Association of Vascular Physical Examination Findings and Arteriographic Lesions in Large Vessel Vasculitis

PETER C. GRAYSON, GUNNAR TOMASSON, DAVID CUTHBERTSON, SIMON CARETTE, GARY S. HOFFMAN, NADER A. KHALIDI, CAROL A. LANGFORD, CAROL A. McALEAR, PAUL A. MONACH, PHILIP SEO, KENNETH J. WARRINGTON, STEVEN R. YTTERBERG, and PETER A. MERKEL, and the Vasculitis Clinical Research Consortium

ABSTRACT. ***Objective.*** To assess the utility of the vascular physical examination to detect arteriographic lesions in patients with established large vessel vasculitis (LVV), including Takayasu's arteritis (TAK) and giant cell arteritis (GCA).

Methods. In total, 100 patients (TAK = 68, GCA = 32) underwent standardized physical examination and angiography of the carotid, subclavian, and axillary arteries. Sensitivity and specificity were calculated for the association between findings on physical examination focusing on the vascular system (absent pulse, bruit, and blood pressure difference) and arteriographic lesions defined as stenosis, occlusion, or aneurysm.

Results. We found 67% of patients had at least 1 abnormality on physical examination (74% TAK, 53% GCA). Arteriographic lesions were seen in 76% of patients (82% TAK, 63% GCA). Individual physical examination findings had poor sensitivity (range 14%–50%) and good-excellent specificity (range 71%–98%) to detect arteriographic lesions. Even when considering physical examination findings in combination, at least 30% of arteriographic lesions were missed. Specificity improved (range 88%–100%) if individual physical examination findings were compared to a broader region of vessels rather than specific anatomically correlated vessels and if ≥ 1 physical examination findings were combined.

Conclusion. In patients with established LVV, physical examination alone is worthwhile to detect arterial disease but does not always localize or reveal the full extent of arteriographic lesions. Abnormal vascular system findings on physical examination are highly associated with the presence of arterial lesions, but normal findings on physical examination do not exclude the possibility of arterial disease. Serial angiographic assessment is advisable to monitor arterial disease in patients with established LVV.
(First Release Dec 15 2011; J Rheumatol 2012;39:303–9; doi:10.3899/jrheum.110652)

Key Indexing Terms:
VASCULITIS TAKAYASU'S ARTERITIS GIANT CELL ARTERITIS
ANGIOGRAM PHYSICAL EXAMINATION

Large vessel vasculitis (LVV) is a group of chronic inflammatory diseases that affect the aorta and its primary branches, resulting in luminal stenosis, vessel occlusion, and/or aneurysmal changes in the large arteries. The 2 most common forms of LVV are Takayasu's arteritis (TAK) and giant cell arteritis (GCA). Despite ethnic, demographic, and clinical differences between TAK and GCA, these disorders share similar arterial histiologic abnormalities and may represent a spectrum of the same disease[1]. Vascular pathology evidenced by arteriographic lesions in the aorta and its primary branch-

From the Vasculitis Center, Section of Rheumatology, and the Clinical Epidemiology Unit, Boston University School of Medicine, Boston, Massachusetts; Department of Biostatistics, University of South Florida, Tampa, Florida; Division of Rheumatology, Mount Sinai Hospital, Toronto, Ontario, Canada; Center for Vasculitis Care and Research, Cleveland Clinic, Cleveland, Ohio; Division of Rheumatology, St. Joseph's Healthcare, McMaster University, Hamilton, Ontario, Canada; Division of Rheumatology, Johns Hopkins University, Baltimore, Maryland; and the Division of Rheumatology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA.

Supported by the Vasculitis Clinical Research Consortium, which has received support from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (U54AR057319 and U01 AR51874 04), the National Center for Research Resources (U54 RR019497), and the Office of Rare Diseases Research. Dr. Grayson receives support from an NIH Training Program in Rheumatic Disease grant (AR 007598).

