Author’s response to reviews

Title: The association of sleep disordered breathing with left ventricular remodeling in CAD patients: a cross-sectional study

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Dear Editors and Reviewers:

Thank you for your letter and for the reviewer’s comments concerning our manuscript entitled “The association of sleep disordered breathing with left ventricular remodeling in CAD patients: a cross-sectional study” (ID: BCAR-D-16-00535) by Audrius Alonderis et al.

Thank you very much for your kind words about our paper. In the following sections, you will find our responses (with line numbers in the revised article) to each of your points and suggestions. We are grateful for the time and energy you expended on our behalf. Now we are looking forward to your response and decision concerning our manuscript.

We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are highlighted in yellow in the revised manuscript.

Yours sincerely

Audrius Alonderis

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Reviewer 1: Editor Comments:

1. Burden of CV risk factors have been largely related to kind of plaque (quote on PMID: 26508517). Potential relationship also with sleep disorder should be added

ANSWER: Following sentences were included into the Background section (line 76) and the references have now been updated.

Pathophysiology of acute coronary syndrome (ACS) deeply differs from stable angina, mainly due to peculiar features of plaque [Iannaccone, 2016]. ACS, which is known to be characterized by a higher conventional CV risk, is caused by the loss of integrity of the protective covering of some atherosclerotic plaques, leading to thrombus formation and subsequent vessel obstruction [Libby, 2001; Iannaccone, 2016]. SA and sleep disruption have also been linked to an imbalance in circulatory thrombotic and anti-thrombotic activity [Terada, 2011].


2. The paper is essentially an association study examining the relationships between sleep apnea and LV remodeling in a CAD cohort. Overall, the study is sound and utilized appropriate and standard statistical methodologies for their data analyses. Their findings and conclusions are consistent with some studies in this field but therein lies the issue as to whether the data is novel or largely derivative. A key sentence to emphasize the novelty of the data would support publication of the paper.

ANSWER: We inserted a new paragraph into DISCUSSION section (line 386):

Previous studies that were not able to fully control for confounding variables suggested that SDB severity is associated with changes in heart structure, including LV hypertrophy. The present study was performed in a large sample of consecutive stable CAD patients characterized by a relatively high degree of comorbidity. This study extends this information with the novel finding that even mild level of SDB strongly predicts LVH with increasing LV thickness (both interventricular septum and posterior wall thickness) and concentric LVH independently of coexisting traditionally recognized risk factors in CAD patients. The risk of concentric hypertrophy did not increase with greater level of SA severity.

3. The strongest limitation of the study is its cross-sectional design from which causal conclusions cannot be derived, though this does not preclude the paper from publication as the authors have already noted, the field is populated with inconsistent findings from differing cohorts. As such, the data in this study warrants interest.

Mechanisms in Discussion were mostly adequate. Ideally, a working hypothesis for the current understanding of sleep apnea and LVH (if any) would provide a better framework to better understand the data.

ANSWER: We agree with your opinion and tried to present the hypothesis more clearly in Background (line 101)
We hypothesized, that in stable CAD patients even mild to moderate SA is independent risk factors for: (1) a higher prevalence of LVH, by wall thickness criteria, with more pronounced both septal and posterior wall thickening; (2) more concentric left ventricle than in patients without SA controlling for traditional recognized risk factors.

5. Minor points:

5.1. Overall, the paper is relatively well-written with occasional syntax and grammatical oddities that require editing. This will improve the flow of the paper. There were instances where I have had to stop and re-read sections to gain a better understanding of the content

ANSWER: We tried to present the results more clearly.

5.2. Check for typos and occasional syntax in Tables and text (eg: Table 4 P-value for LVEDD and Line 317 text).

ANSWER: In statistical analysis we had explained the analysis by SA severity: First, to identify demographic, polysomnographic and echocardiographic characteristics we compared non-SA versus SA patients to standard definition, i.e., non-SA (AHI<5) versus SA (AHI≥5). Subsequently, we compared patients according to SA severity as defined according to the apnea-hypopnea index (AHI) as mild (5-14.9), moderate (15-29.9), and severe (≥30 events/h). We reported only p value for trend in last column Table 4.

