

Obstructive Sleep Apnea Hypopnea Syndrome as a Reason for Active Management of Pulmonary Embolism

Jiang Xie¹, Yong-Xiang Wei², Shuang Liu¹, Wei Zhang¹, Xiang-Feng Zhang¹, Jie Li¹

¹Department of Pulmonary Medicine, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China

²Department of Otolaryngology - Head and Neck Surgery, Beijing Anzhen Hospital, Capital Medical University, Beijing 100029, China

Abstract

Background: Obstructive sleep apnea hypopnea syndrome (OSAHS) constitutes an independent factor for high warfarin dose for patients with pulmonary embolism (PE). The aim of this study was to investigate whether the 6-month anticoagulation treatment by warfarin is enough for patients with PE complicated by OSAHS.

Methods: We investigated 97 PE patients, 32 of them had OSAHS and 65 non-OSAHS. Warfarin was administered for 6-month if no abnormal circumstances occurred. All patients were followed up for 18 months. Adverse events (AE) included death, major bleeding, hospitalization due to heart failure or pulmonary hypertension, and recurrence or aggravation of PE (including deep vein thrombosis). Recurrence rate of PE after warfarin cessation was compared between the two groups.

Results: OSAHS patients required a significantly higher dose of warfarin than their non-OSAHS counterparts (4.73 mg vs. 3.61 mg, $P < 0.001$). During warfarin treatment, no major bleeding and aggravation of PE occurred among OSAHS patients, and the rates of various AE were not significantly different between the OSAHS and non-OSAHS groups. PE recurrence was higher in OSAHS than non-OSAHS groups after withdrawal of warfarin (21.43% vs. 6.78%, $P = 0.047$). Compared with non-OSAHS patients, OSAHS group had lower international normalized ratio (INR) value but higher plasminogen on baseline and INR resumed to a relatively low level after warfarin discontinuation.

Conclusions: OSAHS patients may present with hypercoagulation and relatively high-risk of recurrence of PE after cessation of 6-month warfarin treatment.

Key words: International Normalized Ratio; Pulmonary Embolism; Obstructive Sleep Apnea Hypopnea Syndrome; Recurrence; Warfarin

INTRODUCTION

A number of studies have reported that obstructive sleep apnea hypopnea syndrome (OSAHS) is more prevalent and severe in patients with pulmonary embolism (PE).^[1-4] Patients with PE complicated by OSAHS have more severe conditions, such as greater lung segment involvement and lower partial pressure of oxygen in arterial blood than their non-OSAHS counterparts.^[2] Therefore, more aggressive treatment is required in patients with PE complicated by OSAHS. Anticoagulant treatment plays a pivotal role in the management of patients with PE, and warfarin is still one of the most reliable anticoagulants.^[5,6]

However, there are few studies regarding the effect of anticoagulants in patients with OSAHS. In our previous study, OSAHS was an independent risk factor for high-dose warfarin use in PE patients. A higher dose of warfarin was required

in patients with more severe OSAHS. Hypercoagulation may be an important factor for high-doses of warfarin.^[4] Empirically, the security issue seems to be solved by close follow-up to maintain international normalized ratio (INR) to a narrow therapeutic range. It is worth noting that, according to current recommended guideline,^[7] OSAHS is not a reason for long-term anticoagulation. However, the intrinsic causes leading to hypercoagulation cannot be eradicated thoroughly by anticoagulation, and hypercoagulable state and related complications may reappear after anticoagulant cessation. The purpose of this study was to investigate whether a routine warfarin treatment duration of 6-month is enough for PE patients complicated by OSAHS.

METHODS

Study subjects

Patients identified as having PE were consecutively recruited from June 2012 to February 2013 for a prospective study conducted at Beijing Anzhen Hospital, a 1500-bed, tertiary care

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DOI:
10.4103/0366-6999.162498

Address for correspondence: Dr. Yong-Xiang Wei,
Department of Otolaryngology - Head and Neck Surgery of Beijing
Anzhen Hospital, Capital Medical University, Beijing 100029, China
E-Mail: Weiyongxiang@vip.sina.com

teaching hospital in Beijing, China. A complete medical history was collected for all patients. Inclusion criteria were patients who were diagnosed with PE and who agreed to participate in the study. Exclusion criteria were: Patients unable or unwilling to participate or to provide consent; patients younger than 18 or older than 80 years; pregnant women; patients diagnosed with malignant tumor, connective tissue disease, and heart failure (class IV of the New York Heart Association functional classification); patients diagnosed with PE caused by infective endocarditis; patients contraindicated to warfarin therapy, and patients receiving thrombolytic therapy because of high-risk PE presenting with cardiogenic shock and/or persistent arterial hypotension. Written informed consent was obtained from all patients, and this study complied with the *Declaration of Helsinki* and was approved by the Institutional Review Board of Anzhen Hospital.

