SUPPLEMENTARY ONLINE CONTENT

eAppendix 1. Additional methods

Multimodality Monitoring

According to a previously described institutional protocol[1]invasive neuromonitoring includes measurements of the following: intracranial pressure, partial brain tissue oxygenation (PbtO2) (by means of insertion of a flexible polarographic LICOX Clark-type probe; Integra Neurosciences, Kiel, Germany), and regional cerebral blood flow (rCBF, Bowman Perfusion Monitor "Hemedex", Cambridge, MA). At the same location as the aforementioned invasive monitoring devices, dEEG electrodes were inserted (AD Tech, Racine, WI; Spencer Probe depth electrodes, 8 Platinum contacts, center-to-center intercontact spacing: 2.2 mm, contact width: 1.32 mm, spacing between electrodes: 0.9 mm).[1]

In patients, in whom the aneurysm was treated by means of coiling, MMM probes were placed ipsilaterally to the aneurysm. This was also the case in patients that underwent aneurysm clipping but had focal structural lesions on the contralateral side. In all other cases, in particular in patients in whom the aneurysm was treated surgically, the probes were placed contralaterally to the aneurysm.[2] SEEG recordings were obtained according to the international 10-20 system.[3]

General Management

Medical/surgical management followed the guidelines set forth by the American Heart Association.[4]MMM followed the guidelines of the Neurocritical Care Society and the European Society of Intensive Care Medicine, as well as local guidelines.[1,5–7]Independent of initial EEG findings, patients were given i.v. phenytoin for one week post hemorrhage. Thereafter, anticonvulsive medication was discontinued unless seizures were detected on sEEG. Isolated seizures detected by sEEG recordings were typically treated with Levetiracetam, and status epilepticus with midazolam infusion.[8]PDs were not deemed seizures and not treated with anticonvulsants. However, patients were maintained on anticonvulsants if PDs occurred during the first 7 days after admission and continued beyond that time, in order to prevent transition to seizure activity. Findings made on dEEG recordings did not alter the anticonvulsive regimen.[1]

Data Collection

Data collection for the prospective SHOP data base has been described previously.[9]To gather digital physiologic data we used a high-resolution data acquisition system; data was sampled at a 0.2-Hz-rate. For EEG recordings we used a digital bedside video monitoring system (XLTEK, Excel-Tech Corp., Natus Medical Incorporated, Oakville, Ontario, Canada).

EEG Monitoring and Classification

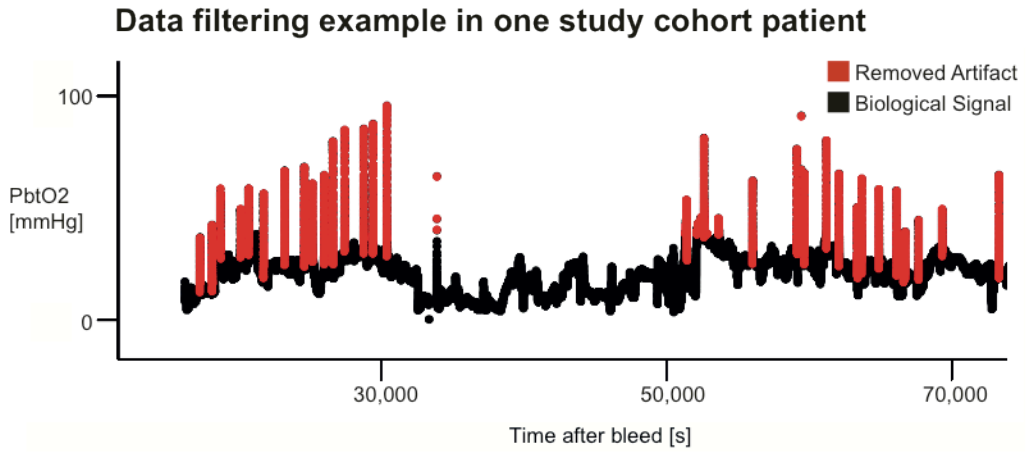
The majority of patients at our institution undergo aneurysm clipping.[9]Therefore most patients were connected to cEEG after removal of tight bandages for scalp incisions, usually on post-bleed day 3. CEEG was rated after visual inspection by two experienced electroencephalographers blinded to the clinical course of patients.[10]Rating was carried out separately for sEEG and dEEG recordings according to published criteria.[11]Studies following the publication of these criteria have shown excellent interrater agreement regarding seizure detection and satisfactory interrater agreement regarding identification of PDs.[12,13]Therefore, in the present study, in cases of doubt, the final rating score was based on consensus between two or three raters.

