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Aortic root diameter, main pulmonary artery diameter/aortic root diameter and pericardial fat volume as predictors of occlusive coronary artery disease

Abdulameer A. Al-Mosawi,¹ Hussein Nafakhi,² Hadeel K. Hameed¹

¹Radiology Department; ²Internal Medicine Department, Medicine College, University of Kufa, Najaf, Iraq

Corresponding author: Hussein Nafakhi, MD, Professor, Internal Medicine Department, Medicine College, Kufa University, P.O. 21, Kufa, Najaf, Iraq. Phone: +964 78 218 41 16; fax: +964 34 09 52; Email: huseinaf.alnaffakh@uokufa.edu.iq

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Informed consent:

Verbal informed consent was obtained from all enrolled participants.

Availability of supporting data: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Abstract

The clinical relevance of aortic root diameter (ARD) and main pulmonary artery diameter (MPAd) or pericardial fat volume (PFV) in the assessment of coronary artery disease (CAD) is largely unknown. We aimed to assess the relationship of pericardial fat volume (PFV), ARD, MPAd, and MPAd/ARD ratio with occlusive CAD (stenosis>50%). This cross-sectional study included patients who had chest pain suggestive of CAD and

underwent a 64-multislice multi-detector CT angiography exam to exclude occlusive CAD presence. A total of 145 patients were enrolled in this study. The mean age was 54 ± 10 years, 51% were males. The mean PFV, ARD, MPAd, and MPAd/ARD ratio in all patients were 155 cm^3 , 29.9 mm, 23.4 mm and 0.8, respectively. On univariate analysis, PFV (OR (CI)=1.1 (1.01-1.3), $P < 0.01$), ARD (OR (CI)=1.2 (1.1-1.4), $P < 0.01$), and MPAd/ARD ratio (OR (CI)= 0.2 (0.1-0.5), $p = 0.02$) showed significant association with occlusive CAD presence. After adjusting for cardiac risk factors, only PFV (OR (CI)=1.1 (1.02-1.3), $p < 0.01$), but not ARD (OR (CI)=0.9(0.3-2), $p = 0.85$) or MPAd/ARD ratio (OR (CI)=0.1(0.1-2), $p = 0.69$), was independently associated with occlusive CAD. In conclusion, increased PFV, but not ARD or MPAd/ARD ratio, showed a significant and independent association with occlusive CAD presence in patients with chest pain suggestive of CAD.

Keywords: aortic root; pericardial fat; coronary artery disease; pulmonary artery; multi-detector computed tomography

Introduction

Overall, the incidence and mortality of coronary artery disease (CAD) are still increasing [1]. Occlusive CAD (>50% stenosis) is more likely associated with myocardial ischemia and adverse cardiac outcome. Thus, early recognition of occlusive CAD by simple and non-invasive imaging markers is essential for better risk stratification [1,2].

The wall of proximal part of thoracic aorta functions as a robust biomechanical structure through a complex interplay between vascular wall cells and the extracellular matrix. This robust homeostatic process can be disturbed through a variety of disease processes, including aneurysmal formation, bicuspid aortic valve or risk factors for CAD [3]. A recent study reported a high prevalence of CAD and narrowing of proximal part of ascending aorta in patients with Homozygous familial hypercholesterolemia [4].

Anatomical and physiological changes in the proximal segments of large arteries, including aortic root and main pulmonary artery, may affect cardiac physiology and performance [2,5]. Progressive changes in aortic root diameter (ARD) and main pulmonary artery

diameter (MPAd) may occur even before cardiac dysfunction, suggesting a possible link between changes in proximal segments of these large arteries and several cardiac diseases [5].

ARD, MPAd, and MPAd/ARD ratio, which were previously reported to be clinically relevant to cardiopulmonary disease and prognosis, are simple, reproducible, and easily measured by non-invasive imaging modalities such as computed tomography of the heart or chest without the need for sophisticated software or advanced expertise [6-8]. The clinical significance of these parameters has been studied in patients with pulmonary hypertension, chronic obstructive pulmonary disease exacerbation, heart failure, and cardiovascular morbidity and mortality [2,6,7]. However, little information is available concerning the association of these parameters with CAD, and their predictive significance remains largely unknown.