P.C. Grayson, MD, MSc; G. Tomasson, MD, Vasculitis Center, Section of Rheumatology, and the Clinical Epidemiology Unit, Boston University School of Medicine; D. Cuthbertson, MS, Department of Biostatistics, University of South Florida; S. Carette, MD, FRCPC, Division of Rheumatology, Mount Sinai Hospital; G.S. Hoffman, MD, MS, Center for Vasculitis Care and Research, Cleveland Clinic; N.A. Khalidi, MD, FRCPC, Division of Rheumatology, St. Joseph's Healthcare, McMaster University; C.A. Langford, MD, MHS, Center for Vasculitis Care and Research, Cleveland Clinic; C.A. McAlear, MA; P.A. Monach, MD, PhD, Vasculitis Center, Section of Rheumatology, and the Clinical Epidemiology Unit, Boston University School of Medicine; P. Seo, MD, MHS, Division of Rheumatology, Johns Hopkins University; K.J. Warrington, MD; S.R. Ytterberg, MD, Division of Rheumatology, Mayo Clinic College of Medicine; P.A. Merkel, MD, MPH, Vasculitis Center, Section of Rheumatology, and the Clinical Epidemiology Unit, Boston University School of Medicine.

Address correspondence to Dr. P.A. Merkel, Vasculitis Center, Section of Rheumatology, Boston University School of Medicine, E533, 72 East Concord St., Boston, MA 02118, USA. E-mail: pmerkel@bu.edu

Accepted for publication September 15, 2011.

es is a universal feature of TAK. Although GCA is often classified on the basis of involvement of the extracranial branches of the carotid arteries, disease in the aorta and its primary branches occurs in a subset of patients with GCA, with an estimated prevalence of radiographic aortitis of at least 20%[2,3,4] and radiographic involvement of arterial branches of the aorta occurring in 10%–70% of cases[5,6].

The vascular physical examination is considered paramount in clinical assessment of patients with established LVV, including both TAK and GCA. Pulse assessment, bruit auscultation, and blood pressure readings are regularly performed at each clinic visit. However, it is unknown to what extent abnormalities detected on vascular physical examinations are reflective of underlying arterial disease using angiography as the "gold standard." New arteriographic lesions in the absence of obvious clinical signs of active disease have been reported in longitudinal studies of patients with TAK[7]. Nevertheless, recent guidelines for the management of patients with established LVV recommended that monitoring for treatment response and diagnosing relapse should be based primarily on clinical assessment, and suggested that the role for periodic angiography to assess disease activity is less clear[8]. Although there are recognized limitations of angiography to assess disease activity[9], serial angiography of the aorta and primary branches in patients with established LVV is often recommended as standard clinical practice to assess ongoing arterial damage[10].

The disagreement regarding the role of serial angiography in patients with LVV in part reflects a lack of evidence of the association between clinical and radiographic assessments in LVV. While the nature and frequency of both abnormalities on vascular physical examination and arteriographic lesions have been described in cohorts of TAK[7,11,12,13,14,15,16,17,18] and GCA[1,3,19], a direct comparison of findings on physical examination to findings on angiography has not been reported in patients with TAK or GCA.

The impetus for this study was to inform clinicians about the relative value of the components of the vascular physical examination in detecting arteriographic lesions in patients with established LVV. While it is unclear whether angiography should be used to screen for thoracic and abdominal arterial disease in patients with newly diagnosed GCA, our objective was not to assess angiography as a screening tool for arterial disease but rather to examine the association of the vascular physical examination and angiography, 2 commonly used modes of clinical assessment in LVV.

MATERIALS AND METHODS

Subject selection. Patients with TAK and GCA enrolled in a longitudinal observational cohort within the Vasculitis Clinical Research Consortium (VCRC; Boston University School of Medicine, Boston, MA, USA; Website: www.RareDiseasesNetwork.org/VCRC) were eligible for participation. The VCRC is an international, multicenter research infrastructure, supported by the US National Institutes of Health, dedicated to conducting clinical research in different forms of vasculitis. Patients with TAK are eligible for inclusion in the VCRC longitudinal cohort if they fulfill the American College of Rheumatology (ACR) criteria for classification of TAK[20] and have arteriographic abnormalities compatible with TAK. Patients with GCA are eligible if they fulfill a modified application of the ACR criteria for classification of GCA[21] including age at disease onset > 50 years (required) and have at least 1 of the other 4 classification criteria or have evidence of LVV by angiogram or biopsy. Patients are excluded from participation in the VCRC longitudinal cohort if arteriographic lesions are felt to be due to atherosclerosis, fibromuscular dysplasia, Cogan's syndrome, Behçet's disease, Kawasaki disease, sarcoidosis, or an infectious form of LVV.

