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Research Article **· Online First ·**

Prevalence of and risk factors for aspirin resistance in elderly patients with coronary artery disease

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Abstract

Objective To assess the prevalence of and related risk factors for aspirin resistance in elderly patients with coronary artery disease (CAD). **Methods** Two hundred and forty-six elderly patients (75.9 ± 7.4 years) with CAD who received daily aspirin therapy (≥ 75 mg) over one month were recruited. The effect of aspirin was assessed using light transmission aggregometry (LTA) and thrombelastography platelet mapping assay (TEG). Aspirin resistance was defined as ≥ 20% arachidonic acid (AA)-induced aggregation and ≥ 70% adenosine diphosphate (ADP)-induced aggregation in the LTA assay. An aspirin semi-responder was defined as meeting one (but not both) of the criteria described above. Based on the results of TEG, aspirin resistance was defined as ≥ 50% aggregation induced by AA. **Results** As determined by LTA, 23 (9.3%) of the elderly CAD patients were resistant to aspirin therapy; 91 (37.0%) were semi-responders. As determined by TEG, 61 patients (24.8%) were aspirin resistant. Of the 61 patients who were aspirin resistant by TEG, 19 were aspirin resistant according to LTA results. Twenty-four of 91 semi-responders by LTA were aspirin resistant by TEG. Multivariate logistic regression analysis revealed that elevated fasting serum glucose level (Odds ratio: 1.517; 95% CI: 1.176–1.957; $P = 0.001$) was a significant risk factor for aspirin resistance as determined by TEG. **Conclusions** A significant number of elderly patients with CAD are resistant to aspirin therapy. Fasting blood glucose level is closely associated with aspirin resistance in elderly CAD patients.

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Keywords: Aspirin resistance; Coronary artery disease; Risk factors

1 Introduction

Ischemic heart disease is predicted to be the leading cause of death worldwide by 2020.[1] The prevalence of coronary artery disease (CAD) increases with advancing age; there is nearly a 2.8-fold higher prevalence among adults aged 65–74 years than among those aged 45–64 years.[2] Aspirin is a cornerstone in the prevention of thromboembolic vascular events. A meta-analysis conducted by the Antiplatelet Trialists' Collaboration showed a 25% reduction in serious vascular events, a 34% reduction in non-fatal myocardial infarction, and a 25% reduction in non-fatal stroke in patients treated with 75–150 mg aspirin daily.[3] However, the antiplatelet effect of aspirin is not uniform in all patients. A previous study estimated that 5.5%–60% of the population does not respond adequately to aspirin therapy.[4] This condition is defined as aspirin resistance or aspirin insensitivity. Recent reviews and meta-analyses have shown that aspirin resistance is associated with an increase in cardiovascular events and is therefore clinically significant.[5,6]

Several studies have shown that aspirin resistance is associated with fasting blood glucose and HbA1c levels in diabetic patients.[7–10] Diabetes is an independent risk factor for CAD and is associated with a marked increase in the prevalence of CAD. Moreover, impaired fasting blood glucose levels in CAD patients are associated with an increased mortality rate.[11] Therefore, we hypothesized that fasting blood glucose levels are associated with aspirin resistance in elderly patients with CAD. However, data regarding aspirin resistance in elderly patients with CAD is scarce. We therefore evaluated the prevalence of aspirin resistance and tested the hypothesis that aspirin resistance is associated with fasting blood glucose levels and other potential risk factors in elderly patients with CAD.

2 Methods

2.1 Ethical approval of the study protocol

This study complied with the Declaration of Helsinki. It

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was approved by the Scientific and Ethics Review Board of the First Geriatric Cardiology Division, Chinese PLA General Hospital (Beijing, China). All patients provided written informed consent to be included in the study.

