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SYSTEMATIC REVIEW

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Prognostication of neurologic outcome in cardiac arrest patients after mild therapeutic hypothermia: a meta-analysis of the current literature

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Abstract *Purpose:* To assess the sensitivity and false positive rate (FPR) of neurological examination and somatosensory evoked potentials (SSEPs) to predict poor outcome in adult patients treated with therapeutic hypothermia after cardiopulmonary resuscitation (CPR).
Methods: MEDLINE and EMBASE were searched for cohort studies describing the association of clinical neurological examination or SSEPs after return of spontaneous circulation with neurological outcome. Poor outcome was defined as severe disability, vegetative state and death. Sensitivity and FPR were determined.
Results: A total of 1,153 patients from ten studies were included. The FPR of a bilaterally absent cortical N20 response of the SSEP could be calculated from nine studies including 492 patients. The SSEP had an FPR of 0.007 (confidence interval, CI, 0.001–0.047) to predict poor outcome. The Glasgow coma score (GCS) motor response was assessed in 811 patients from nine studies. A GCS motor score of 1–2 at 72 h had a high FPR of 0.21 (CI 0.08–0.43). Corneal reflex and pupillary reactivity at 72 h after the arrest were available in 429 and 566 patients, respectively. Bilaterally absent corneal reflexes had an FPR of 0.02 (CI 0.002–0.13). Bilaterally absent pupillary reflexes had an FPR of 0.004 (CI 0.001–0.03). *Conclusions:* At 72 h after the arrest the motor response to painful stimuli and the corneal reflexes are not a reliable tool for the early prediction of poor outcome in patients treated with hypothermia. The reliability of the pupillary response to light and the SSEP is comparable to that in patients not treated with hypothermia.

Keywords Cardiac arrest · Prognostication · SSEP · Therapeutic hypothermia

Introduction

Outcome studies in patients with anoxic-ischaemic encephalopathy after cardiopulmonary resuscitation (CPR) focus on the early prediction of an outcome no better than a vegetative state or severe disability. In 2006 Wijdicks et al. [1] described a number of clinical, electrophysical and laboratory tests which reliably predict a poor neurologic outcome in the practice parameter for the American Academy of Neurology (AAN). These parameters are widely used to determine the outcome in comatose patients after cardiac arrest.

On the basis of two prospective randomized trials in 2002, the International Liaison Committee on Resuscitation (ILCOR) advised to use therapeutic hypothermia in unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest when the initial rhythm was ventricular fibrillation (VF) [2]. Since then, hypothermia has been widely adopted in patients after cardiac arrest. Hypothermia has a marked effect on the pathophysiological cerebral changes that occur during the post-cardiac arrest period by influencing metabolism, cerebral blood flow, inflammatory response and neuroexcitatory pathways [3]. These hypothermia-induced changes may influence the time to recovery of the brain. Hypothermia also modifies the metabolism of most sedatives, with accumulation of these sedatives and/or their metabolites, resulting in an unpredictably prolonged sedative effect. Most currently used guidelines for the prognostication of patients after cardiac arrest are mainly based on patients not treated with hypothermia. The AAN practice parameter identified four reliable methods for predicting a poor prognosis: (1) clinical neurological examination (including corneal reflexes, pupillary reflexes and motor response); (2) myoclonic status epilepticus; (3) somatosensory evoked potential (SSEP) and (4) neuron-specific enolase (NSE) serum levels [1]. There is increasing evidence that therapeutic hypothermia alters the positive and negative predictive value of these parameters.

The aim of this meta-analysis was to assess the sensitivity and false positive rate (FPR) of clinical neurological examination and SSEP parameters to predict poor outcome in adult patients treated with mild therapeutic hypothermia after CPR. The focus was directed to analysis of recently published studies and data were directly obtained from authors of these original studies.

Methods

This systematic review was performed in accordance with the meta-analysis of observational studies in epidemiology (Moose) guidelines [4].

Search strategy

The literature search was performed by MK on 12 December 2011 and repeated on 1 March 2012. We performed a literature search using the electronic database Medline via PubMed (1966–March 2012) and Embase via OVID (1974–March 2012) with the search terms "cardiac arrest" or "heart arrest" and "hypothermia, induced" and "prognosis" or "outcome" with the limits "human" and "adult". Additional search terms used were "cardiac arrest" or "heart arrest" and "SSEP". We included full-text articles of any prospective or retrospective cohort study that reported the association between clinical neurological examination after return of spontaneous circulation (ROSC) or SSEP and outcome. All identified studies were screened on the basis of abstract or title. Reference lists of review articles and eligible primary studies were checked to identify cited articles not captured by electronic searches. All primary authors were contacted and asked to participate in this meta-analysis. When no response was obtained, senior authors were contacted by email.

Study selection

Two reviewers (MK and CH) checked the titles and abstracts identified by the search strategy and examined any publication that potentially met the inclusion criteria. Final in-/exclusion decisions were made after independent duplicate examination of the full manuscripts of selected references. In case of disagreement between the two reviewers, a third reviewer (JH) was contacted and the differences were discussed until consensus was reached. We included all prospective and retrospective cohort studies including at least five patients.

