Recurrence risk of ictal asystole in epilepsy

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ABSTRACT

Objective: To determine the recurrence risk of ictal asystole (IA) and its determining factors in people with epilepsy.

Methods: We performed a systematic review of published cases with IA in 3 databases and additionally searched our local database for patients with multiple seizures simultaneously recorded with ECG and EEG and at least one IA. IA recurrence risk was estimated by including all seizures without knowledge of the chronological order. Various clinical features were assessed by an individual patient data meta-analysis. A random mixed effect logistic regression model was applied to estimate the average recurrence risk of IA. Plausibility of the calculated IA recurrence risk was checked by analyzing the local dataset with available information in chronological order.

Results: Eighty patients with 182 IA in 537 seizures were included. Recurrence risk of IA amounted to 40% (95% confidence interval [CI] 32%–50%). None of the clinical factors (age, sex, type and duration of epilepsy, hemispheric lateralization, duration of IA per patient) appeared to have a significant effect on the short-term recurrence risk of IA. When considering the local dataset only, IA recurrence risk was estimated to 30% (95% CI 14%–53%). Information whether IA coincided with symptoms (i.e., syncope) or not was given in 60 patients: 100 out of 142 IAs were symptomatic.

Conclusion: Our data suggest that in case of clinically suspected IA, the recording of 1 or 2 seizures is not sufficient to rule out IA. Furthermore, the high short-term recurrence risk favors aggressive treatment, including pacemaker implantation if seizure freedom cannot be achieved.

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GLOSSARY

CI = confidence interval; **IA** = ictal asystole.

Ictal asystole (IA) is a rare but potentially devastating complication of epileptic seizures, affecting about 0.3% of patients with refractory epilepsy who underwent video-EEG monitoring.[1] Most recent studies define IA as an RR interval longer than 3 seconds.[1–3] IA can cause traumatic falls due to syncope with sudden loss of muscle tone.[2–4] IA should not be diagnosed based on clinical grounds only, as its symptoms can easily be obscured by other ictal signs.[2,5] Identification of IA, however, has important clinical implications, because the implantation of a cardiac pacemaker may prevent syncope-related falls and injuries.[3,6] Therefore, simultaneous video-EEG and ECG is required to establish diagnosis when IA is clinically suspected.[2] However, to date, the recurrence risk remains unclear and it is therefore not known how many seizures one should record in order to confirm or reject the clinical hypothesis of IA.[7] In this study, we aimed to estimate the recurrence risk and potential influencing factors in patients with IA during simultaneous EEG and ECG recordings.