2.2 Participants

A total of 246 patients with stable CAD were recruited from the Wangshoulu area of Beijing and enrolled in the study from April 2008 to June 2010. All participants were from a public medical insurance system, which covers only prescriptions from hospitals instead of OCT. Compliance of drug therapy was ensured. Patients were aged ≥ 65 years and were receiving regular treatment with enteric coated aspirin (75–100 mg daily over one month). All patients were diagnosed with stable CAD according to the American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines on chronic angina.[12] Exclusion criteria included the use of clopidogrel, ticlopidine, dipyridamole, or other non-steroidal anti-inflammatory drugs; use of heparin or low-molecular-weight heparin; a major surgical procedure within one week prior to study enrollment; a family or personal history of bleeding disorders; platelet count < 150×10^3/μL or > 450×10^3/μL; hemoglobin level < 8 g/dL; a history of myeloproliferative disorders; or a history of drug-induced thrombocytopenia.

2.3 Blood sampling

Blood samples were drawn 2 h to 12 h after administration of the last dose of aspirin to eliminate the effects of circadian variations on platelet function. Blood was drawn by venipuncture through a 21-gauge needle; the first two milliliter of blood was discarded. Tubes of whole blood, anti-coagulated with 3.2% sodium citrate, were used for light transmission aggregometry (LTA) and thrombelastography (TEG). One tube that contained lithium heparin was also used for TEG. In addition, one tube of whole blood was anti-coagulated with a clavicular tilt angle difference (CTAD; a mixture of citrate, theophylline, adenosine and dipyridamole) and was used to measure CD62P (P-selectin) and PAC-1 (activated GP IIb/IIIa receptors). Four conventional collection tubes were used to collect blood for measurement of high-sensitivity C-reactive protein, type-B natriuretic peptide, homocysteine, and protein C, percent activity of anti-thrombin III, routine blood components and blood lipids, and other biochemical parameters. All assays were processed within two hours of blood collection.

2.4 Light transmission aggregometry

Platelet aggregation was assessed in platelet-rich plasma at 37°C by LTA, which was measured using a ChronoLog Aggregometer (Chronolog, Havertown, PA, USA). Aggregation was induced by addition of arachidonic acid (AA; 0.5 mmol/L) and adenosine diphosphate (ADP; 10 μmol/L) using platelet-poor plasma as a reference. This methodology was described previously.[13]

2.5 Thrombelastography platelet-mapping assay

The TEG platelet mapping assay from Haemoscope Corporation (Niles, IL, USA) is a quantitative analysis of platelet function based on the measurement of clot strength. We used AA (1 mmol/L) as a platelet agonist to measure the degree of thromboxane A2 (TXA2)-induced platelet aggregation, as previously described.[14]

2.6 Markers of platelet reactivity

We used flow cytometry (BD Biosciences, San Jose, CA, USA) as previously described to evaluate platelet surface expression of PAC-1 and CD62P after natural activation.[15] The antibodies R-phycoerythrin-conjugated anti-CD62P (recognizes P-selectin), fluorescein isothiocyanate (FITC)-conjugated PAC-1 (recognizes the active GPIIb/IIIa receptor), and R-phycoerythrin-conjugated CD61 (recognizes the total population of GPIIb/IIIa receptors) were obtained from BD Biosciences. The expression levels of CD62P and PAC-1 are expressed as percentage.

2.7 Definition of aspirin resistance

Aspirin resistance was defined as ≥ 20% AA and ≥ 70% ADP-induced aggregation, as determined by LTA. Aspirin semi-responders were defined as meeting one, but not both, of the criteria described above.[16,17] The definition of aspirin resistance in TEG assays was ≥ 50% aggregation induced by AA.[14]

2.9 Statistical analyses

Continuous variables are expressed as the mean ± SD. Categorical data and proportions were compared using the χ^2 test; if the expected cell frequencies were small, exact tests were used. Univariate or Kruskal–Wallis tests were used to compare continuous variables among three groups (if the distribution was not normal). The Student's *t*-test or Mann-Whitney *U* two-sample tests were used to compare continuous variables between two groups (if the distribution was not normal). A value of $P < 0.05$ was considered significant. Parameters significantly related to the presence of aspirin resistance were determined using binary logistic regression analyses (SPSS, Windows, version 14.0, Chicago, IL, USA).

