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Peripheral Calcification and Coronary Artery Disease

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Abstract

Objective: Determine whether presence of peripheral calcification on lower extremity roentgenogram correlates with current diagnosis of Coronary Artery Disease (CAD).

Methods: 2000 plain films between January 2018 to October 2018 of lower extremities reviewed for presence of calcification in women and men ages 50 to 75 (Part A). Case subjects matched by age and gender with control subjects. Past medical history investigated for current diagnosis CAD. Data analyzed and then additional 2000 plain film entries reviewed of both genders 65 to 75 years old (Part B). Low case numbers in Part A, 50 to 64 y/o females and males, therefore Part B included both genders ages 65 to 75. Odds Ratio (OR), Confidence Interval (CI) and p-value computed.

Results: Part A =400 + Part B =464 subjects. Low yield case subjects in the 50 to 59 bracket for females and males therefore low powered. Peripheral calcification present in males in the 60 to 69 (65% and 87%) with OR 2.31. Females 60 to 69 y/o had OR of 2.23 respectively. Of males in the 70 to 75 y/o OR 4.78 and females 1.59. Part B results of 65 to 75 y/o females OR 1.82 and male results OR 2.73. P value was significant for males in Part A 70 to 75 y/o (0.002) and male 65 to 75 y/o in Part B (<0.001) with 95% CI of 1.52- 4.91.

Conclusion: Presence of calcification on peripheral roentgenogram demonstrate significant odds ratio to known coronary artery disease in men 65 to 75 y/o.

Introduction

Cardiovascular Disease (CVD) continues to be the number one cause of death in the United States. According to the Centers for Disease Control, Coronary Artery Disease (CAD) is the most common type of heart disease, killing 366,000 in 2017 [1]. Given this fact, healthcare providers are working in partnership with patients to identify, address, and modify CVD risk factors. Although CVD risk calculators, based on clinical and laboratory data, are used to determine the need for lipid modifying medications, these calculators do not determine the presence of active disease. Coronary Artery Calcium (CAC) Computed Tomography (CT) has been evaluated as a predictor of active disease, with supporting evidence listed as Level IIB based on the 2013 ACC/AHA (American College of Cardiology/American Heart Association) guidelines on risk assessment in patients for whom risk assessment or the decision to initiate statins is uncertain].

The CAC score has emerged as the strongest risk prediction tool (for CAD) according to the 2016 SCCT/STR (Society of Cardiovascular Computed Tomography/Society of Thoracic Radiology) guidelines [2]. It represents calcific atherosclerosis in the coronary arteries and correlates well with the overall burden of coronary atherosclerosis. In 2017, Ferencik et al. conducted a large cohort study and found "distribution and increased number of involved arteries with CAC predict Coronary Heart Disease (CHD) events independent of the traditional Agastson score" [3]. The CAC score was incorporated into the 10-year CHD prediction tool through the MESA risk score by McClelland et al. in 2015 and provided improved accuracy of risk assessment [4].

Chowdhury et al. 2017 completed a retrospective study analyzing CT peripheral calcification and found patients in the highest quartile of calcification scoring (measured by peripheral imaging evidence of calcium) had a statistically significant risk of current ischemic heart disease (p=0.028) [5]. It is unknown whether peripheral extremity calcification can be used as a predictor of CAD. Therefore, the purpose of this study was to examine the feasibility of using peripheral extremity plain films to determine the presence of calcification and its association with current diagnosis of CAD.

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Methods

Outlines of the proposed project were presented to the IRB (Internal Review Board) at Aspirus Wausau Hospital and permission was granted to proceed.

Retrospective data were gathered on male and female patients, between the ages of 50 to 75 years, who had lower extremity plain film radiographs from January 2018 to October 2018. The data consisted of 6,000 lower extremity plain film set entries. If a patient had more than 1 anatomic site imaging of plain films available, all lower extremity films were evaluated by principal investigator for the presence only of calcification. The degree of calcification was not determined. Patients with calcification present were classified as case subjects and those without calcification were classified as control subjects. Case subjects were then matched for comparison with subjects of the same age and gender to generate control subjects for the purposes of investigating past medical history and analyzing the data.

A list of the case and control subjects was created by the principal investigator and blinded to the research colleagues regarding calcification status. The research colleagues then examined the patient's electronic medical record to determine an existing diagnosis of CAD. The diagnosis was based on the past medical history or cardiology procedure/imaging with interpretation by Cardiologist. Part A consists of evaluation of the first 3000 film set entries of patients 50 to 75 years old. Of the 3,000 film entries only 2,000 utilized due to lack of digital access. Review of the volume of case subjects in Part A revealed minimal calcification present in those 50 to 60 years old. The statistical analysis was completed and reviewed for Part A.

