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Impacts of serum P-selectin on blood pressure control after PCI in patients with coronary heart disease complicated with hypertension

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Abstract. – OBJECTIVE: We analyzed the impact of potent anti-hypertension or anti-thrombotic therapy after PCI in patients with coronary heart disease complicated with hypertension, whilst to reflect the prognosis by testing P-selectin.

PATIENTS AND METHODS: A total of 177 patients with coronary heart disease (CHD) complicated with hypertension was continuously enrolled in this study and randomly divided into traditional anti-hypertension group (group A: 130/80 mm Hg ≤ BP ≤ 140/90 mm Hg; anti-hypertensive drugs: β blockers and angiotensin converting enzyme inhibitor, *n*=84) and potent anti-hypertension group (group B: BP <130/80 mm Hg; dosage and frequency in group B > group A, *n*=93). This study was approved by the Ethics Committee of Shaoxing People's Hospital. Signed written informed consents were obtained from all participants before the study. Patients who need a stent placed (CAG shows narrowed vascular diameter ≥75%) have to continuously be followed-up for one year. Standard anti-hypertension (fluctuation of BP <5 mm Hg measured for 3 successive days) was detected respectively at admission and inpatient. The blood pressure, low-density lipoprotein cholesterin (LDL-C), high-sensitivity C-reactive protein (hs-CRP) and P-selectin levels were tested 1 month and 1 year after discharge; the time of adverse events (AEs) was also recorded.

RESULTS: There were no statistical differences between the occurrence times of AEs between group A and B (*p*=0.946). The P-selectin [(83±21) *vs.* (69±16) μg/L, *p*=0.038], systolic pressure [(134±8) *vs.* (119±13) mm Hg, *p*<0.001] and diastolic pressure [(85±6) *vs.* (70±5) mm Hg] in group A were higher (*p*=0.001) than those of group B. Compared with P-selectin ≥50.00 μg/L, the median survival time (>12 *vs.* 10 months, χ^2=3.621, *p*=0.047) of P-selectin <50.00 μg/L was longer. By comparing P-selectin in different SBP grading (<120 mm Hg, 120-130 mm Hg, 130-140 mm Hg), the difference was statistically significant (χ^2=12.912, *p*=0.002).

CONCLUSIONS: Potent anti-hypertension may influence the occurrence time of AEs after PCI in patients with coronary heart disease complicated hypertension. P-selectin can be a sensitive indicator. SBP has an apparent "J-curve effect" and an appropriate anti-hypertensive scope (120-130 mm Hg).

Key Words
Hypertension, Coronary heart disease (CHD), Percutaneous coronary intervention (PCI), J curve effect, P-selectin, Thrombus.

Introduction

Coronary heart disease (CHD) is referred to as "the first killer of human health". Its incidence is rising year by year and patients tend to be getting younger. Independent risk factors include age, sex, smoking, hypertension, diabetes and renal failure[1]. Hypertension is a common and frequently-occurring disease. There are 160 million patients who have suffered from hypertension nationwide. Both awareness rate and control rate are lower[2]. For patients with hypertension concomitant with CHD high-risk factors, their anti-hypertensive target ≤130/80 mmHg[1-3]. However, related studies proved that it is not "the lower the better" but rather a "J-curve effect"[4,5]. Along with rapid development of PCI[6], it is very important that dual anti-platelet therapy is given without delay when seeing a doctor and that the postoperative enhanced anti-coagulation is used to prevent instent thrombosis about patients with moderate and severe CHD. However, bleeding risks should be weighed against the risks of anticoagulant therapy. Individualized anticoagulant program has significant meanings to direct clinical practice.

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Researchers in the past rarely investigated the advantages and disadvantages of potent anti-hypertension regarding the impact of anti-hypertension on anti-coagulation after PCI in patients with coronary aheart disease complicated hypertension. A total of 177 patients with CHD complicated with hypertension was enrolled in this study to analyze the impact of potent anti-hypertension on anti-coagulation after PCI and reflecting the prognosis via testing P-selectin.

