Pulse Waves in the Lower Extremities as a Diagnostic Tool of Peripheral Arterial Disease and Predictor of Mortality in Elderly Chinese

Abstract—Patients with peripheral arterial disease may have elongated upstroke time in pulse waves in the lower extremities. We investigated upstroke time as a diagnostic tool of peripheral arterial disease and predictor of mortality in an elderly (≥60 years) Chinese population. We recorded pulse waves at the left and right ankles by pneumoplethysmography and calculated the percentage of upstroke time per cardiac cycle. Diagnostic accuracy was compared with the conventional ankle-brachial index method (n=4055) and computed tomographic angiography (34 lower extremities in 17 subjects). Upstroke time per cardiac cycle at baseline (mean±SD, 16.4±3.1%) was significantly (P<0.0001) associated with ankle-brachial index in men (n=1803; r=−0.44) and women (n=2252; r=−0.32) and had an overall sensitivity and specificity of 86% and 80%, respectively, for the diagnosis of peripheral arterial disease (upstroke time per cardiac cycle, ≥21.7%) in comparison with computed tomographic angiography. During 5.9 years (median) of follow-up, all-cause and cardiovascular deaths occurred in 366 and 183 subjects, respectively. In adjusted Cox regression analyses, an upstroke time per cardiac cycle ≥21.7% (n=219; 5.4%) significantly (P<0.0001) predicted total and cardiovascular mortality. The corresponding hazard ratios were 1.98 (95% confidence interval, 1.48–2.65) and 2.29 (1.58–3.32), respectively, when compared with those of 2.10 (1.48–3.00) and 2.44 (1.57–3.79), respectively, associated with an ankle-brachial index of ≤0.90 (n=115; 2.8%). In conclusion, pulse waves in the lower extremities may behave as an accurate and ease of use diagnostic tool of peripheral arterial disease and predictor of mortality in the elderly. (Hypertension. 2016;67:527-534. DOI: 10.1161/HYPERTENSIONAHA.115.06666.) • Online Data Supplement

Keywords: aged ■ ankle-brachial index ■ China ■ mortality ■ peripheral arterial disease ■ pulse wave transit time

Current guidelines recommend ankle-brachial blood pressure index (ABI) as a screening diagnostic tool of peripheral arterial disease (PAD).1-3 Pulse waves obtained by the plethysmography technique are usually used as a noninvasive method to position the site of atherosclerotic stenosis.1,3 Already in 1968, pulse waves in the ankles were found equally accurate and useful in the diagnosis of PAD.4 In contrast to the currently recommended and widely used ABI,1-3 pulse waves were, however, much less investigated and rarely used in the diagnosis of PAD,5-7 probably because of the technical difficulty and complexity in obtaining high-quality pulse waves by the use of various pulse volume recording techniques.

Recent oscillometric cuff technology allows accurate pulse volume recording and derives high-quality pulse waveforms in the ankle.8 The foot-to-peak upstroke time (ie, crest time) can then be derived from these pulse waves and standardized by the cardiac cycle. This advanced technology makes the pulse waves in the lower extremities applicable for the diagnosis of PAD in the research setting and in clinical practice. In this study, we investigated in an elderly Chinese population the usefulness of pulse waves in the lower extremities as a diagnostic tool of peripheral arterial oblitative disease and predictor of total and cardiovascular mortality.

Methods

Study Population

Our study was conducted in the framework of the Chronic Disease Detection and Management in the Elderly (≥60 years) Program supported by the municipal government of Shanghai.9-11 In a newly urbanized suburban town, 30 km from the city center, we invited all residents aged ≥60 years to take part in comprehensive examinations of cardiovascular disease and risk. The Ethics Committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine approved the study protocol. All subjects gave written informed consent.

A total of 4203 subjects (participation rate, 90%) were enrolled in the period from 2006 to 2011 and followed up for vital status and cause of death till June 30, 2013. We excluded 148 subjects from the present analysis because the pulse waves were not recorded (n=63) or because of missing other information (n=85). The number of participants included in the present analysis was 4055.
Pulse Wave Recording and ABI Measurement

We performed pulse wave recording and ABI measurement by the use of the Vascular Profiler-1000 device (Omron, Kyoto, Japan), which operates the oscillometric cuff technique and has been validated previously.11,12 Trained technicians or physicians placed the pressure cuffs on both arms and both ankles and performed the measurements, after the subject had rested for >10 minutes in the supine position in a temperature-controlled room in the range of 20 to 24°C.12 The device simultaneously and automatically recorded pulse waves in both ankles and measured blood pressure in the 4 limbs.