Studies were included if they originally included adult patients (age at least 18 years) that were comatose after ROSC and were treated with mild therapeutic hypothermia for 12–24 h after cardiac arrest due to any cause. Studies were eligible if they reported any of the clinical parameters or SSEP results in combination with a clear description of outcome, based on the Glasgow outcome scale (GOS), modified Rankin scale (mRS) or cerebral performance category (CPC) scale. The clinical parameters included pupillary reactions, corneal reflexes and Glasgow coma score (GCS) motor response. Corneal and pupillary light responses were dichotomized as bilaterally absent or not bilaterally absent. Motor score was dichotomized, according to the GCS, as motor score of 2 or less or above 2. Results of the cortical N20 responses of median nerve SSEPs were recorded as assessed by the local clinical neurophysiologists and documented as "absent" (bilaterally absent cortical N20 responses after left and right median nerve stimulation, in the presence of a cervical potential), "present" (cortical N20 response

present on at least one side) or "undeterminable" (technically insufficient recording).

Articles were excluded if they were animal studies, included only patients under the age of 18, had no clear description of a clinical parameter or SSEP, or if they were lacking outcome data. Case series describing less than five patients, abstracts without full-text publications, and conference reports were excluded.

Study quality was determined by analysing the methods of the original study for completeness of the data.

Data collection and analysis

The authors of the trials received a designed data extraction form to provide the necessary data. These data were collected by CH and MK and entered into the local database and were verified by JH. After consensus was reached over the results, the data were included in the meta-analysis.

Outcome measures

The outcome was defined as outcome at hospital discharge or thereafter and scores were dichotomized as favourable or unfavourable based on the GOS (1–3 unfavourable, 4–5 favourable outcome), mRS (5–6 unfavourable, 0–3 favourable) and CPC scales (3–5 unfavourable, 1–2 favourable outcome). This depended on the scale used in the manuscript included. The timing of outcome assessment for each study was recorded.

Statistical analysis

The reference standard was defined as a favourable versus an unfavourable outcome. This resulted in a two-by-two table for each study: positive or negative test result for each one of the two reference values. Studies reporting insufficient data for the construction of a two-by-two table were excluded from the final analyses.

The SSEP, GCS motor response and corneal and pupillary reflexes at 72 h were tested for their sensitivity, specificity and FPR in predicting a poor outcome. The data of the two-by-two tables were used to calculate sensitivity and specificity for each study. FPR was defined as 1 − specificity. All results are expressed as proportion with 95 % confidence intervals (CI). We present individual study results graphically by plotting the estimates of sensitivity and specificity (and their 95 % CIs) in forest plots. A positive index test was defined as a bilaterally absent cortical N20 response, bilaterally absent pupillary or corneal reflexes or a GCS motor score of 1 or 2 at 72 h after the arrest. All other test results, including the undeterminable SSEP recordings were considered as negative index test results.

We used a bivariate random effects approach for the meta-analysis of the pairs of sensitivity and specificity [5]. The random effects approach is used to incorporate unexplained variability as such is expected due to imprecision by which sensitivity and specificity have been measured within each study; variation beyond chance in sensitivity and specificity between studies; and any correlation that might exist between sensitivity and specificity.

The bivariate random effects approach enabled us to calculate summary estimates of sensitivity and specificity, while correcting for the aforementioned sources of variation. Heterogeneity was investigated using Higgins I^2 [6].

Analyses were performed in Stata ver.10.0 using the additional package Metandi (Science Plus, the Netherlands). Figures were plotted using the R-statistical platform with the additional package DiagMeta.

Results

Results of the literature search

We identified 445 articles in our primary search and added two articles by review of references (Fig. 1). After exclusion of duplicates, case reports and reviews, 252 abstracts were assessed for eligibility. After exclusion of 236 articles based on subject, we included 16 studies in a qualitative analysis. We excluded another six studies because in three cases the authors did not respond to our questionnaire, one study lacked a clear outcome description and two studies because of identical patient population.

Study characteristics

Ten studies representing a total of 1,153 patients were included; among these ten studies, eight described prospective patient cohorts and two described retrospective cohorts (Table 1) [7–16]. All studies included adult patients after cardiac arrest treated with mild therapeutic hypothermia. Additional inclusion criteria were coma or a specified GCS in seven studies. One study limited inclusion to patients with VF as cause of the arrest [17]. Patients with a severe pre-existing or concomitant (neurological) disease were excluded in four out of ten studies. Three studies excluded patients that died within the first 72 h or achieved brain death within 48 h. The percentage of patients with a (presumed) cardiac origin of the arrest varied between studies (53–100 % of total number of included patients). The GOS, CPC or mRS

