Original Article

Arterial Stiffness and QT Interval Prolongation in a General Population: The Hisayama Study

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Few population studies have addressed the association of QT interval prolongation with clinical or subclinical arterial disease. The primary objective here was to examine the relationship between the pulse wave velocity (PWV) and the heart rate-corrected QT interval duration (QTc). This is a cross-sectional study, based on a survey of a general population of Japanese. We examined 2,666 community-dwelling individuals without history of cardiovascular disease, aged 40 or over. The PWV was measured between the brachial and ankle regions (baPWV). QTc was estimated using Bazett's equation. The age-adjusted mean values of QTc increased progressively with rising baPWV levels for either sex: for men, 397, 401, 403, and 406 ms for quartile groups defined by baPWV values of less than 1,369, 1,370 to 1,560, 1,561 to 1,840, and 1,841 or greater cm/s, respectively ($p < 0.0001$ for trend); for women, 406, 410, 414, and 417 ms for quartile groups defined by baPWV of less than 1,269, 1,270 to 1,493, 1,494 to 1,821, and 1,822 or greater cm/s, respectively ($p < 0.0001$ for trend). When male and female subjects were combined, this positive relationship between baPWV and QTc remained significant, even after controlling for age, sex, hypertension, ECG abnormalities, dyslipidemia, diabetes, obesity, serum calcium and potassium, alcohol intake, and smoking habits ($p < 0.0001$ for trend). In conclusion, baPWV is independently associated with QT interval prolongation. (*Hypertens Res* 2008; 31: 1339–1345)

Key Words: pulse wave velocity, QT interval duration, epidemiology

Introduction

The QT interval duration on an ECG represents the duration of ventricular depolarization and repolarization (1, 2). It has been suggested that disturbance of cardiac ion channels (1, 2), decreased autonomic tone (3), and myocardial ischemia/infarction (4) extend the QT interval duration, but the etiology of the acquired form of QT interval prolongation has not been

clearly defined. Recently, several epidemiological studies have shown that QT interval prolongation predicts the risks of clinical arterial disease (5–9) as well as sudden cardiac death (5). Likewise, a few cross-sectional studies have suggested a positive association between QT interval prolongation and subclinical arterial disease, such as carotid intima media thickness (10–12). However, there is significant uncertainty about the association between QT interval prolongation and other forms of subclinical arterial disease.

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Table 1. Age-Adjusted Mean Values or Frequencies of Relevant Factors According to Brachial-Ankle Pulse Wave Velocity Quartiles in 1,089 Men

Variables	Brachial-ankle pulse wave velocity (cm/s)				<i>p</i> for trend
	963–1,369 (<i>n</i> =270)	1,370–1,560 (<i>n</i> =273)	1,561–1,840 (<i>n</i> =276)	1,841–3,690 (<i>n</i> =270)	
Age (years)	51.4±8.4	55.6±9.6	60.2±9.7	68.9±8.9	<0.0001
Heart rate (bpm)	60.1±9.9	63.4±9.9	65.2±10.0	70.4±9.9	<0.0001
Systolic blood pressure (mmHg)	116.4±16.4	126.9±14.9	138.9±15.0	151.2±16.4	<0.0001
Diastolic blood pressure (mmHg)	71.1±9.9	78.6±9.9	84.6±10.0	91.2±9.9	<0.0001
Hypertension (%)	11.8	29.4	60.8	89.5	<0.0001
Antihypertensive drugs (%)	5.1	13.6	22.2	21.2	<0.0001
β-Blocker (%)	2.3	2.8	5.7	3.5	0.15
Calcium channel blocker (%)	4.3	9.3	20.7	16.5	<0.0001
ACE inhibitor (%)	0.9	2.8	5.0	5.1	0.0014
ARB (%)	1.8	5.6	3.0	4.1	0.65
ECG abnormalities (%)	11.5	14.5	17.4	18.9	0.001
Total cholesterol (mmol/L)	5.0±0.9	5.0±0.9	5.1±0.9	5.1±0.9	0.23
HDL cholesterol (mmol/L)	1.5±0.4	1.5±0.4	1.4±0.4	1.5±0.4	0.46
LDL cholesterol (mmol/L)	3.1±0.9	3.1±0.8	3.0±0.8	3.0±0.9	0.25
Triglyceride (mmol/L)	1.3±1.4	1.5±1.3	1.9±1.3	1.9±1.5	<0.0001
Dyslipidemia (%)	46.6	50.5	55.4	59.8	0.002
Fasting plasma glucose (mmol/L)	5.8±1.5	6.1±1.4	6.3±1.3	6.7±1.5	<0.0001
HbA1c (%)	4.9±0.8	5.0±0.8	5.1±0.8	5.3±1.0	<0.0001
Diabetes (%)	12.6	15.0	20.5	43.7	<0.0001
BMI	23.0±3.3	23.4±3.3	23.8±3.3	23.8±3.3	0.01
Obesity (%)	30.2	29.5	32.0	53.2	0.09
Serum calcium (mmol/L)	2.3±0.1	2.3±0.1	2.3±0.1	2.3±0.1	0.10
Serum potassium (mmol/L)	4.4±0.3	4.4±0.3	4.3±0.3	4.3±0.3	0.08
Alcohol intake (%)	65.7	65.1	74.2	75.5	0.0006
Habitual smoking (%)	55.7	45.1	45.1	37.3	0.04

