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Could intensive anti-hypertensive therapy produce the "J-curve effect" in patients with coronary artery disease and hypertension after revascularization?

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Abstract. – OBJECTIVE: Intervention and prospective long-term follow-up was performed to observe the presence of the "J-curve effect" in patients with Coronary Artery Disease (CAD) who underwent intensive anti-hypertensive therapy after (PCI or CABG).

PATIENTS AND METHODS: Four hundred and thirty-six successive CAD patients were included in this study, 67 patients with CAD only (Group A) and the 369 patients with both CAD and hypertension who were randomly assigned to Group B (no control of blood pressure (BP), n=72), Group C (n=83, target BP 130-140/80-90 mmHg), Group D (n=78, target BP 120-130/75-80 mmHg), Group E (n=74, target BP 110-120/70-75 mmHg) and Group F (n=62, target BP <110/70 mmHg). All patients had undergone revascularization and anti-hypertensive therapy. The composite endpoint was the end of the follow-up, i.e. major adverse cardiac events (MACE) (cardiac death, nonfatal myocardial infarction and target vessel revascularization) and stroke.

RESULTS: 1) Results showed that smoking, total cholesterol (Tc), low density lipoprotein-C (LDL-C), high-sensitivity C-reactive protein (hs-CRP), β-blockers, ACEI or ARB (except for Group A and Group B), diuretics and follow-up duration among the 6 groups were not significantly different, However significantly lower than those results on admission ($p<0.05$). The difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP) was significant, $p<0.05$, both BP achieved target values. 2) The "J-curve effect" was present in the actual occurrence of composite endpoint and MACE for SBP and DBP, with a reasonable BP-lowering range of 120-130/75-80 mmHg, while the "J-curve effect" was absent in the occurrence of stroke.

CONCLUSIONS: For the patients who had CAD and hypertension, intensive anti-hypertensive therapy could produce the "J-curve effect" after revascularization with the optimal blood pressure (BP) range being 120-130/75-80 mmHg.

Key Words:

Intensive anti-hypertensive therapy, Coronary artery disease, J-curve effect, Major adverse cardiac events, Stroke.

Introduction

CAD is known as "the biggest killer of human health", with an increasing yearly incidence in the young. The independent risk factors of CAD include age, gender, smoking, hypertension, diabetes, and renal insufficiency[1]. Hypertension is a common disease in China, with approximately 160 million of hypertensive patients. However the awareness rate and compliance rate is lower[2]. Chinese Guidance for the Management of Hypertension in 2010 recommended a target blood pressure ≤ 130/80mm Hg for patients with CAD and hypertension. However, relevant studies demonstrated that "the lower the BP, the better anti-hypertension" was not the truth, indicating the "J-curve effect"[3-5]. Most supportive studies were respective, open-label, small scale, or subgroup analysis of large studies, and were limited by confounding factors, leading to different conclusions. Those with opposite views denied the "J-curve effect" in intensive anti-hypertensive therapy, they believed greater cardiovascular benefit with a lower BP[6]. The development of the coronary intervention, especially the application of drug-eluting stent (DES), has improved the quality of life of CAD patients, reduced hospitalization rate, morbidity and mortality. The presence of the "J-curve effect" in intensive anti-hypertensive therapy on the basis of dual antiplatelet therapy after revascularization has been less studied[7]. This study included patients with high-risk CAD and hypertension who were evaluated using the

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"J-curve effect" in intensive anti-hypertensive therapy at different anti-hypertensive level after revascularization through prospective and long-term clinical follow-up, and aimed to provide a reasonable and individualized guide.

