Pulse wave amplitude reduction: A surrogate marker of micro-arousals associated with respiratory events occurring under non-invasive ventilation?

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KEYWORDS
Pulse wave amplitude; Micro-arousals; Chronic respiratory insufficiency; Non-invasive ventilation; Polysomnography; Monitoring

Summary
Introduction: Respiratory events occurring under non-invasive ventilation (NIV) may produce sleep fragmentation. Alternatives to polysomnography (PSG) should be validated for providing simple monitoring tools for patients treated at home with NIV.
Objectives: To study the value of pulse wave amplitude (PWA) reduction as a surrogate marker of cortical micro-arousals associated with respiratory events occurring during NIV.
Methods: 27 PSG tracings under NIV recorded in 9 stable patients with Obesity Hypoventilation Syndrome (OHS), under 3 different ventilator modes (no back-up rate, low or high back-up rate) were analyzed. For all respiratory events (obstructive, central, or mixed event), the association with EEG-micro-arousals, PWA reduction of more than 30% and the presence of associated SpO2 desaturation ≥4% was recorded.
Results: 2474 respiratory events during NREM sleep were analyzed. 73.6% were associated with an EEG-MA, 91.4% with a ≥4% decrease in SpO2, and 74.9% with a significant PWA reduction. Sensitivity of PWA for the detection of an EEG-micro- arousal related to a respiratory event was 89.1% [95%CI: 76.7–95.3]. Positive predictive value (PPV) was 87.0% [95%CI: 75.0–94.0]. Sensitivity of PWA was highest in the S mode, compared to both other S/T modes, \( p = <0.001 \). Sensitivity of PWA was also higher for central and mixed events, compared to obstructive respiratory events, \( p = <0.05 \).

Conclusions: PWA reduction is a sensitive marker with a high PPV for the detection of EEG-MA associated with respiratory events during NREM sleep in stable OHS patients treated by NIV. In this situation, PWA could be used to improve scoring of hypopneas and allow an appropriate assessment of sleep fragmentation related to respiratory events.

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**Introduction**

Home non-invasive ventilation (NIV) is presently recognized as standard care for patients with chronic alveolar hypoventilation. The importance of appropriate monitoring of patients under long term NIV has been recently emphasized [1]. Several reports have shown that patients under NIV may develop patient–ventilator asynchrony [2,3], unrewarded inspiratory efforts [4], unintentional leaks [5], periodic breathing [3] and respiratory events of obstructive, central or mixed origin during their sleep [6]. These abnormal respiratory events may cause disrupted sleep architecture, sleep fragmentation and excessive daytime sleepiness [5,7]. Sleep disturbances can easily be detected and quantified by nocturnal polysomnography (PSG) under NIV, allowing appropriate adjustments of ventilator settings [4,6]. However, quantification of sleep fragmentation by PSG with assessment of EEG-micro-arousals (EEG-MA) is time-consuming, expensive and not always available depending on local health care resources [8]. The use of simplified monitoring tools such as type III portable sleep monitors (polygraphy: PG) with surrogate markers of micro-arousals (MA) and inspiratory effort related to respiratory events may be an alternative option [9].

In a recent review [10], respiratory events occurring under NIV were considered clinically relevant if they induced a drop in SpO2, an increase in PtcCO2, an MA, or any combination of these items. PtcCO2 is rarely contributive because of a lag time which precludes detection of short events. Association of a respiratory event with a drop in SpO2 is easily detected. Conversely, association with an EEG-MA requires PSG. Pulse wave amplitude (PWA) is strongly correlated to EEG-MA in healthy subjects and in patients with obstructive sleep apnea (OSA) [11–13]. Arousals induce sympathetic activation and peripheral vasoconstriction mainly through adrenergic alpha-receptors [14] inducing transient drops in PWA [12,15,16] that can be measured non-invasively by photoplethysmography. This technique uses absorption of red and infrared light across the finger. The pulsation of arterial blood flow passing through an artery modulates light absorption and generates a signal that can easily be derived from a conventional pulse oximeter. In untreated OSA, a PWA drop is considered as a reliable marker of changes in cortical activity using EEG spectral analysis [17]. Furthermore, PWA added to conventional PSG improves the detection of respiratory events and cortical arousals [18].