Values are age-adjusted means±SD or frequencies. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

Aortic pulse wave velocity (PWV) is an established marker for subclinical arterial disease (13, 14) as well as for arterial stiffness (15). Brachial-ankle PWV (baPWV) has also been shown to be closely associated with aortic PWV and to be an excellent functional marker for subclinical arterial disease (16).

The present cross-sectional study evaluates the association of baPWV with heart rate-corrected QT interval duration (QTc) in a general population of Japanese.

Methods

Study Population

The Hisayama Study is an ongoing population-based epidemiological study designed to investigate the morbidity and mortality of cardiovascular disease and its risk factors in the town of Hisayama, Japan. The design of the Hisayama Study has been described in detail elsewhere (17). The present

cross-sectional study was based on a screening survey conducted in 2002 and 2003. A total of 3,328 residents aged 40 years or over (77.6 % of the total population of this age group) participated in the examination and underwent a comprehensive assessment including baPWV and ECG. Of these, 242 subjects for whom there was no information on baPWV or ECG, 54 subjects who were likely to have peripheral arterial disease (ankle-brachial index <0.9), 189 subjects with atrial fibrillation or intraventricular conduction disturbance (QRS interval >120 ms), 30 subjects with elevated heart rate (>100 beats/min), 22 subjects who did not take a fasting blood test, 16 subjects taking medication affecting the QT interval duration (*i.e.*, antiarrhythmic drugs, antibiotics, antipsychotic agents or antihistamines) (2), 111 subjects with a history of cardiovascular disease (myocardial infarction, coronary revascularization or stroke), and 30 subjects who refused to participate in the present study were excluded from the analyses. The final study group comprised 2,666 subjects (1,089 men and 1,577 women).

Table 2. Age-Adjusted Mean Values or Frequencies of Relevant Factors According to Brachial-Ankle Pulse Wave Velocity Quartiles in 1,577 Women