Within the VCRC cohort, patients with TAK routinely undergo serial angiography of the aorta and its primary branches. Patients with GCA undergo angiography presumably if there is clinical suspicion for extracranial arterial disease, although information on specific reasoning for obtaining an angiogram was unavailable.

Between 2006 and 2010, all patients with TAK or GCA in the VCRC cohort who underwent standardized physical examination and had an angiogram of the aorta and its primary branches within 3 months of the physical examination were included in this analysis. Patients who previously underwent surgical vascular intervention including angioplasty, stenting, graft placement, or bypass were excluded from analysis.

Data collection. Baseline demographic information was recorded for each subject including age, sex, race, ethnicity, disease duration, age at onset of disease, study site location, and type of angiogram. Disease onset was defined as the date of initial identification of vascular symptoms that were subsequently determined to be compatible with LVV and not attributable to comorbid conditions.

Analysis focused on the common carotid, subclavian, and axillary arteries, where the dataset was most complete and where disease prevalence is known to be high in LVV[7]. Patients underwent a standardized vascular physical examination performed by experienced clinicians with expertise in LVV. Pulse assessment defined as absent or present was recorded for the radial and carotid arteries. The carotid and subclavian arteries were auscultated for the presence or absence of bruits. Systolic blood pressure was measured in both arms with a sphygmomanometer. The presence or absence of upper extremity claudication was recorded at all study visits. All patients underwent either a magnetic resonance, computerized tomographic, or catheter-based angiogram of the aorta and its primary branches. Angiograms were assessed both by clinical radiologists and by study investigators at each participating institution. Arteriographic lesions, defined as stenosis, occlusion, or aneurysm, were recorded using standardized data collection forms. A study visit to record physical examination findings was linked to an angiogram performed within 3 months of the physical examination. For patients who had multiple study visits, the most recent visit with an associated angiogram was selected.

Analytic methods. The prevalence of each physical examination finding abnormality (absent pulse, bruit, blood pressure difference) was calculated in the total cohort and separately in the TAK and GCA subgroups. The prevalence of each type of angiographic abnormality for each vessel of interest was calculated in the total cohort and separately in the TAK and GCA subgroups. Proportions were compared using Fisher's exact test.

The association between physical examination and arteriographic findings was tested in the entire cohort and in disease subgroups. For each artery of interest, sensitivity and specificity were calculated for the association between relevant physical examination findings and the presence of arterial lesions. To determine whether physical examination findings accurately localized arterial lesions, a physical examination finding (e.g., left subclavian bruit) was compared to angiogram findings both in the anatomically correlated vessel (e.g., left subclavian artery) and in all vessels within the region (carotid or subclavian or axillary arteries). To determine an optimal clinical approach to the physical examination, sensitivity and specificity were calculated for the association between combinations of physical examination findings and the presence of angiographic lesions in each artery of interest.

Regression analysis was used to assess the relative value of 3 different

components of the physical examination (pulse assessment, bruit auscultation, and inter-arm systolic blood pressure difference) to predict the presence of anatomically correlated arteriographic lesions. Because analysis was restricted to the common carotid, subclavian, and axillary arteries, each study participant could contribute up to 6 outcome measures. To account for clustered data within patients, we performed logistic regression using generalized estimated equations and specified a Poisson distribution[22] to calculate prevalence ratios for the association between the examination component and the presence of arteriographic lesions.

All statistical analyses were done using SAS 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Subject characteristics. One hundred patients (TAK = 68, GCA = 32) recruited from 6 study sites were included for analysis. Baseline demographic data are recorded in Table 1. Most of the study patients were women (92%) and white (87%). The mean ages of the participants were 40 years (TAK) and 68 years (GCA). The average disease duration was 8.7 years (TAK) and 2.9 years (GCA). The majority of patients underwent magnetic resonance angiography (82%), although some patients underwent computed tomographic angiography (16%) or catheter-based angiography (2%).

Physical examination findings. Sixty-seven percent of the total cohort (74% TAK, 53% GCA) had at least 1 physical examination abnormality. Prevalence of the 3 physical examination components was similar (bruit 46%; ≥ 15 mm Hg systolic blood pressure difference 45%; and absent pulse 40%) among patients with LVV. Frequencies of examination findings are detailed in Table 2.