Scoring hypopneas requires the presence of either a decrease in flow ≥50%, or a 30% decrease in flow of at least with a drop in SpO2 ≥ 4% and/or an EEG-MA [19]. Because type III portable sleep monitors do not provide EEG-MA, hypopnea scores are underestimated when compared to PSG. The aim of this study was to show that PWA drops associated with respiratory events could be used as surrogate markers of EEG-MA in patients under NIV, and thus could allow a more appropriate scoring of hypopneas with type III portable sleep monitors. The originality of the present study was to assess the interest of PWA under NIV, a specific situation where respiratory events associated or not with SpO2 desaturations are highly prevalent. Because Obesity Hypoventilation Syndrome (OHS) represents one of the most frequent indications for NIV in Western Europe [20,21], this study focused on PSG tracings performed in this population.
Patients and methods

Patients with OHS treated by long term nocturnal NIV, in stable clinical condition and followed by the Division of Pulmonary Diseases of Geneva University Hospital were included. OHS was defined as the association of morbid obesity (BMI >30 kg/m²), and daytime hypercapnia without any other obstructive or restrictive pulmonary pathology. Exclusion criteria were: age <18 years; Obstructive lung disease defined by FEV₁/FVC <70%; history of an acute episode of cardiac and/or respiratory failure within the past 3 months; poor adherence defined as average daily use of ventilator <4/00 h, according to ventilator software [22]. Use of any medication with cardiovascular effects was recorded (anti-hypertensive, anti-arrhythmic, diuretics).

Selection of tracings

Patients included had participated in a study by our group focusing on the impact of changes in back-up respiratory rate (BURR) on respiratory events during sleep under NIV [6]. Briefly, each patient (n = 10) underwent, in a random sequence, 3 consecutive PSG recordings under NIV without any change in pressure settings but with three different back-up rates. All PSG recordings were performed with patients using the same NIV device (VPAP III ST-A™; ResMed; North Ryde, Australia). The second objective of this study was to explore the association between PWA and EEG-MA in patients under NIV. All PSG recordings were considered for the present study (n = 30). Tracings from one patient were discarded because of poor PWA signal quality. Therefore, 27 tracings from 9 patients were included for analysis.

Sleep recordings

Overnight PSG (Embla N7000™, Embla Systems, Broomfield, USA), performed under NIV, included standard electroencephalography (7 electrodes, F3, F4, C3, C4, Cz, O1, O2), left and right electro-oculography and submental electro-myography (EMG). Left and right anterior tibialis EMG was used to detect leg movements and a bipolar electrocardiogram was used for cardiac monitoring. Airflow (using a pneumotachograph), thoracic and abdominal movements, SpO₂, body position and video were simultaneously and continuously monitored (Remlogic 1.1™, Embla). Nocturnal transcutaneous CO₂ partial pressure (PtcCO₂) was recorded using a transcutaneous capnograph with an ear probe heated at 43 °C (Tosca 500™, Radiometer, Switzerland).

Scoring and definition of respiratory events

Sleep and micro- arousals were scored according to AASM criteria [19] by an experienced investigator blinded to the PWA channel. Micro-arousals were defined as an abrupt shift of EEG frequency including alpha, theta waves and/or frequencies greater than 16 Hz lasting at least 3 s.

Respiratory events under NIV were scored when flow drop was associated with a SpO₂ desaturation of ≥4% and/or micro-arousals. Respiratory events where then categorized as central sleep apneas or hypopneas, obstructive sleep apneas or hypopneas, and mixed sleep apneas or hypopneas.

PWA signal was analyzed blinded to all other channels. Finger PWA was determined as the difference between the peak and the nadir values of the corresponding photoplethysmogram pulse wave for each cardiac cycle. A sampling frequency of 100 Hz was used without filtering. Automatic analysis was obtained first using Remlogic 1.1. Two experienced investigators subsequently scored the PWA signal for the whole night. Based on previous reports a decrease of ≥30% of PWA scored visually was considered as significant [16,24]. If the difference between the peak and the nadir values was uncertain, an electronic ruler provided by the company was used to measure PWA reduction.

Only PWA drops associated with respiratory events were analyzed. Decreases in PWA occurring without any respiratory event were not taken into account. Our study aimed to determine whether PWA drops could be used as surrogate markers for EEG-MA associated with respiratory events in PG recordings, and thus allow scoring of hypopneas even in the absence of a significant oxygen desaturation.

