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Abrupt Shift of the Pattern of Diurnal Variation in Stroke Onset With Daylight Saving Time Transitions

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Background—Stroke onset shows a pattern of diurnal variation, with a peak in morning hours. Rhythmic changes in blood pressure, hormones, and other parameters have been suggested as underlying mechanisms, but exogenous factors such as increasing physical activity after awakening may also be of relevance. To characterize the impact of external clock changes on the rhythmic variation in stroke onset, this parameter was recorded in patients during transition periods into and out of Daylight Saving Time (DST).

Methods and Results—The present study was based on a prospective stroke registry in Germany that contains time points of stroke onset from 44 251 patients admitted between 2000 and 2005. To achieve a uniform timeline, time points of stroke onset were set back from Central European Summer Time (CEST) to Central European Time (CET) for patients admitted during DST periods. Compared with the last week before the clock change, transition to or from DST resulted in an immediate shift of stroke onset time points within the first week after the clock change in reference to the uniform timeline (transition from CET to CEST -60 minutes for the time points in both the 25th and 50th percentiles of the diurnal pattern, $P<0.001$; transition from CEST to CET $+60$ minutes for the time points in both the 25th and 50th percentiles, $P<0.001$; patients pooled on a weekly basis). A significant shift was already present the first and second day after the transitions (ie, Monday and Tuesday).

Conclusions—Transition to or from DST is coupled with an immediate shift in the time pattern of stroke onset. This strengthens the idea that exogenous factors associated with awakening are important determinants of the pattern of diurnal variation of stroke onset, because entrainment of the human circadian clock within hours is unlikely. (*Circulation*. 2008;118:284-290.)

Key Words: circadian rhythm ■ stroke ■ patients

Stroke onset shows a characteristic pattern of diurnal (day/night) variation, with a peak occurring during morning hours.¹⁻³ A large number of publications have focused on identifying the underlying pathophysiological mechanisms and have reported rhythmic variation in blood pressure, vascular tone, platelet function, blood viscosity, fibrinolysis, cerebral vasomotor activity, and concentrations of hormones and coagulation factors to be of relevance in this context.³⁻¹³ Furthermore, time-of-day-dependent variations in neuronal vulnerability to cerebral ischemia may also provide an explanation for temporal differences in stroke onset.^{14,15} Most of these rhythms are governed by the circadian clock, which generates an endogenous rhythm via clock genes that interact in transcriptional/translational feedback loops.¹⁶⁻²¹ The rhythmic variation in stroke onset may thus reflect the impact of the circadian clock. In addition, exogenous factors such as increasing physical activity after awakening in combination with gaining an upright body position have been discussed as factors that influence the timing of stroke

onset.^{3,22} However, some authors have raised concerns about the rhythmic nature of stroke onset, pointing out the possibility that the observed morning peak in stroke onset might be at least in part an epiphenomenon that mirrors the time point (ie, the morning hours) at which as yet undetected nighttime strokes are diagnosed.²³

Clinical Perspective p 290

Daylight saving time (DST) is used in many countries far from the equatorial zone to gain daylight in the evening by the convention of advancing clocks.²⁴ Typically, clocks are advanced 1 hour near the start of spring and are adjusted backward in autumn. Transition into or back from DST constitutes a sudden and arbitrary interference with the natural time pattern in which noon is approximately coincidental with the local culmination time of the sun. The present study was performed to characterize the effects of external clock change on the rhythmic pattern of stroke onset and to gain insight into which factors and mechanisms are its most relevant determinants.