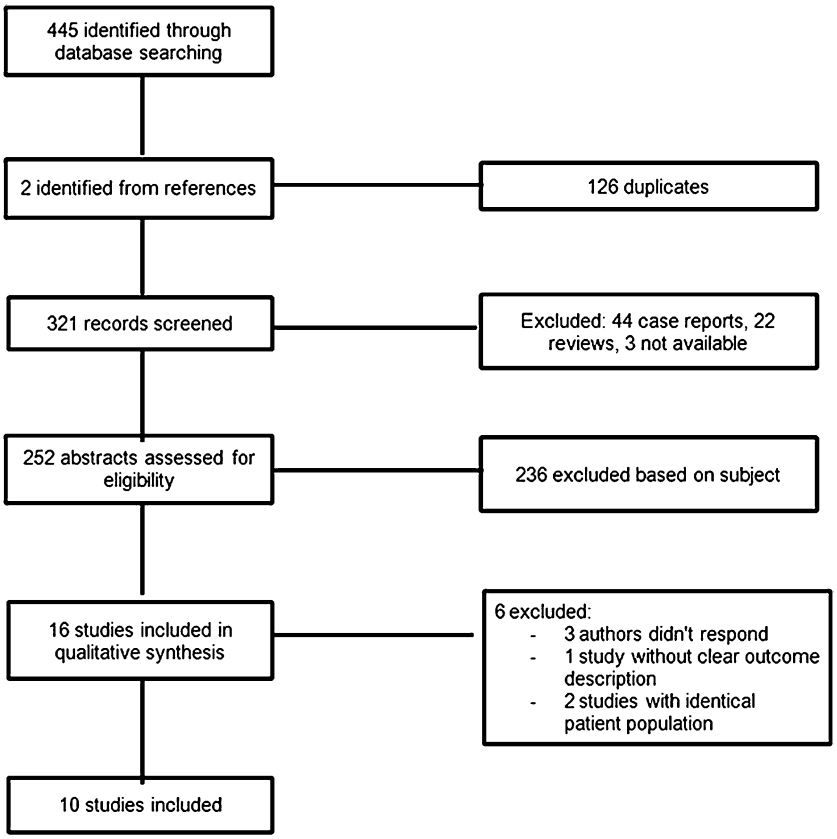

Fig. 1 Study selection

scale were used to describe outcome at variable time points after the arrest (ranging from ICU discharge to 6 months). The percentage of patients with an unfavourable outcome varied between 44 and 79 % between the studies.

Patient treatment

All patients were treated with mild therapeutic hypothermia for 24 h targeting a temperature between 32 and 34 °C. Hypothermia was most frequently induced by infusion of cold fluids in combination with surface cooling (Table 2). Rewarming to normothermia was controlled in five studies; passive rewarming was used in the remaining five studies. Midazolam and fentanyl were the most frequently used drugs for sedation and analgesia. Muscle relaxants were frequently added to treat or prevent shivering, either as a bolus or continuous infusion. Sedation was stopped at 35 °C or at normothermia or was tapered after rewarming.

The SSEP was performed at different time points: at normothermia, at 72 h after the arrest or at 72 h after normothermia was achieved. A bilaterally absent cortical N20 response led to withdrawal of treatment in all patients.

Clinical neurological examination was performed in nine studies and usually consisted of brainstem reflexes together with the GCS and was performed at 72 h (eight studies) or at 72 h after normothermia was reached (one study). Clinical examination resulted in withdrawal of treatment in case of GCS motor score 1–2, or bilaterally absent pupillary reflexes (one study); GCS motor score 1–2; GCS motor score 1–2, in combination with bilaterally absent pupillary reflexes and bilaterally absent corneal reflexes (one study); or no clinical improvement after at least 72 h, together with incomplete recovery of all brainstem reflexes (one study), or the AAN guidelines (one study). Treatment decisions were not strictly guided by protocol in five studies and in one study the decision to withdraw life support was made in conjunction with the family.

SSEP

The prognostic value of SSEP could be calculated from nine studies including 492 patients (Table 3). The sensitivity of SSEP was low [0.50 (0.42–0.27)] (Fig. 2). One of 152 patients with a bilaterally absent cortical N20 response regained consciousness and normal cognitive function [12]. The FPR for bilaterally absent SSEP to predict a poor outcome was 0.007 (0.001–0.047) (Table 4).

Table 1 Study characteristics

Author	Study type	*N*	Inclusion criteria	Exclusion criteria	Cardiac origin of the arrest *N* (%)	Neurological examination during admission	Outcome	Poor outcome *N* (%)
Bisschops [7]	Retrospective single-centre	103	GCS $\leq$ 8		77/103 (75 %)	Intensivist and/or neurologist	GOS at 3 months	67/103 (65 %)
Bouwes [9]	Prospective multicentre	77	Coma	Brain death before treatment Concomitant TBI Discontinuation of hypothermia Impossibility to perform SSEP Absence of informed consent	69/77 (90 %)	Intensivist and/or neurologist	GOS 30 days after admission	51/77 (66 %)
Bouwes [8]	Prospective multicentre	391	Coma	Pre-existing diseases with life-expectancy <6 months Severe disability before CPR CPR due to hypovolemic shock Absence of informed consent	299/391 (76 %)	Intensivist and/or neurologist	GOS 1 week, 1 month, 6 months	199/391 (51 %)
Cronberg [10]	Prospective single-centre	111	GCS < 8 after regaining normothermia	Death <72 h	18/34 (53 %)	Neurologist	CPC 6 months	53/111 (48 %)
Fugate [11]	Prospective single-centre	128	Ventricular fibrillation	Discontinuation of hypothermia	90/128 (70 %)	Neurologist	CPC hospital discharge	56/128 (44 %)
Leithner [12]	Retrospective single-centre	112			49/70 (70 %)	Intensivist and/or neurologist	CPC ICU discharge	65/112 (58 %)
Rossetti [14]	Prospective single-centre	34			27/34 (79 %)	Neurologist	CPC 2 months	20/34 (59 %)
Rossetti [13]	Prospective single-centre	111	Coma	Brain death <48 h	95/111 (86 %)	Neurologist	CPC 3–6 months	66/111 (59 %)
Samaniego [15]	Prospective single-centre	53	Coma (defined as GCS E_1M_5 or worse)	Pre-existing DNR Severe coexisting systemic disease with limited life expectancy Brain death Death <72 h Severe coagulopathy Hemodynamic instability with RR_{syst} < 90 mmHg	37/53 (70 %)	Neurologist	GOS 3 months	32/53 (60 %)
Wu [16]	Prospective single-centre	33	Coma (defined as GCS $E_2M_4V_1$ or worse)	Traumatic cause of coma Pre-existing coma due to medication Cerebral haemorrhage or stroke on CT Imaging of poor quality or performed >72 h after cardiac arrest	33/33 (100 %)	Neurologist	mRS 3 and 6 months	26/33 (79 %)