PWA drops were considered as linked to an EEG-MA if they were superimposed within a 10s timeframe. PWA drop was considered as linked to a respiratory event if it started after the beginning of the respiratory event or if the nadir of the PWA coincided with the hyperventilation phase which followed the respiratory event [25].

Selection of respiratory events for analysis

For each PSG recording, the first 100 respiratory events under NIV occurring during NREM sleep were selected for analysis. We excluded respiratory events occurring during REM sleep because of a high baseline sympathetic activity and a huge variation of all cardiovascular markers of autonomic activation (heart rate, blood pressure, PWA, PTTR) during this sleep stage [26]. Each respiratory event was classified according to its’ association with a micro-arousal, and/or a drop in SpO₂ and/or a drop in PWA (Fig. 1).

Statistical analysis

This study analyses the diagnostic value of PWA drops in the presence of respiratory events, using EEG-MA as reference standard. Analysis was performed on 3 PSG recordings per patient. Sensitivity (Sn), specificity (Sp) positive predictive value (PPV) and negative predictive value (NPV) were computed for each subject directly from the frequencies of PWA drops and EEG-MA. Then, to compute an overall Sn, Sp, PPV and NPV which takes into account the dependence of data from the same subject, a mixed-effects logistic regression model was used. To test whether there were differences in sensitivity and specificity between NIV modes, a three-level categorical variable (one for each mode) was introduced, as well as the interaction between this variable and the variable "EEG-MA". The same analysis was performed for differences between predictive values but with an interaction between the "NIV mode" variable and that coding for PWA drops. To test for differences in sensitivity and specificity between the type of respiratory event, the same method was applied with another three-
level categorical variable (obstructive, mixed and central). Patients’ characteristics were reported as median and IQR due to the limited sample size. Friedman’s test was used to compare mean of repeated data. The significance level was fixed at 5%. All analyses were performed using R for Windows [27] (version 2.15.1) with the package lme4 [28] (version 0.999999-0) for the Generalized Linear Mixed Models and ggplot2 [29] (version 0.9.2.1).

The study protocol was approved by the Ethics Committee for Medical Research of Geneva University Hospitals (IRB CER-08-131) and written informed consent was obtained from all participants. The trial was registered at www.clinicaltrials.gov (NCT01130090).

Results

Patients (n = 9) were aged (median [IQR]) 52 years [51; 59], had a BMI of 46 kg/m² [45; 53], and had been on NIV for 19.5 months [16.5; 59]. Key polysomnographic results for the 3 ventilatory modes are shown in Table 1 (adapted from reference [6]).

None of the ventilator settings was modified during the 3 consecutive PSG recordings (IPAP: 20.5 ± 3.7 cmH₂O; EPAP: 9.2 ± 1.8 cmH₂O; Rise time: 155 ± 65 ms) albeit for back-up rate (BURR). AHI was significantly higher (p = 0.006; Friedman’s test) during NIV with the “S” mode (60/h; [44; 77]) than during “ST” modes (low or high BURR: respectively: 19/h [9; 40] and 12/h [3; 26]) as previously reported [6].

A total of 2474 respiratory events out of 2700 expected events were analyzed because we were not able to collect 100 events from all 3 sleep studies in two patients. 1330 (53.8%) were obstructive apnea or hypopnea, 1003 (40.5%) were central and 141 (5.7%) mixed apnea or hypopnea. Of the 2474 respiratory events, 1822 (73.6%) were associated with an EEG-micro-arousal, 2261 (91.4%) with a decrease in SpO₂ of ≥4% and 1854 (74.9%) with a significant PWA drop. Two by two tables plotting respiratory events according to EEG-MA and PWA drops are displayed for each patient in Fig. 2 as a graphical illustration of raw data. A Supplementary table showing individual data for true positive, true negative, false positive and false negative results of PWA drop to detect EEG-MA is available as an Online supplement. Among 213 respiratory events associated with an EEG-MA but no drop in SpO₂, 62.4% (133) had a synchronous drop in PWA.

