Clinical question.
In adult patients who are comatose after cardiac arrest (prehospital or in-hospital) (P), does the use of biochemical markers (I) as opposed to standard of care (C) allow accurate prediction of outcome (O) (eg survival)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Prognosis

State if this is a proposed new topic or revision of existing worksheet: New topic

Conflict of interest specific to this question
Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

Search strategy (including electronic databases searched).
Cochrane, medline, scopus, AHA Endnote master library: “Cardiac arrest” “coma” “neurological outcome” and “biochemical markers”

Date of recent search Nov 2009

Medline Search:
#1: Search Heart arrest 36180
#2 Search cardiac arrest 40592
#3 Search prognostication 1973
#4 Search #1 and #3 39
#5 Search coma 33299
#6 Search #2 and #3 34
#7 Search #2 and #5 843
#8 Search #1 and #5 1054
#9 Search #7 and #3 14
#10 Search #8 and #3 16
#11 Search biochemical markers 442104
#12 Search #1 and #3 and #11 4
#13 Search neurological outcome 19396
#14 Search #1 and #11 and #13 28

Scopus Search
#1: Search Heart arrest 39318
#2 Search cardiac arrest 24172
#3 Search prognostication 2630
#4 Search #1 and #3 36
#5 Search coma 42832
#6 Search #2 and #3 35
#7 Search #2 and #5 777
#8 Search #1 and #5 1168
#9 Search #7 and #3 16
#10 Search #8 and #3 17
#11 Search biochemical markers 30399
#12 Search #1 and #3 and #11 5
#13 Search neurological outcome 23918
#14 Search #1 and #11 and #13 12

AHA Master Library
#1: Search Heart arrest 2985
#2 Search cardiac arrest 0
#3 Search prognostication 14
#4 Search #1 and #3 11
#5 Search coma 449
#6 Search #2 and #3 0
#7 Search #2 and #5 0
#8 Search #1 and #5 157
#9 Search #7 and #3 0
#10 Search #8 and #3 5
#11 Search biochemical markers 32
#12 Search #1 and #3 and #11  1
#13 Search neurological outcome       134
#14 Search #1 and #11 and #13        2

Cochrane Search
#1 Search hear arrest 92
#2 search cardiac arrest 111
#3 search prognostication 3
#4 search coma 126
#5 search biochemical markers 140
#6 search #1 and #5       5
#7 search #1 and #4 and #5   0

• State inclusion and exclusion criteria
The following studies were excluded: reviews, not cardiac arrest, single cases, no neurologic outcome documented.

• Number of articles/sources meeting criteria for further review:
26 articles met criteria for further review: 25 were PLOEP2, 1 was PLOEP 4.
## Summary of evidence

### Evidence Supporting Clinical Question

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<td>Pfeifer 2005, 49 (NSE, S-100) CD</td>
<td>Piazza 2005, 477 (S-100) CE</td>
<td>Stelzl 1995, 24 (NSE) CE</td>
<td>Zingler 2003, 79 (NSE, S-100) CDE</td>
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<td>A = Return of spontaneous circulation</td>
<td>C = Survival to hospital discharge</td>
<td>E = Other endpoint</td>
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### Evidence Neutral to Clinical question

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- **A** = Return of spontaneous circulation  
- **B** = Survival of event  
- **C** = Survival to hospital discharge  
- **D** = Intact neurological survival  
- **E** = Other endpoint  

*Italics = Animal studies*

### Evidence Opposing Clinical Question

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*Italics = Animal studies*
### Reviewer's Final Comments and Assessment of Benefit / Risk:

#### Discussion:

Several studies have looked at the value of serum markers in prognostication following cardiac arrest. Different markers were studied: NSE, S-100, CK-BB, procalcitonin, NCAM, cortisol, CRP, WBC, fibrinogen. The majority of studies (n=19) focused on S-100 and/or NSE. All the studies were prospective studies with one exception. Tianinen 2003, 2881 was a RCT substudy of HACA trial. All studies have shown an elevation of S-100 and NSE following cardiac arrest and demonstrated that both markers have strong predictions of poor outcome. Despite the plethora of evidence cutoff values have varied between studies.

**S-100 as a poor prognosticator:**
- Levels varied depending on the study:
  - S-100 > 1.10 ug/L (Bottiger 2001, 2694) (100% specificity for poor outcome)
  - S-100 >0.44 ug/L (Fries 2003, 104) (100% specificity for poor outcome)
  - S-100 > 1.2 ug/l (Grubb 2007, 1268) 100% specificity for mortality
  - S-100 >0.29 ug/L (Grubb 2007, 1268) 100% specificity for memory decline
  - S-100 > 0.217 ug/L (Rosen 2001, 183) 100% PPV

- The cutoff value was different depending on the outcome selected whether poor outcome or mortality.

