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The effect of radial pulse spectrum on the risk of major adverse cardiovascular events in patients with type 2 diabetes

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ABSTRACT

Radial pulse spectrum has been shown to correlate with coronary stenosis in patients with type 2 diabetes mellitus (T2DM). In academia, it has not been demonstrated that the radial artery pulse spectrum is an independent risk factor for major adverse cardiovascular events (MACE), including myocardial infarction, stroke, and all-cause mortality. The primary objective of this study is to assess the risk of MACE, in patients with T2DM and to determine if an increase in MACE would be associated with a first harmonic (C1) increase in the radial artery pulse. 1972 consecutive patients with T2DM were enrolled. All subjects received measurements of radial pulse waves at baseline. Harmonic analysis of radial pressure wave was performed. The hazard ratios for MACE and its 95% confident interval were estimated using Cox proportional hazard model. The follow-up period lasted for one year. MACE was detected in 232 (11.8%) of those with T2DM. The log-rank test demonstrated that the cumulative incidence of patients with C1 above 0.96 was greater than those with C1 bellow 0.96. Comparing the patients with C1 smaller than first quartile to the patients with C1 greater than third quartile, higher C1 increased the cardiovascular risks as follows: MACE (Hazard ratio,1.93; 95% CI,1.31–2.86), stroke (Hazard ratio, 1.61; 95% CI, 0.90–2.90), myocardial infarction (Hazard ratio, 2.23; 95% CI, 1.33–3.74). The risk for the composite MACE increased continuously as C1 increased ($P < 0.001$ for trend). The hazard ratio and trend for all-cause mortality were not significant. Increased C1 resulted in increased risk for nonfatal stroke, and nonfatal myocardial infarction among patients with T2DM. Our results indicate that the degree of C1 is a risk factor for nonfatal MACE. Therefore, the radial pulse spectrum could identify patients with T2DM at high risk of nonfatal MACE.

1. Background

Patients with type 2 diabetes are at increased risk for major adverse cardiovascular events (MACE), including stroke, myocardial infarction, and all-cause mortality.[1,2] Type 2 diabetes mellitus (T2DM) is a main risk factor for the occurrence of cardiovascular events and all-cause mortality after adjusting age, sex, and levels of conventional risk factor.[3,4] Hazard ratios for coronary artery disease (CAD)[5] and ischemic stroke[3] among patients with diabetes were 2- to 4-fold as compared with those without diabetes at baseline. Furthermore, cardiovascular complications occur 2 to 5 times in patients with T2DM than in the general population and contribute to a leading cause of death in those patients.[5,6]

In addition, a large proportion of patients with T2DM and at high risk of MACE are "silent." Patients with T2DM are more often without history or symptoms of coronary artery disease until the onset of MI or sudden cardiac death.[7] Asymptomatic diabetic patient has been manifesting 20–35% prevalence of silent CAD[8,9] and 10–67% prevalence of silent myocardial ischemia. Silent brain infarction also more frequently occurred in patients with T2DM.[10] The silent effects would make the patients with T2DM more vulnerable to MACE, leading to the poor prognosis outcomes,[11–15] if no appropriate investigation and treatment were given. Therefore, one of the critical issues for patients with T2DM were to build up early predictors to screen the high-risk patients with T2DM and to provide a risk stratification of MACE. Thus, patients with T2DM

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and at high risk of MACE may benefit from screening and further medical intervention to prevent sudden cardiac death or adverse cardiovascular events.

Radial pulse spectrum combining harmonic analysis is one of the emerging non-invasive and non-radiative technology to screen the risk of cardiovascular events. The harmonic analysis had been introduced to translate the pressure pulse and flow pulse into a numerical Fourier series,[16] which is a complete quantitative expression of pulse waveform.[17] Several studies performed harmonic analysis to compare the pulse pressure between peripheral artery and aortic artery,[18] to assess vascular properties,[19,20] to screen for aging effects,[21] and to study vasodilator drug.[22] Reddy et al. had pointed out the possibilities of harmonic components to monitor the heart disease.[23] CHEN's study supports this concept and found that the second and third harmonics of radial pulse spectrum is affected during the onset of acute myocardial infarction.[24] The further cross-sectional study showed that the second and third harmonics of radial pulse spectrum had the independent association with ischemic heart symptom.[25,26] The radial pulse spectrum had also demonstrated its ability to identify the CAD and Silent CAD in patients with T2DM.[27]