After controlling for between patient variability using a Generalized Linear Mixed Model, sensitivity of PWA for identifying EEG-micro-arousals related to respiratory events was 89.1% [95%CI: 76.9–95.3] and positive predictive value (PPV) was 87.0% [95%CI: 75.0–94.0]. Specificity was 40.7% [95%CI: 21.6–63.2] and negative predictive value (NPV) was 45.8% [95%CI: 27.0–65.9]. Table 2 shows individual data for sensitivity and PPV.

Sensitivity of PWA varied from patient to patient, from one ventilator mode to another, and with the type of respiratory event (central, mixed or obstructive). Sensitivity was lowest for patients 5, 6 and 9. Patient 5 was treated with diltiazem a potent vasodilator drug that may buffer microcirculatory vascular response to autonomic arousal; patients 6 and 9 had no vaso-active, anti-hypertensive or anti-arrhythmic drugs. Sensitivity for all patients was higher under S mode (95.5%; 95%CI [89.4–98.1]) than under low BURR (87.3%; 95%CI [73.8–94.1]) or high BURR (80.8%; 95%CI [63.4–91.1]), p < 0.001 (Table 2). Sensitivity was also demonstrated to be higher with central (91.5%; 95%CI [80.8–96.5]) and mixed respiratory events (94.6%; 95%CI [84.4–98.3]), compared to obstructive respiratory events (87.0%; 95%CI [72.7–94.4]) when data was analyzed...
according to the type of respiratory event ($p < 0.05$). Of note, SpO2 drops were on average of greater magnitude in S mode compared to other modes.

**Discussion**

This study constitutes the first description of the diagnostic value of PWA drops as a surrogate marker of EEG-MA related to respiratory events during NIV. Our results suggest that a decrease in PWA of more than 30% occurring in association with a respiratory event is a sensitive (89.1% [95%CI: 76.7–95.3]) marker of cortical arousals during nocturnal NIV with a high PPV (87.0% [95%CI: 75.0–94.0]). Changes in sensitivity were associated with ventilator mode and with the type of respiratory events. This finding may be related to the magnitude of desaturations according to ventilator mode, i.e. S mode was associated mostly with central respiratory events and profound desaturation dips (Table 1).

### Table 1  Baseline characteristics and polysomnographic results according to ventilator mode.

<table>
<thead>
<tr>
<th></th>
<th>S mode</th>
<th>S/T mode with low BURR</th>
<th>S/T mode with high BURR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI</td>
<td>60 [44; 77]</td>
<td>19 [9; 40]</td>
<td>12 [3; 26]</td>
</tr>
<tr>
<td>Central AHI</td>
<td>17.7 [13.7; 37.6]</td>
<td>0.8 [0.1; 4.1]</td>
<td>0.2 [0; 4.4]</td>
</tr>
<tr>
<td>Mixed AHI</td>
<td>9.5 [4.7; 13.2]</td>
<td>0.1 [0; 1.7]</td>
<td>0 [0; 0.6]</td>
</tr>
<tr>
<td>Obstructive AHI</td>
<td>22 [15.3; 37.3]</td>
<td>17.2 [4.1; 36.5]</td>
<td>8.6 [1.8; 21.6]</td>
</tr>
<tr>
<td>Average SpO2</td>
<td>92 [91; 94]</td>
<td>92 [91; 93]</td>
<td>92 [91; 94]</td>
</tr>
<tr>
<td>SpO2 &lt; 90% (% TST)</td>
<td>13 [4; 27]</td>
<td>11 [5; 27]</td>
<td>7 [2; 23]</td>
</tr>
<tr>
<td>ODI (&gt;4%/h)</td>
<td>59.5 [52; 71]</td>
<td>26 [15; 39]</td>
<td>19 [7; 36]</td>
</tr>
<tr>
<td>Mean desaturation per RE (%)</td>
<td>7.93 [5.5; 15]</td>
<td>6.33 [4.9; 11]</td>
<td>5.81 [4.5; 11]</td>
</tr>
</tbody>
</table>

BMI: body mass index; AHI: apnea–hypopnea index; SpO2: oxygen saturation of hemoglobin measured by pulse oximetry; TST: total sleep time; RE: respiratory event. Data presented as median [IQR].

Adapted from O. Contal et al. [6].