Computer tomographic pulmonary angiography (CTPA) was used to diagnose PE, but when CTPA was negative, and there was a high clinical suspicion for PE, pulmonary angiography was used for diagnosis. Arterial and venous blood was taken for blood gas analysis and biochemical testing. Echocardiography and ultrasonography (for deep vein) were finished for everyone.

Polysomnography

Polysomnography (Compumedics, Abbotsford, Victoria, Australia), which has been described in detail in a previous study,^[4] was performed during hospitalization for all patients with PE several days before discharge from hospital and when they are stable. The sleep lab is located beside the ward, which allows the patients to be covered by the clinician in the ward. An oronasal thermal airflow sensor and nasal pressure transducer were used to monitor airflow to identify apnea and hypopnea, respectively. Arterial oxyhemoglobin saturation (SaO₂) was recorded using a pulse oximeter, and electrocardiograph recordings were taken from a single modified lead II. All sleep studies were manually interpreted by a sleep technician according to the 2007 guidelines of the American Academy of Sleep Medicine (AASM).^[8] Apnea was defined as >90% decrease in airflow relative to baseline flow lasting >10 s. Hypopnea were defined as >30% decrease in airflow with 4% desaturation lasting >10 s (AASM recommendation criteria). The apnea-hypopnea index (AHI) was defined as the average number of apnea and hypopnea episodes per hour and subjects with AHI \geq 5 events/h were considered to have OSAHS. The remaining patients were classified as non-OSAHS patients. Patients with an AHI of between 5 and 15 events/h should also have daytime symptoms for a diagnosis of OSAHS.

Antithrombotic strategies

Antithrombotic strategies have been described in the previous study.^[4] Warfarin was initiated at a dose of 3 mg/day. For the 11 patients older than 75 years or those with a high-risk of bleeding (e.g., uncontrolled hypertension, stroke, renal and hepatic dysfunction, and recent bleeding), a warfarin dose of 2 mg/day was prescribed. The INR value was tested 3 days after warfarin treatment and dosage adjustment

was made according to INR: INR < 1.5 = increase dose by 0.5 mg/day for 7 days; INR 1.5–2.0 = no change for 7 days; INR < 2.0 (after 7 days) = increase dose by 1 mg/day for 3 days. A dosage of 0.5–1.0 mg/day was added or reduced, as necessary, according to the patient's INR. The antithrombotic target was deemed to be achieved if the INR level was verified to be within the range of 2.0–3.0 based on 2 measurements. Low molecular weight heparin was used simultaneously with warfarin for at least 4–5 days.

All patients accepted the suggestion that high consumption of Vitamin K-containing foods, such as green leafy vegetables, and ingestion of alcohol should be actively avoided. A dietary handbook was given to all patients, which listed the Vitamin K content in 100 different vegetables. However, overly strict control of vegetable intake was not advisable. Patients were advised to maintain a stable diet and not to change the kinds and amounts of vegetables they typically eat.

Follow-up

A study team was responsible for the follow-up. Patients were asked to visit the outpatient department every 15 days after hospital discharge. Information on patients' health status and medication were gathered at follow-up. The time and category of adverse events (AEs), including death, major bleeding, hospitalization due to pulmonary hypertension or heart failure, and recurrence or aggravation of PE or deep vein thrombosis (DVT), were also recorded. Major bleeding was diagnosed in the case of a fall in hemoglobin levels to >2 g/dl, the need for transfusion, or intracranial hemorrhage. Aggravation of PE (or DVT) was defined as worsening symptoms with a deterioration observed upon imaging during anticoagulation, while recurrence means reappearance of embolism (or DVT) upon imaging with or without symptoms after warfarin discontinuation.

