

## Original Article

# Effect of continuous positive airway pressure on blood pressure in hypertensive patients with coronary artery bypass grafting and obstructive sleep apnea

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Received August 28, 2014; Accepted October 23, 2014; Epub November 15, 2014; Published November 30, 2014

**Abstract:** Background: Previous studies have documented that obstructive sleep apnea (OSA) increases the incidence of hypertension, respiratory failure and unexpected post-operative deaths during night in coronary artery bypass grafting (CABG) patients. We hypothesized that continuous positive airway pressure (CPAP) reduces blood pressure in these patients. Methods: We conducted a prospective, controlled study in 51 patients. The subjects received CPAP treatment were defined as CPAP group, whereas those refused to use CPAP were served as controls. Blood pressure was measured by 24 h ambulatory blood pressure at baseline and at six months. Results: Fifty-one patients completed the study. CPAP group and controls had similar characteristics. Compared with the control group, the 24-h SBP and 24-h DBP in the CPAP group had a tendency towards lower levels, but the differences were not statistically significant. But the change of SBP in CPAP treatment was significantly higher than controls (CPAP:  $10.0 \pm 13.5$  mm Hg vs. Control:  $2.9 \pm 10.5$  mm Hg,  $P = 0.040$ ). The rate of hypertension control was improved in the CPAP treatment, but had no statistical difference compared to the controls (CPAP, 76.0% vs. Control, 61.5%;  $P = 0.260$ ). Compared with controls, the proportion of non-dipping hypertension had a markedly improvement in the CPAP group (Control, 46.2% vs. CPAP, 16.0%;  $P = 0.034$ ). Conclusions: CPAP therapy decreased SBP and improved the status of non-dipping hypertension and alleviated daytime somnolence in hypertensive patients with CABG and OSA on standardized antihypertensive treatment. But DBP and hypertension control did not significantly change compared with the control group.

**Keywords:** Continuous positive airway pressure, hypertension, obstructive sleep apnea, coronary artery bypass grafting

## Introduction

Obstructive sleep apnea (OSA) is a disorder characterized by recurrent upper airway collapse that occurs during sleep, resulting in sleep fragmentation and oxyhemoglobin desaturation [1]. The prevalence of obstructive sleep apnea in general population has been reported to be 9% in females and 25% in males [2]. OSA is associated with various cardiovascular disease [3-5]. A recent research demonstrates that 67% patients received coronary artery bypass grafting (CABG) have OSA [6]. Previous studies have documented that OSA increases the incidence of respiratory failure and unexpected post-operative deaths during night in CABG patients [7, 8]. A study has shown that over 20% of hypertensive patients exhibit OSA,

whereas prevalence of hypertension in the setting of OSA exceeds 50% [9]. It is conceivable that the hypertension in subjects with CABG and OSA has a higher incidence. Some studies [10-13] suggested that continuous positive airway pressure (CPAP) reduces systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) in patients with OSA. However, other researches indicated that it is unclear whether CPAP application is associated with better blood pressure (BP) control rates [14-16]. To the best of our knowledge, there is a paucity of data about the effect of CPAP on BP in hypertensive patients with CABG and OSA under standardized antihypertensive medications. The better hypertension control is crucial for the improved prognosis of the specific population. Therefore, we conducted a prospective,

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controlled study to determine whether CPAP decreases BP in hypertensive patients with CABG and OSA.

### Methods

#### *Study design and setting*

We performed a single centre, prospective, controlled study of 64 patients attending our hospital by matching the two groups for age, gender, body mass index (BMI) and the severity of OSA. Patients that refused to use CPAP treatment for worrying about the side effects from CPAP, served as a control group, whereas patients accepted CPAP application were allocated to the group of CPAP. This study was approved by the ethics committee of The Fourth Affiliated Hospital of Harbin Medical University. Informed consent was obtained from each patient.

