Hypertensive crisis in patients with obstructive sleep apnea-induced hypertension

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Abstract
Background: Hypertensive crisis is an urgent/emergency condition. Although obstructive sleep apnea (OSA) in resistant hypertension has been thoroughly examined, information regarding the risk factors and prevalence of hypertensive crisis in co-existing OSA and hypertension is limited. This study thus aimed to determine prevalence of and risk factors for hypertensive crisis in patients with hypertension caused by OSA.

Methods: The inclusion criteria were age of 18 years or over and diagnosis of co-existing OSA and hypertension. Those patients with other causes of secondary hypertension were excluded. Patients were categorized by occurrence of hypertensive crisis. Factors associated with hypertensive crisis were calculated using multivariate logistic regression analysis.

Results: There were 121 patients met the study criteria. Of those, 19 patients (15.70%) had history of hypertensive crisis. Those patients in hypertensive crisis group had significant higher systolic and diastolic blood pressure at regular follow-ups than those without hypertensive crisis patients (177 vs. 141 mmHg and 108 vs. 85 mmHg; p value < 0.001 for both factors). After adjusted for age, sex, and Mallampati classification, only systolic blood pressure was independently associated with hypertensive crisis with adjusted odds ratio (95% CI) of 1.046 (1.012, 1.080).

Conclusions: The prevalence of hypertensive crisis in co-existing OSA and hypertension was 15.70% and high systolic blood pressure or uncontrolled blood pressure associated with hypertensive crisis in patients with OSA-associated hypertension.

Keywords: Systolic blood pressure, Obstructive sleep apnea, Hypertensive urgency, Hypertensive emergency

Introduction
Obstructive sleep apnea (OSA) is a disease that is commonly encountered in clinical practice. Its estimated prevalence is approximately 26% in the population between 30 and 70 years of age [1]. It causes intermittent desaturations during sleep, which can result in various cardiovascular diseases such as hypertension, heart failure, atrial fibrillation, coronary artery disease, and stroke [2].

In 2003, OSA was found to be a common cause of hypertension [3]. The prevalence of OSA in hypertensive patients is approximately 50% and ranges from 30–80% [4]. The prevalence of OSA in patients with resistant hypertension is up to 71% which was similar to that in those with hypertensive crisis [5–7]. Large neck

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circumference, snoring, and age are predictors of OSA in these patients with adjusted odds ratios of 4.7 (1.3–16.9), 3.7 (1.3–11.0), and 5.2 (1.9–14.2), respectively [6]. However, although OSA in resistant hypertension has been thoroughly examined, information regarding the risk factors and prevalence of hypertensive crisis in co-existing OSA and hypertension is limited. This study thus aimed to determine prevalence of and risk factors for hypertensive crisis in patients with hypertension caused by OSA.

Methods
This was a retrospective study conducted at Khon Kaen University Hospital Hypertension clinic in Thailand. The inclusion criteria were age of 18 years or over and diagnosis of co-existing OSA and hypertension. The diagnosis of hypertension was based on the criteria proposed in the JNC 7 [3], while that of OSA was made according to the apnea-hypopnea index (AHI: five or more apnea or hypopnea events per hour). Although hypertension can have various causes, this study examined only patients with hypertension caused by OSA and excluded all others. The study period was between 2015 and 2016.

We collected clinical data from the medical charts of all eligible patients recorded at the last follow-up including clinical features, symptoms and signs of OSA, co-morbid diseases, cardiovascular diseases, and laboratory investigation results. The outcome of this study was presence of hypertensive crisis at the Emergency Department, which was diagnosed as systolic and/or diastolic blood pressure greater than 180/110 mmHg [8]. Cases in which there was acute target organ damage from hypertensive crisis, such as heart failure or papilledema, were defined as hypertensive emergency, while those in which there was no acute target organ damage from hypertensive crisis were recorded as hypertensive urgency.

