Background: Carotid atherosclerosis (CA) is a common disease in middle-aged and elderly people, which is closely related to cardiovascular and cerebrovascular disease. In this study, we investigated the benefits of the electrocardiogram (ECG)-based R wave pulse wave index (ERWVI) for the diagnosis of CA.

Material/Methods: According to CA examinations by color Doppler ultrasound, patients were assigned to positive and negative groups. The ECG R wave-Pulse wave transit time (ERWPTT) was obtained by synchronously collecting ECG signals (R wave in ECG) and the time variations in maximum finger pulse oxygen (DOP) on the ECG monitor.

Results: ERPWI was positively correlated with sex, age, BMI, diastolic/systolic blood pressure, fasting blood glucose, uric acid, cholesterol and triglyceride levels, LDL-cholesterol, non-alcoholic fatty liver disease (NAFLD), creatinine, and homocysteine, and was negatively correlated with HDL-cholesterol (P<0.05). With the increase of ERPWI, the incidence of CA significantly increased to various degrees among the subgroups (P<0.05). The binary logistic regression model showed that ERPWI was an independent risk factor for atherosclerosis. The ROC curve showed that when ERPWI was above 0.505, the incidence of CA increased significantly.

Conclusions: There is a close relationship between ERPWI and CA. ERPWI is an independent risk factor for CA. ERPWI ≥0.505 can be used as a diagnostic threshold for CA and a reference index for the diagnosis of CA.
Background

Atherosclerosis is a common disease in middle-aged and elderly people, which is closely related to cardiovascular and cerebrovascular disease [1]. Color Doppler ultrasound is the most direct and common method for the diagnosis of atherosclerosis at present, but it requires expensive equipment and good technical conditions [2]. Recently, the role of pulse wave velocity (PWV), one of the classical indicators of arterial elasticity in atherosclerosis, has attracted increased attention [3]. The electrocardiogram (ECG)-R wave-Pulse wave Velocity (ERPWV) and ERWPTT can be simultaneously obtained through assessment of photoelectric pulses in the toes and the times between peak R waves.

Several studies have shown that the ECG R wave-Pulse wave transit time (ERWPTT) can be obtained by simultaneously collecting the time difference between the peak of R wave in ECG and the peak of photoelectric pulse wave in toes, and then ERWPTT can be calculated [4–6]. This method is feasible and economical. However, due to the influence of blood pressure and nerve inputs, the accuracy of ERPWV for the assessment of atherosclerosis is low and its use is not practical. The present study investigated the elasticity index of vessels (an intrinsic hardness index of blood vessels that is independent of blood pressure) through initial measurements of ERPWV. We set the vascular elasticity index calculated by ERPWV as the ERPWI. By comparing with the results of CA detected by color Doppler ultrasound, we assessed the accuracy and practicability of ERPWI in the diagnosis of CA. Finally, the diagnostic threshold of ERPWI for CA was obtained.

Material and Methods

Patients

From July 2016 to 2018, a total of 885 patients from the physical examination population of Ganzhou Municipal Hospital and Ganzhou People's Hospital were randomly selected for participation. Among the 885 participants, the following conditions led to exclusion: incomplete clinical data, atrial fibrillation, frequent premature systole, severe aortic valve disease, severe organic and conductive heart disease (e.g., heart failure, severe respiratory failure, and severe renal insufficiency), peripheral vascular disease, limb tremor, and limb disability or deformity. Finally, 846 patients were recruited. The study conformed to all ethics standards outlined in the Declaration of Helsinki and approval was provided by the hospital Ethics Committee. Subjects gave informed consent after details on the aims and study protocol were explained. Carotid artery detections were performed using color Doppler ultrasound, and patients were sub-divided into CA-positive and CA-negative (no atherosclerosis) groups.

