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ORIGINAL RESEARCH

Upstroke Time Is a Useful Vascular Marker for Detecting Patients With Coronary Artery Disease Among Subjects With Normal Ankle-Brachial Index

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BACKGROUND: Upstroke time is the transit time from the nadir to peak of the waveform of pulse volume recording. The purpose of this study was to determine whether upstroke time at the ankle is a useful vascular marker for detecting patients with advanced atherosclerosis in combination with ankle-brachial index (ABI).

METHODS AND RESULTS: We measured upstroke time and ABI in 2313 subjects (mean age, 61.2±15.3 years). The prevalence of coronary artery disease (CAD) was significantly higher in patients with prolonged upstroke time (≥180 ms) than in subjects with normal upstroke time (<180 ms) (29.6% versus 11.8%; $P<0.001$), with a significant association between prolonged upstroke time and an increased risk of CAD (odds ratio [OR], 1.61; 95% CI, 1.07–2.44; $P=0.02$). In 1954 subjects with normal ABI ($1.00 \leq ABI \leq 1.40$), the prevalence of CAD was significantly higher in patients with prolonged upstroke time than in subjects with normal upstroke time (29.5% versus 10.6%; $P<0.001$), with a significant association between prolonged upstroke time and CAD (OR, 2.33; 95% CI, 1.41–3.87; $P=0.001$), whereas there was no significant association between upstroke time and CAD in subjects with low ABI (<1.00) (OR, 1.24; 95% CI, 0.72–2.16; $P=0.44$).

CONCLUSIONS: Upstroke time may be a useful vascular marker for detecting patients with CAD, especially in subjects with normal ABI who are usually considered not to have advanced atherosclerosis by ABI measurement alone. More attention should be paid to upstroke time for detecting patients with advanced atherosclerosis.

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Key Words: atherosclerosis ■ biomarker ■ coronary artery disease

Ankle-brachial index (ABI) measurement is a useful screening method for detecting peripheral artery disease (PAD). In the current major guidelines for diagnosis and management of PAD, the normal range of ABI has been defined as 1.00 to 1.40.[1,2] In addition to PAD detection, ABI can be used as a cardiovascular risk marker because ABI is also an indicator of systemic atherosclerosis.[3,4] Therefore, subjects with normal ABI are usually considered to be at lower cardiovascular risk than subjects with abnormal ABI (<1.00 or >1.40).[3,4] However, the ABI method does not always provide reliable data for cardiovascular risk assessment because the ABI value is falsely elevated despite the presence of occlusive arterial lesions in the lower extremities in patients with noncompressible lower limb arteries,[5]

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CLINICAL PERSPECTIVE

What Is New?

- Among subjects with a normal ankle-brachial index, the prevalence of coronary artery disease was significantly higher in patients with prolonged upstroke time than in subjects with normal upstroke time.

What Are the Clinical Implications?

- Upstroke time may be a useful vascular marker for detecting coronary artery disease in individuals with a normal ankle-brachial index who are usually considered not to have advanced atherosclerosis by measurement of the ankle-brachial index alone.

potentially leading to incorrect cardiovascular risk assessment.

Waveforms of pulse volume recording obtained by using a plethysmography technique have been used as a noninvasive method for PAD detection.[6–8] Recent advancement of oscillometric cuff technology has enabled easy and accurate pulse volume recordings in a short time, resulting in clinical application of vascular parameters calculated from high-quality waveforms of pulse volume recordings. Upstroke time, one of the vascular parameters calculated from the waveform of pulse volume recording, is transit time from the nadir to peak of the waveform. Because there is little information on the usefulness of upstroke time alone or in combination with ABI for detecting patients with advanced atherosclerosis as a vascular marker, we investigated the association between upstroke time and coronary artery disease (CAD) to determine whether upstroke time alone or in combination with ABI is useful for detecting patients with advanced atherosclerosis in a large number of well-characterized subjects.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Subjects

This study was a cross-sectional study. Between January 2008 and December 2019, a total of 2753 subjects were recruited for measurements of ABI and pulse volume recording for calculation of upstroke time from participants who visited the outpatient cardiology clinic or who underwent health-screening examinations at Hiroshima University Hospital. Participants with severe aortic stenosis or aortic regurgitation (n=35), atrial fibrillation (n=183), PAD defined as critical limb ischemia (n=56), a history of major amputation (n=55) or minor amputation (n=12), or previous intervention, including angioplasty or bypass graft (n=76), and those with missing information on a history of CAD (n=23) were excluded. Finally, 2313 participants (1437 men and 876 women; mean age, 61.2±15.3 years) were enrolled in this study. Hypertension was defined as treatment with oral antihypertensive drugs or systolic blood pressure of >140 mm Hg and/or diastolic blood pressure of >90 mm Hg, in a sitting position, on at least 3 different occasions without medication.[9] Diabetes mellitus was defined according to the American Diabetes Association recommendation.[10] Dyslipidemia was defined according to the third report of the National Cholesterol Education Program.[11] Smoking status was classified into 3 categories: never smoker, ex-smoker, and current smoker. CAD was defined as a history of myocardial infarction and/or angina pectoris. Myocardial infarction was defined as organic occlusion of at least 1 coronary artery confirmed by coronary angiography with or without a history of a coronary revascularization procedure, including percutaneous coronary intervention and/or coronary artery bypass grafting. Angina pectoris was defined as organic stenosis (≥50%) of at least 1 coronary artery confirmed by coronary angiography and a history of chest pain with

