Delirium Detection Using EEG What and How to Measure

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> **BACKGROUND:** Despite its frequency and impact, delirium is poorly recognized in postoperative and critically ill patients. EEG is highly sensitive to delirium but, as currently used, it is not diagnostic. To develop an EEG-based tool for delirium detection with a limited number of electrodes, we determined the optimal electrode derivation and EEG characteristic to discriminate delirium from nondelirium.

> **METHODS:** Standard EEGs were recorded in 28 patients with delirium and 28 age- and sexmatched patients who had undergone cardiothoracic surgery and were not delirious, as classified by experts using *Diagnostic and Statistical Manual of Mental Disorders, 4th edition,* criteria. The first minute of artifact-free EEG data with eyes closed as well as with eyes open was selected. For each derivation, six EEG parameters were evaluated. Using Mann-Whitney U tests, all combinations of derivations and parameters were compared between patients with delirium and those without. Corresponding P values, corrected for multiple testing, were ranked.

> **RESULTS:** The largest difference between patients with and without delirium and highest area under the receiver operating curve (0.99; 95% CI, 0.97-1.00) was found during the eyes-closed periods of the EEG, using electrode derivation F8-Pz (frontal-parietal) and relative δ power (median [interquartile range (IQR)] for delirium, 0.59 [IQR, 0.47-0.71] and for nondelirium, 0.20 [IQR, 0.17-0.26]; *P* = .0000000000018). With a cutoff value of 0.37, it resulted in a sensitivity of 100% (95% CI, 100%-100%) and specificity of 96% (95% CI, 88%-100%).

CONCLUSIONS: In a homogenous population of nonsedated patients who had undergone cardiothoracic surgery, we observed that relative δ power from an eyes-closed EEG recording with only two electrodes in a frontal-parietal derivation can distinguish among patients who have delirium and those who do not. CHEST 2015; 147(1):94-101

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ABBREVIATIONS: APACHE = Acute Physiology and Chronic Health Evaluation; CAM-ICU = Confusion Assessment Method for the ICU; CCI = Charlson comorbidity index; IQR = interquartile range; PACU = postanesthesia care unit; RASS = Richmond Agitation and Sedation Scale

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Delirium is an acute disturbance of attention and cognition.¹ It is a common disorder in postoperative and critically ill patients and associated with higher mortality and long-term cognitive impairment.^{2,3} Despite its frequency and impact, recognition of delirium by ICU physicians appeared to be poor (sensitivity, 29%).⁴ Therefore, several delirium assessment tools have been developed. The delirium assessment tool with the highest sensitivity in postoperative patients was the Nursing Delirium Symptom Checklist (sensitivity, 29%-95%),^{5,6} whereas the Confusion Assessment Method for the ICU (CAM-ICU) had the highest sensitivity in patients in the ICU (64%-100%).^{4,7-9}

It should be noted, however, that in these studies, delirium assessments were performed by a limited number of dedicated research nurses, and it is questionable whether these findings can be generalized to routine, daily practice, where numerous bedside nurses use these tools. The sensitivity of the Nursing Delirium Symptom Checklist in a real-life, postoperative setting has never been investigated,⁵ whereas the sensitivity of the CAM-ICU in routine ICU care appeared to be much lower than in a research setting.¹⁰ In a multicenter study in which teams of three delirium experts (psychiatrists, geriatricians, and neurologists) acted as the reference standard, the sensitivity of the CAM-ICU for delirium in routine, daily practice was low (< 47%), whereas the specificity was high (98%).¹⁰ However, a study from the same institution where the CAM-ICU was developed showed a higher sensitivity

(81%; specificity, 81%), but this was a single-center study in which research nurses acted as the reference standard.¹¹ Furthermore, the CAM-ICU cannot be used to quantify the severity of delirium. As a consequence, delirium recognition is impaired and treatment is delayed, which may impair outcome.¹²