![Figure 2](image-url)  

Figure 2  Graphical illustration of agreement between PWA drops and EEG-MA during NIV in 9 patients. For each individual patient, data from 3 sleep studies under NIV with different back-up rate are plotted together. Data was jittered to avoid overplotting and to provide a visual impression of the test characteristics. Upper left box: false negative results; upper right: true positive results; lower left: true negative results; lower right: false positive results. 0 = absent; 1 = present.
We also found that there was an inter-subject variability in PWA sensitivity to detect EEG-MA for which there was no obvious explanation.

The AASM recently recommended the systematic use of PSG for NIV titration, in all subjects with chronic alveolar hypoventilation [30]. Indeed, there is an increasing awareness of complex patient–ventilator interactions during sleep [2–4]. The importance of a detailed analysis of these interactions, by respiratory polygraphy or polysomnography has been recently emphasized [10]. However, in many European countries, PSG is not readily available for initiating or adjusting NIV. Also, EEG scoring is expensive and time-consuming. The use of respiratory polygraphy is a reasonable alternative but suffers from two major drawbacks: the lack of a reliable signal of inspiratory effort to discriminate between obstructive and central hypopneas, and a reliable surrogate marker of micro-arousals. Pulse transit time (PTT) has been shown to provide a reliable assessment of inspiratory effort under NIV in normal subjects, and subjects with OHS, but these results have to be confirmed with different softwares and portable devices [9]. PWA is a surrogate marker of MA in diagnostic studies for sleep disordered breathing, but its use is yet unexplored under NIV. If well correlated with EEG-micro-arousals related to respiratory events, it would allow detection and scoring of respiratory events (hypopneas). It gives no indication as to its overall specificity for detecting EEG-MA by PWA sensitivity. In particular, it would not be appropriate to negate a direct effect of ventilator mode on PWA sensitivity as modification of BURR was the sole random founding factor and that the association between ventilatory mode and PWA sensitivity may in fact be driven by the magnitude of SpO2 desaturation. However, our data do not allow us to further enhance causal inference for PWA sensitivity. In particular, it would not be appropriate to negate a direct effect of ventilator mode on PWA sensitivity as modification of BURR was the sole random intervention made in stable OHS patients for the purpose of this study.

Specificity of PWA reported in this study was low. Noteworthy is the fact that, because of the design of our study, specificity reported refers only to the detection of EEG-MA by PWA in the presence of a respiratory event, and gives no indication as to its overall specificity for detecting EEG-MA. A plausible explanation for this low specificity was suggested by Delessert et al.: PWA can be associated with subtle changes in cortical activity even in the absence of visually scored EEG arousals [17]. Other markers of sympathetic nerve activity also exhibit the same properties. For instance, upper airway obstruction in OSA is associated with reduced amplitude of peripheral arterial tonometry (PAT) signal in the absence of detectable EEG arousal [31]. These autonomic arousals, often referred to as “sub-cortical” arousals, may not be recorded by conventional EEG leads and thus are not detected by visual inspection of EEG [32]. They can be detected by methods of quantitative EEG-analysis such as spectral analysis [17]. They are scored as “false positives” of PWA, i.e. drops in PWA not associated with micro-arousals related to respiratory events. The consequences of these “sub-cortical” arousals in terms of quality of sleep, and related morbidity are to date not well

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### Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>NIV all modes</th>
<th>NIV with &quot;S&quot; mode</th>
<th>NIV with &quot;low BURR ST&quot; mode</th>
<th>NIV with &quot;high BURR ST&quot; mode</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PWA Sn (%)</td>
<td>PWA PPV (%)</td>
<td>PWA Sn (%)</td>
<td>PWA PPV (%)</td>
</tr>
<tr>
<td>1</td>
<td>83.6</td>
<td>99.6</td>
<td>97.0</td>
<td>99.0</td>
</tr>
<tr>
<td>2</td>
<td>96.2</td>
<td>71.0</td>
<td>97.1</td>
<td>68.7</td>
</tr>
<tr>
<td>3</td>
<td>91.2</td>
<td>88.3</td>
<td>86.4</td>
<td>92.1</td>
</tr>
<tr>
<td>4</td>
<td>94.6</td>
<td>64.1</td>
<td>96.2</td>
<td>38.1</td>
</tr>
<tr>
<td>5</td>
<td>68.5</td>
<td>83.7</td>
<td>89.4</td>
<td>78.7</td>
</tr>
<tr>
<td>6</td>
<td>47.9</td>
<td>82.3</td>
<td>93.9</td>
<td>63.3</td>
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<tr>
<td>7</td>
<td>95.8</td>
<td>92.6</td>
<td>100</td>
<td>95</td>
</tr>
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<td>8</td>
<td>97.8</td>
<td>80.0</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>66</td>
<td>83.2</td>
<td>75</td>
<td>77.6</td>
</tr>
<tr>
<td>All</td>
<td>89.1</td>
<td>87</td>
<td>95.5</td>
<td>83.2</td>
</tr>
</tbody>
</table>

