Immediate postarousal sleep dynamics: an important determinant of sleep stability in obstructive sleep apnea

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Younes M, Hanly PJ. Immediate postarousal sleep dynamics: an important determinant of sleep stability in obstructive sleep apnea. J Appl Physiol 120: 801–808, 2016. First published December 30, 2015; doi:10.1152/japplphysiol.00880.2015.—Arousability from sleep is increasingly recognized as an important determinant of the clinical spectrum of sleep disordered breathing (SDB). Patients with SDB display a wide range of arousability. The reason for these differences is not known. We hypothesized that differences in the speed with which sleep deepens following arousals/awakenings (postarousal sleep dynamics) is a major determinant of these differences in arousability in patients with SDB. We analyzed 40 preexisting clinical polysomnography records from patients with a range of SDB severity (apnea-hypopnea index 5-135/h). Sleep depth was determined every 3 s using the odds ratio product (ORP) method, a continuous index of sleep depth (0 = deep sleep, 2.5 = full wakefulness) that correlates strongly (r = 0.98) with arousability (Younes M, Ostrowski M, Soiferman M, Younes H, Younes M, Raneri J, and Hanly P. Sleep 38: 641–654, 2015). Time course of ORP was determined from end of arousal until the next arousal. All arousals were analyzed (142 ± 65/polysomnogram). ORP increased from 0.38 ± 0.32 during sleep to 1.67 ± 0.35 during arousals, ORP immediately (first 9 s) following arousals/awakenings (ORP-9) ranged from 0.21 (very deep sleep) to 1.71 (highly arousable state) in different patients. In patients with high ORP-9, sleep deepened slowly (over minutes) beyond 9 s but only if no arousals/awakenings recurred. ORP-9 correlated strongly (r = 0.87, P < 2E-13), the arousal/awakening index (r = 0.68, P < 5E-6), and with the apnea-hypopnea index (r = 0.60, P < 0.001). ORP-9 was consistent within each patient and did not change on continuous positive airway pressure despite marked improvement in sleep architecture. We conclude that postarousal sleep dynamics are highly variable among patients with sleep-disordered breathing and largely determine average sleep depth and continuity.

odds ratio product; arousal index; obstructive sleep apnea sleep quality

AN UPPER AIRWAY THAT COLLAPSES in the absence of pharyngeal dilator muscle activity is essential for the development of obstructive sleep apnea (OSA) (28) and likely also contributes to the development of central sleep apnea (2, 29). However, the severity of the mechanical abnormality, as assessed by closing pressure, appears to play a relatively minor role in the clinical expression of upper airway instability during sleep (14, 30), which ranges from simple snoring, to recurrent apneas with variable frequency [apnea-hypopnea index (AHI) 5–150/h], to the obesity hypoventilation syndrome (OHS). Rather, the clinical outcome is primarily determined by how respiratory control mechanisms respond to the obstructive events and the threshold for arousal from sleep (see Refs. 28 and 32 for reviews).

The role of arousability in determining the clinical expression of OSA has been extensively studied (see Refs. 10, 28, and 32 for reviews). Given time without arousal, pharyngeal muscle dilators ultimately respond to the increase in chemical drive and can open the airway without arousal in most patients (15, 18, 30, 33, 34). The chemical drive at which the dilators respond [effective recruitment threshold (TER)] varies considerably between patients (18, 34). The relationship between arousal threshold and TER appears to be critical in determining the clinical outcome (28, 32).

The increase in inspiratory effort required to elicit arousal (arousal threshold) in OSA patients ranges widely from <10 to >70 cmH₂O (4, 8, 9, 21, 23, 24, 34). The reasons for this variability are not known. An improved understanding of the mechanisms that determine the arousal threshold would provide further insight into the pathogenesis of OSA, which may lead to new and innovative therapeutic strategies for this common sleep disorder.

