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Pulmonary Arterial Hypertension

Relationship between Peripheral Arterial Stiffness and Estimated Pulmonary Pressure by Echocardiography in Systemic Sclerosis

Burabha Pussadhamma,[1] Wannipa Suwannakrua,[1] Panorkwan Toparkngarm,[1] Chaiyasith Wongvipaporn,[1] Chingching Foocharoen[2] and Ratanavadee Nanagara[2]

Background: Pulmonary hypertension (PH) is an important lethal manifestation of systemic sclerosis (SSc). Evidence of an association between peripheral and pulmonary arterial vasculopathy in SSc has been demonstrated. We hypothesized that peripheral arterial stiffness could predict PH in SSc.

Methods: We performed a cross-sectional study among patients with SSc who underwent Cardio-Ankle Vascular Index (CAVI, VaSera VS-1000; Fukuda Denshi, Tokyo, Japan) and transthoracic echocardiography (TTE) examination to evaluate peripheral arterial stiffness and PH, respectively. The correlation between CAVI score and PH hemodynamics [right ventricular systolic pressure (RVSP) and tricuspid regurgitation velocity (TRV)] was studied.

Results: A total of 145 patients underwent both CAVI and TTE evaluation. The mean (standard deviation, SD) patient age was 51.5 (12.3) years; female patients constituted 72% of the subjects. Diffuse SSc occurred in 75% of the cases. The mean (SD) CAVI score was 7.6 (0.9), and the mean (SD) RVSP was 29.9 (11.2) mmHg. Correlation coefficient (r) between CAVI score and RVSP in overall, limited, and diffuse SSc were 0.107 (p = 0.200), 0.040 (p = 0.815), and 0.194 (p = 0.043), respectively. CAVI scores were borderline or abnormal (≥ 8) in 30.3% of subjects. PH was classified intermediate or high probability (TRVmax ≥ 2.9 m/s) in 19.3% of the subjects. Among the overall population, the odds ratios (95% CI) of CAVI score ≥ 8 for TRVmax ≥ 2.9 m/s in univariate and multivariate analysis were 1.23 (0.46-3.21, p = 0.678), and 0.54 (0.10-2.84, p = 0.471), respectively.

Conclusions: Peripheral arterial stiffness, as measured by CAVI, has a correlation trend with the level of pulmonary arterial pressure assessed by TTE, specifically in the diffuse SSc subgroup.

Key Words: Cardio-Ankle Vascular Index • Peripheral arterial stiffness • Pulmonary hypertension • Systemic sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune connective tissue disease with potentially serious consequences, and pulmonary arterial hypertension (PAH) is one of its major manifestations.[1] A study undertaken by Songsak et al. (2007) found PAH in 36.4% of patients with SSc in Northeast Thailand.[2]

Systemic sclerosis-related pulmonary arterial hypertension (SSc-PAH) is a condition with a poor prognosis and high mortality.[3] However, early diagnosis and treatment can improve hemodynamics and reduce the risk of progression.[4] Nevertheless, asymptomatic or mildly symptomatic patients may go unrecognized.[5] Hence, screening for SSc-PAH is warranted.

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[1]Division of Cardiology and Queen Sirikit Heart Center of the Northeast; [2]Division of Allergy-Immunology-Rheumatology, Srinagarind Hospital, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
Corresponding author: Dr. Burabha Pussadhamma, Division of Cardiology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand. Tel: 66-43-363-664, 6689-6179959; Fax: 66-43-203-058; E-mail: pussadhamma@gmail.com

Transthoracic echocardiography (TTE) has been recommended as a standard tool for pulmonary hypertension (PH) screening by evaluating right ventricular systolic pressure (RVSP) and tricuspid regurgitation maximal velocity (TRVmax).[6,7] A good correlation between right ventricular to right atrial pressure gradient measured by TTE and pulmonary artery systolic pressure (PASP) measured by cardiac catheterization has been demonstrated.[8] But there are some obstacles in the use of TTE, e.g. the inadequacy of equipment, shortage of skilled-operators, unavoidable inter- and intra-observer variability, and discrepancies of screening algorithm among guidelines.[5-7] All of these limit the routine use of TTE for screening.