Patients and Methods

Patients

Four hundred and thirty-six successive CAD patients were admitted into the Cardiology Department of the hospital from January 2010 to January 2011, with 254 males and 182 females, aged 67.23±10.15 years, 369 patients with both CAD and hypertension, 67 patients with CAD only (Group A). Those patients with both CAD and hypertension were randomly assigned into Group B (no control of BP, n=72), Group C (n=83, target BP 130-140/80-90 mmHg), Group D (n=78, target BP 120-130/75-80 mmHg), Group E (n=74, target BP 110-120/70-75 mmHg) and Group F (n=62, target BP <110/70 mmHg). These patients were followed until January 2013, with a mean follow-up duration of 28.4±10.3 months. All the included patients met the diagnosis criteria of ischemic coronary heart disease and had coronary angiography indication[1], which demonstrated target vascular stenosis ≥75%. These patients had been inserted with an Excel DES. For those patients had unprotected left main disease, multivessel coronary artery disease, long diffuse lesion or calcified lesion, which were not suitable for percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) was recommended. The patients who underwent PCI, received dual antiplatelet therapy (Clopidogrel 75 mg/d, at least 1 year; Bayaspirin 100 mg/d, long term), all patients received intensive lipid-lowering therapy (Rosuvastatin). The patients with both CAD and hypertension received intensive BP-lowering therapy, including β-blockers (Metoprolol extended release tablets, 47.5 mg), angiotensin converting enzyme inhibitors (ACEI) (Imidapril Tablets, 10 mg/d) or angiotensin receptor blockers (ARB) (Irbesartan, 150 mg), calcium channel blockers (Nifedipine Sustained Release Tablets (II), 20 mg/d) and diuretics (Indapamide sustained-release capsules, 1.5 mg/d). All patients received intensive secondary prophylactic treatment for CAD, including controlling blood sugar and diet, smoking cessation, physical exercise and weight reduction. Exclusion criteria: Non-CAD, such as heart failure, valvular heart disease, primary myocardial disease, myocarditis, pericardial disease and rheumatologic diseases, recent major surgery (except for CABG), massive haemorrhage, cancer, severe liver and kidney diseases, poor follow-up compliance. Informed consent was obtained from all included patients.

Methods

Selected patients underwent intensive anti-hypertensive therapy before the diagnosis of hypertension. The intensive anti-hypertensive therapy was continued after surgery until the blood pressure achieved the correspondent target value in each group, when maintenance treatment was provided. If the patients failed to achieve target BP3 months after admission, they were transferred into the correspondent group based on BP grading criteria. The follow-up endpoint was the composite endpoint, i.e. major adverse cardiac events (cardiac death, nonfatal myocardial infarction and target vessel revascularization) and stroke. Mercury sphygmomanometers that met measurement standard were used to measure BP.

A mercury sphygmomanometer that met measurement criteria was used to measure BP, while the subject was in a sitting position for at least 5 min. During deflation, the vertical height of mercury convex at the first Korotkoff sound and disappearing sound was recorded as SBP and DBP, respectively. The measurement was repeated every 1-2 min, the mean value of 2 measurements was used. If the difference between 2 measurements of SBP or DBP was > 5 mmHg, then the 3rd measurement was performed and mean value of the 3 measurements was used. BP values were obtained through telephone interviews or measurement in clinics during monthly follow-ups. Each BP value was the mean of successive 3 monthly BP values, the monthly BP values were the mean of successive 3 daily BP values at the same time and in the same place, and BP variability was ≤ 5 mmHg.

Statistical Analysis

Quantitative data were represented by $\bar{x} \pm s$ and analyzed by one-way analysis of variance. Categorical data was represented by case number or percentage, and analyzed by chi-square test. $p<0.05$ indicated a significant difference. All statistical analysis was performed by SPSS 17.0 software (IBM, NY, USA).

Results

Baseline Information

As shown in Table I, the differences in sex, age, smoking, diabetes, total cholesterol (Tc), low density lipoprotein-C (LDL-C), high-sensitivity