After reviewing results of the first set of data the author resumed investigation into the second half of the 6,000 film set entries (Part B) to include only patients 65 to 75 years old men and women to increase the yield of case subjects (and thus the power of the study) for comparison. Once again only 2,000 of the remaining 3,000 X-ray entries were examined due to lack of digital access. This process is shown in Figure 1. The results of Part A and Part B were presented separately and then data on 65 to 75 years-old from Part A and B were combined. To avoid fatal flaw, 10% of the cases and control subjects were reviewed separately from the principal investigator by another physician with near complete agreement on interpretation of films with and without calcification.

Charts were generated to visualize the statistical results of the different age groups and genders. Excel software was utilized to create graphs to compare numerical values of the case *vs.* control in each gender. Analysis included determination of specificity, sensitivity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of presence of calcification with diagnosed CAD. The statistics for Confidence Interval (CI), p value, and Odds Ratio (OR) were obtained through MDCalc.org. Results were confirmed by Statistician Professor.

Results

The initial portion of the study was completed after 2,000 film sets were reviewed retrospectively for presence of calcification from January to October 2018 in patients 50 to 75 years old. From the 2,000 films, the 199 case subjects and 201 control subjects were matched based on age and gender (Table 1). The men and women were separated and further assessed in age brackets based on the prevalence tendencies of CAD historically according to the CDC.gov (Tables 2, 3).

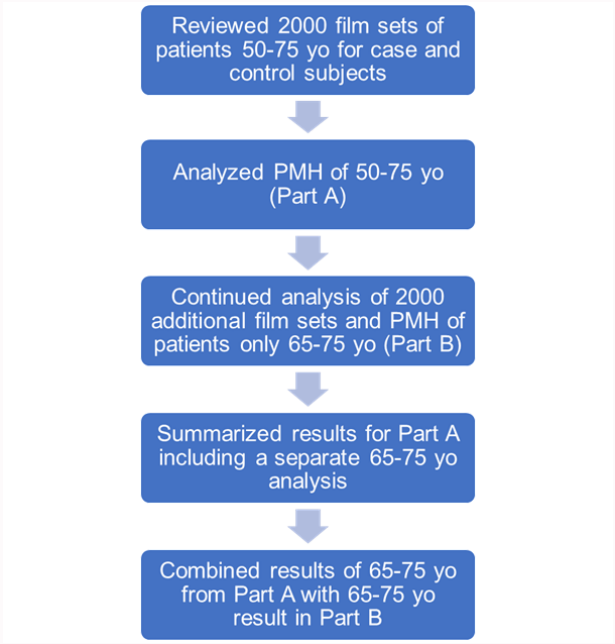

Figure 1: Flow chart of research data acquisition.

Table 1: "Part A" total incident numbers (case + control).

Age	Women	Men	Ratio (F:M)
50-59 yrs	14	32	1:02
60-69 yrs	64	119	1:02
70-75 yrs	72	99	3:04
Cumulative	150	250	3:05

Looking at Table 2, 3 the 50 to 59-year-old group for both men and women, there was low yield given the lack of peripheral calcification noted in this age group (14 women and 32 men). The statistical results of this age group are essentially not significant due to the low power.

In the 60 to 69 years old group from Table 2, 3, although the detection of calcification was more robust with 64 women and 119 men, the sensitivity was determined at 67% and specificity at 53% for presence of diagnosed CAD. PPV was 19% and NPV was 91%. OR ratio was calculated as 2.23 with the 95% confidence interval of 0.51-9.84 and the p value of 0.29. There was a trend towards significance for men aged 60 to 69 years with sensitivity of 65%, specificity of 55%, PPV value of 26% and NPV of 87%. OR for presence of CAD and peripheral calcification in 60 to 69 years old men were 2.31 with 95% CI 0.9-5.96 and p value 0.083.

In the age group 70 to 75 years (Table 1), the authors identified 72 women with peripheral calcification and 99 men. With comparison to controls and looking at Table 2, 3, the sensitivity for presence of CAD was 58% and the specificity 53% for women. PPV was 28% and NPV was 81%. OR for presence of existing CAD in 70 to 75-year-old women was 1.59 with CI of 0.53-4.79 and p value of 0.41. For men aged 70 to 75 years old, demonstrated sensitivity was 75%, specificity 59%, PPV 40%, NPV 87% with OR 4.78, CI 1.72-13.31 and a significant p value 0.003.

A comparison of statistics was completed for all ages of women and men (Table 4). For women, the sensitivity was 63%, specificity

Table 2: "Part A" – Women statistical results.