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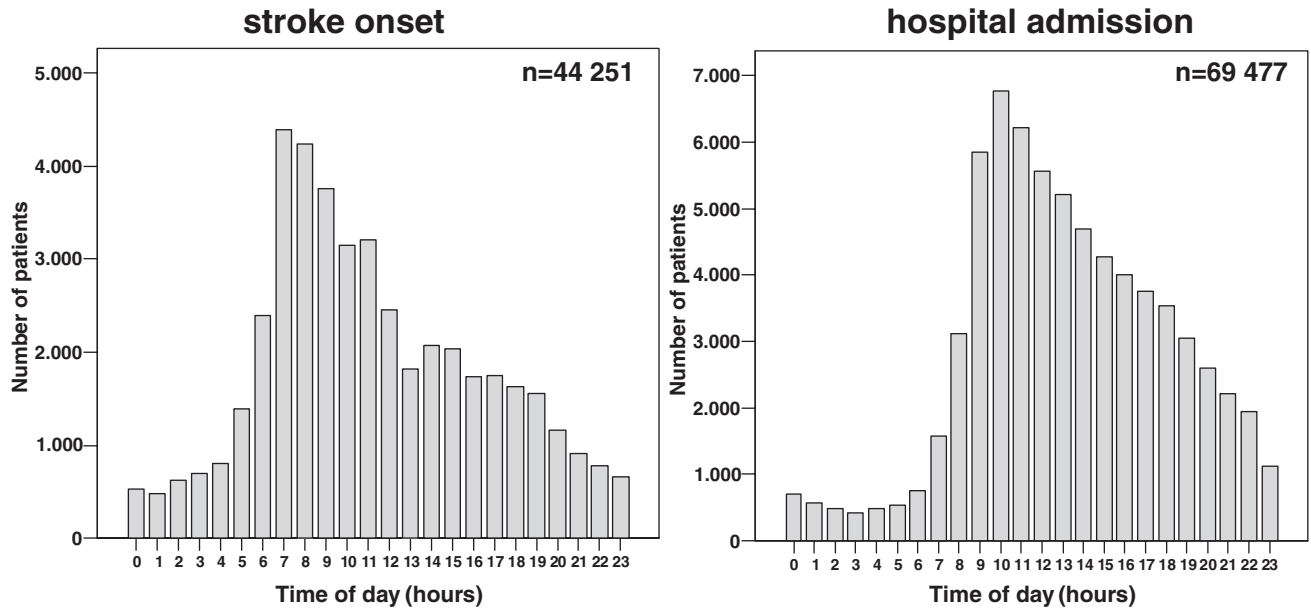


Figure 1. Diurnal pattern of stroke onset and hospital admission (raw data, ie, CET in non-DST periods and CEST in DST periods, categorized on an hourly basis).

Methods

Stroke Registry

The present study was based on a large prospective stroke registry provided by the Arbeitsgruppe Schlaganfall Hessen (Stroke Study Group of Hesse; for details, see www.gqhnet.de).²⁵ This standardized, computerized registry is a countrywide quality-assurance measure based on state law in which all hospitalized stroke patients are supposed to be documented anonymously. Informed consent was not required before enrollment in the registry. At present, more than 100 hospitals participate in enrolling patients with a final diagnosis of transient ischemic attack (International Classification of Diseases, 10th Revision code G45), ischemic stroke (International Classification of Diseases, 10th Revision code I63), or intracerebral hemorrhage (International Classification of Diseases, 10th Revision code I61). All parameters relevant to the present analysis, including admission date, admission time, time of symptom onset (if known), gender, age, and severity of clinical symptoms on hospital admission (assessed with the modified Rankin scale), are recorded prospectively. For the present analysis, we screened data sets from patients admitted to the hospital between January 1, 2000, and December 31, 2005 ($n=85\,868$). The time of hospital admission was reported in $n=69\,477$ data sets, and this information was used for inclusion in the present study. In addition to the time of hospital admission, $n=44\,251$ data sets also reported the time of stroke symptom onset.

Daylight Saving Time

In the European Union, Central European Time (CET, Coordinated Universal Time plus 1 hour) was transitioned into Central European Summer Time (CEST) for the following DST periods: March 26 to October 29, 2000; March 25 to October 28, 2001; March 31 to October 27, 2002; March 30 to October 26, 2003; March 28 to October 31, 2004; and March 27 to October 30, 2005. For every period, DST started after advancement of the clock from 2:00 AM CET to 3:00 AM CEST on the spring index day and ended after the clock was set back from 3:00 AM CEST to 2:00 AM CET on the autumn index day.

