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The first harmonic of radial pulse wave predicts major adverse cardiovascular and microvascular events in patients with type 2 diabetes

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ABSTRACT

This brief report take a further look on the first harmonic of radial pulse wave (C1) after the 1.8 ± 0.5 years follow-up and demonstrated that the quartile level of C1 independently predicts the risk of cardiovascular death, major adverse cardiovascular events, and microvascular outcomes in 2324 patients with type 2 diabetes.

1. Introduction

Radial pulse wave and its harmonics provide insight into nature of cardiovascular physiology and pathology.[1–3] Lin et al. had established a PR wave model [4] to describe the phenomena of resonance observed in animal studies[5,6], and to illustrate the relationship between radial pulse waves and status of ventricular-arterial system.[7] Harmonic analysis is one of the most complete mathematical analysis methods for analyzing arterial pulses[8], which uses the Fourier series method to decompose the pulses into harmonic components. [9] Wang et al. further utilized harmonic analysis and considered these harmonic components as a set of basic physical features to describe the state of the entire arterial system.[10] Therefore, changes in harmonics reveal changes in the state of the arterial system, which has proven to be a useful method in several cardiovascular studies. [1]

The first harmonic amplitude of the radial pulse wave (C1) is the fundamental component of the pulse signal. [11,12] Studies have shown that the C1 is associated with arterial stiffness[13], angina symptoms[14], and signs of myocardial ischemia and left ventricular dysfunction[15]. Our previous studies further demonstrate that C1 is an independent risk indicator for the composite endpoint of non-fatal major adverse cardiovascular events in patients with type 2 diabetes mellitus (T2DM).[16] However, two problems have not been clarified by this previous study: 1) C1 was associated with stroke events by chi-square test, but the univariate Cox regression model did not show significant results (P = 0.07). 2) The relationship between cardiovascular mortality and C1 was not significant in the 12-month follow-up. Therefore, the purpose of this brief report was to further investigate the impact of C1 on the risk of cardiovascular events, including major adverse cardiovascular events and microvascular events.

Conflict of interest statement: The authors declare that they have no competing interests.

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2. Methods

2.1. Participants

To verify the significant effects of C1, we obtained extension approval for this ongoing observational prospective cohort study from the Institutional Review Board (IRB number: ISRCTN14306167). A total of 2324 patients with T2DM participated in the study between 2017 and 2019. The study was conducted in accordance with the Helsinki Declaration and all subjects signed the informed consent.

2.2. Radial pulse wave measurement

Each subject received a radial pulse wave measurement at baseline using a medical grade device TD01C (MII-ANN Technology, Taiwan) and followed the standard protocol described in previous studies. [11] The TD01C is a non-invasive instrument that detects the blood pressure pulse of the radial artery and analyzes the pressure pulses in the frequency domain. This system recorded radial pulse waves in 12 s at a sampling rate of 400 data points per second (Fig. 1). The C1 value is calculated using the Fourier series method as follows:

$$C1 = \frac{1}{M}\sum_{m=1}^{M}\frac{A_{1,m}}{A_{0,m}}$$

where $A_{1,m}$ was the 1st amplitude coefficient of Fourier series of the m^{th} radial pulse within one measurement. $A_{0,m}$ is the mean value of the m^{th} radial pulse and M is the total number of successive pulses within this 12-second pulse measurement.

We then divided the enrolled patients into quartile groups based on C1 value (<0.89, 0.89 to 0.96, 0.96 to 1.07, and >1.07). Compared with previous study[17], the mean follow-up time was extended from 1.2 years to 1.8 years.