Patients and Methods

Patients

A total of 177 patients with coronary heart disease (CHD) complicated with hypertension that was admitted into the Cardiology Department of our hospital between January 2014 and January 2015 were continuously enrolled and randomly divided into traditional anti-hypertension group (group A: 130/80 mmHg≤BP≤140/90 mm Hg; anti-hypertensive drugs: β blockers and angiotensin converting enzyme inhibitor, *n*=84) and potent anti-hypertension group (group B: BP <130/80 mm Hg; dosage and frequency in group B > group A, *n*=93). All subjects met the diagnostic criteria (1) of ischemic CHD with CAG indications. CAG showed when targeted narrow vascular diameter ≥75%; patients with excel drug-eluting stent have to continuously carry out a 1-year follow-up. Exclusion criteria included acute myocardial infarction complicated with diabetes, renal failure and cerebral infarction; also, patients who have experienced surgery, bleeding, tumor, severe liver disease, etc. Anti-hypertensive drugs include β blockers and angiotensin converting enzyme inhibitor (ACEIs) (Yangzijiang, Taizhou, China). Patients had no contraindications of β blockers and ACEIs tolerance. Angiotensin receptor blockers (ARBs) could be an alternative for patients with ACEIs intolerance. Anticoagulants, such as clopidogrel and aspirin, and lipid-lowing agents such as rosuvastatin, will be administrated after PCI.

Study Methods

Standard anti-hypertension (fluctuation of BP <5 mm Hg measured for 3 successive days) was detected respectively at admission and inpatient; the blood pressure, low-density lipoprotein cholesterin (LDL-C), high-sensitivity C-reactive protein (hs-CRP) and P-selectin levels were tested 1 month and 1 year after discharge. The time of adverse events was also recorded. All LDL-C, hs-CRP and P-selectin need fasting blood samples in the early morning. hs-CRP is tested by kits (Thermo Fisher Scientific, Waltham, MA, USA), using micro-particle enhanced transmission and immunonephelometry via Hi-tachi911 analyzer. P-selectin was tested by kits (Shanghai Yu Ping Biotechnology Limited Company, Shanghai, China) and analyzed by dual-antibody one-step sandwich enzyme-linked immunosorbent assay (ELISA) (Thermo Fisher Scientific, Waltham, MA, USA). Blood pressure was measured by standard mercury sphygmomanometer (Yuyue, Zhenjiang, China). Subjects rested for at least 5 min in a sitting position. SBP and DBP were recorded as hearing the first and last sound that affected the height of a column of mercury during deflation, and measured again after 1-2 min to record the mean value of two readings. If those two readings of SBP or DBP differed by 5 mm Hg or more, they were measured again and the mean value of three readings was recorded.

Adverse Events and Provisions of BP not up to Standard at Hospital

Patients who need to be hospitalized due to refractory angina after PCI meet the angina criteria (1) of American Heart Association/American College of Cardiology (AHA/ACC). Provisions of BP not up to standard: it is deemed as not reaching the standard if two measurements of SBP or DBP, or both are greater than the target value among three readings measured at hospital, 1 month and 1 year after discharge in patients who are enrolled in group A and B. The classification of hypertension refers to Guidelines on Hypertension Management in China. Stratification analysis for P-selectin refers to related articles (7) and statistical data (see detailed result analysis) in this study.

Definition of Smoking and Drinking Amount

Smoking amount refers to a number of years in smoking × daily amount, namely years × quantity; drinking amount means number of years in drinking × daily amount, namely years × quantity (unit: jin (1/2 kg).

Statistical Analysis

SPSS 17.0 software (Version X; IBM, Armonk, NY, USA) was used. Measurement data are shown by ($\bar{x} \pm s$) using *t*-test or rank-sum test. Enumeration data are expressed by cases number or percentage

Table I. Baseline data between two groups.