Patients received a fixed maintenance dose of warfarin everyday and had their INR value tested every 15 or 30 days. If INR was too high or too low, and the adjusted warfarin dose was different from the dose taken at hospital discharge, then the dose which could maintain the longest duration of target INR value was accepted in our study for analysis.

All patients with symptomatic OSAHS and all OSAHS patients with AHI >15 times/h were advised to use a positive airway pressure (PAP) device during sleep. Doctors helped select a suitable PAP (manual titration) and appropriate mask, according to their medical and financial conditions. PAP adherence was deemed to be achieved if the patient was on therapy for at least 4 h/night, 70% of the nights of the week.^[9] Two patients were asked to postpone their surgery for OSAHS, because of the diagnosis of PE and their anticoagulant state.

Patients who had no adverse effects for 6-month and no signs of thrombosis on CTPA and ultrasonography were evaluated carefully by doctors to exclude any diseases needing long-term anticoagulation, such as a malignant tumor, connective tissue diseases, atrial fibrillation, residual

lesions and pulmonary hypertension, and then warfarin therapy was discontinued. Patients were closely followed for the next 12-month. Medical assistance was available if any abnormal symptoms appeared. Four patients who were verified to have residual embolism were asked to prolong anticoagulation and were not followed up.

Statistical analysis

Continuous variables are described as mean with standard deviation or median with an interquartile range (IQR) for skewed data, whereas dichotomous variables are described as numbers and percentages. Differences between patients in OSAHS and non-OSAHS groups were analyzed by independent *t*-test for continuous data or Mann–Whitney for samples with nonnormal distributions and Chi-square tests for dichotomous data. Body weight and INR values were selected as covariates, and analysis of covariance was used to compare the difference in warfarin dosage in the OSAHS and the non-OSAHS groups. Chi-square test was used to determine the difference in the incidence of various AE for the two groups. All statistical analyses were carried out using SPSS software version 16.0 (SPSS Inc., Chicago, Illinois, USA). A *P* < 0.05 was considered as statistically significant.

RESULTS

Clinical characteristics

The study design is shown in Figure 1. A total of 133 patients with PE were screened, and 32 OSAHS and 65 non-OSAHS patients were included in the study.

Versus the non-OSAHS group, the OSAHS group had more male patients, with a much higher body mass index and body weight [Table 1]. In our study, 78.13% of OSAHS patients had a history of hypertension versus 55.39% for non-OSAHS patients. There was no significant difference between the two groups in the percentages of concomitant use of aspirin (or clopidogrel), biguanides, antacids, quinolones, cephalosporin and macrolide antibiotics.

Compared with mild OSAHS patients with AHI < 15 events/min, the moderate-to-severe patients with AHI ≥ 15 (events/min) had lower minimum SaO₂ during sleep, longer apneas duration, higher arousal index with bad sleep efficiency [Table 2].

Therapeutic INRs for the OSAHS group required a comparatively higher dose of warfarin [Table 3]. This difference still existed between the two groups after adjusting for covariates (achieved INR value and weight) (*P* = 0.024). Only 4 patients achieved the recommended levels of PAP adherence. According to the changes of INR value during follow-up, one of these 4 subjects was able to take a lower dose of warfarin to maintain the INR range of 2.0–3.0, while the other 3 kept the same daily maintenance dose as before.

Safety and effectiveness of the high-dose warfarin for obstructive sleep apnea hypopnea syndrome patients

During 6-month of warfarin treatment, the incidence of AE (including residual embolism) was 12.5% for OSAHS

