

Pulse transit time as a measure of respiratory effort under non-invasive ventilation

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Contribution of authors to study:

Olivier Contal was involved in: study design and protocol, recording and analysis of data, writing and revision of manuscript

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Abbreviation List

BMI: Body Mass Index

EPAP: Expiratory Positive Airway Pressure

FEV₁: Forced Expiratory Volume in 1 second

FVC: Forced Vital Capacity

IPAP: Inspiratory Positive Airway Pressure

NIV: Non-Invasive Ventilation

OHS: Obesity hypoventilation syndrome

PaCO₂: Arterial Partial Pressure of Carbon Dioxide

PaO₂: Arterial Partial Pressure of Oxygen

Pes: Esophageal pressure

PTT: Pulse Transit Time

PSG: Polysomnography

SB: Spontaneous Breathing

VC: Vital Capacity

ABSTRACT (198 words)

Rationale: Among respiratory events which may occur during nocturnal non-invasive ventilation (NIV), differentiating between central and obstructive events requires appropriate indicators of respiratory effort.

Objective: To assess pulse transit time (PTT) as an indicator of respiratory effort under NIV in comparison with esophageal pressure (Pes).

Methods: 1: During wakefulness, PTT was compared to Pes during spontaneous breathing and under NIV with or without induced leaks in 11 healthy individuals.

2: Contribution of PTT versus Pes for differentiating central from obstructive respiratory events occurring under NIV during sleep was evaluated in 10 patients with obesity hypoventilation syndrome (OHS).

Results: 1: From spontaneous breathing to NIV without leaks, respiratory effort decreased significantly whereas, with increasing level of leaks, there was a significant increase in respiratory effort. Changes in PTT accurately reflected changes in Pes.

2: In OHS patients during nocturnal NIV, intraclass correlation coefficients between Pes and PTT were 0.970 for total number of events and 0.970 for percentage of central events.

Conclusion: PTT accurately reflects the unloading of respiratory muscles induced by NIV and the increase in respiratory effort during leaks. PTT during sleep is also useful to differentiate central from obstructive respiratory events occurring under NIV.

Clinical trial registration number: NCT00983411.

Introduction

Non-invasive ventilation (NIV) is widely accepted as a long term treatment for chronic hypercapnic respiratory failure. Monitoring of the efficacy of long term NIV usually relies on medical history, daytime arterial blood gases, and nocturnal pulse-oximetry, sometimes coupled with transcutaneous capnography [1]. Recently, an increasing awareness of nocturnal respiratory events occurring under NIV has led to a wider use of respiratory polygraphy (PG) and polysomnography (PSG) to improve adjustment of long term NIV settings [2-5]. The most frequent problems detected are unintentional leaks (i.e. not related to exhalation valve of interface), patient-ventilatory asynchrony, and obstructive or central events (either residual or induced by NIV) [4].

Differentiating between central and obstructive events on PG or PSG tracings under NIV is more challenging than in spontaneous breathing and requires appropriate measurements of respiratory effort. Esophageal pressure (Pes) is the “gold standard” for quantifying variations in intra-thoracic pressure resulting from respiratory efforts. However, measuring Pes is invasive, frequently unaccepted or poorly tolerated by the patient's and interferes with sleep quality. Pulse transit time (PTT) has been proposed as an alternate means for quantifying respiratory effort by detecting changes in blood pressure oscillations associated with pleural pressure swings [6]. PTT refers to the time it takes for a pulse wave to travel between two arterial sites. The speed at which this arterial pressure wave travels is inversely proportional to blood pressure. The variation of PTT between inspiration and expiration reflects the intensity of corresponding changes in intra-thoracic pressure. Our group has previously demonstrated that PTT can be used during PSG to analyze respiratory effort and, moreover, that it is specific when defining certain respiratory events occurring during spontaneous breathing (hypopneas, upper airway resistance episodes and central events) [7-9]. However, to date, no study has addressed the interest of PTT for characterizing nocturnal respiratory events occurring under NIV. Because NIV

modifies intra-thoracic pressures, and thus may affect blood pressure oscillations associated with pleural pressure swings, the contribution of PTT measurements in this setting must be evaluated. Also, NIV reduces respiratory effort, which may therefore affect the sensitivity of PTT in detecting changes in inspiratory effort [10].

We undertook the present study to assess the reliability of PTT for: (I) quantifying respiratory effort in comparison with Pes in healthy awake individuals, while breathing spontaneously, then under NIV with or without unintentional leaks, and (II) for differentiating central from obstructive events occurring during sleep under NIV in patients with obesity hypoventilation syndrome.

Materials and Methods

Part 1: Daytime assessment of respiratory effort in healthy individuals (Figure 1)

The objective of this experiment was to analyze the contribution of PTT to identify and quantify changes in respiratory muscle effort using Pes as “gold standard”.

Set-up and Measurements

Healthy subjects were studied during wakefulness while breathing spontaneously or under NIV. Respiratory effort was measured by Pes as reference method and compared to PTT as previously described [7, 8]. Respiratory flow and mask pressure (pneumotachograph), thoracic and abdominal movements, SaO₂ and electrocardiogram were monitored by polygraphy (DeltamedTM, San Carlos, USA).

After 5 minutes of recording during spontaneous breathing, subjects were ventilated consecutively with two different bi-level pressure support devices (GoodKnight 425ST, Tyco Healthcare Inc. Nancy, France and VPAP III ST, ResMed; North Ryde, Australia). Two devices were used because we hypothesized that their pressurization characteristics and thus their impact on respiratory effort might differ. The same settings were used in all the situations: Inspiratory Positive Airway Pressure (IPAP): 15 cmH₂O; Expiratory Positive Airway Pressure (EPAP): 5 cmH₂O; Backup rate: 8/minute; Inspiratory Time: 1.8 seconds. A leak generator was used as described in a previous study [11]. The system included a computer-driven solenoid valve which could be opened from 0 to 10 mm, thus generating a maximal unintentional leak of 60L/min at 15 cmH₂O of Inspiratory Positive Airway Pressure (IPAP). Four levels of leaks were generated (0; 24; 40; and 60 L/min) in a random order for five minutes each.