A new approach to detect delirium, which may fit better in the culture of the postanesthesia care unit (PACU) and ICU, is to monitor physiologic alterations. Delirium is a manifestation of encephalopathy with altered function of neural networks.13 It has been known for decades that during delirium, EEG shows slowing of background activity.14 To use EEG for daily delirium screening is, however, time-consuming and unpractical, as it can only be performed and interpreted by trained personnel. EEG monitoring with automatic processing has become technically feasible.15 EEG-based detection with a limited number of electrodes and automatic processing is more practical and could possibly increase recognition of delirium. However, it is unclear which combination of EEG characteristic and electrode derivation would be the best in differentiating delirium from nondelirium.¹⁶ The objective of this study was to determine the electrode derivation and EEG characteristic that have the best capability to distinguish patients with delirium from patients without delirium. As a first step, we focused on a homogeneous population of patients who underwent cardiothoracic surgery and were admitted postoperatively to the ICU.

Materials and Methods

Study Design and Patients

In this single-center observational study, EEGs were recorded in patients who had undergone cardiothoracic surgery and had or did not have delirium and who were matched, on group level, for age and sex. The included patients were admitted postoperatively to the ICU of the University Medical Center Utrecht. The institutional review board approved the study protocol (number 11-073), and written informed consent was obtained at the preoperative outpatient clinic or at hospital admission prior to surgery. Patients aged \geq 50 years were eligible for this study if they were to undergo cardiothoracic surgery. We excluded patients with a history of any neurologic or psychiatric disease that may confound the diagnosis of delirium or the EEG. Patients with a previous cerebrovascular event were not excluded unless the event resulted in focal EEG alterations. In that case, the patient was replaced by another patient after evaluation of the EEG recording.

Delirium Diagnosis and Data Collection

Daily mental status assessment, including delirium screening, was conducted by research nurses and physicians using the Richmond Agitation and Sedation Scale (RASS) and CAM-ICU during the first five postoperative days.^{7,17} When surgery was complicated, daily mental status assessment was performed on the first 5 days that the patient was not in a comatose state, defined by a RASS score < -3 or a Glasgow coma score $< 9.^{17,18}$ Patients positive for delirium by CAM-ICU received

a neuropsychiatric evaluation conducted by a geriatrician, neurologist, or psychiatrist based on revised Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision, criteria for delirium.1 This neuropsychiatric evaluation included assessment of the level of consciousness, attention, orientation, memory, language, and disorganized thinking. When the delirium expert classified the patient as "definite delirium," the patient received an EEG recording. When the delirium expert had a different classification (delirium or nondelirium) based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision, criteria than the research nurse or physician based on the CAM-ICU, the patient was excluded. After matching on group level for age and sex, patients who were negative by the CAM-ICU also received a similar neuropsychiatric evaluation. When one of these patients was classified as "definite no delirium" by the delirium expert, an EEG recording was conducted. Several patient characteristics were registered: age, sex, APACHE (Acute Physiology and Chronic Health Evaluation) IV score,19 Charlson comorbidity index (CCI),20 European System for Cardiac Operative Risk Evaluation,21 surgery type, bypass time, and medication use during and in the 24 h prior to the EEG recording.

EEGs lasting 30 min were recorded in which patients were asked to keep their eyes open for 15 min and close them for the last 15 min of the recording. The ability to open and close eyes on command was not required for study inclusion. To avoid sleep during the EEG recording, patients were asked to conduct tasks like squeezing their hands at several time points during the recording. In addition to these tasks, patients

with delirium received multiple reminders for eyes-closed and eyesopen instructions to optimize adherence to the protocol. EEG recordings were conducted according to the international 10/20 system, with an extra electro-oculogram electrode below the right eye. Recordings were performed with a Micromed EEG system (Micromed S.p.A.) using a sample frequency of 512 Hz and FzCz as the ground electrode. Analog filter settings were set between 0.1 and 70 Hz. The data were preprocessed using a band-pass finite impulse response filter with cutoff frequencies of 0.5 and 30 Hz. The signal processing toolbox EEGlab (version 9.0.4.5s; http://sccn.ucsd.edu/eeglab/)²² was used for preprocessing of the EEG data in combination with MATLAB (Matlab, version 7.9.0.529; The MathWorks Inc).