Recently, it was found that the first harmonic of the radial pulse wave reflects cardiovascular risk. Wang et al. revealed that first harmonics increased along with the aging process from 20 to 80 years old healthy person.[21] Reddy's study is consistent with this concept, indicating that aortic stiffness in older mice results in a significant increase in first harmonic impedance.[19] Segers' research also revealed that an increase in cardiac afterload results in an increase in first harmonic impedance and an increase in stroke work, which is calculated from the pressure-volume loop of the heart pumping.[28] In addition, Pepine's study also showed that the first harmonic aortic impedance of patients with heart failure was significantly higher than that of patients without heart failure.[29] A brief summary, the first harmonic impedance increases with aortic atherosclerosis or with cardiac afterload, resulting in increased heart burden. The more stroke work from heart pumping, the more oxygen consumption from myocardium needed and the higher risk of myocardial ischemia or myocardial infarction existed. Thus, increasing the first harmonic impedance could be a response to an increased cardiac burden and causes an increase in the first harmonic amplitude of the arterial pulse. In a cross-sectional study, the population mean of C1 values for patients with T2DM with ischemic heart disease had a significantly larger mean compared with the C1 values for patients with T2DM and with no ischemic myocardium ($P < 0.01$).[25] In follow-up research, the longitudinal results also confirmed that the asymptomatic patients with T2DM and with new onset of more than 5% ischemic myocardium had a higher population mean of C1, compared with the patients with T2DM and without symptoms and signs of myocardial ischemia ($P < 0.05$).[30] Since C1 correlates with both symptoms and signs of myocardial ischemia, the follow-up question is whether C1 affect the future cardiovascular events.

Based on the previous results, this report aimed to explore further whether the first harmonic of the radial pulse wave is a risk factor for the hard cardiovascular outcome, MACE, in a longitudinal cohort study. Our objective was to assess the effect of the first harmonics of the radial pulse spectrum on the composite endpoint of stroke, myocardial infarction, and all-cause mortality, separately.

2. Methods

2.1. Study population

Individuals, who had already entered a diabetes management program in the Division of Endocrinology & Metabolism of Zhongxiao Branch of Taipei City Hospital, were eligible for the study if they had a history of T2DM. Individuals were excluded if the radial pulse wave measurement could not be performed due to the severer diseases or acute symptoms such as end-stage renal disease or liver disease. 1972 consecutive patients (1170 men and 802 women) were studied between January 2017 and March 2018 in Taiwan, with a median 12 months follow-up. The study was approved by the Institutional Review Board of Taipei City Hospital (IRB number: ISRCTN14306167). We gave both oral and written information about the study for the enrolled patients. All participants signed written informed consent and were investigated while taking regular medications.

2.2. Study design

Patient demographic data, the status of T2DM, and other clinical variables were determined by medical history and physical examination. Radial pulse spectrum was measured in all 1972 study participants at baseline. The followed up period lasted for 12 months after the radial pulse measurement. Myocardial infarction, stroke, and all-cause death were documented.

Assessment of the radial pressure wave was performed noninvasively using a pulse wave analyzer TD01C (MII-ANN Technology, Taiwan). In the radial pressure wave measurement, each participant was required to lie down in a supine position and rest for 5 min before the assessment. Briefly, a piezoresistive sensor is used to record pressure waveforms from the radial artery of the wrist. TD01C proved its intrinsic reliability using artificial pulse generator.[31] The intra-observer and inter-observer reliability of TD01C has also been demonstrated in the previous clinical study.[32] The sampling rate of pressure data was 400 data points per second. For 12-s measurement, approximately 10–20 continuous pulse waveforms obtained, the harmonic analysis was used to transform the pressure waves into harmonic components. The degree of first harmonic (C1) of radial pulse wave was expressed as followed:

$$C_1 = \sum_{i=1}^{N} \frac{A_{1,i}}{A_{0,i}}$$

, where $A_{0,i}$ is the mean value of ith radial pulse wave and $A_{1,i}$ is the first coefficient of Fourier series of the ith radial pulse wave within one measurement. C_1 was used as a representative first harmonic amplitude value.

2.3. Outcome assessment

The primary composite endpoint of the study was the first occurrence of stroke, myocardial infarction, and all-cause mortality. Patients visit the research hospital every 4–6 months and events were documented by the reviews of electronic hospital record. Each of those cardiovascular outcomes was also analyzed separately. Source data were derived from the database of the diabetes management program in Zhongxiao Branch of Taipei City Hospital and were verified by independent monitors.