Diagnostic criteria

Standardized questionnaires were used for interviews. The contents of the questionnaires included age, sex, history of major cardiovascular diseases, and smoking history. Height was measured by tape rulers, accurate to 1 cm, weight was measured by calibrated platform scales to an accuracy of ~0.1 kg. BMI = body weight in kg/height$^2$ (m$^2$). The subjects sat up in chairs and we measured their blood pressure with a mercury sphygmomanometer. Blood pressure was assessed after 5-min intervals. Data are presented as the means of 2 measurements. All biochemical indicators were detected through an automatic analyzer (Olympus, AU 400, Japan); smoking was divided into non-smoking (no cigarettes in the last calendar year) and smoking (lifetime consumption of ≥20 packs of cigarettes, lifetime tobacco use ≥500 g, or at least 1 cigarette per day for 1 year). The diagnosis of fatty liver was based on the results of abdominal ultrasonography (Philips IU 22), which was performed by trained technicians and general technicians. According to the Asia-Pacific Working Group on Fatty Liver and the Chinese Association for the Study of Liver Diseases [7,8], ultrasound examination of fatty liver revealed at least 2 abnormal manifestations in the following 3 categories: (A) increased liver: kidney echo; (B) decreased liver echo; and (C) poor structure after the exclusion of excessive alcohol abuse and other liver diseases.

Inclusion criteria

The following inclusion criteria were met: (1) men and women 21–80 years old, (2) healthy lower limbs, (3) good general condition to meet the demands of the various examinations, (4) color Doppler ultrasonography of the carotid artery showed favorable outcomes, and (5) intima-media of the carotid artery was clear.

Exclusion criteria

Patients were excluded if the following occurred: (1) atrial fibrillation, (2) frequent premature contraction, (3) severe aortic valve disease, (4) severe heart failure, (5) severe respiratory failure, (6) severe renal insufficiency, (7) other serious organic and conductive heart diseases, (8) peripheral vascular disease, limb tremors, limb disability or deformities, and (9) missing clinical information.

Grouping standards

We used a Philips IU 22 full digital color Doppler ultrasound diagnostic instrument (6–11 MHz, wall filter 50–100 MHz). After resting in supine position for at least 10 min, patients placed their necks in a straightened position and bilateral carotid artery imaging was performed. The carotid atherosclerosis group...
had a carotid intima thickness (IMT) \(\geq 1.2 \text{ mm} \) or IMT \(\leq 1.2 \text{ mm} \) with the intima of the carotid artery being rough with uneven thickening. The normal carotid artery group had an IMT <1.2 mm with smooth carotid intima, dark zones in the middle layer, uniform thickness, and bright adventitia.

**Calculation of ERPWI**

**Calculation of ERPWV**

Subjects were asked to lie flat for 5 min and were assessed by a trained doctor: The distance from the second rib of the sternum to the toes (L) was measured \(^9\) (Figure 1). ECGs and pulse oxygen waveforms of the left toes were synchronously recorded on an ECG monitor (Phillips UT4000C-1). The distance between the R waves and pulse oxygen peaks was also assessed and ERWPTT was calculated (Figure 2) using the formula: Pulse Wave Velocity (PWV)=L/ERWPTT.

Unlike the PWV, which can be affected by blood pressure, the vascular elasticity index \(\beta\) is an intrinsic measure of blood pressure hardness \(^10\) \(\beta=\ln \left(\frac{\text{systolic blood pressure (Ps)}}{\text{diastolic blood pressure (Pd)}}\right) \times 2\pi/(\text{Ps–Pd}) \times (L/\text{ERPWV})^2\) (1).

If Ps/Pd=1n, the blood density \(\rho=1.05 \text{ kg/L} \) \(^11\).

The ERPWV was calculated according to the formula: ERPWV=L/ERWPTT (2).