For quantitative analysis, we selected the first 60 s of artifact-free data with patients' eyes open as well as the first 60 s of artifact-free data with patients' eyes closed. When specific electrode channels still contained artifacts, these channels were removed from the data. Eyes-open and eyes-closed data were analyzed separately. For eyes-open data, only occipital and parietal electrodes (P8, P3, P4, P7, O1, O2) were analyzed to avoid artifacts due to eye movements or blinking. For eyes-closed data, all 21 electrode channels were used (F10, F9, Fp2, Fp1, F8, F4, Fz, F3, F7, T8, C4, Cz, C3, T7, P8, P4, Pz, P3, P7, O2, and O1). For eyes-open and eyes-closed data separately, all EEG electrodes were combined with each other to create all possible bipolar EEG derivations. This resulted in 15 EEG derivations for eyes-open recordings and 210 EEG derivations for eyes-closed recordings. Based on previous literature, the most promising EEG characteristics were determined a priori, and these included the relative power in the δ (0.5-4 Hz), θ (4-8 Hz), α (8-13 Hz), and β (13-30 Hz) frequency bands, the peak frequency, and the slowfast ratio ([relative δ + relative θ]/[relative α + relative β]).¹⁶ These six EEG characteristics were calculated per patient for every EEG derivation for both eyes-open and eyes-closed recordings.

Sample-Size Calculation

The sample-size calculation was based on differences in EEG power spectral analyses. Unfortunately, there was no study that provided EEG spectral data of a similar cardiothoracic surgery population. Therefore, data from a related study were used.¹⁴ The minimal difference between the delirium group (with no apparent CNS disease) and the control group in this study for the relative power in the α band (weakest of various parameters) was 7.5%, assuming the mean for the delirium group was 17% (SD, 11.8%), and 9.5% (SD, 4.7%) for the control group.

Results

Fifty-eight patients were initially selected, but two equivocal cases were excluded after neuropsychiatric evaluation (Fig 1). In total, 56 patients remained, of whom 28 were delirious and 28 were not delirious. Of the patients with delirium, 14 had a hypoactive subtype (negative RASS scores), seven had a hyperactive subtype (positive RASS scores), and seven had a mixed subtype (both positive RASS and negative RASS scores) during the EEG registration. Five patients with delirium did not show an artifact-free epoch of 1 min with eyes open and were excluded for eyes-open analysis only. One patient with delirium did not have a 1-min epoch of artifact-free data with eyes closed and was excluded for eyes-closed analysis.

Patient characteristics are shown in Table 1. Patients with delirium differed from those without in APACHE IV

We defined the minimal clinically relevant difference around 7.5% because other EEG studies in delirium also resulted in differences of 5% to 8.5%.^{23,24} When the statistical power was assumed to be 0.8 and the significance level 0.05, 19 subjects per group were needed. However, the data used for this sample-size calculation originated from a general population of patients who were delirious and in the hospital and 19 nonhospitalized, healthy control subjects, and the contrast between these groups was larger than between the two groups of patients in our study who had undergone cardiac surgery and were in the ICU. Therefore, we wanted to include at least 25 participants per group, instead of 19 per group, to achieve the desired power.

Statistical Analysis

Patient characteristics were tested for normality using the Kolmogorov-Smirnov test. Continuous, normally distributed variables were presented using the mean and SD and compared using a *t* test. Continuous, not normally distributed variables were described with median and interquartile range (IQR) and compared using a Mann-Whitney *U* test. Categorical variables were compared using a χ^2 test or Fisher exact test. Statistical analysis of patient characteristics was conducted with SPSS (SPSS Statistics, version 20; IBM Corp).

In explorative analyses, all possible combinations of EEG derivations and characteristics were compared between patients who were delirious and those who were not delirious. It was assumed that not all EEG characteristics were normally distributed and, therefore, all comparisons were conducted using the Mann-Whitney U test. A Bonferoni correction was applied to correct for multiple testing. For eyes-closed data, this resulted in an α adjusted of 4.0 \times 10⁻⁵ and for eyes-open data, an α adjusted of 5.6 \times 10⁻⁴. For registrations with eyes closed and eyes open separately, all P values were ranked and the smallest P value was assumed to be the optimal EEG derivation and optimal EEG characteristic to distinguish patients who were delirious from those were not. For the 10 most optimal combinations of a certain EEG characteristic and derivation, a receiver operating curve was created and the area under the curve was determined. Using the function "perfcurve" in Matlab, the optimal operating point of the receiver operating curve was calculated and the corresponding cutoff value was used to determine the sensitivity and specificity. In addition to these analyses, we compared patients with delirium with and without haloperidol for the most optimal EEG derivation and EEG characteristic. The statistical analyses of the EEG data were performed with Matlab.