2.4. Statistical analysis

Baseline values are expressed as mean ± standard deviation or prevalence rate. The Kaplan-Meier curves of the estimated time to the first occurrence of MACE according to the quartile levels of C1 were plotted. The log-rank test was performed to demonstrate whether the significant influence of C1 on the risk of MACE existed. All the subjects were then dived into quartiles of C1 levels. This report used a Cox proportional hazards model to compare hazard ratios of clinical events among quartile groups with reference to the first quartile. To demonstrate whether the C1 was predictive of the cardiovascular outcomes, the hazard ratio of stroke, myocardial infarction, all-cause mortality, and the primary composite endpoint, MACE, were calculated using univariate Cox regression analysis. The unadjusted hazard ratio and its 95% confidence intervals of the above outcomes in each quartile were

reported. We also used the Cox proportional hazards model to test the linear trend across quartiles of the C1 level. This report also presented the results by calculating the number and crude rates of events within the 4 subgroups. All statistical analyses were performed using Matlab version 9.2 (MathWorks Inc., USA).

3. Results

The detailed description of the baseline clinical characteristics of 1972 patients was shown in Table 1. The mean age of participants was 62 ± 12 years, all Asian people. 59.3% of the participants were male. The mean systolic and diastolic blood pressure was 128 ± 11 and 75 ± 21 separately. The mean Hba1c level was 7.0 ± 1.1%. The mean systolic and diastolic blood pressure was 128 ± 11 and 75 ± 21 separately. The mean LDL and HDL was 82 ± 26 and 50 ± 15 separately. Data of two groups for the composite endpoint, MACE, within 1 year followed up were presented as a Kaplan-Meier curve in Fig. 1. Comparing to the low-risk group (C1 ≦ 0.96), the cumulative incidence of MACE increased from about 9% to 14%. The results indicated that C1 influences the risk of MACE.

To stratify risk of MACE in T2DM patients with C1, the enrolled patients were divided into quartiles of C1, with 493 patients in each group. Patients were followed for a median 1.0 ± 0.2 years and a total of 1966 patient-years. Table 2 listed the incidence and hazard ratio of stroke, myocardial infarction, all-cause mortality, and MACE. The rates of adverse cardiovascular events were 50.4 per 1000 patient-years of follow-up for stroke, 70.7 for myocardial infarction, 6.1 for all-cause mortality, and 118.0 for the composite endpoint (MACE). The results in Table 2 manifested a graded relationship between the baseline C1 and the risk of the primary composite outcome. The hazard ratio of MACE for each quartile compared with the first quartile (C1 ≦ 0.89) was 1.41 (95% CI, 0.93–2.13) for a C1 of 0.89 to 0.96, 1.86 (95% CI, 1.25–2.76) for an C1 of 0.96 to 1.05, and 1.93 (95% CI, 1.31–2.86) for a C1 > 1.05. The linear trends were significant for MACE ($P < 0.001$) and myocardial infarction ($P = 0.001$). The test for trends was less significant for stroke ($P < 0.1$) and non-significant for all-cause mortality ($P = 0.8$).

4. Discussion

To the best of our knowledge, this report is the first study to prospectively evaluate the effect of radial pulse spectrum on MACE in a large group of patients with T2DM. A growing number of studies have discovered the relationship between radial pulse waveform and risk of cardiovascular diseases.[24,25,33–35] The data of this report support the previous report and further demonstrated that C1 is a strong risk factor for MACE. Within the MACE, myocardial infarction showed the strongest correlation with C1. The hazard ratio of myocardial infarction for each quartile compared with the first quartile (C1 ≦ 0.89) was 1.48 (95% CI, 0.85–2.58) for a C1 of 0.89 to 0.96, 1.98 (95% CI, 1.17–3.35) for a C1 of 0.96 to 1.05, and 2.23 (95% CI, 1.33–3.74) for a C1 > 1.05. The linear trends were significant for MACE ($P < 0.001$) and myocardial infarction ($P = 0.001$). The previous cross-sectional cohort study had shown that C1 was correlated with myocardial ischemia symptom.[25] The lack of myocardial perfusion, reflecting on the radial pulse spectrum, may be one of the reasons that the patients with higher C1 resulted in higher incidence of myocardial infarction at 12-month follow-up.

