The epidemiology of subclavian artery calcification

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Objectives: The purpose of the present study was to determine the prevalence and risk factor associations for subclavian artery calcification.

Background: Arterial calcification is a marker of atherosclerosis, and its presence portends an adverse prognostic risk. The prevalence and associated risk factors for aortic arch, carotid, renal, and coronary calcification have been well described. Fewer data are available for subclavian artery calcification.

Methods: Electron-beam computed tomography was used to evaluate the extent of vascular calcification in multiple arterial beds in 1387 consecutive individuals who presented for preventive medicine services at a university-affiliated disease prevention center. Laboratory values for blood pressure, lipids, anthropomorphic data, and self-reported medical history were obtained.

Results: Subclavian artery calcification was present in 439 of 1387 individuals (31.7%). Those with subclavian artery calcification were significantly older, had a smaller body mass index, and were more likely to also have calcification of nonsubclavian vascular beds. When adjusted for cardiovascular disease risk factors, the presence of subclavian artery calcification was significantly associated with age (prevalence ratio [PR], 1.04; P < .001), hypertension (PR, 1.20; P = .01), history of smoking (PR, 1.21; P = .01), and calcification in nonsubclavian vascular beds (PR, 1.58; P = .01). Subclavian artery calcification was also associated with an increased pulse pressure (β-coefficient = 2.2, P = .008).

Conclusions: Subclavian artery calcification is relatively common and is significantly associated with age, smoking, hypertension, and nonsubclavian vascular calcification. There may be a relationship between vascular stiffness, as manifested by a widened pulse pressure, and the presence of subclavian artery calcification. (J Vasc Surg 2011;54:1408-13.)

Arterial calcification represents the culmination of a complex series of molecular and pathophysiologic mechanisms.1,2 Calcification associated with atherosclerosis has an important relationship to overall cardiovascular risk. Specifically, the detection of calcium in different arterial beds, including the coronary circulation, carotid and renal arteries, and the thoracic and abdominal aorta, has been associated with a variety of cardiovascular risk factors and with an adverse prognosis.3-5 Moreover, calcification of the aortic arch is an independent risk factor for coronary heart disease (CHD).6,7 Because the subclavian arteries are relatively close to the aortic arch, examination of the presence and extent of subclavian artery calcification (SAC) would expand current knowledge about the distribution of atherosclerosis in the major vessels. Notably, risk factors for SAC have not been previously described.

The present study was conducted to determine the prevalence and risk factor associations for SAC. We hypothesized that risk factors and disease associations for calcification of the subclavian vessels would be similar to that described in the literature for aortic and carotid calcification. Specifically, we hypothesized that aging, diabetes, and a history of hypertension would be related to the presence of SAC.

METHODS

The protocol for this study was approved by the Human Research Protection Program at the University of California, San Diego, which granted a waiver of informed consent to conduct this retrospective analysis of existing clinical data.

Participants. From February 1, 2001, to June 29, 2001, 1387 consecutive individuals presented for preventive medicine services at a university-affiliated disease prevention center in San Diego, California, and had complete data available for the current analysis. Most patients were self-referred or referred from local physicians to obtain detailed preventive health information and testing.

Participants completed a detailed health history questionnaire that collected information on history of hypertension, diabetes, high cholesterol, smoking, medications, family history of CHD, diet, exercise, and prior operations. All individuals underwent whole-body electron-beam computed tomography (CT) imaging and were evaluated for the extent of vascular calcification in the coronary, subclavian, thoracic aorta, renal, abdominal aorta, and iliac vessels. Data on a subgroup of these individuals have been previously reported.6,9

Laboratory measurements. Casual serum levels of total, high-density (HDL), and low-density (LDL) cholesterol, and glucose measurements were obtained by fingerstick using the Cholestech LDX system (Cholestech, Hayward, Calif). Individuals with a total/HDL cholesterol ratio >5 or who reported using a medication to treat high
cholesterol were classified as dyslipidemic. Diabetes was defined by current use of prescribed antihyperglycemic medications or a random glucose level >200 mg/dL.

**Blood pressure.** Blood pressure was measured after the participants had rested for 5 minutes while seated. Trained individuals obtained systolic (SBP) and diastolic (DBP) blood pressures in the right arm by automated oscillometry. Mean arterial pressure (MAP) was calculated using the following equation: MAP = DBP + 1/3 × (SBP – DBP). Pulse pressure was the difference between SBP and DBP. Hypertension was defined as an SBP or DBP >140 or 90 mm Hg, respectively, or a self-reported history of physician-diagnosed hypertension and current use of an antihypertensive medication.