The elasticity index of the blood vessels was obtained from the combination of formulas (1) and (2):

\[
\text{ERPWI}=\beta=\ln \left(\frac{\text{Ps}}{\text{Pd}}\right) \times 2\pi/(\text{Ps–Pd}) \times (L/\text{ERPWV})^2.
\]

**Statistical analyses**

All data were analyzed using SPSS 22.0. Quantitative data of normal or approximate normal distributions were expressed as the mean±standard deviation (\(\bar{x} \pm s\)). We used the \(t\) test for inter-group comparisons. Frequencies (%) were used for qualitative data, while the chi-square test was used for inter-group comparison. One-way ANOVA was used for group comparisons. Pearson correlation analysis and Spearman correlation analysis were used for normal and non-normal data distributions, respectively. ROC curves were used to evaluate diagnostic indicators. The Youden index, AUC, and ERPW1 specificity and sensitivity for the diagnosis of CA were measured. \(P\) values <0.05 were deemed statistically significant.

**Results**

**Biochemical assessments**

Patients were divided into control and experimental groups according to Doppler US assessments. Biochemical indices were then compared between the groups. Significant higher age, systolic and diastolic blood pressure, fasting blood sugar, creatinine, serum cholesterol, triglycerides, homocysteine, and LDL-cholesterol levels were observed in the CA group compared to the control group. NAFLD was significantly higher in the CA group compared to healthy controls (\(P<0.05\)). No significant differences in BMI, uric acid, HDL-cholesterol, and smoking history were observed between the 2 groups (\(P>0.05\)) (Table 1).

**Clinical indicators**

ERPWI was positively correlated with sex, age, BMI, systolic and diastolic blood pressure, cholesterol, triglyceride, fasting blood sugar, uric acid, LDL-cholesterol, creatinine, homocysteine, and NAFLD. EWPWI was negatively correlated with HDL-cholesterol (\(P<0.05\)). No significant differences in the ERPWI values were observed according to smoking status (\(P>0.05\)) (Table 2).

**ERPWI subgroups with CA**

Patients were divided into Q1, Q2, and Q3 subgroups according to the levels of ERPWI. The occurrence of CA significantly differed across these subgroups. Increasing ERPWI values
Table 1. Comparison of general data and clinical indicators of the subjects.

|                | Normal group | Experimental group | P     | Total  |
|----------------|--------------|--------------------|-------|--------|
| N              | 583          | 263                | <0.001| 846    |
| Male           | 370 (69.68%) | 161 (30.32%)       | <0.001| 531 (62.8%) |
| Female         | 213 (67.62%) | 102 (32.38%)       | <0.001| 315 (37.2%) |
| Age (year)     | 48.8±9.00    | 55.98±8.90         | <0.001| 51.06±9.56 |
| BMI (kg/m²)    | 22.9±3.21    | 22.94±2.73         | 0.92  | 22.95±3.07 |
| SBP (mmHg)     | 120.58±12.81 | 122.64±14.21       | 0.037 | 121.22±13.29 |
| DBP (mmHg)     | 65.22±8.10   | 63.73±9.20         | 0.018 | 64.76±8.48 |
| GLU (mmol/L)   | 5.34±0.56    | 5.53±0.80          | <0.001| 5.40±0.65 |
| UA (umol/L)    | 309.5±84.88  | 308.41±75.07       | 0.853 | 309.19±81.92 |
| TC (mmol/L)    | 5.30±0.92    | 5.55±1.01          | <0.001| 5.37±0.95 |
| TG (mmol/L)    | 1.29±0.84    | 1.44±0.90          | 0.027 | 1.34±0.86 |
| LDL-C (mmol/L) | 3.25±0.80    | 3.43±0.84          | 0.003 | 3.31±0.82 |
| HDL-C (mmol/L) | 100.6±16.90  | 98.01±17.44        | 0.056 | 99.85±17.10 |
| CRP (mmol/L)   | 0.46±0.05    | 0.53±0.06          | <0.001| 0.48±0.06 |
| ERPWI          | 4.44±0.39    | 4.74±0.45          | <0.001| 4.54±0.43 |
| Smoking (%)    | 133 (22.81%) | 47 (17.87%)        | 0.104 | 180 (21.28%) |
| NAFLD (%)      | 146 (25.04%) | 87 (33.08%)        | 0.015 | 233 (27.54%) |