We recently proposed a continuous index of sleep depth, the odds ratio product (ORP), with a range of zero (deep sleep) to 2.5 (full wakefulness) (35). ORP is very strongly correlated (r = 0.98) with the likelihood of an arousal/awakening (A/AW) occurring within 30 s (35). ORP allows sleep depth to be monitored continuously, every 3 s (35). Average ORP during non-rapid eye movement (REM) sleep (ORP₉₉) varied considerably between patients (0.1–1.6), reflecting the wide range of arousal threshold. While validating the ORP, we noticed considerable differences between patients in the rate at which sleep deepens (i.e., ORP declines) following A/AWs. We hypothesized that these differences may be responsible for the differences in ORP₉₉ and, hence, differences in susceptibility to arousal among OSA patients. Figure 1 presents the rationale for this hypothesis. It outlines two different ORP dynamics following an A/AW. In both cases ORP increases during the arousal and there is an immediate step decrease in ORP following the A/AW. The difference is the level to which ORP decreases immediately (first 9 s) following the A/AW (ORP-9; Fig. 1). In one case ORP decreases immediately to a very low level, where susceptibility to another arousal is very low. In the other case, ORP immediately following arousal is high and decreases slowly to a deep sleep level only if no other arousal occurs. However, since ORP remains at a high level for some time, the likelihood of another arousal occurring is high. Thus, one arousal sets the stage for another until, per chance or with continuous positive airway pressure (CPAP) therapy, no sufficiently strong arousal stimulus occurs for a sufficient period of time to allow progression to deep sleep.
METHODS

We analyzed the preexisting polysomnogram records (PSGs) of the 37 patients with sleep apnea (4 with central apnea) that were used in the ORP validation study (35) and added 4 new patients with severe OSA who received split-night studies to increase the number of studies in which we could compare ORP-9 before and during CPAP. In total, 24 patients received split-night studies. The original studies were approved by the Research Ethics Board of the University of Calgary. PSG monitoring included six EEG electrodes, chin and eye electrodes, signals from chest and abdomen bands, thermistor flow, nasal pressure, and oxyhemoglobin saturation (35). PSGs were scored by two senior technologists. For the current study, another senior technologist was asked to identify onset and end of arousals/awakenings. One patient was excluded because his awake alpha-rhythm was in the theta range, thereby corrupting the ORP calculation (see Ref. 35 for details).

Analyses: ORP values obtained from C3 and C4 signals were generated at 3-s intervals as described previously (35). Briefly, a fast Fourier transform was applied to the EEG signal. Total power in the delta, theta, alpha/sigma, and beta frequency ranges was calculated. The power in each range was assigned a rank (0–9) based on its association with one of three ranges of peak ORP during the arousals: 0.5–1.2, 1.2–1.9, and >1.9; 4) associated with one of these ranges of arousal duration: 3–10, 10–20 and 20–30 s (average ORP-9 was calculated separately for awakenings 30–180 and >180 s in duration); and 5) occurring before and during CPAP application in split studies (n = 24).

The effects of sleep stage, arousal duration, and peak arousal ORP (arousal intensity) on ORP-9 were determined by comparing (paired t-test) average ORP-9 in the different conditions in records containing data from more than one condition. The impact of different variables on average ORP-9 in each PSG was determined using multiple linear

For each A/AW in non-REM sleep we tabulated event duration and the sleep stage preceding the event (Stage). Onset and end of each A/AW were manually located in the ORP table. The highest ORP reached during arousal (peak ORP; reflecting arousal intensity), and average ORP in the 9 s following the end of A/AW (ORP-9) were obtained and tabulated. For observations with a long interarousal interval (>30 s), we tabulated ORP values from the end of the A/AW to the earlier of next A/AW or 5 min. These observations were used to determine the time course of ORP in the absence of subsequent arousals. REM arousals were not examined in view of their small number and the need to average several observations to properly evaluate ORP-9.

The rationale for using the average of three ORP values (9-s) following arousal is as follows: in preliminary analysis of the time course of ORP following arousals that were separated from the next arousal by several minutes, it was clear that there is an immediate step decrease in ORP from its peak value during the arousal and a second slow nonlinear phase (e.g., Fig. 2). In transitional states between wakefulness (or arousal) and sleep, 3-s ORP values are highly unstable (35), so that one 3-s value is not representative. It was, therefore, necessary to either average a number of epochs following the end of arousals, or obtain the corner ORP from the intercept of the nonlinear function established during long interarousal intervals. The latter approach was not feasible since long interarousal intervals (>2 min) were uncommon (<5 in some patients). A 9-s postarousal interval was chosen as a compromise because it was common to all arousals, thereby allowing a large number of determinations.