N number of participants, *TBI* traumatic brain injury, *DNR* do not resuscitate, RR_{syst} systolic blood pressure, *GCS* Glasgow coma score, *GOS* Glasgow outcome scale, *CPC* cerebral performance Category, *mRS* modified Rankin scale

Table 2 Treatment characteristics

Author	Duration of MTH (h)	Cooling method	Target temperature (°C)	Rewarming	Sedation and/or analgesia	Treatment withdrawal
Bisschops [7]	24	Infusion of cold fluids and surface cooling	32–34	Passive rewarming	Midazolam and/or propofol to a Ramsay score of 6 Shivering treated with extra sedation, analgesia or rocuronium Discontinuation at normothermia	Bilaterally absent cortical N20 response at 72 h or Motor score m1–2 in combination with absent pupillary reactions and absent corneal reflexes at 72 h
Bouwes [9]	24		32–34	Passive rewarming	Not specified in study protocol	Bilaterally absent cortical N20 response at normothermia
Bouwes [8]	24		32–34	Not specified	Sedative drugs in accordance with the local protocol: Midazolam, propofol and opiates Discontinuation not specified in study protocol	Bilaterally absent cortical N20 response at normothermia No clinical guidelines for withdrawal
Cronberg [10]	24	Infusion of cold fluids and surface cooling or catheter-based technique	33	Rewarming over 8 h	Midazolam or propofol and fentanyl Discontinuation at normothermia	Bilaterally absent cortical N20 response at 72 h after normothermia or GCS motor score 1–2, or PR absent bilaterally at 72 h after normothermia
Fugate [11]	24	Infusion of cold fluids and surface cooling	33	Controlled rewarming at 0.25 °C/h	Midazolam IV bolus of 0.03 mg/kg followed by an infusion starting at 1 mg/h Fentanyl IV infusion at 25 μg/h Paralysis with atracurium 0.4 mg/kg bolus followed by 4 μg/kg/min Discontinuation at normothermia	Withdrawal of treatment based on neurologic assessment or critical systemic illness
Leithner [12]	24	Infusion of cold fluids and surface cooling	33	Controlled rewarming at 0.25 °C/h	Combination of midazolam (0.125 mg/kg/h) and fentanyl 0.002 mg/kg/h with dose adjustment as needed Muscle relaxation with repetitive administration of pancuronium (0.1 mg/kg) in order to prevent shivering	Repeated neurological examination, NSE, bilaterally absent cortical N20 response at normothermia, waiting period of several days
Rossetti [14]	24	Infusion of cold fluids and surface cooling	33	Passive rewarming	Midazolam (0.1 mg/kg/h) and fentanyl 1.5 μg/kg/h Vecuronium (0.1 mg/kg) bolus to control shivering Discontinuation at 35°C	Bilaterally absent cortical N20 response at normothermia or no clinical improvement after at least 72 h, together with incomplete recovery of all brainstem reflexes
Rossetti [13]	24	Infusion of cold fluids and surface cooling	33	Passive rewarming	Midazolam 0.1 mg/kg/h and fentanyl 1.5 μg/kg/h Vecuronium 0.1 mg/kg bolus for shivering Discontinuation at 35°C	AAN guidelines
Samaniego [15]	24	Surface cooling or catheter-based techniques	33	Passive rewarming over 8–12 h	Fentanyl (25–100 μg/h) iv, midazolam 2–6 mg/h IV Vecuronium to avoid shivering: bolus 0.1 mg/kg followed by 0–5 mg/h Sedation tapered off after rewarming	Goals of care were addressed with each patient's next of kin on multiple occasions and the decision to withdraw life support was made in conjunction with them
Wu [16]	24	Infusion of cold fluids and surface cooling	32–34	Controlled rewarming over 8–12 h	Midazolam and vecuronium 0.1 mg/kg bolus, followed by 0–5 mg/h infusion. Midazolam 0.1 mg/kg/h	Treatment decisions guided by pupillary, corneal and motor responses at 72 h, absent SSEP N20 responses at 48 h

MTH mild therapeutic hypothermia, *GCS* Glasgow coma score motor response

Table 3 Total of included patients per study compared to the included patients per test