Lin had built up a hemodynamic model[36] and an arterial pressure wave equation[37] to interpret the collective behavior of the ventricular-arterial system. According to this model, the loading condition of the organs and physical properties of the large artery will be reflected on the arterial pulse spectrum and can be assessed by the harmonic analysis of the pulse waveform.[38,39] This model was developed and evolved from the animal study of renal artery ligation.[40,41] Recently, longitudinal study supports this concept by manifesting the interaction between radial pulse spectrum and renal function loss.[42]

Atherosclerosis in an aging process is a serious issue since the stenosis of carotid artery,[43] and coronary artery[44] will influence the perfusion condition of brain and myocardium. Thus, atherosclerosis is an important risk factor for developing MACE. Wang et al. had found that first harmonic of radial pulse wave increases along with the aging process from 20 to 80 years old and pointed out that atherosclerosis may play an important role in this process.[21] An animal study supported this concept and proved that aortic stiffness in older mice resulted in significant increase in first harmonic impedance and reflected on arterial pulse waveform.[19] In this study, we demonstrated that C1 could be a risk marker for future MACE using Cox regression model. Atherosclerosis may be one of the possible mechanism. However, more studies are needed to confirm the results of this report and to investigate more about the interaction between the radial pulse spectrum and cardiovascular disease.

The limitation of this study existed. First, the measurement of C1 only at baseline and the reliabilities of the radial pulse spectrum using the different pulse measurement methods[31,32] were the limitations of this report. However, the large sample size and the strong statistical correlation between C1 and the risk of nonfatal MACE made the radial pulse spectrum worth a further investigation. Second, the chi-square test demonstrated the correlation between stroke and quartile levels of C1 (chi-square statistic: 11.4162, $P < 0.01$); however, the Cox regression model only showed 93% confidence for existing linear trend between stroke and quartile levels of C1.Therefore, longer follow-up studies and larger scales of enrolled patients are needed to confirm the linear trend relationship between stroke and quartile levels of C1. Third, this study is a prospective observational cohort study, based on the consecutive patients with T2DM and with regular medications. The drug treatment and history of cardiovascular diseases could bias the results. Therefore, we put C1, statin treatment, aspirin treatment, hypertension, peripheral artery disease, microalbuminuria, and previous CAD into the Cox regression model. The results still showed a linear trend between C1 and primary composite endpoints, MACE ($P = 0.002$). Cox regression analysis also showed that aspirin treatment ($P < 0.001$), hypertension ($P < 0.001$), peripheral artery disease ($P < 0.05$), microalbuminuria ($P < 0.05$), and history of CAD ($P < 0.001$) also affected the MACE. The correlation between MACE and C1 is strongly significant ($P < 0.01$) and remains unchanged either using a single-variable model or several multi-variable models analysis. The results manifested that C1 is associated with MACE and is independent of those risk factors. However, this is a short-term follow-up and the independence of C1 as a predictor for MACE only based on about 200 events. More longitudinal research is needed to confirm the

Table 1
Baseline clinical characteristics of the study population.

Clinical characteristics	Patients with type 2 diabetes
N	1972
Male (%)	59.3
Age (year)	62 ± 12
BMI (kg/m^2)	27.3 ± 8.0
SBP (mmHg)	128 ± 11
DBP (mmHg)	75 ± 21
HbA1C (%)	7.0 ± 1.1
LDL (mg/dl)	82 ± 26
HDL (mg/dl)	50 ± 15
TG (mg/dl)	129 ± 81
Heart rate (beats/min)	73 ± 11
Duration of diabetes (years)	10.3 ± 8.4
Statin treatment	76%
Aspirin treatment	20%
Hypertension	43%
Peripheral artery disease	8%
Microalbuminuria	12%
Previous CAD	3%

BMI = body mass index, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, HbA1c = Glycated hemoglobin, LDL = low density lipoprotein cholesterol, HDL = high density lipoprotein cholesterol, TG = triglycerides, CAD = coronary artery disease.