Groups	Case number (M/F)	Age (y)	Smoking amount (yearsxquantity)	Drinking amount (yearsxquantity)
A	69 (46/23)	61.3±10.8	373±72	3.12±1.54
B	73 (49/24)	57.8±10.7	364±80	2.73±1.68
p-value	0.954	0.168	0.350	0.717

Notes: A: traditional anti-hypertension group; B: potent anti-hypertension group.

using χ^2-test. Comparison between groups was done using One-way ANOVA test followed by Post-Hoc Test (Least Significant Difference). Kaplan-Meier (K-M method) was introduced for survival analysis and tested by Log Rank test χ^2-method. $p<0.05$ means that the result is statistically significant.

Results

Baseline Data

Group A enrolled 74 patients who needed the stent implantation through CAG and 80 in group B. At the end of the study, 69 patients completed the follow-up in group A and 73 in group B. The utilization of data is 92.21% (142/154). Statistical analysis was carried out for sex, age, smoking and drinking amount, number of stents, number of years in hypertension at admission and hypertensive classification, respectively, between two groups. The difference was statistically significant (Table I).

BP, LDL-C, hs-CRP, P-selectin and Occurrence Time of AEs

Standard BP in group A was higher than group B. The difference was statistically significant. The difference of standard SBP and DBP between two groups or at different time points was statistically significant. The difference between LDL-C and hs-CRP was not statistically significant between two groups or at different time points. The difference of P-selectin was statistically significant ($p=0.038$) between two groups but was not statistically significant between different time points ($p=0.412$). The difference in occurrence times of AEs was not statistically significant in group A and B. Median survival time (MST) was approximately 11.0 months ($p=0.946$). The difference of MST in mean P-selectin (i.e. mean value of four measurements) <50.00 μg/L and ≥50.00 μg/L was not statistically significant ($p=0.047$) (Table II).

Comparisons of SBP and DBP Grading

Mean SBP (i.e. mean value of three measurements after up to standard) is divided into 3 scopes (<120, 120-130 and 130-140 mmHg) to compare to the corresponding P-selectin. The difference was statistically significant ($p=0.002$) (Table III). Mean DBP (i.e. mean value of three measurements after up to standard) is divided into 3 scopes (<80, 80-85 and 85-90 mmHg) to compare with corresponding P-selectin. The difference was not statistically significant ($p=0.163$) (Table IV).

Table II. BP, LDL-C, hs-CRP, P-selectin and occurrence time of AEs.

Groups	Case number (BP up to standard)	SBP (mm Hg)	DBP (mm Hg)	LDL-C (mmol/L)	hs-CRP (mg/L)
A	56 (81.16%)	134±8	85±6	2.45±0.64	1.24±0.33
B	48 (65.75%)	119±13	70±5	2.78±0.52	1.08±0.54
p-value	0.038	<0.001	0.001	0.904	0.051

Groups	Occurrence time of AEs (months)	P-selectin (μg/L)	Case number (P-selectin <50.00/≥50.00 μg/L)
A	11.0	83±21	5/51
B	11.0	69±16	8/40
p-value	0.946	0.038	0.234

Table III. P-selectin in Different SBP Grading.

SBP (mmHg)	Total number of subjects	P-selectin <50.00 μg/L [μ(%)]	P-selectin ≥50.00 μg/L [n(%)]
130-140	59	3 (5.08)	56 (94.92)
120-130	37	12 (32.43)	25 (67.57)
<120	8	2 (25.00)	6 (75.00)