Recently, pericardial fat, owing to its anatomical proximity to the heart and coronary arteries and its local and systemic adverse effects, has potential diagnostic and predictive values in assessing cardiovascular risk and CAD risk stratification [9,10]. Local adverse effects of pericardial fat, through its paracrine and endocrine roles, may mediate anatomical and functional changes on coronary arteries, aortic valve, and aortic root leading to coronary atherosclerosis and increased aortic diameter and stiffness, but the exact pathophysiologic mechanism was still unclear and there is a paucity of data concerning the association of pericardial fat volume (PFV) and occlusive CAD among different ethnic groups with different risk factors for CAD [1,11].

We aimed to assess the potential relationship of PFV, ARD, MPAd, and MPAd/ARD ratio with occlusive CAD (stenosis severity >50%) in patients with chest pain suggestive of CAD.

Materials and Methods

The present study was a single-center, cross-sectional study conducted at AL-Sader Teaching Hospital in AL-Najaf City, Iraq between July 2021 and February 2022. Patients

who had chest pain suggestive of CAD and underwent a 64-multislice multi-detector CT angiography exam to determine if there was any occlusive CAD were included in this study. A history of cardiac risk factors for CAD was obtained from each patient at the time of MDCT examination, including age, sex, hypertension, diabetes mellitus, smoking, family history of premature CAD, dyslipidemia, and BMI as described in detail in our previous study [10].

MDCT examination

CT coronary angiography was performed with a 64-slice scanner (Aquilon 64, v. 4.51 ER 010; Toshiba Medical Systems, Tochigi, Japan), with retrospective electrocardiography gating, as described in detail previously [10]. For the measurement of PFV, the amount of fat within the pericardial sac (PFV) was quantified in a 3D manner with the help of contrast-enhanced imaging. To create a 3D image of the heart, we manually traced the layer of the pericardium. Then, we calculated the total volume of tissue within the pericardium whose CT density ranged from -250 to -20 HU to quantify the PFV. This was done using a dedicated workstation (Vitre[®] 2 workstation; Vital Image Inc., Plymouth, MN) for image analysis. Occlusive CAD was defined as a mean lumen diameter reduction of > 50% in a single vessel by comparing the lumen diameter of the narrowest segment with that of a more proximal or distal normal segment in two orthogonal projections. MPAd was measured at the pulmonary artery bifurcation level (Figure 1). ARD was measured at the level of the sinuses of Valsalva (Figure 2). For better assessment of ARD, measurements of the axial plane of aortic root are taken using three lines (one line from each sinus), and an average value is calculated for each case. The largest transverse diameter of both arteries perpendicular to their long axis was measured using oblique multiplanar reconstruction. Two independent radiologists with more than 5 years of experience in coronary MDCT angiography interpretation performed all data analyses respectively. In the case of disagreement in the measurements between the two readers, the final decision was made by consensus. Verbal informed consent was obtained from all enrolled participants. The study was approved by our medicine college board.

Statistical analyses

Continuous data are presented as mean \pm standard deviation, and the categorical data are presented as numbers with percentages. The correlation between PFV with ARD, MPAd, and MPAd/ARD was performed using the Pearson correlation test. Univariate was employed to assess the effects of PFV, MPAd, and MPAd/ARD ratio in predicting occlusive CAD presence. A multivariate regression analysis was used to assess the associations between MDCT markers and occlusive CAD, after adjusting for cardiac risk factors (age, sex, hypertension, diabetes mellitus, smoking, dyslipidemia, family history of premature CAD, and BMI). A p-value of <0.05 was considered statistically significant. All analyses were performed using the SPSS for Windows ver. 23.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 145 patients with chest pain suggestive of CAD were enrolled in this study. The mean age was 54 ± 10 years, 51% were males with nearly half of the patients had $BMI \geq 30$. Baseline comorbidities included diabetes mellitus (30%), hypertension (56%), dyslipidemia (32%), family history of premature CAD (11%), and smoking (20%). Around 30% of entire patients had occlusive CAD. The mean PFV, ARD, MPAd, and MPAd/ARD ratio in all patients were 155 cm^3 , 29.9 mm, 23.4 mm, and 0.8, respectively. The baseline clinical characteristics are shown in Table 1.