Data preparation

Data preparation and all analyses were performed using the R software (v3.0.2., R Project). For each of the physiologic measures we defined a filter to remove the most common artifacts, based on clinical knowledge about their time of onset, time course, and morphology.

For PbtO2, ICP, and CPP we used sliding time-windows between 2 and 15 minutes, across which unnaturally large deviations of activity were identified as artifact and removed. Only one window length was used for rCBF (10 minutes). For an example of these filters please see the E-Figure 1. In a second step, after application of filters, improbably high values were removed based on cumulative distribution functions. Finally, physiologic data were averaged over each minute, matching the MMM values to the coded EEG data.

eFigure 1. Filtering



Brain oxygen (PBtO2) data of the entire hospital stay from one example patient showing data identified as artifact (red) and biological signal (black). Algorithm based on a sliding time-windows, across which large deviations of activity were identified as artifact and removed.

eAppendix 2. Additional study cohort characteristics

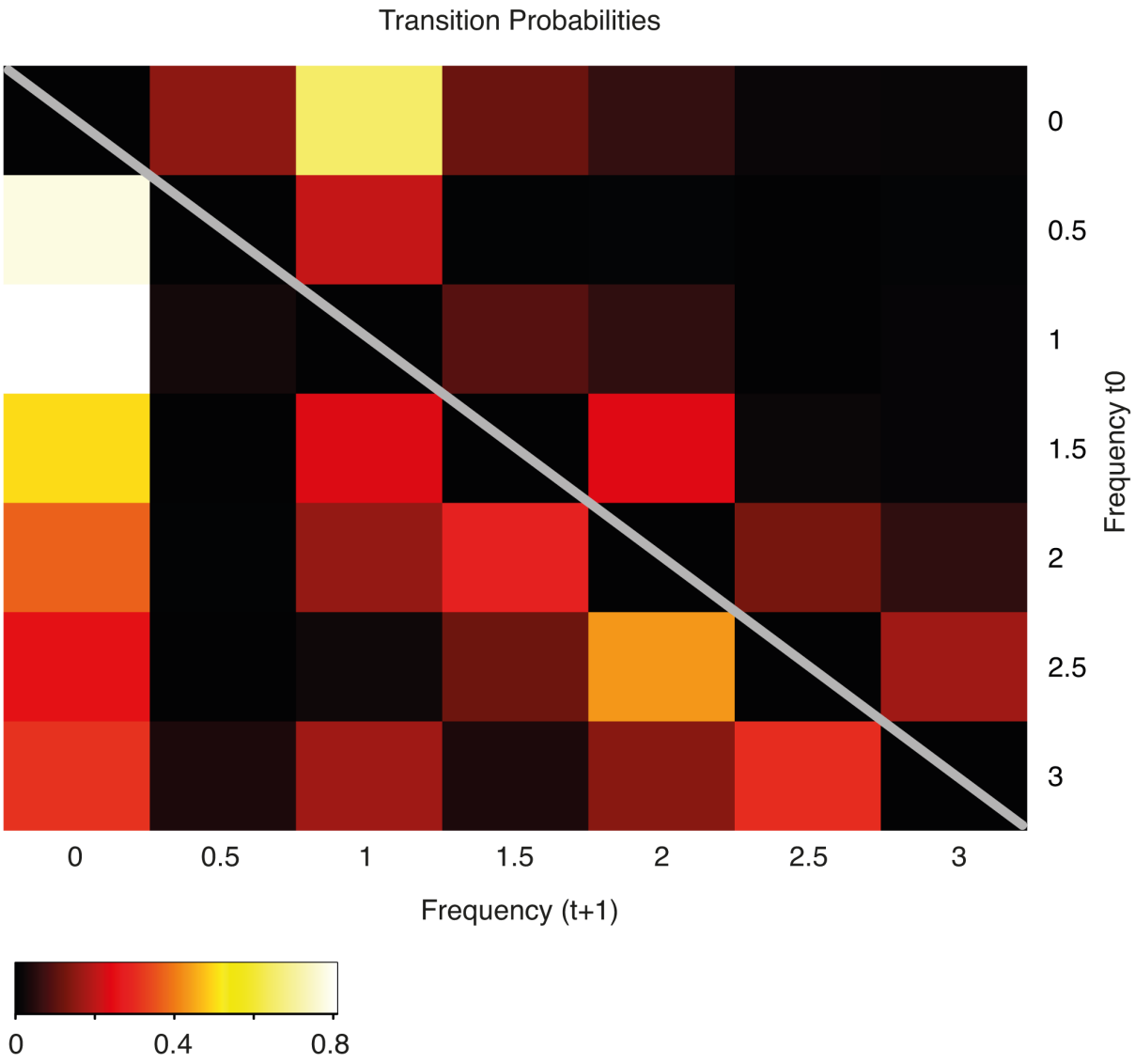
During the study period 666 patients with spontaneous subarachnoid hemorrhage were admitted to our center. 52 patients died within 48 hours of admission and 410 patients had a GCS of greater than 8 making them ineligible for placement of MMM according to our institutional protocol. Of those alive at 48 hours, 204 had a GCS on admission of 8 or lower and were potential candidates. Among these 204, 90 patients were included in the study (see Baseline Characteristics in Table 1), and 114 were not, most frequently for anticipated improvement of GCS within 48 hours, expected death within 48 hours, severe coagulopathy, or lack of consent by relatives or legal representatives. E-table 1 provides a comparison of baseline characteristics of patients included and those not included in the current study. In the study cohort the incidence of delayed cerebral ischemia (DCI) was higher and patients with unprotected aneurysms were less frequent. Baseline characteristics of these two cohorts were otherwise comparable.