We tried to present the results more clearly.

(line 304) – Post hoc analysis (data not shown) demonstrated that only the LVEDD was marginally significantly higher in severe SA patients compared with mild SA patients (mild-SA vs severe-SA p=0.044 (not shown), model F=3.03 p for trend =0.05) (Table 4).

(line 322) – There were not found statistically significant differences in left atrial diameter, in thickness of IVST and LVPWT, in value of LVM and LVMI (g/m-2 and g/m2.7) among patients included in any of the categories of SA severity suggesting that SA severity according to AHI categories was not inducing changes in their LV thickness and mass (ANOVA main effect for SA severity groups p for trend >0.05, Table 4).

3. Figure 1 appears redundant if same data is shown in Table 4 unless for visual effect.

ANSWER: We agree, that figure 1 is redundant, but set it for visual effect
Reviewer 2:

1. Was this prospective study registered at clinicaltrials.gov or some other clinical trial registration platform?

ANSWER: The Lithuanian Bioethics Committee is the main national institution authorized to register and issue approvals for biomedical research and coordinate ethical review of biomedical research in the country. As was already acknowledged in Ethic section (line 127), the study and its consent procedures were approved by the Lithuanian Bioethics Committee (Certificate No. BE-2-21 issued at 2007-04-13) and conform to the ethical guidelines of the 2000 Declaration of Helsinki. Written informed consent was obtained from each study patient.

2. The authors should state a comment on how untreated SDB influences the results as if they were unknown or unidentified in the study subjects investigated.

ANSWER: Thank you for this comment. This is now added to the Discussion section (line 522):

In spite of the differences in the diagnostic procedures as well as different AHI cut-off values for definitions of SA, there seems to be enough evidence to warrant overnight sleep screening in individuals with CAD, given that concomitant SA may worsen long-term outcomes. Furthermore, several subsequent studies have demonstrated that patients with untreated severe SA exhibit an increased incidence of fatal and nonfatal cardiovascular events (including MI and ACS) compared with those without SA or even with those with untreated mild to moderate SA [14, 16, 6]. In a longitudinal study of 408 patients with CAD, Mooe and co-workers (2001) noted that SA independently increased the risk for incident cerebrovascular events [13]. However, such an association suggests but does not demonstrate a causal relationship, and the role of treating SA to prevent CV diseases remains unclear [6]. SA is prevalent in our study population, especially in its mild form. Although severe SA is associated with adverse health consequences, the association with mild disease is unclear, and reports differ regarding the clinical relevance of mild SA. Improved diagnostic techniques and evidence based approaches to management in mild SA require further research.

3. The authors find a very low prevalence of SDB in their study, only 39 %? Other others in big studies found higher prevalence the authors should add this literature of well-known high prevalence of SDB in patients with cardiovascular disease:


ANSWER: These sentences we included into the discussion section and the references have now been updated according to recent findings (line 431).

Recently, Fox et al. (2016) investigating the prevalence of SDB in cardiac rehabilitation patients, reported a prevalence of SDB (AHI≥15) by different cardiac condition. They find that patients who had undergone coronary artery bypass graft (CABG) had a higher prevalence of SDB and more severe SDB compared with patients with stable CAD or ACS (prevalence of 53%, 46% and 45% respectively) [Fox, 2016].

4. Also the authors should add:


It is well known, that CAD and especially heart failure patients have no complaints of concomitant SDB and that SDB patients are more likely men, older and have hypertension (not new).

ANSWER: These sentences we included into the discussion section and the references have now been updated according to recent findings (line 436).

As noted, patients with heart failure and SA (in particular CSA) do not generally present with symptoms that distinguish them from heart failure patients without SA. Arzt et al reported a prevalence of 46 % in a large representative population of patients with stable chronic HF receiving optimized medical treatment [Arzt, 2016].

