



CORRESPONDENCE

REVISED **N-terminal pro-brain natriuretic peptide: a potential follow-up biomarker of mandibular advancement device efficacy on cardiac function in obstructive sleep apnea [version 2; referees: 1 approved, 1 approved with reservations]**

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Abstract

Interrelationships between obstructive sleep apnea (OSA) and cardiovascular diseases are now recognized, but some underlying pathophysiological mechanisms remain controversial. Circulating cardiac biomarkers are diagnostic tools that can help understand them, in particular the N-terminal pro-brain natriuretic peptide (NT-proBNP), a marker of myocardial stretch, and a potential indicator of subclinical cardiac stress in OSA. Continuous positive airway pressure (CPAP), the first-line treatment of moderate to severe OSA, may be considered as uncomfortable, resulting in poor adherence, and reduced effectiveness. In this case, mandibular advancement devices (MAD) are an effective alternative therapy, more comfortable, and generally well accepted, with higher compliance. To date, few studies have compared the cardiovascular effects of CPAP and MAD. From recent literature reviews, it emerges that both therapies are effective in blood pressure reduction. However, the effects of MAD on other cardiovascular outcomes are conflicting, in particular as regards to its impact on circulating cardiac biomarkers. In a recent ancillary study from a randomized controlled trial, Recoquillon *et al* concluded that two months of MAD treatment had no effect on NT-proBNP plasma levels in patients with severe OSA. The present discussion analyses this result from a biological, statistical, and analytical standpoint, in light of results from other studies evaluating natriuretic peptides in MAD-treated OSA, with the aim to support further longitudinal studies designed with a high methodological quality.

Keywords

N-terminal pro-brain natriuretic peptide, mandibular advancement device, obstructive sleep apnea, cardiac biomarker

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Invited Referees

1 2

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report



report

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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED Amendments from Version 1

As suggested by the referee 2, this new version reminds the lack of consensus regarding the interest of natriuretic peptides in the evaluation of cardiac function in OSA, or regarding the impact of CPAP in this context. From a statistical standpoint, the potential effect of outliers on final results is also reminded, especially when groups include few subjects and when biomarkers concentrations display too wide standard variations.

See referee reports

Mandibular advancement devices (MADs) are an effective alternative to continuous positive airway pressure (CPAP) in the treatment of obstructive sleep apnea (OSA). OSA is associated with increased cardiovascular morbidity and mortality, and an increasing number of studies highlight the efficacy of MADs in terms of both sleep apnea, and cardiac outcomes¹⁻³. Unlike CPAP-related studies, few studies to date have focused on cardiac biomarkers under MAD therapy in OSA.

In a recent randomized controlled trial, Recoquillon *et al.* evaluated the effect of two months of MAD treatment on N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) plasma levels in patients with severe OSA⁴. Compared to a sham device, the high treatment adherence (6.6 hours/night) significantly reduced the mean apnea-hypopnea index (AHI), and the oxygen desaturation index. Nevertheless, according to their model, the authors stated that MADs had no effect on NT-proBNP levels, nor on other inflammatory and metabolic biomarkers. To our knowledge, to date only two studies have investigated the natriuretic peptides in such contexts^{5,6}. Given their scarcity, any type of study looking at relevant cardiac biomarkers of MAD efficacy must be encouraged, and designed in as detailed and robust a manner as possible. In this way, some issues have to be discussed regarding the evaluation of NT-proBNP from Recoquillon *et al.*

1) Biological standpoint.

