Identification of biomarkers suitable for predicting cognitive decline in patients undergoing cardiac surgery

Douglas S. Pfeil Ph.D.[1], Harry L. Graber Ph.D.[2], Jeremy D. Coplan M.D.[3], Yong Xu Ph.D.[2], Randall L. Barbour Ph.D.[1,2], Daniel C. Lee M.D.[4]

[1]Dept. of Pathology, SUNY Downstate Medical Center, Brooklyn, NY 11203 USA [2]NIRx Medical Technologies, Glen Head, NY 11545, USA
[3]Dept. Of Psychiatry, SUNY Downstate Medical Center, Brooklyn, NY 11203 [4]Dept. of Surgery, U. of Oklahoma, Oklahoma City, OK 73126 USA

Introduction

- Postoperative cognitive decline (POCD) remains significantly high in patients undergoing cardiac surgery[1,2]
- At discharge, 50-80% of patients exhibit POCD, persisting in 20-50% of patients 6 weeks after surgery[3].

- Currently available cerebral oximeters (e.g. INVOS) that use near-infrared spectroscopy (NIRS) for patient monitoring are based on small-area, low-density arrays
- Utilize *declines in cerebral hemoglobin saturation (Hbsat / rSO2) to predict POCD*
- Demonstrated *poor sensitivity[4]*

- We hypothesize that large, high-density arrays (HDA) of NIRS probes, used in combination with biomarkers based on *cerebral autoregulation, will provide better predictions of POCD*

Methods

- 17 patients undergoing elective cardiac surgery
- Patients performed neurocognitive tests before surgery and at time of discharge.
  - Trail Making Part A & B
  - Grooved Pegboard
  - Symbol Digit Modalities
  - MMSE/Animal naming/Short story recall from Community Screening Interview for Dementia
  - Modified Word List Learning
- >20% decrease in performance in at least 2 of the tests was considered to be a POCD[5]

- Intra-operatively, patients monitored with HDA of 48 optical sources and 32 detectors
- HDA arranged into 104 overlapping source-detector pairs (channels), inter-optode distance of 4cm - Figure 1

- Several biomarkers (Results) derived from NIRS data were tested using rank-sum tests to differentiate those with and without POCD
- Biomarkers were tested using smaller partial arrays to determine if a smaller system can be used in the future.

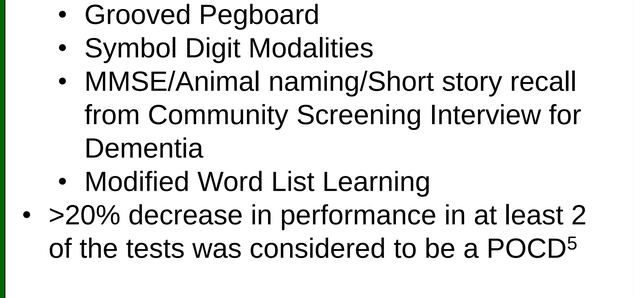

Figure 1: a) Picture of the new patient interface on an anthropomorphic head. b) Picture of the new patient interface on a patient in the OR with an overcap in place. c) Schematic representation of the array to illustrate the 2x2 source-detector block design

Results

- 11 out of 17 patients able to complete pre and post-operative testing and had NIRS and mean arterial pressure (MAP) data suitable for analysis

- ARRAYS ANALYZED – values of each biomarker were averaged across a given array for each patient (Figure 2 identifies each partial array location with colored dots)
  - Global: All good channels for a given patient (ranges from 19 to 103)
  - 12 good: the 12 channels that had good data quality for all 11 patients
  - Forehead: An 8-channel array with optodes over the forehead region
  - INVOS-mimic: a 2-channel array located over the forehead in a position similar to that used by INVOS.

