

Relationship between breast arterial calcification on mammography with coronary CT angiography findings

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BACKGROUND: Breast arterial calcification is a frequently benign finding on mammography that usually is not reported. An increasing attention has been formed to determine the association between breast arterial calcification (BAC) and Coronary artery disease. In the current study we have aimed to evaluate the relationship between BAC on mammography with coronary CT angiography findings.

METHODS: The case control study was carried out on 60 women; 30 CAD and 30 healthy subjects as control, admitted to Golestan hospital radiology department. The mammography was performed in two views; Craniocaudal (CC) view and mediolateral oblique (MLO) and BAC was graded based on the severity and extent of calcifications. Coronary Arterial Calcification (CAC) were scored by Agatston criteria.

RESULTS: Overall, 36 patients (60%) were positive for BAC. Twenty six out of them (72%) were CAD. There was a positive significant correlation between BAC and CAD. The sensitivity and specificity of BAC for CAD were 69% and 47%, respectively. Moreover, the severe BAC scores were significantly higher in CAD patients than non-CAD.

CONCLUSION: Our findings in line with several previous studies indicated the positive significant association between BAC and CAD occurrence. While the sensitivity and specificity of BAC in diagnosis of CAD is low, suggested the using of BAC just as a CAD risk factor. The relatively low sample size is the major limitation of the study.

Keywords breast arterial calcification, CAD, angiography

Introduction

Coronary artery disease (CAD) known as a first leading cause of death in the world. Indeed, one-third of deaths in people aged over 35 years is due to CAD. Based on the recent World Health Organization (WHO) project, the CAD burden reach to 47 million disability adjusted life years by the 2020 year (Kandaswamy et al., 2018). The highest rate of cardiovascular disease related deaths in the world is reported from the Middle East and some Eastern Europe countries. Moreover, it has been shown a higher burden of the disease in Iran than other countries in this region (Sarrafzadegan et al., 2013). Although, several risk factors have been proposed for CAD including family history, hypertension, hypercholesterolemia,

diabetes mellitus and smoking, they could not sufficiently predict the CAD incidence. Hence, new risk factors were suggested (Akhabue et al., 2014). The coronary artery calcium score (CAC) is a new emerging risk factor to predict the incidence of CAD. It has been proposed as one of the strongest marker in risk prediction of cardiovascular diseases. It could be used either in risk stratification or monitoring atherosclerosis development (Pletcher et al., 2004; Polonsky et al., 2010; Zeb and Budoff, 2015). Two different computed tomography (CT) procedures could be used to CAC quantification, electron beam (EBCT) and multidetector computed tomography (MDCT) that EBCT provided more quick imaging (Becker et al., 2001; McEvoy et al., 2010).

Coronary calcium defined when Hounsfield units reach to above than 130 in at least 3 adjacent pixels. Several CAC quantification criteria have been proposed. The Agatston score that presented in Agatston units (AU), is the most popular criteria that was frequently used in clinical settings. Agatston units figured out by the calcified plaque area and

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maximal calcium lesion density (McEvoy et al., 2010). CAC testing by CT angiography is relatively expensive and not supported by the insurance. Therefore, its application as a screening tool for CAD risk assessment is very limited.

After the worldwide introduction mammography as a screening test at the late of 1980s, millions of women do the mammogram test annually (Arleo et al., 2017). Based on the Guideline of Ministry of Health (MOHME, 2011) women older than 40 years should be performed mammography every two years (Shirzadi et al., 2017). One of the most common findings in mammography is Breast arterial calcifications (BACs) that do not report because of its clinical insignificance. Nowadays, there are increasing attention to determine the association between breast arterial calcification (BAC), that easily determined in a standard mammogram, and the risk of CAD (Rotter et al., 2008).

Although several of authors reported the considerable association between BAC and CAD (Crystal et al., 2004; Topal et al., 2007; Rotter et al., 2008; Abi Rafeh et al., 2012; Mostafavi et al., 2015; Chadashvili et al., 2016), some others failed to find the correlation (Henkin et al., 2003; Akinola et al., 2011). So, there are still a controversy in using of BAC as an independent marker for estimating the risk of CAD. Therefore, in the current study we aimed to evaluate the relationship between BAC on mammography with coronary CT angiography findings.

Material and methods

Study design

The case control study was carried out on patients admitted to radiology department of Imam Khomieni Hospital, Ahvaz during March 2017 to Feb 2018. The female patients that underwent CT angiography were included. While, patients with breast trauma or surgery, breast cancer, history of stroke and renal failure were excluded. The study protocol has explained for the patients and signed informed was given prior to participate. The study was approved by ethical committee of Ahvaz Jundishapour University of Medical Sciences.

