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Original Article

Characterisation of sleep disturbances in postural orthostatic tachycardia syndrome: a polysomnography-based study

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ABSTRACT

Background and Aim: Postural orthostatic tachycardia syndrome (PoTS) has been frequently associated with sleep disturbances but objective sleep data are lacking. In addition, although regional autonomic denervation has been described, less is known about autonomic nervous activity overnight in these patients.
Patients/Methods: A full polysomnography and heart rate variability were performed on 37 patients diagnosed with PoTS . In addition, a multiple sleep latency test (MSLT) was conducted on a subgroup of patients with excessive daytime sleepiness.
Results: The polysomnographic data did not show major pathological findings except the percentage spent in rapid eye movement (REM) sleep which was slightly reduced at 18.4%. The MSLT did not confirm excessive daytime sleepiness as median mean sleep latency was 14.4 min (11.8–17.5). When comparing patients with and without subjective daytime sleepiness, it was found that the latter had a reduced parasympathetic activation at night as expressed by the average high frequency [6936.5 ms^2 (6028.2–8675.5) vs. 4689.5 (3922.7–7685.2) $p < 0.05$].
Conclusion: Patients with PoTS do not exhibit polysomnographic findings consistent with relevant sleep pathologies nor objective daytime sleepiness. Subjective daytime sleepiness is associated with enhanced activation of the parasympathetic nervous system.

1. Background and aim

Postural orthostatic tachycardia syndrome (PoTS) is characterized by clinical features of orthostatic intolerance and an excessive increase in heart rate (by ≥30 or to ≥120 bpm) when upright [1].

Typical complaints include palpitations, weakness, blurred vision, chest pain, diurnal or nocturnal sweating, dizziness, presyncope, shortness of breath, tremulousness and fatigue [2].

The aetiology of PoTS remains a matter of debate. The mechanisms causing PoTS vary and include regional autonomic denervation, typically in the lower limbs [3]. Studies on patients with PoTS demonstrate signs of an attenuated response of the sympathetic nervous system (SNS) after Valsalva and other physiological manoeuvres [4,5]. Microneurographic studies performed by Bonyhay and colleagues showed that patients with PoTS exhibited a greater increase in sympathetic nerve activity (both burst frequency and burst incidence) during a hypotensive challenge with nitroprusside [6].

Therefore, the current view is that an increased sympathetic outflow response occurs in patients with PoTS during a hypotensive challenge, but the lack of a concomitant increase in mean burst area is suggestive of sympathetic denervation.

The accepted, although arbitrary, definition of PoTS does not include sleep disturbance. However, recent studies have shown that sleep problems are common in patients with PoTS [7–9].

Bagai et al. studied 44 patients with PoTS and showed that, compared to healthy subjects, they exhibited higher subjective daytime sleepiness, fatigue and worse sleep- and health-related quality of life, although no objective measures of sleep were undertaken [7]. The same group subsequently showed that patients with PoTS exhibited poor sleep efficiency as assessed by wrist actigraphy [8].

Similar findings were confirmed by Mallien et al., who undertook full polysomnography in 38 patients with a diagnosis of PoTS [9]. Polysomnographic findings did not demonstrate significant differences in terms of sleep parameters and the total sleep time, with the exception of a higher proportion of stage 2 sleep in patients with PoTS in comparison to healthy subjects. These results are somewhat surprising, given that the patients with PoTS in this study reached a significantly higher score in Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) compared to the control group.

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Despite data demonstrating alterations in peripheral sympathetic activity, few data are available on the central effects of nocturnal autonomic nervous system changes. Heart rate variability (HRV) is an indirect measure of autonomic nervous system balance through the analysis of changes in heart rate over time [10]. In healthy subjects, HRV permits the distinction between rapid eye movement (REM) and non-REM (NREM) sleep, but, in patients with PoTS, these changes are less evident, suggesting an autonomic imbalance [9]. Indeed, Mallien et al. [9] demonstrated that the known changes of HRV seen in normal subjects (higher sympathetic activation in REM sleep and greater parasympathetic activation in NREM sleep) are not present in patients with PoTS, suggesting that these patients have altered HRV at night.