**Imaging.** Data on the imaging techniques used for these individuals have been previously described in detail. Briefly, imaging was conducted using an Imatron C-150 scanner (General Electric, San Francisco, Calif). Images for each vascular bed (carotid, subclavian, aorta, coronaries, renals, and iliac) were obtained from a single scan and proceeded caudally from the base of the skull to the symphysis pubis. Each bed was obtained by a distinct scan of the segment in question by using slice thicknesses of 3 mm for the coronary bed, 5 mm for the thorax, and 6 mm through the neck, abdomen, and pelvis. Imaging of the heart, thorax, and abdomen was conducted during separate breath holds at 50% maximal inspiration.

Quantitative calcium scores were determined according to the method described by Agatston et al. Atherosclerotic calcium was defined as a plaquelike area 1 mm² with a density of 130 Hounsfield units. The total calcium score was determined by summing the lesion scores from all of the slices for that segment. The degree of subclavian calcification was derived by grouping the calcium scores for the right subclavian, innominate, and left subclavian arteries. The right subclavian artery was identified from the root of the aorta as the brachiocephalic, and subsequent subclavian, artery. The left subclavian was identified from the root of the aorta. Both arteries were examined through the mediastinum to where they arched over the top of the lung.

**Statistical analysis.** Baseline characteristics were compared within gender for SAC using analysis of variance, χ², or Kruskal-Wallis tests, as appropriate. SAC was examined as a dichotomous outcome (yes/no) and as a continuous outcome among those with any subclavian calcium. In this study, the prevalence of SAC was >10%. Because odds ratios from logistic regression will overestimate the prevalence ratios in this case, log-binomial models were used to assess associations of risk factors with SAC >0 vs SAC = 0. If issues with convergence of the log-binomial models were encountered, a Gaussian link with robust standard errors was used. Because SAC scores >0 were skewed, these were natural log-transformed, and linear regression was used to assess the association of risk factors with these outcomes. In models examining the association of SAC with blood pressure outcome, linear regression was also used. For these models, univariate associations of SAC with each blood pressure outcome were evaluated first, and then staged models were used to examine potential confounders. Traditional cardiovascular risk factors and variables that have been associated with subclinical atherosclerosis in our previous studies were included in the regression models, including age, sex, body composition, smoking, diabetes, hypertension, family history of CHD, dyslipidemia, and nonsubclavian calcification. SAS 9.1.3 software (SAS Institute, Cary, NC) was used for statistical analysis.

**RESULTS**

**Prevalence of SAC.** SAC was found in 439 of 1387 participants (31.7%). Individuals with SAC were older than those without SAC (63 ± 11 vs 54 ± 11 years, respectively; P < .001). The characteristics of the study cohort and the presence of SAC adjusted for age and sex are reported in Table I. Those with SAC had a slightly smaller body mass index (26 ± 6 vs 27 ± 4 kg/m², P < .001) and less percentage of body fat (28.7% vs 30.1%, P < .001) vs individuals without SAC. The prevalence of hypertension by history was no different in participants with SAC vs those without SAC: Although the two groups had similar SBPs, those with SAC had lower DBP (79 ± 11 vs 81 ± 11 mm Hg, P = .02). The prevalence of arterial calcification in the carotid, coronary, renal, iliac arteries, and total aortic vascular beds was 24.6%, 60.3%, 18.2%, 58.9%, and 62.5%, respectively. Calcification in the nonsubclavian vascular beds was significantly more common in those with SAC (P < .001 for the carotids, coronaries, renal arteries, and iliac arteries; P = .002 for the total aorta; Fig).

**Multivariable risk factor analysis for SAC.** In a multivariable logistic regression model containing age, body mass index, body fat, sex, former or current smoking, hypertension, diabetes, family history of CHD, dyslipidemia, and calcium presence in the nonsubclavian vascular beds (Table II), the presence of SAC was significantly associated with age (prevalence ratio [PR], 1.04 per year, 95% confidence interval [CI], 1.03-1.04; P < .001), BMI (PR, 0.97; 95% CI, 0.95-1.00; P = .02), a history of smoking (PR, 1.21; 95% CI, 1.04-1.40; P = .01), hypertension (PR, 1.20; 95% CI, 1.04-1.39; P = .01), and calcification in other vascular beds, including carotid, coronary, aortic, renal, or iliac arteries (PR, 1.58; 95% CI, 1.11-2.25; P = .01). For the individual vascular beds, the presence of SAC was associated with calcification of the carotids (PR, 1.36; 95% CI, 1.16-1.60; P < .001), aorta (PR, 1.40; 95% CI, 1.05-1.86; P = .02), renal (PR, 1.60; 95% CI, 1.35-1.88; P < .001), and coronary arteries (PR 1.27; 95% CI, 1.00-1.61; P = .05). The association with diabetes was of borderline significance (PR 1.25; 95% CI, 1.08-1.46; P = .07).