Measurements

Demographic informations including age, menopausal status and parity were asked and registered. Moreover, patients were evaluated in terms of CAD risk factors, diabetes mellitus (DM), hypertension (HTN) and hyperlipidemia. Coronary CT angiograms were performed using Single multi detector 64-slice CT scanner (Siemens medical solutions, Erlangen, Germany). Iodinated contrast agent was administrated by routine clinical protocol; 80–100 mL, 4–5 mL/s (Isovue 370, Bracco, Milan, Italy). The single expert physicians in coronary angiography, has reviewed the angiograms for

grading CAD severity. The patients were divided into 4 groups based on the arteries stenosis; 1. absence of stenosis, 2. scarce or single arterial calcification with stenosis < 10%, 3. calcificated or non-calcificated arterial plaque with stenosis < 50%, 4. calcificated or non-calcificated arterial plaque with stenosis > 50%. The groups of three and four considered as CAD positive. CAC were scored by Agatston criteria as follow: no evidence of CAD: 0 Calcium score, minimal evidence of CAD: 1–10 Calcium score, Mild evidence of CAD: 11–100: Calcium score, moderate evidence of CAD: 101–400 Calcium score, severe evidence of CAD: Calcium score > 400.

The mammography was performed in two views, Cranio-caudal (CC) view and mediolateral oblique (MLO). The mammograms were evaluated by an expert radiologist. A four point scale was used for grading the BAC (BAC) based on the severity and extent of calcifications, 1) No vascular calcifications, 2) Few punctate vascular calcifications, 3) Coarse vascular calcifications affecting < 3 vessels, 4) Coarse or tram track calcifications affecting ≥ 3 vessels. The BAC grades of 3 and 4 considered as BAC positive.

Statistical analysis

All of statistically analysis was performed in IBM SPSS Statistics package version 22 and GraphPad Prism ver 6. The data was presented as mean, S.D and frequency. The Kolmogorov–Smirnov test was used for detaining the data distribution. Based on the data normality we used *t*-independent test or Mann–Whitney U test to compare them. Moreover, Chi square test was used for comparing categorical variables. BAC sensitivity ($\text{true-positives} \times 100 / [\text{true-positives} + \text{false-negatives}]$), specificity ($\text{true-negatives} \times 100 / [\text{true-negatives} + \text{false-positives}]$), positive predictive value ($\text{true positives} \times 100 / [\text{true-positive} + \text{false-positives}]$), negative predictive value ($\text{true-negatives} \times 100 / [\text{true-negatives} + \text{false-negatives}]$) for detecting CAD were calculated.

Results

The study evaluated 60 subjects that consist equal CAD and non-CAD patients. The patients did not significantly differ in terms of age (53.06 vs 50.7, $p = 0.13$). While, the prevalence of DM, HTN and hyperlipidemia was significantly higher in CAD than non-CAD patients. Moreover, our results indicated that there are a significant difference in terms of CAC score between the groups ($p < 0.0001$). On other words, the severe CAC scores were significantly higher in CAD patients than non-CAD (Table 1).

At the next step, we evaluated the association between semi-quantified BAC and CAC scores. Our results showed a significant positive correlation between the BAC and CAC scores, that means that higher BAC scores presented in patients with increased CAC score (Table 2).

Table 1 Comparative analysis of cases and controls characteristics

Variables		CAD n = 30	Non-CAD n = 30	p value
Age		53.066±6.15	50.70±0.6.01	p = 0.137
Underlying Diseases	Diabetes	26(86.7%)	0(0%)	p < 0.0001
	HTN	12(40%)	3(10%)	p = 0.008
	Hyperlipidemia	6(20.7%)	0(0%)	p = 0.012
CAC score	0 Degree	0(0%)	27(87.1%)	p < 0.0001
	Minimal	4(13.3%)	19(63.3%)	
	Mild	6(20%)	4(13.3%)	
	Moderate	7(23.3%)	7(23.3%)	
	Severe	12(40%)	0(0%)	

Table 2 Association of CAC score and BAC grade

Variables		Mammogram calcification score				p value
		No vascular Calcification	Few Punctate vascular calcification	Coarse or Tram Track calcification < 3	Coarse or Tram Track calcification > 3	
CAC	0 Calcium score	6(31.6%)	7(36.8%)	6(31.6%)	0(0%)	p < 0.0001
	Minimal	0(0%)	4(50%)	0(0%)	4(50%)	
	Mild	0(0%)	7(53.8%)	6(46.2%)	0(0%)	
	Moderate	0(0%)	0(0%)	8(66.7%)	4(33%)	
	Severe	0(0%)	0(0%)	0(0%)	8(100%)	

Overly, 36 patients (60%) were positive for BAC, that 26 out of them (72%) were CAD. There was a positive significant correlation between BAC and CAD (Table 3) (Fig. 1). The sensitivity and specificity of BAC for diagnosis of CAD were 69% and 47%, respectively. Moreover its NPV and PPV were 83% and 72%. The odds ratio and relative risk of BAC for predicting incidence of CAD were 13 and 4.3, respectively (Table 4).