2.3. Outcomes

The primary outcome was a composite of major adverse cardiovascular events, including nonfatal stroke, nonfatal myocardial infarction, hospitalization for heart failure, and cardiovascular death, analyzed jointly and separately. The secondary outcome was a composite of microvascular events, including the major adverse kidney events (composite endpoints of double serum creatinine, end-stage renal disease, and kidney failure), macroalbuminuria, retinopathy, and polyneuropathy. The follow-up procedure was described in our previous studies.[16]

2.4. Statistical methods

We used log rank test and Cox proportional hazard model analysis to verify the impact of C1 on those cardiovascular complications. The survival time from baseline radial pulse measurement to the first occurrence of relevant events was used in each Cox model. All statistical analyses were done by using Matlab version 9.2(MathWorks Inc., USA). The p value of the statistical testing <0.05 was considered to be significant.

3. Results

Among the 2324 subjects enrolled, the mean age, body mass index, and duration of diabetes were 62 ± 12 years, 27 ± 8 kg/m^2 and 10 ± 8 years. Their mean systolic blood pressure, diastolic blood pressure and Hba1c were 128 ± 11 mmHg, 74 ± 8 mmHg and 7.0 ± 1.1%. During the average of 1.8 years of follow-up, 444 patients had major adverse cardiovascular events (Table 1). The log-rank test manifested that comparing to the patients with C1 < 0.89, those patients with C1 > 1.07 had the higher cumulative incidence of major adverse cardiovascular events (P < 0.001), and the hazard ratios (HR) were listed as follows: Primary outcomes (HR, 2.04; 95% CI, 1.55–2.67), nonfatal stroke (HR, 1.97; 95% CI, 1.17–3.34), nonfatal myocardial infarction (HR, 2.00; 95% CI, 1.42–2.80), hospitalization for heart failure (HR, 2.61; 95% CI, 1.47–4.66),

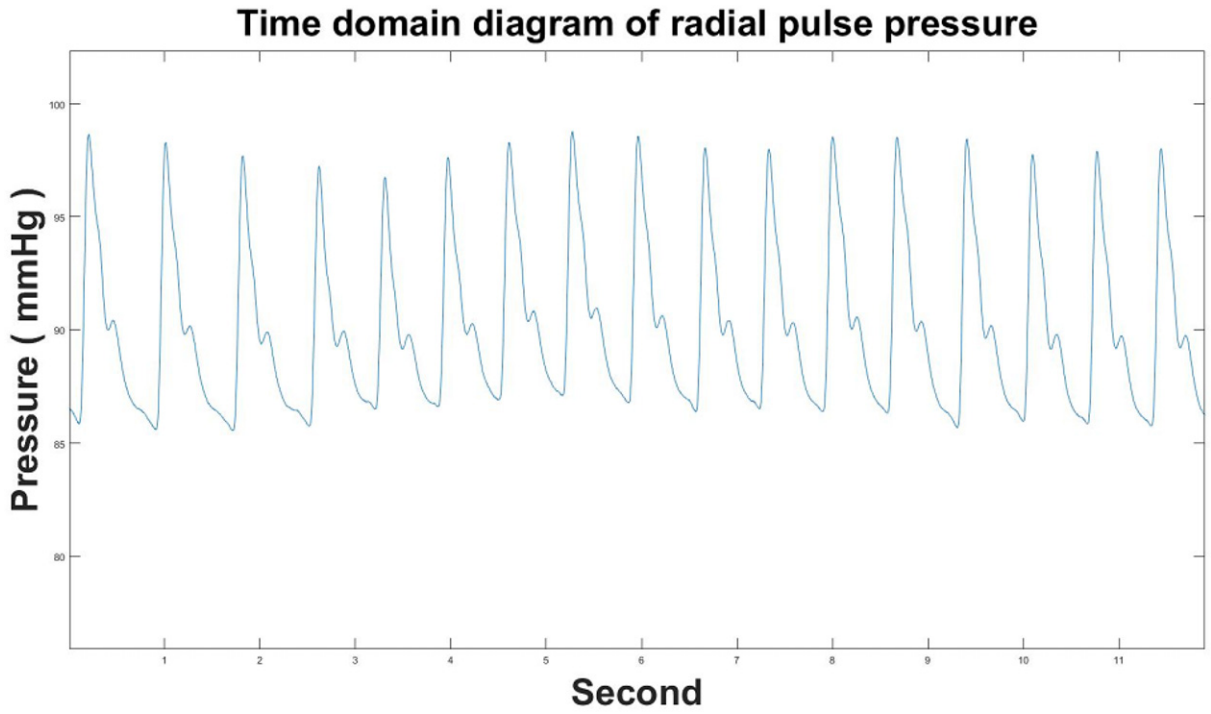

Fig. 1. Typical 12-second radial pulse wave recorded by TD01C system at a sampling rate of 400 Hz.