3 Results

3.1 Patient characteristics

As shown in Table 1, patients were grouped by aspirin resistance (by both tests) and aspirin sensitive (not resistance by both tests). No significant differences exist with respect to age, female gender, current smoker status, presence of hypertension, diabetes, or cerebrovascular disease, use of medications, blood chemistry, or baseline platelet count. Fasting serum glucose level and the number of patients with peripheral arterial occlusive disease was lower among aspirin sensitive patients than among aspirin-resistant patients ($P = 0.040$ and $P = 0.048$).

Table 1. Characteristics comparison between aspirin resistance patients and aspirin sensitive patients as determined by both LTA and TEG.

	Aspirin resistant ($n = 19$)	Aspirin sensitive ($n = 114$)	*P*
Demographic data			
Age (yrs)	78.89 ± 6.76	75.91 ± 7.39	0.102
Female, *n* (%)	3 (15.8)	33 (28.9)	0.232
Current smoker, *n* (%)	2 (10.5)	7 (6.1)	0.481
BMI (kg/m^2)	24.77 ± 3.43	25.01 ± 3.57	0.784
Medical conditions			
Hypertension, *n* (%)	13 (68.4)	87 (76.3)	0.566
Cerebrovascular disease, *n* (%)	12 (63.2)	55 (48.2)	0.229
Diabetes, *n* (%)	6 (31.6)	33 (28.9)	0.816
PAOD, *n* (%)	4 (21.1)	8(7.0)	0.048
Blood chemistry			
Homocysteine (μmol/L)	17.38 ± 3.73	17.79 ± 11.46	0.732
BNP (pg/mL)	162.57 ± 192.77	137.21 ± 170.68	0.557
hs-CRP (mg/dL)	0.34 ± 0.32	0.40 ± 0.71	0.721
CD62P (%)	10.30 ± 19.75	16.92 ± 22.31	0.227
PAC-1 (%)	39.53 ± 30.22	36.65 ± 27.50	0.678
Protein C activity (%)	105.52 ± 35.87	114.58 ± 34.56	0.296
Anti-thrombin III activity (%)	97.83 ± 18.47	102.50 ± 13.58	0.207
Creatinine (μmol/L)	88.56 ± 28.76	83.24 ± 23.75	0.375
Fasting serum glucose (mmol/L)	6.27 ± 1.05	5.81 ± 0.89	0.040
Total cholesterol (mmol/L)	4.52 ± 0.89	4.77 ± 1.41	0.469
Triglyceride (mmol/L)	1.52 ± 0.85	1.53 ± 0.67	0.974
HDL cholesterol (mmol/L)	1.32 ± 0.45	1.34 ± 0.38	0.818
LDL cholesterol (mmol/L)	2.68 ± 0.71	2.71 ± 0.80	0.911
Uric acid (μmol/L)	337.52 ± 101.01	320.70 ± 90.07	0.460
Platelet count (×10^3/μL)	205.63 ± 80.46	200.53 ± 51.75	0.716
Medications taken			
Statins, *n* (%)	9 (47.4)	39 (34.2)	0.269
ACEIs/ARBs, *n* (%)	7 (36.9)	40 (35.0)	0.882
CCBs, *n* (%)	10 (52.6)	50 (43.9)	0.477
Daily aspirin dose, *n* (%)			
75 mg	5 (26.3)	31 (27.2)	0.936
100 mg	14 (73.7)	83 (72.8)	0.936

ACEIs: angiotensin-converting enzyme inhibitor; ARBs: angiotensin receptor blocker; BMI: body mass index; BNP: type-B natriuretic peptide; CCBs: calcium-channel blockers; hs-CRP: high-sensitivity C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LTA: light transmission aggregometry; PAOD: peripheral arterial occlusive disease; TEG: thrombelastography platelet mapping assay.

