Atherosclerosis Plus 52 (2023) 18–22

Contents lists available at ScienceDirect

Atherosclerosis Plus

journal homepage: www.elsevier.com/locate/atherosclerosis

Long term aortic arch plaque progression in older adults

David Leibowitz [a, d], Yuriko Yoshida [a], Zhezhen Jin [b], Carlo Mannina [a], Shunichi Homma [a], Koki Nakanishi [c], Mitchell S.V. Elkind [e, f], Tatjana Rundek [g, h, i], Marco R. Di Tullio [a, *]

[a] Department of Medicine, New York, NY, USA
[b] Department of Biostatistics, Columbia University, New York, NY, USA
[c] Department of Cardiovascular Medicine, The University of Tokyo, Tokyo, Japan
[d] Heart Institute, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel
[e] Department of Neurology, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA
[f] Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA
[g] Department of Neurology, Evelyn F. McKnight Brain Institute, Miller School of Medicine, University of Miami, FL, USA
[h] Department of Public Health Sciences, USA
[i] Clinical and Translational Science Institute, Miller School of Medicine, University of Miami, FL, USA

ARTICLE INFO

Article history:
Received 29 March 2023
Received in revised form
5 May 2023
Accepted 19 May 2023
Available online 20 May 2023

Keywords:
Aortic arch plaques
Echocardiography
Elderly

ABSTRACT

Background and aims: The presence of aortic arch plaques (AAP) is significantly associated with increased cardiovascular morbidity and mortality. Few studies have examined the incidence of AAP progression and factors which may contribute to it using transthoracic echocardiography (TTE). The objective of this study was to utilize sequential imaging of the aortic arch using TTE to examine the rate of AAP progression and its risk factors in a cohort of older adults.

Methods: Participants enrolled in both the Cardiovascular Abnormalities and Brain Lesion study (years 2005–2010) and the Subclinical Atrial Fibrillation and Risk of Ischemic Stroke study (2014–2019) who underwent TTE with assessment of aortic arch plaques at both time points represent the study cohort.

Results: 300 participants were included in the study. Mean age was 67.8 ± 7.5 years at baseline, and 76.7 ± 6.8 years at follow-up; 197 (65.7%) were women. At baseline, 87 (29%) had no significant AAP, 182 (60.7%) had evidence of small AAP (2.0–3.9 mm) and 31 (10.3%) had evidence of large (≥4 mm) AAP. At the time of follow-up assessment, 157 (52.3%) of participants exhibited progression of AAP with 70 (23.3%) having mild progression and 87 (29%) having severe progression. There were no significant demographic or clinical predictors of AAP progression except baseline plaque thickness itself which was significantly lower in the group with AAP progression.

Conclusions: Our study demonstrates a high prevalence of AAP on TTE exam in a population-based cohort of older adults with a high incidence of AAP progression. TTE is a useful test for baseline and follow up imaging of AAP, even in subjects with no or little AAP at baseline.

1. Introduction

The presence of aortic arch plaques (AAP) is significantly associated with an increased risk of stroke and overall mortality [1–3]. The number and size of AAP increase with age and are common in the general elderly population with a particularly high incidence in patients with embolic events [4,5]. Risk factors for AAP are generally similar to traditional risk factors for atherosclerotic vascular disease and include age, hypertension, diabetes and hyperlipidemia [6–9]. Few studies have examined the incidence of AAP progression and factors which may contribute to it [10–12]. The studies that exist mainly utilized transesophageal echocardiography (TEE) and have focused on a select population of patients referred for TEE evaluation of clinical embolic events. TEE, while generally safe, is semi-invasive and not suitable for routine clinical follow-up of AAP. Other imaging modalities such as CT or MRI are expensive, and require the use of radiation as well as intravenous contrast agents. Transthoracic echocardiography (TTE) is noninvasive and accurately detects AAP when compared to TEE [13,14]. Very limited data have examined progression of AAP using TTE [15]. As progression of

* Corresponding author. Division of Cardiology, Columbia University Medical Center, 630 W 168th St, New York, NY, 10032, USA.
E-mail address: md42@cumc.columbia.edu (M.R. Di Tullio).

https://doi.org/10.1016/j.athplu.2023.05.001

AAP is significantly associated with recurrent vascular events including death, there is an important clinical need to evaluate its incidence and causes using a suitable noninvasive method [10]. The objective of this study was to utilize serial imaging of the aortic arch using TTE to examine the rate of AAP progression and its risk factors in a population-based cohort of older adults.

