Author's response to reviews

Title: Comparison of cardiovascular co-morbidities and CPAP use in patients with positional and non-positional mild obstructive sleep apnea

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Ms Ma. Celine Zapanta
Editor,
BMC Pulmonary Medicine

Re: MS: 4037933321057996

Dear Ms Ma. Celine Zapanta,

Thank you for your kind review of our manuscript and for the valuable reviewer comments. We have revised our manuscript titled “Comparison of cardiovascular co-morbidities and CPAP use in patients with positional and non-positional mild obstructive sleep apnea” to address the Reviewers’ comments. All changes to the manuscript are indicated in the following list of responses.

We hope that with these changes, the manuscript will be acceptable for publication in your journal. If you have any questions, please contact us.

Sincerely,

Mei-Chen Yang, MD
RESPONSE TO REVIEWERS' COMMENTS

(Reviewers’ comments are in italics)

Reviewer #1

*The paper asks an interesting question; whether the positional-dependent or not mild sleep apnea patients have differences in blood pressure. In order to answer that questions, they did a retrospective study of about 800 patients and found 70 who fullfilled the criteria. They found that the two groups have no differrence in BP and that the adherence to the therapy was very small.*

Although the study is well written, mit sound data and adherance to the relevant standards for reporting, I would like to make two comments:

**Discretionary Revisions:**

1. It would be interesting to see how the patients with moderate and severe sleep apnea behave, and it would be interesting to see a comparison between these three groups. I am sure that in a pool of 800 patients, it would be no problem to gather adequate patients to perform statistical analyses.

**Response:** We have now added the data regarding patients with moderate and severe apnea and also did a comparison across the different groups. In the revised manuscript, a total of 371 patients with OSA were included for analysis and divided into 6 groups according to positional-dependency status and severity of OSA: positional mild (n = 52), positional moderate (n=29), positional severe (n=24), non-positional mild (n = 18), non-positional moderate (n=70) and non-positional severe group (n=178).

The new analysis found that positional mild OSA had less cardiovascular co-morbidities (P=0.007) and lower morning blood pressure (P=0.018) compared with the other 5 groups. CPAP acceptance of mild OSA, independent of positional-dependency status, was also lower compared with the other groups (P<0.001), but CPAP adherence and CPAP compliance was similar to that of acceptors with moderate or severe OSA. The data is presented in the results and Tables 1-3.

2. The adherence rate is small. How do the authors explain the low adherence rate? I would like to see a bit more discussion about this limitation and comparison to other studies.

**Response:** With the new analysis, the adherence/compliance rate of patients who were receiving CPAP treatments was relatively high (range 66.7% to 100%), and the overall adherence/compliance was 71% (120/169) among all OSA patients (mild+moderate+severe). The number is around average compared to other studies. Moreover, in Taiwan CPAP is not covered by national or commercial
insurance, and consequently it is paid out-of-pocket at a 2-3 time higher price than that in other countries. Due to this, we believe 71% adherence/compliance is a positive outcome. We have added greater discussion regarding acceptance and adherence/compliance to the Discussion (see paragraph 5).

Reviewer's report #2:

General Comments:
In this paper by Huang and colleagues, blood pressure measurements in the evening and morning in patients with mild positional OSA were compared to patients with mild non-positional OSA. Although it appeared that several parameters of sleep architecture were worse in those with non-positional OSA, BP parameters were not different between the two groups. Generally, the paper is well written and organized, and easy to follow. It does appear that the overall findings are valid. However, some of the conclusions and clinical recommendations may be somewhat premature. My concerns are outlined below under specific comments.

Specific Comments:

Minor Essential

1 Background, 2nd Sentence: To be fair, I think that whether mild OSA is causally related to hypertension and CVD is still up for debate. Longitudinal cohort studies are not consistent in this regard, and a recent RCT (Barbe et al, JAMA, see supplemental tables) did not find OSA related to incident hypertension. You may want to be less dogmatic about this.

Response: We have revised the sentence as suggested and cite to prospective randomized longitudinal studies that address this issue (Barbe et al., JAMA, 2012;307:2161-2168 and Martinez-Garcia, JAMA 2012; 310:2407-2415). Both studies did not find an association of hypertension of CVD with OSA.

2 Discussion: You recommend that patients with poor sleep quality irrespective of OSA severity status should receive “optimal” treatment. Does “optimal” mean CPAP? Regardless, although sleep quality is associated with hypertension, I know of no evidence that improving sleep quality lowers BP.