Upstroke time was reported by the device as the pulse foot-to-peak transit time. We calculated the percentages of upstroke time per cardiac cycle (UTCC) in pulse waves in the left and right ankles separately and selected the greater one for the diagnosis of PAD and prediction of mortality. ABI was reported by the device as the ratio of the lower ankle over the higher brachial systolic blood pressures.

We performed reproducibility study in 17 subjects and 34 lower extremities and calculated the coefficient of variation as the ratio of the mean difference between the 2 repeated measurements to the SD of the within-subject differences multiplied by 100.13 The intersession coefficient of variation was 1.60% for UTCC and 0.94% for ABI.

Field Work

One experienced physician measured each participant’s blood pressure 3× consecutively using a validated Omron 7051 oscillometric blood pressure monitor (Omron, Kyoto, Japan) on the nondominant arm, after the subjects had rested for at least 5 minutes in the sitting position. The same observer also administered a standardized questionnaire to collect information on medical history, lifestyle, and use of medications. Hypertension was defined as a sitting blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic or as the use of antihypertensive drugs.14

A trained technician measured body height and body weight. Body mass index was calculated as the body weight in kilograms divided by the body height in meters squared.

Venous blood samples were drawn after overnight fasting for the measurement of plasma glucose and serum total cholesterol. Diabetes mellitus was defined as a plasma glucose concentration of at least 7.0 mmol/L fasting or 11.1 mmol/L at any time or as the use of antidiabetic agents.15

Computed Tomographic Angiography

We performed computed tomographic angiography (CTA) on the arteries of the right and left lower extremities in 17 subjects selected according to ABI (ABI ≥0.90, n=15 and ABI <0.90, n=19), using a 64-detector CT scanner (General Electric, Fairfield, CT) with 100 mL of intravenous contrast material Optiray 320 (Ioversol injection 68%: Mallinckrodt Pharmaceuticals, Damastown, Mulhuddart, Dublin, Ireland) at a speed of 3 mL/s. Scanning covered the whole lower extremities with 5-mm slice thickness from common abdominal aorta to planta pedis. However, the images are insufficient for the determination of the degree of luminal stenosis for arteries below the knee. PAD was, therefore, defined as stenosis of ≥50% in the superficial femoral arteries,6,17 The CTA images were evaluated by an experienced radiologist.

Follow-Up

Information on vital status and the cause of death was obtained from the official death certificate, with further confirmation by the local Community Health Center and family members of the deceased people. The International Classification of Diseases Ninth Revision was used to classify the cause of death. Cardiovascular mortality included deaths attributable to stroke, myocardial infarction, and other cardiovascular diseases (International Classification of Diseases Ninth Revision, 390.0–459.9).

Statistics

For database management and statistical analysis, we used SAS software (version 9.13, SAS Institute, Cary, NC). Means and proportions were compared with the Student t test and Fisher exact test, respectively. The receiver operating characteristic (ROC) curve was used to show sensitivity and specificity of UTCC or ABI (≤0.90) for the diagnosis of PAD, defined by CTA-detected stenosis, and to compare the predictive value of UTCC and ABI for total and cardiovascular mortality.