Digital Signal Processing and Analysis of polygraph recordings:

All the digital signal processing and analysis was performed using dedicated engineering Matlab software (Version 6.5.0, The MathWorks Inc., Natick, USA). We first selected by visual analysis valid portions of the tracings with at least 10 cycles with no artefacts on any

of the analyzed signals (Flow, PTT and Pes). Limits of each respiratory cycle were automatically defined on the flow signal as previously described by Bachy et al. [12]. The Pes signal classically presents a specific high frequency noise generated by the heart beats: this could affect quantification of effort when calculating the area under the curve of the negative deflection of the Pes signal. Adaptive filtering using a “Least Mean Square” algorithm was used to solve this problem. The beginning of the respiratory cycle was used to readjust the zero level for each cycle on the Pes signal. This was necessary to correct for the intermittent drift that occurred for the Pes signal. The area under the curve of the inspiratory Pes signal was then calculated, for each cycle. PTT swings were quantified as previously described [13] by measuring the difference between the expiratory peak and the inspiratory nadir for each cycle (figure 1C)

Part 2: Use of PTT as a surrogate marker of inspiratory effort to discriminate between central and obstructive respiratory events during sleep in patients with obesity hypoventilation syndrome (OHS)

The aim of this experiment was to determine if it was possible, based on PTT to determine whether decreases in flow occurring under NIV during sleep were of “central” or “obstructive” nature, using Pes as “gold standard.”

Set-up, definition of events and measurements

Patients with OHS chronically treated at home with nocturnal bi-level positive pressure ventilation for at least 3 months were included. OHS was defined as the association of obesity ($BMI > 30 \text{ kg/m}^2$), and daytime hypercapnia without any other obstructive or restrictive pulmonary pathology [14, 15]. Exclusion criteria were: age < 18 years; $FEV_1/FVC < 70\%$; history of an acute episode of cardiac and/or respiratory failure within the past 3 months; allergy to latex, and a history of oesophageal varices precluding the use of an esophageal probe. Polysomnography under NIV was performed as previously

described by our team [16, 17] using a single bi-level device (VPAP ST III, ResMed, Sydney, Australia) with the patients' usual ventilator settings (Table 2). Respiratory events under NIV were scored manually according to criteria proposed by Gonzalez-Bermejo J et al. [4].

Data analysis (Figure 2)

Scoring of respiratory events focused on central, mixed and obstructive events.

Figure 2 shows representative examples of how events were identified as either “central” or “obstructive” (partial or total upper airway obstruction with or without reduction of ventilatory drive) by using PTT and Pes.

First, respiratory events were scored by one observer based on Pes alone while blinded to the PTT signal. Secondly, events were scored using the PTT signal as indicator of respiratory effort, while the same observer was blinded to Pes tracing.

All subjects provided written informed consent. Study protocol was approved by the Ethics Committee of Grenoble University Hospital Center. Clinical trial registration number (clinicaltrials.gov): NCT00983411

Statistical Analysis:

Normality of the data was checked using tests of Skewness and Kurtosis and equality of variance was assessed by Levene's test. Data are expressed as median and inter-quartile range [25%;75%] when appropriate. PTT and Pes values are reported as percentage of value during spontaneous breathing (SB).

Comparisons between experimental conditions were analyzed by two-way repeated measures ANOVA with a repeated factor “condition” (no leaks, calibrated leaks of 24L/min, 40L/min and 60 L/min versus spontaneous breathing), and a repeated factor “ventilator”

(GoodKnight 425ST versus VPAP III). Bonferroni's correction was used for the paired T-Tests.

Comparisons between PTT and Pes for the total number of events and percentage of central events occurring under NIV in OHS patients was expressed as proposed by Bland and Altman [18]. The agreement between PTT and Pes for events occurring during sleep was quantified using an intra-class correlation coefficient (ICC) calculated with SPSS Statistics 17 (SPSS Inc, Chicago, IL) [19]. ICC values between 0.51 and 0.70 describe moderate reproducibility, and values above 0.71, good reproducibility. Correlations were assessed by Pearson's or Spearman's coefficients depending upon the normality of distribution.

For all tests, a level of significance of $p < 0.05$ was used. Statistical analysis was performed with NCSS 97 software (Kaysville, Utah, USA).

Results

Part 1: Daytime assessment of respiratory effort in healthy individuals

Eleven subjects (6 male, aged: 31 ± 9 years; BMI: 22.3 ± 2.5 Kg/m²) were included. Respiratory effort was assessed simultaneously by esophageal probe and PTT. Subjects were recorded 1/ *during* spontaneous breathing, 2/ under NIV without leaks and 3/under NIV with induced calibrated leaks applied in a random order. The mathematical processing of PTT and Pes is shown in figure 1. A two-way repeated measures ANOVA with a repeated factor “condition” (no leaks, calibrated leaks of 24L/min, 40L/min and 60 L/min at inspiratory pressure versus spontaneous breathing), and a repeated factor “ventilator” (GoodKnight 425ST versus VPAP III) showed no effect related to the ventilator. As such, figure 3 and table 1 present mean values for the two ventilators. There was a significant decrease in respiratory effort when shifting from spontaneous breathing to NIV without leaks (Figure 3). This change was highly significant with either PTT or Pes. When leaks were increased (from 0 to 60L/min), increase in respiratory effort was documented similarly by PTT and Pes (Table 1).

Part 2: During sleep assessment of OHS patients

Ten patients with OHS (6 male, aged: 56 ± 12 years; BMI: 35 ± 5 kg/m²) were included in the night time study. Table 2 summarizes respiratory function, blood gases and usual NIV settings of these patients.

Based on Pes, we found that our patients had a total number of respiratory events on NIV of 43 ± 48 per night. These events were predominantly obstructive in nature (85.8% of total number of events). The total number of events and the percentage of central events scored when using PTT alone or Pes alone were highly significantly correlated ($r=0.98$ and $r=0.86$ respectively, $p=0.001$) (Figure 4 A and B). On the corresponding Bland and Altman, the mean systematic bias was respectively 5 events [limits of agreement: -19.3;29.3] and -

3.4 % [limits of agreement: -14.9;8.2]. The intraclass correlation coefficients (ICC) between Pes and PTT were 0.970 (95% CI: 0.889;0.992, $p<0.0001$) for total number of events and 0.970 (95% CI: 0.871;0.993, $p<0.0001$) for percentage of central events (table 3).

An additional interest of PTT was its ability to describe changes in respiratory effort when respiratory cycles were triggered or not by the patients (see figure 5).