Discussion

Breast arterial calcification is a frequently benign finding during mammography. Its prevalence varies in different

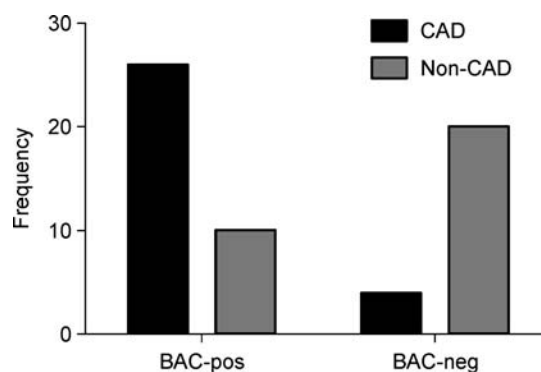


Figure 1 Correlation of BAC and CAD.

Table 3 Sensitivity and specificity table

	CAD	Non-CAD	Total
BAC-pos	26	10	36
BAC-neg	4	20	24
Total	30	30	60

populations. The healthy population based studies reported the prevalence range between 10% to 12%. Whiles it could be increased to 60%–70% among elderly females (Endriks et al., 2015). There are several reports that suggested BAC as an independent risk factor for CAD (Crystal et al., 2004; Topal et al., 2007; Rotter et al., 2008; Abi Rafah et al., 2012;

Table 4 Accuracy analysis of BAC in diagnosis CAD

Sensitivity and specificity	Percent	95% confidence interval	
		Upper	Lower
Sensitivity	0.87	0.69	0.96
Specificity	0.67	0.47	0.82
Positive predictive value	0.72	0.54	0.85
Negative predictive value	0.83	0.62	0.95
Strength of association			
Relative risk	4.33	1.73	10.8
Odds ratio	13.00	3.5	47.6

Mostafavi et al., 2015; Chadashvili et al., 2016). In this case-control study we have evaluated 60 patients in respect to determine the potency of BAC in detecting CAD patients.

Our results showed a positive significant correlation between BAC and CAD, that means that the patients positive for BAC had more higher risk of CAD. Although the role of BAC as a risk factor for CAD is currently uncertain, our findings were in line with majority of previous studies (Crystal et al., 2004; Topal et al., 2007; Rotter et al., 2008; Abi Rafeh et al., 2012; Mostafavi et al., 2015). Moreover, Eva et al. in the most recent meta analysis study reported the significant associating between BAC and increased risk of cardiovascular diseases (Endriks et al., 2015). Medial arterial calcification (MAC) known Monckeberg's sclerosis is pathophysiological cause of BAC that occurred in the media part of the arteries. It is completely different from the intima arterial calcification that affected medium to large sized arteries and recognized as 'typical' atherosclerosis (Kim et al., 1999). MAC is also morphologically different from intimate calcifications in radiographic assessment, and presented likes railroad tracks (Reddy et al., 2005). Interestingly, several investigations reported a relationship between BAC and CAD risk factors including hypertension, diabetes mellitus (DM) and carotid intima thickening (Yildiz et al., 2014). Currently, it has not been understood that how BAC increased CAD risk. But, it can just simply show previous long-term exposure to well known CAD risk factors. On the other hand, BAC could also reflect the medial calcification in other veins. Moreover, MAC leads to vascular stiffness and it may be defined the correlation of BAC and CAD (Polonsky and Greenland, 2017). More studies are needed to define the distinct role of BAC in increasing CAD incidence.

Henkin et al. in contrast with our findings have failed to find any association between BAC and CAD. They studied on females aged 50-70 that could be increased the prevalence of BAC and make a selection bias. The higher BAC prevalence decreased the sensitivity of test. Moreover, they did not match the groups in terms of age. These limitations falsified the results (Henkin et al., 2003). Similarly, Akinola et al. have also reported that BAC in mammogram could not predict cardiovascular diseases. The low sample size and poor statistical analysis caused a difficulty to compare that with our findings (Akinola et al., 2011). Besides, Zgheib et al. in contrast with our results failed to show any correlation between BAC and CAD. They considered all of patients with any visible calcium deposits in mammogram as BAC positives, this mistake leads to increase of BAC positive patients (Polonsky and Greenland, 2017).

In summary, our findings in line with several previous studies indicated the positive significant association between BAC and CAD occurrence. While the sensitivity and specificity of BAC in diagnosis of CAD are low, suggested the using of BAC just as a CAD risk factor. The relatively low sample size is the major limitation of the study.

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Compliance with ethical standards

The authors declared no conflict of interest. All procedures have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was signed prior to participation in the study.

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