Statistical Analysis

To gain a uniform CET timeline, the time points of symptom onset and hospital admission were set back from CEST to CET values for patients admitted during DST periods. In the first step, we aimed to assess how stable the pattern of diurnal variation is over time and how this pattern is influenced by external clock change. To do so, we

pooled patients according to their admission dates on a weekly basis over a 5-week period that either ended 1 day before the clock change or began 1 day after the clock change. Public holidays scheduled on weekdays (eg, Good Friday, Easter Monday) were excluded. Time points of both symptom onset and hospital admission were calculated in minutes after midnight. For descriptive purposes, the time points that reflected the 25th and 50th percentiles of the respective diurnal pattern were determined. The Mann-Whitney U test and Kruskal-Wallis test were used for statistical comparison of the overall diurnal patterns.

In a second step, we focused on characterizing the pattern of diurnal variation within the first week after external clock change to identify any gradual or stepwise adjustment. To do so, we pooled all patients admitted on the first and second day (ie, Monday and Tuesday) or on the fourth and fifth day (ie, Thursday and Friday) after the clock change and compared the time points of their symptom onset and hospital admission with those of the patients admitted on Monday/Tuesday or Thursday/Friday during the last 5 weeks before the clock change.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Mean age of the patients was 72 ± 13 years, and 50.2% were female. Twenty-five percent of the patients were documented as having transient ischemic attack, 64% as having ischemic stroke, and 8% as having intracerebral hemorrhage, whereas 4% could not be classified. Forty-five percent revealed slight to moderate neurological deficits on hospital admission (modified Rankin scale 0 to 2), and 54% had moderate to severe deficits (modified Rankin scale 3 to 5; 1% not classified). Seventy-six percent of patients were classified as having arterial hypertension and 29% as having diabetes mellitus.

Figure 1 displays the diurnal variation of the time points of symptom onset ($n=44\,251$) and hospital admission ($n=69\,479$) for the entire data set (raw data, ie, CET in non-DST periods and CEST in DST periods). For both stroke onset and hospital admission, a diurnal rhythm with a