The aim of this study was to objectively assess patients with PoTS with polysomnography in order to understand if subjective daytime sleepiness can be objectively verified. An additional aim was to understand the relationship between autonomic nervous system imbalance at night, derived from HRV, and perceived daytime sleepiness.

2. Patients and methods

Patients diagnosed with PoTS were seen in our Sleep Centre (Guy's and St. Thomas' Sleep Disorders Centre, London, UK) between January 2012 and December 2014 for assessment. All patients were seen by a sleep physician, and demographic data were recorded along with past medical history. Subjective daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) [11].

All patients with a definite diagnosis of PoTS according to the standard criteria were included [12]. Patients with electrocardiogram (ECG) abnormalities, incomplete/corrupted PSG data or those unable to undergo polysomnographic assessment were excluded from this study. For the analysis, patients were divided into two groups: those without subjective daytime sleepiness (ESS ≤ 10), and those with subjective daytime sleepiness (ESS > 10).

All clinical studies conformed to the principles of the Declaration of Helsinki. The study was approved by the local institutional review board (registration number: 4593).

2.1. Polysomnography

All participants underwent full nocturnal polysomnography (NPSG) (Embla® N7000), and the montage included frontal (F3 and F4), central (C3 and C4) and occipital (O1 and O2) electrodes with auricular reference electrodes, two electro-oculographic channels, two submental electromyographic channels, ECG, electromyographic channel on anterior tibialis bilaterally, pulse oximetry, nasal cannula, and respiratory inductance plethysmography with chest and abdominal belts. Sleep stages were scored by expert sleep technologists using 30-sepochs according to standard criteria by the American Academy of Sleep Medicine [13].

All NPSGs were analysed with Embla® RemLogic™ PSG Software, and standard sleep indexes were calculated: total sleep time (TST), sleep efficiency (SE), wake after sleep onset (WASO), sleep latency (SL), REM sleep latency (REML), number of awakenings, percentage of each sleep stage over total sleep time, oxygen desaturation index (ODI), apnoea–hypopnoea index (AHI), mean oxygen saturation, total arousals, arousal index (AI), limb movements (LM), limb movement index per hour of sleep (LMI), periodic limb movements (PLMs) and periodic limb movement index per hour of sleep (PLMI).

2.2. Multiple sleep latency test

A subgroup of the patients with subjectively recorded daytime sleepiness (ESS > 10) underwent multiple sleep latency test (MSLT) following the NPSG. Using frontal (F3 and F4), central (C3 and C4) and occipital (O1 and O2) electrodes for the montage, with auricular reference electrodes, two electro-oculographic channels, two submental electromyographic channels and electrocardiography, the MSLT was performed according to standard guidelines [14].

Using 30-s epochs according to standard criteria of the American Academy of Sleep Medicine [13], sleep stages were scored by the expert sleep technologists. Each patient underwent four or five naps, with a 2-h interval between them.

The MSLT was performed in the morning following the NPSG if at least 6 h of polysomnographically defined sleep was recorded, no evidence of other sleep pathology was present and the patient had been off any sleep-affecting drug for at least 15 days. A sleep log or actigraphy for a 2-week period prior to the MSLT was also required.

All MSLTs were analysed to determine the mean sleep latency (MSL) and number of sleep-onset REM periods (SOREMPs).

2.3. Heart rate and HRV analysis

The following heart rate parameters were derived from the NPSG ECG recording: mean heart rate, supine heart rate, non-supine heart rate, REM heart rate and NREM heart rate. HRV data were calculated from the ECG traces extracted from NPSG recordings.

All ECG traces were visually controlled for artefacts and extra systoles. HRV was analysed by the Embla® RemLogic™ PSG Software according to the 'Recommendations of the International Federation of Clinical Physiology for the Practice of Clinical Neurophysiology' [15,16].

The following time domain indexes were calculated: Average RR interval (ANN); Standard Deviation of NN intervals (DSNN), which reflects total HRV; Average of 5-min standard deviations of NN intervals, which reflects average short-term HRV and combined SNS and parasympathetic nervous system (PNS) influences (SDNNIDX); Root mean square of successive differences of NN intervals which reflects vagal activity with normal sinus rhythm (rMSSD); Percent of NN intervals >50 ms different from previous NN, which reflects vagal activity with normal sinus rhythm (pNN50); Standard deviation of AVNN for 5-min intervals, which reflects primarily circadian HRV (SDANN).