Pulmonary endothelial dysfunction leading to pulmonary vasculopathy is one of the main pathobiologic mechanisms of PH in SSc.[9] Reichenberger et al.[10] found a high level of endothelin (ET), a marker of vasoconstriction and vascular damage, in bronchoalveolar lavage fluid from patients with SSc, while Kadono et al.[11] and Vancheeswaran et al.[12] also found an increased level of plasma ET in patients with SSc. Peled et al.[13] found a trend towards increased peripheral arterial stiffness among 10 SSc-PAH patients. And a report based on 33 Thai patients with SSc revealed a significant correlation between peripheral arterial stiffness and PASP.[14] Therefore, it is possible that there is an association between pulmonary and peripheral arterial vasculopathy in SSc, and detection of peripheral arterial vasculopathy might indicate the likelihood of PH among patients with SSc.

The purpose of our study was to evaluate the correlation between peripheral arterial stiffness as measured by Cardio-Ankle Vascular Index (CAVI) and PH as measured by TTE in a SSc population larger than in the previous study in Thailand. This would allow us to assess whether or not CAVI had the potential to predict the presence of PH among patients with SSc.

MATERIALS AND METHODS

A cross-sectional analytic study was conducted between April, 2012 and April, 2013 at Srinagarind hospital, Khon Kaen University, in Khon Kaen, Thailand. The study was approved by the Khon Kaen University Ethics Committee in human research.

Study population

Patients with SSc who had undergone TTE evaluation were recruited from the SSc clinic. All patients were over 18 years of age and a diagnosis of SSc had been made based on criteria established by the American College of Rheumatology.[15] The SSc was classified as either the limited or the diffuse type according to LeRoy, et al.[16] Patients were excluded if: 1) they had limb defects making CAVI measurement impracticable; 2) the arterial pulse of the extremities could not be measured by Doppler ultrasonography; and 3) they exhibited conditions causing overestimation of CAVI measurement including; end-stage renal disease with or without hemodialysis, metabolic syndrome, obesity with BMI > 30, diabetics mellitus, obstructive sleep apnea, or were current smokers. All patients provided written informed consent.

Transthoracic echocardiography

The TTE (AlokaProSound F75 or AlokaProSound α10 sonographic system; Hitachi-Aloka Medical, Ltd, Tokyo, Japan) was performed by two cardiologists. Left ventricular systolic function was represented by left ventricular ejection fraction (LVEF, Teichholz method). Left ventricular diastolic function was represented by E velocity, deceleration time, A velocity, and E' velocity, respectively.[17] RVSP was calculated from TRVmax using a modified Bernoulli equation; RVSP = $4 \times \text{TRVmax}^2$ + right atrial pressure (RAP), with the mean RAP estimated to be 3, 8, or 15 mmHg, according to the inferior vena cava dimension and its collapsibility.[18]

Cardio-Ankle Vascular Index

The CAVI automated vascular device (VaSera VS-1000; Fukuda Denshi, Tokyo, Japan) was used to evaluate the peripheral arterial stiffness. The subjects lay on their backs for five minutes, then arterial cuffs were applied on their arm and leg on the same side. An electrocardiogram electrode was placed on the arm and the microphone on the sternum to obtain the phonocardiography measurement. The machine automatically calculated the CAVI score according to a formula using the distance from the aortic valve to the ankle artery and the time that the pulse wave took to travel from the

aortic valve to the brachium, i.e., CAVI = a $\{(2\rho/\Delta P) \times \ln(P_s/P_d)PWV^2\}$ + b.[19] In this formula, a and b are constants, ρ is blood density, P_s and P_d are systolic and diastolic blood pressure, respectively, ΔP is P_s-P_d, and PWV is the pulse wave velocity between heart and ankle. This formula was derived from Bramwell-Hill's equation and the stiffness parameter. The CAVI measurement was performed on both sides of the body using the same method and the average used as the CAVI score. CAVI is the blood pressure-independent parameter,[20] and vessels with lower compliance have higher arterial pressure and higher blood flow velocity distally, resulting in a higher CAVI.[17] According to the manufacturer's judgment criteria, a CAVI < 8.0 is considered normal, a CAVI ≥ 9.0 raised a suspicion of atherosclerosis, whereas a CAVI ≥ 8 but < 9 is considered borderline.[21]

The clinical evaluation and CAVI measurement were done either on the same day as the TTE evaluation or less than six months apart in patients whose functional class was stable. The CAVI was performed by a single research assistant. One hundred thirty-one out of 145 TTE procedures (90%) were performed by one cardiologist, with the remainder by another.