References	Study[b]		Included patients per test (sum of TP, FP, TN, FN), *n* (%)			
	N	Study design	SSEP[c] 72 h	Motor[d] 72 h	Cornea[e] 72 h	Pupil[f] 72 h
Bisschops [7][a]	103	R	43 (42)	91 (88)	29 (28)	90 (87)
Bouwes [9][a]	77	P	32 (42)	73 (95)	63 (82)	65 (84)
Bouwes [8]	391	P	129 (33)	284 (73)	130 (33)	195 (50)
Cronberg [10][a]	111	P	29 (26)	34 (31)	21 (19)	31 (28)
Fugate [11][a]	128	R	18 (14)	110 (86)	110 (86)	110 (86)
Leithner [12]	112	R	70 (63)	NA	NA	NA
Rossetti [14]	34	P	32 (94)	34 (100)	NA	NA
Rossetti [13]	111	P	100 (90)	109 (100)	NA	NA
Samaniego [15][a]	53	P	39 (74)	53 (100)	53 (100)	52 (98)
Wu [16]	33	P	NA	23 (70)	23 (70)	23 (70)
Total	1,153		492 (37)	811 (71)	429 (37)	566 (49)

NA not available, *TP* true positive, *FP* false positive, *TN* true negative, *FN* false negative

[a] All tests available

[b] Study design *R* retrospective, *P* prospective

[c] Somatosensory evoked potentials after 72 h

[d] GCS motor score after 72 h

[e] Corneal reflexes after 72 h

[f] Pupillary light responses after 72 h

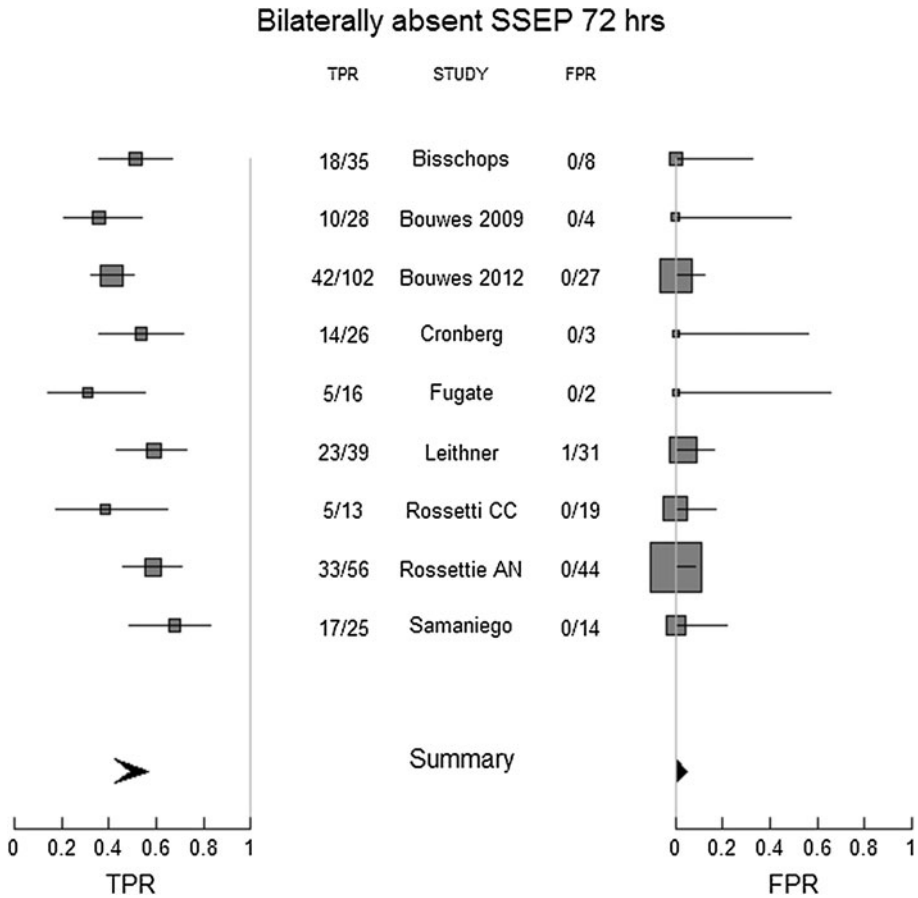

Fig. 2 TPR and FPR of bilaterally absent N20 response at 72 h after the arrest. *TPR* true positive rate, proportion of patients with a unilaterally or bilaterally present cortical N20 response while having a favourable outcome; *FPR* false positive rate, proportion of patients with a bilaterally absent cortical N20 response while having a favourable outcome. Heterogeneity between studies as determined by Higgins I^2 0 %

Table 4 Summary measures of sensitivity and false positive rate

Tests (72 h)	Sensitivity (95 % CI)	FPR (95 % CI)
Bilaterally absent SSEP	0.50 (0.42–0.57)	0.007 (0.001–0.047)
GCS motor score 1–2	0.80 (0.63–0.91)	0.21 (0.08–0.43)
Bilaterally absent corneal reflexes	0.32 (0.27–0.39)	0.02 (0.002–0.13)
Bilaterally absent pupillary reflexes	0.22 (0.18–0.27)	0.004 (0.001–0.03)