Angiogram findings. All 68 patients with TAK had at least 1 arteriographic lesion detected in the aorta or its primary branches. An angiogram was performed in 32 (21%) of 150 patients with GCA within the VCRC observational cohort. Twenty-four (75%) patients with GCA had at least 1 arteriographic abnormality in the aorta or its primary branches, and 7 of the 15 patients with GCA who did not have a recorded vascular physical examination abnormality had at least 1 arteriographic lesion. There was a significant difference between sex and the presence of arteriographic disease in patients with GCA: all patients with GCA who had extracranial, arteriographic disease were women, whereas female prevalence was 80% among patients with GCA within the total VCRC observational cohort (p = 0.004).

When analysis focused on the common carotid, subclavian, or axillary arteries, 76% of patients with LVV (82% TAK, 63% GCA) had at least 1 arteriographic lesion. Luminal stenosis (72%) was the most common type of arterial lesion, followed by vessel occlusion (14%) and aneurysm (3%). The left subclavian was the most commonly affected single artery in patients with TAK (70%). Axillary artery disease was more prevalent in GCA compared to TAK (left: 42% vs 22%, respectively; p = 0.069; right: 43% vs 12%; p = 0.005). Notably, the left axillary artery in 11 patients and the right axillary artery in 4 patients could not be accurately assessed due to stenosis or occlusion of the adjacent distal subclavian artery, preventing adequate inflow of contrast material into the axillary artery. Otherwise, any missing angiographic data were due to incomplete visualization of the entire artery. The frequencies of arterial lesions are detailed in Table 3.

Sensitivity/specificity of physical examination and angiogram findings for arterial lesions. Individual physical examination findings had poor sensitivity (range 14%–50%) and good-excellent specificity (range 71%–98%) to detect angiographic lesions in the anatomically correlated artery of interest. If individual physical examination findings were compared to a group of regional arteries rather than to a single anatomically correlated artery, sensitivity worsened (range 7%–30%) and specificity improved (range 91%–100%). Sensitivity improved (range 52%–70%) and specificity worsened (range 59%–85%) if any of the 3 findings of the peripheral vascular examination (absent pulse or bruits or ≥ 15 mm Hg inter-arm systolic blood pressure difference) considered in combination were abnormal. Sensitivity worsened (range 6%–25%) and specificity improved (range 93%–100%) if 2 or

Table 1. Baseline demographics of study patients.

Variable	Total, n = 100	Takayasu's Arteritis, n = 68	Giant Cell Arteritis, n = 32
Age, yrs, mean (range)	49.7 (9–89)	40.1 (9–60)	68.7 (55–89)
Sex (% female)	92/100 (92)	64/68 (94)	28/32 (88)
Race (%)			
White	87/100 (87)	58/68 (85)	29/32 (91)
Asian	6/100 (6)	5/68 (7)	1/32 (3)
Black	6/100 (6)	5/68 (7)	2/32 (6)
Unknown	1/100 (1)	1/68 (1)	0
Age at onset, yrs, mean (± SD)	44.3 (± 20.5)	33.6 (± 13.6)	66.6 (± 7.1)
Disease duration, yrs, mean (range)	6.7 (0–31)	8.7 (0–31)	2.9 (0–13)
Type of angiogram (%)			
Magnetic resonance	82/100 (82)	59/68 (87)	23/32 (72)
Computed tomography	16/100 (16)	7/68 (10)	9/32 (28)
Catheter-based	2/100 (2)	2/68 (3)	0

Table 2. Frequency of vascular physical examination findings.