6. The authors mention the impact of SDB on cardiovascular disease, but in the introduction they should point out the importance of SDB in regard of mortality! And add the literature therefore:


ANSWER: This sentence is now added to the Introduction section (line 73) and the references was updated
SDB and nocturnal hypoxaemia are highly prevalent in stable heart failure with reduced left ventricular function and were identified as independent predictor of all-cause mortality in these patients [Oldenburg, 2015].

7. 1027 patients were enrolled in the study, but only 772 were analyzed. The authors mention technical difficulties during investigations, none accurate interpretations of echocardiography or polysomnography results. What does this mean? What are technical difficulties? Why were so many patients excluded? Please explain!

ANSWER: Only several echocardiograms and PSG were technically inadequate (n=6, 0.5%).

This text that details the study participant’s recruitment now added to the Methods section (line116):

137 (13.3%) of the patients were excluded from the study for meeting the criteria of being older than 80 years and having cognitive disorientation and communicative disabilities, having other severe diseases or not consent to participate in the program. In total, 887 (86.3%) participants had successful echocardiographic data, 775 (75.4%) participants had successful PSG of which 772 also had PSG data in conjunction with echocardiographic and ESS data (the other 115 with successful echocardiography data either elected not to undergo PSG or were ineligible due to medical reasons). The several echocardiograms and PSG were technically inadequate (n=6, 0.5%). Although the inclusion rate for eligible patients for study analysis was 772 (75%), the inclusion design was consecutive, and there were no significant differences in baseline characteristics with regard to comorbidities.

8. What rules for scoring SDB were used? AASM? European? What exact definitions were used?

ANSWER: Use of different definitions of hypopnea significantly affected calculated apnea-hypopnea indices and measured prevalence of sleep apnea. We used AASM 2007 protocol. This is already described in the Methods:

(line 155) – Overnight fully attended polysomnography (PSG) monitoring was performed with the “Alice 4” Polysomnography System (Respironics Inc., USA) in the Sleep laboratory using standard recording techniques according to AASM (American Academy of Sleep Medicine) and precise protocol of PSG monitoring [34]. Apnea was defined as the disappearance of airflow for over 10 s; hypopnea was defined as a 50% or greater decrease in airflow lasting for more than 10 s associated with arousal or a 3% or greater decrease in arterial oxygen saturation from the baseline level.
(line 173) – SA was defined as five or more episodes of apnea and hypopnea per hour of sleep (AHI ≥ 5 n/h).

9. ESS is known to be inaccurate in cardiovascular patients. Please add therefore this novel reference:


ANSWER: The references have now been updated according to recent findings (line 401):

The limitations of ESS are known in cardiovascular patients and the existence of patients with severe SA without excessive sleepiness is controversial [41, 42 Somnologie, 2017].

10. What influence on the results does have the fact, that none SDB patients had less BMI? Do they have less risk of cardiovascular disease because of not having SDB?

ANSWER: Thank you for this question. We think that physicians should view SDB and obesity as independent clinical problems. (eg INTERPRETATION of regression model: at a given all predictors (age, sex, BMI, hypertension etc) at a fixed value, we will see 2 fold increase in the odds of getting LVH in patient under the same condition plus mild SA).

This paragraph has been including in DISCUSSION section (line 403):

Our results discovered that even mild SA had additive effect in changes in the heart’s shape, similar to the effects of both hypertension and obesity. This effect includes increased mass and thickening of the heart wall. The fact that patients with stable CAD and with SA often do not show typical SA symptoms, suggest that the presence of one or more established predictors of LVH on the basis of wall thickness criteria or concentric LVH, such as male sex, older age, higher BMI, ejection fraction >45%, or SA may be the independent risk factors for adverse long-term outcomes. With the increasing recognition of SA as an independent, additive or even synergistic risk factor for CAD, there is a need for early identification of high-risk individuals and a consensus regarding well defined treatment strategies in such patients.

11. All abbreviations in the tables need to be fully announced in a table footnote

ANSWER: This is now added and clarified.

Thank you for taking the time and energy to help us improve the paper. We hope that our supplementary analyses and revised focus helps to improve your opinion of work.