#### *Patient selection*

We recruited consecutive patients from outpatient and inpatient departments of our hospital from January 2012 to December 2013. Patients diagnosed with moderate to severe OSA documented by polysomnography [17], hypertension (hypertension is defined as systolic pressure  $\geq 140$  mm Hg and/or diastolic pressure  $\geq 90$  mm Hg at rest, or treatment with antihypertensive medication.) and a confirmation of the CABG in the medical record were enrolled into this study. Also, the following criterion needs to be met: at least 3-month optimal treatment for hypertension but with uncontrolled hypertension. The subjects were excluded if they had secondary hypertension, history of significant chronic renal, or hepatic failure or severe pulmonary disease, central sleep apneas, diagnosed with malignant cancer with a life expectancy of less than 1 years, regular use of drugs that can affect BP (including corticosteroids, sedative drugs and some traditional Chinese medicine), severe psychiatric disease, uncontrolled alcohol use, current use of CPAP treatment for OSA or pharyngeal surgery for OSA, declined to participate or were unable to give informed consent.

#### *Study protocol*

Patients diagnosed as hypertension and CABG with a suspicion of OSA were screened and per-

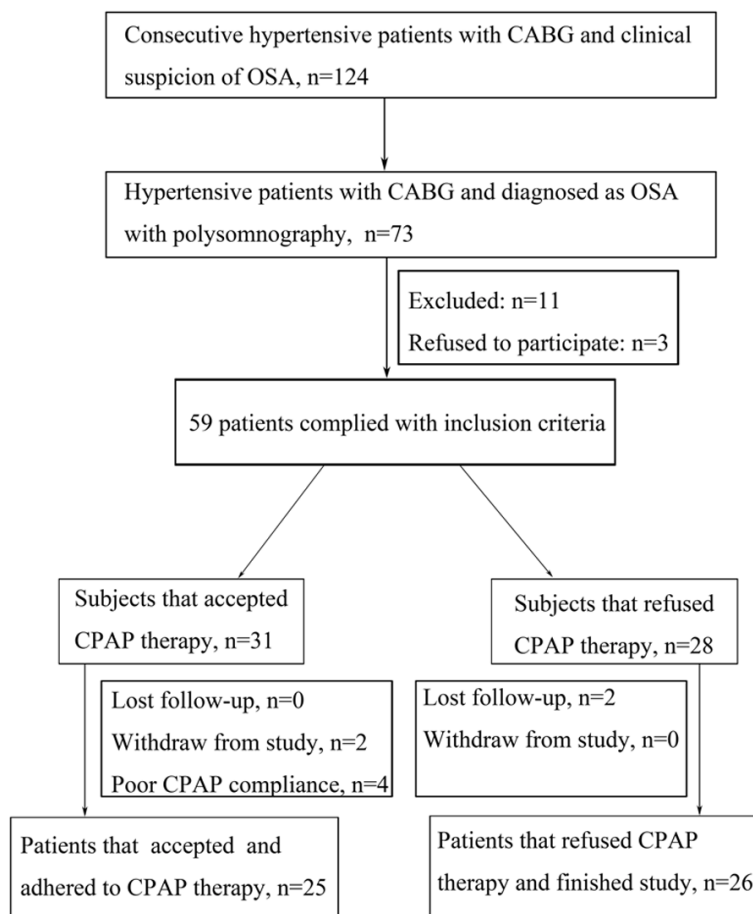
formed by evaluation of relevant daytime and nighttime symptoms. Patients who were diagnosed with moderate to severe OSA were included in the present study. At baseline, 24-h ambulatory BP monitoring (ABPM) was measured, demographic data including age, sex, medical history, therapeutic regimen, lifestyle habits, height (cm) and weight (kg), waist circumference (cm), hip circumference (cm), and neck circumference (cm) were recorded, and BMI was calculated as weight divided by height squared (kilograms per square meter,  $\text{kg}/\text{m}^2$ ). The daytime somnolence of patients was assessed by the Epworth sleepiness scale (ESS) [18], a self-completed questionnaire specific to symptoms of daytime sleepiness in various daytime situations. Patients underwent regular clinical examination and laboratory tests to exclude secondary hypertension. After the initial evaluation, physician would give lifestyle advice (including smoking cessation and discontinue heavy drinking). Participants were assigned antihypertensive and CABG drug treatment according to current guidelines in a 3-month run-in period that allowed for modifications in therapeutic schedule. Patients were not allowed to change their therapeutic regimen after 3-month run-in period.