Examination Findings	Total (%)	Takayasu's Arteritis (%)	Giant Cell Arteritis (%)
Absent pulse (any)	40/100 (40)	26/68 (41)	12/32 (38)
Carotid			
Left	7/100 (7)	4/68 (6)	3/32 (9)
Right	3/100 (3)	2/68 (3)	1/32 (3)
Radial			
Left	29/99 (29)	21/68 (31)	8/31 (25)
Right	20/100 (20)	11/68 (16)	9/32 (28)
Bruit (any)	46/100 (46)	37/68 (54)	9/32 (28)
Carotid			
Left	21/100 (21)	20/68 (29)	1/32 (3)
Right	24/99 (24)	20/68 (29)	4/31 (13)
Subclavian			
Left	28/100 (28)	22/100 (22)	6/32 (19)
Right	16/100 (16)	12/68 (18)	4/32 (13)
BP difference, mm Hg*			
≥ 10	52/98 (53)	39/67 (58)	13/31 (42)
≥ 15	44/98 (45)	35/67 (52)	9/31 (29)
≥ 20	40/98 (41)	32/67 (48)	8/31 (26)
Any examination abnormality	67/100 (67)	50/68 (74)	17/32 (53)

* Difference in systolic blood pressure between arms.

Table 3. Frequency of arteriographic lesions by vessel and lesion type.

Arterial Lesion	Total	Takayasu's Arteritis	Giant Cell Arteritis
Left common carotid (%)	24/90 (27)	20/62 (32)	4/28 (14)
Stenosis	22	18	4
Occlusion	2	2	0
Aneurysm	0	0	0
Right common carotid (%)	18/89 (20)	15/61 (25)	3/25 (11)
Stenosis	17	14	3
Occlusion	1	1	0
Aneurysm	0	0	0
Left subclavian (%)	64/96 (67)	46/66 (70)	18/30 (60)
Stenosis	53	36	17
Occlusion	10	10	0
Aneurysm	1	0	1
Right subclavian (%)	47/95 (49)	31/66 (47)	16/29 (55)
Stenosis	42	26	16
Occlusion	4	4	0
Aneurysm	1	1	0
Left axillary (%)	23/81 (28)	12/55 (22)	11/26 (42)
Stenosis	19	10	9
Occlusion	3	1	2
Aneurysm	1	1	0
Right axillary (%)	19/86 (22)	7/58 (12)	12/28 (43)
Stenosis	17	6	11
Occlusion	2	1	1
Aneurysm	0	0	0
Left subclavian/axillary (%)	65/98 (66)	46/67 (69)	19/31 (61)
Stenosis	55	37	18
Occlusion	13	11	2
Aneurysm	2	0	1
Right subclavian/axillary (%)	48/97 (49)	31/66 (47)	17/31 (55)
Stenosis	54	36	18
Occlusion	5	4	1
Aneurysm	1	1	0
Stenosis in any vessel (%)	72/100 (72)	53/68 (78)	19/32 (59)
Occlusion in any vessel (%)	14/100 (14)	12/68 (18)	2/32 (6)
Aneurysm in any vessel (%)	3/100 (3)	2/68 (3)	1/32 (3)
Any type of arterial lesion in any vessel (%)	76/100 (76)	56/68 (82)	20/32 (63)

more of the physical examination findings were abnormal. These findings are summarized in Table 4.

When stratified by disease subgroup (TAK or GCA), similar patterns of association between physical examination and arteriographic findings were observed. Although analyses were restricted to common carotid, subclavian, and axillary arteries, repeat analyses with inclusion of angiographic data from the branchiocephalic artery, ascending aorta, and aortic arch did not significantly change the results (data not shown).

Value of examination components. Abnormalities in all 3 examination components (pulse assessment, bruit auscultation, inter-arm systolic blood pressure difference) were significantly associated with the presence of arteriographic arterial lesions (Table 5). Absent pulse had the largest risk estimate for the presence of arterial lesions (prevalence ratio 2.73, 95% CI 2.02 to 3.69), followed by bruit (prevalence ratio 1.74, 95% CI 1.25 to 2.45) and inter-arm systolic blood pressure difference (prevalence ratio 1.39, 95% CI 1.04 to 1.86). In a multivariate model with all 3 examination components included, absent pulse (prevalence ratio 2.38, 95% CI 1.69 to 3.38) and

Table 4. Association of physical examination findings and angiographic arterial lesions.