A fast Fourier transform (FFT)-based algorithm was used for the spectral analysis of HRV to calculate the frequency domains. Spectral analysis allows discrimination between sympathetic and parasympathetic activation, which are represented by the low-frequency (LF) and the high-frequency (HF) components of the HRV signal. The LF band reflects a combination of sympathetic and parasympathetic influences and baroreflex function, whilst the HF band reflects parasympathetic activity. The resulting LF to HF ratio serving as a quantitative index of the sympathovagal balance was calculated.

The following frequency domain indexes were calculated: Total power, which reflects total HRV (TP); very-low-frequency power which measures rhythms between 0.003 Hz and 0.04 Hz, reflecting vagal and renin–angiotensin system effects on HR (VLF); low-frequency power, measuring HR rhythms from 0.04 Hz to 0.15 Hz, averaged over 5 min or less, reflecting the combination of SNS and PNS influences as it captures baroreflex rhythms (LF); and high frequency power, capturing variations in HR due to respiratory sinus arrhythmia at 0.15–0.4 Hz and, under normal circumstances, reflecting vagal activity (HF). The calculated low-frequency to high-frequency ratio (LF/HF) reflects the SNS/PNS balance.

2.4. Statistical analysis

Statistical analysis was performed using the SPSS statistical analysis programme (SPSS 17.0). Data are reported as median and interquartile range as non-normally distributed. Patients with normal

and high ESS were compared with a non-parametric *t*-test. Regression analysis was conducted to understand the determinants of frequency domain HRV parameters: LF, HF and LF/HF were analysed as dependent variable, whilst age, sex, BMI and ESS were the independent variables.

A $p < 0.05$ was considered to be statistically significant.

3. Results

This study included 47 patients diagnosed with PoTS; seven were excluded due to lack of NPSG, one due to corrupted NPSG data and two patients were excluded as the HRV analysis could not be performed due to ECG abnormalities. Finally, analysis was conducted on 37 patients.

3.1. Demographic data

Table 1 summarises the baseline characteristics. Our cohort of patients was predominantly non-obese young females (30 females, median age 27 years, median BMI 23.6 kg/m^2). Patients totalling 27% had Ehlers–Danlos syndrome type III; chronic fatigue syndrome, asthma and migraines were each seen in 8.1% of patients. Coexisting depression, fibromyalgia, and irritable bowel syndrome were each seen in 5.4% of patients. Epilepsy or overt autonomic dysfunction was seen in 2.7% of patients. The median ESS was 13 (7.5–16) points, and 16 patients (43.2%) had an ESS >10 implying subjective EDS. Only one patient had significant sleep-disordered breathing accounting for a prevalence of 2.7%. None of the patients had significant periodic limb movements.

3.2. Polysomnographic data

The polysomnographic data showed a median total sleep time of 374.5 min with a sleep efficiency of 83.4% (Table 2). Respiratory indexes were within the normal range, and sleep latencies were slightly delayed (median sleep latency 17.9 min and REM sleep latency 135.25 min).

Patients spent normal percentages of time in sleep stage 1 (N1), sleep stage 2 (N2), and sleep stage 3 (N3) sleep, whilst percentage spent in REM was slightly reduced at 18.4%. Limb movement statistics showed a number of limb movements of 57.5 across the night and limb movement index and periodic limb movement index were within normal limits.

Table E1 shows the analysis of nocturnal heart rate and HRV in the on line supplement.

Table 1
Demographics and co-morbidities of the patients studied expressed as median and IQ range (square brackets) or as an absolute number and percentage (round brackets).