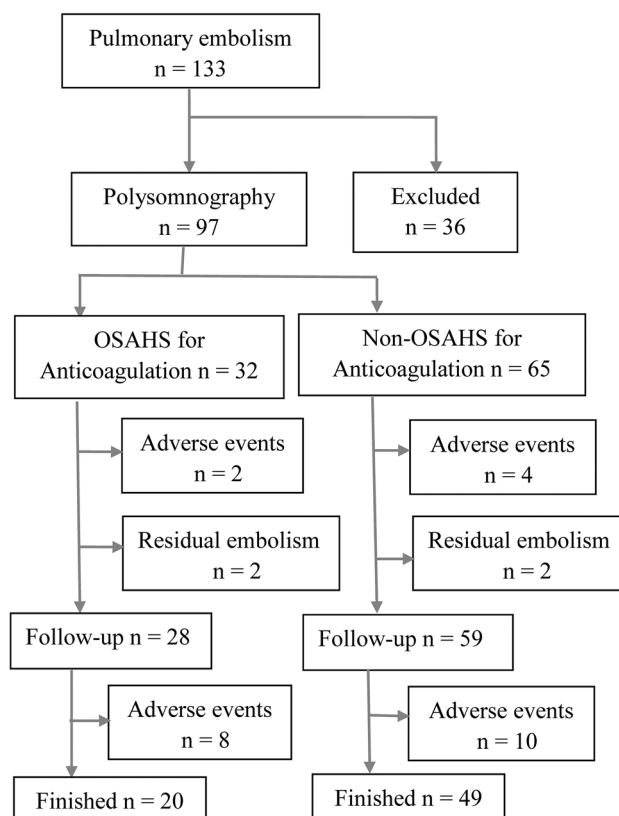


Figure 1: Flow diagram of a study investigating the effects of warfarin on patients with pulmonary embolism complicated by obstructive sleep apnea hypopnea syndrome (OSAHS) versus those without OSAHS. Finished: Patients finished the antithrombotic treatment and follow-up with no adverse events during 18 months.

patients, and 9.23% for non-OSAHS patients ($\chi^2 = 0.241$, *P* = 0.623). OSAHS patients had no major bleeding or PE aggravation [Table 4]. Noticeably, 3 major bleeding events occurred among non-OSAHS patients, including 2 within the 1st month. Two patients with major bleeding had an INR value within the therapeutic range. One OSAHS patient died from heart failure within 6-month, but no non-OSAHS patient died in the same period. There was no significant difference in the incidence of hospitalization for heart failure or pulmonary hypertension between the two groups (3.13% vs. 1.54%, *P* = 0.616). After anticoagulation, each group had 2 patients with confirmed residual embolism but with no clinical manifestation (silent residual) (6.25% vs. 3.08%, *P* = 0.473).

Pulmonary embolism relapses after warfarin discontinuation

As shown in Table 5, after successful treatment for 6-month, 28 OSAHS, and 59 non-OSAHS patients were allowed to discontinue anticoagulation and enter into close follow-up observation. No significant difference existed between the two groups in terms of the total number of adverse effects after warfarin termination (28.57% vs. 16.95%, *P* = 0.214). However, OSAHS patients had more recurrence of PE than non-OSAHS (21.43% vs. 6.78%, *P* = 0.047). Notably, the recurrence of PE constituted 75% of the AE after warfarin

Table 1: Baseline characteristics of OSAHS and non-OSAHS patients

Variables	OSAHS (n = 32)	Non-OSAHS (n = 65)	P
Age (years)	59.97±12.91	62.99±12.75	0.278
Male (n, %)	20 (62.50)	25 (38.46)	0.009
Heart rate (beats/min)	73.50±13.44	75.57±14.14	0.493
SBP (mmHg)	129.22±19.91	125.38±16.17	0.312
DBP (mmHg)	80.19±16.19	74.85±11.69	0.067
Weight (kg)	83.98±13.69	69.59±11.35	<0.001
BMI (kg/m ²)	30.74±5.41	26.14±4.10	<0.001
Total cholesterol (mmol/L)	4.65±1.01	4.70±0.95	0.834
Triglyceride (mmol/L)	2.22±1.27	1.66±1.03	0.024
Arterial PO ₂ (mmHg)	76.59±12.78	77.30±13.70	0.807
Arterial PCO ₂ (mmHg)	38.92±9.36	34.98±5.46	0.011
LVEF (%)	64.97±7.94	65.25±5.65	0.841
Hypertension (case/morbidity)	25/78.13%	36/55.39%	0.043
Diabetes (case/morbidity)	14/43.75%	9/13.85%	0.064
DVT (case/morbidity)	7/21.88%	19/29.23%	0.452

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; LVEF: Left ventricular ejection fraction; DVT: Deep vein thrombosis; PaO₂: Partial pressure of oxygen; PaCO₂: Partial pressure of carbon dioxide; OSAHS: Obstructive sleep apnea hypopnea syndrome.