Statistical analysis

According to the sample size estimation for correlations with pre-specified confidence interval (CI), by the correlation coefficient value equals the square root of R-squared value, where R-squared value was 0.39, then the calculated correlation coefficient value was 0.62. And with the CI for correlation to estimate the sample size with 95% CI of 0.2 wide, then the calculated sample size was about 150 cases using the PASS 2008 statistical package program. Continuous variables are presented as the mean, minimum, maximum, and standard deviations. Categorical variables are presented as frequency and percentages, and the correlation between CAVI score with clinical characteristics and non-invasive parameters of TTE was analyzed using Pearson's correlation test. The Chi-square or Fisher's exact test was used as necessary to differentiate between clinical features in categorical data in diffuse SSc and limited SSc. The continuous variables were tested using the Two-sample t-test or the Wilcoxon Rank-sum test, as appropriate. The univariate and multivariate analysis of predictors for TRVmax ≥ 2.9 m/s were performed and presented by odds ratio (OR) and 95% confidence intervals (CI). Stata version 10.0 (Stata Corp., College Station, Texas, USA) was used for the analysis. All statistical tests were two-tailed and a p value < 0.05 was considered statistically significant.

RESULTS

One hundred and forty-five patients were enrolled (104 female; 72%, 109 diffuse SSc; 75%). The mean ± standard deviation (SD) for age was 51.5 ± 12 years. Over half of the patients (57%) were asymptomatic [World Health Organization functional class (WHO FC) I] and about one-third (39%) were mildly symptomatic (WHO FC II). The means ± SDs for RVSP, TRVmax, LVEF, and CAVI score were 29.9 mmHg ± 11.2, 2.51 m/s ± 0.48, 66.9% ± 7.6, and 7.60 ± 0.91, respectively (Table 1). Subjects with diffuse SSc had statistically significant higher mean Rodnan scores than subjects with limited SSc (12.28 versus 5.1; p = < 0.001), higher prevalence of digital pitting scars (28.4% versus 5.6%; p = 0.009), higher rates of internal organ involvement (47.7% versus 5.6%; p =< 0.001), and higher age (52.8 years versus 47.5 years; p = 0.025).

According to the arbitrary criteria using TRVmax,[6] 117 patients (80.7%) were classified as low probability for PH, while 22 patients (15.2%) and 6 patients (4.1%) were classified intermediate and high probability for PH, respectively. According to the CAVI score judgment criteria, 101 (69.7%), 32 (22%), and 12 (8%) subjects were regarded as normal, borderline, and suspected for atherosclerosis, respectively (Table 1). The correlation coefficient (r) between CAVI score and RVSP among all patients, those with limited type SSc, and those with diffuse type SSc were 0.107 (p = 0.200), 0.040 (p = 0.815), and 0.194 (p = 0.043), respectively (Figure 1 and Table 2).

Statistically significant weak and moderate positive correlations between CAVI score and RVSP were also noted in female patients (r = 0.202, p = 0.039) and absence of Raynaud's phenomenon (r = 0.328, p = 0.021). There were also non-significant, positive correlation between CAVI score and RVSP among those with absence of digital pitting scar (r = 0.165, p = 0.082) and presence of anti-Scl-70 antibody (r = 0.217, p = 0.062) (Table 2).

