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Fourth harmonic of radial pulse wave predicts adverse cardiac events in asymptomatic patients with type 2 diabetes

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ABSTRACT

Aims: Studies have shown that the fourth harmonic of the radial pulse wave (C4) is associated with atherosclerotic processes and myocardial ischemia. We sought to investigate whether C4 is an independent predictor of adverse cardiac events (ACE).
Methods: The baseline C4 is calculated using the Fourier series method. 1968 asymptomatic patients with type 2 diabetes were followed up for 1.8 ± 0.4 years and survival analysis were performed using Cox proportional hazard model.
Results: The Cox regression analysis showed that the C4 value is independent and inversely related to ACE both before and after adjusting for age, sex, smoke, systolic blood pressure, dyslipidemia, and Hba1c. (P for trend < 0.001)
Conclusions: Decreasing C4 is associated with an increased risk of ACE in asymptomatic patients with type 2 diabetes.

1. Introduction

Diabetes is an important risk factor for cardiovascular disease.[1] A cross-sectional study showed that some asymptomatic patients with type 2 diabetes mellitus (T2DM) have myocardial ischemia or coronary heart disease and are not recognized by traditional risk factors.[2] Therefore, strategies for further assessment of cardiac risk in asymptomatic patients are needed prior to cardiac stress testing. Harmonic analysis of arterial pulse waves provides insight into the atherosclerosis and hemodynamic status of arterial system through resonance effects.[3,4] Recent studies of harmonics of radial pulse waves have shown great potential for assessing cardiovascular disease.[5,6] Wan et al. proved that C4 is related to the aging process and the augmentation index.[7] Our previous clinical studies have further demonstrated that C4 is associated with myocardial ischemia by myocardial perfusion imaging with single photon emission computed tomography.[8] Therefore, the purpose of this study was to investigate whether C4 is an independent predictor of ACE in asymptomatic patients with T2DM.

2. Methods

2.1. Study population

The RPWT2DM study is an ongoing prospective observational cohort study in Taipei City Hospital. The initial target size of the study was 2000 patients, accounting for about two-fifths of the patients participating in the Endocrinology and Metabolism Diabetes Management Program at the Zhongxiao Branch of the Taipei Hospital. We look forward to finding novel non-invasive indicators that can be regularly assessed to improve cardiac risk assessment in asymptomatic diabetic patients.

Patients who participated in the diabetes management program and met the inclusion/exclusion criteria were enrolled. The inclusion criteria were: 30 years of age or older; T2DM was diagnosed according to American Diabetes Association criteria; willing to participate in the study and receive regular follow-up from the research hospital; signed informed consent. Exclusion criteria were: symptoms of heart disease, such as chest discomfort, dyspnea and angina-related symptoms;

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abnormal electrocardiogram; history of cardiovascular disease. After receiving approval from the Taipei City Hospital Institutional Review Board (IRB number: ISRCTN14306167), the study received 1968 asymptomatic patients with T2DM from February 2017 to December 2018, with an average follow-up of 1.8 years. All enrolled patients signed the informed consent.

2.2. Radial pulse wave measurement and C4 calculation

After the standard assessment of radial pulse wave at baseline,[9,10] continuous pulse data is obtained in 12 s with a sampling rate of 400 data points per second. Then we further used the Fourier transform to calculate C4, which is defined as follows:

$$C4 = \frac{1}{M}\sum_{m=1}^{M}\frac{A_{4,m}}{A_{0,m}}$$

where $A_{4,m}$ was the fourth amplitude coefficient of Fourier series of the mth radial pulse in one measurement.[11,12] $A_{0,m}$ is the mean value of the mth radial pulse, and M is the total number of consecutive pulses in the 12 second measurement.

2.3. Outcomes

The primary study outcome was a composite of myocardial infarction, heart failure, and cardiovascular death. Each of these outcomes was also analyzed separately. The source data was obtained from the diabetes management project database of the Zhongxiao Branch of Taipei City Hospital, which was verified by independent monitoring personnel. Myocardial infarction was diagnosed by cardiologists, when at least two of the following three characteristics existed: (1) Elevated cardiac troponin levels (higher than the 99th percentile) reflecting cardiomyocyte death. (2) Abnormal electrocardiogram. (3) Angina related Symptoms.