Variables	Brachial-ankle pulse wave velocity (cm/s)				<i>p</i> for trend
	900–1,269 (<i>n</i> =395)	1,270–1,493 (<i>n</i> =392)	1,494–1,821 (<i>n</i> =396)	1,822–4,128 (<i>n</i> =394)	
Age (years)	49.7±6.8	56.0±8.4	62.7±9.2	71.5±8.4	<0.0001
Heart rate (bpm)	62.9±11.9	64.9±9.9	68.6±10.0	72.8±11.9	<0.0001
Systolic blood pressure (mmHg)	107.5±17.9	121.7±15.8	135.2±15.9	150.5±19.9	<0.0001
Diastolic blood pressure (mmHg)	63.9±11.9	73.5±9.9	80.2±10.0	87.4±11.9	<0.0001
Hypertension (%)	3.2	16.9	50.2	85.5	<0.0001
Antihypertensive drugs (%)	2.5	7.4	25.7	47.5	<0.0001
β-Blocker (%)	0.2	1.4	2.6	6.0	0.0001
Calcium channel blocker (%)	1.9	6.1	20.5	38.1	<0.0001
ACE inhibitor (%)	0.0	0.5	7.3	6.9	<0.0001
ARB (%)	0.2	0.9	5.1	9.8	<0.0001
ECG abnormalities (%)	3.0	8.4	10.3	30.9	<0.0001
Total cholesterol (mmol/L)	5.2±1.0	5.5±0.9	5.6±0.9	5.4±1.0	0.01
HDL cholesterol (mmol/L)	1.8±0.5	1.8±0.4	1.7±0.4	1.6±0.5	0.0002
LDL cholesterol (mmol/L)	3.2±0.9	3.4±0.8	3.4±0.8	3.3±1.0	0.15
Triglyceride (mmol/L)	0.9±0.8	1.1±0.7	1.3±0.7	1.4±0.9	<0.0001
Dyslipidemia (%)	49.2	53.5	58.8	68.4	0.0001
Fasting plasma glucose (mmol/L)	5.4±1.2	5.8±1.1	6.0±1.1	6.4±1.3	<0.0001
HbA1c (%)	4.8±0.8	5.0±0.6	5.1±0.6	5.3±0.8	<0.0001
Diabetes (%)	3.1	8.6	12.4	34.3	<0.0001
BMI	21.7±4.0	22.8±4.0	23.6±4.0	24.0±4.0	<0.0001
Obesity (%)	28.4	24.6	30.5	39.6	0.0004
Serum calcium (mmol/L)	2.3±0.1	2.3±0.1	2.3±0.1	2.3±0.1	0.01
Serum potassium (mmol/L)	4.3±0.4	4.3±0.4	4.3±0.4	4.2±0.4	0.003
Alcohol intake (%)	22.5	29.3	31.1	29.3	0.69
Habitual smoking (%)	21.0	6.3	9.4	4.7	0.49

Values are age-adjusted means±SD or frequencies. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

Measurements of QTc and baPWV

Standard, resting 12-lead ECG was performed using an ECG device (FCP-4266; Fukuda Denshi, Tokyo, Japan) in the supine position in the morning. Heart rate (bpm) and QT interval duration (ms) were determined automatically using the PI-10 ECG Analysis Program (Fukuda Denshi). The program calculated the QT interval duration from the beginning of QRS to the end of the T wave. The QT interval duration was corrected for heart rate by calculating QTc according to Bazett's equation (18).

$$QTc = QT \text{ interval duration [ms]} / (60/\text{heart rate})^{1/2}$$

The baPWV was measured in the supine position after at least 5 min of rest using a volume-plethysmographic apparatus (Form PWV/ABI; Colin, Komaki, Japan), as described previously (19). Briefly, cuffs to measure baPWV were wrapped on both brachia and ankles. PWV at the brachia and ankles were recorded using a semiconductor pressure sensor. Volume waveforms were stored with automatic gain analysis

and quality adjustment. BaPWV was automatically calculated according to the following equation: $baPWV = (L_a - L_b)/T$, with L_a being the distance from the heart to each ankle, L_b the distance from the heart to the right upper arm, and T the time delay from the right brachial waveform to each ankle waveform.

All clinical examinations including 12-lead ECG, measurement of baPWV and blood test were conducted on the same day.

Relevant Factors

At baseline examination, a self-administrated questionnaire concerning current drug use including antihypertensive agents (*e.g.*, β-blocker, calcium channel blocker, angiotensin converting enzyme inhibitor or angiotensin receptor blocker), smoking, and alcohol intake was completed in advance by each participant and was checked by trained interviewers at the screening. These variables were classified as being either habitual or not. Blood pressure was measured three times