Discussion

Data presented in the present study show that, in normal subjects, in spite of the changes in intra-thoracic pressure and hemodynamics induced by positive pressure ventilation, pulse transit time (PTT) accurately reflects the unloading of respiratory muscles induced by non-invasive ventilation (NIV) as well as the increase in respiratory effort accompanying leaks during NIV. This may be of interest when seeking to unload the respiratory muscles during daytime titration of NIV. We also showed that the analysis of PTT during sleep studies allows an appropriate classification of respiratory events occurring under NIV as being either central or obstructive in nature (i.e. partial or complete upper airway obstruction with or without reduction of ventilator drive) [4]. These results support the use of PTT as a surrogate marker of inspiratory muscle effort under NIV.

Complex respiratory events occurring during sleep under NIV, which may have a detrimental effect on both quality of sleep and control of nocturnal hypoventilation, have been the focus of several recent studies and reviews [2, 20]. In a PSG study, 40% of obese patients using NIV showed a high index of periodic breathing, mostly occurring in light sleep and associated with sometimes severe nocturnal hypoxaemia [5]. Identification of these events is important in order to select the appropriate changes in ventilator settings and/or interface. Whether systematic PSG is necessary for titrating NIV, as suggested by the American Academy of Sleep Medicine [2] is a subject of debate: this option is not supported in a recent review on monitoring of home NIV [21]. However, when PSG or PG are performed, determining whether events are primarily “central” or “obstructive” is often critical (i.e.: with a decrease or increase in respiratory drive). This is especially the case in the presence of partial reduction of airflow: detecting whether persisting inspiratory efforts are increasing, suggesting upper airway obstruction, or not, suggesting a decrease in respiratory drive, requires an indicator of inspiratory effort, with P_{es} being the gold standard [4]. This is a key issue as both events lead to different strategies in terms of

ventilator setting adjustment. Pes has been validated both in the intensive care unit for improving ventilators settings and in the field of sleep medicine as a marker of inspiratory effort [22]. However, as previously mentioned, routine use of Pes is questionable because of associated sleep disruption and leaks around the mask induced by the esophageal probe. PTT has been suggested as a surrogate marker of inspiratory effort [23]. It has been documented as a reliable marker of inspiratory efforts in sleep studies performed in children with sleep-disordered breathing [9, 24, 25] and in adults [23, 26]. Our data support the use of PTT as a marker of inspiratory effort under bi-level positive pressure ventilation. Using PTT for quantifying changes in inspiratory effort induced by NIV may also be of interest. It is usually admitted that efficacy of long term NIV relies on resting the respiratory muscles, reducing the load against which the respiratory muscle pump must work and restoring central drive to breathe [27]. However, the tools currently available to assess muscle rest and load reduction all have significant limitations. As mentioned, esophageal probes are poorly tolerated by patients and used only in specialized centers. Diaphragm or intercostal electromyograms are difficult to quantify, and require a level of expertise to be of practical interest. Data presented that PTT may provide a simple marker for assessing the degree of respiratory muscle rest provided when titrating pressure support under NIV. The changes in Pes and PTT were obvious during NIV without leaks, a situation associated with a complete rest of respiratory muscles. In response to leaks some normal subjects exhibited a higher percentage of triggered cycles and frankly increased their respiratory effort. This was nicely demonstrated by Pes but less clearly showed by PTT. This means that the PTT technique is easier to tolerate for the patients but probably less sensitive to detect subtle increases in respiratory effort.

Limitations of the study

There are a certain number of limitations to the use of PTT. First, the quality of the signal is directly related to the quality of the ECG and pulse-oximetry: these signals may easily become unstable, leading the analysis of PTT useless on bouts of PG or PSG tracings. Signal processing may also vary according to software and PSG or PG devices used: this warrants further clinical testing. Secondly, there is significant variation in PTT between individuals as a result of differences in blood pressure and vascular compliance. This does not unduly affect interpretation as it is the pattern of Δ PTT change by which respiratory events are scored. From our own anecdotal experience it is known that cardiac arrhythmias such as atrial fibrillation render the PTT signal almost uninterpretable. This is potentially a major drawback in some patients.

The sample size of our study was relatively limited but we performed systematic measurements of esophageal pressure both during diurnal and sleep experiments. Such an experimental design is difficult to implement in larger populations. At the end, we were able to draw significant conclusions from this well defined population. Owing to a limited number of included subjects, we decided to investigate a homogeneous population of obesity hypoventilation syndrome. These patients appeared of particular interest as exhibiting both central and obstructive respiratory events during sleep. We anticipate that the ability of PTT to estimate respiratory effort will be the same in COPD and thoracic cage restrictive diseases. More questionable is the situation of patients with neuromuscular disorders producing only moderate respiratory effort. A specific study in this population is desirable.

PTT has the ability to quantitatively assess respiratory effort. However, during this study we did not try to separate hypopneas related to pharyngeal collapses from hypopneas owing to decrease in ventilatory command associated with glottis closures.

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Conclusion and perspectives

Taking into account the above-mentioned caveats, PTT is a promising tool for non-invasively assessing inspiratory muscle effort under bi-level positive pressure ventilation, and distinguishing between central and obstructive events under NIV not only in the sleep laboratory but also potentially in domiciliary sleep studies (polygraphy). The choice of softwares and their evolution is certainly critical to the development of PTT. Further studies are also required to assess PTT as a tool for identifying ineffective efforts under NIV and its capacity to be used for adjusting trigger sensitivity. The ability of PTT to estimate respiratory effort under NIV should be established in other patient's population such as COPD and thoracic cage restrictive diseases.