Heart failure was diagnosed by cardiologists, including structural and functional abnormalities, according to the New York Heart Association (NYHA) functional classification and the American College of Cardiology guidelines.[13,14] The enrolled patients were followed every 4 to 6 months after baseline radial pulse wave measurements. Our previous study details the baseline clinical variables, follow-up scenarios and the definition of each outcome.[15]

2.4. Data and statistical analysis

All subjects were ranked in descending order of quartile levels of C4 value (>0.17, 0.14 to 0.17, 0.11 to 0.14, and <0.11). Our aim was to use the Cox proportional hazard model and the log-rank test to study whether the quartile level of C4 value can independently predict adverse cardiac events.

2.4.1. Cox proportional hazards model

The Cox proportional hazards model was used to compare hazard ratios of clinical events across quartile groups, with the first quartile as a reference (C4 > 0.17). Table 1 listed the numbers of patients with new heart failure, myocardial infarction, and cardiovascular death in each quartile level of C4 and their incidence (%) during follow-up. The number of patients with the new occurrence of primary composite endpoint in each quartile level of C4 and those incidence during the follow-up period were also listed (Table 1). The unadjusted hazard ratio and 95% confidence intervals (CIs) of all outcomes in each quartile were recorded. (Table 1)

The Cox proportional hazards model for multivariable analysis was used to assess the independent relationship between the C4 quartiles and future ACE. Linear trend tests were before and after adjusting for age, gender, smoking, systolic blood pressure, dyslipidemia and Hba1c. For each cardiac outcome and primary composite outcome, the *p*-values for the linear trend across the C4 quartiles were listed in the last two columns of Table 1. The Cox model analysis was performed mainly based on the function "coxphfit ()" of Matlab software (version 9.2).

2.4.2. Kaplan Meier curve and log-rank test

To determine if the significant influence of C4 on the risk of ACE existed, the curves of Kaplan Meier for primary composite cardiac endpoints, ACE, were plotted on Fig. 1 according to the quartile levels of C4. The log-rank test was performed to determine if there was a significantly different primary composite outcome incidence among the quartiles of C4. The Kaplan Meier curve was plotted and the log-rank test was performed, based on the function "ecdf()" and the function "logrank()" using version 9.2 of Matlab software (MathWorks Inc., USA). Statistical significance was accepted at $p < 0.05$.

3. Results

The results indicate a reverse grading relationship between baseline C4 quartile level and the risk of facing future ACEs. The cumulative incidence of primary composite endpoint increased from 8.3% to 10.2% to 14.0% to 18.7% according to quartiles of C4 levels (>0.17, 0.14 to 0.17, 0.11 to 0.14, and <0.11) in descending order. The listed incidence and hazard ratios were written in Table 1. Compared to the first quartile (C4 > 0.17), the hazard ratio of primary composite endpoint for each quartile were 1.24 (95% CI, 0.82–1.87) for C4 of 0.14 to 0.17, 1.73 (95% CI, 1.17–2.54) for C4 of 0.11 to 0.14, and 2.38 (95% CI, 1.64–3.43) for a C4 <0.11. The linear trends were significant for ACE before and after

Table 1
The incidence and hazard ratios of outcomes according to C4 quartile in 1968 asymptomatic patients with type 2 diabetes. Primary composite endpoints combined the new onset of heart failure, myocardial infarction, and cardiovascular cause mortality.

Endpoint	C4 quartiles in descending order				*p* for trend*	*p* for trend #
C4 values	>0.17	0.14 to 0.17	0.11 to 0.14	<0.11		
Primary composite endpoints						
Patients, n (%)	41 (8.3%)	50 (10.2%)	69 (14.0%)	92 (18.7%)		
Hazard ratio (95% CI)	1	1.24 (0.82–1.87)	1.73 (1.17–2.54)	2.38 (1.64–3.43)	$p = 0.0001$	$p = 0.0007$
Heart failure						
Patients, n (%)	11 (2.2%)	15 (3.0%)	28 (5.7%)	36 (7.3%)		
Hazard ratio (95% CI)	1	1.38 (0.63–3.00)	2.61 (1.30–5.25)	3.38 (1.72–6.64)	$p = 0.0003$	$p = 0.02$
Myocardial infarction						
Patients, n (%)	31 (6.3%)	34 (6.9%)	43 (8.7%)	64 (13.0%)		
Hazard ratio (95% CI)	1	1.11 (0.68–1.80)	1.40 (0.88–2.22)	2.13 (1.39–3.28)	$p = 0.0002$	$p = 0.002$
Cardiovascular-cause mortality						
Patients, n (%)	4 (0.8%)	5 (1.0%)	4 (0.8%)	8 (1.6%)		
Hazard ratio (95% CI)	1	1.25 (0.34–4.66)	1.00 (0.25–4.00)	2.01 (0.61–6.69)	$p = 0.28$	$p = 0.32$