In univariate analysis, significant predictors for

Table 1. Baseline characteristics of patients

Characteristic	Total (n = 145)	Limited (n = 36)	Diffuse (n = 109)	p value
Age (year)	51.5 ± 12.3 (18-79)	47.5 ± 14.5 (19-71)	52.8 ± 11.3 (18-79)	0.025
Female	104 (71.7)	30 (83.3)	74 (67.9)	0.116
Body mass index (kg/m^2)	20.9 ± 3.7 (10.2-29.8)	21.3 ± 3.1 (16.2-29.8)	20.8 ± 3.7 (10.2-29.6)	0.460
Rodnan score	11 ± 8.5 (1-36)	5 ± 3.4 (1-13)	12 ± 9.0 (1-36)	< 0.001
Raynaud's phenomenon	96 (66.2)	27 (75.0)	69 (63.3)	0.279
Digital pitting scar	33 (22.8)	2 (5.6)	31 (28.4)	0.009
Internal organ involvement*	54 (37.2)	2 (5.6)	52 (47.7)	< 0.001
Anti-Scl-70 antibody	77 (78.9)	12 (63.2)	63 (82.9)	0.116
Comorbidities				
Hypertension	10 (6.9)	2 (5.6)	8 (7.3)	> 0.999
Hypercholesterolemia	48 (33.1)	11 (30.6)	37 (33.9)	0.865
Significant left-sided VHD	3 (2.1)	0	3 (2.8)	0.574
WHO FC				
FC I	82 (56.6)	25 (69.4)	57 (52.3)	0.108
FC II	56 (38.6)	10 (27.8)	46 (42.2)	0.179
FC III	6 (4.1)	1 (2.8)	5 (4.6)	1.000
FC IV	1 (0.7)	0	1 (0.9)	1.000
Medications use				
ACEI/ARB	9 (6.2)	1 (2.8)	8 (7.4)	0.451
Beta-blocker	1 (0.7)	0	1 (0.9)	> 0.999
CCB	118 (81.9)	30 (83.3)	88 (81.5)	> 0.999
Statins	5 (3.5)	0	5 (4.6)	0.332
SBP (mmHg)	115 ± 14.7 (90-159)	117 ± 14.2 (90-148)	115 ± 14.9 (90-159)	0.347
DBP (mmHg)	71 ± 9.4 (37-96)	74 ± 9.5 (60-96)	70 ± 9.2 (37-94)	0.019
Heart rate (beat per minute)	76 ± 14.1 (42-122)	74 ± 13.0 (56-99)	77 ± 14.3 (42-122)	0.224
TRVmax (m/sec)	2.5 ± 0.5 (1.6-4.6)	2.5 ± 0.5 (1.6-4.1)	2.5 ± 0.5 (1.7-4.6)	0.326
Mean RAP (mmHg)	4.1 ± 2.5 (3-15)	4.2 ± 2.7 (3-15)	4.1 ± 2.4 (3-15)	0.875
RVSP (mmHg)	30 ± 11.2 (12.6-86.5)	29 ± 12.2 (12.6-73.6)	31 ± 11.4 (14.2-86.5)	0.459
PH classification according to TRV max				0.116
< 2.9 m/s (low probability)	117 (80.7)	32 (88.9)	85 (78.0)	
2.9-3.4 m/s (intermediate probability)	22 (15.2)	2 (5.6)	20 (18.4)	
> 3.4 m/s (high probability)	6 (4.1)	2 (5.6)	4 (3.7)	
LVEF (%)	66.9 ± 7.6 (46.1-84.9)	67.8 ± 6.8 (46.3-79.0)	66.6 ± 7.9 (46.1-84.9)	0.411
Diastolic dysfunction[#]	76 (53.5)	18 (48.7)	58 (55.2)	0.490
CAVI score	7.6 ± 0.9 (5.8-10.0)	7.4 ± 1.0 (5.8-10.0)	7.7 ± 0.9 (5.8-10.0)	0.200
CAVI score[†]				
< 8 (normal)	101 (69.7)	27 (75.0)	74 (67.9)	0.552
8-8.99 (borderline)	32 (22.1)	7 (19.4)	25 (22.9)	0.837
≥ 9 (abnormal)	12 (8.3)	2 (5.6)	10 (9.2)	0.738
PWV (m/s)	18.3 ± 1.7 (13.7-22.5)	18.4 ± 1.8 (14.9-22.2)	18.3 ± 1.6 (13.7-22.5)	0.775
Hemoglobin (g/dl)	12.3 ± 1.5 (9.1-15.7)	12.6 ± 1.3 (9.6-15.7)	12.2 ± 1.5 (9.1-15.7)	0.210
Hematocrit (%)	37.4 ± 4.6 (15.2-48.8)	38.4 ± 3.4 (29.6-47.3)	37.0 ± 4.9 (15.2-48.8)	0.073
Serum creatinine (mg/dl)	0.8 ± 0.3 (0.3-2.5)	0.8 ± 0.3 (0.5-2.5)	0.8 ± 0.3 (0.3-1.9)	0.873
ALT (mg/dl)	20 ± 15.1 (2-133)	20 ± 14.7 (5-88)	20 ± 15.3 (2-133)	0.896
AST (mg/dl)	28 ± 26.4 (1-244)	34 ± 42.4 (3-244)	26 ± 17.9 (1-137)	0.276
Fasting blood glucose (mg/dl)	95 ± 21.4 (66-200)	93 ± 16.4 (71-146)	96 ± 22.8 (66-200)	0.523
Total cholesterol (mg/dl)	194 ± 41.4 (108-310)	190 ± 35.4 (112-266)	195 ± 43.3 (108-310)	0.495

Data are presented as mean ± SD (range) or n (%).

ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; CAVI, Cardio-Ankle Vascular Index; CCB, calcium channel blocker; DBP, diastolic blood pressure; LVEF, left ventricular systolic function; PH, pulmonary hypertension; PWV, pulse wave velocity; RAP, right atrial pressure; RVSP, right ventricular systolic pressure; SBP, systolic blood pressure; SSc, systemic sclerosis; TRVmax, tricuspid regurgitation maximal velocity; VHD, valvular heart disease; WHO FC, World Health Organization functional class.

* Internal organ involvement is defined as one or more of the following: pulmonary fibrosis, alveolitis, pulmonary arterial hypertension, stomach or intestinal dysfunction, or myositis. [#] According to the criteria of ASE/EAE recommendations for the evaluation of left ventricular diastolic function by echocardiography.[17] [†] Average score of left and right CAVI.

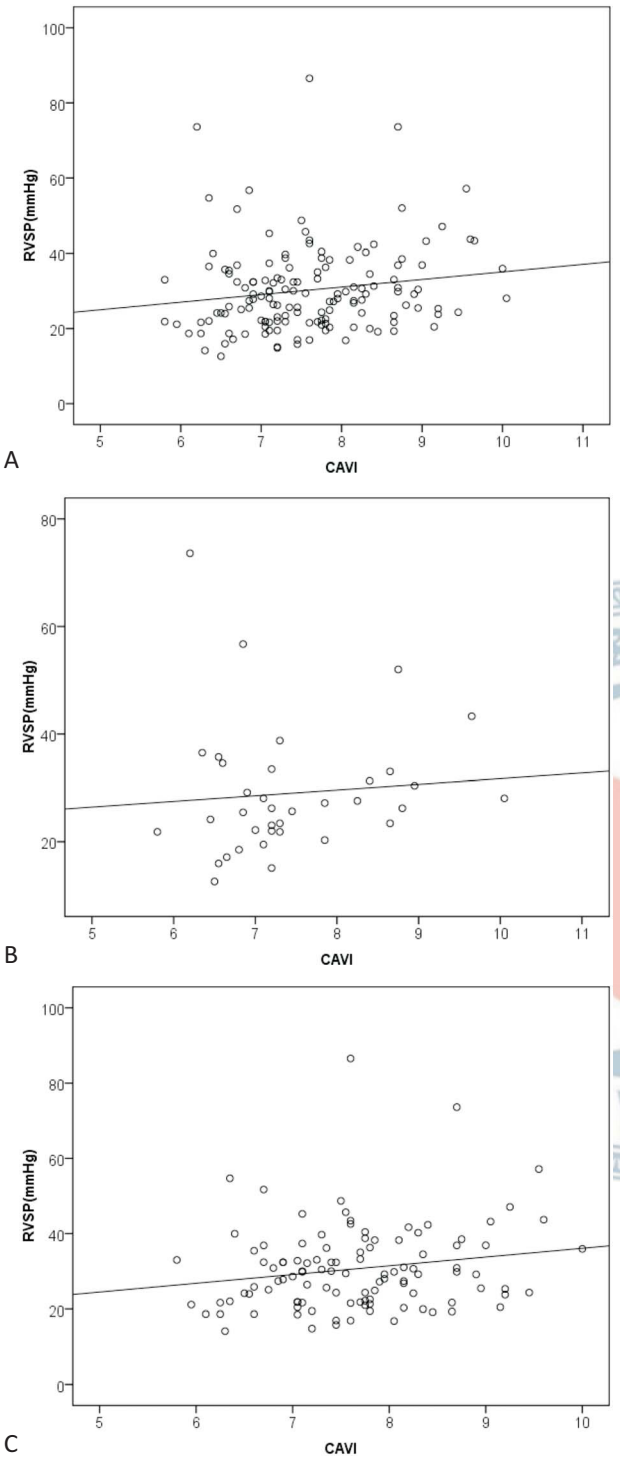

Figure 1. *Correlations between CAVI score and RVSP. Cardio-Ankle Vascular Index (CAVI) score had no significant correlation with right ventricular systolic pressure (RVSP) as determined by transthoracic echocardiography (TTE) in overall population (r = 0.107, p = 0.200) (A), and in limited systemic sclerosis (SSc) subgroup (r = 0.040, p = 0.815) (B). The significant weak correlation, however, was found in diffuse SSc subgroup (r = 0.194, p = 0.043) (C).*

Table 2. Correlation between CAVI score and RVSP according to subgroup characteristics

Characteristic	Correlation coefficient (r)	p value
Female	0.202	0.039
Type of SSc		
Limited SSc	0.040	0.815
Diffuse SSc	0.194	0.043
Rodnan score ≥ 21 (more skin thickness)	0.203	0.436
Absence of Raynaud's phenomenon	0.328	0.021
Absence of digital pitting scar	0.165	0.082
Presence of internal organ involvement	0.220	0.110
Presence of anti-scl-70 antibody	0.217	0.062
WHO functional class		
FC I	0.063	0.573
FC II	0.114	0.402
FC III-IV	0.638	0.123

FC, functional class; SSc, systemic sclerosis; WHO, World Health Organization.