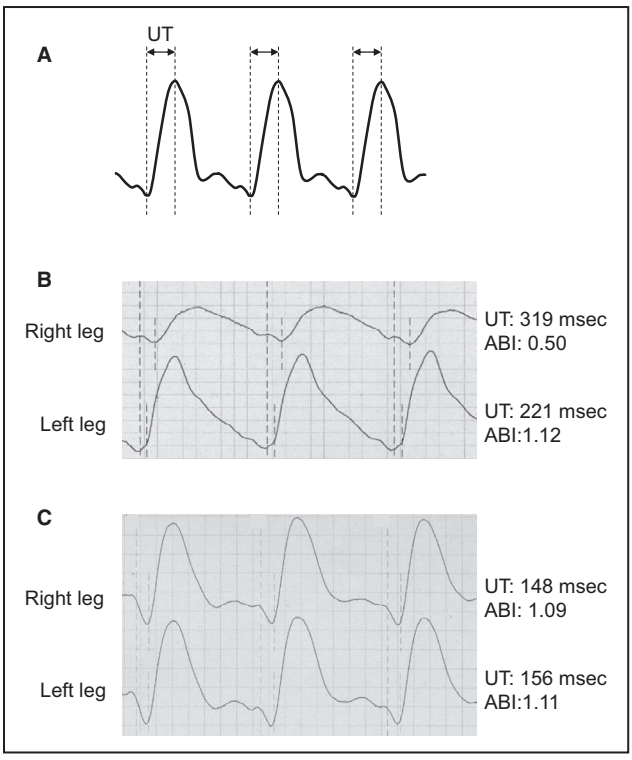

Figure 1. Waveforms of pulse volume recording (A). Representative waveforms of pulse volume recording with prolonged upstroke time (UT) (**B**) and normal UT (**C**). ABI indicates ankle-brachial index.

Table 1. Clinical Characteristics of Subjects

Variables	All (n=2313)	Low ABI (n=274)	Normal ABI (n=1954)	High ABI (n=85)	*P* Value	Normal UT (n=1992)	Prolonged UT (n=321)	*P* Value
Age, y	61.2±15.3	64.3±16.2	60.8±15.3	61.9±12.4	0.002	60.1±15.3	68.1±13.4	<0.001
Men, n (%)	1437 (62.1)	175 (63.9)	1198 (61.3)	64 (75.3)	0.02	1254 (63.0)	183 (57.0)	0.04
Body mass index, kg/m^2	24.0±4.0	23.0±4.2	24.1±3.9	25.2±3.9	<0.001	24.1±4.0	23.0±3.6	<0.001
Systolic blood pressure, mm Hg	132.4±18.9	134.2±21.1	132.4±18.5	127.9±20.1	0.02	132.1±18.5	134.5±20.9	0.03
Diastolic blood pressure, mm Hg	78.2±12.5	75.3±12.1	78.7±12.5	75.3±12.7	<0.001	78.9±12.5	74.0±12.0	<0.001
Heart rate, bpm	69.5±12.1	74.2±13.3	68.9±11.9	66.9±8.7	<0.001	70.1±12.2	65.5±10.5	<0.001
Total cholesterol, mmol/L	4.94±0.97	4.75±0.97	4.97±0.96	4.88±1.05	0.007	4.97±0.96	4.78±1.01	0.004
Triglycerides, mmol/L	1.61±1.23	1.57±0.98	1.60±1.24	1.82±1.60	0.27	1.60±1.19	1.63±1.46	0.74
HDL cholesterol, mmol/L	1.53±0.4	1.54±0.52	1.54±0.43	1.42±0.45	0.07	1.54±0.44	1.53±0.48	0.77
LDL cholesterol, mmol/L	2.84±0.84	2.63±0.84	2.87±0.83	2.87±0.95	<0.001	2.87±0.84	2.66±0.80	<0.001
Glucose, mmol/L	6.40±2.22	7.63±3.53	6.23±1.94	6.66±1.95	<0.001	6.23±1.92	7.54±3.37	<0.001
HbA1c, %	5.6±0.9	6.1±1.2	5.5±0.9	5.5±0.8	<0.001	5.5±0.9	5.9±1.0	<0.001
Creatinine, μmol/L	84.2±85.4	113.9±135.3	77.4±60.5	150.7±226.0	<0.001	80.4±76.1	108.4±126.7	<0.001
Smoking status, n (%)								
Never smoker	1043 (45.4)	99 (36.4)	918 (47.3)	26 (31.0)	<0.001	906 (45.8)	137 (42.7)	0.26
Ex-smoker	816 (35.5)	111 (40.8)	663 (34.1)	41 (50.0)		689 (34.8)	127 (39.6)	
Current smoker	440 (19.1)	62 (22.8)	362 (18.6)	16 (19.1)		383 (19.4)	57 (17.8)	
Complication, n (%)								
Hypertension	1908 (82.5)	218 (79.6)	1619 (82.9)	71 (83.5)	0.41	1646 (82.6)	262 (81.6)	0.66
Dyslipidemia	1663 (72.0)	213 (77.7)	1393 (71.3)	57 (67.1)	0.04	1417 (71.2)	246 (76.6)	0.04
Diabetes mellitus	653 (28.3)	121 (44.2)	509 (26.1)	23 (27.4)	<0.001	507 (25.5)	146 (45.5)	<0.001
Coronary artery disease	329 (14.2)	67 (24.5)	240 (12.3)	22 (25.9)	<0.001	234 (11.8)	95 (29.6)	<0.001
Previous myocardial infarction	140 (6.1)	37 (13.6)	89 (4.6)	14 (16.5)	<0.001	95 (4.8)	45 (14.1)	<0.001
Angina pectoris	274 (11.8)	50 (18.3)	204 (10.4)	20 (23.5)	<0.001	197 (9.9)	77 (24.0)	<0.001
Prior coronary revascularization procedure	259 (11.2)	53 (19.3)	190 (9.7)	16 (18.8)	<0.001	186 (9.3)	73 (22.7)	<0.001
Hemodialysis	39 (1.7)	16 (5.9)	14 (0.72)	9 (10.7)	<0.001	25 (1.3)	14 (4.4)	<0.001
Medications, n (%)								
Antihypertensive drugs	1564 (67.6)	179 (65.3)	1329 (68.0)	56 (65.9)	0.64	1342 (67.4)	222 (69.2)	0.52
Lipid-lowering drugs	872 (37.7)	141 (51.5)	701 (35.9)	30 (35.3)	<0.001	693 (34.8)	179 (55.8)	<0.001