Table 2: Sleep and breathing parameters of the patients with OSAHS

Variables	AHI < 15 (events/min) (n = 13)	AHI ≥ 15 (events/min) (n = 15)	P
AHI (events/h)	9.15±3.62	36.14±20.88	<0.001
Minimum SaO ₂ (%)	83.61±3.40	76.53±7.46	0.004
Longest hypopnea (s)*	39.5 (33.7, 60.9)	58 (41.8, 86.2)	0.279
Longest apnea (s)*	17.3 (13.0, 20.0)	44.4 (28.4, 75.5)	<0.001
Sleep efficiency (%)	87.08±4.37	78.47±5.68	<0.001
Arousal index (events/h)	9.23±3.3	37.20±23.28	<0.001

*Skewed data expressed as median (IQR) and compared with Mann-Whitney test. AHI: Apnea-hypopnea index; SaO₂: Oxyhemoglobin saturation; OSAHS: Obstructive sleep apnea hypopnea syndrome; IQR: Interquartile range.

Table 3: Comparison of warfarin dosage between OSAHS and non-OSAHS

Warfarin dose	Mean (CI)		P
	OSAHS	Non-OSAHS	
Needed dose*	4.73 (4.19–5.28)	3.61 (3.31–3.90)	<0.001
Dose in model 1	3.71 (3.38–4.04)	4.52 (4.03–5.01)	0.012
Dose in model 2	4.64 (4.20–5.08)	3.65 (3.34–3.96)	0.001
Dose in model 3	4.45 (3.97–4.93)	3.75 (3.43–4.06)	0.024

*Warfarin dose needed to maintain INR between 2 and 3. Model 1 adjusts body weight; Model 2 adjusts achieved INR value; Model 3 adjusts both body weight and achieved INR value. CI: Confidence interval; INR: International normalized ratio.

discontinuation for the OSAHS group. In the 10 patients that experienced a PE recurrence, 60% occurred within 3 months of warfarin discontinuation, and 90% occurred within 6-month.

Table 4: Comparison of adverse events between OSAHS and non-OSAHS patients during anticoagulation (n (%))

Events	OSAHS (n = 32)	Non-OSAHS (n = 65)	Total (n = 97)	P
Bleeding	0	3 (4.62)	3 (3.09)	0.118
PE aggravation	0	0	0	-
Heart failure*	1 (3.13)	1 (1.54)	2 (2.06)	0.616
Death	1 (3.13)	0	1 (1.03)	0.135
Total incidence	2 (6.25)	4 (6.15)	6 (6.19)	0.985
Silent residual†	2 (6.25)	2 (3.08)	4 (4.12)	0.473

*Patients hospitalized due to heart failure or pulmonary hypertension; †Confirmed residual embolism with no clinical manifestation. OSAHS: Obstructive sleep apnea hypopnea syndrome; PE: Pulmonary embolism.

Table 5: Comparison of adverse events between OSAHS and non-OSAHS patients after anticoagulation cessation (n (%))

Events	OSAHS (n = 28)	Non-OSAHS (n = 59)	Total (n = 87)	P
PE recurrence	6 (21.43)	4 (6.78)	10 (11.49)	0.047
Heart failure	0	2 (3.39)	2 (2.30)	0.209
Death	2 (7.14)	3 (5.08)	5 (5.75)	0.705
Others	0	1 (1.70)	1 (1.15)	0.376
Total incidence	8 (28.57)	10 (16.95)	18 (20.69)	0.214

OSAHS: Obstructive sleep apnea hypopnea syndrome; PE: Pulmonary embolism.

None of the 4 patients achieving recommended levels of PAP adherence had PE relapse after warfarin discontinuation.

Obstructive sleep apnea hypopnea syndrome patients present with hypercoagulation

Figure 2a demonstrates that OSAHS patients had lower INR value than non-OSAHS counterparts on admission (0.96 mg vs. 1.03 mg). The plasminogen (PLG) value was significantly higher in OSAHS groups than in non-OSAHS (115.85 vs. 103.77, $P = 0.040$). During anticoagulation, two groups maintained equivalent INR value [Figure 2b], and the INR returned to the value similar to baseline respectively for each group 1-month after warfarin discontinuation [Figure 2c].