Editorial, page 756

Supplemental data at Neurology.org

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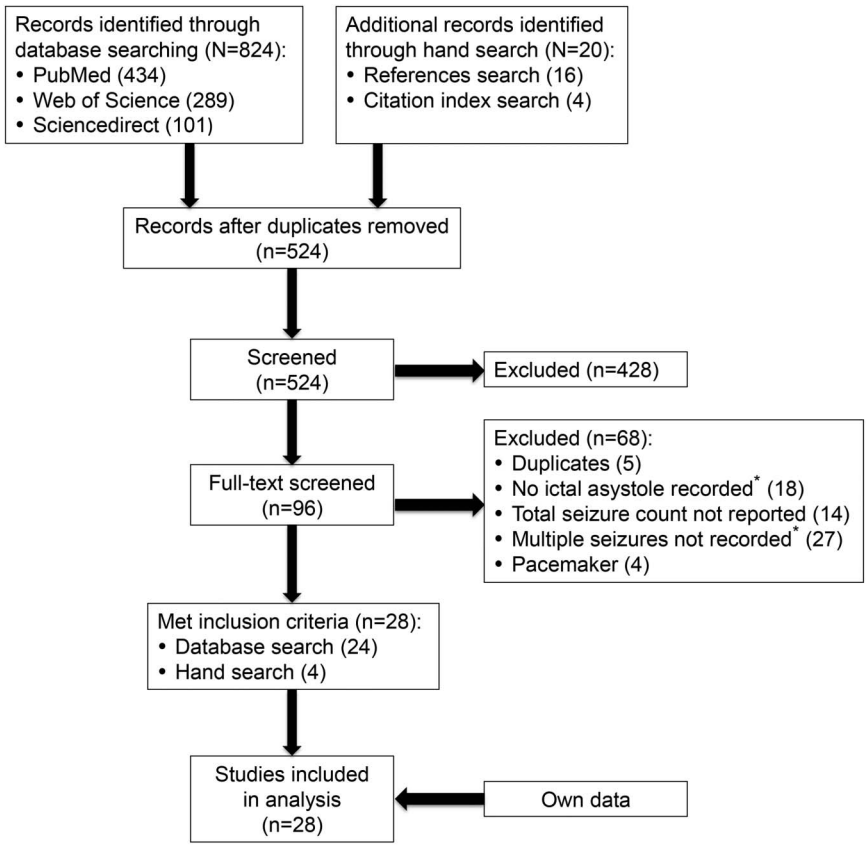
METHODS **Literature search strategy and data acquisition.** We systematically reviewed the literature using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and the Patient Intervention/Exposure Comparison Outcome criteria.[8,9] We used a combination of the following keywords: (1) arrest or asystole or syncope, (2) epilepsy, (3) human, (4) electrocardiogram or ECG or monitoring, and (5) electroencephalogram or EEG or monitoring. Publications were identified in 3 of the databases: PubMed (first date available to February 9, 2016), Web of Science (first date available to February 15, 2016), and ScienceDirect (first date available to February 1, 2016) (figure 1A). K.G.H. screened all titles and abstracts. K.G.H. and R.S. independently screened the 96 full-text articles. Furthermore, a hand search of the reference lists and citation indices of these articles was performed. In addition, we searched our database at the Department of Epileptology (Bonn, Germany) for patients with IA during video-EEG or long-term EEG recordings from January 1, 1993, to December 31, 2015. If available, original records were reviewed; otherwise, data were taken from previously published case series from our center.[10,11] IA was defined as RR interval longer than 3 seconds and at least twice as long as the previous RR interval.[4] The inclusion criteria for the final analysis were (1) epilepsy patients with at least one IA simultaneously recorded with EEG and ECG, (2) more than one seizure simultaneously recorded with EEG and ECG, and (3) report of the total number of recorded seizures and IAs. Exclusion criteria were seizures induced by electrical stimulation (during presurgical assessment using intracranial EEG electrodes), intoxication, status epilepticus, subclinical seizures, nonepileptic events, pacemakers, and acute diseases like encephalitis. The study reporting was done in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines.[12]

Standard protocol approvals, registrations, and patient consents. This work was carried out in accordance with the local ethics committee and the Declaration of Helsinki. Due to the retrospective nature, no informed consent was required.

Statistical analysis. We applied a random mixed effect logistic regression model using adaptive Laplace approximation to estimate the average recurrence risk of IA and to evaluate possible influencing factors.[13] We have chosen to perform an individual patient data meta-analysis instead of a regular meta-analysis, as this approach allowed us to evaluate possible influencing factors on an individual patient level.[14] The null model was used to estimate the average risk for recurrence of IA. As dependent variable we entered occurrence of IA as the binary outcome (1 indicating presence and 0 indicating absence of IA) into the model. As fixed effects, we entered sex, type of epilepsy (temporal or extra temporal), hemispheric lateralization (left, right, or bilateral), age, duration of epilepsy, and mean duration of IA per patient. In addition, we adjusted for the total number of seizures recorded per patient to control for a possible bias; this was because we observed a decreasing risk of IA with increasing numbers of recorded seizures per patients. As random effects, we included patients to account for nonindependence in the data (more than one seizure from the same patient). The variables were selected by forward and backward selection. Quantitative variables were

Figure 1 **Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of search strategy and study selection**



*With at least 1 ictal asystole and more than 1 seizure simultaneously recorded with EEG and ECG.