As shown in Table 2, PFV showed a significant correlation with ARD ($r=0.5$, $p<0.01$) and MPAd/ARD ($r=-0.3$, $p<0.01$) while no significant association was noted between PFV and MPAd ($r=0.1$, $p=0.11$). On univariate analysis, PFV (OR (CI)=1.1 (1.01-1.3), $p<0.01$), ARD (OR (CI)=1.2 (1.1-1.4), $p<0.01$), and MPAd/ARD ratio (OR (CI)=0.2 (0.1-0.5), $p=0.02$) showed significant association with occlusive CAD presence, as in Table 3. After adjusting for cardiac risk factors in multivariate regression analysis, only PFV (OR (CI)=1.1 (1.02-1.3), $p<0.01$), but not ARD (OR (CI)=0.9 (0.3-2), $p=0.85$) or MPAd/ARD ratio (OR (CI)=0.1(0.1-2), $p=0.69$), independently associated with occlusive CAD, as in Table 4.

Discussion

Our results show that increased PFV, but not ARD or MPAd/ARD ratio, is independently associated with occlusive CAD (stenosis severity >50%) presence. The independent association of PFV with severe CAD is consistent with previous studies that have reported the predictive role of increased cardiac adiposity in CAD progression and development owing to the unique anatomical and functional properties of cardiac adipose tissue. As well as on the development of CAD, PFV assessment could provide helpful data about the cardiovascular prognosis, helping to detect those at risk of adverse outcomes and monitoring patients with metabolic diseases during clinical follow-up [9,10-12]. A case-cohort study enrolled 998 community-based middle-aged and older adults, who were randomly selected from 6814 multi-ethnic study of atherosclerosis individuals, reported that increased PFV assessed by cardiac computed tomography predicts a higher risk of future CAD independent of conventional risk factors, including BMI [13]. The mechanism underlying the relation between pericardial fat and coronary heart disease may be due to its proximity to coronary arteries and local release of several inflammatory cytokines and mediators. This local inflammatory cytokines release may not be related to the plasma concentrations of circulating cytokines and seems to be independent of other coronary risk factors [14].

A recent comprehensive meta-analysis of 21 studies, involving 846 patients with severe CAD (coronary stenosis $\geq 50\%$) and 1762 non-CAD patients, reported that severe stenosis group had a larger PFV when compared to the coronary stenosis <50% group ($p < 0.001$), supporting the association between increased PFV and the development of CAD [15].

Anatomically, MPA and proximal aorta share a common embryonic origin and several confounding variables such as sex, degeneration of media layer, or body surface area influence the MPA and ARD equally. Thus, using MPAd/ARD ratio might provide an internal standardization and show the overall interaction of different risk factors influencing the prognosis of the cardio-respiratory system [16]. Moreover, both MPAd and ARD can be measured on just one axial slice at the site of pulmonary artery bifurcation [17]. The common embryonic origin and similarity in the remodeling process involving the arterial wall of MPA and the proximal aorta may explain the clinical use of both arteries

as a diagnostic or prognostic tool in pathologic processes related to the cardio-respiratory system [16,18].

Although we observed a significant association between ARD and MPAd/ARD with PFV and between ARD and MPAd/ARD ratio with and occlusive CAD in the univariate analysis, the association of ARD and MPAd/ARD with occlusive CAD did not persist after adjusting for cardiac risk factors. Previous clinical studies showed that increased ARD, in the absence of aneurysmatic alterations, was associated with several cardiovascular risk factors and was predictive of worse cardiovascular prognosis [19-21].