Patients visited the sleep research laboratory at 1 month, 3 months and 6 months after starting treatment. Follow-up was carried out in all cases by the same investigator. The physician responsible for the assessment of subjects was blinded to the CPAP status of the patients. Every medical appointment involved protocol-based assessments of the following: heart rate recorded by electrocardiogram after the patient rested for 10 min, adherence to CPAP, medical compliance, lifestyle habits, height, weight, waist circumference, hip circumference, neck circumference, and ESS.

#### *BP measurement*

24-h ABPM was evaluated with a SpaceLabs Healthcare device (model 90202) ambulatory blood pressure monitor. An appropriately sized cuff was applied. Blood pressure was registered every 15 min during daytime (awake) and every 30 min during nighttime (asleep) on the basis of the patient's reports on their activities during day and night. The percentage of fall in SBP at night was calculated by dividing the difference between mean daytime and mean

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**Figure 1.** Flow-chart of the study. CABG, coronary artery bypass grafting; OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure.

nighttime systolic blood pressures by the mean daytime SBP [19]. Non-dipping hypertension was defined as a BP decrease of < 10% during sleep compared with the awake period. Bedtime and the time of awakening from sleep were recorded in diaries. Therefore, data are based on 24-h ABPM using actual sleep and wake times recorded by participants. BP was considered to be controlled in those patients with 24-h mean blood pressure values < 135/85 mm Hg [20].

### Sleep evaluation

All patients underwent overnight polysomnography (Embla-Flaga hf. Medical Devices). Polysomnography data were scored manually by trained personnel. Apneas were defined as airflow reduction to 10% or less of the baseline value for 10 s or more. Hypopnea was defined as a 30% to 90% reduction in oronasal airflow for more than 10 seconds, associated with an

oxygen desaturation of 4% or higher [21]. Central sleep apnea was defined as at least 50% of respiratory events having a pattern of apnea or hypopnea without thoracic and abdominal movement. The severity of OSA was quantified numerically as the number of apnea-hypopnea index (AHI). Moderate OSA was defined as an AHI of 15-29 episodes/h and severe OSA as an AHI at least 30 episodes/h. Subjective daytime somnolence was assessed with the ESS questionnaire. A total score > 10 was considered excessive daytime sleepiness.

### CPAP application

For patients agree to use nasal CPAP group received fixed-level CPAP titration using an automated pressure setting device for one night. The optimal CPAP pressure for each patient in the CPAP group was set at the minimum pressure required to abolish snoring, obstructive respiratory

events, and airflow limitation for 95% of the night. The fixed pressure was then maintained throughout the study in those patients used the CPAP machine. CPAP compliance was objectively measured by the built-in compliance software of CPAP devices from the regular examination of follow-up. Patients are generally considered adequately adherent to their CPAP treatment if the mean CPAP use was at least 4 hours per night. Each patient received standardized instructions by one investigator specialized in OSA and by a home health care provider at the start of the CPAP treatment. A specialist OSA team assisted patients with telephone or outpatient advice for any difficulties with CPAP during the study and masks were adjusted as necessary.

### Statistical analysis

Continuous variables with normal distribution were expressed as mean  $\pm$  SD and as median

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**Table 1.** Baseline anthropometrics and clinical characteristics between CPAP and control groups