Hazard ratios of outcomes with the reference to the largest quartile of C4 (>0.17) were calculated using the Cox proportional hazard model analysis. *p* for trend presented the *p* values in the linear trend tests across C4 quartiles using Cox regression analysis, before(*) and after(#) adjusting for age, sex, smoke, systolic blood pressure, dyslipidemia, and Hba1c.

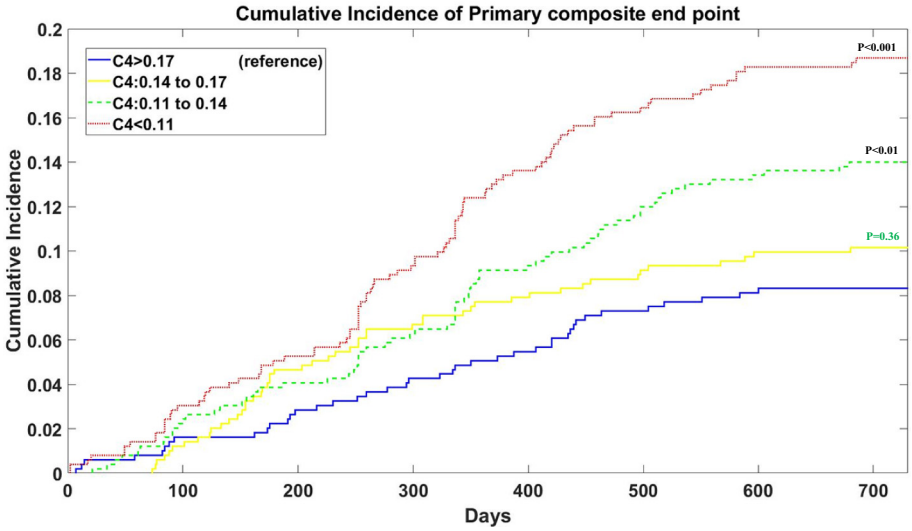

Fig. 1. Kaplan-Meier event rates of primary composite outcomes. Primary composite endpoints combined the adverse heart events, including new onset of heart failure, myocardial infarction, and cardiovascular mortality ($N = 1968$); p values were the result of the log-rank test. The reference group for log-rank test is the first quartile of C4 in the descending order (>0.17).

controlling for age, sex, smoking, systolic pressure, dyslipidemia, and Hba1c ($p < 0.001$).

4. Discussion

C4 has been shown correlated with atherosclerotic process[7] and myocardial ischemia.[8] In this study, we further demonstrated that C4 levels significantly predict the ACE using the Cox model (Table 1). Log-rank test also demonstrated that the patients with lowest quartile of the C4 level had the highest cumulative incidence of ACE, compared with the patients the greatest quartiles of C4 levels. After adjusting risk factors, including age, sex, smoke, systolic blood pressure, dyslipidemia, and Hba1c, C4 still independently predicted ACE.

The resonance effect of whole ventricular-arterial coupling system may be one of the reasons for the relationship between radial pulse and heart function.[3,4] In the phantom study of the ventricular-arterial system, arterial stiffness and the mechanical loading can alter the harmonics.[16–18] Lin had built up a multi-rank model[19] to illustrate how the arterial pulse transmits through the arterial wall and reveals the condition of ventricular-arterial system[20,21] Therefore, harmonic analysis of arterial pulse wave could provide additional information and pave the way for future personalized cardiovascular risk assessment.[22]

In conclusion, this report demonstrated that C4 give independent predictive value for ACE risk stratification in asymptomatic patients with T2DM. Due to the convenience and non-invasiveness of radial pulse measurements, C4 can provide an attractive strategy for routine assessment of cardiac function prior to further cardiac testing, particularly for type 2 diabetic patients who have neither angina nor history of cardiovascular disease.

List of abbreviations

T2DM	type 2 diabetes mellitus
ACE	adverse cardiovascular events
HF	heart failure
MI	myocardial infarction
HbA1C	glycated hemoglobin

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Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

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 was 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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