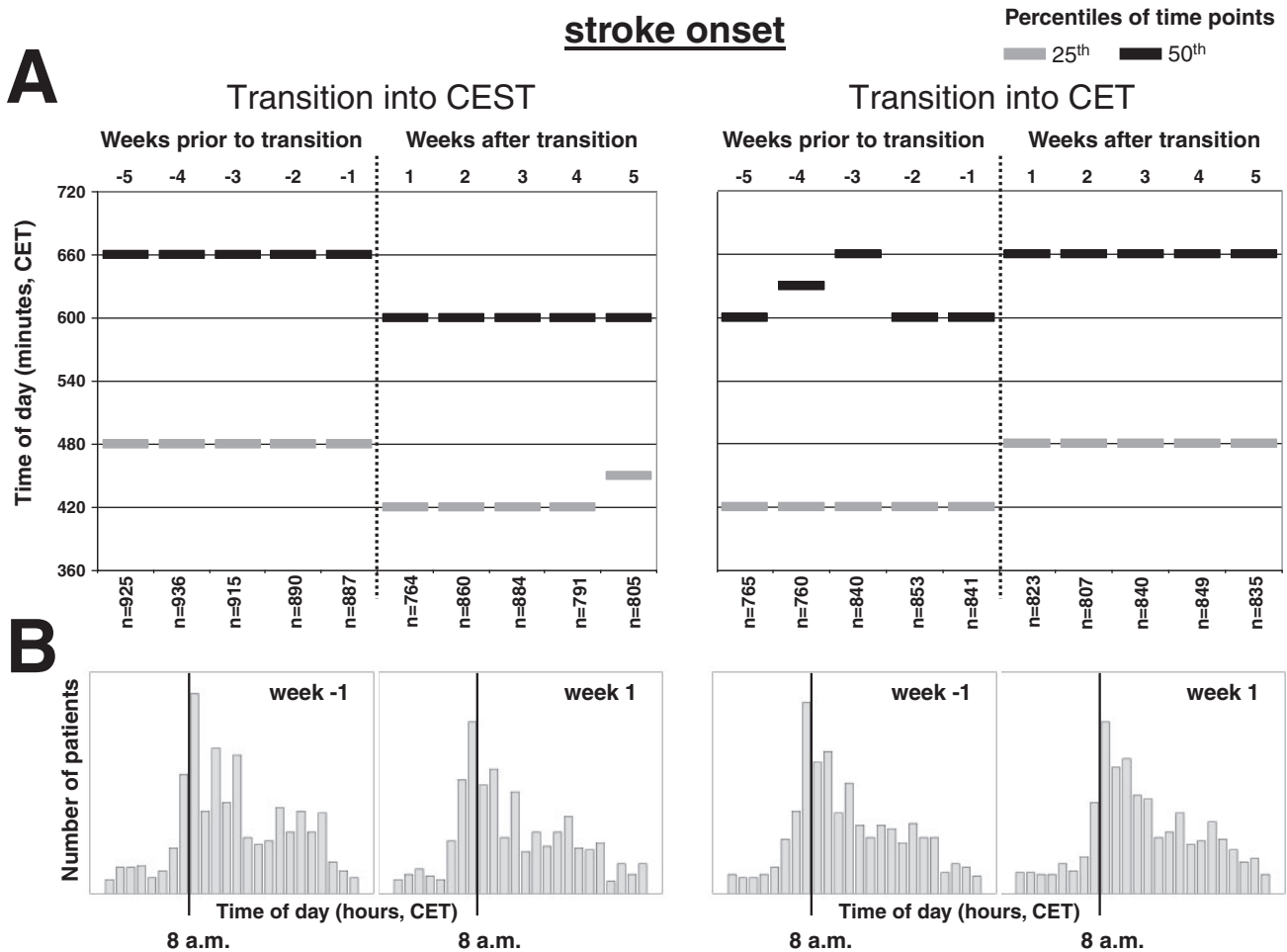


Figure 2. Shift of the time points of stroke onset during transition into and back from CEST. Patients were pooled on a weekly basis. A uniform timeline was established by referencing the time points from patients documented in DST periods to CET. A, Time points are given in minutes after midnight. Bars represent the time points in the 25th (gray) and 50th (black) percentile of the diurnal pattern, respectively. N indicates number of patients per week. B, Frequency diagrams plotting the number of patients vs the time of day (categorized on an hourly basis) for the last week before the transition and the first week thereafter. The 1-hour shift of the morning peak is easy to discern.

morning peak was obvious. The time point that reflected the 25th percentile of the diurnal pattern of stroke onset corresponded to minute 480 after midnight (8:00 AM), and the time point that reflected the 50th percentile corresponded to minute 660 after midnight (11:00 AM). The respective values of the time points of hospital admission were minute 650 after midnight (10:50 AM) and minute 823 after midnight (1:43 PM).

As shown in Figures 2 and 3, the pattern of diurnal variation of stroke onset and hospital admission was found to be stable within the 5-week periods before and after the external clock change (Kruskal-Wallis test, all $P=NS$); however, transition into DST resulted in a highly significant advancement of the time points of stroke onset within the first week after external clock change compared with the last week before the time shift, in reference to the uniform time line (ie, CET timeline; -60 minutes for the time points in both the 25th and 50th percentiles of the diurnal pattern; Mann-Whitney U test, $P<0.001$). Conversely, setting the external clock back from CEST to CET at the end of the DST periods delayed the time points of stroke onset significantly (by 60

minutes, respectively; $P=0.001$) within the first week after external clock change. Respective values for the time points of hospital admission were -46 and -23 minutes for the transition into DST (from CET to CEST; $P<0.001$) and 53 and 36 minutes for the transition back from CEST to CET ($P<0.001$). The shift of the time points of symptom onset and hospital admission remained significant when we selected males, patients with ischemic stroke, and patients with moderate and severe neurological deficits, respectively (Table).