Discussion

P-selectin, namely CD62P, is an adhesive protein that is expressed in megakaryocytes, active platelets and endothelial cells. It participates with active platelets in thrombosis and adheres to phagocytes as well as stimulated vascular endothelial cells under inflammation. It has strong sensitivity and specificity[7,8] in early detection of thrombosis. The widespread use of drug-eluting stents in CHD increases the incidence (advanced and extremely advanced incidence 0.3%-0.6%)[9,10] of in-stent thrombosis while reducing in-stent restenosis resulting in acute myocardial infraction and psychogenic death. In-stent thrombosis may be associated with local artery injuries by breaking atherosclerotic plaques and intimal injuries. It may even lead to median damages such as exposing the subcutaneous coagulation mechanism, activating platelet and prothrombin and triggering intrinsic and extrinsic coagulation pathways after stent implantation. Therefore, it has important clinical significance[11] to test whether the blood is in a hypercoagulable state in case severe complications emerge after PCI. The difference of P-selectin is statistically significant between groups in this trial, but the difference was not statistically significant at different time points. Our results suggest that P-selectin may reach a steady state (likely associated with enhanced anti-platelet therapy) after a period (only one year for observation). Difference between groups indicates that different BP may influence the expression levels of P-selectin in the serum. The MST in AEs was the same between groups, which may be related to a selection bias of excluding the major adverse cardiac events (MACE) such as myocardial infarction and psychogenic death. The reason for this exclusion is that only one-year observation was conducted. Moreover, all patients with CHD admitted into our hospital received the enhanced anti-platelet therapy after PCI and, therefore, the occurrence of MACE was lower. Patients with postoperative refractory angina that needed hospitalized were chosen as adverse events that either had clinically practical significance or caused a reduction in sample size. However, it also may lead to the difference of MST of AEs in two groups not being statistically significant. Further analysis shows that the MST with P-selectin <50.00 μg/L is significantly longer than that of P-seletin ≥50.00 μg/L. For a number of patients with different P-selectin values between groups, the difference was not statistically significant. It partly explains the not statistically significant difference of occurrence time of AEs between two groups. By referring to the "J-curve effect" tested in previous clinical studies[12,13], the mean SBP is classified (according to 10 mm Hg as an interval). After recording the number of patients with corresponding P-selectin, it was found that the difference was not statistically significant. Along with a reduction of SBP, the survival rate (expressed based on percentage of P-selected ≥50.00 μg/L) dropped rapidly and then rose slowly. SBP has a relatively appropriate anti-hypertensive scope (120-130 mm Hg). Further dividing more grading ranges may obtain more suitable anti-hypertensive scopes[14,15] of SBP. Mean DBP is classified (based on 5 mm Hg as an interval) and the difference was not statistically significant according to method above. Further

Table IV. P-selectin in Different DBP Grading.

DBP (mm Hg)	Total number of subjects	P-selectin <50.00 μg/L [n(%)]	P-selectin ≥50.00 μg/L [n(%)]
185-90	33	9 (27.27)	24 (72.73)
80-85	37	16 (43.24)	21 (56.76)
<80	34	8 (23.53)	26 (76.47)

dividing more grading ranges may obtain more suitable anti-hypertensive scopes[16,17] of DBP. The "J-curve effect" was first reported in 1979. After nearly 30 years of large-scale clinical trials and meta-analysis, it was found that the occurrence of cardiovascular events (CVE) is accordingly decreased when BP (SBP or DBP) falls to a specific value or interval during anti-hypertensive therapy. Instead, the occurrence of CVE is somewhat increased after further lowering the blood pressure. Due to the small sample size and less observation time in this study, the difference may have no statistical significance (DBP). With respect to the impact of anti-hypertension on P-selectin expression levels, studies on mechanisms are also needed to be further designed, tested and discussed.

Conclusions

Potent anti-hypertension influences the occurrence time of adverse events after PCI in patients with coronary heart disease complicated hypertension. P-selectin can be a sensitive indicator. SBP has an apparent "J-curve effect" and an appropriate anti-hypertensive scope (120-130 mmHg).