(*Continued*)

Table 1. Continued

Variables	All (n=2313)	Low ABI (n=274)	Normal ABI (n=1954)	High ABI (n=85)	*P* Value	Normal UT (n=1992)	Prolonged UT (n=321)	*P* Value
Antidiabetic drugs	466 (20.1)	96 (35.0)	354 (18.1)	16 (18.8)	<0.001	337 (16.9)	129 (40.2)	<0.001
Right ABI	1.15±0.13	0.94±0.20	1.17±0.78	1.36±0.13	NA	1.17±0.11	1.04±0.21	<0.001
Left ABI	1.14±0.14	0.90±0.16	1.17±0.79	1.45±0.16	NA	1.16±0.11	1.03±0.23	<0.001
Right ankle UT, ms	146.0±28.0	176.1±44.8	141.8±21.5	144.8±29.2	<0.001	137.7±15.6	196.9±33.2	NA
Left ankle UT, ms	146.0±27.8	177.2±43.8	141.8±21.7	141.8±23.5	<0.001	137.8±16.0	196.5±32.0	NA

Data are given as mean±SD unless otherwise indicated. ABI indicates ankle-brachial index; bpm, beats per minute; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable; and UT, upstroke time.

or without a history of a coronary revascularization procedure. Stroke included ischemic stroke, hemorrhagic stroke, and transient ischemic attack. The vascular tests were performed without withholding medications. The ethical committees of our institutions (Hiroshima University Hospital institutional review board) approved the study protocol. Written informed consent for participation in the study was obtained from all subjects.

Study Protocol

The subjects fasted the previous night for at least 8 hours and abstained from consuming alcohol and caffeine and from smoking. The subjects were kept in the supine position in a quiet, dark, air-conditioned room (constant temperature of 22°C–26°C) throughout the study. A 23-gauge polyethylene catheter was inserted into the left deep antecubital vein to obtain blood samples. ABI measurement and pulse wave recording were performed at least 5 minutes after maintaining the supine position. Vascular tests were performed by skilled and trained physicians without detailed knowledge of baseline clinical characteristics of the subjects.

ABI Measurement and Pulse Volume Recording

ABI measurement and pulse volume recording for calculation of upstroke time were performed using a volume-plethysmographic apparatus (Form PWV/ABI; Omron Health Care Co, Kyoto, Japan). Four oscillometric cuffs were wrapped around both upper arms and lower legs. The cuffs were connected to an oscillometric pressure sensor for measurements of blood pressure and to a plethysmographic sensor for pulse volume recordings. Blood pressure in each limb was automatically and simultaneously measured, and then waveforms of pulse volume recording in the lower limbs

Figure 2. Bar graphs show the proportions of subjects with prolonged upstroke time (UT ≥180 ms) according to ankle-brachial index (ABI) in right and left legs.

Table 2. Multiple Logistic Regression Analysis of the Relationships Between Prolonged Upstroke Time and Variables

Covariates	Right Ankle		Left Ankle	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Age, y	1.04 (1.02–1.05)	<0.001	1.03 (1.02–1.04)	<0.001
Men (yes/no)	0.76 (0.52–1.13)	0.17	0.60 (0.41–0.89)	0.01
Body mass index, kg/m^2	0.98 (0.94–1.03)	0.47	0.96 (0.91–0.99)	0.04
Heart rate, bpm	0.94 (0.93–0.95)	<0.001	0.94 (0.92–0.95)	<0.001
Hypertension (yes/no)	0.71 (0.46–1.09)	0.12	0.92 (0.60–1.42)	0.70
Dyslipidemia (yes/no)	1.20 (0.81–1.78)	0.36	1.11 (0.76–1.63)	0.58
Diabetes mellitus (yes/no)	1.95 (1.40–2.71)	<0.001	2.03 (1.46–2.81)	<0.001
Ex-smoking (yes/no)	1.45 (0.96–2.18)	0.07	1.31 (0.87–1.97)	0.20
Current smoking (yes/no)	1.34 (0.80–2.25)	0.27	1.58 (0.96–2.60)	0.07
Hemodialysis (yes/no)	6.48 (2.66–15.8)	<0.001	2.96 (1.07–8.15)	0.04
ABI	0.93 (0.92–0.94)	<0.001	0.93 (0.91–0.94)	<0.001

ABI indicates ankle-brachial index; and bpm, beats per minute.

were automatically and simultaneously recorded. This device distinguished between pulses of the anterior tibial artery, posterior tibial artery, and peroneal artery by using frequency analysis and automatically selected and displayed the pulse with the highest oscillation. ABI was automatically calculated by dividing the ankle systolic blood pressure of the right and left sides by the higher brachial systolic blood pressure of either arm. Upstroke time is transit time from the nadir to peak of the pulse wave (Figure 1A). Upstroke time should be prolonged with hemodynamically significant stenosis or occlusion (Figures 1B and 1C). Waveforms of pulse volume recording were obtained by holding cuff pressure at 54 mm Hg in subjects with diastolic blood pressure >62 mm Hg and by holding cuff pressure at 8 mm Hg below diastolic blood pressure in subjects with diastolic blood pressure <62 mm Hg to minimize the influence of cuff pressure on hemodynamics. Pulse waveforms in the lower limbs were recorded and stored for 10 s. Upstroke time was calculated for each pulse waveform, and the mean of upstroke times obtained in the 10-s recording was used for analyses. A beat with a pulse interval 25% shorter or longer than the previous beat interval was excluded because of the possibility of arrhythmia or body movement. Upstroke time was not calculated when the number of available pulses for calculation was <3.[12] The reproducibility of upstroke time (on visit 1 and visit 2) was assessed in 30 subjects. Pearson correlation coefficients of upstroke time between visit 1 and 2 were 0.83 (P<0.001) in the right leg and 0.84 (P<0.001) in the left leg, and the coefficients of variation were 4.6% in the right leg and 5.2% in the left leg.