Physical Examination Findings	Angiogram Comparison Vessel	No.	Sensitivity, %	Specificity, %
Individual examination findings with anatomically correlated vessel				
Absent Pulse				
Common carotid	Ipsi CC	179	14	98
Radial	Ipsi SA	193	40	94
Bruit				
Common carotid	Ipsi CC	179	45	82
Subclavian	Ipsi S	191	27	91
Blood pressure				
BP difference	Bilat SA	96	50	71
Combined examination findings with anatomically correlated vessel (any 1 abnormal)				
Carotid bruit no carotid pulse	Ipsi CC	179	52	80
Subclavian bruit no radial pulse	Ipsi SA	195	53	85
Subclavian bruit BP difference	Ipsi SA	195	64	59
No radial pulse BP difference	Ipsi SA	195	63	61
Subclavian bruit BP difference no radial pulse	Ipsi SA	195	70	59
Individual examination findings with regional correlated vessels (unilateral and bilateral)				
Absent pulse				
Common carotid	Ipsi CC/SA	195	7	99
Common carotid	Bilat CC/S	196	7	100
Bruit				
Common carotid	Ipsi CC/SA	194	30	88
Common carotid	Bilat CC/S	195	27	91
Subclavian	Ipsi CC/SA	195	30	91
Subclavian	Bilat CC/S	196	29	98
Combined examination findings with anatomically correlated vessel (2 or more abnormal)				
Carotid bruit no carotid pulse	Ipsi CC	179	7	100
Subclavian bruit no radial pulse	Ipsi SA	195	14	98
Subclavian bruit BP difference	Ipsi SA	195	13	93
No radial pulse BP difference	Ipsi SA	195	25	95
Subclavian bruit BP difference no radial pulse	Ipsi SA	195	6	99

BP: blood pressure; Ipsi: ipsilateral; Bilat: bilateral; CC: common carotid; SA: subclavian/axillary; S: subclavian; BP difference: systolic blood pressure difference between arms.

Table 5. Prevalence ratios for 3 physical examination components. Multivariate analyses are adjusted for the other respective physical examination components.

Examination Component Findings	Univariate Analysis Prevalence Ratio (95% CI)	p	Multivariate Analysis Prevalence Ratio (95% CI)	p
Absent pulse	2.73 (2.02–3.69)	< 0.001	2.38 (1.69–3.38)	< 0.001
Bruit present	1.74 (1.25–2.45)	0.0011	1.51 (1.08–2.13)	0.0174
≥ 15 mm Hg BP difference	1.39 (1.04–1.86)	0.0272	1.18 (0.86–1.63)	0.3133

BP difference: systolic blood pressure difference between arms.

bruit (prevalence ratio 1.51, 95% CI 1.08 to 2.13) were significantly associated with the presence of arterial lesions, while ≥ 15 mm Hg systolic blood pressure difference (prevalence ratio 1.18, 95% CI 0.86 to 1.63) was not a significant predictor of arterial disease.

Claudication compared to vascular physical examination. Left arm claudication was present in 43/90 patients (48%), and right arm claudication was present in 33/90 patients (37%). A history of upper extremity claudication was 60% sensitive and 85% specific to detect angiographic lesions involving either the ipsilateral subclavian or axillary arteries. Assessment of claudication in combination with the vascular physical examination did not further improve the performance characteristics of the physical examination.

DISCUSSION

This study examined the association of vascular physical examination findings with angiographic findings in a cohort of 100 patients with established LVV, including TAK (n = 68) and GCA (n = 32). Vascular physical examination findings had low sensitivity but high specificity in detecting arteriographic disease. Abnormal physical examination findings were highly associated with the presence of arterial lesions, but normal physical examination findings did not rule out the possibility of arterial disease. Even when considering physical examination findings in combination, at least 30% of arteriographic lesions were missed. Specificity of examination findings in detecting arterial disease improved when physical examination findings were evaluated in association with a broader region of arterial lesions rather than a specific anatomically correlated vessel, suggesting that examination findings did not always accurately localize disease. Among the individual examination components, absent pulse was more predictive of arterial lesions than bruits or ≥ 15 mm Hg inter-arm systolic blood pressure differences. The presence of claudication was more sensitive but less specific than individual physical examination findings to detect arterial disease in the upper extremities. However, claudication assessment did not improve upon the combination of physical examination findings to detect arterial disease. While valuable in the assessment of arterial disease in patients with established LVV, the physical examination should not form the sole basis of assessment for arterial lesions and should be supplemented by angiography.