2. Patients and methods

2.1. Study population

The Cardiovascular Abnormalities and Brain Lesion (CABL) study was a community-based epidemiological study conducted to investigate the cardiovascular predictors of subclinical cerebrovascular disease in the community. CABL based its recruitment on the Northern Manhattan Study (NOMAS), a prospective population-based cohort that enrolled from the residents of northern Manhattan between 1993 and 2001. The study design and recruitment details of NOMAS have been described previously [16]. NOMAS participants who were ≥50 years old, had no previous diagnosis of stroke and no contraindications to magnetic resonance imaging (MRI) were invited to participate in a brain MRI sub-study from 2003 to 2008. From September 2005 to July 2010, NOMAS-MRI participants who voluntarily agreed to undergo a more extensive cardiovascular evaluation including transthoracic echocardiography were included in the CABL study (n = 1004). From August 2014 to December 2019, NOMAS participants who agreed to undergo a more extensive cardiovascular evaluation were included in the Subclinical Atrial Fibrillation and Risk of Ischemic Stroke (SAFARIS) study (n = 536). Four hundred participants who were enrolled in both CABL and SAFARIS and underwent transthoracic echocardiographic studies at both time points represent the initial study cohort for the present report; of them, 300 had adequate imaging of the aortic arch at both time points and represent the study cohort for the present report. All studies were approved by the institutional review boards of Columbia University and the University of Miami and participants provided informed consent.

2.2. Risk factor assessment

Hypertension was defined as systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg at the time of the visit, or a patient's self-reported history of hypertension or antihypertensive medication use. Diabetes mellitus was defined by the patient's self-report, current use of insulin or hypoglycemic agents, or a fasting blood glucose ≥126 mg/dL on ≥2 occasions in each participant. Hypercholesterolemia was defined as total serum cholesterol >240 mg/dL, a patient's self-report of hypercholesterolemia or the use of lipid-lowering medication. Smoking status was defined as cigarette smoking at any time in the past or present. Body mass index was calculated as: weight/(height)^2 and expressed in kg/m^2.

2.3. Assessment of aortic arch plaques

Transthoracic echocardiography was performed by trained registered sonographers following a standardized protocol with a commercially available system (iE33; Philips Medical Systems, Andover, MA, USA) equipped with a 2.5-MHz to 3.5-MHz transducer. All the tests were stored on digital media for subsequent analysis. Measurements were performed offline using an electronic caliper included in a dedicated echocardiography analysis software (Siemens Syngo Dynamics Workplace, VA2OF_20.0.0.2935). Imaging of the aortic arch was obtained from a suprasternal window. The aortic arch was defined as the portion of the aorta between the curve at the end of the ascending portion and the takeoff of the left subclavian artery. A plaque was defined as a discrete protrusion of the intimal surface of the vessel at least 2 mm in thickness, different in appearance and echogenicity from the adjacent intact intimal surface [17]. The presence of any increase in AAP thickness from the first to the second examination was recorded. Based on the accepted classification of the French Study of Aortic Plaques group, AAP up to 3.9 mm were defined as small and those equal to or greater than 4 mm were defined as large [1]. (Fig. 1). Progression was defined as an increase in AAP thickness on the second TTE of at least 1 mm from baseline. Progression by 1 mm−1.9 mm was defined as mild; progression by 2 mm or greater was defined as severe. All images were interpreted by a single experienced echocardiographer (MDT) blinded to the patients' clinical data and to the results of baseline AAP measurements. Intraobserver variability for AAP measurement was low (correlation coefficient 0.95) [18].

2.4. Statistical analysis

Comparison of the clinical characteristics was performed using the Student t-test for normally distributed continuous variables, the Wilcoxon or Mann-Whitney u test for non-normally distributed variables and the Chi-Square or Fisher's exact test for categorical variables. Sequential multivariable logistic regression models were used to evaluate the association of independent variables with AAP progression: model 1 adjusted for age and sex; model 2 adjusted for variables included in model 1 plus use of anti-hypertensive medications and statin use; model 3 adjusted for variables included in model 2 plus BMI, hypertension, diabetes, hyperlipidemia and time interval between tests. Finally, model 4 was adjusted for parameters associated with AAP progression at $p < 0.20$ on univariable analysis. A p value of <0.05 was considered statistically significant for all analyses. The sample size of 300 subjects achieved 80% power at significance level of 0.05 to detect an odds ratio of 0.723 with the observed 52.3% progression of AAP and the standard deviation of 1.3 mm in the measurement of baseline AAP thickness.