Using the same modeling strategy, the amount of SAC was associated with age (% difference in SAC, 6.0%; 95% CI, 4.6-7.3; P < .001), a history of smoking (26.7%; 95% CI, 0.5-56.0; P = .04), hypertension (66.1%; 95% CI, 30.7-111.2; P < .001), carotid calcification (77.8%; 95% CI 57.4-130.1; P < .001), renal artery calcification (63.8%; 95% CI 25.9-112.9; P < .001), and coronary calcium presence (36.3%; 95% CI, 0.2.1-85.3; P = .05).
Association of SAC presence and amount with blood pressure. After adjustment for age, sex, and cardiovascular risk factors (except hypertension), the presence of SAC was associated with SBP (β-coefficient = 2.0, $P = .05$) and pulse pressure (PP; β-coefficient = 2.2, $P = .008$; Table III). After the same adjustments, the amount of SAC was most strongly associated with decreasing DBP (β-coefficient = −1.2, $P = .04$) and mean arterial pressure (β-coefficient = −1.1, $P = .08$).
Table II. Multivariate models for the presence and extent of subclavian artery calcification (SAC)

<table>
<thead>
<tr>
<th>Variable</th>
<th>SAC presence (n = 1387)*</th>
<th>SAC extent (n = 439)b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PR (95% CI)</td>
<td>% Difference in SAC (95% CI)</td>
</tr>
<tr>
<td>Age, per 1 year</td>
<td>1.04 (1.03-1.04)</td>
<td>.001</td>
</tr>
<tr>
<td>BMI, per 1 unit</td>
<td>0.97 (0.95-1.00)</td>
<td>.02</td>
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<tr>
<td>Body fat, per 1%</td>
<td>1.00 (0.98-1.01)</td>
<td>.52</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.87 (0.71-1.06)</td>
<td>.17</td>
</tr>
<tr>
<td>History of smoking</td>
<td>1.21 (1.04-1.40)</td>
<td>.94</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.20 (1.04-1.39)</td>
<td>.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.25 (0.98-1.60)</td>
<td>.07</td>
</tr>
<tr>
<td>Family history CHD</td>
<td>1.03 (0.88-1.20)</td>
<td>.74</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.03 (0.86-1.23)</td>
<td>.74</td>
</tr>
<tr>
<td>Presence of Any calcium</td>
<td>1.58 (1.11-2.25)</td>
<td>.01</td>
</tr>
<tr>
<td>Carotid calcium</td>
<td>1.36 (1.16, 1.60)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Iliac calcium</td>
<td>1.22 (0.96, 1.55)</td>
<td>2.8</td>
</tr>
<tr>
<td>Aortic calcium</td>
<td>1.40 (1.05-1.86)</td>
<td>.02</td>
</tr>
<tr>
<td>Renal artery calcium</td>
<td>1.60 (1.35-1.88)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Coronary calcium</td>
<td>1.27 (1.00-1.61)</td>
<td>.05</td>
</tr>
</tbody>
</table>

CHD, Coronary heart disease; CI, confidence interval; PR, prevalence ratio.

* Those with Agatston score >0 only – % difference in SAC (100 × [exp(coefficient – 1)]).

† Current or former smoking.

‡ Presence in any other nonsubclavian vascular bed, including carotid, iliac, aortic, renal, or coronary arteries.

Table III. Association of subclavian artery calcification presence and amount with blood pressure

<table>
<thead>
<tr>
<th>Variable</th>
<th>SBP (95% CI)</th>
<th>DBP (95% CI)</th>
<th>PP (95% CI)</th>
<th>MAP (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>3.3 (1.3-5.4)</td>
<td>.001</td>
<td>–1.3 (–2.6 to 0.01)</td>
<td>.06</td>
</tr>
<tr>
<td>+ Age/sex</td>
<td>0.4 (–1.7 to 2.6)</td>
<td>.69</td>
<td>–1.6 (–3.0 to –0.2)</td>
<td>.03</td>
</tr>
<tr>
<td>+ CHD risk factors*</td>
<td>2.0 (–0.02 to 3.9)</td>
<td>.05</td>
<td>–0.6 (–1.9 to 0.8)</td>
<td>.42</td>
</tr>
<tr>
<td>Amount*</td>
<td>2.4 (1.2-3.5)</td>
<td>&lt;.001</td>
<td>–0.9 (–2.0 to 0.1)</td>
<td>.07</td>
</tr>
<tr>
<td>+ Age/sex</td>
<td>0.7 (–0.7 to 2.0)</td>
<td>.35</td>
<td>–1.2 (–2.4 to –0.1)</td>
<td>.03</td>
</tr>
<tr>
<td>+ CHD risk factors*</td>
<td>0.2 (–1.1 to 1.6)</td>
<td>.73</td>
<td>–1.2 (–2.3 to –0.1)</td>
<td>.04</td>
</tr>
</tbody>
</table>