Table I. Baseline information

	Group A	Group B	Group C	Group D	Group E	Group F
Male [n (%)]	42 (62.7)	39 (54.2)	51(61.5)	45(57.7)	40(54.1)	37(59.7)
Age (years)	59.6±9.2	65.6±10.5	68.7±6.9	69.4±11.4	67.2±8.6	69.9±12.1
Smoking [n (%)]	15 (22.4)	9 (12.5)	22 (26.5)	11 (14.1)	12 (16.2)	8 (12.9)
Diabetes mellitus [n (%)]	7 (10.4)	6 (8.3)	10 (12.0)	12 (15.4)	8 (10.8)	4 (6.5)
Tc (mmol/L)	4.6±1.5	5.1±1.7	4.8±0.8	4.5±0.9	5.2±1.3	5.0±1.1
LDL-C (mmol/L)	3.4±0.7	3.5±0.5	3.6±0.8	3.7±0.9	3.6±1.2	3.8±1.3
hs-CRP (mg/L)	3.0±1.3	3.2±1.4	3.3±1.6	3.2±1.7	3.4±1.5	3.5±1.8
ACS [n (%)]	37 (55.2)	40 (55.6)	46 (55.4)	43 (55.1)	39 (52.7)	35 (56.5)
PCI [n (%)]	62 (92.5)	66 (91.7)	78 (94.0)	74 (94.9)	69 (93.2)	58 (93.5)
Number of stent (n)	0.9±0.5	1.4±0.4	1.7±0.6	1.8±0.3	1.6±0.5	1.5±0.2
SBP (mm Hg)	118.5±11.3[§]	159.7±12.4	163.8±13.7	161.5±10.9	165.2±13.4	164.8±9.7
DBP (mm Hg)	75.3±6.7[§]	106.7±9.2	108.5±6.8	109.1±6.2	107.4±7.5	99.5±10.3

Note: Group A, CAD patients without hypertension; Group B, patients without BP control; Group C, target BP 130-140/80-90 mmHg; Group D, target BP 120-130/75-80 mmHg; Group E, target BP 110-120/70-75 mmHg; Group F, target BP < 110/70 mmHg; Tc, Total cholesterol; LDL-C, low density lipoprotein-C; hs-CRP, high-sensitivity C-reactive protein; ACS, acute coronary syndrome; PCI, Percutaneous coronary intervention; SBP, systolic blood pressure; DBP, diastolic blood pressure; [§]indicates that the SBP and DBP in Group A were significantly different from those in other 5 groups, $p<0.05$.

C-reactive protein (hs-CRP), acute coronary syndrome (ACS), PCI proportion, number of stent, SBP (except for Group A) and DBP (except for Group A) among 6 groups were not significant.

Risk Factors and Antihypertensive Agents

As shown in Table II, smoking, Tc, LDL-C, hs-CRP, β-blocker, ACEI or ARB (except for Group A and Group B), diuretics and follow-up duration among 6 groups were not significantly different, however significantly lower than those on admission ($p<0.05$). The usage frequency of CCB was highest in Group F and lowest in Group A, the difference was significant, $p=0.028$. SBP and DBP were significantly different ($p<0.05$), and both SBP and DBP achieved the target value.

The "J-curve effect" in SBP and DBP

Based on the grading criteria of BP, 6 patients in Group F didn't achieve target SBP, 3 of these patients were assigned to Group E and 3 patients to Group D. Six patients in Group E didn't achieve target SBP, 4 of these patients were assigned to Group D and 2 patients to Group C. Therefore, the numbers of patients who achieved target SBP

Table II. Risk factors and antihypertensive agents.

	Group A	Group B	Group C	Group D	Group E	Group F
Smoking [n (%)]	6 (9.0)	4 (5.6)	10 (12.0)	5 (6.4)	6 (8.1)	3 (4.8)
Tc (mmol/L)	3.2±1.1	3.4±1.3	3.3±1.2	3.0±1.5	3.6±1.7	3.5±1.4
LDL-C (mmol/L)	2.0±0.5	2.2±0.7	2.3±0.8	2.4±1.1	2.5±0.5	2.4±0.9
hs-CRP (mg/L)	2.1±1.1	2.3±1.2	2.4±1.5	2.3±1.6	2.5±1.3	2.6±1.6
SBP (mm Hg)*	116.6±12.4	153.6±12.1	136.7±10.6	125.9±9.5	116.7±8.9	106.9±7.8
DBP (mm Hg)*	73.6±6.5	98.6±9.3	86.5±6.5	78.6±6.3	74.9±7.4	68.9±5.8
β-blockers [n (%)]	59 (88.1)	65 (90.3)	74 (89.2)	69 (88.5)	65 (87.8)	56 (90.3)
ACEI (ARB) [n (%)]	5 (7.5)[§]	6 (8.3)[§]	32 (38.6)	35 (44.9)	39 (52.7)	37 (59.7)
CCB [n (%)]*	2 (3.0)	3 (4.2)	9 (10.8)	12 (15.4)	17 (23.0)	18 (29.0)
Diuretics [n (%)]	0	0	2 (2.4)	2 (2.6)	3 (4.1)	3 (4.8)
Follow-up duration (month)	26.8±12.6	27.3±13.6	28.1±15.3	29.0±16.3	27.6±12.9	26.7±11.5