Results are presented as proportions
FPR false positive rate

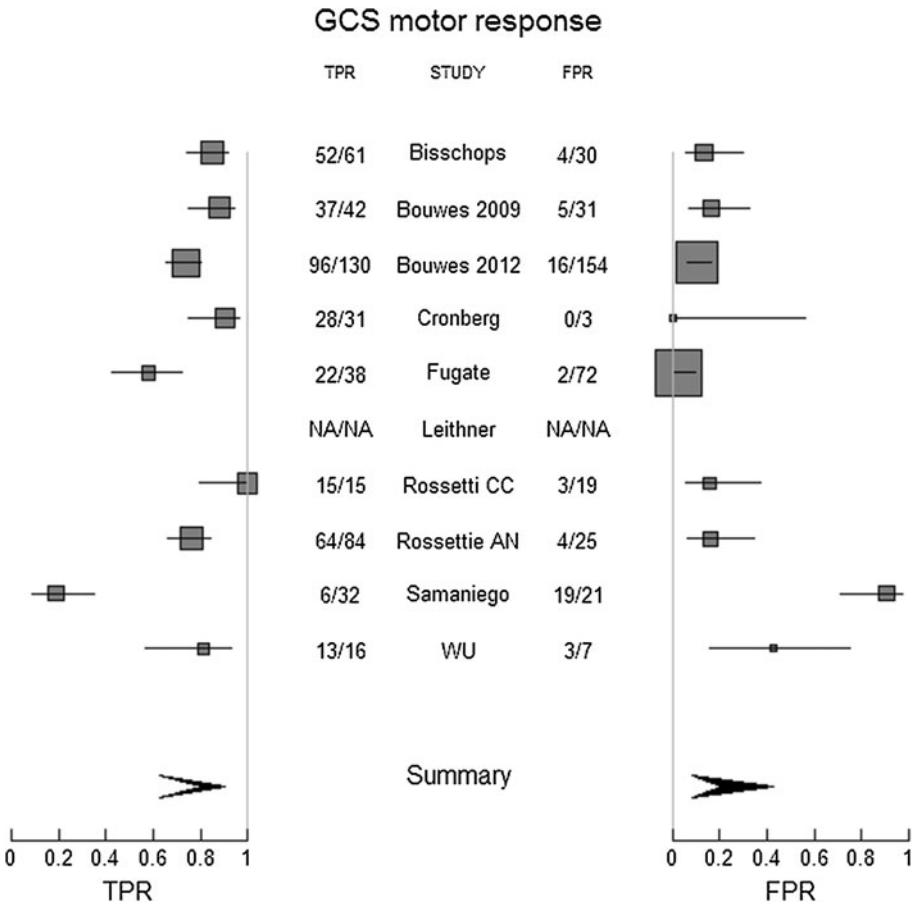

Fig. 3 TPR and FPR of Glasgow coma score motor response 1–2 at 72 h after the arrest. *TPR* true positive rate, proportion of patients with a Glasgow coma score motor response >2 while having a favourable outcome; *FPR* false positive rate, proportion of patients with a Glasgow coma score motor response 1–2 while having a favourable outcome. Heterogeneity between studies as determined by Higgins I^2 28 %

Clinical neurological tests

The GCS motor response at 72 h after the arrest was assessed in 811 patients from nine studies (Table 3). We found a high FPR of 0.21 (CI 0.08–0.43) for absent motor response. The heterogeneity between the studies as assessed using Higgins I^2 was 28 % (Fig. 3). The lowest FPR was calculated in the studies by Cronberg and Fugate [10, 11] and the highest FPR in the study by Samaniego et al. [15]. The corneal reflex at 72 h after the arrest was available in 429 patients from seven studies. The overall FPR for absent corneal reflex was 0.02 (CI 0.002–0.13) (Fig. 4). The study by Bisschops et al. [7] had relatively high FPR compared to all other studies. The pupillary response to light was tested in 566 patients at 72 h after the arrest. The overall FPR for absent pupillary reactivity was 0.004 (CI 0.001–0.03) (Fig. 5).

Discussion

Therapeutic hypothermia changes the validity of the currently used electrophysiological and clinical parameters. This meta-analysis clearly indicates that the GCS motor score and the corneal reflexes at 72 h after the arrest are unreliable parameters to predict a poor outcome. Bilaterally absent pupillary reflexes and a bilaterally absent cortical N20 response both have low FPR, with narrow 95 % confidence intervals. The validity of the SSEP and