CHD, Coronary heart disease; CI, confidence interval; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure.

*Body mass index, body fat, diabetes, smoking, dyslipidemia, family history of CHD.

†Modeled per standard deviation (SD) where SD = 159.6 for DBP and MAP; modeled as per log-unit for SBP and PP.

DISCUSSION

In this study of a relatively large cohort of individuals with a low frequency of established cardiovascular disease (CVD), atherosclerotic calcification was found in the subclavian arteries of nearly one-third of the patients. Of the traditional CVD risk factors, age, a history of smoking, and a history of hypertension were independently associated with the presence and amount of SAC. In addition, elevated SBP, a widened PP, and extrascapular vascular bed calcification also appear to be related to the presence of SAC. The amount of SAC was significantly associated with age, lower DBP, a history of smoking, and a history of hypertension.

Prevalence of SAC and comparison with calcification of other vascular beds. Numerous studies have examined the prevalence of coronary artery calcification in the general population. The presence of coronary calcification is a marker for subclinical atherosclerosis, and the degree of calcification may provide important prognostic information, even in asymptomatic individuals. Comparatively fewer studies have examined the prevalence and predictive value of peripheral vascular calcification. Our group has previously reported the frequency of renal artery calcification derived from a cohort similar to the one in the present study. The prevalence of renal artery calcification was 18%, and evidence of renal artery calcification was significantly associated with age, male sex, hypertension, and calcification in other beds.

A larger body of data describes the epidemiology of aortic arch and carotid calcification. Given that the left and right (as a continuation of the innominate artery) subclavian arteries are in direct continuum with the ascending aortic arch, it is
unknown whether there is a unique epidemiology for SAC. Aortic arch calcification has been studied extensively and appears to be more common than coronary calcification. Using radiographic evidence of calcification in a large population-based sample of >116,000 individuals, Iribarren et al demonstrated a 1.9% occurrence of aortic arch calcification in men and 2.6% in women, with independent associations with age, smoking, and hypertension. The prevalence in those aged >65 years was 11% in men and 16% in women. Furthermore, arch calcification was related to CVD outcomes, specifically to the risk of coronary artery disease in men and stroke in women. Although not directly comparable to the isolated aortic arch, our own group, using data derived from electron-beam CT demonstrated a prevalence of thoracic aortic calcification of 63% to 69% (women, men, respectively) in 60 to 70 year olds and in 96% to 98% in those aged >70 years. Furthermore, these data confirmed the previously described risk factor associations, specifically, the strong association of age and hypertension with calcification of the aorta.

Calcification of the carotid arteries has also been an area of extensive research. In this regard, calcific plaque involving the common or internal carotid artery, or both, is an adverse predictor of cardiovascular events. Prabhakaran et al examined the prevalence and prognostic significance of carotid calcification by vascular ultrasound in a stroke-free cohort of seniors and noted a 20.1% prevalence of carotid artery calcification. Calcified plaque was associated with age, diabetes, hyperlipidemia, and coronary disease, and at a follow-up of almost 3 years, calcified plaque (vs noncalcified or no plaque) was independently associated with the highest likelihood of vascular death, myocardial infarction, or stroke. Using more sensitive methods, Odink et al examined CT-derived Agatston scores in a senior population sample and noted the presence of calcification in 83% of men and 77% of women. Within this senior cohort, increasing calcification was associated with increasing age.

Our group's analysis of the pattern of calcification in a wider age range cohort demonstrated the importance of age as a risk factor for the presence of carotid calcification. The prevalence of carotid calcification in the 60 to 70 age range was 26% to 30% in women and 42% to 45% in men. Smoking and hypertension were also strongly associated with carotid calcification in men but less so in women.