Patient characteristics ($n = 37$)	
Age (years)	2700 [20–32]
Sex (M/F)	07/30
BMI (kg/m^2)	23.6 [20.8–26.4]
ESS (points)	13 [7.5–16]
Co-morbidities	
Ehlers–Danlos syndrome(n and %)	10 (27)
Irritable bowel syndrome(n and %)	2 (5.4)
Chronic fatigue syndrome(n and %)	3 (8.1)
Migraine(n and %)	3 (8.1)
Depression(n and %)	2 (5.4)
Fibromyalgia(n and %)	2 (5.4)
Asthma(n and %)	3 (8.1)
Epilepsy(n and %)	1 (2.7)
Autonomic dysfunction(n and %)	1 (2.7)

Table 2
Polysomnographic data of the patients in the study expressed as median and IQ range (square brackets) or as an absolute number and percentage (round brackets).

Polysomnographic data	
Total sleep time (minutes)	374.5 [321–436]
Wake after sleep onset (minutes)	42.6 [26.3–88.8]
Sleep efficiency (%)	83.4 [67.4–90.4]
Number of awakenings	23 [17–27]
Sleep latency to N1 (minutes)	17.9 [9.5–40.5]
Sleep latency to REM (minutes)	135.25 [90.5–185.5]
Apnoea-hypopnoea index (events/hour)	0.1 [0–0.5]
Oxygen desaturation index (events/hour)	0 [0–0.5]
N1 sleep of total sleep time (%)	8.4 [5.5–12]
N2 sleep of total sleep time (%)	44.1 [37.2–51.7]
N3 sleep of total sleep time (%)	26.8 [21.4–36.5]
REM sleep of total sleep time (%)	18.25 [13.9–19.7]
Total arousals (n)	101 [66–145]
Arousal index (events/hour)	18.4 [13.1–22.7]
Mean oxygen saturation (%)	96.6 [95.6–97]
Limb movement statistics	
Limb movements (n)	57.5 [33–93.5]
Limb movement index (events/hour)	9.75 [5.8–15.1]
Periodic limb movements (n)	2 [1–5.2]
Periodic limb movement index (events/hour)	0.3 [0.1–0.8]

3.3. Multiple sleep latency test data

In a subgroup of patients [$n = 14$, 12 females, median age 56 (19.5–27), median BMI 24.2 (21.1–27.6)] with ESS >10 [16 (13.2–17.7)], additional MSLT was performed.

The MSLT data did not show evidence of objective daytime sleepiness or polysomnographic features of central hypersomnia: the mean sleep latency (MSL) was 14.4 min [11.8–17.5], and 13 of the 14 patients did not enter REM sleep in any of the naps. Only one patient exhibited one SOREMP during four naps; in this patient, the resulting MSL was normal at 14.6 min, again not suggesting EDS.

3.4. Comparison between subgroups with and without excessive daytime sleepiness

Fourteen patients had an ESS ≤10 whilst 22 had an ESS >10. The two subgroups were matched for age and BMI. Females were overrepresented in the group with an increased ESS (64.2% vs. 90.9%, $p < 0.05$) (Table 3).

Polysomnographic data of the two groups did not differ significantly, although there was a trend towards an increased proportion of N3 sleep in patients with an ESS < 10 in comparison to the group of sleepy patients. Comparison of HRV data of the two subgroups showed that patients with a normal ESS had a reduced parasympathetic activation at night as expressed by the decreased average HF in comparison to subjectively sleepy patients [4689.5 (3922.7–7685.2), vs 6936.5 (6028.2–8675.5), $p < 0.05$] (Table 4).

3.5. Regression analysis

Multiple regression analysis was performed using the average HF and LF and the LF to HF ratio as dependent variables. Age, sex, BMI, and ESS were the independent variables. ESS was an independent predictor of both average HF and LF but not of LF to HF ratio (standardized β-coefficients 0.389 and 0.411, respectively, $p < 0.05$) (Table E2 – Online supplement).

In addition, age was an additional independent predictor of both HF and LF to HF ratio (standardized β-coefficients – and 0.457 respectively, $p < 0.05$) and sex was an independent predictor of average LF and LH/HF ratio (standardized beta coefficients –0.512 and –0.480, respectively, $p < 0.01$).

Table 3
Demographic and polysomnographic data of the two subgroups expressed as median and IQ range (square brackets). One patient was not included in the analysis as the patient did not complete the ESS form.