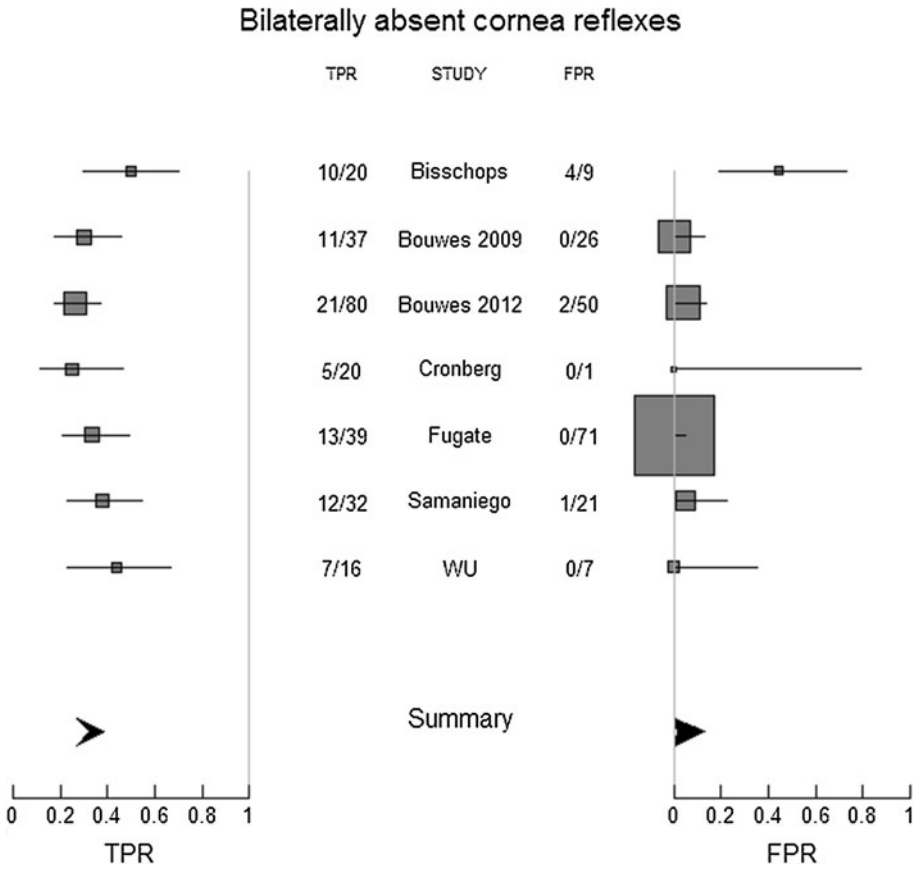

Fig. 4 TPR and FPR of bilaterally absent corneal reflexes at 72 h after the arrest. *TPR* true positive rate, proportion of patients with a unilaterally or bilaterally present corneal reflexes while having a favourable outcome; *FPR* false positive rate, proportion of patients with bilaterally absent corneal reflexes while having a favourable outcome. Heterogeneity between studies as determined by Higgins I^2 <1 %

the pupillary reflexes is comparable to that reported in patients not treated with hypothermia.

Early prognostication after cardiac arrest focuses on the prediction of an outcome no better than a vegetative state or severe disability. To avoid withdrawal of treatment in patients with a potentially favourable outcome, prognostic tests must have a high specificity for predicting a poor prognosis with a narrow confidence interval. The results of this meta-analysis strongly indicate that not all currently used clinical parameters can be applied to patients after hypothermia.

Hypothermia has a marked effect on the cerebral changes that occur during the post-cardiac arrest period by influencing metabolism, cerebral blood flow, inflammatory response and neuro-excitatory pathways [18]. These hypothermia-induced changes by themselves may prolong the time to recovery of the brain.

The elimination of sedatives such as midazolam and fentanyl, which were most frequently used for sedation and analgesia in this meta-analysis, are strongly influenced by temperature. Midazolam plasma concentrations increased fivefold in traumatic brain injury patients treated with hypothermia compared to normothermia control [19]. This may be explained by the depressed CYP3A4 and CYP3A5 activity during hypothermia [20]. Fentanyl is also metabolized by CYP3A4 and serum concentrations are increased in patients treated with hypothermia [21]. Hypothermia thus results in an unpredictable increase in the concentrations of circulating sedatives, analgetics and their metabolites. The motor response to painful stimuli and the corneal reflexes were less reliable in predicting a poor outcome in our meta-analysis compared to earlier reports from normothermic patients [1]. As these parameters are strongly influenced by sedation, the higher FPR may at least to some extent be explained by the effect of prolonged sedation. Cronberg et al. [10] performed the clinical neurological tests at 72 h after rewarming to normothermia and cessation of sedation. In that study, the prognostic value of the GCS motor score was higher compared to other studies. Both the pupillary reflexes to light and the SSEP are relatively unaffected by sedation, and had a better prognostic value comparable to that described in normothermic patients [1]. The wide confidence interval found for bilaterally absent corneal reflexes indicates the uncertainty for this test, and limits its safe use for prognostication. The prognostic value of the GCS motor score and corneal reflexes when tested later than 72 h after the arrest has to be established in this population.

The SSEP is considered a robust test that is relatively insensitive to sedation, muscle relaxation and temperature [9]. Bilateral absence of the N20 cortical response in the