TRVmax ≥ 2.9 m/s were WHO FC II-IV in overall population [odds ratio (OR) 0.5, 95% confidence interval (CI) 0.29 to 0.84, p = 0.009], WHO FC II-IV in diffuse SSc subgroup (OR 0.67, 95% CI 0.05 to 0.49, p = 0.001), and heart rate in the overall population (OR 1.04, 95% 1.00 to 1.06, p = 0.031). The CAVI score ≥ 8 (borderline or abnormal) showed an association with TRVmax ≥ 2.9 m/s, which was not statistically significant, in the overall population (OR 1.23, 95% CI 0.46 to 3.21, p = 0.678), limited SSc subgroup (OR 1.44, 95% CI 0.12 to 16.42, p = 0.767), and diffuse SSc subgroup (OR 1.16, 95% CI 0.40 to 3.32, p = 0.785) (Table 3). After adjustment for other variables in multivariate analysis, the independent predictors were Rodnan score ≥ 21 in overall population (OR 0.29, 95% CI 0.09 to 0.95, p = 0.042), presence of anti-Scl-70 antibody in overall population (OR 0.08, 95% CI 0.01 to 0.29, p = 0.004) and in diffuse SSc subgroup (OR 0.06, 95% CI 0.01 to 0.48, p = 0.008), WHO FC II-IV in overall population (OR 4.63, 95% CI 1.26 to 16.89, p = 0.021) and in diffuse SSc subgroup (OR 5.39, 95% CI 1.24 to 23.39, p = 0.025), and diastolic dysfunction in overall population (OR 4.42, 95% CI 1.02 to 19.01, p = 0.046) and in diffuse SSc subgroup (OR 6.16, 95% CI 1.06 to 35.58, p = 0.042). CAVI score ≥ 8 showed the non-statistical significant association in the overall population (OR 0.54, 95% CI 0.10 to 2.84, p = 0.471) and diffuse SSc subgroup (OR 0.88, 95% CI 0.14 to 4.82, p = 0.877) (Table 3).

Table 3. Odds ratios for TRVmax ≥ 2.9 m/s (univariate and multivariate analysis)*

Variables	Univariate analysis						Multivariate analysis			
	Total		Limited		Diffuse		Total		Diffuse	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.00 (0.96-1.03)	0.965	0.96 (0.89-1.03)	0.277	1.00 (0.96-1.04)	0.717	-	-	-	-
Male sex#	1.01 (0.40-2.53)	0.969	NA†	-	1.07 (0.40-2.81)	0.884	-	-	-	-
BMI#	1.05 (0.93-1.18)	0.395	0.43 (0.03-5.18)	0.505	1.03 (0.90-1.16)	0.676	-	-	-	-
Rodnan score ≥ 21	0.57 (0.23-1.36)	0.206	NA†	-	0.66 (0.25-1.69)	0.385	0.29 (0.09-0.95)	0.042	0.28 (0.06-1.12)	0.072
Raynaud's phenomenon	0.90 (038-2.13)	0.811	NA†	-	0.76 (0.30-1.92)	0.568	0.37 (0.10-1.35)	0.133	0.24 (0.05-1.06)	0.061
Digital pitting scar	1.84 (0.73-4.56)	0.191	NA†	-	1.72 (0.65-4.48)	0.268	1.83 (0.46-7.29)	0.470	2.29 (0.53-9.97)	0.266
Internal organ involvement	1.93 (0.83-4.43)	0.124	10.33 (0.50-210.58)	0.129	1.39 (0.59-3.46)	0.474	3.61 (0.81-15.96)	0.091	2.93 (0.57-14.99)	0.198
Anti-Scl-70 antibody	0.49 (0.15-1.51)	0.214	1.20 (0.08-16.23)	0.891	0.34 (0.09-1.23)	0.101	0.08 (0.01-0.29)	0.004	0.06 (0.01-0.48)	0.008
WHO FC II-IV	0.50 (0.29-0.84)	0.009	0.39 (0.04-3.21)	0.383	0.67 (0.05-0.49)	0.001	4.63 (1.26-16.89)	0.021	5.39 (1.24-23.39)	0.025
SBP#	1.02 (0.98-1.04)	0.299	0.99 (0.91-1.06)	0.739	1.02 (0.99-1.05)	0.168	-	-	-	-
DBP#	1.02 (0.97-1.06)	0.457	1.00 (0.89-1.11)	0.950	1.03 (0.98-1.08)	0.239	-	-	-	-
Heart rate	1.04 (1.00-1.06)	0.031	1.06 (0.96-1.16)	0.241	1.03 (0.98-1.06)	0.070	1.00 (0.97-1.01)	0.485	1.00 (0.97-1.01)	0.621
LVEF#	1.02 (0.97-1.08)	0.293	1.05 (0.88-1.23)	0.590	1.03 (0.96-1.08)	0.412	-	-	-	-
Diastolic dysfunction	1.47 (0.63-3.40)	0.371	3.40 (0.31-36.27)	0.264	1.24 (0.49-3.11)	0.640	4.42 (1.02-19.01)	0.046	6.16 (1.06-35.58)	0.042
CAVI score ≥ 8	1.23 (0.46-3.21)	0.678	1.44 (0.12-16.42)	0.767	1.16 (0.40-3.32)	0.785	0.54 (0.10-2.84)	0.471	0.88 (0.14-4.82)	0.877

