Decreased fat oxidation during exercise in severe obstructive sleep apnoea syndrome

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Abstract

Aim. – To assess whether the severity of obstructive sleep apnoea syndrome (OSAS) is associated with altered fat oxidation (FO) during physical exercise in men with type 2 diabetes (T2DM) and/or the metabolic syndrome (MetS).

Methods. – A total of 105 consecutive overweight or/and T2DM male patients were hospitalized for metabolic check-ups including bioimpedancemetry to measure lean body mass (LBM), standardized exercise calorimetry to assess FO, maximum fat oxidation (MFO) and carbohydrate oxidation (CHO), and OSAS screening using respiratory polygraphy. Twenty patients were classified as having severe OSAS, according to the apnoea/hypopnoea index (AHI), with greater than 30 events/h (mean AHI: 45.2 ± 14.3 events/h). They were group-matched for age, BMI, and the presence of T2DM and/or MetS with two other OSAS groups: mild (AHI < 15 events/h [n = 20]; mean AHI: 8.8 ± 4.5 events/h); and moderate (AHI > 15 events/h and < 30 events/h [n = 20]; mean AHI: 23.7 ± 4.2 events/h).

Results. – MFO adjusted for LBM was severely decreased in the severe OSAS group (1.6 ± 1.0 mg.min⁻¹.kgLM⁻¹) compared with the moderate (2.5 ± 0.9 mg.min⁻¹.kgLM⁻¹; P = 0.008) and mild (2.9 ± 0.8 mg.min⁻¹.kgLM⁻¹; P = 0.003) groups. All exercise-intensity levels (20%, 30%, 40% and 60% of the theoretical maximum aerobic power) showed reduced FO levels between the severe and mild-to-moderate OSAS groups. However, no differences in CHO were seen at any level of exercise between groups. Pearson’s correlation analysis showed that AHI and the oxygen desaturation index were negatively associated with MFO corrected for LBM (r = 0.41 and r = 0.37, respectively; P < 0.005).

Conclusion. – OSAS severity is associated with altered FO during exercise.

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Keywords: Obstructive sleep apnoea syndrome; Exercise and substrate oxidation; Fat oxidation; Type 2 diabetes mellitus; Metabolic syndrome; LIPOXmax; Fatmax

Résumé

Réduction de l’oxydation des lipides durant l’exercice physique chez les patients atteints d’un syndrome d’apnées obstructives du sommeil.

Objectif. – Évaluer si la sévérité du syndrome d’apnées obstructives du sommeil (SAOS) est associée avec une altération du débit d’oxydation lipidique (OL) pendant l’exercice physique chez des sujets de sexe masculin présentant un syndrome métabolique (SMet) et/ou un diabète de type 2 (DT2).

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1. Introduction

Obstructive sleep apnoea syndrome (OSAS) is associated with metabolic alterations such as insulin resistance, visceral obesity, the metabolic syndrome (MetS) and type 2 diabetes (T2DM) [1–3] that can alter the nature of the substrates oxidized during exercise. Exercise calorimetry can help to predict the quantity of lipids that will be oxidized during steady-state exercise at a given intensity. This can be used to target training, and to measure the ability to oxidize lipids during exercise that is impared in some diseases and improved by training, and which is correlated with muscle physiological status. Increased sympathetic activation resulting from sleep fragmentation and intermittent hypoxia, as found in OSAS, can alter carbohydrate metabolism [4,5] and energy expenditure during physical exercise [6]. For this reason, it was hypothesized that OSAS severity, as reflected by the apnoea–hypopnoea index (AHI), can modify fat oxidation (FO) during exercise and especially the maximum fat oxidation rate (MFO), leading to resistance to weight loss in apnoeic patients. In the present study, indirect calorimetry was used to quantify FO during exercise in OSAS patients divided into three groups according to severity, and matched for age, body mass index (BMI), and the presence of T2DM and/or MetS.