Cutoff Values of ABI and Upstroke Time

The 2016 American Heart Association/American College of Cardiology guidelines on the management of PAD recommend that ABI in the range of 1.00 to 1.40 should be classified as normal for the diagnosis of PAD.[1] In addition, a previous study has shown that low ABI (<1.00) and high ABI (≥1.40) were associated with higher incidence of cardiovascular events than was normal ABI (1.00–1.40).[4] Therefore, participants were divided into 3 groups based on those cutoff values of ABI: patients with low ABI when either side of ABI was <1.00, subjects with normal ABI when ABIs on both the left and right sides were within the range of 1.00 to 1.40, and patients with high ABI when either side of ABI was >1.40.

To our knowledge, there has been no report in which a cutoff value of upstroke time for cardiovascular disease was proposed. Therefore, in accordance with the recommended cutoff value of upstroke time for diagnosis of PAD in the 2013 Japanese Circulation Society guidelines for a noninvasive vascular function test and cutoff values proposed in recent studies in which the optimal cutoff value of upstroke time for diagnosis of PAD was investigated,[9,12,13] participants were divided into 2 groups: subjects with normal upstroke time when the upstroke times on both the left and right sides were <180 ms and patients with prolonged upstroke time when upstroke time on either side or upstroke times on both sides were ≥180 ms. In the present study, these cutoff values of ABI and upstroke time were used for severity assessment of atherosclerosis but not for diagnosis of PAD.

Statistical Analysis

All reported probability values were 2 sided, and a probability value of <0.05 was considered statistically significant. Continuous variables are summarized as means±SD and were compared by using unpaired Student *t* test. Categorical variables are presented as frequencies and percentages and were

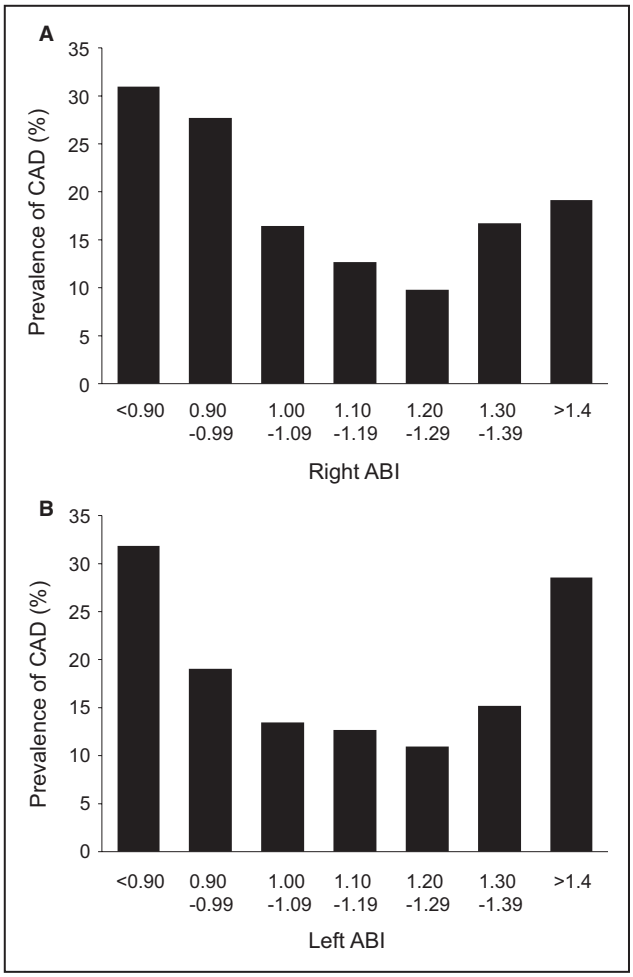

Figure 3. Bar graphs show the prevalence of coronary artery disease (CAD) according to ankle-brachial index (ABI) in right (A) and left (B) legs.

compared by means of the χ^2 test. The Cochran-Armitage trend test was used to assess the trend of ordered categorical variables for the association between ABI and proportion of subjects with prolonged upstroke time and the association between upstroke time and prevalence of CAD. Multiple logistic regression analyses were performed to identify independent variables associated with upstroke time or CAD. Age, sex, body mass index, heart rate, hypertension, dyslipidemia, diabetes mellitus, smoking status, hemodialysis, and ABI were entered as covariates into the model of the relationships between prolonged upstroke time and variables. Age, sex, body mass index, heart rate, systolic blood pressure, antihypertensive drug treatment, dyslipidemia, diabetes mellitus, glucose level, smoking status, and hemodialysis were entered into the model for the association between CAD and ABI. In addition to those variables, ABI was also entered into the model for the association between CAD and upstroke time. Upstroke time was entered into the models as a categorical variable (normal and prolonged upstroke time) or a continuous measure (every 1-SD increase of upstroke time). Subgroup analyses were performed separately for subjects with normal, low, and high ABI. Multivariate analysis was not performed because of the small number of patients with CAD among patients with high ABI (n=22). The data were processed using JMP version pro 14 (SAS Institute, Cary, NC).

