Author's response to reviews

Title: Heart rate variability in non-apneic snorers and controls before and after continuous positive airway pressure

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Author's response to reviews: see over
Reviewer 1:

We thank Dr. Quan for his comments. We have responded to each comment in a point by point fashion.

(1) If the authors' findings are true, would not individuals who chronically snore be protected from adverse effects of snoring, and only those who intermittently snore be at risk.

Those who snore intermittently could be at greater risk because of the increase in the number of non-snoring segments. However, because the frequency of the perturbation (i.e. snoring) that leads to changes in autonomic function would be intermittent only minor alterations in autonomic function during non-snoring periods (either during sleep or wakefulness) would be expected and the risk would be minimal.

From a strictly autonomic point of view those who snore chronically could be protected from the adverse affects of snoring during the act itself. However, the risk compared to intermittent snorers would be significantly greater during periods of non-snoring or during transitions from sleep to wakefulness.

(2) The use of a 2% oxygen desaturation to define hypopnea is not common. Please justify.

We chose to employ a 2% oxygen desaturation criteria (rather than 3 or 4%) in order to ensure that snoring associated with small changes in oxygen saturation were identified. Based on the use of this criterion we reasoned that if the number of events was similar between snoring and control subjects and less than 5, we could be reasonably confident that the subjects recruited for this study were truly non-apneic.
Reviewer 2: We thank Dr. Lofaso for his comments. We have responded to each comment in a point by point fashion.

(1) This study showed very few information concerning the subjects characteristics, concerning the age, BMI. A table is necessary . . .

We have now provided a table (table 1 in the revised manuscript) that includes each subject’s age, BMI, sex and mean arterial pressure during both wakefulness and NREM sleep. As the table shows these subjects overall were young. They were not on any medications and did not complain of any physical ailments with the exception of snoring.

(2) The authors tell us that snorers were matched to control groups, but how is it possible when the number of patients and the subjects are not the same? What were they matched for? Were the ages similar between snorers and non-snorers? . . .

The reviewer is correct that the term matched is confusing because 12 controls and 11 snorers participated in our study. Thus we have deleted the word “matched”. However, as shown in table 1, 11 snorers and 11 controls were similar in age and sex. One control subject was not matched with a snoring subject. Nevertheless, we chose to include this subject because the addition of this data had no impact on our findings (i.e. statistically significant changes were found whether or not the 12th control subject was included in the statistical analysis of the data).

(3) It is commonly admitted that sleep apnea patients (idem for snorers) who were normotensive in the daytime can be considered to have the same cardiovascular risks as hypertensive patients because they experience higher nocturnal blood pressures compared to measures obtained during the day. Therefore, if the authors want to show that a very early phenomenon may occur with snoring in a population without any arterial pressure abnormalities, they should check at first, in their normal snorers, that the dipping of the nocturnal pressure exists in a 24h ambulatory pressure.

We have now provided average values of mean arterial pressure that were calculated from beat-to-beat blood pressure measures obtained during NREM sleep when the preliminary sleep study was completed to confirm that subjects were either non-apneic snorers or control subjects.

(4) I completely disagree with the discussion and the conclusion of the authors. It could be considered that in fact, these results showed an adaptive physiological phenomenon in order to maintain a normal PNSA/SNSA ratio during sleep rather than an alteration of the autonomic nervous system and in conclusion there is no risk for these snorers who could be considered to have normal PNSA/SNSA activity. To my point of view, the discussion and the conclusion should be modified and rewritten according to this point of view.

It is suggested that snoring itself poses no potential risk because PNSA and SNSA were similar compared to control. However, this similarity occurred because snoring caused a reduction in SNSA and an increase in PNSA, which were elevated and reduced respectively during nCPAP application (trial 2) or during periods of non-snoring in trial 1 in the non-apneic snorers. In order for snoring not to be a risk factor for alterations in autonomic activity some other mechanism would have to be responsible for the increases in SNSA and decreases in PNSA that were observed. We have considered two possible alternative explanations to the explanation provided in the initial submission of the manuscript. One, it is possible that that the snoring subjects responded differently to CPAP compared to control. We believe this is unlikely since SNSA was increased and PNSA was decreased in our snoring subjects during non-snoring periods that we
analyzed in the non-CPAP trial. This data is now included in the revised version of the manuscript. Second, it is possible that the snoring subjects are genetically predisposed to increases in SNSA and decreases in PNSA and that snoring alters this predisposition. We cannot discount this possibility and thus have added it to the discussion section. However, we cannot disregard completely that mechanisms activated during snoring may lead to increases in SNSA and decreases in PNSA, although its impact is masked during the act of snoring itself. We believe this is plausible for at least two reasons. First, termination of snoring leads to increases in blood pressure and heart rate, compared to measures obtained during snoring, independent of cortical arousal (e.g. Lofaso et al. Chest 1998, 113:985-91; see Figure 1- grade 0c). These increases likely mirror “autonomic arousal” in the absence of cortical arousal. As hypothesized by others (Krieger et al. Rev Neurol (Paris) 159:6S107-12, 2003) this autonomic arousal may originate from mechanoreceptors. If this is the case, it seems highly unlikely that this stimulus would not be present throughout snoring. If so, why are extended periods of snoring often observed without “autonomic arousal” (blood pressure and heart rate may in fact be reduced) but evident immediately after termination of snoring despite the absence of cortical arousal? We believe this is so because vagal afferents are activated during snoring and these afferents inhibit SNSA and mask the potential excitatory impact that mechanoreceptors (via brainstem arousal) have on SNSA exist. This possibility is supported by findings that SNSA is inhibited in response to activation of vagal afferents even in the presence of stimuli known to activate SNSA.

5) The second comment is strengthened by the fact that the mechanism generally proposed to explain hypertension in snorers, is the occurrence of repeated abrupt increases of SNSA with transient elevations of systemic arterial blood pressure, when arousals related to abnormal respiratory efforts occurred. In other words, it is generally well accepted that snorers who risk developing hypertension are the patients with upper airway resistance syndrome. This discussion has been completely omitted. Therefore, the study presented here is not well positioned in the literature and therefore not well discussed.

We now outline the typical symptoms of individuals suffering from upper airway resistance syndrome which includes brief cortical arousal. However, we also comment that snoring may induce increases in heart rate and blood pressure (“autonomic arousal”) independent of cortical arousal.