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Du J, Zhang D, Yin Y, Zhang X, Li J, Liu D, Pan F, Chen W. The personality and psychological stress predict major adverse cardiovascular events in patients with coronary heart disease after percutaneous coronary intervention for five years. Medicine (Baltimore) 2016; 95: e3364.
2) Bertoia ML, Waring ME, Gupta PS, Roberts MB, Eaton CB. Implications of new hypertension guidelines in the United States. Hypertension 2011; 58: 361-366.
3) Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. 2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007; 25: 1105-1187.
4) Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, Cifkova R, Clement D, Coca A, Dominiczak A, Erdine S, Fagard R, Farsang C, Grassi G, Haller H, Heagerty A, Kjeldsen SE, Kiowski W, Mallion JM, Manolis A, Narkiewicz K, Nilsson P, Olsen MH, Rahn KH, Redon J, Rodicio J, Ruilope L, Schmieder RE, Struijker-Boudier HA, Van Zwieten PA, Viigimaa M, Zanchetti A. Reappraisal of European guidelines on hypertension management: a European society of hypertension task force document. Blood Press 2009; 18: 308-347.
5) Ji AL, Chen WW, Huang WJ. Clinical study on influences of enteric coated aspirin on blood pressure and blood pressure variability. Eur Rev Med Pharmacol Sci 2016; 20: 5017-5020.
6) De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C, Collet JP, Halvorsen S, Huber K, Jespersen J, Kristensen SD, Lip GY, Morais J, Rasmussen LH, Ricci F, Sibbing D, Siegbahn A, Storey RF, Ten BJ, Verheugt FW, Weitz JI. Oral anticoagulants in coronary heart disease (Section IV). Position paper of the ESC working group on thrombosis--task force on anticoagulants in heart disease. Thromb Haemost 2016; 115: 685-711.
7) Ho JA, Jou AF, Wu LC, Hsu SL. Development of an immunopredictor for the evaluation of the risk of cardiovascular diseases based on the level of soluble P-selectin. Methods 2012; 56: 223-229.
8) Tuttolomondo A, Di Raimondo D, Pecoraro R, Serio A, D'Aguanno G, Pinto A, Licata G. Immune-inflammatory markers and arterial stiffness indexes in subjects with acute ischemic stroke. Atherosclerosis 2010; 213: 311-318.
9) Ong AT, McFadden EP, Regar E, de Jaegere PP, van Domburg RT, Serruys PW. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. J Am Coll Cardiol 2005; 45: 2088-2092.
10) Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005; 293: 2126-2130.
11) Kvasnicka J, Horak J, Zenahlikova Z, Kvasnicka T, Simek S, Kovarnik T, Malikova I, Linhart A, Aschermann M. Reduced thrombin generation and soluble P-selectin after intravenous enoxaparin during PCI. Cardiovasc Drugs Ther 2011; 25: 243-250.
12) Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, Kolloch R, Benetos A, Pepine CJ. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? Ann Intern Med 2006; 144: 884-893.

13) Zanchetti A, Grassi G, Mancia G. When should antihypertensive drug treatment be initiated and to what levels should systolic blood pressure be lowered? A critical reappraisal. J Hypertens 2009; 27: 923-934.
14) JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients. Hypertens Res 2008; 31: 2115-2127.
15) Messerli FH, Panjrath GS. The J-curve between blood pressure and coronary artery disease or essential hypertension: exactly how essential? J Am Coll Cardiol 2009; 54: 1827-1834.
16) Protogerou AD, Safar ME, Iaria P, Safar H, Le Dudal K, Filipovsky J, Henry O, Ducimetiere P, Blacher J. Diastolic blood pressure and mortality in the elderly with cardiovascular disease. Hypertension 2007; 50: 172-180.
17) Fagard RH, Staessen JA, Thijs L, Celis H, Bulpitt CJ, de Leeuw PW, Leonetti G, Tuomilehto J, Yodfat Y. On-treatment diastolic blood pressure and prognosis in systolic hypertension. Arch Intern Med 2007; 167: 1884-1891.