eTable 1 Selection bias analysis comparing patients included in the study and those that were eligible but were not included.

Patients Fulfilling MMM Eligibility Criteria			
	Included in Study (N=90)	**Not Included in Study (N=114)**	**P-Value**
Demographics			
Age	55 +-15	59 +-18	N.S.
Female Gender	64 (71)	78 (68)	N.S.
Caucasian Ethnicity	27 (30)	39 (35)	N.S.
Admission Findings			
Hunt & Hess Grade	4 (4-5)	4 (4-5)	N.S.
APACHE-II Physiologic Score	22 +-7	22 +-7	N.S.
IVH Sum Score	4 +-4	4 +-3	N.S.
Global Cerebral Edema	43 (46)	47 (41)	N.S.
Aneurysm Treatment			
Aneurysm Clipping	53 (60)	53 (49)	N.S.
Aneurysm Coiling	24 (28)	22 (20)	N.S.
Not Protected	13 (12)	39 (31)	**0.023**
Hospital Course			
Delayed Cerebral Ischemia	49 (59)	45 (41)	**0.014**
Worst Hunt&Hess	5 (4-5)	4 (4-5)	N.S.
Functional Outcome at 3 months			
Modified Rankin Score	5 (3-6)	5 (3-6)	N.S.

Data are represented as No. (%), mean ± standard deviation, or median (interquartile range)
N.S. Not Significant

eFigure 2. Transition probabilities between PD frequencies.



Probability of transitioning from PD frequency at time t0 (vertical axis) to frequency at time t+1 minute (horizontal axis). We only considered runs of PDs with a minimum duration of two minutes. All entries above the grey diagonal line represent increases in PD frequency, while all elements below the diagonal represent decreases. For example, the lower left box denotes the probability of 3Hz PD runs to be followed by 0Hz (i.e., no PDs) and the right upper box the probability of 0Hz PD runs to be followed by 3Hz.

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