Demographic data	ESS ≤10 (n = 14)	ESS >10 (n = 22)	P value
Age (years)	23 [20–29.2]	27 [20.2–32.7]	0.703
Sex (M/F)	5/9	2/20	0.049
BMI (kg/m^2)	23.4 [20.5–25.4]	24.2 [21.4–27.2]	0.927
Polysomnographic data			
Total sleep time (minutes)	352.3 [313.8–444]	382.2 [339.3–419.7]	0.861
Wake after sleep onset (minutes)	51.6 [29.5–82.4]	34.2 [24.1–84.6]	0.625
Sleep efficiency (%)	81 [63.8–90.7]	84.8 [69.5–90.2]	0.721
Number of awakenings	22 [15.5–26]	25 [18.2–27]	0.618
Sleep latency to N1 (minutes)	15 [9.6–40]	18.4 [9.8–34.2]	0.829
Sleep latency to REM (minutes)	109.8 [89.5–158]	138.5 [100–186.5]	0.568
Apnoea–hypopnoea index (events/hour)	0.1 [0–0.4]	0.1 [0–0.5]	0.789
Oxygen desaturation index (events/hour)	0 [0–0.4]	0.2 [0–0.4]	0.567
N1 sleep of total sleep time (%)	9.5 [6.9–12]	6.9 [4.5–11]	0.895
N2 sleep of total sleep time (%)	40 [36.3–44.7]	47.1 [41.6–52.2]	0.103
N3 sleep of total sleep time (%)	30 [25.2–41.2]	25.7 [18.7–31.3]	0.074
REM sleep of total sleep time (%)	18.3 [14.1–20.8]	17.7 [13.7–19.1]	0.991
Total arousals (n)	98 [69.5–140.7]	103.5 [66–143.5]	0.821
Arousal index (events/hour)	15.7 [13.2–28.8]	19 [12.9–22.6]	0.779
Mean oxygen saturation (%)	96.8 [96.3–97.3]	96.3 [95.4–96.7]	0.265
Limb movement statistics			
Limb movements (n)	73.5 [49.2–96.5]	57 [27–88]	0.332
Limb movement index (events/hour)	12.1 [7.5–17]	8.4 [5.6–14.1]	0.295
Periodic limb movements (n)	2 [1–6.5]	2 [1–5]	0.971
Periodic limb movement index (events/hour)	0.3 [0.1–0.9]	0.3 [0.1–0.8]	0.875

4. Discussion

This polysomnography-based study contributes to the current knowledge of sleep quality in patients with PoTS. In this cohort of patients, a high proportion of individuals presented with subjective complaints of EDS as assessed with the ESS (43.2%). These data were consistent with the data from Bagai et al. study where the prevalence of subjective daytime sleepiness was 51% [7]. Polysomnographic results did not demonstrate relevant sleep pathologies and, importantly, the MSLT did not confirm objective EDS in the subgroup of 14 patients with subjective EDS.

This discrepancy is of clinical interest, as a different approach to EDS in patients with PoTS could be suggested. Indeed, patients with PoTS do complain of fatigue which may be misinterpreted as daytime sleepiness [2]. However, although the MSLT is viewed as the gold standard for objective measurement of EDS, it is well known that there is poor agreement between the MSL and ESS, which may simply be a reflection of the multidimensional nature of sleepiness [17]. In addition, MSL values vary in different disease populations [18]. Significantly shorter MSL values are seen in narcolepsy, allowing for strong discriminatory power in the right clinical context, but studies on MSL ranges in different disease populations are essential [19].

Comparison of sleepy and non-sleepy patients with PoTS did not demonstrate differences in sleep parameters. However, on comparing HRV, average HF was greater in patients with an ESS >10, suggesting that patients with subjective complaints of daytime sleepiness exhibit increased parasympathetic activity at night compared with patients with no EDS. In a similar study, Lombardi et al. [20] compared patients with and without daytime sleepiness and found that patients with daytime sleepiness had a reduced baroreflex sensitivity and an increased cardiac sympathovagal balance over the whole night, with an impaired modulation of the LF to HF power ratio among sleep stages. They did not find significant differences in HF or LF. However, it is important to note that this cohort of patients had sleep-disordered breathing which could alter the sympathovagal balance during the night and therefore have a significant impact on HRV.