Sample size calculation. A previous report found the prevalence of hypertensive crisis in the Emergency Department to be 11.5% [9]. Based on a formula for a single population, we determined that the expected prevalence of hypertensive crisis in OSA patients was likely to be 20%. Thus, the required sample size was 77 to reach the expected OSA prevalence of 20% in hypertensive crisis with a confidence of 90% and power of 80%.

All eligible patients were classified by the presence of hypertensive crisis. Clinical factors of patients in both groups were compared using descriptive statistics. Factors associated with hypertensive crisis were calculated using logistic regression analysis. Univariate logistic regression analysis was used to identify the risk factors for hypertensive crisis. Those with p values less than 0.20 or clinically significant were included in the subsequent multivariate logistic regression analysis. Results of the logistic regression analyses were presented as unadjusted and adjusted odds ratio (OR) with 95% confidence interval (CI). All analyses were performed using STATA version 10.1 (College Station, Texas, USA).

Results
During the study period, there were 121 patients with hypertension caused by OSA. Of those, 19 (15.70%) had a history of hypertensive crisis, categorized as either hypertensive urgency (15 patients) or hypertensive emergency (four patients). There were two significant factors that differed between patients with and without history of hypertensive crisis (Table 1): systolic and diastolic blood pressure. Those with a history of hypertensive crisis had higher median systolic and diastolic blood pressure than those without (systolic: 177 vs. 141 mmHg; diastolic: 108 vs. 85 mmHg). Symptoms and signs of OSA, co-morbid diseases, and cardiovascular diseases were comparable between the two groups.

There was no significant difference between the two groups in terms of laboratory results (Table 2). The hypertensive crisis group had a lower average apnea hypopnea index score than those without hypertensive crisis (14.5 vs. 19.5 events/hour; p value 0.363). After adjusting for age, sex, and Mallampati classification, only systolic blood pressure was independently associated with hypertensive crisis, with an adjusted odds ratio (95% CI) of 1.046 (1.012, 1.080).

Discussion
Hypertensive crisis (particularly hypertensive emergency) has been associated with high morbidity and mortality. A French study reported 15 deaths out of 46 patients (33%) within three months after admission with hypertensive emergency [10]. Previous studies have found the general prevalence of hypertensive crisis in hypertensive patients to be approximately 1–2%, of which 25% presented with hypertensive emergency [11, 12]. The population in this study was patients with hypertension caused by OSA. The prevalence of hypertensive crisis in this setting was much higher than in the general population (15.70% vs. 1–2%), but the proportion of patients with hypertensive emergency was comparable between this study and general population (21.1% vs. 25%) [11]. These results may indicate that patients with hypertension caused by OSA are at higher risk for hypertensive crisis. A previous study also confirmed this with evidence that OSA was a cause of hypertensive crisis in 70% of the161 patients examined [7].

One previous study in 89 hypertensive patients found female sex and obesity to be significantly associated with hypertensive crisis [13]. Our study found that in patients with co-existing OSA and hypertension, baseline systolic blood pressure was a significant risk factor...
Table 1 Clinical features of patients with hypertension secondary to obstructive sleep apnea (OSA) categorized by presence of hypertensive crisis (HTC)