In each PSG we calculated the average ORP-9 following A/AW: 1) in the entire PSG record; 2) in different non-REM sleep stages; 3) associated with one of three ranges of peak ORP during the arousals: 0.5–1.2, 1.2–1.9, and >1.9; 4) associated with one of three ranges of arousal duration: 3–10, 10–20 and 20–30 s (average ORP-9 was calculated separately for awakenings 30–180 and >180 s in duration); and 5) occurring before and during CPAP application in split studies (n = 24).

The primary purpose of this study was to document the relationship between ORP-9 and average sleep ORP in patients with OSA. In addition, we examined the effect of arousal characteristics, sleep stage, and resolution of OSA with CPAP on ORP-9.
regression with backward elimination, eliminating the variable with the highest \( P \) value, until all remaining variables were significant \((P < 0.05)\). ORP-9 values before and during CPAP were compared (paired \( t \)-test) in split-night studies.

RESULTS

The PSGs belonged to 40 patients (21 female) with an average age of 54.2 \(\pm\) 12.4 (range 26–73) years and body mass index (BMI) of 38.2 \(\pm\) 11.5 (range 26–71). AHI ranged from 5 to 135/h (38.4 \(\pm\) 32.2). Four patients were clinically diagnosed as OHS because of gross obesity (BMI 39–56) and daytime hypercapnia and somnolence. Four other patients (3 with congestive heart failure) had central apneas (AHI 45–86/h). A/AW index ranged from 12 to 120/h (46.0 \(\pm\) 22.8/h), sleep efficiency ranged from 40 to 94% (67.9 \(\pm\) 15.3%), stage 1 non-REM sleep (N1) ranged from 3 to 55% total sleep time (TST) (22.4 \(\pm\) 13.0%), and stage 3 non-REM sleep (N3) ranged from 0 to 75% TST (15 \(\pm\) 19%).

An average 142 \(\pm\) 65 arousals and short awakenings (defined earlier and subsequently referred to as arousals) were analyzed per PSG (range 28–334). ORPNR ranged from 0.10 to 1.64 in different records (0.62 \(\pm\) 0.35). ORP increased to 1.68 \(\pm\) 0.37 during arousals (range 0.68–2.28 in different PSGs). ORP decreased immediately following arousals (ORP-9) to very different levels, including very low levels in several records (range 0.23–1.74; 0.70 \(\pm\) 0.32). In the absence of subsequent arousals, ORP decreased slowly beyond the first 9 s (Fig. 2).

Figure 3 contrasts EEG tracings from a patient whose ORP-9 was 0.31, showing fast return of ORP to a very low level following an arousal (Fig. 3A), with those from the patient with an ORP-9 of 1.01 (Fig. 3B).

Relationship between ORP-9 and average ORP during non-REM sleep. There was an excellent correlation \((r = 0.87, P = 2E-13)\) between ORP-9 and ORPNR (Fig. 4). To determine whether other variables contributed to ORPNR, multiple linear regression with backward elimination was performed with ORPNR as dependent variable and ORP-9, A/AW index (A/AWI), AHI, age, gender, BMI, arousal duration, and peak arousal ORP as independent variables. Only ORP-9 and A/AWI remained significant, accounting for 83% of variability in ORPNR. The final equation was: ORPNR \(= 0.66 \times \text{ORP-9} - 0.006 \times \text{A/AWI} - 0.14 \) \((P = 1E-16)\). Thus, for an ORP-9 of 0.3 and an A/AWI of 20, expected ORPNR is 0.19 (deep sleep), whereas with an ORP-9 of 1.0 and A/AWI of 50, expected ORPNR is 0.84 (light sleep) (35).

Relationship between ORP-9 and obstructive apnea severity. There was a highly significant correlation between pre-CPAP
CPAP essentially normalized breathing and sleep architecture and A/AWI index are values obtained prior to institution of complications. In patients who received a split study (n = 24) ORP-9, AHI and A/AWI index are values obtained prior to institution of continuous-positive airway pressure.