handled as continuous data and missing data were handled by performing available-case analysis. In addition, to validate our results, we performed a regular random-effects meta-analysis using restricted maximum likelihood to estimate the average recurrence risk of IA. For most published cases, we lacked information on the chronological order of the seizures with and without IA. Therefore, we estimated IA recurrence risk by analyzing all seizures and IA including the index IA. To check for plausibility, we additionally calculated the IA recurrence risk using the local dataset from Bonn for which information on chronologic order was available. In this particular analysis, all seizures occurring before the index IA as well as the index IA (that led to the inclusion of the patient) were excluded from the calculation. Statistical analysis and graphical presentation were performed with R version 3.1.3 (R Foundation of Statistical Computation, Vienna, Austria).

RESULTS Selection process and search strategy. The comprehensive search strategy resulted in 844 articles (figure 1). After removing duplicates, 524 titles and abstracts were screened. We excluded 428 articles because they did not meet the inclusion criteria. Afterwards, we performed full text screening on the remaining 96 articles; from those, 68 were removed for the following reasons: 27 studies did not record or

Table 1 Study characteristics

Study reference[a]	No. of patients[b]	No. of IAs	No. of seizures	No. of sIAs	Definition of IA	Duration of IA, s
S1	1	5	9	5	No	8-21
S2	1	4	13	NR	No	3-9
S3	1	2	4	NR	No	~16
16	9	25	55	14	RR interval >3 s and ≥2-fold as the previous one	3-48
S5	2	7	10	NR	No	10-96
S6	1	3	3	NR	No	~27
S7	1	1	5	NR	No	8
S8	1	3	3	NR	No	8.5-24.5
7	5	9	30	5	RR interval >4 s	4-36
S10	1	2	3	NR	No	8-9
S11[c]	1	1	3	NR	No	4
S12	1	4	4	1	No	39-40
S13	4	8	30	NR	No	9-25
S14	1	2	2	2	No	8-10
S15	1	1	5	NR	No	16
2	9	26	103	26	RR interval >3 s	3-25
Own data	9	15	32	5	RR interval >3 s and ≥2-fold as the previous one	4-28
S17	1	1	2	NR	No	22
5	1	2	7	2	No	21-28
S20	2	3	8	3	No	10-30
S21	1	3	3	3	No	7-8
S22	3	4	51	NR	No	4.6-18
4	9	20	53	7	RR interval >3 s and ≥2-fold as the previous one	3.9-26
S24	1	1	5	NR	No	19
S25	1	2	2	NR	No	22-29
3	10	24	86	23	RR interval >3 s	3-33
S27	1	3	3	3	No	24-38
S28	1	1	3	1	No	20
Total	80	182	537	100	6/28	

Abbreviations: IA = ictal asystole; NR = not reported; sIA = reported symptomatic ictal asystole.
[a] For full references, see supplemental material.
[b] With at least 1 ictal asystole and more than 1 seizure simultaneously recorded with EEG and ECG.
[c] One IA was excluded due to a duration of 2 seconds.

report more than one seizure simultaneously with ECG and EEG, 18 studies had not recorded any IA occurring simultaneously with ECG and EEG, and 14 studies did not report the total number of recorded seizures. Furthermore, 5 case series were removed, because they were subsequently included in larger studies. Finally, 4 cases recorded after implantation of a pacemaker were excluded, because this intervention prevented IA. A total of 28 studies (13 case reports and 15 case series) met the inclusion criteria. In addition, 9 patients from our local database were included in the final analysis after removing duplicates from 2 previously published case series from our center.[10,11]

Included studies and patient characteristics. A total of 80 patients from 28 studies with 182 IAs in 537 seizures simultaneously recorded with ECG and EEG were included (including 9 patients with 15 IAs in 32 seizures from our local database; table 1). Six studies provided a precise definition of IA. Table 2 summarizes the clinical data of the included patients.