2. Research design and methods

Between May 2008 and December 2010, 105 overweight or obese male patients with or without T2DM were screened for OSAS by overnight respiratory polygraphy during a brief hospitalization for a metabolic check-up. All subjects underwent a complete medical history review with measurement of subjective daytime sleepiness [7], anthropometric measurements and standardized exercise calorimetry (described below). Twenty subjects were classified as having severe OSAS (AHI > 30 events/h), and were matched by age, BMI and the presence or not of T2DM and/or MetS with 20 subjects with moderate OSAS (AHI 5–14.9 events/h) and 20 subjects with mild OSAS (AHI 15–29.9 events/h). A total of 24 patients were identified as having T2DM while 45 patients had the MetS [8], including nine patients with both conditions. Oral antidiabetic treatment (n = 22) was withheld for 12 h prior to the test. For those receiving insulin (n = 4), the last injection was given no later than 2000 h the night before.

2.1. Overnight polygraphy

Measurement of sleep apnoea–hypopnoea was performed by overnight respiratory polygraphy (Embletta PDS, ResMed Corp., Poway, CA, USA). Measurements of respiratory events were made by a sleep specialist according to the American Academy of Sleep Medicine (AASM) guidelines [9]: apnoea (> 90% nasal flow reduction for ≥10 s) and hypopnoea (≥50% reduction in nasal flow associated with ≥3% desaturation). None of these patients were being treated with a continuous positive airway pressure (CPAP) mask.

2.2. Anthropometric and biological measurements

Body composition, weight, height, and waist and neck [10] circumferences were measured in the morning after greater or equal to 12-h fast. A multifrequency bioelectrical impedance analysis (BIA) instrument (Bodystat Quadscan 4000, Bodystat Ltd, Douglas, Isle of Man, UK) was used at the following frequencies: 5, 10, 50 and 100 kHz. Analysis was performed using the Geneva equation [11]. A venous blood sample was obtained to measure lipid profile, plasma glucose and insulin resistance (homeostasis model assessment for insulin resistance or HOMA-IR).

2.3. Exercise calorimetry

Subjects performed graded exercise on an electromagnetically braked cycle ergometer (Ergoline GmbH, Bitz, Germany) connected to a breath-by-breath measuring device (Viasys Healthcare, Höchberg, Germany) for gas-exchange measurements (VO₂ and VCO₂ with volume expressed in mL·min⁻¹). For individualization, each increment of exercise workload at each step was calculated from the theoretical maximum
aerobic power (\(\text{thP}_{\text{max}}\)) corresponding to the theoretical \(\text{VO}_{2\text{max}}\) given by Wasserman’s equations [12]. The revolution rate of cycling was maintained at 60–70 rev.min\(^{-1}\) throughout the test. Every 6-min period of steady-state workload at 20%, 30%, 40% and 60% of the \(\text{thP}_{\text{max}}\) was performed with continuous electrocardiography monitoring. Ventilation and gas-exchange parameters were determined as the means of measurements taken during the last 2 min of each workload period. The FO rate during exercise was calculated according to equations of non-protein respiratory quotient [13]. Given that protein oxidation can be considered to be negligible during a 24-min exercise period (FO [mg.min\(^{-1}\)] = 1.6946 \(\text{VO}_2\)−1.7012 \(\text{VCO}_2\)), FO was further normalized for lean mass (LM) and expressed in mg.min\(^{-1}\).kgLM\(^{-1}\). The MFO was also calculated as described elsewhere [14].

2.4. Statistical analysis

Subjects were categorized into three OSAS severity groups according to AHI. Quantitative data were expressed as means ± standard deviation (SD). Group differences were assessed using one-way analysis of variance (ANOVA) and Bonferroni’s post-hoc test for differences between the severe and mild-to-moderate groups. If normality was not established, ANOVA by ranks (Kruskal–Wallis) and Tukey’s post-hoc test were used for differences between the two groups. Correlations were assessed by Pearson’s correlation analysis.