Age	Sensitivity	Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	OR	CI (95%)	p Value
50-59	100%	54%	14%	100%	3.46	(.12-100)	0.47
60-69	67%	53%	19%	91%	2.23	(.51-9.84)	0.29
70-75	58%	53%	28%	81%	1.59	(.53-4.79)	0.41

Table 3: "Part A" – men statistical results.

Age	Sensitivity	Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	OR	CI (95%)	p Value
50-59	0%	48%	0%	94%	0.31	(.01-8.28)	0.49
60-69	65%	55%	26%	87%	2.31	(.90-5.96)	0.083
70-75	77%	59%	40%	87%	4.78	(1.72-13.31)	0.003

Table 4: "Part A" – CUMULATIVE Results.

Age	Sensitivity	Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	OR	CI (95%)	p Value
Women 50-75	63%	53%	27%	87%	1.91	0.81-4.49	0.141
Men 50-75	70%	56%	28%	88%	2.91	1.5-5.66	0.002

Table 5: "Part B" TOTAL Incident Numbers (case + control): The ratio of women to men was not equal (similar to Part A) with ratio of 1:2.

Age	Women	Men
65-75 yrs	158	306

53%, PPV 27%, NPV 87%, OR 1.91, 95% CI 0.81-4.49 and P value 0.141. The cumulative statistics for men were sensitivity 70%, specificity 56%, PPV 28%, NPV 88%, OR 2.91, CI 1.5-5.66 and significant p value of 0.002.

In Part B, 2000 additional plain film sets of females and males from the age group 65 to 75 were analyzed for peripheral calcification and then presence of CAD was determined. In Part B, the age range was narrowed based on the improved statistical results seen in older patients from Part A. Data from Part A participants 65 to 75 years old were added to the data from additional patients gathered from the second search of films of patients 65 to 75 years (Table 5). For women 65 to 75 years, the sensitivity was 62%, specificity 53%, PPV 23%, NPV 86%, OR 1.82, 95% CI 0.80-4.17 and p value 0.14 (Table 6). For men age 65 to 75, sensitivity was 69%, specificity 55%, PPV of 29%, NPV of 87%, OR 2.73, 95% CI 1.52-4.91 and p value of 0.0008 (Table 6). Just as in Part A, the older age bracket of men demonstrated a higher NPV and significant p value.

Discussion

We found that the presence of peripheral calcification on plain film increased the odds of a diagnosis of CAD in men, particularly those aged 65 to 75 years. The absence of such calcification had a high negative predictive value for CAD in both men and women. A strength of this study is the inclusion of men and women increases the applicability of findings. Additional study strengths include matching of the control subjects with case subjects based on gender and age. Despite insignificant results generated in men 50 to 59 and 60 to 69, the cumulative data for men demonstrated a better NPV compared to separate age categories and a significant p value that was improved compared to any separate age category.

Further strengths include the fact that the principal investigator was blinded to the patient's medical history when reviewing extremity roentgenograms. In addition is the principal investigator was not involved in extracting the health history to determine presence or lack of CAD thus decreasing possibility of bias. The associates who gathered the medical history information were also blinded to the knowledge of whether the patient was a control or a case subject, thus decreasing the possibility of bias. 10% of the cases and 10% of the control plain film sets were examined by University of Wisconsin faculty with near complete agreement in interpretation. Ethnicity and socioeconomic status, were unknown by the principal investigator.

Why do we care about calcification and specifically coronary artery calcification? Coronary artery calcium determination and scoring has been available in the medical community since the 1990's. In early 2000's, several papers were published evaluating CAC scores compared to Framingham score (FS) for risk prediction.

- In 2004, Greenland et al. found that high CAC scores "can modify predicted risk obtained from FS in the intermediate category". The additional information can then be utilized for clinical decisions [6].

- The study by Arad and Kondos demonstrated prediction of coronary events in those with significant coronary calcification [7,8].

- A cohort study by Budoff in 2007 analyzed 25,000 persons and found "CAC was an independent predictor of mortality in a multivariable model controlling for age, gender, ethnicity, and cardiac risk factors" based on relative risk ratio [9].

The progression of coronary artery calcium in patients with elevated CAC score has also been shown to significantly predict all-cause mortality by Budrow [10]. Similar findings were demonstrated by Shaw et al [11]. Thus, the presence of calcification can be used to determine health risk and not solely cardiovascular events. In addition, CAC determined by CT was shown to predict future cardiovascular events in multiple populations [12,13].

Table 6: "Part B" – cumulative results.