Recurrence risk of IA and potential influencing factors. On average, the short-term recurrence risk of IA amounted to 40.4% (95% confidence interval [CI] 32.4%–49.8%). This result was verified by the random-effects meta-analysis, which yielded a similar short-term IA recurrence risk of 43.7% (95% CI 34.2%–53.7%). When considering the local dataset only (for which information on chronological order of IA occurrence was available and that allowed exclusion of seizures prior to the index IA), IA recurrence risk was estimated as 30% (95% CI 14%–53%) (see table e-1 at Neurology.org for more detailed analysis).

The recurrence risk of IA seemed to decrease with the total number of recorded seizures per patient (figure 2A). None of the clinical factors (age, sex, type and duration of epilepsy, hemispheric lateralization, duration of IA per patient) appeared to have a significant effect on the recurrence risk of IA (table 2). Figure 2B shows the distribution of the number of IA vs the total number of recorded seizures per patient. Importantly, information on whether IA was symptomatic (i.e., associated with syncope) was given in 60 patients with 398 seizures (table 1). In these 60 patients, a total of 142 IAs occurred, of which 100 were symptomatic. The proportion of symptomatic vs asymptomatic IA in those with recurring IA amounted to 63.8% (95% CI 55.7%–72.8%).

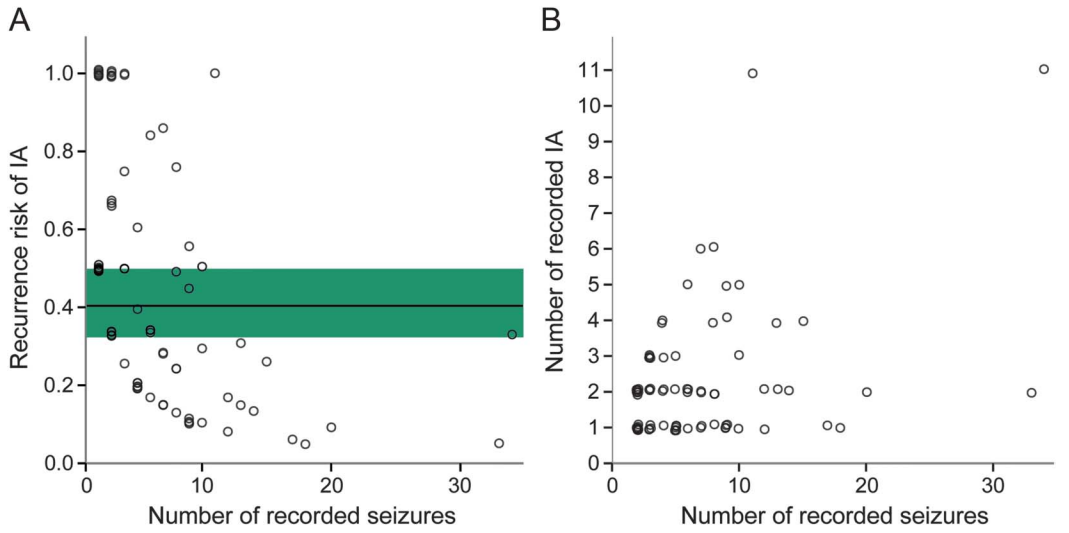
DISCUSSION The exact mechanism of IA is not fully understood, but may be due to involvement of

Table 2 Summary data of clinical characteristics

Variable	Mean ± SD	OR (95% CI)[a]	*p* Value[a]	OR (95% CI)[b]	*p* Value[b]
Age, y	40.1 ± 15.7 (9 NR)	1.01 (0.99–1.04)	0.34	1.01 (0.99–1.03)	0.17
Duration of epilepsy, y	17.1 ± 14.7 (11 NR)	0.99 (0.96–1.02)	0.46	0.99 (0.97–1.02)	0.70
Average asystole duration per patient, s	15.8 ± 13.3 (12 NR)	1.01 (0.96–1.05)	0.78	1.01 (0.98–1.04)	0.38
No. of patients[c]					
Sex					
Female[d]	31				
Male	40	0.98 (0.42–2.27)	0.97	1.39 (0.72–2.69)	0.33
NR	9				
Epilepsy type					
Temporal lobe epilepsy[d]	60				
Extratemporal lobe epilepsy	9	1.84 (0.52–6.55)	0.34	0.86 (0.33–2.26)	0.76
NR	11				
Hemispheric lateralization					
Left[d]	28				
Right	23	1.20 (0.53–2.71)	0.66	0.71 (0.33–1.52)	0.38
Bilateral	14	2.23 (0.84–5.90)	0.11	1.49 (0.62–3.56)	0.37
NR	15				