A comparison of the pattern of diurnal variation on the first and second day (ie, Monday and Tuesday) after external clock change with that on Mondays and Tuesdays of the 5 weeks immediately preceding the clock change revealed a significant shift for the time points of both symptom onset and hospital admission (all $P<0.05$; Figure 4). The extent of this shift did not change on the fourth and fifth day (Thursday and Friday) after external clock change (values from the first and second day were compared with those of the fourth and fifth day and were assessed by means of z values derived from Mann-Whitney U tests; Figure 4). Thus, the difference in diurnal profiles between the DST and non-DST groups was

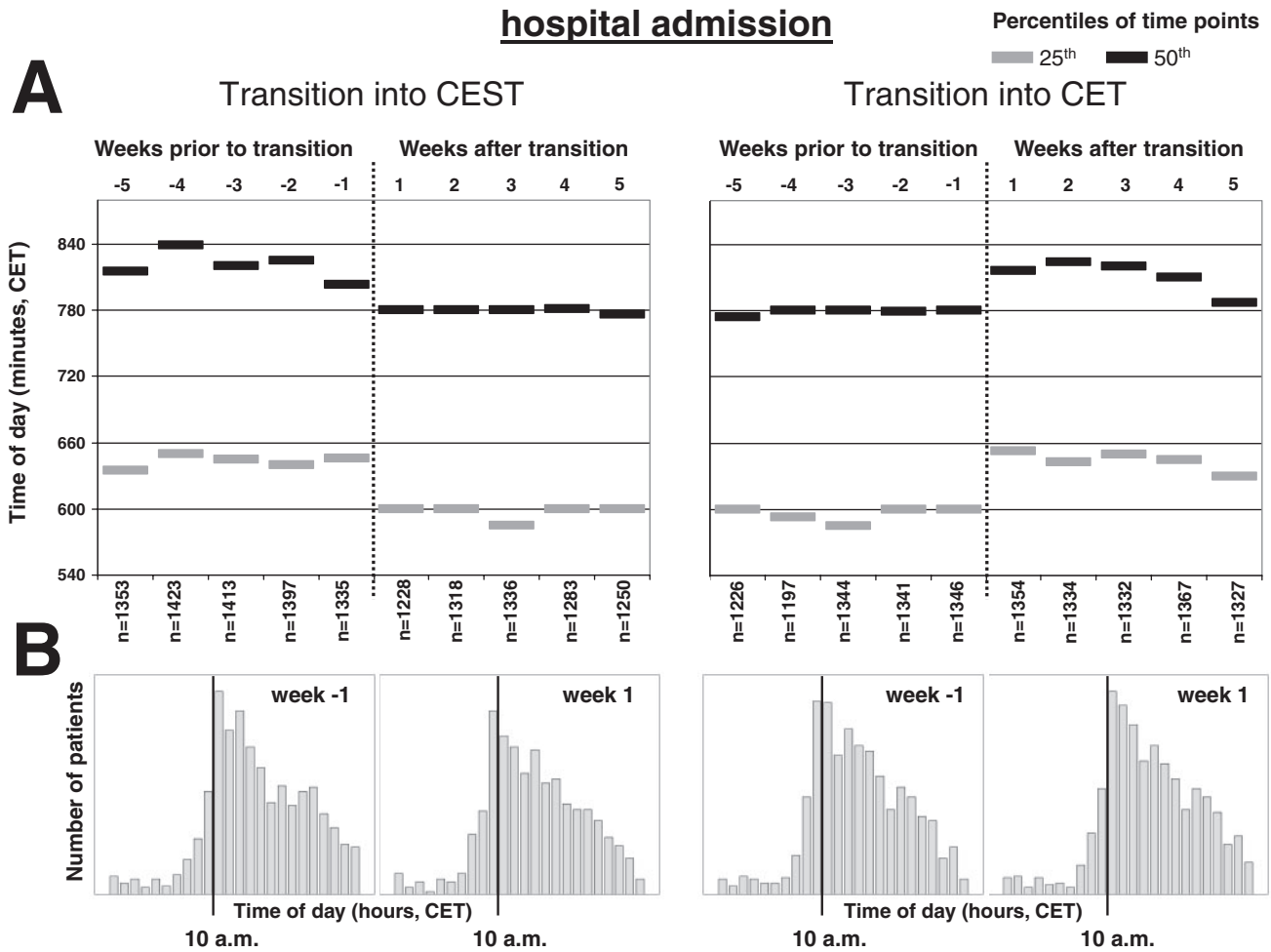


Figure 3. Shift of the time points of hospital admission during transition into and back from CEST. For more details, see Figure 2.