The data from the present study demonstrate that similar to the carotid circulation, age, smoking, and hypertension were important risk factors for the presence of SAC. Furthermore, the presence and extent of SAC appeared to be related to carotid artery calcification. The similarities in anatomic location of the great vessels from the arch may subject these vessels to similar aging- and hypertension-related changes in vascular stiffness and hemodynamic flow disturbances.

Role of vascular stiffness in SAC. In the present study, a history of hypertension, the presence of an elevated SBP, and a widening of the PP were associated with the presence of SAC. A decrease in DBP also appeared to be associated with the amount of SAC present. These data suggest that increasing vascular stiffness, as reflected by systemic pressure measurements, may be related to SAC. The degree of vascular stiffness is strongly associated with aging and the presence of hypertension. Our group previously noted an independent association between widening of the PP and increasing SBP with the presence of arterial calcification in the carotid and coronary arteries and in the thoracic and abdominal aortas. These relationships were much stronger in those aged >60 vs those aged <60 years. Furthermore, other investigators have demonstrated that increasing aortic stiffness, as measured by pulse wave velocity analysis, and decreasing carotid distensibility have both been correlated with increasing calcification of the aortic arch and carotid arteries, respectively. Calcification of the subclavian and carotid vessels may create reflection sites that augment the PP difference in older individuals. This process likely represents concurrent mechanisms that may be additive to one another and related to a complex interplay between vascular remodeling, inflammation, and atherosclerotic plaque deposition. Additional studies will need to be performed to determine if SAC is related to more specific measures of vascular stiffness.

Study limitations. In the present study, blood pressures were not obtained in both arms; therefore, the prevalence of subclavian artery stenosis in conjunction with SAC cannot be determined. Given this limitation, the association between SAC and cuff blood pressure data may be inaccurate if the measurements were obtained in an arm with concomitant subclavian artery stenosis. However, this scenario would result in lower SBP readings and likely underestimate the association seen in our analysis. The relationship between SAC and elevated blood pressures could also be influenced by the association of SAC with increased arterial stiffness. Specifically, converse to the potential effect of subclavian artery stenosis, increased arterial stiffness secondary to SAC could elevate SBPs in the affected arm. In addition, we did not obtain ankle-brachial index measurements and therefore cannot comment on the relationship between lower extremity peripheral arterial disease and SAC.

The number of individuals with diabetes in the study was lower than that reported in the general population, and definite conclusions about the interaction between diabetes and SAC are less certain. The lifetime burden of cigarette smoking (pack/years) was not assessed; therefore, a more precise relationship between total volume of smoking and SAC could not be determined.

Lastly, the data are limited by a large proportion of self-referred individuals; therefore, the findings may not be applicable to other populations.

Clinical and epidemiologic significance. The present study provides further evidence of the systemic effect of hypertension, smoking, and aging on vascular calcification. These data provide the first evidence that these risk factors are associated with SAC. We have demonstrated that calcification of this bed is common (affecting about one-third of individuals), even in a cohort with a low rate of established CVD. CT imaging of the chest is increasing in frequency in
the United States.\textsuperscript{21} To date, clinicians or epidemiologists have not been given information about the significance of incidental SAC seen on these scans.

The current study has begun the evaluation of this vascular bed and sets the stage for further determination of the prognostic effect of SAC on cardiovascular outcomes. If a link between SAC and adverse outcomes is found, a finding of incidental SAC on a CT scan could, for instance, trigger evaluation of additional vascular beds (coronaries or carotids) or modify cardiovascular risk. In addition, the potential relationship between SAC and subclavian artery stenosis (a clinically relevant disease) is important and will also need to be explored before the full relevance of SAC can be elucidated.

Furthermore, it is important to understand the relationship between SAC and blood pressure, given that blood pressure is measured in the clinic in the arm. If SAC is associated with increases or decreases in blood pressure in the arm, then this could influence the results of cuff pressure measurements and therefore screening for hypertension.

CONCLUSIONS

The data from the present study demonstrate that the risk factor profile of SAC—specifically, aging, smoking, and hypertension—shares similarities with calcification in other vascular distributions, including the aorta and carotid arteries. However, the presence of SAC may have additional epidemiologic associations with widening of the PP. These data suggest a potential link between the presence of SAC and increased vascular stiffness. The prognosis and clinical significance of SAC are still poorly defined and require further study.

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AUTHOR CONTRIBUTIONS

Conception and design: MA
Analysis and interpretation: CW, NJ, AP, MA
Data collection: MA
Writing the article: AP, MA
Critical revision of the article: AP, MA, CW
Final approval of the article: MA
Statistical analysis: CW
Obtained funding: MA
Overall responsibility: MA

REFERENCES