The log-rank test was used to compare the cumulative incidence of mortality between groups with Kaplan–Meier survival function to show the time to death. Multiple Cox regression analysis was performed to compute hazard ratios (HRs) with their 95% confidence intervals (CIs). HRs (95% CI) for mortality were computed for each quintile against the total study population in a single model. In additional analyses, we calculated at all cutoff points ranging from the fifth to 95th percentile distribution of UTCC the HR for both total and cardiovascular mortality in those exceeded the cutoff point versus the total study population. We plotted these HRs and their CIs against the corresponding cutoff points and identified the cutoff point where the lower confidence limit exceeded 1.18 In sensitivity analyses, we studied the heterogeneity between subgroups according to baseline characteristics. We performed the net reclassification analysis,19 while accounting for the European SCORE.20

Results

Characteristics of the Study Participants

At baseline, the 4055 participants (1803 [44.5%] men) had a mean (±SD) age of 68.5±7.5 years and included 2448 (60.4%) hypertensive patients and 353 (8.7%) diabetic patients. Table 1 shows the baseline characteristics by sex. Men and women differed significantly (P<0.02) in all characteristics except for the use of antihypertensive drugs (39.5%; P=0.18) and the prevalence of hypertension (65.4%; P=0.87) and PAD diagnosed by ABI (≤0.90; 2.8%; P=0.72).

Overall, UTCC had a slightly but significantly skewed distribution (P<0.01; Figure S1 in the online-only Data Supplement), with a mean±SD of 16.4%±3.1%. Men, compared with women, had significantly (P<0.0001) shorter upstroke time (−5.8 ms), slower heart rate (−1.9 bpm), and accordingly a smaller UTCC (−0.9%). UTCC was not different (P>0.20) between users of single-pill combinations of hydrochlorothiazide plus reserpine or clonidine (n=859), calcium-channel blockers (n=319), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (n=114), or nitrates (n=19).

Diagnostic Accuracy of Pulse Waves When Compared With ABI and CTA

UTCC was significantly (P<0.0001) and negatively associated with ABI in men (n=1803; r=−0.44) and women (n=2252; r=−0.32; Figure 1), and in men and women combined was significantly greater in patients with an ABI of ≤0.90 than subjects with a normal ABI (20.9% versus 16.2%; P<0.0001).

We performed CTA on the arteries of 34 lower extremities in 17 subjects selected according to ABI (ABI≤0.90, n=15; ABI>0.90; n=19). Of the 34 lower extremities, 14 had PAD on CTA, with arterial stenosis of ≥50% or total occlusion. We studied the accuracy of ABI and UTCC against CTA for the diagnosis of PAD using the ROC curve method. The area under the ROC curve, sensitivity, and specificity were 88%, 85%, and 86%, respectively, for ABI (≤0.94), and 93%, 86%, and 80%, respectively, for UTCC (≥21.7%).
Prediction of the Pulse Waves for Mortality

During 5.9 years (median) of follow-up, the cumulated number of person-years was 20,459, and all-cause and cardiovascular deaths occurred in 366 and 183 subjects, respectively.

In analyses adjusted for age, sex, body mass index, current smoking, alcohol intake, hypertension, diabetes mellitus, and serum total cholesterol, we first investigated the risk of mortality associated with UTCC being above the cutoff point defined by CTA (≥21.7%; n=219, 5.4%). The HRs were 1.98 (95% CI, 1.48–2.65) and 2.29 (95% CI, 1.58–3.32) for total and cardiovascular mortality, respectively (Table 2), when compared with that of 2.10 (95% CI, 1.48–3.00) and 2.44 (95% CI, 1.57–3.79), respectively, associated with an ABI of ≤0.90 (n=115; 2.8%).

Further analyses according to the quintile distributions of UTCC demonstrated a J-shaped relationship with the incidence rate of total and cardiovascular mortality (Figures 2 and 3). Subjects in quintiles 3 (15.3%–16.8%) and 5 (>18.6%), respectively, had the lowest and highest risks of mortality. The incidence rate per 1000 person-years from quintile 1 to 5 was 9.9, 10.8, 12.7, and 30.0, respectively, for total mortality, and 5.4, 4.4, 4.3, 6.2 and 19.2, respectively, for cardiovascular mortality. In adjusted analyses, the HRs in quintile 5 versus the average risk in the whole-study population were 1.95 and 5.4, 4.4, 4.3, 6.2 and 19.2, respectively, had the lowest and highest risks of mortality. The value for UTCC determined at all cutoff points ranging from the fifth to 95th percentile the HR for both total and cardiovascular mortality remained unaltered.