| Factors                        | No HTC n = 102 | HTC n = 19 | p value |
|--------------------------------|----------------|------------|---------|
| **Basic characteristics**      |                |            |         |
| Age, years                     | 50.5 (39.0–59.0) | 42.0 (33.0–52.0) | 0.062   |
| Male sex                       | 56 (54.90)     | 9 (47.37)  | 0.620   |
| BMI, kg/m²                     | 29.3 (26.0–35.6) | 30.6 (26.3–34.8) | 0.017   |
| SBP, mmHg                      | 141 (130–150)  | 177 (150–190) | <0.001  |
| DBP, mmHg                      | 85 (79–93)     | 108 (90–121) | <0.001  |
| Previous alcohol consumption*  | 14 (31.82)     | 3 (30.00)  | 0.999   |
| Current alcohol consumption    | 9 (20.45)      | 1 (10)     | 0.667   |
| Previous smoker*               | 7 (15.91)      | 2 (20.00)  | 0.667   |
| Current smoker                 | 3 (6.98)       | 0 (0.00)   | 0.999   |
| Wearing dentures               | 3 (5.56)       | 0 (0.00)   | 0.999   |
| No. of antihypertensive drugs  | 1 (1–2)        | 2 (1–3)    | 0.081   |
| Statin therapy                 | 56 (60.22)     | 11 (61.11) | 0.999   |
| **Signs and symptoms of OSA**  |                |            |         |
| Snoring                        | 61 (98.39)     | 12 (92.31) | 0.319   |
| Median snoring duration, years | 8.0 (3.5–10.0) | 2.0 (2.0–20) | 0.500   |
| Witnessed apnea                | 26 (70.27)     | 5 (83.33)  | 0.659   |
| Nocturia, times/night          | 2 (1–3)        | 2.5 (1–4)  | 0.419   |
| Morning headache               | 19 (50.00)     | 3 (75.00)  | 0.608   |
| Unrefreshing sleep             | 26 (78.79)     | 5 (71.43)  | 0.645   |
| Excessive daytime sleepiness   | 47 (87.04)     | 6 (75)     | 0.328   |
| Mallampati classification      |                |            |         |
| @1                             | 0 (0)          | (7.69)     |         |
| @2                             | 22 (35.48)     | (23.08)    |         |
| @3                             | 29 (46.77)     | (46.15)    |         |
| @4                             | 11 (17.74)     | 2 (15–38)  |         |
| Macroglossia                   | 30 (61.08)     | 6 (66.67)  | 0.384   |
| Tonsil palatins                | 8 (32.00)      | 2 (28.57)  | 0.999   |
| Tonsil mandibularis            | 6 (25.00)      | 1 (14.29)  | 0.999   |
| Tonsil enlargement (%)         | 7 (21.88)      | 1 (14–29)  | 0.999   |
| Retroglossa (%)                | 5 (22.73)      | 2 (28.57)  | 0.999   |
| Median neck circumference, cm  | 41.0 (38.0–44.7) | 37.0 (35.0–38.0) | 0.089   |
| **Co-morbid diseases**         |                |            |         |
| Diabetes mellitus              | 33 (35.48)     | 4 (26.67)  | 0.572   |
| GERD                           | 32 (39.51)     | 6 (40.00)  | 0.999   |
| Allergic rhinitis              | 20 (50.00)     | 3 (33.33)  | 0.472   |
| Cardiovascular events          |                |            |         |
| Stroke                         | 8 (8.89)       | 1 (7.69)   | 0.999   |
| Coronary artery disease        | 8 (8.89)       | 2 (14.29)  | 0.621   |
| Heart failure                  | 9 (10.00)      | 2 (13.33)  | 0.656   |
| Atrial fibrillation            | 2 (2.22)       | 1 (7.14)   | 0.355   |
| Other arrhythmias              | 2 (2.25)       | 1 (7.69)   | 0.339   |

Data recorded at the last follow-up at the clinic prior to HTC occurrence for HTC group and last follow-up at the clinic during study period for the no HTC group; data presented as numbers (percentage) or median (1st to 3rd quartile range)

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, GERD: gastroesophageal reflux disease
* Indicated no alcohol consumption or smoking at all after cessation

Table 2 Laboratory results of patients with hypertension secondary to obstructive sleep apnea categorized by presence of hypertensive crisis (HTC)