Age	Sensitivity	Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	OR	CI (95%)	p Value
Women 65-75	62%	53%	23%	86%	1.824	(0.8-4.17)	0.154
Men 65-75	69%	55%	29%	87%	2.73	(1.52-4.91)	0.0008

Coronary calcification studies have assessed the risk of future cardiovascular events in patients with high CAC scores. An early metanalysis by Pletcher identified significant relative risk in persons with elevated CAC score and CHD events [14]. In the study by Raggi, those in the highest quartile of calcium score demonstrated an odds ratio of 21.5 for future hard cardiovascular events [15]. In addition, those subjects in the St Francis Heart Study with scores >400 were at a 30-fold increase in CAD, death, or myocardial infarction [16]. Based on the Prospective Army Coronary Calcium Project, young patients underwent EBT (Electron Beam Tomography) and followed prospectively. Coronary artery calcium was associated with 12-fold increased risk for CHD events even after controlling for Framingham risk score [17]. This emphasizes the importance of physical evidence of disease as a better predictor of future events compared to a risk calculator.

Shin et al. evaluated the CT presence of peripheral calcification and found this to significantly correlate with CAD extent. Lower extremity calcium scores were higher in those with significant CAD than those with non-significant CAD ($p<0.001$). "In receiver operating characteristic curve analysis, the diagnostic performance of lower extremity calcium score was 0.807 (95% confidence interval =0.724-0.891, $p<0.001$) for predicting multivessel CAD [18]. A recent article by Taylor et al demonstrated that the presence of arterial calcifications on hand plain films indicated 6.2-fold increased odds of CAD [22]. In an earlier article from Bannas et al. assessing the correlation of aortic arch calcification gradient with CAC, the authors found that aortic arch calcification grading on chest radiography was reliable and positively associated with CAC scoring [23].

Practically speaking, CT scans, specifically for CAC screening, may be unavailable in rural locations. Plain film radiography is accessible, portable, and inexpensive. Based on "fairhealthconsumer.org" a lower extremity roentgenogram in our area of the United States costs $40/$80 (in/out of network) for the image *vs*. $220/$490 (in/out of network) for a CT chest image. Radiation exposure with lower extremity roentgenogram is insignificant at 0.001 mSV *vs.* chest CT radiation exposure is 1 mSV. The low cost, accessibility, and applicability are all factors that argue in favor and meet expectations of a useful screening test.

The goal of this study was to evaluate an association between peripheral artery calcification on roentgenograms and current diagnosis of CAD. Risk calculators that are routinely used to decide on treatment decisions, are not physical evidence of disease. The physical evidence of calcification peripherally may provide more useful information for deciding on the treatment approach for patients in the category of intermediate risk for atherosclerotic disease. Based on results for men 65 to 75 years, including NPV of 87% and p value of 0.0008, plain films may be considered a worthwhile screening test for those in the intermediate risk range as a screening tool.

The results from this project suggest that peripheral extremity plain films may assist in identifying men aged 65 to 75 years at lower risk for CAD based on lack of peripheral calcification. The statistical results from this study are not significant for women in any age group. Small numbers of both men and women in the 50-year-old age group limited the power of the statistical findings. Possibly the yield would have been improved on prospective study targeting men in the age group 50 to 59 years with 1 or more CAD risk factors.

The cumulative data for men years 50 to 70 years and cumulative data for men years 65 to 75 years were statistically significant, however there was no statistical significance for men in their 50's and 60's. An important factor to note, in all data groups the negative predictive value was 81% or higher. A negative peripheral film for calcification in men 65 to 75 years with an ASCVD (Atherosclerotic Cardiovascular Disease) risk calculated at greater than 7.5% may be useful in the decision-making process of prescribing a statin. A future study could include a cohort study in which men 60 years and older in the intermediate cardiovascular risk category are provided a plain film of the lower extremity and then prospectively followed for development of cardiovascular events. Previous papers have identified CAC scores in the elderly with intermediate risk as a means of reclassifying them into appropriate categories [19] and as an improved predictor of coronary events and disease [19,20].

Future studies should consider the limitations of this study. Despite films from more than 4,000 patients, we could evaluate only a small number of control patients. Statistical results for those in their 50's in Part A data likely represent type 2 error due to low power. Imaging studies were obtained from patients who had musculoskeletal concerns; thus, the data were not necessarily a reflection of the general population. The odds ratio might increase using a prospective study design comparing the CAD rate of those screened who have CAD risk factors *vs.* the general population for both cases and control subjects. Finally, the yield for case subjects with peripheral calcification was low; however, the number of case subjects may have been higher if the patients were selected based on risk factors.

Conclusion

The presence of calcification on peripheral roentgenogram in men aged 65 to 75 years resulted in a statistically significant OR for existing CAD of 2.73. The high negative predictive value in all ages and both genders is also noteworthy. The results from this study justify further investigation such as a cohort study comparing extremity plain films of those with intermediate 10-year ASVD risk to those subjects who are considered low risk (or high risk).

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