already evident on the first 2 days after external clock change and did not tend to increase further within the first week.

Finally, we performed a cross-check and compared the diurnal pattern of stroke onset on the first and second day

after external clock change with that on Mondays and Tuesdays of the last 5 weeks before the clock change using the “raw” time points of stroke onset as documented in the registry (ie, CET values in non-DST periods and CEST

Table. Shift of Time Points in the 25th and 50th Percentiles of the Pattern of Diurnal Variation of Stroke Onset and Hospital Admission During Transition to and From DST

	Transition into CEST			Transition into CET		
	25th Percentile	50th Percentile	<i>P</i>	25th Percentile	50th Percentile	<i>P</i>
Δ Time of symptom onset, min						
All	-60	-60	<0.001	60	60	0.001
Males	-60	-60	0.005	60	60	0.002
Ischemic stroke	-60	-60	0.003	60	60	0.003
mRS 3–5	-60	-60	0.003	60	90	0.003
Δ Time of hospital admission, min						
All	-46	-23	<0.001	53	36	<0.001
Males	-57	-49	<0.001	44	15	0.021
Ischemic stroke	-56	-20	<0.001	45	18	0.005
mRS 3–5	-40	-19	0.002	39	30	0.029

mRS indicates modified Rankin scale.

For DST periods, CEST values were counted back to CET values to gain a uniform CET timeline. The comparison was performed between the last week before the external clock change and the first week thereafter (patients pooled on a weekly basis). The figures express the difference between the respective percentiles. *P* values result from Mann–Whitney *U* test.