3. Results

300 participants were included in the study. Mean age was 67.8 ± 7.5 years at baseline, and 76.7 ± 6.8 years at follow-up; 197 (65.7%) were women. At baseline assessment, 87 (29%) had no significant AAP, 182 (60.7%) had evidence of small AAP and 31 (10.3%) had evidence of large AAP. Table 1 demonstrates the clinical characteristics of participants without and without AAP at baseline. Subjects with evidence of AAP at baseline were significantly older, more commonly hypertensive and more often receiving medical treatment for hypertension as well as statin therapy.

At the time of follow-up assessment (mean 8.9 ± 2.0 years), 157 (52.3%) of participants exhibited progression of AAP with 70 (23.3%) having mild progression and 87 (29%) having severe progression. Mean AAP thickness in the cohort as a whole was 2.0 ± 1.3 mm at baseline examination and increased at the time of follow up to 3.1 ± 1.0 mm. Significantly greater increase in AAP thickness was observed in subjects with no significant AAP at baseline (Table 1). Table 2 shows characteristics of participants with and with AAP progression. There were no significant demographic or clinical predictors of AAP progression except baseline plaque thickness itself, which was significantly lower in the group with AAP progression.

Table 3 shows the univariable associations of demographic and clinical variables with AAP progression; only AAP thickness at baseline was associated (inversely) with any degree of AAP progression, whereas AAP thickness at baseline, statin treatment and total cholesterol at baseline were inversely associated with severe AAP progression.

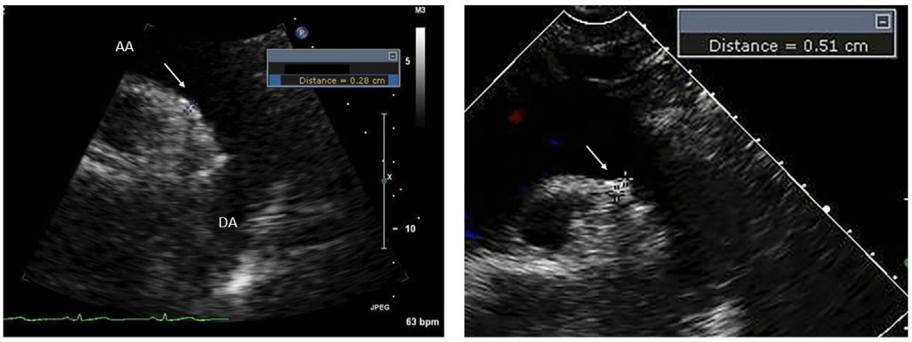

Fig. 1. Example of aortic arch plaque progression.

Table 1
Characteristics of the study cohort according to AAP presence at baseline.

	No AAP (N = 87)	Any AAP (N = 213)	P value
AAP thickness at baseline, mm	0.23 ± 0.42	2.74 ± 0.81	N/A
Age, years	65.0 ± 7.8	69.0 ± 7.0	<0.001
Male sex	26 (29.9)	77 (36.2)	0.300
Time interval, years	9.1 ± 1.8	8.8 ± 2.1	0.262
Body mass index, kg/m^2	29.1 ± 4.5	28.2 ± 4.5	0.105
Systolic blood pressure, mmHg	133 ± 18	136 ± 16	0.182
Diastolic blood pressure, mmHg	80 ± 9	79 ± 9	0.722
Pulse pressure, mmHg	54 ± 13	57 ± 14	0.063
Hypertension	59 (67.8)	171 (80.3)	0.021
Use of anti-hypertensive meds	49 (56.3)	154 (72.3)	0.008
Diabetes mellitus	19 (21.8)	54 (25.4)	0.520
Hypercholesterolemia	54 (62.1)	152 (71.4)	0.115
Statin use at baseline	29 (33.7)	108 (51.9)	0.004
Total cholesterol, mg/dL	193 ± 41	201 ± 38	0.132
LDL cholesterol, mg/dL	118 ± 34	121 ± 34	0.496
HDL cholesterol, mg/dL	53 ± 17	52 ± 17	0.803
Change in AAP thickness, mm	2.41 ± 1.01	0.49 ± 1.24	<0.001
Any AAP progression	81 (93.1)	76 (35.7)	<0.001
Severe AAP progression	60 (69.0)	27 (12.7)	<0.001

Table 2
Characteristics of the study cohort with and without AAP progression.