The pathophysiological mechanisms underlying non-aneurysmal dilatation of the proximal aorta are complex and may be not related to atherosclerosis, but may be linked to the interplay of other hemodynamic and non-hemodynamic factors, such as wall stress, inflammatory processes, growth factors imbalance, sympathetic nervous system dysfunction, or extracellular matrix disturbances [22].

In the Chin-Shan Community Cardiovascular Cohort study, the predictive role of aortic root diameter on cardiovascular morbidity and mortality was assessed in 1,851 Chinese participants over a median follow-up period of up to 13 years. Increased ARD was associated with an increased risk of cardiovascular adverse outcomes in univariate analysis. However, this positive association was confounded by age and other conventional cardiovascular risk factors in multivariate regression analysis, suggesting a minor role of atherosclerosis in the dilatation of the proximal aorta [19].

Furthermore, a multicenter, population-based study sponsored by the National Heart, Lung, and Blood Institute found that ARD was positively associated with left ventricular hypertrophy and mass, increased risk for congestive heart failure, stroke, cardiovascular disease mortality, and total mortality, but not with incident myocardial infarction after adjustment for other cardiovascular risk factors [20].

Taken together, these previous findings along with our findings may suggest that increased ARD can be regarded as a marker of later consequences of the impact of several cardiac risk factors, such as older age, diabetes mellitus, or PFV, rather than a mediator of coronary atherosclerosis or acute coronary events [20-22].

The possible strength of the present study is the 3D volumetric measurement of fat deposition in the pericardial sac and MDCT assessment of proximal large arteries and CAD were performed concurrently. In addition, MDCT combined with retrospective electrocardiogram gating provide heart images with high time resolution and reconstruct multiphase images of the whole cardiac cycle for assessing the ARD and MPAd accurately without motion artifacts in comparison to echocardiography measurement [23].

The present study has some limitations. This is a single-center study that included patients with chest pain suggestive of CAD. Therefore, our findings may not be generalizable to other populations. Also, we assessed the association of imaging parameters with occlusive CAD but not acute coronary events. Furthermore, the hemodynamic significance of functional severity of occlusive coronary lesions was not assessed in this study (using CT-derived coronary fractional flow reserve). ARD and MPA measurements were performed without indexing to body surface area. However, the MPAd/ARD ratio may allow for normalization of the effect of body surface area by accounting for the baseline great vessel size. The causal association between PFV with occlusive CAD cannot be confirmed because of the cross-sectional design of the study, which may not reflect this association over time. Our findings should be prospectively tested for further validation.

In conclusion, increased PFV, but not ARD or MPAd/ARD ratio, showed a significant and independent association with occlusive CAD presence in patients with suspected of CAD.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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Table 1. Baseline clinical characteristics.

Variable	n (%) or mean \pm SD
Age, years	54 \pm 10
Obese, BMI \geq 30	73(50)
Male	74(51)
Hypertension	82(56)
Diabetes mellitus	43(30)
Dyslipidemia	46(32)
Family history of premature CAD	16(11)
Smoking	29(20)
Occlusive CAD	44(30)
PFV, cm ³	155 \pm 70
ARD, mm	29.9 \pm 3
MPAd, mm	23.4 \pm 2
MPAd/ARD	0.8 \pm 0.09

Table 2. The correlation of PFV with ARD, MPAd, and MPAd/ARD ratio.

	PFV	
	r	p
ARD	0.5	<0.01
MPAd	0.1	0.11
MPAd/ARD	-0.3	<0.01

Table 3. Univariate correlation analysis for the association between occlusive CAD with PFV, ARD,MPA, and MPA/ARD.

Predictors	Occlusive CAD	
	OR (CI)	p
PFV	1.1(1.01-1.3)	<0.01
ARD	1.2(1.1-1.4)	<0.01
MPAd	1(0.9-1.2)	0.22
MPAd/ARD	0.2(0.1-0.5)	0.02

Table 4. Multivariate regression analysis for occlusive CAD.