3. Results

3.1. Patients’ characteristics

As expected, the three groups were similar in terms of age (54.2 ± 11.0 years, 55.5 ± 9.5 years and 55.4 ± 7.7 years) and BMI (33.6 ± 5.9 kg/m\(^2\), 33.4 ± 5.4 kg/m\(^2\) and 33.8 ± 3.5 kg/m\(^2\)) for the mild, moderate and severe OSAS groups, respectively. All patients were sedentary (< 2 h of moderate physical activity per week). The proportions of type 2 diabetics and MetS patients were also similar between groups. In addition, HbA1c, fasting plasma glucose, HOMA-IR, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglycerides did not differ across the three groups (Table 1).

3.2. Polygraphic analysis

Mean AHI (8.8 ± 4.5 vs 23.7 ± 4.2 vs 45.2 ± 14.3 events/h) and oxygen desaturation indices (7.4 ± 3.4 vs 14.6 ± 9.4 vs 37.2 ± 15.1 events/h) differed across all three groups (\(P<0.005\) for each). The mean nocturnal pulse oxygen saturation (SpO\(_2\); 93.4 ± 1.4% vs 93.8 ± 1.8% vs 92.0 ± 1.7%) also differed between the mild and severe groups (\(P=0.016\), and between the moderate and severe groups (\(P=0.002\)). The percentage of time spent at less than 90% (5.2 ± 13.8% vs 5.3 ± 10.2% vs 20.5 ± 18.0%) differed between the mild and severe groups (\(P<0.001\)) and between the moderate and severe groups (\(P<0.001\)).

3.3. Fat oxidation during exercise

FO was compared among the three groups at rest, and at 20%, 30%, 40% and 60% of the \(\text{thP}_{\text{max}}\) (Table 2). The intensity level identified for MFO was closest to the 20% of the \(\text{thP}_{\text{max}}\) for each OSAS group (Fig. 1). A progressive decrease was noted in MFO adjusted for LM from the mild to moderate to severe OSAS groups (2.9 ± 0.8 vs 2.5 ± 0.9 vs 1.6 ± 1.0 mg.min\(^{-1}\).kgLM\(^{-1}\), respectively). In addition, the FO adjusted for LM was significantly decreased at 20% (\(P=0.001\)), 30% (\(P=0.001\)), 40% (\(P=0.004\)) and 60% (\(P=0.05\)) of the \(\text{thP}_{\text{max}}\) in the severe OSAS group compared with the mild group, and at 20% (\(P=0.007\)), 30% (\(P=0.009\)) and 40% (\(P=0.03\)) of the \(\text{thP}_{\text{max}}\) compared with the moderate group. No difference was found in carbohydrate oxidation (CHO) adjusted for LM for the three groups whatever the intensity of exercise (Fig. 2).

Table S1 (see supplementary material associated with this article online) presents the crude values of power (in watts) for each exercise step, the \(\text{thP}_{\text{max}}\) and the theoretical maximum oxygen consumption rate (\(\text{thVO}_{2\text{max}}\)) for each of the three groups. No differences were found between groups at each power and at the \(\text{thVO}_{2\text{max}}\). AHI and oxygen desaturation indices were negatively correlated with MFO corrected for LM (\(r=0.41\) and \(r=0.37\), respectively; \(P<0.005\); Fig. S1; see supplementary material associated with this article online). Post-hoc correlation analysis confirmed the relationship between the HOMA-IR and AHI (\(r=0.82\); \(P<0.01\)), but no correlation was found between the HOMA-IR and MFO.

4. Discussion

The primary objective of this cross-sectional study was to investigate whether OSAS severity can influence substrate
metabolism during exercise independently of the well-identified modifying factors such as age, gender, BMI and T2DM. Based on previous studies using calorimetry during steady-state workloads, an exercise test was developed comprising five 6-min submaximum steps, during which lipid oxidation from gas exchanges was calculated during the 5th and 6th min of each step. Using this technique, a marked decrease was seen in the capacity to oxidize lipids during exercise in the MetS and/or T2DM patients with severe OSAS compared with those with mild and moderate OSAS. In addition, negative correlations were also found between MFO and both the AHI and oxygen desaturation index. These findings favour the idea that the ability of muscle to oxidize substrates is indeed influenced by the obstructive respiratory events encountered in OSAS.