BMI, body mass index; CAVI, Cardio-Ankle Vascular Index; DBP, diastolic blood pressure; LVEF, left ventricular systolic function; SBP, systolic blood pressure; TRVmax, tricuspid regurgitation maximal velocity; WHO FC, World Health Organization functional class.

* The multivariate analysis of the patients with limited systemic sclerosis was totally unavailable due to the insufficiency of event for the analysis.

Data are not included in the multivariate analysis. † NA, not available due to insufficiency of event for the analysis.

DISCUSSION

This study evaluated the utility of CAVI for predicting the presence of PH by comparing parameters from TTE among patients with SSc at a single center. The mean age (51.5 years) and the preponderance of females (72%) in our study populations matches the usual demographic situation for SSc.[22] The higher Rodnan scores and higher prevalence of digital pitting scars and internal organ involvement among diffuse type patients, is also typical. However, the proportion of Anti-Scl 70 positive individuals (78.9%) was much higher than the 19.6% reported from a large US population.[23]

In our study population, 30.3% of the subjects had abnormal peripheral arterial stiffness (CAVI score ≥ 8). This was slightly higher than found in a previous study of 34 Thai patients with SSc, in which 8 patients (23.53%) had CAVI score > 8.[24] This small difference is probably a consequence of sample size. Nevertheless, there is no other report concerning the prevalence of CAVI-measured peripheral arterial stiffness from other ethnicities.

The pulse wave velocity (PWV), which is one of the parameters indicating for peripheral arterial stiffness, was not different between 2 groups of patient. However, the normal value of PWV among patients with SSc had never been study. Comparing with PWV, the CAVI has advantages for being blood pressure-independent test and reflecting both organic and functional stiffness (smooth muscle dysfunction), whereas PWV was affected by blood pressure (reflected the change of blood pressure rather than smooth muscle contraction) and was not able to reflect the early atherosclerotic change.

Prevalence of PH (intermediate or high probability) was 11.1% in patients with limited SSc, and 22.0% in patients with diffuse SSc. However, these prevalences were not statistically different. Compared with a large

cohort of 3656 patients with SSc,[25] however, the prevalence of PH in patients with limited SSc in our study was lower (11.1% versus 20.5%), while in patients with diffuse SSc, prevalences in the two studies were nearly the same (22.0% versus 22.3%).

There was no significant positive correlation between CAVI score and RVSP in the overall group (r = 0.107, p = 0.200). In subgroup analysis, however, a significant weak positive correlation was found in diffuse SSc subgroup (r = 0.194, p = 0.043) but not in limited SSc subgroup (r = 0.040, p = 0.815). The differences might be explained by differing pathogenesis of PH in the two forms of SSc. In limited SSc, PH usually results from localized pulmonary vascular abnormalities (isolated PAH),[25,26] in which peripheral arteriopathy might not play a role. In contrast, PH in diffuse SSc is much more associated with pulmonary fibrosis and isolated PAH is less common.[25] PH in diffuse SSc might be a consequence of generalized vasculopathy, affecting both pulmonary and peripheral vascular, and leading to the trend of positive correlation between CAVI and RVSP.