RESULTS

Baseline Clinical Characteristics

The baseline clinical characteristics of the subjects are summarized in Table 1. Of the 2313 participants, 329 (14.2%) had CAD. Mean values were 1.15±0.13 for right ABI, 1.14±0.14 for left ABI, 146.0±28.0 ms for right ankle upstroke time, and 146.0±27.8 ms for left ankle upstroke time. The proportion of patients with prolonged upstroke time (≥180 ms) was increased in relation to a decrease in ABI in both the left and right legs (P<0.001) (Figure 2). Multiple logistic regression analyses revealed that more advanced age, lower heart rate, diabetes mellitus, hemodialysis, and lower ABI were

Table 3. Association Between Coronary Artery Disease and ABI

Variable	Odds Ratio (95% CI); *P* Value			
	Unadjusted	Model 1*	Model 2†	Model 3‡
Normal ABI	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Low ABI	2.31 (1.70–3.14); <0.001	2.00 (1.44–2.78); <0.001	1.87 (1.29–2.70); <0.001	1.79 (1.18–2.70); 0.006
High ABI	2.50 (1.51–4.13); <0.001	2.26 (1.33–3.86); 0.003	2.61 (1.43–4.75); 0.002	1.85 (0.96–3.57); 0.07

ABI indicates ankle-brachial index.
*Model 1: adjusted for age and sex.
†Model 2: adjusted for age, sex, body mass index, heart rate, hypertension, dyslipidemia, diabetes mellitus, and smoking status.
‡Model 3: adjusted for age, sex, body mass index, heart rate, systolic blood pressure, antihypertensive drug treatment, dyslipidemia, diabetes mellitus, glucose level, smoking status, and hemodialysis.

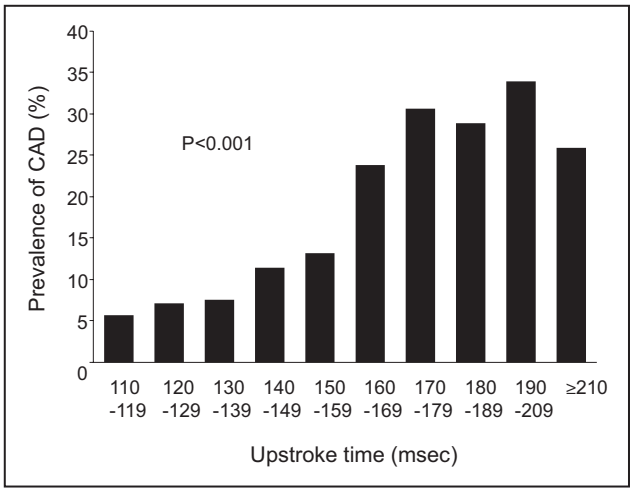

Figure 4. Bar graphs show the prevalence of coronary artery disease (CAD) according to upstroke time.

significantly associated with prolonged upstroke time in both the left and right legs (Table 2).

Association Between ABI and CAD

The prevalence of CAD according to ABI had a reverse J-shaped distribution in both the right and left legs (Figure 3A and 3B). We divided the participants into 3 groups according to ABI (low ABI: ABI <1.00; normal ABI: 1.00 ≤ ABI ≤ 1.40; and high ABI: ABI >1.40). The baseline clinical characteristics are summarized in Table 1. Of the 2313 subjects, 274 (11.8%) had low ABI and 85 (3.7%) had high ABI. The prevalence of CAD was higher in patients with low ABI and patients with high ABI than in subjects with normal ABI (24.5% in the low ABI group versus 12.3% in the normal ABI group versus 25.9% in the high ABI group; *P*<0.001) (Table 1). Multiple logistic regression analysis revealed that low ABI was significantly associated with an increased risk of CAD (odds ratio [OR], 1.79; 95% CI, 1.18–2.70; *P*=0.006) after adjustments for other traditional cardiovascular risk factors (Table 3).

Association Between Upstroke Time and CAD

The higher upstroke time value of either side was used for analysis. The prevalence of CAD increased in relation to an increase in upstroke time (*P*<0.001) (Figure 4). We divided the participants into 2 groups according to upstroke time (normal upstroke time: <180 ms; prolonged upstroke time: ≥180 ms). The baseline clinical characteristics are summarized in Table 1. Of the 2313 subjects, 321 (13.9%) had prolonged upstroke time. The prevalence of CAD was significantly higher in patients with prolonged upstroke time than in subjects with normal upstroke time (29.6% versus 11.8%; *P*<0.001) (Table 1). Multiple logistic regression analysis revealed that prolonged upstroke time was significantly associated with an increased risk of CAD (OR, 1.61; 95% CI, 1.07–2.44; *P*=0.02) after adjustments for other traditional cardiovascular risk factors (Table 4). Every 1-SD increase of upstroke time was significantly associated with an increased risk of CAD (OR, 1.32; 95% CI, 1.11–1.56; *P*=0.002) after adjustments for other risk factors (Table 4).

Association Between Upstroke Time and CAD in Subjects With Normal ABI

Next, we divided the subjects with normal ABI into 2 groups according to upstroke time. The clinical characteristics are summarized in Table 5. Of the 1954 subjects with normal ABI, 173 (8.9%) had prolonged upstroke time. The prevalence of CAD was significantly higher in patients with prolonged upstroke time than in subjects with normal upstroke time (29.5% versus 10.6%; *P*<0.001) (Figure 5). Multiple logistic regression analysis revealed that prolonged upstroke time was significantly associated with an increased risk of CAD

Table 4. Association Between Coronary Artery Disease and Upstroke Time

Variable	Odds Ratio (95% CI); *P* Value			
	Unadjusted	Model 1*	Model 2†	Model 3‡
Normal upstroke time	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Prolonged upstroke time	3.16 (2.40–4.16); <0.001	2.65 (1.96–3.59); <0.001	2.11 (1.51–2.95); <0.001	1.61 (1.07–2.44); 0.02
Every 1-SD (30.3-m/s) increment of upstroke time	1.62 (1.47–1.80); <0.001	1.52 (1.27–1.71); <0.001	1.45 (1.27–1.64); <0.001	1.32 (1.11–1.56); 0.002

*Model 1: adjusted for age and sex.
†Model 2: adjusted for age, sex, body mass index, heart rate, hypertension, dyslipidemia, diabetes mellitus, and smoking status.
‡Model 3: adjusted for age, sex, body mass index, heart rate, systolic blood pressure, antihypertensive drug treatment, dyslipidemia, diabetes mellitus, glucose level, smoking status, hemodialysis, and ankle-brachial index.