The classical physiological modifiers of the balance of substrates during exercise measured at fasting under standardized conditions are gender [16,17] and exercise-training status. Among the diseases that modify this balance of substrates, the majority of studies report that, in obese [14,20] and T2DM [18–20] subjects, the intensity of exercise that elicits maximum lipid oxidation (also called the LIPOXmax) is markedly shifted to lower intensities with lower MFO.

In our present study, there was a decrease in lipid oxidation that was uncompensated for by an increase in CHO. In fact, Fig. 2 should mirror Fig. 1, and the CHO rate should be significantly lower than the FO rate to match energy requirements. However, such findings were not seen, as no differences were reported among the crude power values at

Table 1
Baseline characteristics of the three groups of patients with mild, moderate and severe obstructive sleep apnoea syndrome (OSAS).

<table>
<thead>
<tr>
<th>Groups</th>
<th>AHI &lt; 15/h</th>
<th>AHI &gt; 15/h and &lt; 30/h</th>
<th>AHI &gt; 30/h</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>54.2 ± 11.0</td>
<td>55.5 ± 9.5</td>
<td>55.4 ± 7.7</td>
<td>0.90</td>
</tr>
<tr>
<td>Type 2 diabetes (n)</td>
<td>8</td>
<td>7</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Metabolic syndrome (n)</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>33.6 ± 5.9</td>
<td>33.4 ± 5.4</td>
<td>33.8 ± 3.5</td>
<td>0.97</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>114.8 ± 12.9</td>
<td>110.9 ± 12.2</td>
<td>115.6 ± 10.3</td>
<td>0.41</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>42.2 ± 1.8</td>
<td>42.6 ± 2.9</td>
<td>44.2 ± 2.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>66.3 ± 7.7</td>
<td>65.2 ± 6.7</td>
<td>68.0 ± 9.7</td>
<td>0.55</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>35 (30–42)</td>
<td>29 (26–41)</td>
<td>36 (28–43)</td>
<td>0.42</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>188 (122–205)</td>
<td>143 (110–238)</td>
<td>190 (170–261)</td>
<td>0.43</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>40 (39–48)</td>
<td>43 (40–58)</td>
<td>45 (37–53)</td>
<td>0.61</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>111 ± 41</td>
<td>120 ± 37</td>
<td>125 ± 34</td>
<td>0.60</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.4 (4.8–6.9)</td>
<td>5.5 (4.9–6.2)</td>
<td>5.8 (5.2–7.7)</td>
<td>0.40</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.87 (2.18–4.00)</td>
<td>1.98 (1.36–3.04)</td>
<td>3.88 (3.49–5.95)</td>
<td>0.06</td>
</tr>
<tr>
<td>Validated time (min)</td>
<td>460 (423–471)</td>
<td>450 (411–464)</td>
<td>462 (424–468)</td>
<td>0.44</td>
</tr>
<tr>
<td>AHI (events/h)</td>
<td>8.4 (5.2–13.7)</td>
<td>24.0 (21.0–27.0)</td>
<td>43.6 (32.6–54.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ODI (events/h)</td>
<td>8.1 (5.5–9.8)</td>
<td>12.0 (9.5–19.9)</td>
<td>34.0 (26.8–43.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean SpO₂ (%)</td>
<td>93.4 ± 1.4</td>
<td>93.8 ± 1.8</td>
<td>92.0 ± 1.7</td>
<td>&lt; 0.002</td>
</tr>
<tr>
<td>Time &lt;90% (%)</td>
<td>5.2 ± 13.8</td>
<td>5.3 ± 10.2</td>
<td>20.5 ± 18.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ESS (per 24 h)</td>
<td>9.2 ± 5.2</td>
<td>9.0 ± 5.5</td>
<td>7.5 ± 3.9</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD; n indicates number of patients. Groups for AHI were validated using a two-way ANOVA and Bonferroni’s post-hoc test for differences between the three groups. The classical physiological modifiers of the balance of substrates during exercise measured at fasting under standardized conditions are gender [16,17] and exercise-training status. Among the diseases that modify this balance of substrates, the majority of studies report that, in obese [14,20] and T2DM [18–20] subjects, the intensity of exercise that elicits maximum lipid oxidation (also called the LIPOXmax) is markedly shifted to lower intensities with lower MFO.