Table 1
Effects of the first harmonic amplitude on all clinical outcomes in 2324 patients with type 2 diabetes.

	C1, first harmonic amplitude of the radial pulse wave					
	<0.89	0.89 to 0.96	0.96 to 1.07	>1.07	P for trend	P for trend*
n	581	581	581	581		
Major adverse cardiovascular events						
No. events	87	114	123	174		
Hazard ratio (95% CI)	1.00	1.35 (1.02–1.78)	1.45 (1.10–1.91)	2.16 (1.67–2.79)	<0.001	<0.001
Stroke						
No. events	21	28	35	41		
Hazard ratio (95% CI)	1.00	1.34 (0.76–2.35)	1.68 (0.98–2.89)	1.97 (1.17–3.34)	<0.01	<0.01
Myocardial infarction						
No. events	51	66	63	98		
Hazard ratio (95% CI)	1.00	1.32 (0.91–1.90)	1.25 (0.865–1.81)	2.00 (1.42–2.80)	<0.001	<0.001
Heart failure						
No. events	16	16	22	41		
Hazard ratio (95% CI)	1.00	1.00 (0.501–2)	1.38 (0.724–2.62)	2.61 (1.47–4.66)	<0.001	<0.001
Cardiovascular death						
No. events	3	8	7	13		
Hazard ratio (95% CI)	1.00	2.67 (0.71–10.1)	2.34 (0.60–9.05)	4.36 (1.24–15.3)	<0.05	<0.05
Microvascular events						
No. events	140	158	175	219		
Hazard ratio (95% CI)	1.00	1.15 (0.92–1.45)	1.29 (1.03–1.61)	1.69 (1.37–2.09)	<0.001	<0.001
Major adverse kidney events						
No. events	33	25	30	59		
Hazard ratio (95% CI)	1.00	0.75 (0.45–1.26)	0.91 (0.554–1.49)	1.83 (1.19–2.80)	<0.01	<0.01
Macroalbuminuria						
No. events	59	56	77	86		
Hazard ratio (95% CI)	1.00	0.95 (0.66–1.37)	1.32 (0.937–1.85)	1.48 (1.06–2.06)	<0.01	<0.01
Retinopathy						
No. events	55	80	86	106		
Hazard ratio (95% CI)	1.00	1.49 (1.06–2.1)	1.61 (1.15–2.26)	2.02 (1.46–2.80)	<0.001	<0.001
Polyneuropathy						
No. events	11	22	15	19		
Hazard ratio (95% CI)	1.00	2.02 (0.98–4.17)	1.37 (0.627–2.97)	1.74 (0.83–3.65)	0.35	0.30

The reference group for hazard ratio is the first quartile of C1 (<0.89).
* P for trend controlling for age, sex, smoking, systolic pressure, dyslipidemia, duration of diabetes, Hba1c, and history of cardiovascular disease.

and cardiovascular death (HR, 4.36; 95% CI, 1.24–15.3). The Cox regression analysis also demonstrated that, as quartile level of C1 value increase, the risk of major adverse cardiovascular events increased before and after adjusting for age, gender, smoking, systolic blood pressure, diastolic pressure, dyslipidemia, duration of diabetes, Hba1c, and history of cardiovascular disease ($P_{for\ trend} < 0.001$).