In contrast to our finding, a previous case-control study of 33 Thai patients with SSc and 15 healthy control individuals found a statistically significant moderate positive correlation between PASP measured by TTE and peripheral arterial stiffness measured by CAVI (r^2 = 0.39, p < 0.001) in the overall population.[14] The proportion of diffuse patients with SSc in the study, however, was not clarified, and it was possible that the majority of studied patients were in this category. The other explanation might be the effect of larger sample size in our study (145 patients).

There was even a statistically significant positive correlation between CAVI score and RVSP among the diffuse SSc subgroup. However, further univariate and multivariate analysis of borderline and abnormal CAVI score (≥ 8) for intermediate or high probability for PH (TRVmax ≥ 2.9 m/s) could not demonstrate a statistically significant association. This might be explained by its weak correlation between peripheral arterial stiffness and pulmonary hypertension or the inadequate of sample size.

Rodnan score ≥ 21, presence of Anti-Scl-70, WHO FC II-IV, and diastolic dysfunction were shown to be statistically significant independent predictors for intermediate or high probability for PH from multivariate analysis in our study. The elevated serum level of vascular endothelial growth factor, which is the marker of neoangiogenesis, had been demonstrated in patients with SSc, and showed a strong association both with skin thickness[27] and PH.[28] This might have explained the association between extensive skin thickness (Rodnan score ≥ 21) and PH in the overall population found in our study, where both conditions resulted from simultaneous vascular damage.

The presence of anti-Scl-70 antibody was found mainly in diffuse SSc and has been associated with interstitial pulmonary fibrosis.[29,30] This may consequently have resulted in PH, which could have explained the association between the presence of anti-Scl-70 antibody and PH. However, this postulation is limited because the presence of pulmonary fibrosis was not explored in our study.

Both left and right ventricular diastolic dysfunction have been seen in patients with SSc, and may have contributed to PH.[31] Left ventricular diastolic dysfunction caused an elevation of left atrial pressure, and subsequently elevated pulmonary artery pressure.[6] A high prevalence of left ventricular diastolic dysfunction among asymptomatic patients with SSc in the northeast of Thailand has been reported, shown to be 60.5% in patients with limited SSc, and 37.7% in patients with diffuse SSc (p = 0.04).[32] This was also observed in our study population, with a prevalence of 48.7% in patients with limited SSc, and 55.2% in patients with diffuse SSc (p = 0.49). This elevated prevalence of diastolic dysfunction could in some way explain the association between diastolic dysfunction and PH as found in our study.

Raynaud's phenomenon, which is characterized by a recurrent, reversible vasospasm of small arteries and arteriole,[33] was commonly found in the majority of patients with SSc, and also in our study population (66.2%). The "pulmonary Raynaud's hypothesis" suggests that pulmonary vasospasm contributes to the development of PH.[34] Nevertheless, the presence of Raynaud's phenomenon could not show the statistically significant association with PH both from univariate and multivariate analysis in our study. Additionally, there was no correlation between CAVI score and RVSP among patients with SSc who had Raynaud's phenomenon, but a moderate positive correlation was found among patients who did not have Raynaud's phenomenon. It was possible that

pulmonary Raynaud's, and peripheral Raynaud's occurred separately and are not associated, or that the pulmonary Raynaud's hypothesis is erroneous.[35]

A major strength of our study was that it represents the first large study ever performed among patients with SSc with the goal to evaluate the clinical utility of CAVI in predicting PH. However, the study did have several limitations, including: 1) it was conducted at only a single center; 2) the study lacked a normal control population; 3) TTE and CAVI were not performed in the same day for 17.9% of the subjects; 4) the inter-observer variability was not validated between the two cardiologists; 5) the skin thickness in SSc might directly affect CAVI results, even though the exact effect remains unknown; 6) the study used TRVmax to define PH, rather than using the mean pulmonary artery pressure from right heart catheterization which is the gold standard, and thus might lead to unreliable results; and 7) the observed correlation between CAVI and RVSP in our study was much lower than the assumed effect size (correlation coefficient of 0.62), suggesting that a larger sample size may be needed to achieve a statistically significant correlation among the overall population.

CONCLUSIONS

In patients with SSc, peripheral arterial stiffness as measured by CAVI had no statistically significant association with PH. Nevertheless, a statistically significant weak positive correlation was found between the CAVI score and RVSP specifically in patients with diffuse SSc. Further study is suggested to evaluate the potential of CAVI to predict the presence of PH in patients with diffuse SSc.

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DISCLOSURES

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