Variable	CPAP (n = 25)	Control (n = 26)	P
Age (years)	62.3 ± 7.2	61.6 ± 7.1	0.743
Male sex (n, %)	20 (80.0)	23 (88.5)	0.465
BMI (kg/m <sup>2</sup> )	28.8 ± 3.2	28.0 ± 2.4	0.337
Smokers (n, %)	15 (60.0)	17 (65.4)	0.691
Diabetes mellitus (n, %)	16 (64.0)	19(73.1)	0.485
Dyslipidemia (n, %)	21 (84.0)	20(76.9)	0.523
Myocardial infarction (n, %)	7 (28.0)	9 (34.6)	0.611
Neck circumference (cm)	41.7 ± 3.4	41.0 ± 2.2	0.349
ESS (points)	9.9 ± 3.3	8.9 ± 3.3	0.287
AHI (events/h)	28.2 ± 12.9	28.1 ± 13.2	0.998
Minimum SaO <sub>2</sub> (%)	77.7 ± 5.5	78.2 ± 5.4	0.777
24-h Heart rate (bpm)	67.4 ± 8.7	65.7 ± 6.3	0.428
24-h SBP (mm Hg)	136.1 ± 13.4	133.7 ± 9.0	0.449
24-h DBP (mm Hg)	84.3 ± 8.0	84.2 ± 7.9	0.968
ACEI (n, %)	7 (28.0)	10 (38.5)	0.428
ARB (n, %)	11 (44.0)	12 (46.2)	0.877
β-Blocker (n, %)	15 (60.0)	18 (69.2)	0.490
CCB (n, %)	12 (48.0)	10 (38.5)	0.492
Diuretics (n, %)	20 (80.0)	19 (73.1)	0.560
Antihypertensive drugs	3.0 ± 0.6	2.9 ± 0.6	0.668
Hypertension control (n, %)	14 (56.0)	17 (65.4)	0.493
Non-dipping hypertension (n, %)	9 (36.0)	11 (42.3)	0.645

Values are mean ± SD or No. (%). CPAP, continuous positive airway pressure; BMI, body mass index; bpm, beats per minute; ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CCB, calcium channel block.

(range) without normal distribution, and categorical variables were reported as absolute numbers and percentages. Comparison between controls and CPAP group, a two-tailed test was used for normally distributed variables and a Mann-Whitney test for non-normally distributed variables. The  $\chi^2$  test was used to compare categorical variables. Fisher's exact test was used if appropriate. SPSS version 13 software (SPSS Chicago, Illinois, USA) was used for statistical analysis. A *P* value <0.05 was considered statistically significant.

### Results

The study flow-chart is depicted in **Figure 1**. Of 124 patients who were screened between January 2012 to December 2013. A total of 73 (58.9%) patients diagnosed with OSA, 3 subjects declined to participate in the study, 11 of them were excluded: 9 patients with AHI < 15

and 2 patient with severe chronic obstructive pulmonary disease, 59 fulfilled inclusion criteria. Of these, 31 patients agreed to use CPAP treatment and 28 subjects refused to follow CPAP application. And 2 participants withdrew from the study at 1 month due to intolerance of CPAP treatment. Additionally, 2 subjects lost to follow-up in the control group. Four participants with very poor CPAP compliance were also excluded. Finally, 25 patients in the CPAP group and 26 subjects in the control group completed the study.

### *Characteristics of the two groups at baseline*

Baseline characteristics were similar in both groups (**Table 1**). The mean age was 61.9 ± 7.1 years. In this study, 43 (84.3%) participants were male and 13 (25.5%) subjects were with obesity,

and 23 (45.1%) patients had daytime sleepiness. The comorbidities between groups were similar. There were no significant differences with respect to drug number and category used by the patients in the two groups. The 24-h SBP in the CPAP treatment group and controls was 136.1 ± 13.4 mm Hg and 133.7 ± 9.0 mm Hg, respectively (*P* = 0.449). And the 24-h DBP in both groups was 84.3 ± 8.0 mm Hg and 84.2 ± 7.9 mm Hg, respectively (*P* = 0.968).

### *Changes of clinical characteristics at six months*

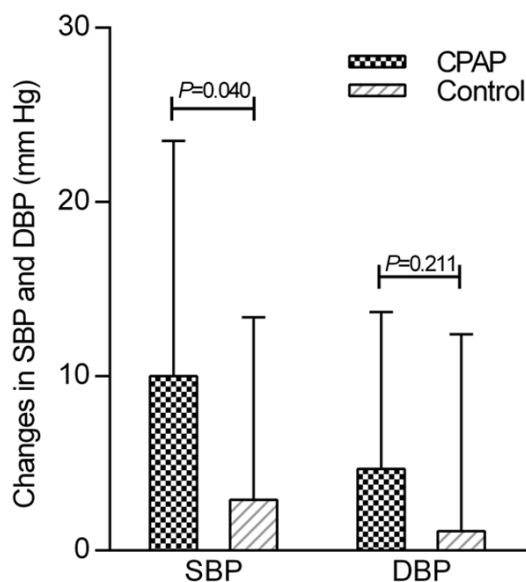
The six-month data are summarized in **Table 2**. There was no significant difference in BMI between groups (28.7 ± 3.1 kg/m<sup>2</sup> vs. 27.9 ± 2.4 kg/m<sup>2</sup>; *P* = 0.339). Moreover, heart rate and neck circumference had also no significant differences in the two groups. The mean time of CPAP treatment was 4.7 ± 1.5 h/night. AHI in