Abbreviations: CI = confidence interval; NR = not reported; OR = odds ratio.
[a] According to the full model with all variables (complete cases n = 38).
[b] Each variable tested separately corrected for the variable seizure count (for age, n = 71; for duration of epilepsy, n = 69; for mean asystole duration per patient, n = 68; for sex, n = 71; for epilepsy type, n = 69; for hemispheric lateralization, n = 65).
[c] Total number of patients = 80.
[d] Reference levels of the model.

Figure 2 Distribution of recurrence risk of ictal asystole (IA) and of number of IAs

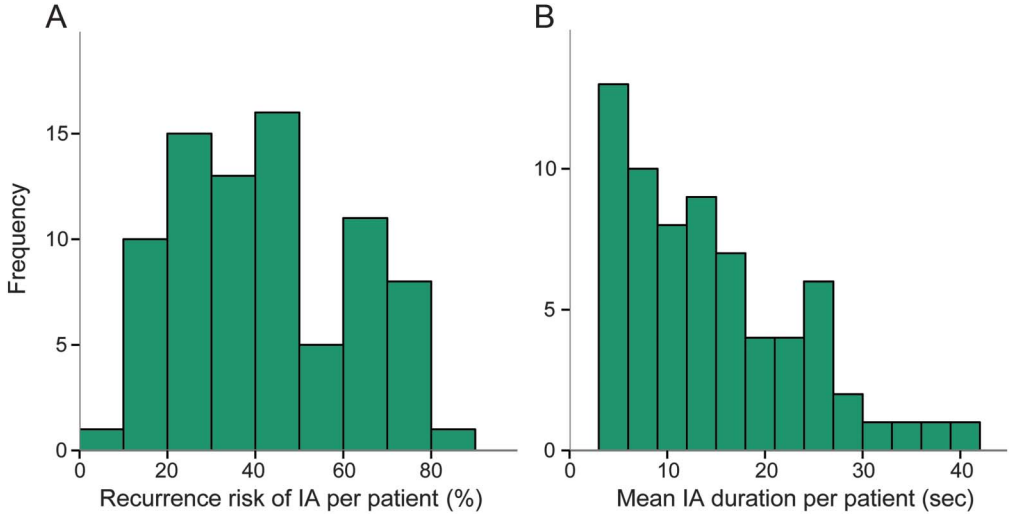


(A) Individual recurrence risk of IA is plotted vs the total number of recorded seizures per patient. A jitter was used to avoid overplotting. The black line indicates the estimated average recurrence risk of IA with the 95% confidence interval (blue rectangle). (B) Individual number of IAs is plotted vs the total number of recorded seizures per patient.

the central autonomic network, which controls the parasympathetic and sympathetic output, or alternatively involvement of vasovagal reflex pathways.[1,15] We did not find any correlation between side of seizure onset and occurrence of IA or recurrence risk. We found that in cases of recorded IA during video-EEG telemetry, the recurrence risk of IA varied from patient to patient (figure 3A), but amounted to 40% on average. This result was verified by the regular meta-analysis. The small difference in the estimate and CI can be explained by the different method and the additional clustering structure for the variable studies. However, testing the additional random effect for the variable studies in the random mixed effect logistic regression model did not improve the model fit. Therefore, we used the simpler model with a random effect for the variable patients only. None of the studied clinical features predicted an increased recurrence risk of IA.