Note: ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; CCB, Calcium channel blocker; *, $p<0.05$; [§]indicates that the number of patients who used AECI or ARB in Group A and Group B was more than the other 4 groups ($p<0.05$).

Table III. The incidence of endpoint events in SBP and DBP in 6 groups.

	Group A	Group B	Group C	Group D	Group E	Group F
SBP compliance (n)	67	72	85	85	71	56
Composite endpoint *[n (%)]	3 (4.48)	11 (10.80)	11 (8.46)	9 (6.11)	8 (6.79)	7 (8.02)
MACE* [n (%)]	3 (4.48)	9 (8.02)	10 (7.24)	9 (6.11)	8 (6.79)	7 (8.02)
Stroke [n (%)]	0	2	1	0	0	0
DBP compliance (n)	67	72	83	81	75	58
Composite endpoint *[n (%)]	3 (4.48)	11 (10.80)	11 (8.77)	8 (5.40)	9 (7.52)	7 (7.59)
MACE* [n (%)]	3 (4.48)	9 (8.02)	10 (7.57)	8 (5.40)	9 (7.52)	7 (7.59)
Stroke [n (%)]	0	2	1	0	0	0

Note: MACE: Major adverse cardiac events; *: The comparison among Group B to Group F, significant difference, $p<0.05$.

were 67, 72, 85, 85, 71 and 56. The prevalence of the composite endpoint, MACE and stroke in Group A was 4.48%, 4.48% and 0%. The actual prevalence of the composite endpoint, MACE and stroke in the remaining groups is equal to (endpoint events minus (events in each group timed the prevalence in Group A) / total number of events in each group [the actual prevalence of composite endpoint in Group B = (11-72×4.48%)]. As shown in Table III and Figure 1, the "J-curve effect" was present in the actual pravalence of composite endpoint and MACE in Group B through to Group F, especially for composite endpoint; while the "J-curve effect" was not present in the prevalence of stroke. Four patients in Group F didn't achieve target DBP, 3 of these patients were assigned to Group E and 1 patient to Group D. Two patients in Group E didn't achieve target DBP, both patients were assigned to Group D. Therefore, the numbers of patients achieving target DBP were 67, 72, 83, 81, 75 and 58. As shown in Table III and Figure 2, the "J-curve effect" was present in the actual prevalence of composite endpoint and MACE in Group B through to Group F, especially for composite endpoint; while the "J-curve effect" was not present in the prevalence of stroke.

Discussion

Stewart[8] first discovered the "J-curve effect" in 1979 and described it as the clinical phenomenon of significantly increasing mortality and morbidity in cardiovascular death when DBP was lower then certain critical value (such as 70-80 mmHg)[8]. Recently, a meta-analysis included 11 relevant clinical studies from 1991 to 2010 confirmed the presence of the "J-curve effect", which was significantly related to the occurrence of cardiovascular events rather than stroke events. Most studies attributed the "J-curve effect" to lower DBP. Recently, some studies found that the "J-curve effect" was related to SBP[10], i.e. SBP < 130 mmHg was significantly related to the occurrence of cardiovascular events rather than stroke events. The sub-group analysis also found that in imaging-confirmed CAD patients, the "J-curve effect" in those patients who hadn't undergone