References

1. Janssens JP, Borel JC, Pepin JL. Nocturnal monitoring of home non-invasive ventilation: the contribution of simple tools such as pulse oximetry, capnography, built-in ventilator software and autonomic markers of sleep fragmentation. *Thorax* epub 2010 oct.: 66(5): 438-445.
2. Berry RB, Chediak A, Brown LK, Finder J, Gozal D, Iber C, Kushida CA, Morgenthaler T, Rowley JA, Davidson-Ward SL. Best clinical practices for the sleep center adjustment of noninvasive positive pressure ventilation (NPPV) in stable chronic alveolar hypoventilation syndromes. *J Clin Sleep Med* 2010: 6(5): 491-509.
3. Fanfulla F, Taurino AE, Lupo ND, Trentin R, D'Ambrosio C, Nava S. Effect of sleep on patient/ventilator asynchrony in patients undergoing chronic non-invasive mechanical ventilation. *Respir Med* 2007: 101(8): 1702-1707.
4. Gonzalez-Bermejo J, Perrin C, Janssens JP, Pepin JL, Mroue G, Leger P, Langevin B, Rouault S, Rabec C, Rodenstein D. Proposal for a systematic analysis of polygraphy or polysomnography for identifying and scoring abnormal events occurring during non-invasive ventilation. *Thorax* epub 2010 oct.
5. Guo YF, Sforza E, Janssens JP. Respiratory patterns during sleep in obesity-hypoventilation patients treated with nocturnal pressure support: a preliminary report. *Chest* 2007: 131(4): 1090-1099.
6. Pitson DJ, Stradling JR. Value of beat-to-beat blood pressure changes, detected by pulse transit time, in the management of the obstructive sleep apnoea/hypopnoea syndrome. *Eur Respir J* 1998: 12(3): 685-692.
7. Argod J, Pepin JL, Levy P. Differentiating obstructive and central sleep respiratory events through pulse transit time. *Am J Respir Crit Care Med* 1998: 158(6): 1778-1783.

8. Argod J, Pepin JL, Smith RP, Levy P. Comparison of esophageal pressure with pulse transit time as a measure of respiratory effort for scoring obstructive nonapneic respiratory events. *Am J Respir Crit Care Med* 2000; 162(1): 87-93.
9. Pepin JL, Delavie N, Pin I, Deschaux C, Argod J, Bost M, Levy P. Pulse transit time improves detection of sleep respiratory events and microarousals in children. *Chest* 2005; 127(3): 722-730.
10. Wilson TA, Angelillo M, Legrand A, de Troyer A. Muscle kinematics for minimal work of breathing. *J Appl Physiol* 1999; 87(2): 554-560.
11. Contal O, Vignaux L, Combescure C, Pepin JL, Jolliet P, Janssens JP. Monitoring of non-invasive ventilation by built-in software of home bi-level ventilators: a bench study. *Chest*.
12. Bachy JP, Eberhard A, Baconnier P, Benchetrit G. A program for cycle-by-cycle shape analysis of biological rhythms. Application to respiratory rhythm. *Comput Methods Programs Biomed* 1986; 23(3): 297-307.
13. Pitson DJ, Sandell A, van den Hout R, Stradling JR. Use of pulse transit time as a measure of inspiratory effort in patients with obstructive sleep apnoea. *Eur Respir J* 1995; 8(10): 1669-1674.
14. Mokhlesi B. Obesity hypoventilation syndrome: a state-of-the-art review. *Respir Care* 2010; 55(10): 1347-1362; discussion 1363-1345.
15. Piper AJ, Grunstein RR. Obesity hypoventilation syndrome: mechanisms and management. *Am J Respir Crit Care Med* 2011; 183(3): 292-298.
16. Borel JC, Tamisier R, Gonzalez-Bermejo J, Baguet JP, Monneret D, Arnol N, Roux-Lombard P, Wuyam B, Levy P, Pepin JL. Noninvasive Ventilation in Mild obesity hypoventilation syndrome: A randomized controlled trial. *Chest* epub 2011 sept.

17. Chouri-Pontarollo N, Borel JC, Tamisier R, Wuyam B, Levy P, Pepin JL. Impaired objective daytime vigilance in obesity-hypoventilation syndrome: impact of noninvasive ventilation. *Chest* 2007; 131(1): 148-155.
18. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1(8476): 307-310.
19. McGraw KO, Wong, S. P. Forming inferences about some intraclass correlation coefficients. *Psychological Methods* 1996; 1(1): 30-46 (Correction, Vol. 31, No. 34, 390).
20. Rabec C, Rodenstein D, Leger P, Rouault S, Perrin C, Gonzalez-Bermejo J. Ventilator modes and settings during non-invasive ventilation: effects on respiratory events and implications for their identification. *Thorax* epub 2010 oct.: 66(2): 170-178.
21. Janssens JP, Borel JC, Pepin JL. Nocturnal monitoring of home non-invasive ventilation: the contribution of simple tools such as pulse oximetry, capnography, built-in ventilator software and autonomic markers of sleep fragmentation. *Thorax* epubs 2010: 66(5): 438-445.
22. Fanfulla F, Delmastro M, Berardinelli A, Lupo ND, Nava S. Effects of different ventilator settings on sleep and inspiratory effort in patients with neuromuscular disease. *Am J Respir Crit Care Med* 2005; 172(5): 619-624.
23. Pepin JL, Tamisier R, Borel JC, Baguet JP, Levy P. A critical review of peripheral arterial tone and pulse transit time as indirect diagnostic methods for detecting sleep disordered breathing and characterizing sleep structure. *Curr Opin Pulm Med* 2009.
24. Brietzke SE, Katz ES, Roberson DW. Pulse transit time as a screening test for pediatric sleep-related breathing disorders. *Arch Otolaryngol Head Neck Surg* 2007; 133(10): 980-984.
25. Huang H, Ye JY, Li YR, Wang XY, Zhang YH, Wang JY, Ding X, Li HG, Han DM. Pulse transit time for quantifying inspiratory effort in patients with obstructive sleep apnea. *ORL J Otorhinolaryngol Relat Spec*: 73(1): 53-60.

26. Poyares D, Guilleminault C, Rosa A, Ohayon M, Koester U. Arousal, EEG spectral power and pulse transit time in UARS and mild OSAS subjects. *Clin Neurophysiol* 2002; 113(10): 1598-1606.
27. Elliott MW. Domiciliary non-invasive ventilation in stable COPD? *Thorax* 2009; 64(7): 553-556.