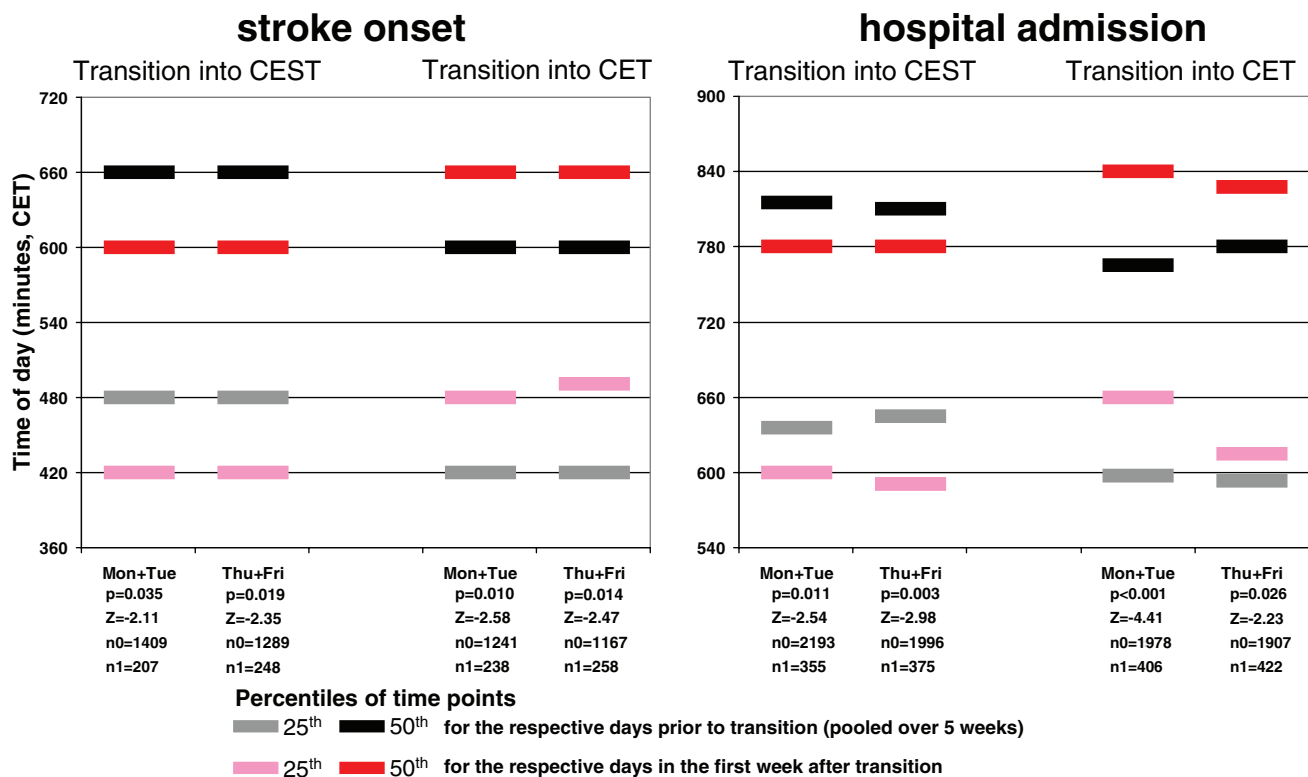


Figure 4. Comparison of the rhythmic pattern of time points of stroke onset and hospital admission on the first and second (ie, Monday and Tuesday [Mon+Tue] and the fourth and fifth (ie, Thursday and Friday [Thu+Fri]) days after the clock change with that recorded on Mondays/Tuesdays and Thursdays/Fridays within the last 5 weeks before the clock change. The gray and black bars indicate time points in the 25th and 50th percentiles before the shift, respectively; pink and red bars indicate time points in the 25th and 50th percentiles after the shift, respectively. *P* values and *z* values are derived from Mann–Whitney *U* comparisons. *N* indicates number of patients per group.

values in DST periods). Despite a 1-hour advancement of the external clock during the transition from CET into CEST, a significant shift of stroke-onset time points was not obvious (0 minutes for the time points in both the 25th and 50th percentiles of the diurnal pattern; $P=0.540$). Respective values for the transition back from DST to CET were also 0 minutes ($P=0.855$).

Discussion

In concordance with previous publications, the present investigation confirms that the time points of both stroke onset and hospital admission reveal a characteristic rhythmic day/night pattern, with a peak in the morning hours.^{1–3} The large number of patients in the present database provided a unique opportunity for studying how these time patterns are influenced by the transitions into and back from DST. The major finding of the present study is that external clock changes from CET to CEST and vice versa evoked immediate shifts of the time points of stroke onset when the time points were referenced to a baseline time system (CET). This finding is of interest for consideration of the mechanisms that underlie the rhythmic pattern of stroke onset.

Several physiological systems and parameters, such as the cardiovascular system, blood pressure, platelet function, serum concentrations of circulating hormones and coagulation factors, blood viscosity, fibrinolytic activity, and cerebral vasomotor activity, reveal a characteristic pattern of day/night

rhythmicity, predominantly peaking during the morning hours.^{3–13} These rhythms are under control of the circadian system that generates endogenous rhythms with a period length of ≈ 24 hours (in humans, 24.2 hours) by molecular clocks comprising clock genes that interact in transcriptional/translational feedback loops.¹⁶ Under natural conditions, the circadian system is entrained to the 24-hour period of the astrophysical day by external stimuli called “zeitgebers.” The most important zeitgeber is the photoperiod, ie, the change between night and day. In humans and mammals, photoperiodic information is transmitted to the circadian clock via the photopic and scotopic systems in the retina and a special set of photoreceptors that are located in the ganglion layer of the retina and that use melanopsin as a photopigment.^{26–29} The transition to or from DST investigated here does not change the environmental photoperiod but represents a social cue. The issue of whether social cues may act as zeitgebers capable of entraining/phase shifting the human circadian system remains controversial.³⁰ Some authors have reported that social cues have negligible, if not zero, direct drive on the human circadian system.³¹ Assuming that social cues would not affect the human circadian clock, the present results suggest that changes of the external clock elicit a direct (masking) effect on rhythmic body functions such as the sleep-wake cycle. In modern civilizations, the sleep-wake cycle is firmly synchronized to the time of the external clock, and external clock change is likely to abruptly shift the