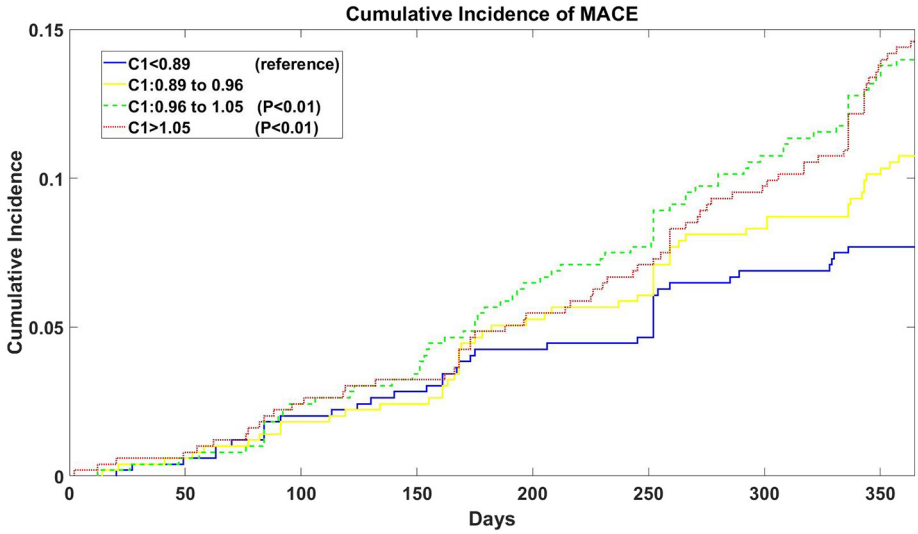

Fig. 1. Kaplan-Meier event rates of the composite outcome of stroke, myocardial infarction, and all-cause mortality in quartile groups according to the first harmonic amplitude level of the radial pulse wave(N = 1972); *P* values were the result of the log-rank test. The reference group for the log-rank test is the first quartile of C1 (<0.89).

independence of C1 as a risk marker in a more general population. We anticipate this assay to be a starting point for the characteristics extraction of radial pulse spectrum as early risk predictors of cardiovascular events. The earlier predictors may provide useful information to identify the patients at high risk of cardiovascular events and lead to early medical treatment or revascularization to prevent adverse cardiovascular events. Moreover, the radial pulse spectrum may help improve our understanding the relationship between the blood pressure and the development of MACE, which may modulate medical therapeutic strategies and therefore enhance prevention of cardiovascular events in the future clinical practice.

5. Conclusion

This report demonstrated that the first harmonics, C1, of radial pulse spectrum is a risk factor for nonfatal MACE. The risk of nonfatal MACE was increased with the increment of quartile graded C1 levels. The results suggested that the radial pulse spectrum may benefit the risk stratification of future nonfatal MACE for patients with T2DM. The assessment of radial pulse spectrum is non-invasive, safe enough to facilitate in routine clinical practice, and cost-effective to repeat within months. Hence, periodic screening for radial pulse spectrum may be a simple test to identify the patients with T2DM at high risk of confronting nonfatal MACE, who may need a further investigation or preventive intervention to reduce the cardiovascular risk.

Abbreviations

T2DM	type 2 diabetes mellitus
MACE	major adverse cardiovascular events
CAD	coronary artery disease
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
LDL	low-density lipoprotein cholesterol
HDL	high-density lipoprotein cholesterol
HbA1C	Glycated hemoglobin

Availability of data and materials

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

Consent for publication

Not applicable.

Table 2
Quartile of the first harmonic of the radial pulse wave as a risk for composite endpoint, stroke, myocardial infarction, and all-cause mortality in 1972 patients with type 2 diabetes.

Endpoint	C1, the first harmonic of the radial pulse wave					
	<0.89	0.89 to 0.96	0.96 to 1.05	>1.05	P for trend	P for trend[#]
Major adverse cardiovascular events						
Patients, n (%)	38 (7.7%)	53 (10.8%)	69 (14.0%)	72 (14.6%)		
Hazard ratio(95% CI)	1.0	1.41 (0.93–2.13)	1.86 (1.25–2.76)	1.93 (1.31–2.86)	P < 0.001	P < 0.001
Stroke						
Patients, n (%)	18 (3.7%)	23 (4.7%)	30 (6.1%)	29 (5.9%)		
Hazard ratio(95% CI)	1.0	1.28 (0.69–2.37)	1.67 (0.93–3.00)	1.61 (0.90–2.90)	P = 0.07	P = 0.07
Myocardial infarction						
Patients, n (%)	21 (4.3%)	31 (6.3%)	41 (8.3%)	46 (9.3%)		
Hazard ratio(95% CI)	1	1.48 (0.85–2.58)	1.98 (1.17–3.35)	2.23 (1.33–3.74)	P < 0.001	P < 0.01
All-cause mortality						
Patients, n (%)	3 (0.6%)	3 (0.6%)	4 (0.8%)	2 (0.4%)		
Hazard ratio(95% CI)	1	1.00 (0.20–4.95)	1.33 (0.30–5.96)	0.67 (0.11–3.98)	NS	NS

The reference group for hazard ratio is the first quartile of C1 (<0.89). NS: non-significant.
P for trend controlling for age, sex, smoke, systolic and diastolic blood pressure, dyslipidemia, and Hba1c.

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.

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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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