**NSE as a poor predictor:**
- Levels varied depending on the study
  - NSE > 25 ug/L (Meynaar 2003, 189) all patient with those values never regained consciousness
  - NSE >65 ng/ml (Pfeifer 2005.49) poor outcome
  - NSE > 27 ug/L (Prohl 2007, 1230) poor outcome
  - NSE >80 ng/ml (Reisinger 2007, 52) 100% PPV for poor outcome
  - NSE >16 ug/L (Shorkhuber 1999, 1598) poor outcome
  - NSE >140 ug/L (Steizl 1995. 24) very poor outcome
  - NSE >43 ug/L (Zingler 2003, 79) poor outcome.

- CSF values of both S-100 and NSE were lower than serum levels. Only one study looked at CSF S-100 (Karkela 1993, 100). Three studies looked at CSF NSE (Karkela 1993, 100; Martens 1996, 126; Roine 1989, 753)

#### False Positive rates of the NSE and S-100.

**S-100:**

- Bottiger 2001, p2694 ----- Predictor Mortality; Cut-off 0.2 ug/l---- FPR 0%
- Hachimi 2002 p 251 ------ Predictor Mortality; Cut-off 0.7 ug/l ---- FPR 13.25 (95% CI: -9-35)
- Grub 2007 p1268 ----- Predictor mortality ; Cutoff varying between 0.29 – 1.2 ug/l ---- FPR 9 (95% CI: -9 - 27)
  ---- Predictor Moderate to severe impairment ; cutoff 0.16-0.29 ug/l ---- FPR 7 (95% CI -82 – 96)
- Pfeifer 2005 p 49 ---- predictor poor neurological outcome; cutoff 1.5 ug/l ---- FPR 3.7%
- Zingler 2003 p79 --- Predictor poor neurological outcome; cutoff 0.2 – 5.2 , FPR 0%
- Tiainen 2003 p2881 --predictor poor neurological outcome; cutoff 0.12- 0.49 ug/l --- FPR 1 (95% CI -0.8 – 3.5)
- Schoerkuber 1999 p1598--- predictor poor neurological outcome; cutoff 14.5 – 17.9 ---- FPR 19 ( 95% CI: 5-33)
- Rosen 2001 p183 --- predictor of poor outcome.; cutoff 0.1 – 0.5 ---- FPR on day 1 20 (95% CI: 18-22); on day 2 FPR was 5 (95% CI -5 – 15), on day 3 FPR was 2 (95% CI: -3, 8).
- Rosen 1998 p473 ---- Predictor of mortality; cutoff 0.2 ----- FRP on day 1 was 19% and on Day 2 was 0%.

**NSE:**

- Grubb 2007 p1268 --- predictor of mortality; cutoff 16 -24 --- FPR 11 (95% CI: -13, 35)
- Meynaar 2003 p189—predictor of regaining consciousness; cutoff 25 ug/l --- FPR 0%
- Pfeifer 2005 p49 --- predictor of poor neurological outcome; cutoff 65 ug/l --- FPR 4%
- Rech 2006 pR133—predictor of poor neurological outcome; cutoff 60 ng/ml --- FPR 0%
Effect of Hypothermia on serum markers:
In one RCT the effect of hypothermia was studied. NSE values were lower in hypothermic patients whereas S-100 did not change. Patient with lower values did neurologically better (Tiainen 2003, 2881)

Several studies had multimodal approach to prognostication. No studies have demonstrated any specific improvement of predictions using serum markers over neurological exam or evoked potential

Grubb 2007, 1268 measured S-100 and NSE in addition to a clinical scoring. Poor clinical score were as predictive as S-100 and NSE.

Meynaar 2003, 189 developped a predictive model that included NSE, GCS and SSEP. The model showed that when GCS and SSEP were added to NSE the prediction increased from 64% to 76%.

The following studies included a combination of neurological exam and serum markers:

Acknowledgements:

Citation List


LOE 5. case report about use of microdialysis in cardiac arrest patients.


LOE4. CK-BB was measured in CSF in 115 consecutive patients with a multitude of neurological problems including brain death, cerebral hemorrhage and ischemia related to cardiac arrest. CSF was collected on admission and over the first 3 days of admission. The test had the most specific and predictive value at 3 days after admission


LOE2 good quality study. 66 patients undergoing CPR were studied. Serum samples were taken during CPR and after ROSC by an independent physician not involved in the care of the patient. Patient survival was assessed regarding ROSC and hospital admission and 14 day survival. Outcome divided into 4 groups: 1) no brain damage (CPC1), 2) documented brain damage, 3) no ROSC 4) patient died soon after ROSC. S-100 was measured at several time points. Significant difference in the levels of S-100 between patient surviving without brain damage and those with brain damage were observed. At 48 hours S-100 levels >1.10 ug/L revealed a
specificity of 100% for brain damage. It seems that the highest positive predictive value of S-100 levels was at 24 hrs. The NPV was 100% all across when 0.2 ug/L level cut-off was used. NSE levels were also measured and it seems that they were elevated in brain damage patients but no cutoff was measured.