after the subject had rested for at least 5 min using a semiautomatic device (BP203RVIII; Colin) based on the cuff-oscillometric principle with the subject in the sitting position. The mean of the three measurements was used for the present analysis. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, or current use of antihypertensive agents. ECG abnormalities were defined as Q wave (Minnesota codes, 1–1, 2, 3), left ventricular hypertrophy (3–1) or ST depression (4–1, 2, 3). Body height and weight were measured in light clothing without shoes, and body mass index (BMI) was calculated as weight in kg divided by height in m squared. Blood samples were collected from an antecubital vein after an overnight fast for the determination of lipids, plasma glucose levels, serum calcium, and potassium. Serum total cholesterol, triglycerides, low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol concentrations were determined enzymatically. Fasting blood glucose levels were measured by the glucose oxidase method. Hemoglobin A1c levels were measured by high-performance liquid chromatography. Dyslipidemia was defined as total cholesterol ≥ 5.68 mmol/L, LDL-cholesterol ≥ 4.13 mmol/L, HDL-cholesterol < 1.03 mmol/L, triglycerides ≥ 1.69 mmol/L, or current use of lipid-lowering agents. Diabetes was defined according to the criteria recommended by the American Diabetes Association (20), in addition to a medical history of diabetes. Obesity was defined as BMI ≥ 25.0 kg/m².

Statistical Analysis

The age-adjusted frequencies of relevant factors in quartile groups defined by baPWV were calculated by means of the direct method using the total study population as a standard and were compared using age-adjusted logistic regression models. The age-adjusted mean values of QTc and relevant factors in quartile groups defined by baPWV were calculated using covariance analysis and compared using multiple regression models. Multivariate-adjusted mean values of QTc in the four baPWV groups were estimated using multiple regression models including age, gender, hypertension, ECG abnormalities, dyslipidemia, diabetes, obesity, serum calcium and potassium levels, alcohol intake, and habitual smoking. Comparisons of the relationships of baPWV with QTc among subgroups were carried out by adding an interaction term to the statistical models. *p* values less than 0.05 were considered statistically significant. Statistical analyses were performed using the SAS program package (SAS Institute, Cary, USA).

Ethical Considerations

The ethics committee of Kyushu University approved this study, all participants provided written informed consent, and the procedures followed were in accordance with national guidelines.

Fig. 1. Age-adjusted mean values of heart rate-corrected QT interval duration according to quartiles of brachial-ankle pulse wave velocity levels for men (solid circles) and women (solid boxes). For men, the quartile groups were defined by baPWV values of less than 1,369, 1,370 to 1,560, 1,561 to 1,840, and 1,841 or greater; and for women, by baPWV of less than 1,269, 1,270 to 1,493, 1,494 to 1,821, and 1,822 or greater. The centers of the circles or boxes are placed at the estimates of mean values. Vertical lines represent SEM for mean values. **p* < 0.01 vs. the lowest quartile group. *p* < 0.0001 for trend in both men and women.

Results

The mean value of QTc was 401.7 ms (SD, 21.5; range, 328.0–494.0) for men and 411.7 ms for women (SD, 23.3; range, 295.0–554.0). Baseline characteristics of male and female participants according to quartile groups defined by baPWV are shown in Tables 1 and 2, respectively. For men, the quartile groups were defined by baPWV values of less than 1,369, 1,370 to 1,560, 1,561 to 1,840, and 1,841 or greater cm/s; and for women, by baPWV of less than 1,269, 1,270 to 1,493, 1,494 to 1,821, and 1,822 or greater cm/s. The subjects with higher baPWV levels were significantly older. The frequencies of hypertension, dyslipidemia, diabetes, obesity, and alcohol intake increased with rising baPWV levels, while an inverse association was observed for the frequency of habitual smoking.

Figure 1 shows the age-adjusted mean values of QTc according to quartiles of the baPWV levels by sex. The age-adjusted mean values of QTc linearly increased with rising baPWV levels for men and women: for men, 396.7, 401.4, 403.2, and 405.6 ms for the 1st to 4th quartile groups, respectively (*p* < 0.0001 for trend); for women, 405.7, 409.9, 413.8, and 417.4 ms for the 1st to 4th quartile groups, respectively (*p* < 0.0001 for trend). When the Friedrich formula was used for estimation of QTc, similar associations were observed between baPWV and QTc in both men and women.