In an effort to define cutoff points of UTCC in a more precise manner for risk stratification in clinical practice, we calculated at all cutoff points ranging from the fifth to 95th percentile the HR for both total and cardiovascular mortality in those exceeded the cutoff point versus the total study population (Figure 4). The lower boundary of the 95% CI of the risk crossed the HR 1 at 15.7% and 16.0% for total and cardiovascular mortality, respectively. The results of these analyses suggest that a value <16% (approximated to the lower limit of quintile 4) of UTCC is probably not associated with increased risk of mortality (Figure 3).

We performed sensitivity analyses on the risk associated with a UTCC of ≥21.7% according to various baseline characteristics (Table 2). None of the interactions were statistically significant (P≥0.10). We also performed analysis after exclusion of 12 subjects with an ABI of ≥1.3. Our findings remained unaltered.

Finally, the ROC curve method showed that UTCC was slightly and nonsignificantly (P≥0.10) better than ABI in the
prediction of total and cardiovascular mortality (Figure 5). The area under the ROC curve for UTCC and ABI was 0.63 and 0.60, respectively, for total mortality, and 0.66 and 0.63, respectively, for cardiovascular mortality.

After accounting for the European SCORE, net reclassification improvement for UTCC of ≥21.7% was significantly (P<0.001) positive for total (9.3%; 95% CI, 4.9% to 13.7%) and cardiovascular mortality (13.4%; 95% CI, 6.4% to 20.4%).

Discussion

Our study demonstrated that the elongated upstroke time in pulse waves in the lower extremities as assessed by plethysmography and standardized by cardiac cycle had similar diagnostic accuracy of PAD as ABI and independently predicted total and cardiovascular mortality. Indeed, the UTCC of ≥21.7% had 86% sensitivity and 80% specificity in comparison with the noninvasive standard CTA method. PAD diagnosed by this method of pulse waves had a prevalence of 5.4% in our elderly Chinese population and was associated with 98% and 129% higher total and cardiovascular mortality, respectively.

In comparison with the currently recommended ABI method,1–3 a major advantage of this pulse wave method is that all the diagnostic information can be obtained on a single limb. In doing so, the diagnostic accuracy would not be influenced by measurement on the upper limbs. On extreme conditions, such as arterial stenosis on both arms, the diagnostic accuracy can still be assured. Another advantage of the pulse volume recording technique is that it is valid even for calcified incompressible arteries. The test does not rely on occlusion of the calcified artery as is necessary for cuff-based blood pressure measurement. Nonetheless, this pulse wave method relies on advanced technology of pneumoplethysmography.

The pulse volume recording technique has been available in clinical practice for a century21 but has become applicable for accurate measurement of upstroke time only within a decade with the new cuff method.8,22 This technical difficulty may to some extent explain why the pulse wave method has not been studied as extensively as the ABI method for the diagnosis of PAD.

Despite that the plethysmography pulse wave method has not been sufficiently studied for clinical usefulness, its accuracy for the diagnosis of PAD had been studied in the early

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The hazard ratios express the risk for the upstroke time per cardiac cycle of ≥21.7% compared with the rest of the study participants. The COX models were adjusted for age, sex, body mass index, current smoking, alcohol intake, hypertension, diabetes mellitus, and serum cholesterol. CI indicates confidence interval; and CVD, cardiovascular disease.
In 1940, a photoelectric plethysmography method was proposed for estimating the arterial blood supply in a case of intermittent claudication. In 1968, the accuracy of pulse waves for the diagnosis of PAD was studied in an adequately designed study, in parallel with ABI, in 146 limbs with angiographically diagnosed PAD. Two parameters of pulse waves, namely, the upstroke time and the width of pulse waves at the half amplitude, were standardized to heart rate. The study clearly indicated that the pulse waves were similarly sensitive (90% for upstroke time versus 80% for ABI).

**Figure 2.** Kaplan–Meier survival curve for total (left) and cardiovascular disease (CVD, right) mortality according to quintile distributions of upstroke time per cardiac cycle (UTCC). The survival curve for the subjects with a UTCC of ≥21.7% is also shown.