Patient selection for participation in this study, particularly with respect to GCA, merits further discussion. Only 32 out of 150 patients with GCA within the VCRC observational cohort underwent angiography. Because patients with GCA in the VCRC cohort underwent angiography presumably on the basis of underlying clinical suspicion for large vessel disease, this study does not provide direct evidence for or against screening for large vessel disease in patients with GCA. However, 7 of the 15 patients with GCA who did not have a recorded vascular physical examination abnormality had an arterial lesion on angiography. Additionally, that only a subset of patients with GCA underwent angiography may have affected the prevalence and extent of arterial disease in the GCA subgroup (verification bias). The direction of any such bias is difficult to interpret given the correlated structure of the dataset. However, with respect to the association of vascular physical examination findings and angiographic findings, similar patterns of association were observed in the GCA and TAK subgroups. Given that issues of verification bias were not applicable in the TAK subgroup, it seems appropriate to have confidence in the same results in the GCA subgroup.

This study has some other limitations to consider. This was a study of patients with established LVV and thus the patterns of association between physical examination and arteriographic findings may not necessarily be applicable in a diagnostic setting. Similarly, by focusing analysis on the common carotid, subclavian, and axillary arteries, the findings may not be generalizable to other vessels. Changes in the vessel wall, e.g., thickening and contrast enhancement, were not incorporated into the definition of arteriographic disease, and if included, sensitivity of examination findings to detect arterial disease would likely have been even lower. However, the prognostic importance of arterial wall abnormalities in the absence of stenosis in LVV is uncertain. The degree of arterial stenosis was not quantified, and the performance characteristics of the physical examination could differ according to the degree of arterial stenosis. Variability of data quality may have occurred due to the collection of data at multiple study sites; however, the physical examination assessments were performed by experienced clinicians with expertise in vasculitis using standardized data collection forms, thus reducing potential inter-examiner variability. Further, the data elements collected were mostly simple dichotomous variables ("absent" or "present" pulses or bruits) or standardized blood pressure readings. Examining physicians were potentially not blinded to angiographic findings that may have biased the association with the physical examination toward higher sensitivity and specificity.

The main strength of this study is that it addresses a series of questions about the relative utility of physical examinations and angiograms for assessment of LVV, issues of interest to both clinicians and researchers in vasculitis. It is not surprising that the physical examination is less sensitive than angiography for detecting arterial disease and is fairly specific when abnormalities are present. However, quantifying the strengths and limitations of the various components of the vascular physical examination in relationship to comparative angiography provides a deeper understanding of the association between these 2 commonly used complementary modes of clinical assessment in LVV. Other strengths include use of a large cohort of patients with a rare disease, evaluation at several centers with expertise in clinical research and management of LVV, and the use of standardized data collection forms with a centralized database.

This study also provides comparative demographic, clinical, and angiographic findings in patients with TAK and a subset of patients with GCA and large vessel involvement sampled from within the same cohort, and allows comparisons to existing descriptive data from other cohorts of patients with TAK and GCA. Ninety-two percent of patients with TAK in our study were women, which is similar to other reports of > 90% female preponderance in TAK[7,11]. The overall reported sex prevalence ratio in GCA is 2:1 female to male[23]. In our study, 100% of patients with GCA who had extracranial, ateriographic lesions were women, a significant association even considering that 88% of patients with GCA within the VCRC cohort were women. An association between female sex and large vessel disease has similarly been reported in other studies of GCA[19,24], and this degree of female preponderance is interestingly similar to that seen in TAK. Luminal stenosis, compared to vessel occlusion and aneurysmal formation, was overwhelmingly the most commonly observed type of arteriographic lesion, a finding consistent with other reports in both TAK[7,11,12,18] and GCA[19]. The prevalence of subclavian disease was high in both TAK and GCA and, as reported in several other cohorts, the highest prevalence of arterial disease in the primary branches of the aorta was found in the left subclavian artery in patients with TAK[7,11,13,16,18]. Consistent with previous angiographic[1] and ultrasonographic[24] studies, axillary artery disease was more prevalent in patients with GCA than in those with TAK.

In patients with established LVV, the physical examination alone is worthwhile to assess the presence of arterial disease but does not reveal the full extent of arterial lesions seen on comparative angiography. Use of angiography as a supplement to the vascular physical examination and complete large vessel imaging with branch vessels rather than focal imaging at the site of physical examination findings are advisable to monitor arterial disease in patients with established LVV.