Our study has some limitations. First, patient and seizure characteristics were only partially reported in the included articles. This possibly reduces the power to detect a significant effect on the recurrence of IA outcome. Therefore, we cannot rule out that we have

Figure 3 Histograms of the individual recurrence risk of ictal asystole (IA) and of mean IA duration per patient



(A) The individual IA recurrence risk (as calculated by the model in %, bin size 10%) is plotted vs the absolute frequencies. (B) The mean IA duration per patient (in seconds; bin size 3 seconds) is plotted vs the absolute frequencies. One observation with an IA of 96 seconds is not included in the graph.

overlooked weak to moderate effects of potential influencing factors. Second, we included studies with different definitions of IA or studies that lacked one (table 1).[2–4,6,16] Because information on the duration of IA was missing, we could not verify in all reported IA which definition was used. However, the summary data showed that most IA lasted longer than 4 seconds and thus met all definition criteria for IA (table 2 and figure 3B). In addition, of all studies that provided information on seizure characteristics, only one asystole had to be excluded due to duration of only 2 seconds. Thus, the lack of definition of IA in most studies had no major influence on our results. Third, an effect of anticonvulsants and their reduction during the monitoring period on the risk of recurrence of IA cannot be ruled out. Furthermore, publication bias may be present. For example, one may expect that cases with higher recurrence risk are more likely to be reported. This might be particularly true for case reports in which only severe seizure-related syncope are described. We assessed this issue by separately analyzing recurrence risk of IA in patients from our local database, yielding a recurrence risk of 53.7% (95% CI 28.2%–77.4%), which is even higher than the estimated risk of the composite data. This finding argues against an overestimation due to publication bias. Another legitimate concern is the lack of information on the chronological order of the seizures with and without IA in most published cases. Therefore, we estimated the recurrence risk both by including and by excluding the index seizure with IA in all seizures and in the seizures from the local database only (table e-1). Importantly, the most conservative calculation yielded an IA recurrence risk of 30% (95% CI 14%–53%), which largely overlaps with the estimation including all available seizures, suggesting that our results are plausible. In this context, it is also important to note that the included reports did not consistently provide information on whether IA was asymptomatic or whether IA was associated with clinical symptoms or syncope. Thus, given the smaller number of reported symptomatic IAs, we are unable to calculate a valid estimation of the recurrence risk of IA-related syncope. Furthermore, temporal lobe epilepsy is likely to be overrepresented in the analyzed studies, because it is more frequently investigated with video-EEG monitoring in an epilepsy surgery setting. Finally, the apparent recurrence risk of IA seems to decrease with higher number of recorded seizures (figure 1B). Patients with fewer seizures recorded tended to have a higher risk than those in whom more seizures were recorded. In addition, in most patients only a few seizures per patient were recorded. Thus, one might think that this study could overestimate the risk of recurrence of IA. However, this observation is most probably not directly related to the total number of seizures recorded, but more likely due to patient selection: in patients with higher risk of IA, physicians were less likely to have recorded more seizures. Instead, these patients would have been referred to cardiology for pacemaker implantation. Taken together, we believe that our study population represents a rather typical mixture of patients with refractory epilepsy seen at specialized epilepsy centers.

The short-term recurrence risk of IA is high and amounts to 40%, therefore requiring special attention. In people in whom seizures cannot be fully controlled by anticonvulsant drugs or alternative treatments (e.g., epilepsy surgery), implantation of a cardiac pacemaker seems advisable to prevent syncope-related injuries.[3,6] In people in whom IA is suspected, our data suggest that the recording of 1 or 2 seizures is not sufficient to rule out IA. If prolonged inpatient video-EEG monitoring is not available, insertion of an insertable cardiac monitor may be an alternative option.

AUTHOR CONTIBUTIONS

Kevin G. Hampel: study design, literature search, data acquisition, statistical analysis, interpretation of the data, writing of the manuscript, drafting the figures. Roland D. Thijs: interpretation of the data, revision of the manuscript for important intellectual content. Christian E. Elger: interpretation of the data, revision of the manuscript for important intellectual content. Rainer Surges: study design, literature search, data acquisition, statistical analysis, interpretation of the data, writing of the manuscript, drafting the figures.

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