TEG results (Table 2) showed that there were no significant differences between the aspirin-resistant and aspirin-sensitive groups with regard to age, current smoker status, presence of hypertension, diabetes, cerebrovascular disease, peripheral arterial occlusive disease, or baseline platelet count. Levels of fasting serum glucose and low density lipoprotein (LDL) cholesterol were higher among patients with aspirin resistance than among patients with aspirin sensitivity ($P = 0.0001$ and $P = 0.045$, respectively).

3.2 Platelet aggregation testing

LTA showed that 23 (9.3%) elderly patients were resistant to aspirin therapy; 91 (37.0%) patients were semi-responders. TEG showed that 61 patients (24.8%) were aspirin resistant. Of the 61 patients who were aspirin resistant by TEG, 19 were aspirin resistant by LTA. Twenty-four of 91 semi-responders by LTA were aspirin resistant by TEG. The kappa statistic between these two methods was 0.366 (95% CI: 0.306–0.426).

3.3 Distribution of aspirin resistance by sex and age group

There were no significant differences with regard to the prevalence of aspirin resistance between age groups (Table 3). We did not investigate significant differences between age groups based on sex in the present study (Table 4).

3.4 Multiple logistic regression analysis

We did not find significant risk factors based on data from LTA. However, using data based on TEG, a binary logistic regression analysis demonstrated that fasting serum glucose level (odds ratio (OR): 1.517, 95% CI: 1.176–1.957, $P = 0.001$) was a significant risk factor for aspirin resistance (Table 5).

4 Discussion

Among elderly patients with CAD, the present study showed that 9.3% to 24.8% of patients are aspirin resistant and an additional 37.0% are aspirin semi-responders. This

Table 2. Association of aspirin resistance with patient characteristics as determined by TEG.

	All patients (*n* = 246)	Aspirin resistant (*n* = 61)	Aspirin sensitive (*n* = 185)	*P*
Age (yrs)	75.9 ± 7.4	76.3 ± 7.3	75.8 ± 7.4	0.620
Female, *n* (%)	79 (32.1)	23 (37.7)	56 (30.3)	0.281
Hypertension, *n* (%)	182 (74)	45 (73.8)	137 (74.1)	0.965
Cerebrovascular disease, *n* (%)	106 (43.1)	30 (49.2)	76 (41.1)	0.268
Diabetes, *n* (%)	74 (30.1)	21 (34.4)	53 (28.6)	0.394
PAOD, *n* (%)	25 (10.2)	10 (16.4)	15 (8.1)	0.063
Current smoker, *n* (%)	15 (6.1)	3 (4.9)	12 (6.5)	0.465
BMI (kg/m^2)	25.05 ± 3.91	25.08 ± 3.12	25.04 ± 4.14	0.945
Homocysteine (μmol/L)	17.80 ± 9.54	17.81 ± 7.48	17.79 ± 10.15	0.992
BNP (pg/mL)	158.06 ± 255.61	158.26 ± 219.05	157.99 ± 267.13	0.994
hs-CRP (mg/dL)	0.44 ± 1.03	0.45 ± 0.71	0.44 ± 1.12	0.938
CD62P (%)	16.54 ± 21.48	20.50 ± 24.95	15.23 ± 20.11	0.097
PAC-1 (%)	40.61 ± 27.38	43.52 ± 29.40	39.63 ± 26.69	0.937
Protein C activity (%)	112.29 ± 37.43	108.96 ± 40.33	113.39 ± 36.47	0.432
Antithrombin III activity (%)	103.26 ± 14.22	104.65 ± 16.49	102.80 ± 13.40	0.378
Creatinine (μmol/L)	82.25 ± 23.26	79.94 ± 23.79	83.01 ± 23.10	0.372
Fasting serum glucose (mmol/L)	6.06 ± 1.23	6.58 ± 1.62	5.89 ± 1.02	0.0001
Total cholesterol (mmol/L)	4.81 ± 1.29	5.08 ± 1.29	4.73 ± 1.28	0.067
Triglyceride (mmol/L)	1.61 ± 0.71	1.71 ± 0.82	1.57 ± 0.68	0.174
HDL cholesterol (mmol/L)	1.30 ± 0.37	1.28 ± 0.38	1.31 ± 0.37	0.687
LDL cholesterol (mmol/L)	2.78 ± 0.87	2.9 ± 1.07	2.72 ± 0.79	0.045
Uric acid (μmol/L)	319.92 ± 92.02	328.41 ± 90.51	317.12 ± 92.58	0.407
Platelet count (×10^3/μL)	203.05 ± 58.52	212.30 ± 74.52	200.00 ± 52.07	0.155
Medications taken				
Statins, *n* (%)	92 (37.4)	24 (39.3)	68(36.8)	0.717
ACEIs/ARBs, *n* (%)	68 (27.6)	17 (27.9)	51(27.6)	0.964
CCBs, *n* (%)	110 (44.7)	27 (44.3)	83(44.9)	0.935
Daily aspirin dose, *n* (%)				
75 mg	82 (33.3)	24 (39.3)	58 (31.3)	0.251
100 mg	164 (66.7)	37 (60.7)	127 (68.7)	0.251

ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; BMI: body mass index; BNP: type-B natriuretic peptide; CCBs, calcium-channel blockers; HDL: high-density lipoprotein; LDL: low-density lipoprotein; PAOD: peripheral arterial occlusive disease; TEG: thrombelastography platelet mapping assay.

Table 3. Age-specific prevalence of aspirin resistance in patients with CAD.

Age group (yrs)	Aspirin resistant (TEG), *n* (%)	Aspirin resistant (LTA), *n* (%)	Aspirin semi-responders (LTA), *n* (%)	Aspirin resistant or semi-responders (LTA), *n* (%)
65–74 (*n* = 85)	17 (20.0)	5 (5.9)	32 (37.6)	37 (43.5)
75–84 (*n* = 138)	40 (29.0)	15 (10.9)	50 (36.2)	65 (47.1)
≥85 (*n* = 23)	4 (17.4)	3 (13)	9 (39.1)	12 (52.2)
P	0.221	0.377	0.954	0.735

CAD: coronary artery disease; LTA: transmission aggregometry; TEG: thrombelastography platelet mapping assay.

Table 4. Distribution of aspirin resistance by age based on sex.

Aspirin resistance by different methods	Age group (years)					
	65–74 (*n* = 85)		75–84 (*n* = 138)		≥ 85 (*n* = 23)	
	Male (*n* = 50)	Female (*n* = 35)	Male (*n* = 101)	Female (*n* = 37)	Male (*n* = 16)	Female (*n* = 7)
Aspirin resistant						
TEG, *n* (%)	9 (18)	8 (22.9)	26 (25.7)	14 (37.8)	3 (18.8)	1 (14.3)
LTA, *n* (%)	4 (8.0)	1 (2.9)	11 (10.9)	4 (10.8)	3 (18.8)	0 (0)
Aspirin semi-responders						
LTA, *n* (%)	22 (44)	10 (28.6)	32 (31.7)	18 (48.6)	6 (37.5)	3 (42.9)
Aspirin resistant or semi-responders						
LTA, *n* (%)	26 (52)	11 (31.4)	43 (42.6)	22 (59.5)	9 (56.3)	3 (42.9)

LTA: transmission aggregometry; TEG: thrombelastography platelet mapping assay.

Table 5. Results of multiple logistic regression analysis.

	B	SE	Wald	df	*P*	Exp(B)	95% CI for EXP(B)	
							Lower	Upper
Fasting serum glucose	0.417	0.130	10.276	1	0.001	1.517	1.176	1.957
LDL cholesterol	0.155	0.270	0.329	1	0.566	1.168	0.688	1.983
PAOD	0.866	0.470	3.394	1	0.065	2.378	0.946	5.978
Total cholesterol	0.128	0.176	0.527	1	0.468	1.137	0.804	1.606
CD62P	0.011	0.007	2.613	1	0.106	1.011	0.998	1.024
Constant	-5.034	1.051	22.937	1	0.000	0.007		

finding suggests that elderly patients do not obtain desirable effects from low doses of aspirin. Considering the strong evidence in favor of aspirin use, this prevalence is particularly noteworthy. Although several studies demonstrate a low prevalence of aspirin-resistance (0–2.8%),[18,19] most studies report a relatively high rate (5.5%–33%) of aspirin resistance in patients with cardiovascular disease.[16,17,20-22] These different data could possibly be due to the lack of a standardized method for determining aspirin resistance.