Table 3. Age- and Sex-Adjusted Mean Values of Heart Rate–Corrected QT Interval Duration According to Brachial-Ankle Pulse Wave Velocity Quartiles and Relevant Factors

	Quartiles of brachial-ankle pulse wave velocity				<i>p</i> for trend	<i>p</i> for homogeneity
	Q1	Q2	Q3	Q4		
Hypertension						
No (<i>n</i> =1,618)	402.4±0.9	405.8±0.9	408.8±1.3	410.8±1.9	<0.0001	0.43
Yes (<i>n</i> =1,048)	402.8±3.9	408.8±2.0	409.7±1.3	412.8±1.2	0.01	
Dyslipidemia						
No (<i>n</i> =1,202)	403.1±1.4	405.9±1.3	410.0±1.4	408.6±1.8	0.03	0.14
Yes (<i>n</i> =1,464)	401.3±1.4	407.0±1.2	408.8±1.1	414.5±1.2	<0.0001	
Diabetes						
No (<i>n</i> =2,243)	402.4±1.0	406.4±0.9	408.7±0.9	411.9±1.2	<0.0001	0.39
Yes (<i>n</i> =423)	404.1±3.8	407.6±2.7	411.7±2.2	412.9±1.9	0.06	
Obesity						
No (<i>n</i> =1,938)	402.7±1.1	406.4±1.0	408.7±1.0	411.2±1.2	<0.0001	0.19
Yes (<i>n</i> =728)	401.7±2.0	406.9±1.7	410.5±1.6	414.8±1.8	<0.0001	
ECG abnormalities						
No (<i>n</i> =2,196)	402.2±1.0	405.8±0.9	409.1±0.9	411.8±1.2	<0.0001	0.43
Yes (<i>n</i> =470)	402.3±3.7	411.1±2.9	410.6±2.3	413.7±2.1	0.04	
Alcohol intake						
No (<i>n</i> =1,504)	404.3±1.4	408.1±1.2	410.6±1.2	413.6±1.3	<0.0001	0.34
Yes (<i>n</i> =1,162)	399.8±1.4	404.4±1.3	407.6±1.3	410.9±1.6	<0.0001	
Habitual smoking						
No (<i>n</i> =2,068)	403.9±1.2	407.2±1.0	409.7±1.0	413.7±1.1	<0.0001	0.21
Yes (<i>n</i> =598)	397.2±1.6	404.1±1.7	408.1±1.8	407.5±2.3	0.0003	

Values are age- and sex-adjusted means±SEM.

Table 4. Age- and Sex-Adjusted Mean Values of Heart Rate–Corrected QT Interval Duration According to Brachial-Ankle Pulse Wave Velocity Quartiles and the Number of Relevant Factors

Number of relevant factors	Quartiles of brachial-ankle pulse wave velocity				<i>p</i> for trend
	Q1	Q2	Q3	Q4	
0–1 (<i>n</i> =903)	406.0±1.6	404.0±1.4	408.1±1.4	411.6±1.7	0.001
2–3 (<i>n</i> =1,313)	402.5±1.4	404.8±1.3	409.4±1.3	410.4±1.5	0.003
4–7 (<i>n</i> =450)	407.4±2.3	407.7±2.2	413.9±2.2	413.5±2.4	0.02

Values are age- and sex-adjusted means±SEM. Relevant factors: hypertension, dyslipidemia, diabetes, obesity, ECG abnormalities, alcohol intake, and habitual smoking.

($p < 0.0001$ for trend in both sexes). In the following analyses, male and female subjects were combined because the relationships of baPWV to QTc were comparable between men and women.

Table 3 shows the age- and sex-adjusted mean values of QTc according to quartiles of the baPWV levels for subgroups of participants defined on the basis of the presence or absence of hypertension, dyslipidemia, diabetes, obesity, ECG abnormalities, alcohol intake, or smoking habits. There were comparable relationships between baPWV and QTc for participants who were and were not hypertensive. Likewise, there were no interactions in the relationships of baPWV with QTc between subgroups defined by every other relevant factor (all p values for interaction > 0.05). There were also com-

parable relationships of baPWV with QTc between participants who were and were not taking antihypertensive agents or lipid-lowering agents (p for interaction > 0.5). We also estimated the age- and sex-adjusted mean values of QTc according to quartiles of the baPWV levels by the number of relevant factors (Table 4). There was a significantly positive relationship between baPWV and QTc in each of the groups defined by a number of cardiovascular risk factors of 0–1, 2–3, and 4–7.