**Table 1. Very severe obstructive sleep apnea vs. obesity hypoventilation syndrome**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OSA</th>
<th>OHS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORP-9</td>
<td>n = 7</td>
<td>n = 4</td>
<td>3E-05</td>
</tr>
<tr>
<td>Apnea hypopnea index</td>
<td>1.30 (0.22)</td>
<td>0.40 (0.14)</td>
<td>0.01</td>
</tr>
<tr>
<td>Arousal/awakening index</td>
<td>68 (27)</td>
<td>28 (14)</td>
<td>0.02</td>
</tr>
<tr>
<td>N1, %total sleep time</td>
<td>29 (18)</td>
<td>8 (9)</td>
<td>0.03</td>
</tr>
<tr>
<td>N3, %total sleep time</td>
<td>10 (12)</td>
<td>51 (28)</td>
<td>0.003</td>
</tr>
<tr>
<td>Average SpO2</td>
<td>91 (3)</td>
<td>88 (1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Minimum SpO2</td>
<td>81 (6)</td>
<td>67 (13)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are means (SD); ORP-9, odds ratio product immediately after arousal; OSA, obstructive sleep apnea with ORP-9 > 0.9; OHS, obesity hypoventilation syndrome; N1, stage 1 non-REM sleep; N3, stage 3 non-REM sleep; SpO2, oxy-hemoglobin saturation.

(3) Their ORP-9 did not change on CPAP (0.68 ± 0.47 vs. 0.67 ± 0.36).

**Impact of sleep stage and arousal characteristics on ORP-9.** The thin lines in Fig. 7 (A–C) show average ORP-9 values within each PSG record when arousals occurred in different sleep stages, and following arousals with different intensities or durations. Overall average ORP-9 (open circles) decreased progressively as sleep stage progressed from N1 to N2 (P = 5E-12) and from N2 to N3 (P = 2E-5) and increased as arousal intensity increased from light to moderate (P = 2E-12) and from moderate to intense (P = 2E-9). It also increased with A/AWI duration (P = 1E-45 by analysis of variance for repeated measures). However, the changes in average ORP-9 were relatively small compared with the overall range of ORP-9, so that there was a very wide range of ORP-9 within any sleep stage or arousal category.

**Impact of age, gender, and BMI on ORP-9.** In univariate analysis, ORP-9 was not correlated with age (r = 0.15, P < 0.4) or BMI (r = 0.21, P < 0.2). There was no significant difference between males (0.74 ± 0.35) and females (0.65 ± 0.26, P = 0.14). Multiple regression analysis that also included AHI, A/AWI, arousal duration, peak arousal intensity, and average sleep stage in the PSG was performed to ensure that these negative results were not due to differences in associated variables that correlated with age, gender, or BMI. Again there was no significant correlation between ORP-9 and age (P = 0.25), gender (P = 0.40), or BMI (P = 0.40). When backward elimination was applied, the only variables that remained significant (P < 0.05) were A/AWI, and peak arousal intensity.

Fig. 5. A: relationship between ORP-9 and the apnea hypopnea index (AHI) in 36 patients with obstructive sleep apnea. Open circles, 4 patients with the obesity hypoventilation syndrome. B: relationship between ORP-9 and the A/AWI index in the same patients. In patients who received a split study (n = 24) ORP-9, AHI and A/AWI index are values obtained prior to institution of continuous-positive airway pressure.

Fig. 4. Relationship between ORP-9 and average non-rapid eye movement (REM) ORP in patients with sleep-disordered breathing (includes 4 patients with central sleep apnea). Each dot represents a separate patient.
Within night variability in ORP-9. During transitions from wakefulness to sleep (as in the immediate postarousal period), 3-s ORP values are highly unstable (35). Accordingly, ORP values following one or few arousals do not properly reflect the prevailing ORP-9. To counter this variability, we obtained a 10-arousal moving average of ORP-9. The standard deviation of this moving average across the night in different PSGs averaged 0.15 ± 0.06, corresponding to 6.0 ± 2.4% of full scale ORP (0.0–2.5).

Fig. 6. Response of ORP-9, apnea hypopnea index, and arousal/awakening index to continuous-positive airway pressure (CPAP) in 24 patients who underwent a split-night study. Values are means ± SD (top) of all patients. Note that ORP-9 did not change on CPAP, despite reduction in the AHI and the frequency of arousals and awakenings.