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**Table 2.** Comparison of characteristics of patients between groups at six months

Variable	CPAP (n = 25)	Control (n = 26)	P
BMI (kg/m <sup>2</sup> )	28.7 ± 3.1	27.9 ± 2.4	0.339
Neck circumference (cm)	42.0 ± 3.2	41.1 ± 2.2	0.257
ESS (points)	3.6 ± 2.2	7.5 ± 2.3	< 0.001
24-h Heart rate (bpm)	65.2 ± 6.2	67.5 ± 6.8	0.200
24-h SBP (mm Hg)	126.0 ± 10.5	130.7 ± 12.3	0.150
24-h DBP (mm Hg)	79.6 ± 6.5	83.2 ± 7.9	0.086
SBP change (mm Hg)	10.0 ± 13.5	2.9 ± 10.5	0.040
DBP change (mm Hg)	4.7 ± 9.0	1.1 ± 11.3	0.211
Hypertension control (n, %)	19 (76.0)	6 (61.5)	0.266
Non-dipping hypertension (n, %)	4 (16.0)	12 (46.2)	0.034

Values are mean ± SD or No. (%). CPAP, continuous positive airway pressure; BMI, body mass index; ESS, Epworth Sleepiness Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; blood pressure change is defined as baseline minus six-month value.



**Figure 2.** The changes in SBP and DBP at six-month in the two groups.

patients with CPAP treatment reduced obviously from  $28.2 \pm 12.9$  events/h to  $2.1 \pm 1.5$  events/h, suggesting that OSA was good control in the CPAP group. Compared to control group, daytime somnolence apparently decreased in the therapeutic CPAP group (ESS,  $7.5 \pm 2.3$  vs.  $3.6 \pm 2.2$ ;  $P < 0.001$ ). The 24-h SBP and 24-h DBP in the CPAP group had a tendency towards lower levels compared with controls, but the differences were not statistically significant (24-h SBP, CPAP:  $126.0 \pm 10.5$  mm Hg vs. Control:  $130.7 \pm 12.3$  mm Hg; 24-h DBP, CPAP:  $79.6 \pm 6.5$  mm Hg vs. Control:  $83.2 \pm 7.9$

mm Hg;  $83.2 \pm 7.9$ ; both  $P > 0.05$ ). The comparison of change of DBP at six months had no significant difference between groups ( $\Delta$  DBP, CPAP:  $4.7 \pm 9.0$  mm Hg vs. Control:  $1.1 \pm 11.3$  mm Hg,  $P = 0.211$ ). But the change of SBP in the CPAP group was significantly higher than in control group (CPAP:  $10.0 \pm 13.5$  mm Hg vs. Control:  $2.9 \pm 10.5$  mm Hg;  $P = 0.040$ , **Figure 2**). The rate of hypertension control was improved in

the CPAP treatment, but had no statistical difference compared to the control group (CPAP, 76.0% vs. Control, 61.5%;  $P = 0.260$ ). Compared with controls, the proportion of non-dipping hypertension had a markedly improvement in the CPAP group (Control, 46.2% vs. CPAP, 16.0%;  $P = 0.034$ ).

### Discussion

To our knowledge, this is the first study specifically designed to investigate the effect of CPAP treatment on BP in hypertensive patients with CABG and OSA. The present study indicated that CPAP therapy decreased SBP and improved the status of non-dipping hypertension and alleviated daytime somnolence in hypertensive patients with CABG and OSA on standardized antihypertensive treatment. But DBP and hypertension control did not significantly change compared with the control group.

Being different from many previous studies [22-25], which either mainly targeted at normotensive patients or evaluated the effect of CPAP in the absence of antihypertensive medications, all the included subjects were hypertensive population with a history of CABG and received standardized antihypertensive medications in the present study.