Previously reported data are inconsistent regarding the association of aspirin resistance to aspirin dose. Gonzalez-Conejero, *et al*.[23] revealed that 33.3% of healthy subjects taking 100 mg/d of aspirin were aspirin resistant as determined by PFA-100. This resistance was overcome by administration of 500 mg/d of aspirin. Gurbel, *et al*.[20] found a significant association between aspirin dose and the platelet response to aspirin as determined by PFA-100 and TXB2. Other studies also demonstrated that increase in aspirin dose decreased the prevalence of aspirin resistance.[18,24] Furthermore, a large systematic review of 42 studies showed that a statistically significant higher prevalence of aspirin resistance was found in studies that used aspirin doses of 100 mg than in those that used 300 mg or more (36% *vs*. 19%, $P < 0.0001$).[25] However, a meta-analysis by the Antiplatelet Trialists' Collaboration reported that a low dose of aspirin (75–150 mg daily) was as effective as higher daily doses in decreasing vascular events.[3] Similarly, compared to lower doses of aspirin (81 mg), higher doses may not provide additional COX-1 inhibition.[26] Further studies are required to ascertain the relationship between aspirin resistance and aspirin dose.

The present study showed that an elevated fasting serum glucose level is an independent risk factor for aspirin resistance. Ertugrul, *et al*.[8] found that aspirin-resistant patients, as determined by impedance platelet aggregometry, were more likely to be diabetic. Aspirin resistance correlated positively with fasting blood glucose levels ($r = 0.224$, $P < 0.001$) and HbA1c levels ($r = 0.297$, $P < 0.0001$).[8] Similarly, Cohen, *et al*.[10] found that aspirin resistance was significantly associated with HbA1c ≥ 8% in a study of 48 diabetic patients. Furthermore, Hovens, *et al*.[27] revealed that suboptimal glycemic control was associated with a higher frequency of aspirin resistance in 40 diabetic patients. These findings suggest that physicians should pay more attention to blood glucose levels and that better glycemic control can improve the antithrombotic effects of aspirin.

Compared to aspirin-sensitive patients, aspirin-resistant patients had higher levels of LDL cholesterol in the present study. Akoglu, *et al*.[28] investigated 83 patients with nephrotic syndrome and found that serum LDL cholesterol levels were closely associated with aspirin resistance. Moreover, Sachika, *et al*.[29] recruited 972 participants from the general Japanese population and showed that collagen-induced platelet aggregation using LTA was correlated with LDL cholesterol levels. Interestingly, Tejskal, *et al*.[30] also reported that aspirin resistance occurred more often in patients with decreased HDL levels, as observed in a study which followed 103 patients with acute coronary syndrome over a period of four years. Furthermore, Tanrikulu, *et al*.[31] showed that HDL cholesterol (OR: 0.974; 95% CI: 0.950–0.999; P = 0.043) was an independent predictor of aspirin resistance in a cohort of patients with chronic renal failure. These results suggest that blood lipid levels should be monitored in patients with dyslipidemia.

The present study had one important limitation. The prevalence of aspirin resistance in elderly patients with CAD was determined for a dose of 75–100 mg/d of aspirin, but we did not investigate the other suggested doses of 162 mg/d and 325 mg/d.

In conclusion, these findings suggest that a significant number of elderly patients with CAD who are resistant to aspirin therapy do not achieve adequate platelet inhibition. Multivariate analysis demonstrated that an elevated fasting blood glucose level is an independent risk factor for aspirin resistance in elderly patients with CAD. Further studies are required to explore the mechanism of aspirin resistance and to provide strategies for antiplatelet therapy in elderly patients with aspirin resistance.

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