Table 2
Differences between nFO rates at each step of the graded exercise test according to severity of obstructive sleep apnoea syndrome (OSAS).

<table>
<thead>
<tr>
<th>Group</th>
<th>AHI &lt; 15/h</th>
<th>AHI &gt; 15/h and &lt; 30/h</th>
<th>AHI &gt; 30/h</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td>1.59 ± 0.54</td>
<td>1.47 ± 0.51</td>
<td>1.30 ± 0.79</td>
<td>0.36</td>
</tr>
<tr>
<td>20% nP₆₄₈</td>
<td>2.89 ± 0.80</td>
<td>2.48 ± 0.87</td>
<td>1.59 ± 0.98</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>30% nP₆₄₈</td>
<td>2.78 ± 1.16</td>
<td>2.39 ± 1.06</td>
<td>1.35 ± 0.99</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>40% nP₆₄₈</td>
<td>2.26 ± 1.51</td>
<td>2.00 ± 1.22</td>
<td>0.96 ± 0.83</td>
<td>0.003</td>
</tr>
<tr>
<td>60% nP₆₄₈</td>
<td>1.07 ± 1.45</td>
<td>0.99 ± 1.06</td>
<td>0.18 ± 0.50</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD; FO rates are adjusted for lean mass (mg·min⁻¹·kgL⁻¹); group differences were assessed using one-way ANOVA and Bonferroni’s post-hoc test for differences between the three groups. The classical physiological modifiers of the balance of substrates during exercise measured at fasting under standardized conditions are gender [16,17] and exercise-training status. Among the diseases that modify this balance of substrates, the majority of studies report that, in obese [14,20] and T2DM [18–20] subjects, the intensity of exercise that elicits maximum lipid oxidation (also called the LIPOXmax) is markedly shifted to lower intensities with lower MFO.

In our present study, there was a decrease in lipid oxidation that was uncompensated for by an increase in CHO. In fact, Fig. 2 should mirror Fig. 1, and the CHO rate should be significantly greater in the group presenting with a lower FO rate to match energy requirements. However, such findings were not seen, as no differences were reported among the crude power values at

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each exercise step (Table S1; see supplementary material associated with this article online). Nevertheless, these data should be interpreted with caution. In fact, the lack of differences could be due to a type-II error. The mild-to-moderate OSAS groups exhibited almost the same balance of substrates, and the level of lipid oxidation was impaired only in the severe OSAS group. This finding probably illustrates a ‘threshold effect’ determined by OSAS severity, with the defect in lipid oxidation appearing with greater than 30 events/h. Two hypotheses favour such a threshold effect: first, the severe OSAS group had the largest neck circumferences as a result of different fat accumulation; and second, the severe OSAS group was characterized by more prolonged sleep time under conditions of hypoxia and more severe intermittent hypoxia (IH). Several studies also suggest that significant oxygen desaturation is required to produce significant metabolic impairment and cardiovascular disease [21,22].

Among the primary physiological disturbances that characterize OSAS, acute periods of hypoxic stress and sleep disruption may potentially have an impact on glucose homoeostasis. Our present study has confirmed the known relationship between the HOMA-IR and AHI \( (r = 0.82; P < 0.01) \), whereas no correlation was found between the HOMA-IR and MFO. As measurements of HOMA-IR were similar in all of our groups, this cannot explain the primary results for lipid oxidation in the present study. Regarding exposure to chronic hypoxia and IH, severe OSAS can generate a low-grade inflammatory state with increased levels of interleukin (IL)-6, tumour necrosis factor (TNF)-alpha and leptin resistance, all of which are factors involved in metabolic impairment. Under normal conditions, leptin increases muscle FO and decreases muscle fat uptake, thereby decreasing intramyocellular lipid stores [23]. In addition, IL-6 enhances glucose disposal, lipolysis and fat oxidation [24].