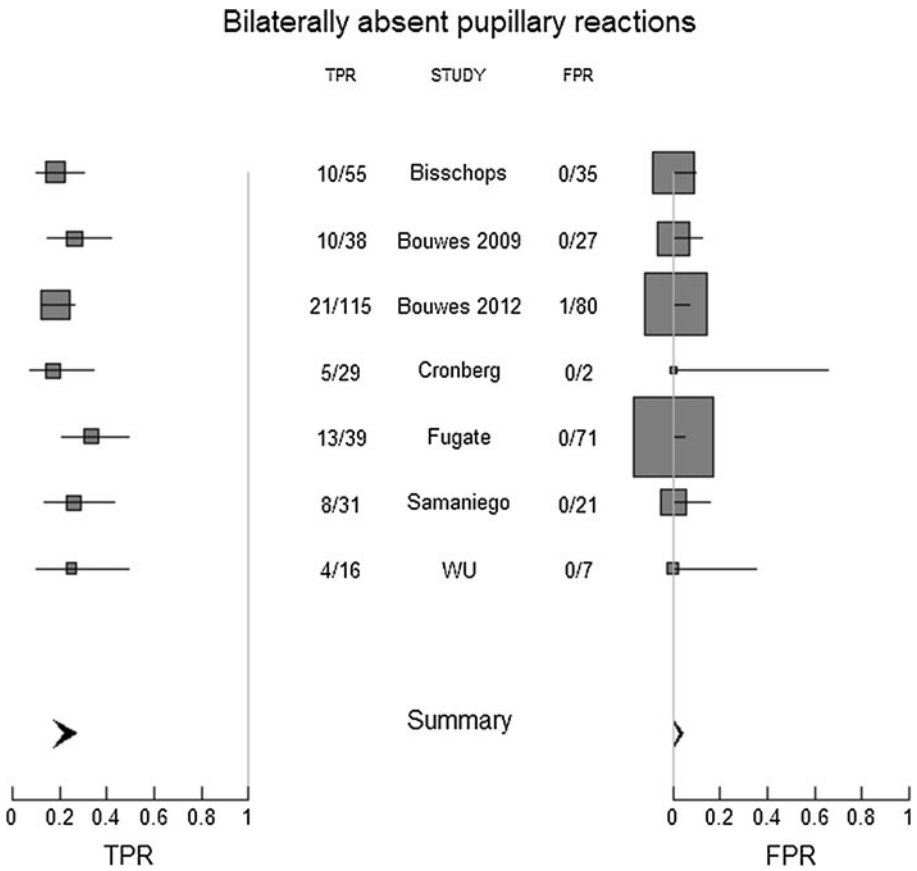

Fig. 5 TPR and FPR of bilaterally absent pupillary reflexes at 72 h after the arrest. *TPR* true positive rate, proportion of patients with a unilaterally or bilaterally present pupillary reflexes while having a favourable outcome; *FPR* false positive rate, proportion of patients with bilaterally absent pupillary reflexes while having a favourable outcome. Heterogeneity between studies as determined by Higgins I^2 0 %

SSEP was considered a valid predictor of poor outcome in patients who are unconscious after circulatory arrest by all authors and consequently, treatment was usually withdrawn in these patients. The FPR of a bilaterally absent N20 response was low in this meta-analysis and comparable with that reported in patients treated with normothermia [1]. These results should be interpreted with caution. Withdrawal of active treatment based upon a test result will automatically result in a self-fulfilling prophecy in which the true prognostic value of that test can no longer be established. We found one patient in a cohort of 492 patients with a bilateral absent N20 response who regained consciousness [12]. This patient was a 43-year-old man with alcoholism, resuscitated from asystole due to sepsis following severe pneumonia. The SSEP was recorded during administration of midazolam and fentanyl. This single case does not significantly change the FPR of the test in our meta-analysis; we found a low FPR and narrow confidence interval. In addition, the interpretation of the SSEP recordings is subject to a significant interobserver variability [22], especially in situations with much noise.

This is the first individual patient data meta-analysis that describes the prognostic value of neurologic examination after induced hypothermia after cardiac arrest. The strength of this individual patient data analysis is that it provides more information than is currently available in study-specific meta-analyses and hence increases the precision of estimates and reduces biases. Unfortunately, not all authors of identified studies responded or were able to provide their data. Data extraction from these studies was not possible because of the lack of detailed described information and they had to be excluded. Therefore not all available studies could be included in the meta-analysis. A maximum of 139 patients could have been added to the 1,153 patients included in this meta-analysis. It is very unlikely that this would have significantly changed our results.

This study has a number of limitations. The percentage of patients with poor outcome varied across studies between 44 and 79 %, reflecting a wide variability in case mix. Diagnostic tests were performed at different time points after the arrest, ranging from 72 h after the arrest to 72 h after restoration of normothermia. Outcome measures were assessed at different points in time, ranging from hospital discharge to 6 months after discharge. All study hospitals treated their patients according to the ILCOR guidelines [2]. As expected, local protocols differed in use of sedation, analgesia and muscle relaxants. Serum concentrations of sedatives and analgesics were not determined in patients in any of the studies. In addition, criteria for withdrawal of active treatment differed between

studies and a number of studies did not have a strict protocol for withdrawal of life-sustaining therapy. These differences may explain some of the heterogeneity between the validity of the studied parameters. A general concern in the design of all studies is the fact that, for obvious ethical reasons, treatment is generally withdrawn on the basis of results of the parameters that are under investigation. This may falsely increase the reliability of the tests that are under investigation. However, the main conclusion of our analysis is that absence of motor response and corneal reflexes at least 72 h after CPR are not reliable enough to predict poor outcome. The true prognostic value of the pupillary reflexes to light and the SSEP cannot be determined with absolute certainty from these studies because of their design.

Conclusions

Early prognostication after cardiac arrest in the hypothermia era is difficult and influenced by the hypothermia itself and use of sedatives. At 72 h after the arrest, the motor response to painful stimuli and the corneal reflexes are unreliable for the early prediction of poor outcome in patients treated with hypothermia. The validity of the pupillary response to light and the SSEP is comparable to that in patients not treated with hypothermia. Studies are needed to elucidate whether the prognostic value of clinical neurological parameters improves if performed later than 72 h after the arrest and to identify the optimal time point for clinical neurological prognostication.

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Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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