	No AAP progression (N = 143)	Any AAP progression (N = 157)	P value
AAP thickness at baseline, mm	2.85 ± 0.90	1.25 ± 1.23	<0.001
Age, years	68.5 ± 7.4	67.1 ± 7.5	0.108
Male sex	49 (34.3)	54 (34.4)	0.981
Time interval, years	8.8 ± 2.1	9.0 ± 1.9	0.375
Body mass index, kg/m^2	28.1 ± 4.4	28.8 ± 4.5	0.169
Systolic blood pressure, mmHg	136 ± 16	135 ± 17	0.750
Diastolic blood pressure, mmHg	79 ± 9	79 ± 10	0.775
Pulse pressure, mmHg	57 ± 14	56 ± 13	0.564
Hypertension	109 (76.2)	121 (77.1)	0.863
Use of anti-hypertensive meds	98 (68.5)	105 (66.9)	0.760
Diabetes mellitus	32 (22.4)	41 (26.1)	0.451
Hypercholesterolemia	100 (69.9)	106 (67.5)	0.653
Total cholesterol at baseline, mg/dL	201 ± 37	196 ± 41	0.299
LDL cholesterol at baseline, mg/dL	121 ± 32	119 ± 35	0.601
HDL cholesterol at baseline, mg/dL	51 ± 16	53 ± 18	0.239
Statin therapy at baseline	72 (51.4)	65 (42.4)	0.113

In multivariable logistic regression analysis, AAP thickness at baseline remained a significant negative predictor in all models examined (Table 4).

4. Discussion

Our study demonstrates a high prevalence of AAP on TTE exam in a population-based cohort of older adults with a high incidence of AAP progression, particularly in participants without significant AAP at baseline. TTE appears to be a useful test for baseline and follow up imaging of AAP in particular in patients without evidence of AAP on initial imaging.

Most previous studies examining AAP progression generally studied patients referred for TEE for clinical evaluation, possibly leading to bias [10]. It is important to note that previous studies have shown a good correlation between assessment of AAP using

Table 3
Univariable associations between clinical variables and any AAP progression or severe AAP progression in the entire cohort.

	Any AAP progression[a]		Severe AAP progression[b]	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age, per year	0.98 (0.94–1.01)	0.106	1.00 (0.96–1.03)	0.805
Male sex	1.01 (0.62–1.62)	0.981	1.25 (0.74–2.10)	0.402
Time interval	1.05 (0.95–1.18)	0.373	0.96 (0.85–1.09)	0.534
Body mass index, kg/m^2	1.04 (0.98–1.09)	0.167	1.04 (0.98–1.09)	0.215
Systolic blood pressure, mmHg	1.00 (0.98–1.01)	0.749	1.00 (0.99–1.02)	0.611
Diastolic blood pressure, mmHg	1.00 (0.98–1.03)	0.774	1.02 (0.99–1.05)	0.155
Pulse pressure, mmHg	1.00 (0.98–1.01)	0.562	1.00 (0.98–1.02)	0.749
Hypertension	1.05 (0.61–1.79)	0.863	1.24 (0.68–2.27)	0.490
Use of anti-hypertensive meds	0.93 (0.57–1.51)	0.760	0.94 (0.55–1.59)	0.813
Diabetes mellitus	1.23 (0.72–2.08)	0.452	1.39 (0.79–2.44)	0.257
Hypercholesterolemia	0.89 (0.55–1.46)	0.653	0.66 (0.39–1.11)	0.117
Statin therapy at baseline	0.69 (0.44–1.09)	0.114	0.58 (0.35–0.97)	0.039
Total cholesterol at baseline, mg/dL	1.00 (0.99–1.003)	0.297	0.99 (0.98–0.999)	0.026
LDL cholesterol at baseline, mg/dL	1.00 (0.99–1.01)	0.600	1.00 (0.99–1.004)	0.320
HDL cholesterol at baseline, mg/dL	1.01 (0.99–1.02)	0.236	0.99 (0.98–1.01)	0.511
AAP thickness at baseline, mm	0.26 (0.19–0.36)	<0.001	0.26 (0.20–0.35)	<0.001

AAP = aortic arch plaque, CI = 95% confidence interval, HDL = high-density lipoprotein, and LDL = low-density lipoprotein.
[a] Compared with no AAP progression.
[b] Compared with no plus mild AAP progression.

Table 4
Association of AAP thickness at baseline with AAP progression - Multivariable analyses.