| Factors                        | No HTC n = 102 | HTC n = 19 | p value |
|--------------------------------|----------------|------------|---------|
| Polysonomography               |                |            |         |
| @AHI, events/hr                | 19.5 (10.0–35.0)| 14.5 (5.0–29.0) | 0.363   |
| @Lowest oxygen saturation (%)  | 81.5 (72.0–88.0)| 83 (72.0–89.0) | 0.712   |
| BUN, mg/dL                     | 12.3 (9.2–16.0) | 12.5 (11.1–15.7) | 0.549   |
| Cr, mg/dL                      | 0.9 (0.7–1.1)  | 0.9 (0.7–1.3) | 0.920   |
| ALT, U/L                       | 30 (21–55)     | 19 (14–43)  | 0.179   |
| AST, U/L                       | 26 (20–42)     | 27 (15–53)  | 0.749   |
| HbA1c, %                       | 6.2 (5.7–7.3)  | 5.8 (5.4–6.3) | 0.143   |
| UACR, mg/d                     | 12 (5–53)      | 403 (39–657) | 0.157   |
| Cholesterol, mg/dL             | 186 (167–212)  | 170 (143–237) | 0.392   |
| Triglyceride, mg/dL            | 120 (101–168)  | 111 (88–163) | 0.508   |
| HDL, mg/dL                     | 46 (40–57)     | 46 (40–53)  | 0.540   |
| LDL, mg/dL                     | 118 (104–150)  | 115 (85–175) | 0.966   |

Data presented as median (1st to 3rd quartile range)

AHI: apnea–hypopnea index, BUN: blood urea nitrogen, Cr: creatinine, ALT: alanine aminotransferase, AST: aspartate aminotransferase, UACR: urine albumin–creatinine ratio, HDL: high density lipoprotein, LDL: low density lipoprotein, RVSP: right ventricular systolic pressure, NA not applicable

for hypertensive crisis (Table 3). The median systolic blood pressure of the hypertensive crisis group was significantly higher than that of the non-hypertensive crisis group (177 vs. 141 mmHg), as shown in Table 1. We found similar results with regard to diastolic blood pressure. These findings were similar to those of a previous report from the US [14], which found that uncontrolled systolic blood pressure in an out-patient setting increased the risk of hypertensive crisis by 1.30 times. Note that the study population in the that report was not limited to OSA patients, as it was in this study.

Other OSA risk factors, such as age over 50 years, large neck circumference, and snoring, have been found to be significant predictors for OSA in cases of resistant hypertension (odds ratios of 5.2, 4.7, and 3.7, respectively) [6]. Our study found, however, that the correlations between these factors and hypertensive crisis varies across studies [15]. In this study, we used those laid out in the GEAR project [8, 10, 16, 17], while some other studies have used diagnostic criteria such as systolic/diastolic
Table 3  Factors associated with occurrence of hypertensive crisis in patients with hypertension secondary to obstructive sleep apnea

| Factors                              | Unadjusted odds ratio (95% confidence interval) | Adjusted odds ratio (95% confidence interval) |
|--------------------------------------|-------------------------------------------------|-----------------------------------------------|
| Age, years                           | 0.970 (0.936, 1.005)                             | 0.996 (0.947, 1.048)                          |
| Male sex                             | 1.353 (0.507, 3.609)                             | 0.908 (0.205, 4.021)                          |
| Systolic blood pressure, mmHg        | 1.074 (1.041, 1.108)                             | 1.046 (1.012, 1.080)                          |
| Mallampati classification            | 1.076 (0.879, 1.317)                             | 1.051 (0.905, 1.222)                          |

Conclusion
The prevalence of hypertensive crisis in patients with co-existing OSA and hypertension was 15.70%. High systolic blood pressure or uncontrolled blood pressure associated with hypertensive crisis in patients with OSA-associated hypertension.

Acknowledgements
The authors would like to thank Dr. Dylan Southard (USA) for his English language editing and the Khon Kaen University Sleep Apnea Research Group and Diamond project, Research Affair, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand (DR64301).

Authors’ contributions
SK and KS designed the study and contributed significantly to manuscript preparation. SK, AC, PL, JC, WS, VS, and YS contributed to data collection, or data interpretation. BS and KS analysed data. All authors read and approved the final manuscript.

Funding
None.

Availability of data and materials
All relevant data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Khon Kaen University Ethics Committee for Human Research (Thailand; HES41373). Written informed consent was not required due to retrospective data collection.

Consent to publish
Not applicable.

Competing interests
The authors declare that they have no conflict of interest.

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