Analysis of the secondary composite endpoint showed that 30% of all enrolled patients experienced new microvascular events (Table 1). The log-rank test proved that taking patients with C1 < 0.89 as reference, those patients with C1 > 1.07 had the higher microvascular events rate($P < 0.001$), and the hazard ratios (HR) were listed as follows: Secondary outcomes (HR, 1.69; 95% CI, 1.37–2.09), major adverse kidney events (HR, 1.83; 95% CI, 1.19–2.80), macroalbuminuria (HR, 1.48; 95% CI, 1.06–2.06), retinopathy (HR, 2.02; 95% CI, 1.46–2.80), and polyneuropathy(HR, 1.74; 95% CI, 0.83–3.65). The Cox regression analysis further demonstrated that, as C1 quartile increase, the risk of microvascular increased before and after adjusting for traditional risk factors mentioned above ($P_{for\ trend} < 0.001$).

4. Discussion

C1 has been shown to be associated with aging[13], atherosclerosis[17], and the impedance of the ventricular-arterial system[18]. Atherosclerosis and increased cardiac afterload may lead to an increase in myocardial burden, which in turn pushes up the risk of cardiovascular disease and is reflected in the increase in first harmonic impedance. The clinical trial of Pepine et al. demonstrated that patients with heart failure had increased first harmonic input impedance due to aortic stiffness relative to the control group[19]. On this basis, our further studies have manifested that for patients with T2DM, either with or without confirmed cardiovascular disease or angina symptoms, C1 is an independent risk marker for non-fatal myocardial infarction and heart failure[16,20]. Huang's study found that in patients with angina pectoris, those with coronary artery stenosis had higher C1 values than those without coronary artery stenosis.[21] However, whether C1 is an independent risk marker for both macro- and micro-vascular disease has not been fully answered.

Compared with the patients with C1 < 0.89, patients with C1 > 1.07 had a about doubled risk of nonfatal stroke, nonfatal myocardial infarction, and retinopathy, a 2- to 3-fold increase in heart failure, a 4 times increase in cardiovascular death, and a >80% increase in major adverse kidney events. We performed the Cox models to adjust for traditional risk markers, including age, gender, smoking, systolic blood pressure, dyslipidemia, duration of diabetes, Hba1c, and cardiovascular disease (Table 1); the linear trend between these complications and quartile C1 remained significant respectively ($P_{for\ trend} < 0.05$). This indicated that C1 added the significant predictive value for those cardiovascular complications. To the best of our knowledge, this study is the first to demonstrate that quartiles of C1 levels can independently predict stroke, cardiovascular mortality, and microvascular events in patients with T2DM. The study also showed the use of C1 in risk prediction for non-fatal myocardial infarction and hospitalization for heart failure, consistent with previous studies. The above results and previous studies convey two important concepts: 1) C1 provides valuable information about the overall physical properties of the arterial system that will influence the progression of cardiovascular disease. 2) C1 shows changes in the function or properties of the microvascular bed of many organs.

We also performed an additional multivariate Cox proportional hazard model to investigate whether clinical features were independent risk markers for major adverse cardiovascular events and microvascular events (Table 2). The results showed that an increase in C1 and age and a decrease in estimated glomerular filtration rate are independent risk markers for major adverse cardiovascular events. The results also showed that an increase in C1, age, systolic blood pressure, and heart rate, and a reduction in estimated glomerular filtration rate respectively

Table 2
Multivariate predictors of major adverse cardiovascular events and microvascular events in patients with T2DM (N = 2324).