scores, CCI scores, and haloperidol use. Two patients without delirium used haloperidol in the 24 h previous to the EEG, because of delirium 2 days before the EEG recording and they were tapering off the haloperidol.

Table 2 lists the 10 combinations of EEG derivations and EEG characteristics with the lowest *P* values for the eyes-closed condition. All combinations were statistically significantly different between delirium and nondelirium. The derivation F8-Pz for relative δ power showed the lowest *P* value (.0000000000018) and the largest area under the receiver operating curve (0.99). Also, neighboring electrodes of both F8 (eg, Fp2) and Pz (eg, P3 or O1) in combination with relative δ power were in the top five of smallest *P* values (Fig 2).

Table 3 shows the 10 combinations with the lowest *P* values for the eyes-open condition. Again, all combinations were statistically significantly different between



Figure 1 – Flowchart of patient inclusion.

delirium and nondelirium. The electrode derivation with the lowest *P* value was P7-P4 in combination with relative α power (*P* = .0000020), which was associated with an area under the receiver operating curve of 0.90.

 TABLE 1] Characteristics of the Study Population

When we restricted our analyses to patients with delirium and compared patients taking haloperidol to patients without haloperidol, there was no difference in the best combination for eyes closed (median relative δ power at F8-Pz: haloperidol, 0.58 [IQR, 0.40-0.70] vs no haloperidol, 0.64 [IQR, 0.53-0.71]; *P* = .39). Furthermore, for the best combination with eyes open (P7-P4, relative α), there also was no difference between patients with delirium with or without haloperidol (median relative α at P7-P4: haloperidol, 0.11 [IQR, 0.08-0.14] vs no haloperidol, 0.15 [IQR, 0.10-0.15]; *P* = .37).

Discussion

In summary, we found that with only two electrodes and 1 min of EEG recording, large differences can be found between patients with and without delirium after cardiothoracic surgery. The largest difference between delirium and nondelirium (ie, the lowest *P* value) was observed in EEG epochs with eyes closed. In this condition, the optimal EEG characteristic and electrode derivation was the relative δ power in F8 (frontal lateral) to Pz (midline, parietal).

This study represents an innovative approach to detecting delirium. Using EEG with a limited number of electrodes and automatic processing may offer an objective tool to detect the encephalopathy that underlies

Characteristic	Patients With Delirium (n = 28)	Patients Without Delirium $(n = 28)$	P Value
Age, mean (SD), y	77 (5.6)	74 (8.6)	.16
Male sex	16 (57)	16 (57)	1.00
APACHE IV score, median (IQR) ¹⁹	58 (45-65)	43 (35-51)	<.01
Charlson comorbidity index, median $(IQR)^{20}$	2 (1-3)	1 (0-1)	.02
EuroSCORE, median (IQR) ²¹	7 (6-9)	7 (5-8)	.17
Surgery type			.49
CABG	3 (11)	5 (18)	
Valve	8 (28)	11 (39)	
Other ^a	17 (61)	12 (43)	
Bypass time, median (IQR), min	129 (95-158)	108 (77-168)	.07
Morphine in past 24 h	10 (36)	10 (36)	1.00
Benzodiazepines in past 24 h	7 (25)	6 (21)	.75
α_2 -Agonist in past 24 h	4 (14)	0 (0)	.11
Haloperidol in past 24 h	17 (61)	2 (7)	<.01
Postsurgical day of EEG, median (IQR)	3 (2-5)	3 (2-4)	.78

Data given as No. (%) unless otherwise indicated. APACHE = Acute Physiology and Chronic Health Evaluation; CABG = coronary artery bypass graft; EuroSCORE = European System for Cardiac Operative Risk Evaluation; IQR = interquartile range.

aOther surgery type refers to cardiothoracic surgery that includes two or more of the following procedures: CABG, valve surgery, or Maze procedure.