Table 5. Clinical Characteristics of Subjects With Normal Ankle-Brachial Index According to UT

Variables	Normal UT (n=1781)	Prolonged UT (n=173)	*P* Value
Age, y	60.3±15.2	66.0±14.9	<0.001
Men, n (%)	1111 (62.4)	87 (50.3)	0.002
Body mass index, kg/m^2	24.1±3.9	23.5±3.6	0.03
Systolic blood pressure, mm Hg	132.3±18.5	132.7±19.0	0.78
Diastolic blood pressure, mm Hg	79.2±12.4	73.8±12.2	<0.001
Heart rate, bpm	69.6±11.9	61.9±9.0	<0.001
Total cholesterol, mmol/L	4.98±0.95	4.83±1.08	0.06
Triglycerides, mmol/L	1.61±1.20	1.58±1.57	0.79
HDL cholesterol, mmol/L	1.54±0.43	1.54±0.44	0.99
LDL cholesterol, mmol/L	2.89±0.83	2.73±0.86	0.02
Glucose, mmol/L	6.16±1.80	6.95±2.95	<0.001
HbA1c, %	5.5±0.9	5.7±0.9	0.03
Creatinine, μmol/L	76.8±58.4	83.6±78.5	0.18
Smoking status, n (%)			
Never smoker	835 (47.2)	83 (48.0)	0.96
Ex-smoker	604 (34.1)	31 (17.9)	
Current smoker	331 (18.7)	59 (34.1)	
Complication, n (%)			
Hypertension	1478 (83.0)	141 (81.5)	0.62
Dyslipidemia	1261 (70.8)	132 (76.3)	0.13
Diabetes mellitus	443 (24.9)	66 (38.2)	<0.001
Coronary artery disease	189 (10.6)	51 (29.5)	<0.001
Previous myocardial infarction	70 (3.9)	19 (11.0)	<0.001
Angina pectoris	159 (8.9)	45 (26.0)	<0.001
Prior coronary revascularization procedure	153 (8.6)	37 (21.4)	<0.001
Stroke	115 (6.5)	16 (9.3)	0.16
Hemodialysis	11 (0.62)	3 (1.73)	0.10
Medications, n (%)			
Antihypertensive drugs	1212 (68.1)	117 (67.6)	0.91
Lipid-lowering drugs	611 (34.3)	90 (52.0)	<0.001
Antidiabetic drugs	296 (16.6)	58 (33.5)	<0.001

Data are given as mean±SD unless otherwise indicated. bpm indicates beats per minute; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and UT, upstroke time.

(OR, 2.33; 95% CI, 1.41–3.87; *P*=0.001) among subjects with normal ABI (Table 6). Every 1-SD increase of upstroke time was significantly associated with an increased risk of CAD (OR, 1.71; 95% CI, 1.36–2.14; *P*<0.001) after adjustments for other risk factors (Table 6).

Association Between Upstroke Time and CAD in Patients With Low ABI

We divided the patients with low ABI into 2 groups according to upstroke time. The clinical characteristics are summarized in Table 7. There was no significant difference in the prevalence of CAD between patients with normal upstroke time and patients with prolonged upstroke time (22.5% versus 26.5%; *P*=0.44) among patients with low ABI (Table 7). Multivariate logistic regression analysis revealed that there was no significant association between upstroke time and CAD (OR, 1.24; 95% CI, 0.72–2.16; *P*=0.44) (Table 6). There was no significant association between every 1-SD increase of upstroke time and CAD (OR, 1.03; 95% CI, 0.86–1.23; *P*=0.75) (Table 6).

Association Between Upstroke Time and CAD in Patients With High ABI

We divided the patients with high ABI into 2 groups according to upstroke time. The clinical characteristics are summarized in Table 8. The prevalence of CAD was significantly higher in patients with prolonged upstroke time than in subjects with normal upstroke time (66.7% versus 19.2%; *P*<0.001).

DISCUSSION

In the present study, we demonstrated that not only abnormal ABI but also prolonged upstroke time at the ankle (≥180 ms) was significantly associated with an increased risk of CAD, indicating that upstroke time is a useful vascular marker to detect patients with

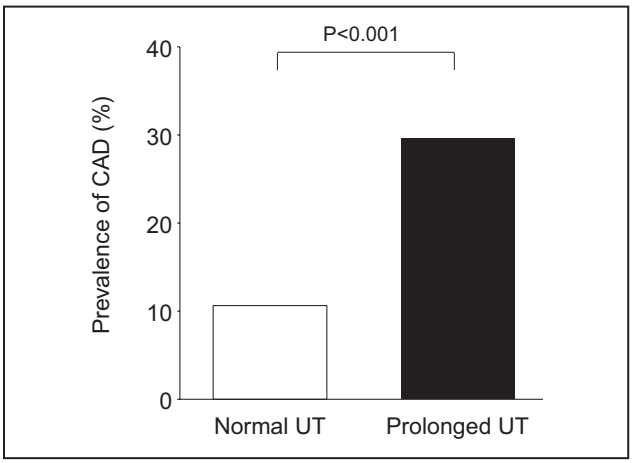

Figure 5. Bar graphs show the prevalence of coronary artery disease (CAD) in subjects with normal upstroke time (UT) and subjects with prolonged UT.