Legends

Figure 1: Diagram of experiments **A:** healthy subject ventilated and monitored with esophageal probe, flow sensor, thoracic and abdominal sensors, electrocardiogram (ECG) and oximetric photoplethysmography (for pulse transit time), computer-driven solenoid valve generating calibrated unintentional leaks; **B:** Tracing during nocturnal experiment in an OHS patient; **C:** Zoom on PPT (measure of time on one cycle “expiratory peak to inspiratory peak”) and Pes (calculation of the area under zero)

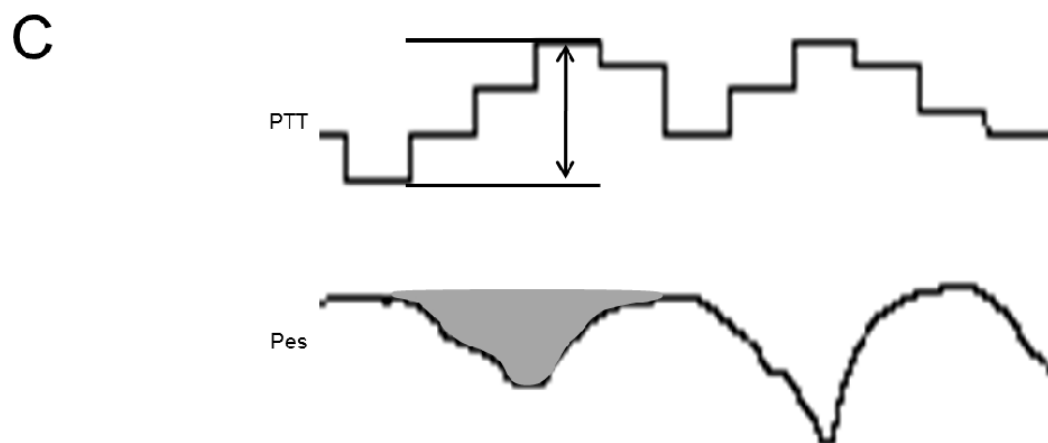
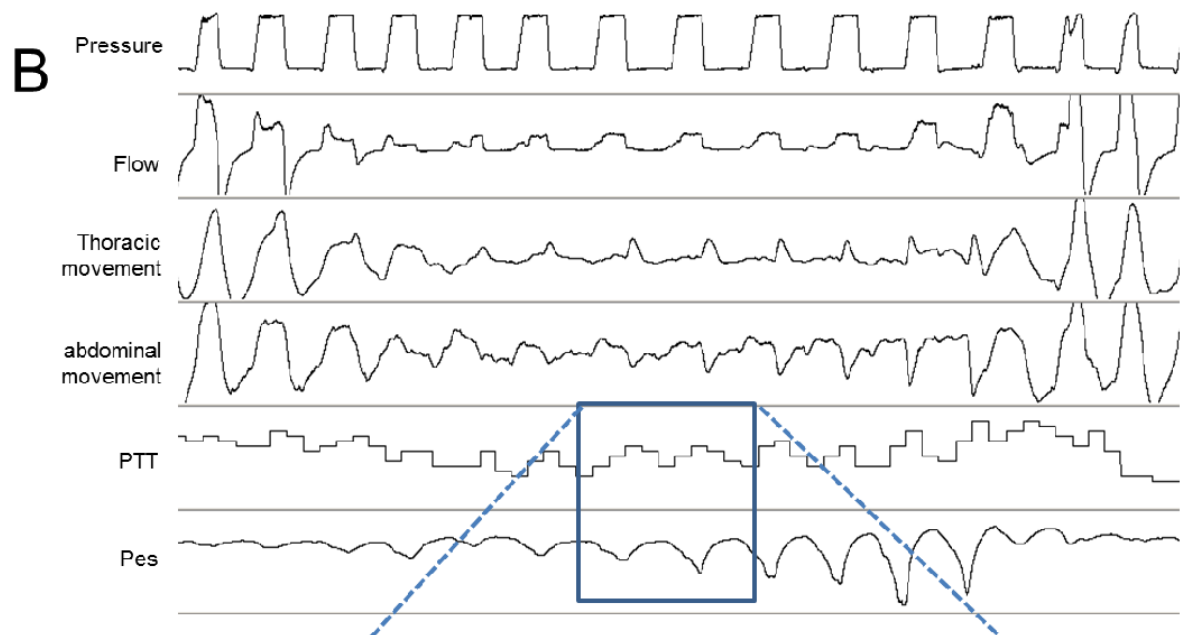
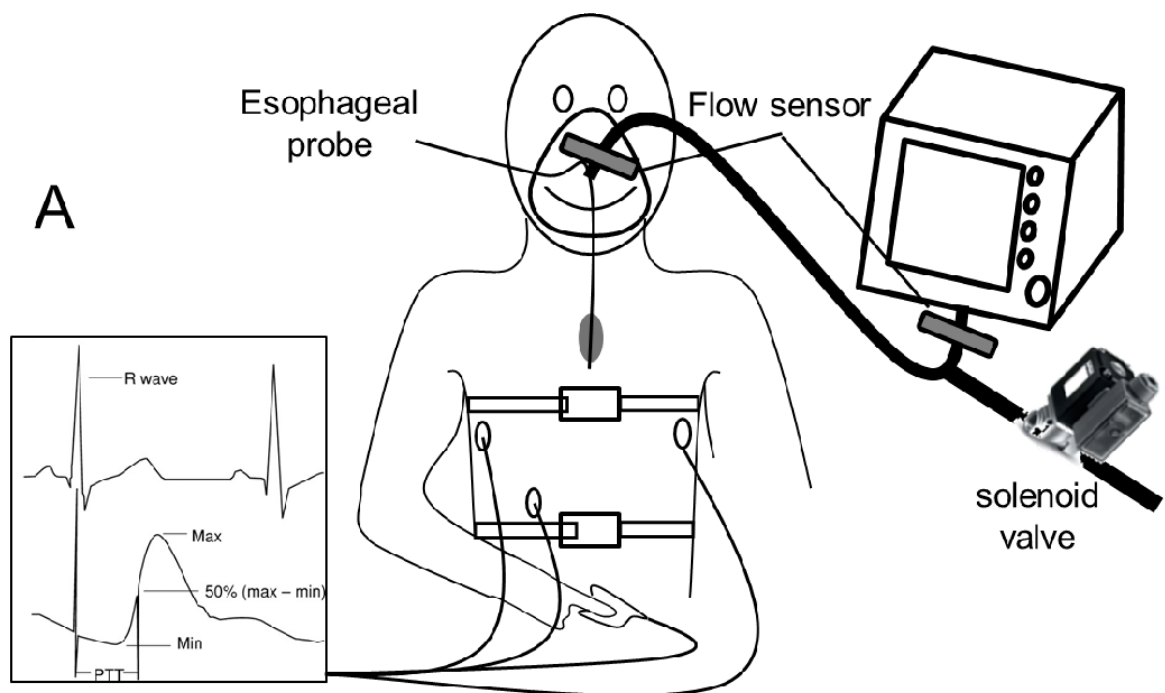


Figure 2: During 3 minutes epoch, illustrative examples of how visual scoring was performed to identify central vs. obstructive events using PTT or Pes

(A) Central respiratory event: for both Pes and PTT signals, respiratory oscillations are markedly reduced or disappear

(B) Obstructive respiratory event: swings of Pes become increasingly negative during an obstructive event, with a simultaneous increase in oscillations of PTT between inspiration and expiration (dark lines).