Occlusive CAD		
Predictors	OR(CI)	p
PFV	1.1(1.02-1.3)	<0.01
ARD	0.9(0.3-2)	0.85
MPAd	1.2(0.3-4)	0.76
MPAd/ARD	0.1(0.1-2)	0.69
Age	1.1(1-1.4)	<0.01
Male sex	1(0.9-1.2)	0.70
Diabetes mellitus	4(1.5-10)	<0.01
Hypertension	1(0.7-1.1)	0.05
BMI	1(0.9-1.1)	0.70
Family history of premature CAD	1.4(0.5-4)	0.71
Dyslipidemia	0.6(0.2-2)	0.43
Smoking	1.7(0.4-6)	0.40

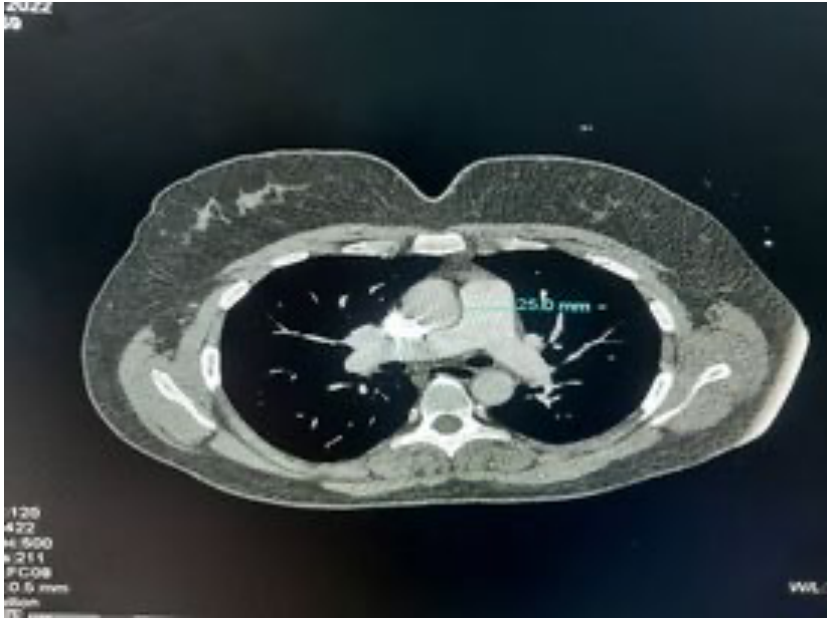


Figure 1. Measurement of main pulmonary artery diameter (MPAd).

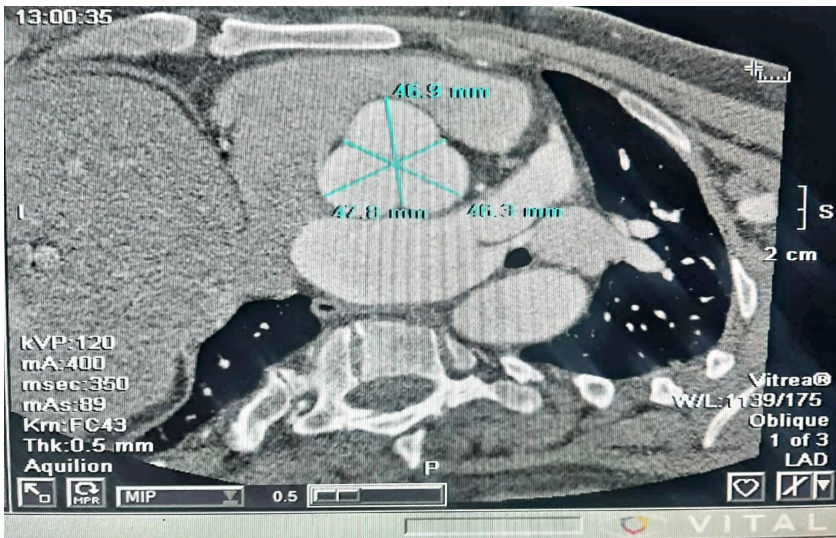


Figure 2. Measurement of aortic root diameter (ARD).