	Cutoff	0.37	0.35	0.42	0.42	0.35	0.37	0.41	0.35	0.42	0.36
	Specificity %, (95% CI)	96 (88-100)	96 (88-100)	96 (87-100)	95 (85-100)	92 (81-100)	95 (87-100)	96 (88-100)	92 (81-100)	95 (87-100)	96 (89-100)
	Sensitivity, % (95% CI)	100 (100-100)	96 (87-100)	96 (87-100)	96 (87-100)	96 (87-100)	96 (87-100)	91 (80-100)	91 (80-100)	100 (100-100)	88 (76-100)
	AUC (95% CI)	0.99 (0.97-1.00)	0.99 (0.96-1.00)	0.99 (0.95-1.00)	0.99 (0.97-1.00)	0.98 (0.94-1.00)	0.99 (0.95-1.00)	0.98 (0.94-1.00)	0.98 (0.94-1.00)	0.99 (0.95-1.00)	0.96 (0.91-1.00)
Eyes Closed	Nondelirium, Median (IQR)	0.20 (0.17-0.26)	0.19 (0.15-0.26)	0.23 (0.18-0.30)	0.27 (0.23-0.36)	0.20 (0.17-0.26)	0.22 (0.17-0.26)	0.26 (0.20-0.33	0.21 (0.17-0.30)	0.28 (0.22-0.36)	0.17 (0.10-0.25)
	Delirium, Median (IQR)	0.59 (0.47-0.71)	0.59 (0.46-0.69)	0.60 (0.49-0.73)	0.66 (0.60-0.75)	0.60 (0.43-0.70)	0.62 (0.48-0.72)	0.57 (0.46-0.67)	0.57 (0.49-0.67)	0.64 (0.53-0.72)	0.50 (0.37-0.57)
	Characteristic	Rel. õ	Rel. õ	Rel. 8	Rel. õ	Rel. 8	Rel. õ				
	Derivation	F8-Pz	F8-P3	F8-02	Fp2-01	F8-F4	F8-01	F8-Cz	F8-C3	Fp2-Pz	Cz-01
	P Value ^a	.000000000018	.000000000037	.00000000011	.00000000015	.00000000017	.000000000022	.00000000024	.00000000024	.00000000029	0200000000000.
	Rank	1	2	м	4	ß	9	7	8	6	10

See Table 1 legend for expansion of other abbreviations. AUC= area under the curve of the receiver operating curve; Rel. 8 = relative power in the 8 frequency band. See Table 1 legend for expansion of other abbrev •AII *P* values were < .00004. Therefore, all combinations in this table showed a statistically significantly difference between delirium and nondelirium. delirium. Patients in the PACU and ICU are monitored for various physiologic alterations. Consequently, EEG-based detection of delirium may fit better in the local culture than cognitive testing. To our knowledge, our study is the first to systematically investigate what the best electrode derivation and EEG characteristic are to detect delirium. We showed that with only two electrodes and 1 min of recording, large differences can be found between patients with and without delirium.

Two previous studies found that delirium can be detected with two electrodes, using T5-O1 (parietal to occipital) or C3-A1 (central to left ear) derivations in combination with EEG frequency analyses. However, the observed differences in these studies were much smaller than the differences found in our investigation.14,25 Our study contrasts with previous investigations in that we determined systematically which combination of bipolar electrode derivation and EEG characteristic showed the largest differences between patients with and without delirium. Unlike previous quantitative EEG studies in delirium, we did not observe that relative θ power was an important characteristic to distinguish patients with delirium from those without.16 These previous studies often stratified the θ frequency band into an upper and a lower part, with only the lower part proving to be significantly different between delirium and nondelirium.^{26,27} We did not use further division of the θ band, as this would have further increased the number of possible combinations to study.