In a recent study in which 12 healthy subjects were exposed to 2 weeks of experimentally reproduced IH stress such as encountered in severe OSAS (30 events/h for 8 h every night), the subjects reached their MFO at a higher level of intensity at the end of the protocol [25]. This was an unexpected result and contrasts with the data from our present study. However, healthy subjects are clearly different from OSAS patients with a long history of altered metabolism and hypoxic stress. Similarly, in two studies [26,27] evaluating the effects of chronic IH in mice, the authors reported insulin resistance, increased lipid utilization and reduced CHO by muscle, although these measurements were made on resting muscle in slim mice. Nevertheless, these studies do not reflect the profound changes induced by exercise, and the ‘insulin-like’ effects that promote glucose transport and uptake by muscle, especially in sedentary subjects in whom the glycolytic pathway is relatively more developed. Furthermore, in our present study, the OSAS patients had been exposed to hypoxic stress for several years.

In addition to hypoxic stress, sleep deprivation can also increase the risk of diabetes [28,29] by decreasing leptin levels and increasing ghrelin levels [30,31]. These changes may lead to a decrease in fat-free mass during a restrictive diet, thus emphasizing the importance of sleep duration in preventing disturbances of glucose homoeostasis [32]. However, neither sleep deprivation nor sleep restriction is likely to be the main explanation for the metabolic disturbances seen in OSAS. One study attempted to mimic the sleep fragmentation classically associated with OSAS by repeatedly arousing healthy volunteers from their sleep for two nights (30–40 times/h) using auditory and mechanical stimuli [5]. This experimentally induced sleep fragmentation protocol resulted in a 20.4% decrease in the intravenous glucose tolerance test (IVGTT) insulin-sensitivity index. Nonetheless, there is a clear need for more clinical and translational research to determine whether sleep fragmentation contributes to the development of insulin resistance.

Our present results further suggest that regular exercise may be able to correct this muscle metabolism defect. Regular endurance exercise at a moderate intensity increases the ability to oxidize lipids at rest, shifting the balance of substrates oxidized over 24 h towards the oxidative use of a larger quantity of lipids [33]. Moreover, physical training has led to increases in the capacity to oxidize lipids over 24 h, which is an independent predictor of exercise-induced weight loss [34]. Finally, a recent study has suggested that regular exercise reduces the severity of OSAS [35], although there were no data on its effect on lipid oxidation.

5. Conclusion

Our present study is the first to show that, in patients with T2DM or MetS, severe OSAS is associated with an important decrease in FO during exercise, as well as with obesity, diabetes itself and growth hormone deficiency [36]. OSAS can also impair the balance of substrates during exercise. In addition, there was a negative correlation between lipid oxidation during exercise and AHI and oxygen desaturation index, suggesting a causal relationship between the alteration of lipid oxidation and
respiratory obstructive events. The next step is to investigate whether or not the treatment of OSAS (including CPAP and exercise training) can normalize lipid oxidation during exercise.

6. Author contributions

M. Desplan wrote manuscript, researched data, contributed to discussion.
J.-F. Brun wrote manuscript, researched data, contributed to discussion.
F. Pillard reviewed/edited manuscript.
C. Fedou researched data.
C. Prefaut contributed to discussion, reviewed/edited manuscript.
Y. Dauvilliers contributed to discussion, reviewed/edited manuscript.
J. Mercier contributed to discussion, reviewed/edited manuscript.
A. Avignon wrote manuscript, contributed to discussion, reviewed/edited manuscript.

Disclosure of interest

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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Appendix A. Supplementary material

Supplementary material (Fig. S1 and Table S1) associated with this article can be found, in the online version, at http://www.sciencedirect.com, at doi:10.1016/j.diabet.2011.12.002.

References