REFERENCES

1. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Takayasu arteritis and giant cell arteritis: A spectrum within the same disease? Medicine 2009;88:221-6.
2. Garcia-Martinez A, Hernandez-Rodriguez J, Arguis P, Paredes P, Segarra M, Lozano E, et al. Development of aortic aneurysm/dilatation during the followup of patients with giant cell arteritis: A cross-sectional screening of fifty-four prospectively followed patients. Arthritis Rheum 2008;59:422-30.
3. Cid MC, Prieto-Gonzalez S, Arguis P, Espigol-Frigole G, Butjosa M, Hernandez-Rodriguez J, et al. The spectrum of vascular involvement in giant-cell arteritis: clinical consequences of detrimental vascular remodelling at different sites. APMIS Suppl 2009;127:10-20.
4. Nuenninghoff DM, Hunder GG, Christianson TJ, McClelland RL, Matteson EL. Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. Arthritis Rheum 2003;48:3522-31.
5. Walter MA, Melzer RA, Schindler C, Muller-Brand J, Tyndall A, Nitzsche EU. The value of [18F]FDG-PET in the diagnosis of large-vessel vasculitis and the assessment of activity and extent of disease. Eur J Nucl Med Mol Imaging 2005;32:674-81.
6. Blockmans D, de Ceuninck L, Vanderschueren S, Knockaert D, Mortelmans L, Bobbaers H. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: A prospective study of 35 patients. Arthritis Rheum 2006;55:131-7.
7. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. Arthritis Rheum 2007;56:1000-9.
8. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2009;68:310-7.
9. Tso E, Flamm SD, White RD, Schvartzman PR, Mascha E, Hoffman GS. Takayasu arteritis: utility and limitations of magnetic resonance imaging in diagnosis and treatment. Arthritis Rheum 2002;46:1634-42.
10. Pipitone N, Versari A, Salvarani C. Role of imaging studies in the diagnosis and follow-up of large-vessel vasculitis: An update. Rheumatology 2008;47:403-8.
11. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottern M, et al. Takayasu arteritis. Ann Intern Med 1994;120:919-29.
12. Vanoli M, Daina E, Salvarani C, Sabbadini MG, Rossi C, Bacchiani G, et al. Takayasu's arteritis: A study of 104 Italian patients. Arthritis Rheum 2005;53:100-7.
13. Ueda H, Morooka S, Ito I, Yamaguchi H, Takeda T. Clinical observation of 52 cases of aortitis syndrome. Jpn Heart J 1969;10:277-88.
14. Nakao K, Ikeda M, Kimata S, Niitani H, Niyahara M. Takayasu's arteritis. Clinical report of eighty-four cases and immunological studies of seven cases. Circulation 1967;35:1141-55.
15. Ishikawa K, Maetani S. Long-term outcome for 120 Japanese patients with Takayasu's disease. Clinical and statistical analyses of related prognostic factors. Circulation 1994;90:1855-60.
16. Lupi-Herrera E, Sanchez-Torres G, Marcushamer J, Mispireta J, Horwitz S, Vela JE. Takayasu's arteritis. Clinical study of 107 cases. Am Heart J 1977;93:94-103.
17. Park MC, Lee SW, Park YB, Chung NS, Lee SK. Clinical characteristics and outcomes of Takayasu's arteritis: Analysis of 108 patients using standardized criteria for diagnosis, activity assessment, and angiographic classification. Scand J Rheumatol 2005;34:284-92.
18. Jain S, Kumari S, Ganguly NK, Sharma BK. Current status of Takayasu arteritis in India. Int J Cardiol 1996;54 Suppl:S111-6.
19. Brack A, Martinez-Taboada V, Stanson A, Goronzy JJ, Weyand CM. Disease pattern in cranial and large-vessel giant cell arteritis. Arthritis Rheum 1999;42:311-7.
20. Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990;33:1129-34.
21. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122-8.
22. Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159:702-6.
23. Nir-Paz R, Gross A, Chajek-Shaul T. Sex differences in giant cell arteritis. J Rheumatol 2002;29:1219-23.
24. Schmidt WA, Seifert A, Gromnica-Ihle E, Krause A, Natusch A. Ultrasound of proximal upper extremity arteries to increase the diagnostic yield in large-vessel giant cell arteritis. Rheumatology 2008;47:96-101.