**Figure 3.** Multivariable-adjusted hazard ratios (95% confidence intervals [CIs]) for total (left) and cardiovascular disease (CVD) mortality (right) by quintiles of upstroke time per cardiac cycle (UTCC). The hazard ratios express the risk in quintiles compared with the average risk in the whole-study population and were adjusted for age, sex, body mass index, current smoking, alcohol intake, hypertension, diabetes mellitus, and serum total cholesterol. The number of deaths and the incidence rate per 1000 person-years are given for each quintile.
for the diagnosis and follow-up of patients with PAD. These previous and several subsequent studies on the use of pulse volume recording used photoelectric plethysmography technique. Our study used a pneumatic plethysmography technique. After standardization to heart rate, the upstroke time achieved similar accuracy as ABI for the diagnosis of PAD.

Our study is the first that has demonstrated significant and independent predictive value of UTCC in pulse waves for mortality. By using the cutoff limit (≥21.7%) identified in the study against CTA, the prevalence of PAD was 5.4%. These patients with PAD had 98% and 129% higher total and cardiovascular mortality, respectively. The predictive value was similar to that of ABI in our study in elderly Chinese and other studies in the elderly. However, in our study, the prevalence of PAD diagnosed by the pulse waves (5.4%) was approximately twice that by ABI (2.8%). The pulse wave method may identify patients who are at high risk but missed by the ABI method (4.1% of the total study population). In addition, a value of ≤16.0%, far lower than the cutoff limit (≥21.7%), was possibly not associated with increased risk of mortality. People whose UTCC was in the interval between 16.0% and 21.7% might also have high cardiovascular risk, such as artherosclerotic plaques or stenosis of <50%. However, the relationship between UTCC and mortality was J-shaped, not linear. Subjects in quintiles 1 and 2 tended to have slightly higher risk of mortality than quintile 3. Similar J-shaped relationship was observed for ABI and mortality previously and in this study (data not shown). Arterial

![Figure 4](image1.png)

**Figure 4.** Multivariable-adjusted hazard ratios (95% confidence intervals [CIs]) for total (left) and cardiovascular disease (CVD) mortality (right) by cutoff points ranging from the fifth to 95th percentile for upstroke time per cardiac cycle (UTCC) in pulse waves. The hazard ratios express the risk in subjects whose UTCC exceeds the cutoff point compared with the average risk in the whole-study population. The hazard ratios were adjusted for age, sex, body mass index, current smoking, alcohol intake, hypertension, diabetes mellitus, and serum total cholesterol.

![Figure 5](image2.png)

**Figure 5.** Receiver operating characteristic curves for the prediction of total (left) and cardiovascular disease (CVD) mortality (right). Solid and dotted lines represent upstroke time per cardiac cycle (UTCC) and ankle-brachial blood pressure index (ABI), respectively. AUC indicates area under curve.
stiffness and calcification may be an explanation why those with a low UTCC or high ABI have increased risk. The exact mechanism for this nonlinear relationship remains under investigation.

Our study demonstrated that the UTCC in the pulse waves predicted not only cardiovascular but also noncardiovascular mortality. This finding remains incompletely understood. A speculative explanation is that elongated upstroke time may also be an indicator of damages in organs other than the heart, brain, and kidneys and therefore predict deaths attributable to noncardiovascular diseases.

Our study should be interpreted within the context of its strengths and limitations. We measured ABI and upstroke time of the pulse waves in a relatively large number of elderly subjects. We studied the diagnostic accuracy of the pulse wave method against the current ABI method and the standard CTA imaging method and the prognostic significance for mortality in the same study population. Nonetheless, the CTA study was only performed in a small number of subjects and lower extremities. CTA studies of large sample size or studies using other imaging techniques, such as digital subtraction angiography, are apparently required. Another limitation was that our analysis was restricted to mortality. Information on nonfatal cardiovascular events was not currently available. Our study included only a small number of patients with an ABI of ≥1.3 and therefore had inadequate power to perform analysis in this group of patients. However, after exclusion of these subjects, our findings remained unaltered. ABI was obtained using oscillometry. This method has been shown to overestimate blood pressure in the ankle and thereby underestimate the prevalence of PAD. Moreover, this technique does not provide information on which vessel (dorsalis pedis or posterior tibialis) is used for the computation of ABI. Finally, we only measured serum total cholesterol but not high-density lipoprotein cholesterol, and hence in our reclassification analysis had to account for the European SCORE instead of the Framingham risk score.