The pathogenesis of EDS in patients with sleep disorders is still a matter of debate. Several studies in patients with obstructive sleep apnoea have found no correlation between EDS and the frequency of apnoea–hypopnoea episodes, the minimum level of nocturnal oxygen saturation or the number of intermittent hypoxemic episodes at night [21], and the only determinant thus far identified remains sleep fragmentation [22].

In our study, however, the degree of sleep fragmentation as represented by the number of awakenings and the arousal index was similar in patients with PoTS with or without EDS, and so does not provide a ready explanation. The arousal index was notably only slightly elevated at 18.4 events/hour, when compared to normative values, and did not differ significantly between patients with and without daytime sleepiness. The only identified differences between the two groups were the HRV measures of parasympathetic activity, reinforcing the hypothesis that deranged cardiac vagal modulation is related to EDS through a complex interaction between dysfunctions in cerebral regions responsible for sleep regulation, daytime vigilance, and autonomic cardiovascular control [20].

Table 4
Heart rate variability (HRV) data of the two subgroups expressed as median and IQ range (square brackets). One patient was not included in the analysis as the patient did not complete the ESS form.

HRV data	ESS ≤10 (n = 14)	ESS >10 (n = 22)	P value
Average RR interval (milliseconds)	939.5 [810.2–1058]	927.5 [836.2–970.2]	0.76
NN standard deviation (milliseconds)	99.5 [61.7–116.7]	107 [91–120.7]	0.99
NN standard deviation index (events/hour)	73 [39.5–102.5]	74 [63–99.5]	0.88
Root mean square of successive differences (milliseconds)	73 [33–98]	56 [46.2–82]	0.57
NN50% count (n)	2544 [841.5–12060.7	6485.5 [3081–11021.7]	0.75
Percent NN50 of total heart rate	8.1 [3.8–48.6]	23.3 [10.3–37.8]	0.88
Standard deviation of all 5-min RR interval means (milliseconds)	75 [48.2–113.7]	61.5 [55.2–84]	0.19
Average total power (milliseconds^2)	26932.5 [19588.7–37640.7]	33270 [23746.7–42741.2	0.22
Average very-low-frequency power (milliseconds^2)	9478 [7213.5–15288.5]	12033.5 [7699.7–16058.7]	0.59
Average low frequency power (milliseconds^2)	9173.5 [5691–15537.7]	11918 [8472.7–17507]	0.38
Average high-frequency power (milliseconds^2)	4689.5 [3922.7–7685.2]	6936.5 [6028.2–8675.5]	0.04
LF/HF ratio	1.6 [1.3–2.6]	1.7 [1.4–2.2]	0.29

This study also confirmed that there are sex- and age-related differences in autonomic modulation of heart rate variability in a cohort of patients with PoTS. This has been already demonstrated in healthy subjects [23] and in patients after myocardial infarction [24].

This study has limitations. Our sample of patients was probably not representative of the sleep characteristics of the whole population of patients with PoTS, because only those with sleep complaints in the first instance were referred for assessment. Furthermore, clinical experience also suggests that some patients with sleep disturbance in PoTS have a clinical picture of psychophysiological insomnia, for which polysomnographic assessment is not clinically indicated. Due to the potential influence of a 'first-night effect' [25] because of the lack of an adaption night, the results of polysomnography need to be interpreted with caution.

However, to our knowledge, our cohort, as with the patients studied by Mallien et al. [9], is the largest cohort of patients with PoTS assessed with full polysomnography. The intriguing finding of differences in measures of autonomic function, between those patients with and without subjective EDS, raises the possibilities either that altered parasympathetic activity precipitates sleepiness, or that sleep disruption due to unknown underlying mechanisms alters autonomic function in these patients. Certainly, it is essential to conduct a more systematic examination of these findings, perhaps by adding the analysis of autonomic arousals.

5. Conclusion

This study suggests that patients with PoTS often complain of subjective EDS which does not seem to be backed up by either polysomnographic confirmation of relevant sleep pathologies or objectively recorded daytime sleepiness. Subjective daytime sleepiness is associated with enhanced activation of the parasympathetic nervous system, implying a possible association between sleep and altered autonomic nervous system in patients with PoTS.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.08.003.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.sleep.2015.08.003.

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