Predictor	Major adverse cardiovascular events		Microvascular events	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
C1 (continuous)	2.388 (1.068–5.338)	0.034	3.646 (2.221–5.985)	<0.001
Male	1.254 (0.863–1.824)	0.236	0.691 (0.509–0.937)	0.017
Age (per year increase)	1.027 (1.012–1.042)	<0.001	1.017 (1.005–1.029)	0.005
Duration of diabetes (per year increase)	1.011 (0.994–1.028)	0.205	1.006 (0.992–1.020)	0.394
BMI	1.025 (0.845–1.243)	0.805	1.038 (0.870–1.238)	0.679
EGFR	0.989 (0.985–0.993)	<0.001	0.985 (0.981–0.989)	<0.001
Smoke	1.135 (0.818–1.574)	0.449	1.166 (0.896–1.517)	0.254
SBP	0.995 (0.984–1.006)	0.373	1.009 (1.001–1.017)	0.034
DBP	1.001 (0.998–1.005)	0.434	1.000 (0.996–1.003)	0.823
HBALC	0.967 (0.854–1.095)	0.597	0.995 (0.896–1.103)	0.917
LDL	0.989 (0.976–1.002)	0.093	1.005 (0.994–1.016)	0.413
TG	0.998 (0.995–1.001)	0.199	1.001 (0.999–1.003)	0.397
TC	1.011 (0.998–1.024)	0.091	0.995 (0.984–1.006)	0.392
HDL	0.994 (0.979–1.008)	0.394	1.008 (0.996–1.021)	0.187
Heart rate (per beat/s increase)	1.452 (0.781–2.700)	0.238	1.761 (1.042–2.978)	0.035
Drug use				
Antihypertensive drug	3.632 (2.834–4.653)	<0.001	1.252 (1.021–1.535)	0.031
Aspirin	1.012 (0.747–1.371)	0.939	1.386 (1.071–1.794)	0.013
Statins	1.452 (0.781–2.700)	0.238	1.761 (1.042–2.978)	0.035

C1 (continuous) = continuous value of first harmonic amplitude of radial pulse wave, BMI = body mass index, EGFR = estimated glomerular filtration rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, Hba1c = glycated hemoglobin, LDL = low density lipoprotein cholesterol, HDL = high density lipoprotein cholesterol, TG = triglycerides, TC = total cholesterol.

and independently predict an increased risk of microvascular events. Therefore, continuous value of C1 and quartile levels of C1 both predict the risk of major adverse cardiovascular events and microvascular events.

In this study, we found that C1 can predict the risk of stroke and microvascular events. In the phantom model of the ventricular-arterial system, the elasticity of the vessel wall and the peripheral perfusion state can change the harmonic components of the radial pulse wave.[12,22,23] In animal and clinical studies, changes in harmonic components have also been shown to be associated with several vascular function or perfusion.[24,25] In our past studies, we have also found that the use of antihypertensive drug[26,27] or the intake of teas[28,29] rich in anti-inflammatory and vasodilating catechins, the harmonic components of radial pulse will change significantly. Furthermore, Hsiu et al found that the harmonic indices of radial pulse waves are related to cerebral microvascular perfusion in stroke patients using laser Doppler flowmetry.[30–33] Thus, the increase in C1 may be due in part to changes in microvascular properties or perfusion caused by atherosclerosis, which is mediated by inflammation in the progression of cardiovascular disease.[34–36] Nevertheless, further researches are needed to explore the core mechanisms that mediate the increase in C1 and its relationship to vascular function and cardiovascular disease progression.

In summary, this study demonstrated that C1 is an independent risk marker for major adverse cardiovascular events and microvascular complications, including major adverse kidney events, macroalbuminuria, and retinopathy in patients with T2DM. Therefore, periodic radial pulse wave measurements and harmonic analysis can improve the identification of patients with T2DM who need further cardiovascular testing or treatment. Further researches on radial pulse spectrum may provide us with new insights into the progression of vascular disease and may pave the new avenues for cardiovascular prevention strategies.

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Ethics approval and consent to participate

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and was approved by the respective Institutional Review Board of Taipei City Hospital according to national and international regulations. IRB number: ISRCTN14306167. All participants provided written informed consent.

Authors' contributions

C.W. contributed to protocol design, analysis and interpretation of the data, and writing the manuscript. K.M. contributed to the design considerations for the trial and were involved in the analysis and interpretation of the data. Y.T. constructed the statistical model. Y.C. and S.H. researched the data. G.C. contributed to the discussion and reviewed/edited the manuscript.

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