Fig. 7. Effect of sleep stage, peak ORP during arousals, and arousal/awakening duration on ORP-9. Thin lines, individual patients; open circles, average change. Note that the average effect of these variables is quite small relative to the range of ORP-9 between patients. *Significantly different from the intermediate value; †significant difference between the different groups by analysis of variance. N1, N2, and N3, non-REM sleep stages 1, 2 and 3.
The main findings in this study are that the pattern of sleep recovery following an arousal or awakening is highly variable among OSA patients and, along with the frequency and strength of arousal stimuli, determines the prevailing sleep depth during non-REM sleep and, by extension, determines susceptibility to arousal and contributes to OSA severity. Furthermore, the pattern of sleep recovery (ORP-9) appears to be predominantly an intrinsic characteristic of the individual.

Relationship between ORP{sub NR} and ORP-9. There was an excellent correlation between ORP{sub NR} and ORP-9 (Fig. 4). It may be argued that ORP-9 is dependent on ORP{sub NR}, rather than the opposite. This is very unlikely. First, in the eight patients with an above average (>0.67) ORP{sub NR} before CPAP and who improved dramatically on CPAP, ORP{sub NR} decreased from 1.08 ± 0.36 to 0.59 ± 0.22 (P < 0.005). Yet, ORP-9 did not change significantly (0.96 ± 0.35 vs. 1.06 ± 0.38; P = 0.10). Second, ORP-9 following long awakenings (>180 min) was highly correlated with ORP-9 following brief arousals (r = 0.76, P = 2E-9), despite the fact that the preawakening and postawakening ORP measurements were separated by several minutes of wakefulness.

We previously reported that ORP{sub NR} differs substantially between patients, even in the same sleep stage (35). The present results indicate that these differences in arousability are largely related to differences in postarousal sleep dynamics.

In addition to being largely determined by ORP-9 (Fig. 4), we found that ORP{sub NR} is also affected by the A/AWI, independent of ORP-9. This can be explained by the fact that, for a given ORP-9, a lower A/AWI, produced by less frequent arousal stimuli, provides more time for ORP to decline before the next arousal.

Range of ORP-9 and its relevance to OSA phenotypes. ORP-9 ranged from 0.21 to 1.71 in different patients. The probability of an A/AWI occurring within 30 s increases from 12% when current ORP is 0.20 to 50% when ORP is 1.75 (Fig. 1) (35). This indicates that arousal stimuli occur frequently but vary in intensity. When ORP is high, arousal stimuli over a wide range of intensities can trigger arousal, whereas with a low ORP only strong stimuli can do so.

The wide range of ORP-9 seen here indicates that, in some patients, sleep returns to an arousal-resistant state immediately following arousal, while in others there is only partial recovery, leaving the patient vulnerable to further arousals. This range of immediate postarousal dynamics provides a credible explanation for the wide range of clinical presentations of obstructive sleep disorders and supports the schema proposed earlier in this respect (28, 32). A high ORP-9 is the perfect setting for producing repetitive events and arousals in such patients, because a progressive arousal stimulus [negative airway pressure, asphyxia (3, 11, 13, 16)] will be initiated immediately upon resumption of sleep, during the period of high arousability. A new arousal will occur with only mild deterioration of blood gas tensions, before the dilators have had a chance to respond. Such patients would then remain normocapnic but have difficulty progressing into deep sleep unless, perchance or through position change or CPAP, an event does not occur for a minute or two, allowing ORP to decrease further and abort the cycling. This scenario is likely very common since, as opposed to earlier determinations (3, 21, 23), in most recent studies the increase in effort that results in arousal is very modest (8, 9, 24, 31, 34). By contrast, when ORP-9 is very low, the arousal stimulus associated with a new obstructive event must increase to a much higher level before an arousal occurs. In the event that reflexes manage to open the airway with relatively small increases in respiratory drive (33), the event will be terminated without arousal and breathing may stabilize (28, 32). This patient (low ORP-9 with responsive airway dilators) would become a snorer and can readily progress to deep sleep (28, 32). On the other hand, with poorly responsive dilators associated with low arousability, the airway may not open until a marked increase in respiratory drive develops. The patient may wake up despite the low arousability or may sleep through the high chemical drive. In either case, hypventilation develops (OHS) (28, 32). The finding that patients with OHS have very low arousability (Fig. 5) further supports this scenario. As seen in Table 1, by comparison to patients with very high AHI, these patients also had more deep sleep, much fewer events, and greater decreases in oxyhemoglobin saturation.