After two months of MAD use, the NT-proBNP plasma concentrations decreased from 296.8 to 252.5 pg/mL (−14.9%) in treated patients, whereas they decreased from 189.8 to 184.3 pg/mL (−2.9%) in patients with the sham device, resulting in a mean adjusted intergroup difference of 12.0 pg/mL (−40.9 to 64.9, 95%CI; $P=0.65$). The question arises as to whether a NT-proBNP decrease of about 15% after treatment is biologically significant. Indeed, according to the specifications of the desirable biological variation database⁷, this decrease should be considered as significant according to the within-subject biological variation (CV_i 10%), but not significant according to the between-subject biological variation (CV_g 16%). In any case, this decrease should be considered as analytically significant since it exceeds the allowable limit of total error, which combines the analytical imprecision and the inter-method inaccuracy, fixed at 13% for NT-proBNP. Moreover, one could argue that a longer treatment period, even one extra month, could be sufficient to significantly lower its circulating level. In support of this assumption, Hoekema *et al.* showed a significant decrease in NT-proBNP (−58%, $P=0.035$) in ten patients with moderate

to severe OSA treated by MAD (adherence 6.8 hours/night, 6.9 nights/week) after a period of 69 to 82 days⁵. For these ten patients, baseline (52 pg/mL, interquartile range (IQR): 13–105), and follow-up NT-proBNP values (22 pg/mL, IQR: 15–33) were within or close to the reference intervals established according to the method⁸, and were thus in accordance with exclusion criteria discarding patients with a history of cardiovascular disease (CVD). Unlike Hoekema *et al.*, NT-proBNP values from Recoquillon *et al.* reached 500 to 700 pg/mL, *i.e.* much higher than the normal values announced by the manufacturer (median 47 pg/mL, min–max: 3.9–155 pg/mL⁹). This is somewhat in contradiction with the exclusion criteria supposed to discard patients with a history of CVD, including heart failure⁴. Another study showed a significant decrease of plasma BNP levels (−24%) after 6 months of MAD therapy in patients with stable, mild to moderate congestive heart failure (CHF), and OSA⁶. Although less stable in plasma than NT-proBNP¹⁰, BNP, the other biomarker of CHF, is still widely and routinely assayed on analyzers in hospital laboratories, and thus remains of potential interest for the follow-up of cardiac function under MAD treatment.

2) Statistical standpoint.

In the supplemental statistical section, Recoquillon *et al.* mentioned that variables with non-continuous distributions are described as median (IQR)⁴. However, NT-proBNP results were expressed as mean (standard deviation (SD)), and reached 296.8 (401.6) pg/mL. Such a wide SD suggests a strong skewness of distribution, with possibly the presence of extreme outliers at baseline and/or at follow-up, in the low values and/or in the high values, which could ultimately false the observed difference in concentrations. The impact of outliers is well-known in research, be they of clinical or laboratory origin^{11,12}; they must be detected through appropriate methods, possibly with adjustment for skewness¹³, and their presence requires investigation, especially for small groups. In the study from Recoquillon *et al.*, a median (IQR) expression would therefore have been more appropriate than mean (SD), and a graph detailing the scatter dot plots for both groups, with connecting lines before and after treatment, would have been required. Moreover, a linear regression analysis was used for the adjustment of baseline values and potential covariates: age, gender, body mass index, and baseline AHI. Nevertheless, these covariates were used for the adjustment of all biomarkers, but no statistical proof was provided as regards to their degree of correlation with NT-proBNP specifically. Furthermore, given the limited number of patients ($n \pm 55$), if NT-proBNP results were not normally distributed (as seems to be the case), nonparametric ANCOVA or robust regression methods would probably have been more appropriate^{14–17}.

3) Analytical standpoint.

Recoquillon *et al.* assayed plasma NT-proBNP using a multiplex electrochemiluminescent immunoassay on a MESO QuickPlex® SQ120 analyzer (MSD, Rockville, USA). Using this technology for assaying this cardiac biomarker is somewhat unusual. Indeed, as reminded by the manufacturer, this method is for research use only, but not for use in diagnostic or therapeutic procedures. It involves three incubation steps, interspersed with three wash sequences, requiring at least five hours of preparation for one 96-well plate. To our knowledge, no studies based on

this assay have been published up to now, not even the eight references cited in the MSD technical sheet of the human NT-proBNP assay kit⁹. Given the long and tedious assay protocol impractical in hospital laboratory routine, and given the absence of hindsight about its analytical performance, the authors should rather have used a most widespread, reliable, and rapid automated method, like the electrochemiluminescent immunoassay method on Roche analyzers (Roche Diagnostics, Mannheim, Germany)¹⁸, which was, moreover, available in the laboratory from one of the five hospital centers participating to the trial (Poitiers Hospital Center¹⁹, NCT01426607²⁰).