Figure 2 shows the multivariate-adjusted mean values of QTc according to quartiles of the baPWV levels. The multivariate-adjusted mean values of QTc significantly increased with rising baPWV levels, even after controlling for age, sex, hypertension, ECG abnormalities, dyslipidemia, diabetes,

Fig. 2. Multivariate-adjusted mean values of heart rate-corrected QT interval duration according to quartiles of brachial-ankle pulse wave velocity levels. The centers of the boxes are placed at the estimates of mean values. Other conventions are the same as in Fig. 1. Mean values and *p* values are adjusted for age, sex, hypertension, ECG abnormalities, dyslipidemia, diabetes mellitus, obesity, serum calcium and potassium, alcohol intake, and smoking habits. **p* < 0.01 vs. the lowest quartile group. *p* < 0.0001 for trend.

obesity, serum calcium, serum potassium, alcohol intake, and smoking habits (*p* < 0.0001 for trend).

Discussion

To our knowledge, this is the first study to address the associations between baPWV and QTc in a general population without preexisting cardiovascular disease. In the present analysis, the mean values of QTc increased with rising baPWV levels for both men and women. These associations remained strong and continuous, even after controlling for traditional cardiovascular risk factors, suggesting an independent relationship between subclinical arterial disease (atherosclerosis) and QT interval prolongation.

In the present study, there were strong and continuous relationships between QTc and baPWV, which has been shown to be a functional marker for subclinical atherosclerotic disease in central and peripheral arteries (16, 21). Ours is the largest study to have investigated the association between subclinical arterial disease and QT interval prolongation, but there have been a few other cross-sectional studies addressing this question using other structural markers of subclinical arterial disease (10–12). The Insulin Resistance Atherosclerosis Study (IRAS) investigated the association between carotid intima media thickness and QTc in 912 nondiabetic subjects without coronary artery disease and found a close association between carotid atherosclerosis and QT interval prolongation (10). The Salzburg Atherosclerosis Prevention Program in Subjects at High Individual Risk also showed a positive correlation

between carotid intima media thickness and QT interval duration in 1,199 clinically healthy subjects (11). These observational data support our hypothesis that subclinical arterial disease is associated with QT interval prolongation.

It is well known that the QT interval is affected by heart rate (18, 22). In order to control for the confounding effects of heart rate, we used QTc, which was estimated by Bazett's formula, and found significant associations between baPWV and QTc. When the Friedrich formula was used for estimation of QTc instead of Bazett's formula, similar associations were observed. We also investigated the association between baPWV and crude QT interval duration and found significantly positive relationships even after adjustment for heart rate, ECG abnormalities, and other cardiovascular risk factors (data not shown). These results suggest that baPWV is significantly associated with QT interval duration and this association is independent of the effects of heart rate.

The mechanism underlying the association between subclinical arterial disease and the acquired form of QT interval prolongation has not been clearly defined. Subclinical arterial disease and subsequent arterial stiffness may increase ventricular load and, as a consequence, may promote myocardial and electrophysiological remodeling, resulting in QT interval prolongation (23, 24). Another possible mechanism is that microvascular atherosclerosis in the coronary artery, which is strongly related to systemic arterial disease, may lead to sub-endocardial ischemia and thus extend QT interval duration (25).

One limitation of our study is that we have no information on subjects with congenital long QT syndrome. However, the prevalence of the congenital long QT syndrome has been reported to be less than 0.1% (26). Furthermore, in our subjects the relationship between baPWV and QTc was strong and continuous, even after excluding participants with QT intervals of 440 ms or more (*p* < 0.0001 for trend). Thus, the influence of congenital long QT syndrome would seem to have been negligible. Another limitation is that information on repeated measurements of baPWV and QTc is limited. This fact made it difficult for us to conduct longitudinal analysis.

In conclusion, we found close associations between baPWV and QTc for men and women without histories of cardiovascular disease. These associations were independent of hypertension, ECG abnormalities, dyslipidemia, diabetes, obesity, alcohol intake, and smoking habits. Thus, subclinical arterial disease appears to contribute to the pathogenesis of QT interval prolongation. Future longitudinal studies are necessary to clarify the causal relationship between subclinical arterial disease and QT interval prolongation.

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