The pulse wave recording technique used in our study has several physiological limitations. First, the pulse wave depends on peripheral blood flow and hence may be influenced by factors other than vessel patency, such as the sympathetic nerve input. Second, severe congestive heart failure may also slow blood flow and mimic inflow disease. Nonetheless, such patient was not included in our study. Third, the pulse wave represents the total blood flow through the area being assessed, and therefore, it cannot provide accurate diagnostic information on where and to what extent a specific artery is diseased. Fourth, the pulse wave recording involves susceptibility to interference from factors, such as patient movement, which can result in artifact in the detection of signal and in subsequent poor quality pulse wave recordings. In addition, the pulse wave recording in the diagnosis of PAD is frequently performed before and shortly after exercise. This was shown to greatly increase the diagnostic capacity of this technique. However, for practical reasons in our elderly population study, pulse wave recording was only performed at rest in the supine position.

In conclusion, pulse waves in the lower extremities, obtained by plethysmography and standardized by cardiac cycle, may behave as an accurate, ease of use screening diagnostic tool of PAD and predictor of mortality in the elderly. Pulse wave recording is feasible with the current pneumoplethysmography technology and may be used for the detection or assessment of PAD, especially in patients who are suspected of PAD but have a normal or unmeasurable ABI. Nonetheless, because the incremental value over and above ABI is modest, we propose this pulse wave method as a complementary tool for the diagnosis of PAD.

**Perspectives**

The prevalence of PAD increases with age advancing. Thus, with the increasing longevity and the increasing prevalence of atherosclerotic risk factors in most countries, there could be an emerging epidemic of PAD. New and advanced technology needs to be further developed to improve the management of this disease. The pulse volume recording technique used in this study might behave as a complementary to or alternative of the ABI method in the diagnosis of PAD, especially when dedicated devices become available. Nonetheless, the clinical usefulness of this technique requires confirmation from other prospective observational or interventional studies. Future studies should also investigate the arterial structural characteristics of the elongated upstroke time in pulse waves.

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**Disclosures**

Ji-Guang Wang reports receiving grants and lecture and consulting fees from Omron Healthcare (Kyoto, Japan). The other authors report no conflicts.

**References**

the ACC/AHA Task Force on practice guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; Trans-Atlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2001;113:e463–e654. doi: 10.1161/CIRCULATIONAHA.106.174526.


Novelty and Significance

What Is New?

• In an elderly population, we investigated the upstroke time of pulse waves in the lower extremities as a diagnostic tool of peripheral arterial disease and predictor of mortality.

What Is Relevant?

• Pulse wave recording is feasible with the current pneumoplethysmography technology and may be used for the detection or assessment of peripheral arterial disease, especially in patients who are suspected of peripheral arterial disease but have a normal or unmeasurable ankle-brachial index.

Summary

We found that the elongated upstroke time in pulse waves in the lower extremities, as assessed by plethysmography and standardized by cardiac cycle, had similar diagnostic accuracy of peripheral arterial disease as ankle-brachial index and independently predict total and cardiovascular mortality.
Pulse Waves in the Lower Extremities as a Diagnostic Tool of Peripheral Arterial Disease and Predictor of Mortality in Elderly Chinese
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Pulse Waves in the Lower Extremities as a Diagnostic Tool of Peripheral Arterial Disease and Predictor of Mortality in Elderly Chinese

Short title: Pulse Waves, Peripheral Arterial Disease and Mortality

Chang-Sheng Sheng, Yan Li, Qi-Fang Huang,

Yuan-Yuan Kang, Fei-Ka Li, Ji-Guang Wang

Centre for Epidemiological Studies and Clinical Trials, Shanghai Key Laboratory of Hypertension, The Shanghai Institute of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.

Corresponding Author and Reprints: Ji-Guang Wang, MD, PhD, The Shanghai Institute of Hypertension, Ruijin 2nd Road 197, Shanghai 200025, China Tel: +86 21 6437 0045 ext 610911; fax: +86 21 6466 2193. Email: jiguangwang@aim.com
Figure S1. Distributions of upstroke time per cardiac cycle (UTCC) in all subjects