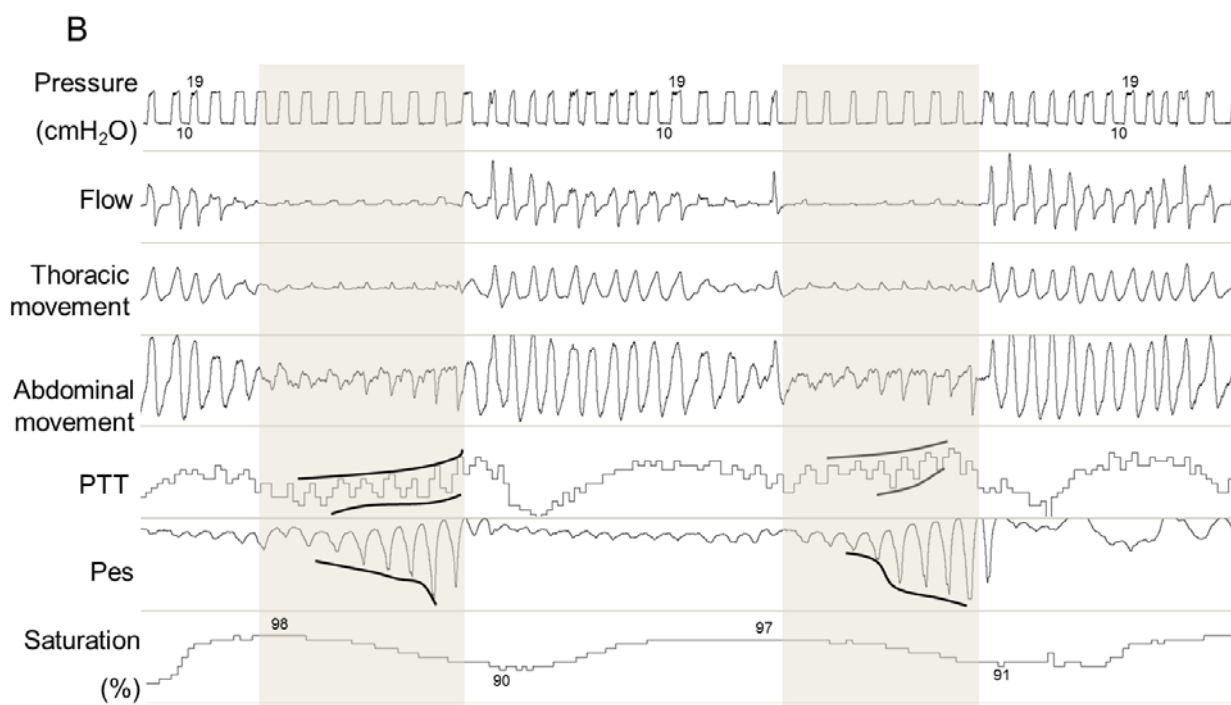
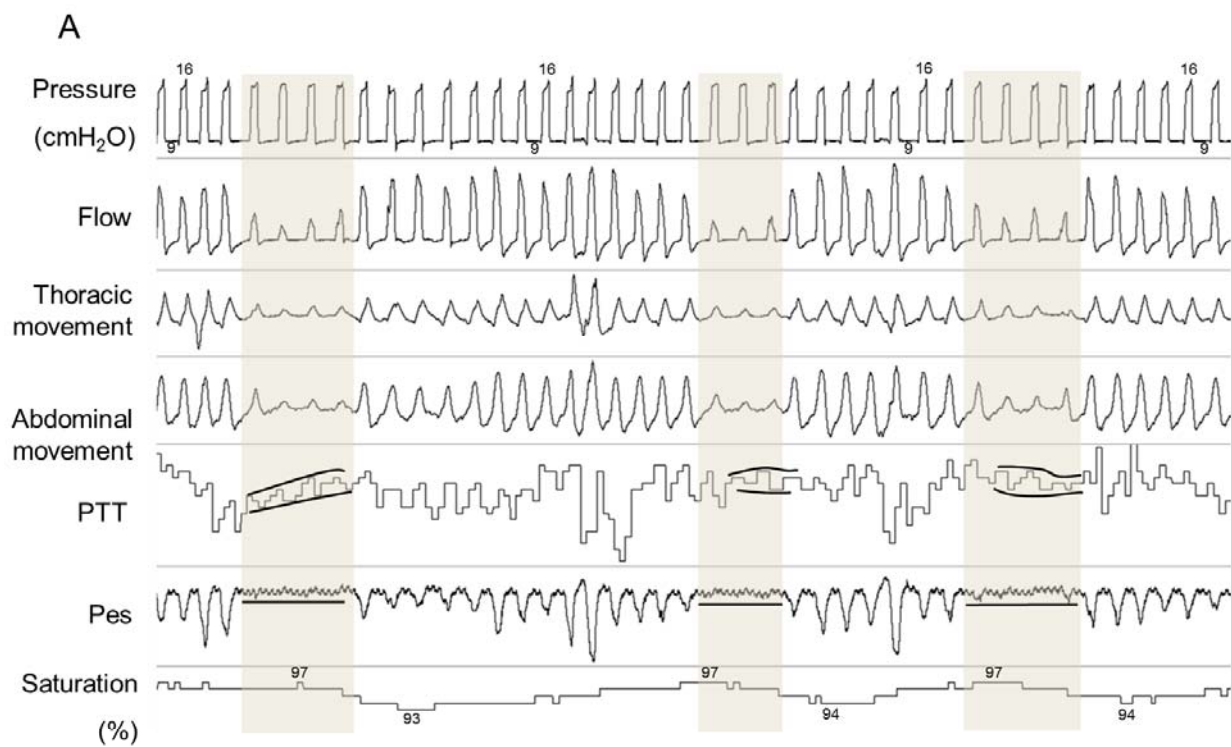


Figure 3: Respiratory effort measured by Pulse transit time (PTT) (Figure 3A) or esophageal pressure (Pes) (Figure 3B) in awake healthy subjects while breathing spontaneously (SB) or under non-invasive ventilation at different levels of leaks (percentage of SB value; SB = 100, mathematical processing analysis of Pes and PTT).