Table 6. Association Between CAD and Upstroke Time in Subjects With Normal ABI and Patients With Low ABI

Variable	Odds Ratio (95% CI); *P* Value			
	Unadjusted	Model 1*	Model 2†	Model 3‡
Normal ABI				
Normal upstroke time	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Prolonged upstroke time	3.52 (2.46–5.05); <0.001	3.48 (2.34–5.18); <0.001	2.53 (1.61–3.97); <0.001	2.33 (1.41–3.87); 0.001
Every 1-SD (30.3-m/s) increment of upstroke time	2.20 (1.88–2.58); <0.001	2.21 (1.85–2.63); <0.001	1.91 (1.56–2.34); <0.001	1.71 (1.36–2.14); <0.001
Low ABI				
Normal upstroke time	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Prolonged upstroke time	1.24 (0.72–2.16); 0.44	0.91 (0.48–1.73); 0.78	0.94 (0.45–1.95); 0.87	0.44 (0.17–1.12); 0.09
Every 1-SD (30.3-m/s) increment of upstroke time	1.03 (0.86–1.23); 0.75	0.93 (0.75–1.15); 0.49	1.01 (0.76–1.34); 0.94	0.81 (0.55–1.19); 0.28

ABI indicates ankle-brachial index; and CAD, coronary artery disease.
*Model 1: adjusted for age and sex.
†Model 2: adjusted for age, sex, body mass index, heart rate, hypertension, dyslipidemia, diabetes mellitus, and smoking status.
‡Model 3: adjusted for age, sex, body mass index, heart rate, systolic blood pressure, antihypertensive drug treatment, dyslipidemia, diabetes mellitus, glucose level, smoking status, hemodialysis, and ABI.

advanced atherosclerosis. In particular, among subjects with normal ABI (1.00 ≤ ABI ≤ 1.40), the prevalence of CAD was significantly higher in patients with prolonged upstroke time than in subjects with normal upstroke time. In addition, multiple logistic regression analysis revealed that there was a significant association between prolonged upstroke time and an increased risk of CAD even after adjustment for other cardiovascular risk factors. These findings indicate that upstroke time may be a useful vascular marker for detecting patients with advanced atherosclerosis in subjects with normal ABI who are usually considered not to have advanced atherosclerosis by ABI measurement alone.

ABI measurement has been used for many years as a noninvasive test for diagnosis and severity assessment of PAD. ABI has also been used as a marker of generalized atherosclerosis and cardiovascular prognosis.[3,4,14–16] Low ABI related to severe occlusive arterial lesions of the lower extremities and high ABI related to poor arterial compressibility attributable to increased stiffness and calcification of lower limb arteries represent markers of advanced systemic atherosclerosis and vascular diseases in other vascular beds. Therefore, patients with low ABI or high ABI are considered to be at high cardiovascular risk, with higher rates of concomitant cardiovascular diseases and higher incidence of cardiovascular events. Consistent with these previous observations, our results showed that the prevalence of clinical CAD according to ABI had a reverse J-shaped distribution and that abnormal ABI (<1.00 or >1.40), especially low ABI (<1.00), was significantly associated with an increased risk of CAD independent of traditional cardiovascular risk factors, supporting that the ABI is an established marker of atherosclerosis. However, ABI can be unreliable as a marker of atherosclerosis in patients with calcified and noncompressible lower limb arteries because oscillometric ABI can be falsely normalized by falsely elevated ankle blood pressure despite the presence of hemodynamically occlusive arterial disease, potentially leading to misclassifying patients with high cardiovascular risk as being at low risk by ABI measurement alone.[17,18] Therefore, an additional vascular parameter should be combined with ABI to improve the accuracy of ABI for detecting subjects with advanced atherosclerosis.

Change in lower limb volume generated by pulsatile arterial inflow can be recorded using plethysmography. With the advanced technology of pneumoplethysmography using the new cuff method, the waveform of pulse volume recording can be easily obtained in a short time, and pulse volume recording parameters, including upstroke time, are automatically calculated by an automated oscillometric device, leading to objective evaluation and clinical application of pulse volume recording parameters. The waveform of pulse volume recording in patients with hemodynamically occlusive arterial disease tends to be blunted with a delayed peak, leading to prolonged upstroke time. Indeed, the proportion of patients with prolonged upstroke time was increased with a decrease in ABI in the present study. Previous studies have shown that a combination of pulse volume recording parameters, including upstroke time, and ABI improves diagnostic accuracy for PAD.[6,12,19]

Table 7. Clinical Characteristics of Subjects With Low Ankle-Brachial Index According to UT

Variables	Normal UT (n=138)	Prolonged UT (n=136)	*P* Value
Age, y	58.1±16.9	70.6±12.7	<0.001
Men, n (%)	50 (36.2)	49 (36.0)	0.97
Body mass index, kg/m^2	23.4±4.7	22.5±3.6	0.09
Systolic blood pressure, mm Hg	130.3±20.2	138.2±21.2	0.002
Diastolic blood pressure, mm Hg	75.5±13.2	75.0±10.9	0.73
Heart rate, bpm	78.3±14.3	70.1±10.8	<0.001
Total cholesterol, mmol/L	4.78±0.99	4.73±0.95	0.71
Triglycerides, mmol/L	1.49±0.77	1.65±1.16	0.23
HDL cholesterol, mmol/L	1.56±0.49	1.52±0.54	0.61
LDL cholesterol, mmol/L	2.68±0.92	2.58±0.75	0.35
Glucose, mmol/L	7.06±3.11	8.21±3.84	0.11
HbA1c, %	5.8±1.2	6.4±1.1	0.007
Creatinine, μmol/L	1.15±1.50	1.42±1.56	0.17
Smoking status, n (%)			
Never smoker	48 (35.3)	51 (37.5)	0.34
Ex-smoker	52 (38.2)	59 (43.4)	
Current smoker	36 (26.5)	26 (19.1)	
Complication, n (%)			
Hypertension	104 (75.4)	114 (83.8)	0.08
Dyslipidemia	106 (76.8)	107 (78.7)	0.71
Diabetes mellitus	47 (34.1)	74 (54.4)	<0.001
Coronary artery disease	31 (22.5)	36 (26.5)	0.44
Previous myocardial infarction	19 (13.8)	18 (13.3)	0.92
Angina pectoris	25 (18.1)	25 (18.4)	0.95
Prior coronary revascularization procedure	21 (15.2)	32 (23.5)	0.08
Stroke	15 (10.9)	34 (25.2)	0.002
Hemodialysis	9 (6.6)	7 (5.2)	0.62
Medications, n (%)			
Antihypertensive drugs	78 (56.5)	101 (74.3)	0.002
Lipid-lowering drugs	57 (41.3)	84 (61.8)	<0.001
Antidiabetic drugs	30 (21.7)	66 (48.5)	<0.001

Data are given as mean±SD unless otherwise indicated. bpm indicates beats per minute; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and UT, upstroke time.