DISCUSSION

To the best of our knowledge and belief, this is the first study to follow-up the results of anticoagulation in patients with PE complicated by OSAHS. To treat PE, the OSAHS group required a comparatively higher dose of warfarin to achieve an INR of 2.0–3.0. The safety and effectiveness of the high-dose warfarin for OSAHS patients were demonstrated in the equivalent event-free survival rate between the OSAHS and non-OSAHS groups. The high recurrence rate of PE after warfarin discontinuation among OSAHS patients implies the rationality of aggressive treatment regimen, namely higher doses of warfarin as well as possibly longer courses of treatment at the same time.

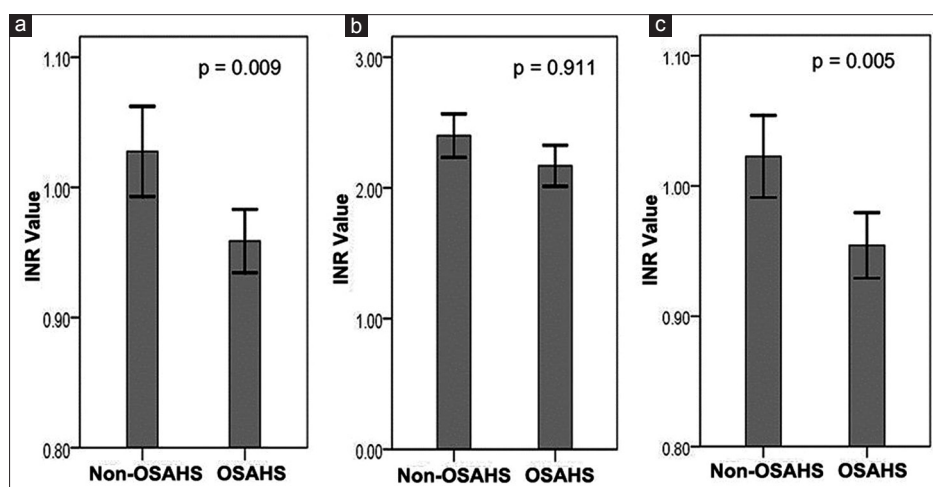


Figure 2: (a) Obstructive sleep apnea hypopnea syndrome (OSAHS) patients had lower international normalized ratio (INR) value than non-OSAHS counterparts on admission; (b) Equivalent INR values were achieved for both groups; (c) INR returned to low value for OSAHS patients after warfarin discontinuation.

In our study, PE patients with OSAHS took high-dose warfarin but did not have a high incidence of bleeding, during treatment revealing that a high-dose anticoagulant does not mean a high-risk of bleeding, if INR is closely monitored. The reported incidence of major bleeding in patients on warfarin ranges from 0.4% to 7.2%/year.^[10-12] Noticeably, most bleeding events happened at very early stage of treatment in our study. Therefore, strict INR monitoring is encouraged as early as the initiation of anticoagulation, regardless of whether the index is stable or fluctuating. Patients should be educated on increased bleeding risk during this period. Proven risk factors for bleeding include advanced age, presence of hypertension, diabetes, anemia, congestive heart failure, and female gender.^[10,13-16] Based on the findings of this study, a high maintenance warfarin dose taken by patients with severe OSAHS does not constitute a risk factor.

In addition to concerns regarding the risk of bleeding, the recurrence of thrombosis constitutes another important concern. The cumulative proportions of patients with incident venous thromboembolism (VTE) with recurrence (including VTE and PE) at 1, 2, 5 and 10 years are 13%, 17%, 23% and 30%, respectively,^[17-20] and 2.0%, 6.4% and 8.0% at 14-, 90- and 180-day, respectively.^[21] Some researchers even tend to argue that it is basically impossible to cure embolism using anticoagulation.^[18,22] In our study, before stopping warfarin, a diagnosis of malignant tumor, connective tissue diseases, atrial fibrillation, residual lesion, and pulmonary hypertension, which need chronic anticoagulation, was excluded. However, there was still a notable proportion of patients presenting with a recurrence of PE or DVT while OSAHS patients had higher rates of recurrence than their non-OSAHS counterparts. Noticeably, most of the recurrence happened early after warfarin discontinuation. It appears that OSAHS patients tended to present with a trend of warfarin resistance, namely no bleeding during warfarin treatment and a high recurrence rate after discontinuation, as well as a favorable benefit/risk ratio for warfarin treatment. The documented risk factors for PE recurrence included

male gender and D-dimer level in previous studies.^[23] Uncontrolled OSAHS can also be a potential risk factor for PE recurrence. This is a meaningful finding, worth noticing.