BURR: Back-up respiratory rate. Values expressed as mean [95%CI].
defined. They may however be associated with daytime vigilance impairment [33]. PWA drops occurring without EEG-defined MA may also relate to other events such as limb movements, external noises, or transient increases in upper airway resistance not fulfilling all criteria for RERA. Finally, PWA drops per se may prove to be more relevant than EEG-micro- arousals when estimating cardiovascular risk. The cumulative time spent with PWA drops reflects increased sympathetic activity induced by recurrent episodes of nocturnal hypoxia, as showed in normal volunteers [34] and in subjects with OSA [35, 36]. OSA which is frequent in OHS patients is also associated with endothelial dysfunction, which predisposes to increased vasoconstriction. Treatment of OSA by nCPAP significantly reduces peripheral vasoconstriction: this may be a marker of a positive impact of positive pressure on cardiovascular risk [36].

There are few limitations to this study. First, although 2474 respiratory events were collected in our database, all respiratory events arise from a limited group of patients followed for OHS. The interest of this group of subjects resides in the wide range of respiratory events detected in their PSGs, which allowed us to document variations of PWA in central, obstructive, and mixed apnea and hypopnea. Leaks were low and episodes of patient–ventilator asynchrony represented a small percentage of TST: they were therefore not included in the present analysis. Conclusions of this study are therefore restricted to subjects with OHS and use of PWA as a surrogate marker of EEG-micro-arousals related to respiratory events should be explored in other diagnostic groups. In future studies, we also plan to explore whether PWA drop analysis can be expanded to REM sleep. Important intrinsic variability of most autonomic signals during REM precludes their immediate transfer into clinical practice. A cutoff value for PWA drop, specific to micro-arousal during REM, will have to be determined by clinical studies designed to answer this question before generalization of the technique. Secondly, the design of our study does not allow the computation of a global PWA sensitivity and specificity for the detection of EEG-micro-arousals because PWA drops not associated with a respiratory event were not recorded. It was a choice of the authors to analyze only EEG-micro-arousals related to respiratory events, in order to estimate the potential performance of PWA drops for improving detection of hypopneas with type III sleep monitors. Our results do however provide an indication as to the contribution of PWA for documenting sleep fragmentation, but sensitivity and specificity must be interpreted only for PWA associated with respiratory events.

In summary, PWA drops are sensitive indicators with a high positive predictive value for the detection of EEG-micro-arousals associated with respiratory events occurring during NREM sleep in stable OHS patients treated by non-invasive ventilation. In this situation, PWA could be used to improve scoring of hypopneas and allow an appropriate assessment of sleep fragmentation related to respiratory events. The rather low specificity of PWA could be explained by "subcortical" arousals which are associated with sympathetic activation. The finding of a patient-to-patient variability in performance of PWA warrants further studies. Items such as duration of decrease of PWA or more "in depth" analysis of the PWA curve should be explored to improve specificity.

**Contribution of authors to this study**

Dan Adler was involved in: study design, analysis of the data, writing and revision of the manuscript.

Pierre-Olivier Brichot was involved in: analysis of the data, revision of the manuscript.

Olivier Contal was involved in: study design, patient recruitment, recording of the data, revision of the manuscript.

Elise Dupuis-Lozeron was involved in analysis of the data, revision of the manuscript.

Marjolaine Georges was involved in: revision of the manuscript.

Elisabeth Claudel was involved in: recording and analysis of the data and revision of the manuscript.

Jean-Louis Pépin was involved in: study design, analysis of the data, writing and revision of the manuscript.

Jean-Paul Janssens was involved in: study design, patient recruitment, analysis of the data, writing and revision of the manuscript.

**Conflict of interest**

All authors declare there is no actual or potential conflict of interest to declare in relation to this article.

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**Appendix A. Supplementary data**

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2013.10.010.

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