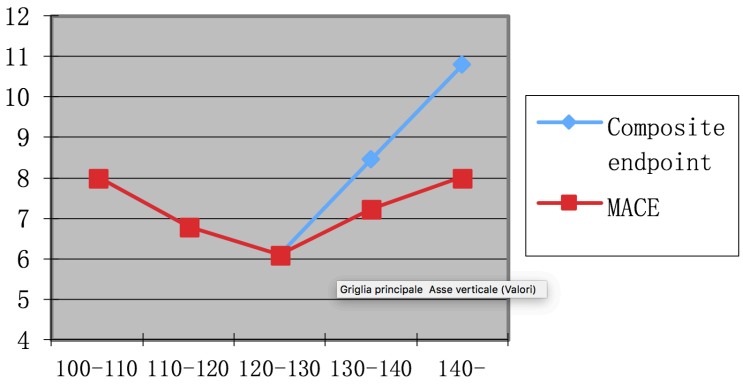

Figure 1. "J-curve effect" in SBP.

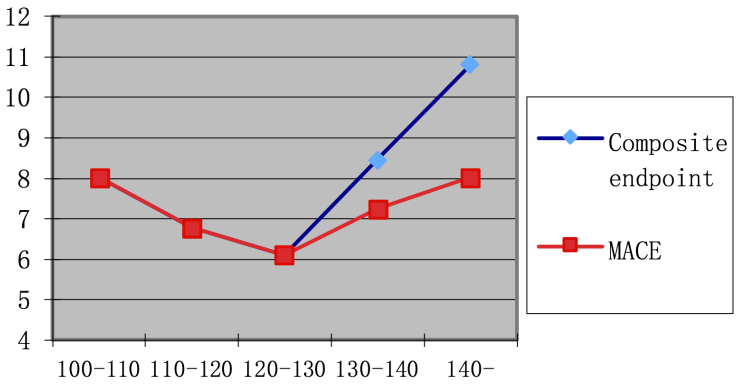

Figure 2. "J-curve effect" in DBP.

revascularization was more obvious than those who had undergone revascularization; this could be explained from a physiological view[11]. The coronary artery was only perfused effectively at diastole. Hemodynamic experiment in dogs found no perfusion in the coronary artery when coronary perfusion pressure was < 40-50 mmHg, this meant 100 % mortality. For CAD patients, coronary artery stenosis resulted in relatively lower perfusion pressure in the distal coronary artery, leading to attenuated physiological effects of self-feedback regulation. The coronary perfusion pressure lower limit may result in myocardial ischemia[12]. However, the occurrence of stroke was negatively related to BP, i.e. if BP was higher than a certain level, the risk of stroke may decrease with decreasing BP. Cerebral perfusion was predominantly dependent on the perfusion pressure in systole, while coronary perfusion was predominantly dependent on the perfusion pressure in diastole[13].

This study randomly assigned patients with CAD and hypertension, who needed and underwent successful revascularization into the groups of different BP-lowering levels and provided interventions, such as intensive anti-hypertensive therapy and secondary prevention of CAD. After a mean follow-up of 28 months, we found that the "J-curve effect" was present in the occurrence of both SBP and DBP as composite endpoint events and MACE, especially for SBP, with a reasonable BP range of 120-130/75-80 mmHg, while no apparent "J-curve effect" present in the occurrence of stroke. This was consistent with previous clinical meta-analysis[14-15]. As the patients undergoing revascularization had been increasing, postoperative intensive antithrombotic therapy was indispensable. The resultant haemorrhage event was a pressing problem for clinicians. The effect of intensive anti-hypertensive therapy on haemorrhage event required further exploration. Further clinical observation was necessary for the presence of the "J-curve effect" in those who had diabetes mellitus and hypertension, hypertension with diabetes and chronic CAD, chronic kidney disease and hypertension, hypertension and stroke, and elderly patients with isolated systolic hypertension[16].

Conclusions

The current recommendation of target BP in clinical guidance was based on the retrospective analysis of observational studies or clinical trials. In order to minimize confounding factors, provide scientific and effective data for establishing target BP; a strictly designed study was needed for the effect of different target BP on clinical outcome. This study may propose more reasonable BP-lowering target levels.

Conflicts of interest

The authors declare no conflicts of interest.

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