	Any AAP progression[a]		Severe AAP progression[b]	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Model 1	0.24 (0.17–0.34)	<0.001	0.20 (0.14–0.29)	<0.001
Model 2	0.24 (0.17–0.34)	<0.001	0.20 (0.14–0.29)	<0.001
Model 3	0.24 (0.17–0.33)	<0.001	0.19 (0.13–0.28)	<0.001
Model 4	0.25 (0.18–0.34)	<0.001	0.27 (0.20–0.37)	<0.001

Model 1: adjusted for age and sex.
Model 2: adjusted for variables as in Model 1 plus anti-hypertensive medication and statin.
Model 3: adjusted for variables as in Model 2 plus baseline body mass index, hypertension, diabetes, hyperlipidemia and interval time.
Model 4: adjusted for parameters associated with AAP progression at $p < 0.20$ in univariable analyses.
[a] Compared with no AAP progression.
[b] Compared with no plus mild AAP progression.

TTE and TEE. For example, in a study of 89 patients, Schwammenthal et al. noted positive and negative predictive values of 91% and 98% for detection of AAP using TTE as compared to TEE [14]. To the authors' knowledge, only one previous study utilized TTE to examine AAP at baseline and with follow up. Geraci and Weinberger performed a small longitudinal study of 89 patients referred for evaluation of neurological symptoms with a limited mean follow up of 7 months [15]. Despite the relatively short follow up, 14% of subjects had progression of AAP, a finding that appears consistent with the 52% progression noted in our study with much longer follow up. Also consistent with our study in a more general population, a high incidence of AAP was noted at baseline with only 16 (18%) subjects having a normal aortic arch. Risk factors for AAP progression were not reported. Interestingly, 7 patients with a normal arch at baseline developed arch disease at follow up, a finding again potentially consistent with our study, as it suggested that no disease at baseline could still be associated with a high incidence of disease progression.

Our findings that age and a history of hypertension were associated with AAP at baseline is consistent with previous studies [6–9] Risk factors for progression of AAP have been more difficult to identify and appear to be distinct from risk factors associated with the incidence of AAP both in our study and previous studies [10,11]. This finding may be considered to be analogous to aortic stenosis, where risk factors for initiation of the valve disease appear to be distinct from risk factors associated with its progression [19]. Our finding of an inverse relationship between baseline AAP thickness and progression of AAP is novel. The reasons for this finding are unclear. Participants with AAP at baseline received more statin and antihypertensive therapy and it is possible that this more aggressive medical treatment contributed to relative lack of AAP progression in this group. In contrast to our findings, Izumi et al. noted that moderate or severe aortic plaques at baseline were predictive of progression [11]. Their study, unlike ours, examined patients using TEE and evaluated plaque in the descending aorta. It retrospectively analyzed patients who were referred for follow up TEE for clinical indications and was not a prospective community-based population. In addition, a high percentage of patients in the Izumi et al. study were receiving anticoagulation, which may have affected the natural history of plaque progression.

The strengths of our study include the relatively large number of subjects with extended follow up. All measurements were performed blinded by an experienced echocardiographer. The main limitation of the study is the performance of serial imaging in only a subset of the main trial; however, selection bias appears unlikely. We cannot rule out the possibility that regression to the mean played a role in our findings of a negative association between baseline AAP thickness and AAP progression over time, as larger AAPs at baseline are more likely to be affected by regression to the mean than smaller ones; also, the study may have been underpowered to detect associations with AAP progression of other risk factors. Finally, the study was not powered to examine associations between echocardiographic findings and clinical events, an important topic for future studies.

In conclusion, older adults have a high frequency and progression over time of AAP, and TTE is a useful imaging technique for their assessment and monitoring. The absence of baseline AAP in this age group is not indicative of low risk and does not exclude the possibility of future development of significant AAP. Future studies are necessary to better understand factors associated with AAP progression and therefore possible preventive strategies.

Financial support

This work was supported by grants from the National Institute of Neurological Disorders and Stroke (grants R01 NS36286 to Dr. Di Tullio and R01 NS29993 to Dr Elkind).

Author contributions

DL, YY and MDT contributed to the conception or design of the work. ZJ, SH, MSE, and TR contributed to the acquisition, analysis, or interpretation of data for the work. DL drafted the manuscript. YY, ZJ, CM, SH, KN, DL, MSE, TR, and MDT critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

The Authors wish to honor the memory of Dr. Ralph L. Sacco, founder of the NOMAS study, for his enormous knowledge, support and invaluable contributions to research over the years.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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