Table 2. Comparison of the 3 subgroups of ERPWI with clinical indicators.

|                | Q1 (n=236) | Q2 (n=304) | Q3 (n=306) | P     |
|----------------|------------|------------|------------|-------|
| Age (year)     | 47.3±9.5   | 50.2±8.7   | 54.8±9.1   | <0.001|
| BMI (kg/m²)    | 21.8±2.7   | 23.0±3.0   | 23.7±3.2   | <0.001|
| SBP (mmHg)     | 113.5±12.0 | 119.1±10.9 | 129.2±12.0 | <0.001|
| DBP (mmHg)     | 61.2±6.3   | 66.5±8.4   | 65.8±9.2   | <0.001|
| GLU (mmol/L)   | 5.2±0.5    | 5.4±0.5    | 5.6±0.8    | <0.001|
| UA (umol/L)    | 281.4±77.6 | 312.9±78.1 | 327.0±83.4 | <0.001|
| TC (mmol/L)    | 5.2±1.0    | 5.4±0.9    | 5.5±1.0    | 0.002 |
| TG (mmol/L)    | 1.0±0.6    | 1.3±0.9    | 1.6±0.9    | <0.001|
| HDL-C (mmol/L) | 1.5±0.4    | 1.4±0.4    | 1.3±0.4    | <0.001|
| LDL-C (mmol/L) | 3.2±0.8    | 3.3±0.8    | 3.4±0.8    | 0.007 |
| CRP (mmol/L)   | 103.3±17.8 | 101.0±16.7 | 96.2±16.3  | <0.001|
| HCY (umol/L)   | 13.0±5.9   | 17.1±8.5   | 19.0±8.1   | <0.001|
| Smoking (%)    | 110 (42.8%)| 123 (40.2%)| 120 (43.0%)| <0.001|
| NAFLD (%)      | 50 (21.2%) | 72 (23.7%) | 58 (19.0%) | 0.361 |
| LIVER(%)       | 23 (9.7%)  | 87 (28.6%) | 123 (40.2%)| <0.001|
were significantly correlated with the increased incidence of CA (P<0.05) (Table 3).

ERPWI and CA

Age, BMI, systolic and diastolic blood pressure, GLU, UA, TC, TG, HDL-cholesterol, LDL-cholesterol, Cr, HCY, sex, LIVER, and other factors are closely related to CA. Binary regression models were used to assess the relationship between ERPWI groupings (co-variant) and atherosclerosis (dependent variable). In the unadjusted model, the risk of CA increased with increased ERPWI (OR=23.0, 95% CI=19.0–27.6, P=0.001). In addition, the relationship between ERPWI and CA was adjusted according to age and sex (OR=22.1, 95% CI=18.2–27.0), (P=0.001). Model II showed increases in both systolic blood pressure and diastolic blood pressure on the basis of model I. The risk ratio of CA was 39.1, 95% CI (32.0–47.4) with each additional unit of ERPWI (P=0.001); model III included serum cholesterol, triglyceride, fasting blood sugar, HDL-cholesterol, LDL-cholesterol, and NAFLD on the basis of model II. The ERPWI increased and remained an independent risk factor for CA (OR=39.8, 95% CI=33.5–50.7, P=0.001) (Table 4).

Diagnostic value of ERPWI for CA

The results showed that ERPWI was a risk factor for CA (OR=2.301, 95% CI=1.754–3.121, P<0.001). ERPWI=0.46±0.05 in the normal group, ERPWI=0.53±0.06 in the CA group, and ERPWI=0.48±0.06 in the general population were compared through Doppler US. The diagnostic potential of the ERPWI was then assessed by ROC curve analysis. When the Youden index was 0.523, the AUC was 0.818 and the 95% CI was 0.786–0.851, indicating significant differences (P<0.001) compared to a chance-diagnosis (AUC=0.5). When the cut-off value of the ERPWI=0.505, the sensitivity and specificity were 0.669 and 0.854, respectively. An ERPWI ≥0.505 can therefore be used as a diagnostic threshold for CA and as a reference index for CA diagnosis (Figure 3).