Table 8. Clinical Characteristics of Subjects With High Ankle-Brachial Index According to UT

Variables	Normal UT (n=73)	Prolonged UT (n=12)	*P* Value
Age, y	60.6±12.7	69.5±7.2	0.02
Men, n (%)	55 (75.3)	9 (75.0)	0.98
Body mass index, kg/m^2	25.6±3.8	22.7±2.9	0.01
Systolic blood pressure, mm Hg	129.4±16.9	118.7±33.4	0.09
Diastolic blood pressure, mm Hg	77.0±11.5	65.2±15.7	0.002
Heart rate, bpm	67.3±8.8	64.8±7.8	0.37
Total cholesterol, mmol/L	4.90±1.10	4.75±0.72	0.66
Triglycerides, mmol/L	1.76±1.44	2.19±2.39	0.41
HDL cholesterol, mmol/L	1.42±0.46	1.42±0.38	0.97
LDL cholesterol, mmol/L	2.92±1.00	2.59±0.57	0.30
Glucose, mmol/L	6.35±1.80	8.42±1.88	<0.001
HbA1c, %	5.4±0.8	5.9±0.5	0.16
Creatinine, μmol/L	128.9±203.3	281.4±312.3	0.04
Smoking status, n (%)			
Never smoker	23 (31.9)	3 (25.0)	0.04
Ex-smoker	33 (45.8)	9 (75.0)	
Current smoker	16 (22.2)	0 (0.0)	
Complication, n (%)			
Hypertension	64 (87.7)	7 (58.3)	0.01
Dyslipidemia	50 (68.5)	7 (58.3)	0.49
Diabetes mellitus	17 (23.6)	6 (50.0)	0.06
Coronary artery disease	14 (19.2)	8 (66.7)	<0.001
Previous myocardial infarction	6 (8.2)	8 (66.7)	<0.001
Angina pectoris	13 (17.8)	7 (58.3)	0.002
Prior coronary revascularization procedure	12 (16.4)	4 (33.3)	0.17
Stroke	5 (6.9)	0 (0.0)	0.35
Hemodialysis	5 (6.9)	4 (33.3)	0.006
Medications, n (%)			
Antihypertensive drugs	52 (71.2)	4 (33.3)	0.01
Lipid-lowering drugs	25 (34.3)	5 (41.7)	0.62
Antidiabetic drugs	11 (15.1)	5 (41.7)	0.03

Data are given as mean±SD unless otherwise indicated. bpm indicates beats per minute; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and UT, upstroke time.

However, there is little information on the usefulness of upstroke time alone or in combination with ABI as a marker of atherosclerosis. In the present study, the prevalence of CAD increased in relation to an increase in upstroke time. In addition, prolonged upstroke time was significantly associated with an increased risk of CAD, indicating that upstroke time

can be used as a marker of atherosclerosis. In particular, the association between prolonged upstroke time and an increased risk of CAD was significant in subjects with normal ABI but not in patients with low ABI, indicating that upstroke time is especially useful for detecting patients with advanced atherosclerosis among subjects with normal ABI who are usually considered not to have advanced atherosclerosis by ABI measurement alone.

Compared with the ABI method, a major advantage of the pulse volume recording method is that the waveform of pulse volume recording that reflects arterial pulsatility may not be significantly affected by the presence of calcified and noncompressible arteries,[20,21] which may contribute to improvement in the diagnostic accuracy of pulse volume recording parameters for PAD in combination with ABI.[6,12,19] Patients with PAD with pseudonormalized ABI attributable to noncompressible lower limb arteries may be included among subjects with normal ABI, leading to an underestimation of the prevalence of PAD and incorrect severity assessment of atherosclerosis by ABI measurement alone.[13,18] Our results suggest that those patients with pseudonormalized ABI can be detected by upstroke time calculated from pulse volume recording, which may not be significantly affected by the presence of noncompressible arteries. Therefore, the recommended procedures for the severity assessment of atherosclerosis by a combination of ABI and upstroke time could be as follows. First, patients with low ABI (<1.00) or high ABI (>1.40) should undergo further evaluation to confirm the presence of CAD. Second, in subjects with normal ABI (1.00 ≤ ABI ≤ 1.40), upstroke time should be checked carefully to detect patients with pseudonormalized ABI who potentially have advanced atherosclerosis. Subjects with normal ABI but with abnormally prolonged upstroke time (≥180 ms) should undergo further evaluation to confirm the presence of CAD.

There are some limitations in the present study. The waveform of pulse volume recording can be profoundly affected by other factors, including heart rate and aortic valve disease. These factors should be taken into account for appropriate interpretation of the results of pulse volume recording. In the present study, patients with severe aortic valve disease were carefully excluded. Stroke is also a lethal cardiovascular condition. The diagnosis of stroke was based on the questionnaire, and we cannot distinguish between the underlying causes of ischemic stroke, including cardioembolic stroke, small-artery occlusion (lacunar infarction), large-artery atherosclerosis, and other determined or undetermined causes in the present study. The prevalence of ischemic stroke associated with atherosclerosis was unknown. Therefore, we only focused on CAD in the present study. It remains unclear whether upstroke time is a useful vascular marker for identifying patients at high risk for incident cardiovascular disease, including CAD. Further study is needed to determine whether upstroke time can be used as a prognostic marker for cardiovascular events in subjects with normal ABI.

In conclusion, upstroke time calculated from pulse volume recording can be used as a marker of atherosclerosis. Upstroke time may be useful for detecting patients with CAD with advanced atherosclerosis among subjects with normal ABI who are usually considered not to have advanced atherosclerosis by ABI measurement alone. More attention should be paid to upstroke time for detecting patients with advanced atherosclerosis, especially in subjects with normal ABI.

ARTICLE INFORMATION

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Disclosures

None.

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