The strong association between the severity of OSA and a higher prevalence and incidence of cardiovascular events has been evidenced for a long time²¹. However, where cardiac biomarkers are useful for the diagnosis of many cardiovascular diseases, the interest of natriuretic peptides in the evaluation of OSA-associated cardiac dysfunction and CPAP effects remain controversial, especially because of uncontrolled co-morbidities, as summarized by Maeder *et al.*^{22,23}. To date, no study has specifically evaluated whether NT-proBNP reflects cardiac dysfunction in OSA or whether NT-proBNP is under the influence of obesity in this context.

An interesting perspective is the ongoing MOSAIC study, whose main objective is to assess the impact of three months of MAD therapy on AHI in Asian patients with heart failure and OSA²⁴. Indeed, one of the planned secondary objectives is the evaluation of cardiac remodeling and of cardiac biomarkers, including NT-proBNP. Meanwhile, the present standpoints remind and emphasize the need for close collaborations between sleep specialists and laboratory practitioners to strengthen the methodological quality and robustness of studies involving biomarkers.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Grant information

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Current Referee Status:



Version 1

Referee Report 31 January 2019

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Micha Maeder

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The present manuscript is a relatively extensive comment on a short original manuscript (brief communication) published in *Thorax*. The key finding of the paper by Recoquillon et al.¹ was a lack of effect of effective OSA treatment by mandibular advancement therapy on NT-proBNP. This finding is in the centre of the comment by Denis Monneret.

From my point of view the result was far away from being statistically significant, and the observed (non-significant) difference may have been the result of chance. Therefore, I cannot fully follow the argument listed under “biological standpoint”. The key problem however is the fact that it is currently unknown what BNP and NT-proBNP reflect in patients with OSA. The literature on this issue has been summarized in detail by Maeder MT et al. in *Clin Chim Acta* (2016)², and the overall summary is that the data is conflicting. No study has in detail evaluated whether NT-proBNP in OSA reflects cardiac dysfunction or whether NT-proBNP is mainly under the influence of obesity in OSA. Variable effects of CPAP on BNP and NT-proBNP in uncontrolled studies have been observed. In the present manuscript I would really like the author to mention these aspects.

With regards to the statistical standpoint I fully agree that BNP and NT-proBNP always display a skewed distribution, and that this should have been taken into account. When using non-parametric tests, the result is even more unlikely to be statistically significant.

With regards to the analytical standpoint I also agree: the use of an established easy to use NT-proBNP assay would have made it easier to check the plausibility of the data and to compare it with the existing literature.

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Is the rationale for commenting on the previous publication clearly described?

Yes

Are any opinions stated well-argued, clear and cogent?

Partly

Are arguments sufficiently supported by evidence from the published literature or by new data and results?

Partly

Is the conclusion balanced and justified on the basis of the presented arguments?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Heart failure, valve disease, coronary disease, OSA

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Referee Report 17 January 2019

<https://doi.org/10.5256/f1000research.18676.r42053>



Gen-Min Lin 

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In general, the comments were written well, as the cited paper is a randomised control trial design and the author made a critical appraisal. Since many readers might not have time to review the original paper, it might be helpful to write a summary before the comments. Otherwise no further comments were made; and the report is suitable to be accepted in current version.

Is the rationale for commenting on the previous publication clearly described?

Yes

Are any opinions stated well-argued, clear and cogent?

Yes

Are arguments sufficiently supported by evidence from the published literature or by new data and results?

Yes

Is the conclusion balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Sleep medicine and cardiovascular disease

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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