Although the number of patients with central apnea in this series was very small, their results, showing an AHI well in excess of what is expected from their arousability, are consistent with central apneas being primarily the result of an elevated chemical control loop gain as opposed to OSA, where arousability is a major underlying mechanism (26).

Determinants of ORP-9. We found no relationship between ORP-9 and age, gender, or BMI. The effect of arousal characteristics on ORP-9 was quite small relative to the wide range of ORP-9 among patients. Furthermore, the effects of sleep stage and arousal duration (<30 s) disappeared when arousal intensity was included in multiple regression analysis. Average ORP-9 changed little through the night. Thus peak ORP during arousal (arousal intensity) remains the main correlate with ORP-9 (Fig. 7).

Although it is possible that more intense arousals are followed by slower recovery dynamics, the opposite is more likely. A higher ORP-9 results in a higher sleep ORP (Fig. 4). Since ORP during arousals is higher than the prevailing sleep ORP, peak arousal ORP must increase with ORP{sub NR}. On the other hand, maximum ORP cannot exceed 2.5 (35). The combined reality that the lowest peak ORP must increase as ORP-9 increases but the maximum cannot increase dictates a good correlation between ORP-9 and arousal intensity.

These data, and the observation that ORP-9 is not altered following treatment of sleep apnea (Fig. 6), suggest that postarousal dynamics are intrinsic to each individual. This is consistent with previous observations that arousal characteristics are highly reproducible (1, 19, 20, 22) and that the tendency of some individuals to have disrupted sleep is heritable (6, 7, 12).

Wang et al. (25) reported a correlation between the improvement in Pco{sub 2} following treatment of OHS and reduction in the delta/alpha ratio of the EEG. Their finding raises the possibility that ORP-9, when measured, may be found to increase after sustained therapy in these patients. It remains to be determined whether the low ORP-9 (fast sleep dynamics) in OHS is itself a premorbid trait that leads to hypercapnia/somnolence or is a consequence of a trait that determines whether arousability will decrease in response to sustained hypercapnia. We previously reported that arousal threshold reversibly increases only in a minority of patients with severe OSA (17), suggesting that the
increase in arousal threshold in response to severe OSA is not uniform among patients. Further studies in which ORP-9 is measured before and after sustained therapy are needed to address this issue.

**Clinical implications.** The pathogenesis of OSA is multifactorial (8, 9, 24, 28, 32, 34). There is much interest in identifying the responsible factor(s) in individual patients, with the idea that targeted therapy could be used to treat the disorder (8, 9, 24, 27, 34). Easy arousability has been identified as one of these factors, and several studies have measured arousal threshold with the idea that patients with a low arousal threshold may respond to sedatives (8, 9, 24, 34). Arousal threshold in OSA is conventionally measured as the negative esophageal or pharyngeal pressure in the inspiratory effort immediately preceding arousal (3, 8, 9, 11, 23, 24). Measuring ORP-9 would provide the relevant information (arousability at the time of events) while avoiding the invasiveness of current methods. ORP-9 has the additional advantage that it can be determined from each arousal with digital automatic analysis in routine diagnostic PSGs.

At present, the only means available to pharmacologically suppress arousals is to use central nervous system (CNS) depressants. In usual therapeutic doses, sedatives or hypnotics have only a modest effect on the arousal threshold, and their impact on the AHI is small, if any (5, 8, 9, 24). Larger doses would have unacceptable side effects. The identification of postarousal sleep dynamics as the main determinant of arousability may open up a new avenue for increasing arousal threshold with the idea that patients with a low arousal threshold may respond to sedatives (8, 9, 24, 34). Arousal threshold in OSA is conventionally measured as the negative esophageal or pharyngeal pressure in the inspiratory effort immediately preceding arousal (3, 8, 9, 11, 23, 24). Measuring ORP-9 would provide the relevant information (arousability at the time of events) while avoiding the invasiveness of current methods. ORP-9 has the additional advantage that it can be determined from each arousal with digital automatic analysis in routine diagnostic PSGs.

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**DISCLOSURES**

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**AUTHOR CONTRIBUTIONS**

Author contributions: M.Y. conception and design of research; M.Y. analyzed data; M.Y. and P.J.H. interpreted results of experiments; M.Y. prepared figures; M.Y. drafted manuscript; M.Y. and P.J.H. edited and revised manuscript; M.Y. and P.J.H. approved final version of manuscript.

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