As to the duration of anticoagulation, acute therapy aims to prevent extension of an acute embolism, insure thrombus has either recanalized or organized, and return the inflammatory/innate immunity system to baseline.^[24] Current guidelines recommend 3–6 months of treatment after initiation of warfarin for PE and DVT.^[25] Beyond 6-month, the aim of continued anticoagulation is to prevent recurrent thrombosis (prophylaxis). Considering the bleeding risk, the appropriateness of prolonged anticoagulation should be continuously re-evaluated, and prophylaxis should be stopped if the benefit no longer exceeds the risk.^[21] For patients with PE complicated by OSAHS, especially severe OSAHS, it would be wise to assess the patients more strictly before deciding to discontinue anticoagulation. Meanwhile, although we consider the routine 3–6 months of anticoagulation as not enough for some OSAHS patients, randomized controlled trials are needed to verify that these patients can really benefit from prolonged duration anticoagulant treatment.

Considering the lower INR and higher PLG values on admission, OSAHS patients appear, to some extent, to have a hypercoagulant state in our study. Actually, OSAHS patients tend to have higher weight and more risks of hypercoagulation due to factors such as sedentary behavior, increased hematocrit levels,^[26] higher blood viscosity,^[27] and increased platelet activity,^[28] all of which tend to permit more aggressive anticoagulation. However, it would not be prudent to use baseline coagulation values to estimate the required warfarin dose, and the dose may be determined by many important genetic and nongenetic factors. Anyway, the OSAHS group resumed a relatively hypercoagulant state 1-month after warfarin cessation in our study, which can be an important risk for recurrence of PE.

There is a very important shortcoming in our study. PAP was suggested for most OSAHS patients, but only 4 patients

actually adhered to PAP during follow-up. In China, not only because of the economic development but also the understanding of OSAHS, acceptance of PAP therapy is quite low. For those who accepted PAP, according to a study completed mostly in China, the reported 12-month adherence rates were only 39%.^[29] Internationally, of OSA patients in whom CPAP is recommended, the initial rejection rates range widely from 5% to 50%.^[30] In China, it is the initiation rather than persistence of PAP constitutes the difficulty for OSAHS control. Failure of health insurance coverage is an important reason. Meanwhile, we had better confess that patients with coronary heart disease receiving percutaneous coronary intervention did have better CPAP adherence to about 40%.^[31] For patients with PE, more effort is needed to convince them the importance of PAP. Previous studies proved that PAP may reduce blood coagulability^[32] and systemic oxidative stress.^[33] It will be very interesting to investigate whether PAP can really eradicate hypercoagulation of OSAHS patients, counteract some dose of their anticoagulant agents or increase warfarin “sensitivity”, or even increase risk of bleeding side effect by taking regular dose of anticoagulant. Meanwhile, as warfarin dose is closely related to genetic background, it is worthy to investigate whether genetic overlap exists between OSAHS and warfarin resistance, which cannot be reversed by CPAP.

In conclusion, OSAHS patients require a comparatively higher maintenance dose of warfarin to maintain an INR of 2.0–3.0. Under close monitoring, the relatively high-dose of warfarin will not increase the bleeding risk. PE and hypercoagulation may recur in some OSAHS patients soon after warfarin termination, and 6-month routine anticoagulation seems not enough for PE complicated by uncontrolled OSAHS.

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Received: 03-12-2014 **Edited by:** Li-Min Chen

How to cite this article: Xie J, Wei YX, Liu S, Zhang W, Zhang XF, Li J. Obstructive Sleep Apnea Hypopnea Syndrome as a Reason for Active Management of Pulmonary Embolism. *Chin Med J* 2015;128:2147-53.

Source of Support: This study was supported by a grant from the Beijing Project of Science and Technology (No. Z101107050210044). **Conflict of Interest:** None declared.