LOE P2 study in which 23 patients who suffered from out-of-hospital cardiac arrest were enrolled. Blood samples were collected within the first hour and on day 1-3 after hospitalization. Both S-100 and procalcitonin (PCT) were measured. A blinded physician to the study assessed Glasgow-Outcome Scale at day 14. GOS<4 was considered bad outcome while GOS 4 and 5 were classified as good neurological outcome. The nonsurvivors had a significantly greater level of PCT than survivors on day 1, 2 and 3 but not at time of hospital admission. S-100 was significantly elevated in patients with bad neurological outcome even on hospital admission. On admission levels of 1.25 ug/L were 100% specific for predicting a bad neurologic outcome but low sensitivity, The sensitivity was the highest on admission. Levels of 0.2 on day 1 and on were associated with good sensitivity and specificity.


LOE P2 good study. 143 survivors of out-of-hospital cardiac arrest were included. The principal outcome measures in this study were memory test score and in-hospital mortality. Three time points for NSE and S-100 were sampled: within 12 hours of cardiac arrest, 24-48 hours, and 72-96 hours. NSE and S-100 were compared to a clinical prognostic score.


LOE P2 good study. Prospective observational study. Outcome was divided into two groups. Group 1 dead and PVS and group 2 regained consciousness. Results of S-100 were blinded to physicians. S-100 was obtained on admission and at 24 h later in all patients. S-100 levels were significantly elevated in comatose patient. A value of >0.7 ug/l at admission was found to be a predictor that consciousness would not be regained.


LOE2 study. Prospective study. 33 consecutive patients were included. A serum cortisol assay and corticotropin test were done 6-36 hr after cardiac arrest. Three outcome groups: 1) survival with full neurologic recovery, 2) early death from refractory shock and 3) later death from neurologic dysfunction. Patient who died of shock had lower response. No cutoff was established.

LOE P2. 20 consecutive patients were included in the study. Follow-up period 2 years. CSF and serum markers CK-BB, NSE and NCAM were measured.


LOEP2. Prospective study. 52 patients. Serum NSE measured.24 hrs after cardiac arrest.


LOE P2. 110 patients included. SSEP measured at 48h post CPR. Blood for NSE measured on admission and every 24 h for 5 days or until discharge from ICU. No patient with serum NSE level >25 ug/l at any time regained consciousness.


LOE P2. 97 patients. Two groups outcome. Poor outcome died or PVS. Group II good or moderate outcome. NSE or S-100 were measured 1-3 times daily for 5 days. NSE serum levels >6 or= 65 ng/ml increased risk of death and PVS by 16.8. S-100 level >or=1.5 increased risk of death and PVS by 12.6.


LOE P2. S100 serum levels assessed at 12 hr. EEG recorded within 24 hours. At hospital discharge outcome divided into two groups. Group 1 bad neurological outcome, group 2 good neurological outcome (GOS 4-5). Sensitivity of S100 was high (100%), specificity was low. Only abstract was reviewed.


LOE P2. Good study. 80 consecutive patients were included. NSE and S100 were measured on days 2, 3, and 4 after cardiac arrest. Neurological exam done at day 2 and 4 after CA. a clinical examination score was developed. Evoked potential were done on day 4. GP-CPC was used to measure outcome at 1 and 6 month. Neuropsych testing was done at 1 and 6 month.


LOE P2. 45 patients were included. NSE was measured between 12 and 36 hours. GOS was measured at 6 month. NSE with a cutoff of 60 ng/ml had a specificity of 100% and sensitivity of 35%. PPV of 100%, NPV of 29%.

LOE P2. good study. 227 consecutive patients were included. Serum NSE measured on admission and daily for 4 days. Physicians not blinded to NSE results, therapy the same regardless of level. Neurological outcome was evaluated using GP-CPC within 6 months. Peak NSE of > 80 ng/ml predicted persistent coma with sensitivity of 63%, PPV 100%, NPV 84%, predictive accuracy of 88%.


LOE P2. 75 patients. CSF samples. Cutoff for CSF NSE >24 ng/ml 24 hours after cardiac arrest.


LOE P2. 22 were included in the study. Lumbar puncture was done on day 12-14. Neurofilament concentration was measured. Examination were planned on admission, day 2-4, days 12-14, day 45, 3 month, and one year. Coma level was assessed using the swedish RLS 85 score.


LOE P2. good study S-100 level of 0.2 was used. Serum samples taken during the first 3 days.


LOE P2. S-100 >0.2 had a PPV of 100%. NSE >15 had a PPV of 100%.


LOE P2. no difference in NSE levels at 6 hours but at 12,24,48 and 72 hours. the ROC curve was the highest at 72 hours. NSE level >16 was the best cutoff level


LOE P2. BNP measured in 155 patients. Outcome at 6 month

**LOE p2. Only thirteen patients**


**LOE P2. Hypothermia patients in cardiac arrest. NSE levels were affected by hypothermia but not S-100**


**LOE P2. Type to achieve hypothermia correlated with high NSE values**


**LOE5. CRP and fibrinogen level were measured.**


**LOE P2. NSE and S100 measured on days 1,2,3 and 7. best cutoff for negative outcome was NSE>43.**