Discussion

Electrocardiogram (ECG)-R wave and pulse wave photoplethysmography is increasingly used to measure pulse wave conduction velocities (ERPWV). Liu et al. [9] measured the ERPWV from the heart to the left and right earlobes, fingers, and toes, revealing the method to be reproducible. Allen et al. [12] revealed the association of the ERPWV with age, in which a faster conduction velocity of the R-pulse wave was observed in older patients. Wu et al. [5] measured the pulse waves of ECG...
signals through multiple channels and found that ERPWV was correlated with carotid intima thickness, blood sugar levels, hypertension, and body weight. Muoz-Tsorrero et al. [13] assessed 260 patients and found that the ERPWV was positively correlated with brachial artery pulse wave velocity. However, Tsai et al. [14] found that ERPWV measurements were strongly influenced by blood pressure and weakly correlated with atherosclerosis. Detection methods that show no response to blood pressure alterations are therefore urgently required to improve CA detections based on ECG R-wave pulse assessments. The vaso-elastic index derived from the Bramwell-Hill equation is less dependent on blood pressure than PWV [15,16] and is a practical tool for the detection of CA [17,18].

The ERWPTT can be assessed through the synchronization of ECG R waves and pulse waves using the photoelectric volume signals obtained through the ECG monitor. In the present study, the distances between the heart and toes were simultaneously measured. The ERPWV was calculated and the elasticity index of the hemorrhagic tube was obtained from the following formula: $\beta = \ln (Ps/Pd) \cdot 2P/(Ps - Pd) \cdot \left(1 + \frac{1}{PWV^2}\right)$. We termed the elastic index of the blood vessels as the ERPWI.

In this study, after adjusting for common cardiovascular risk factors, ERPWI was identified as a risk factor for CA (OR=39.8, 95% CI=33.5–50.7, P<0.001). The ERPWI in the normal group was 0.46±0.05, which was significantly lower than the 0.53±0.06 observed in the CA group (P<0.001). The ERPWI in the general population was 0.48±0.06. When the Youden index was 0.523, the AUC was 0.818 and the 95% CI was 0.786–0.851, demonstrating a significant difference from a chance-diagnosis (AUC=0.5, P<0.001). At a cut-off values of ERPWI=0.505, the sensitivity was 0.669 and the specificity was 0.854. The ERPWI thus had clinical value in CA diagnosis. An ERPWI ≥0.505 can be used as a diagnostic threshold of CA.

In this study, the elastic index of vessels was introduced to reduce the influence of blood pressure on pulse wave conduction velocity. Since atherosclerosis usually not a homogeneous process in different parts of the body vessel, it is not valid to evaluate the changes of systemic atherosclerosis by measuring the pulse wave velocity in an isolated area of the body. There are regional differences in PWV at different locations [19], and these pulse signals are also affected by limb position [20]. The ERPWI is obtained through measurements in the time differences between peaks of R waves and photovoltaic pulse wave peaks in the toes. Using this method, pulse waves pass through the great, middle, small, and micro-arteries, and finally to the toes, which can reflect the elastic strength information of the whole artery more comprehensively and accurately [14]. However, due to the delayed time from the generation of R wave to the opening of aortic valve, ERWPTT [21] is increased to a certain extent, which reduces the true conduction velocity. Moreover, because the diameter of blood vessels in different parts of the artery is different, the structure of blood vessels in each segment and the wall of the artery is complex and diverse, and the transmission of R wave pulse wave is also controlled by autonomic nerves, and the conduction velocity of pulse wave in different vessels is also different [16,22]. All of these factors were likely to have affected our research results.

Conclusions

In conclusion, our results confirm that the ERPWI is an independent predictor of CA risk and can be measured independently of blood pressure. Higher ERPWI values indicate a higher risk of CA. When ERPWI is ≥0.505, it can be used as a diagnostic threshold for CA. The ECG R wave vascular index therefore is a non-invasive index for CA detection.

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