Delirium is a common disorder with a prevalence (ie, pretest probability) of up to 45% in the PACU and 32% when both the PACU and in-patient surgical ward are combined.⁵ In patients in the ICU, the prevalence may be even higher and ranges between 60% and 80% for patients on mechanical ventilation and 20% to 50% for those not mechanically ventilated.²⁸ Although prevalence is high, multiple studies reported that in clinical practice, > 50% of patients with delirium were missed using delirium screening tools such as the CAM-ICU.^{5,10} Specificity was high in these studies. A new diagnostic tool, therefore, should increase sensitivity to > 50% to improve our current recognition of delirium. When validating the method proposed in this study to discriminate delirium from nondelirium, it should be determined whether the sensitivity is, indeed, better than current methods. When this technique is validated in unselected populations with varying pretest probabilities of delirium, we will be able to calculate how sensitive and specific the technique needs to be for a negative result to lower the

TABLE 2] The 10 Combinations of EEG Derivation and Characteristic That Showed the Lowest P Value in Discriminating Delirium From Nondelirium With



Figure 2 – Most optimal electrode combinations for delirium detection, based on first four rankings of the eyes-closed condition. The thickness of the connecting line corresponds with the rank of the electrode combination: The thickest line represents the highest rank.

posttest probability to a threshold below which it is acceptable to miss delirium.

Some limitations of the present study should be acknowledged. This study describes only the first step toward an objective delirium-detection tool. Due to the study design, in which only definitive cases were included, we cannot derive the incidence of delirium in this population. Therefore, parameters such as the area under the receiver operating curve, sensitivity, and specificity may be too optimistic and should be interpreted with caution. In our study, artifact-free data were manually selected for analysis and not automatically chosen. Automatic artifact-detection programs are available and already implemented in single-channel, sleep EEG analysis programs.²⁹ A comparable automatic detection algorithm needs to be implemented in a future objective delirium-detection tool. The homogenous study population of patients who had undergone cardiothoracic surgery did not have residual sedation, which may be an issue in delirium detection in a general population of patients in the ICU. Besides, the etiology of delirium after cardiothoracic surgery differs from the etiology of

ICU delirium.³⁰ It is, therefore, unclear whether our findings can be extrapolated to a general ICU population. Another possible limitation of this study may be that differences in haloperidol use between the delirium and the nondelirium groups could have affected the results. It is, however, unlikely that this explains our findings, as we found no differences between users and nonusers of haloperidol within the group of patients with delirium. As delirium is caused by an underlying disease, unsurprisingly, there was a difference in APACHE IV score and CCI between patients with and without delirium. Furthermore, we cannot exclude that the results might be affected due to the problem that patients with delirium needed more reminders to keep their eyes closed or open than those without delirium. As both groups needed reminders to open or close their eyes, and only 1 min of EEG recording was analyzed, we expect that a possible effect of this problem will only be minimal. In this explorative study, patients with neurologic or psychiatric disease were excluded as well as doubtful cases, because these are the patients for whom making a diagnosis of delirium is the most difficult. In future validation studies, it should be explored whether

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All P values were < .00056. Therefore, all combinations in this table showed a statistically significantly difference between delirium and nondelirium. See Table 1 and 2 legends for expansion of other abbreviations.

the technique proposed in this study can also be applied to these subgroups.

A serious limitation of this study is that the proposed method for discriminating delirium from nondelirium was not tested in an independent study population, which will be necessary to prove that this technique can be used as a diagnostic test for delirium. Therefore, future studies should validate the results of this study and investigate whether our findings can be generalized to an unselected population of patients in the ICU and to a general population of postoperative patients. To generalize the findings, future validation studies should be conducted in unselected populations with blinding of the physician making the delirium diagnoses to the results of the EEG-based delirium monitor. The effects of residual sedation and automatic data selection should also be considered in these studies.

In conclusion, we showed that with two electrodes and 1 min of EEG data, delirium can be discriminated from nondelirium under certain circumstances. This opens the prospect of EEG-based detection of delirium.

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authors have reported to *CHEST* the following conflicts of interest: Drs van der Kooi and Slooter hold a patent (pending) through the University Medical Center of Utrecht entitled "Method and system for determining a parameter which is indicative for whether a patients is delirious" (Application No.: PCT/EP2013/069521). Drs Zaal, Klijn, Koek, Meijer, and Leijten have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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