The changes in Pes and PTT were obvious during NIV without leaks, a situation associated with a complete rest of respiratory muscles. In response to leaks some normal subjects exhibited a higher percentage of triggered cycles and frankly increased their respiratory effort. This was nicely demonstrated by Pes but less clearly showed by PTT.

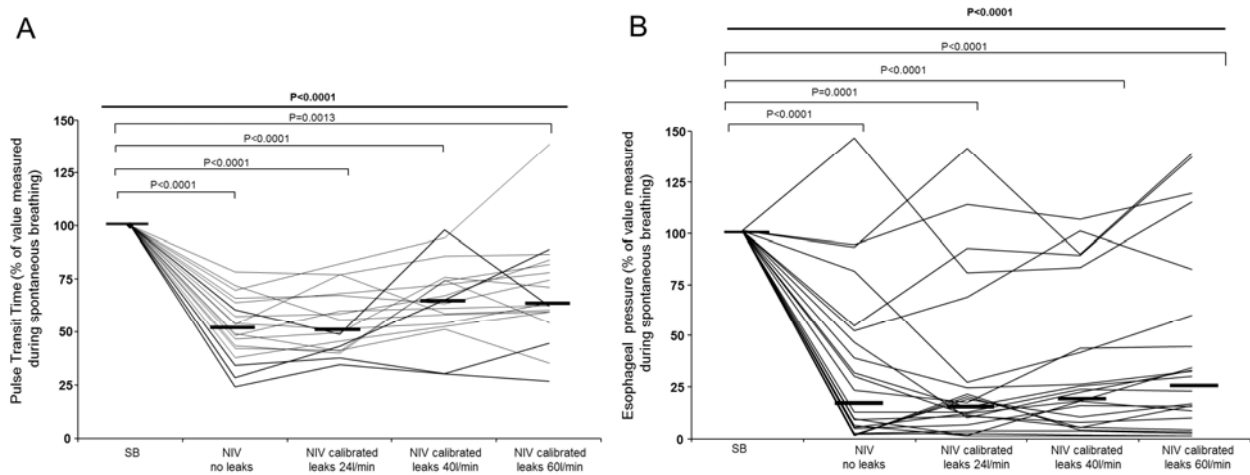


Figure 4: Representation of scoring of all respiratory events and percentage of central events ($r=0.98$ and $r=0.86$ respectively, $p=0.001$) **A:** Correlation between total number events scored when using PTT alone versus Pes alone. **B:** Correlation between percentage of central events scored when using PTT alone versus Pes alone.

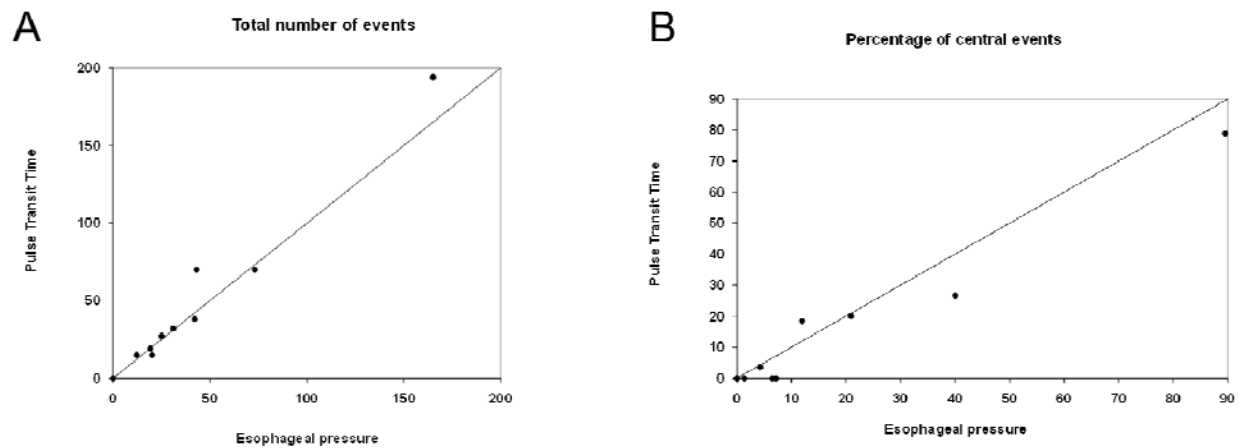


Figure 5: Ability of pulse transit time to characterize respiratory effort during respiratory cycles triggered or not by the patients

- A- Box 1: respiratory cycles are triggered by the patient. Box 2: There is no inspiratory effort from the patient, all respiratory cycles are controlled by the ventilator.
- B- 1-Respiratory cycles are triggered by the patient as demonstrated by the changes in pressure signal before pressurization (see arrow). There is a clear increase in respiratory effort as demonstrated by esophageal pressure and an increase in inspiratory-expiratory differences on PTT signal.
- 2-All the respiratory cycles are controlled by the ventilator with an obvious reduction in effort both on PTT and Pes as compared to figure 5B-1.