Response: We mean optimal treatment would be surgery for patients that are candidates for surgery and CPAP for those patients who are not surgical candidates. We have clarified this point (see Discussion, paragraph 1). Until recently, there was no evidence that improving sleep lowers blood pressure. However, Huang et al (Sleep Medicine 2013;13:263-268) found that the blood pressure of poor sleepers was significantly reduced compared to pretreatment values following zolpidem treatment (P<0.05) and more poor sleepers treated with zolpidem were converted from nondipping hypertension to dipping.
hypertension. We have added this information to the Discussion (see paragraph 3).

3 Discussion: You recommend that patients with mild OSA should receive “active and effective therapy”. Unfortunately, I think this is a debatable issue because it is still unsettled whether mild OSA leads to hypertension or CVD. The ATS has assembled a working group to examine the literature on this point given its controversy.

Response: There is growing evidence supporting the use of CPAP in sleepy patients with mild OSA (see Peker, 2012), however, the findings are mixed and CPAP treatment of mild OSA as only a treatment option (see Kushida et al. Sleep 2006;29(3):375-80). Given the findings that there is an association of mild OSA with hypertension and mild OSA tends to worsen over time, we recommend treatment for these patients. Further studies are required to better understand the potential benefit of CPAP in treating mild OSA and hypertension. We have added this information to the Discussion (see paragraph 6).

Major Compulsory

4. Methods: It appears that airflow during the PSG was only ascertained using a thermistor. AASM standards now require a nasal pressure transducer. Use of only a thermistor may underestimate the severity of OSA. In the case of this study, misclassification of patients as mild OSA may have occurred. You should explain how lack of a nasal pressure transducer signal could have impacted your results.

Response: The reviewer makes a good point. We have now added to the Discussion the comment that not using a nasal pressure transducer and esophageal manometry may have resulted in an under-estimation of the severity of OSA and consequently misclassification of patients in the mild to moderate OSA groups.

5. Methods: In what position were the BP measurements taken? Supine, sitting, standing?

Response: BP was measured in the supine position. We have added this to the Methods (see paragraph 5).

6. Methods: I am little concerned that BP measurements were taken with an automated device. Were these devices calibrated and/or validated against manual measurements performed with a Hg sphygmomanometer?

Response: A Welch Allyn Vital Signs Monitor300 Series device was used. The automated sphygmanometer was regularly calibrated at least every year by the technician from the manufacture who calibrated and/or validated the instrument against manual measurement performed with a standard mercury sphygmomanometer. We have added this information to the Methods (see paragraph 5).

7. Results: There was a high prevalence of hypertension in both groups with the non-positional group having a greater prevalence than the positional group. However, I
am surprised that only 1 patient in each group was receiving BP medications at bedtime (Table 1). If actually more patients were on BP medications (i.e., taken earlier in the day), then this represents a major potential confound, and you should then perform a sensitivity analysis using only those patients not on anti-hypertensive meds. The paper indicates that you controlled for hypertension, but you don’t indicate whether hypertension status was a significant independent variable in explaining the results.

Response: Most of diurnal HTN medicines are long-acting, hence patients taking diurnal BP drugs did not take a pill at bedtime. For patients taking short-acting medicine, they are usually recommended to take the medicine twice or thrice a day in order to maintain the therapeutic efficacy; these patients usually did not take medicine before going to bed. Considering the reasonableness, we replaced the variable ‘anti-HTN drugs at bedtime’ with “anti-HTN medicine usage” in the revised manuscript.

We tried to re-do analysis after excluding patients using anti-HTN drugs (n=184) and found similar results except for no differences in sex and smoke distributions for baseline characteristics as well as similar morning BP among all groups (data were not shown). Although HTN medication may have an influence on OSA, this point is not what we concern in this article. Therefore, it was treated as a covariate and corresponding results were not reported. When doing analysis, it was CV co-morbidity, rather than HTN, was put into the multivariable model for adjustment as we noted a strong correlation between HTN and CV co-morbidity ($\Phi = 0.852$, $p<0.001$) and a high percentage of taking anti-HTN medicine in HTN patients (182/209=87.08%). According to the results from 371 patients, the effect of CV co-morbidity was significant on sleep efficacy, S1, SaO2 mean, evening SBP, morning SBP, morning DBP, morning MABP, change of MABP and change of DBP.