A number of studies have analyzed the effect of CPAP on BP but with conflicting results. Rauscher and colleagues analyzed 60 hypertensive patients (33 accepted CPAP and 27 refused) for 512 days, and showed that the

improvements in BP correlated with changes in BMI but not with CPAP use [26]. It is noticeable that some important variables (including the number and category of antihypertensive drugs and ESS) associated with outcomes did not mention in their study. Recently, Kasiakogias et al. [27] conducted a long-term study about the effect of CPAP on BP and indicated that CPAP treatment is not associated with lower BP levels or a need for less antihypertensive drugs for BP control in nonsleepy, hypertensive, OSA patients on conventional antihypertensive treatment. However, the study has some obvious drawbacks. First, the patients in their study had a significant difference in severity of OSA at baseline ( $P = 0.005$ ). Second, the proportion of diuretics use in their study was only 36.3% and the mean number of antihypertensive medications is less than 3. Furthermore, these included patients had no subjective complaints of sleepiness. There are two studies suggesting that the ESS is closely related to the responsiveness of subjects to the CPAP treatment [10, 28].

Consistent with our findings, A few nonrandomized studies have consistently indicated that CPAP treatment in OSA patients with resistant hypertension mainly resulted in reductions in SBP (from 5.2 to 11 mm Hg) [29-31]. What is more, Montesi et al. [9] and Schein et al. [28] performed the systematic review and meta-analysis of randomized controlled trials demonstrated that treatment with CPAP promoted significantly but small reductions in blood pressure in the individuals with OSA. The results of the present study are important because international guidelines [32] have pointed out that even minimal reductions in the SBP (2-3 mm Hg) in the older population could have a clinically significant effect by greatly reducing subsequent cardiovascular mortality (between 6%-8% for stroke and 4%-5% for coronary heart disease), and therefore a significant potential reduction in cardiovascular mortality and morbidity should be expected in these patients. Seif and colleagues' study showed that OSA and diurnal nondipping hemodynamic led to an increased cardiovascular risk [33]. And our finding that CPAP application improved the status of non-dipping hypertension in patients with CABG and OSA, and may improve the prognosis of the specific subjects under long-term CPAP therapy. Furthermore, ESS score in patients adhered to use CPAP had a significant reduc-

tion from  $9.9 \pm 3.3$  at baseline to  $3.6 \pm 2.2$  at six-month. Choi and colleagues showed that a higher ESS score was significantly related to lower stroke index and cardiac index even after controlling for age, sex, ethnicity, respiratory disturbance index, and mean sleep oxygen saturation [34]. Nishihata and colleague have shown that moderate to severe OSA not treated with CPAP was an independent risk factor for relapse of a CVD event, and adequate CPAP treatment improved cardiovascular outcomes in elderly patients [35].

### *Study limitations*

Our study has some limitations. First, the study sample size was relatively small. However, it is difficult to recruit the large uncontrolled hypertensive subjects with CABG and OSA. Second, this was a nonrandomized study. Because the available evidence on the effect of CPAP not allow us to perform a randomized study for a long-term follow-up ethically, especially in CABG population. Third, the lack of blinding may have had an impact on the outcomes of the trial. The study investigator responsible for the assessment of participants, however, was blind to allocation of CPAP. It is useful to avoid observer bias.

### **Conclusions**

In summary, our findings has demonstrated that CPAP treatment in hypertensive patients with CABG and OSA receiving standardized antihypertensive treatment CPAP therapy decreased SBP and improved the status of non-dipping hypertension and alleviated daytime somnolence in hypertensive patients with CABG and OSA on standardized antihypertensive treatment. But DBP and hypertension control did not significantly change compared with the control group. In the future, a large scale, long-term prospective trial is needed to clarify the impact of CPAP on the prognosis of patients with CABG and OSA.

### **Acknowledgements**

We thank Pengna Wei for her contribution in the statistical analysis and the relentless efforts of the sleep laboratory personnel, technicians Xiumei, Li. This work was supported by grants from the Youth Science Fund of Heilongjiang Province (NO. QC2012C129).

**Disclosure of conflict of interest**

None.

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