sleep-wake cycle of most individuals. Thus, the sleep-wake cycle and factors associated with awakening, including an increased physical activity, gaining a posture body position, and diagnosis of thus far undetected nighttime strokes, may be critical determinants of the diurnal time pattern of stroke onset. In our opinion, the latter point is particularly strengthened by the finding that heterogeneous types of stroke (ie, ischemic stroke, intracerebral hemorrhage, and transient ischemic attack) and different subtypes of ischemic stroke (ie, cardioembolic, large artery, and lacunar) all show a very similar pattern of diurnal variation of stroke onset despite a considerably different pathophysiology.^{1-3,23} Unfortunately, it was not explicitly stated in the present database how many patients noticed their symptoms at the time of awakening. Thus, further studies are needed to investigate the influence of reduced awareness during sleep on the morning peak of stroke onset and hospital admission.

We cannot rule out the possibility that the changing of the external clock represents a zeitgeber that entrains the human circadian clock. If so, this entrainment by a social cue would occur rather rapidly, ie, within the first 24 hours after the stimulus provided by the external clock change. Notably, a rapid entrainment of the human circadian clock (within 24 hours) has also been observed when light stimuli at nighttime were applied as zeitgebers and shifts in melatonin rhythms were analyzed as readouts.³²

Missing data constitute a limitation of the present study. Although documentation is mandatory for all hospitals in Hesse, Germany, it is likely that a certain proportion of stroke patients were not registered. For instance, we cannot rule out that patients arriving during the night were less often documented than daytime patients. However, the present study did not investigate the diurnal profile of stroke onset and hospital admission per se but focused on profile shifts associated with DST transitions. It would be unreasonable to assume that patients were more likely to be entered into the database before the DST transition than afterward, or vice versa. Thus, we do not believe that missing data would have significantly influenced the present results.

In summary, the present study is the first to demonstrate that transition into or out of DST is coupled with an immediate shift of the time pattern of stroke onset. This suggests that exogenous factors associated with awakening are important determinants of the pattern of diurnal variation of stroke onset. As an alternative explanation, a rapid entrainment of the human endogenous clock within hours is unlikely. Future studies may investigate whether the diurnal variations in the frequency of onset of acute myocardial infarctions are influenced by external clock changes in a similar way.³³

Disclosures

None.

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CLINICAL PERSPECTIVE

In the present study, we analyzed the influence of Daylight Saving Time transitions on the circadian pattern of stroke onset and identified abrupt shifts of stroke onset time points in reference to the time effective before the transitions. Simply put, after the transition into Daylight Saving Time, patients appeared to have their strokes roughly 1 hour earlier than in the weeks before, whereas the transition back from Daylight Saving Time into standard time delayed stroke onset for \approx 1 hour. Our investigation suggests that the circadian profile of stroke onset is coupled with the actual time of day. In modern civilizations, the sleep-wake cycle is firmly synchronized with the actual time of day, and clock change is likely to abruptly shift the sleep-wake cycle of most individuals. Thus, the sleep-wake cycle and factors associated with awakening (eg, the identification of as yet unrecognized nighttime strokes) appear to be the most important determinants of the diurnal pattern of stroke onset. Conversely, it is well known that physiological parameters such as blood pressure, platelet function, serum concentrations of circulating hormones, and coagulation factors reveal a pattern of diurnal rhythmicity that is governed by the molecular clock and clock genes. However, the rapid shift of stroke onset time points after Daylight Saving Time transitions does not support the hypothesis that these endogenous factors play a major role in determining the circadian profile of stroke onset, because an entrainment of the human circadian clock within hours is unlikely.