Nakano M, Otsuka F, Stolzmann P, Scheffel H, Ferencik M, Kriegel M, Seifarth H, Virmani R, Hoffmann U: The Napkin-ring Sign Indicates Advanced Atherosclerotic Lesions in Coronary CT Angiography. [submitted 2011].

3. Jensen JK, Medina H, Noergaard BL, Oevrehus KA, Jensen JM, Nielsen LH, **Maurovich-Horvat P**, Engel LC, Januzzi JL, Hoffmann U, Truong QA: Association of Ischemic Stroke to Coronary Artery Disease Using Computed Tomography Coronary Angiography. Int J Cardiol. 2011 May 2. **IF: 6.802**

4. Stolzmann P, Goetti P, Desbiolles L, **Maurovich-Horvat P**, Feuchtner G, Hoffmann U, Flohr T, Leschka S, Alkadhi H: Predictors of Image Quality in High-Pitch Coronary CT Angiography. AJR Am J Roentgenol. 2011 Oct;197(4):851-8. **IF: 2.797**

5. Mekkaoui C, Huang S, Dai G, Reese TG, Thiagalingam A, **Maurovich-Horvat P**, Ruskin J, Hoffmann U, Jackowski MP, Sosnovik DE: A Quantitative Framework for Diffusion MRI Tractography of the Heart. [submitted 2011].

6. Stolzmann P, Subramanian S, Abdelbaky A, **Maurovich-Horvat P**, Scheffel H, Tawakol A, Hoffmann U: Complementary Value of Cardiac FDG PET and CT for the Characterization of Atherosclerotic Disease. Radiographics. 2011 Sep-Oct;31(5):1255-69. **IF: 2.760**

7. Donnelly P*****, **Maurovich-Horvat P***, Vorpahl M, Nakano M, Kaple RK, Tanaka A, Tearney G, Virmani R, Hoffmann U: Multi Modality Imaging Atlas of Coronary Atherosclerosis. JACC Cardiovascular Imaging 2010; 3(8): 876-880. **IF: 5.528**

8. **Maurovich-Horvat P**, Ghoshhajra B, Ferencik M: Coronary Computed Tomography Angiography for the Detection of Obstructive Coronary Artery Disease. Curr Cardiovasc Imaging Reports 2010; 3(6): 355-365.

9. **Maurovich-Horvat P**, Móri T, Kerecsen G, Fövényi J, Sallai T, Soós P, Préda I, Merkely B, Jermendy G: Assessment of coronary artery calcification using dual-source computed tomography in adult asymptomatic patients with type 1 diabetes mellitus. Med Sci Monit 2010; 16(7): MT59-64. **IF: 1.543**

10. Vago H, Toth A, Apor A, **Maurovich-Horvat P**,Toth M, Merkely B: Images in cardiovascular medicine. Cardiac contusion in a professional soccer player: visualization of acute and late pathological changes in the myocardium with magnetic resonance imaging. Circulation 2010 Jun; 121(22): 2456-2461. **IF: 14.816**

11. Truong QA, Yared K, **Maurovich-Horvat P**, Siegel E, Cubeddu RJ, Etta M, King E, Heist EK, Mansour M, Holmvang G: Double Chamber Right Ventricle with Situs Inversus Dextrocardia. Circulation 2010; 121(9): e229-e232. **IF: 14.816**

12. **Maurovich-Horvat P**, Hoffmann U, Vorpahl M, Nakano M, Virmani R, Alkadhi H: The Napkin-Ring Sign: CT signature of high risk coronary atherosclerotic plaques? JACC: Cardiovascular Imaging 2010; 3(4): 440-444. **IF: 5.528**

13. van der Giessen AG, Toepker MH, Donelly PM, Bamberg F, Raffle C, Irlbeck T, Schlett CL, Lee H, van Walsum T, **Maurovich-Horvat P**, Gijsen FJH, Wentzel JJ, Hoffmann U: Reproducibility, Accuracy, and predictors of accuracy of advanced computed tomography to detect coronary atherosclerotic plaque according to plaque

composition - A comparison to IVUS in an ex vivo setting. Investig Radiol 2010; 45(11): 693-701. **IF: 4.850**

14. Szelid Zs, Kerecsen G, **Maurovich-Horvat P**, Lux Á, Marosi E, Kovács A, Kiss RG, Préda I, Merkely B: Determination of coronary in-stent restenosis using dual source computed tomography angiography. Interv Med Applied Sci 2010; 2(1): 5-9.

15. **Maurovich-Horvat P**, Ferencik M, Bamberg F, Hoffmann U: Methods of Plaque Quantification and Characterization by Cardiac Computed Tomography. J Cardiovasc Comp Tomography 2009; 3(Suppl 2): S91-S98.

16. Becker D, **Maurovich-Horvat P**, Barczi Gy, Szabo Gy, Fulop G, Nagy A, Molnar L, Apor A, Belicza E, Merkely B: Life after coronary stent thrombosis. Med Sci Monit 2009; 15(5): CR236-241. **IF: 1.543**

17. Abbara S, Pena AJ, **Maurovich-Horvat P**, Butler J, Sosnovik DE, Lembcke A, Cury RC, Hoffmann U, Ferencik M, Brady TJ: Feasibility and optimization of aortic valve planimetry with MDCT. Am J Roentgenol 2007; 188(2): 356-60. **IF: 2.470**

18. Ferencik M, Nomura CH, **Maurovich-Horvat P**, Hoffmann U, Pena AJ, Cury RC, Abbara S, Nieman K, Fatima U, Achenbach S, Brady TJ: Quantitative parameters of image quality in 64-slice computed tomography angiography of the coronary arteries. Eur J Radiol 2006; 57(3): 373–379. **IF: 1.332**

19. Soós P, Merkely B, **Maurovich Horvát P**, Zima E, Schauerte P: Determinants and effects of electrical stimulation of the inferior interatrial parasympathetic plexus during atrial fibrillation. J Cardiovasc Electrophysiol 2005; 16(12):1362-1367. **IF: 3.285**