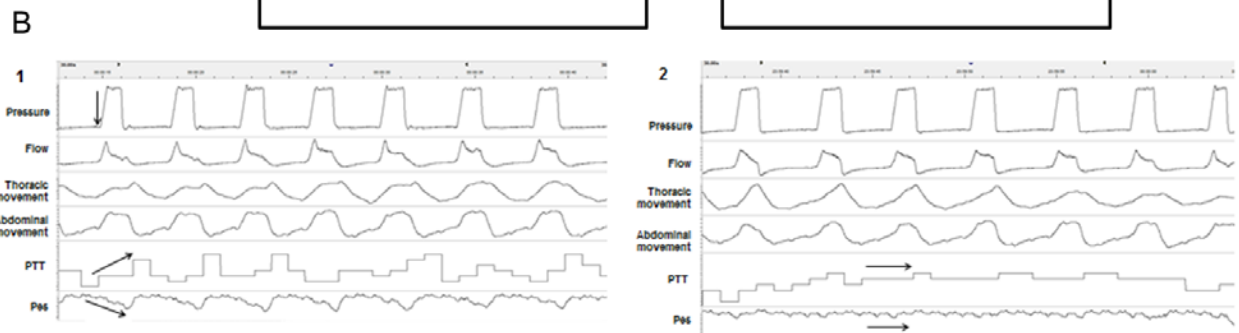
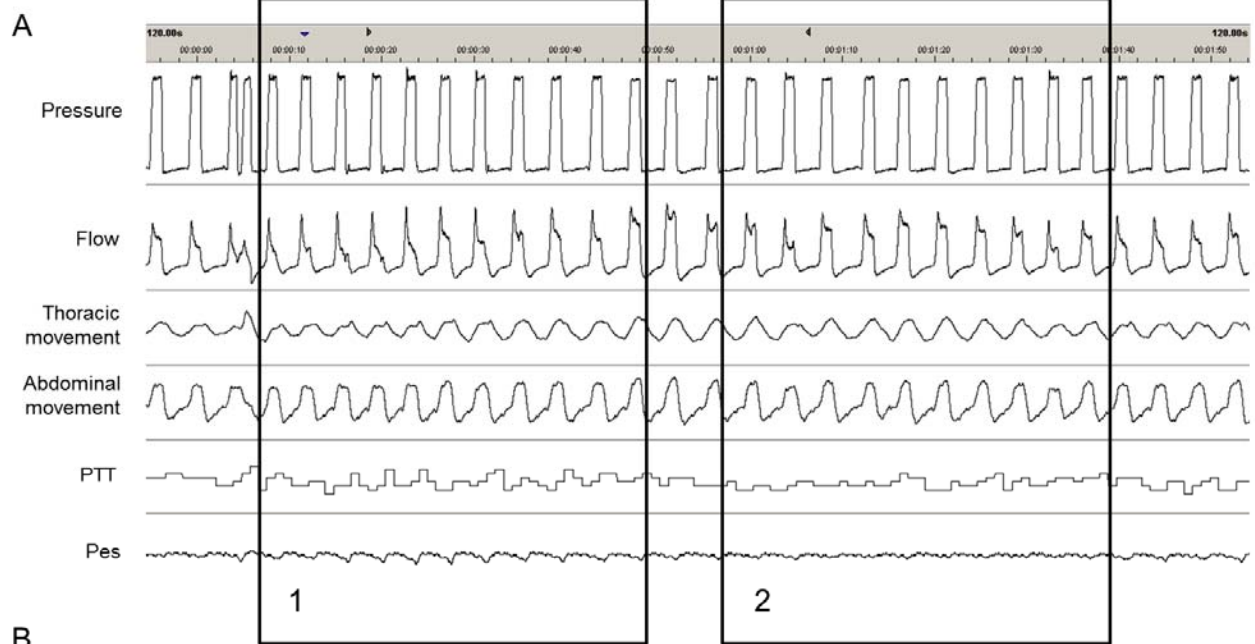


Table 1: Respiratory effort measured by Pulse transit time (PTT) (Figure 3A) or esophageal pressure (Pes) (Figure 3B) in awake normal subjects while breathing spontaneously (SB) or under non-invasive ventilation at different levels of leaks (expressed as percentage of SB value (=100), see text for mathematical processing of Pes and PTT signals)

| | SB | NIV no leaks | NIV Calibrated leak of 24l/min | NIV Calibrated leak of 40l/min | NIV Calibrated leak of 60l/min | P-value |
|-----|-----|---------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|----------|
| PTT | 100 | 51.3 [41.2-64.3] | 50.6 [41.3-67.4] | 64.3 [53.7-75.0] | 63.1 [58.2-82.3] | < 0.0001 |
| Pes | 100 | 16.8 [3.3-51.8] | 15.1 [8.3-36.4] | 19.2 (4.4-52.5) | 25.5 [7.5-64.3] | < 0.0001 |

Values presented as Median [interquartile range]:

PTT: Pulse Transit Time; Pes: Esophageal Pressure; SB: Spontaneous Breathing; NIV: Non Invasive Ventilation. p value two-way repeated measures ANOVA.

Table 2: Respiratory function, blood gases (room air) and NIV settings of patients with OHS

| | Mean | SD |
|----------------------------------------|------|------|
| VC (L) | 3.2 | 1 |
| VC (%predicted) | 88 | 23 |
| FEV ₁ (L) | 2.4 | 0.8 |
| FEV ₁ (%predicted) | 83 | 25 |
| FEV ₁ / VC | 79.3 | 8.6 |
| FEV ₁ / FVC (%predicted) | 94.3 | 1.1 |
| <u>Arterial blood gases</u> | | |
| pH | 7.40 | 0.03 |
| PaO ₂ (kPa) | 10 | 1.7 |
| PaCO ₂ (kPa) | 5.9 | 0.8 |
| HCO ₃ ⁻ (mmol/l) | 27 | 1.7 |
| SaO ₂ (%) | 95 | 1.7 |
| <u>NIV settings</u> | | |
| Back-up rate (cycles per minute) | 13 | 2 |
| IPAP (cmH ₂ O) | 19 | 2 |
| EPAP (cmH ₂ O) | 11 | 2 |

VC: vital capacity; FEV₁: forced expiratory volume in 1 s; PaO₂: arterial oxygen partial pressure; PaCO₂: arterial carbon dioxide partial pressure; HCO₃⁻: bicarbonates; SaO₂: arterial oxygen saturation; IPAP: inspiratory positive airway pressure; EPAP: expiratory positive airway pressure.

Table 3: Percent of respiratory events scored using either esophageal pressure (Pes) or pulse transit time (PTT) as indicators of respiratory effort

| | Measurement of respiratory effort | | | |
|--------------------|---------------------------------------------------------------------|---------------------------------------------------------------------|-------------------------------------------------------|---------|
| | Pes mean number of events (% of total number of events) | PTT mean number of events (% of total number of events) | Intraclass correlation coefficients (95% CI) | P-value |
| Obstructive events | 36.9 (85.8%) | 42.5 (88.5%) | 0.990 (0.912;0.998) | <0.0001 |
| Mixed events | 1.1 (2.6%) | 1 (2.1%) | 0.636 (0.021;0.897) | 0.023 |
| Central events | 5 (11.6%) | 4.5 (9.4%) | 0.970 (0.871;0.993) | <0.0001 |