- BIOMARKERS ANALYZED – values derived from the NIRS data that were used in attempts to separate patients with and without POCD
  - Sat < 65%: the number of time frames when saturation fell below 65%
  - Sat/Tot < 20% BL: the number of time frames when saturation or Hbtot fell more than 20% of the baseline value
  - Autoreg: The number of overlapping 5-minute intervals (i.e., minutes 0-5, 1-6, 2-7,…) with Pearson correlation between Hbsat and MAP > 0.4[6]. High correlation implies a loss of autoregulation - Figure 3
  - Tot-MAP: analogous to Autoreg but utilizing Hbtot instead

- Autoregulatory marker distinguishes the groups, for ALL arrays
- Use of subtraction-based superficial correction methods produced a reduction in statistical significance

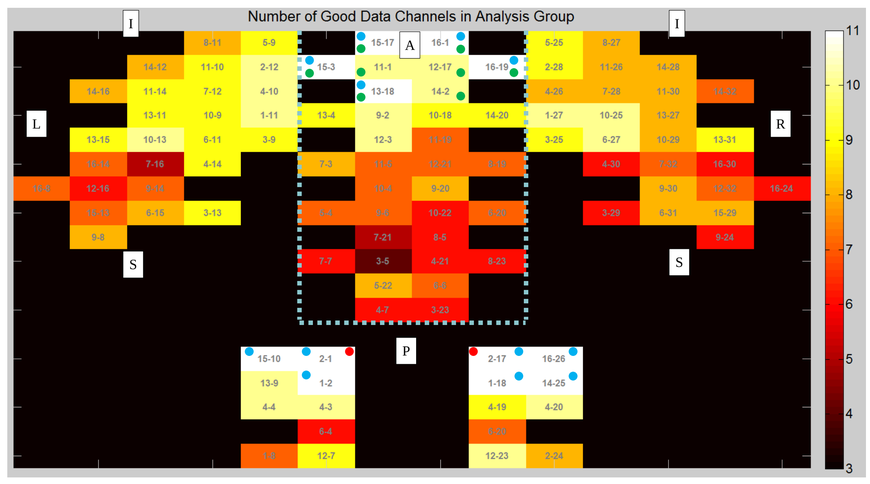

Figure 2: Topographic map displaying the number of times each data channel was marked good across the 11 analysis patients. Blue dots represent the 12 good channels across all 11 patients. Green dots represent the channels used in the 8-channel forehead array. Red dots represent the INVOS-mimic array. A = anterior, P = posterior, I = inferior, S = superior, L = left, R = right

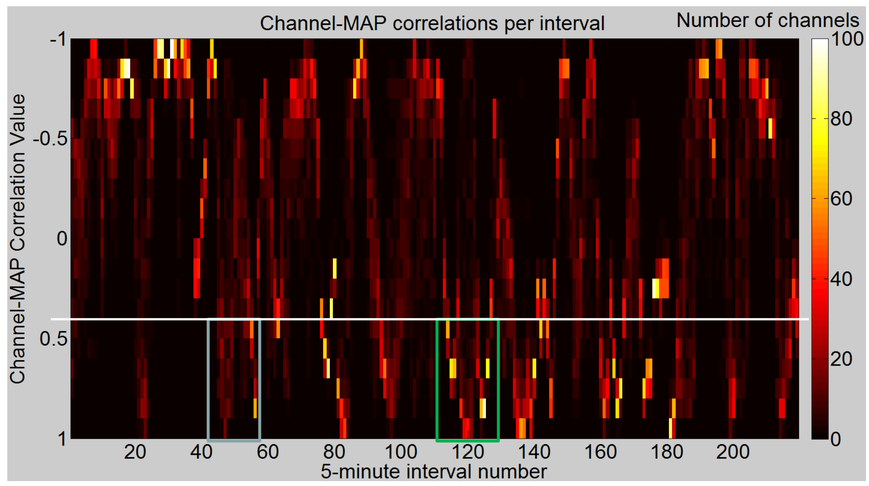

Figure 3: Colorplot showing the number of channels with a particular Hbsat channel-MAP correlation value during all 5-minute overlapping intervals for patient 09. Channel-MAP correlations BELOW the white line represent channels where autoregulation has failed. The blue box highlights the transition onto bypass, when many hemodynamic shifts are present. The green box highlights a period when the surgeon was replacing the patient's heart valve.

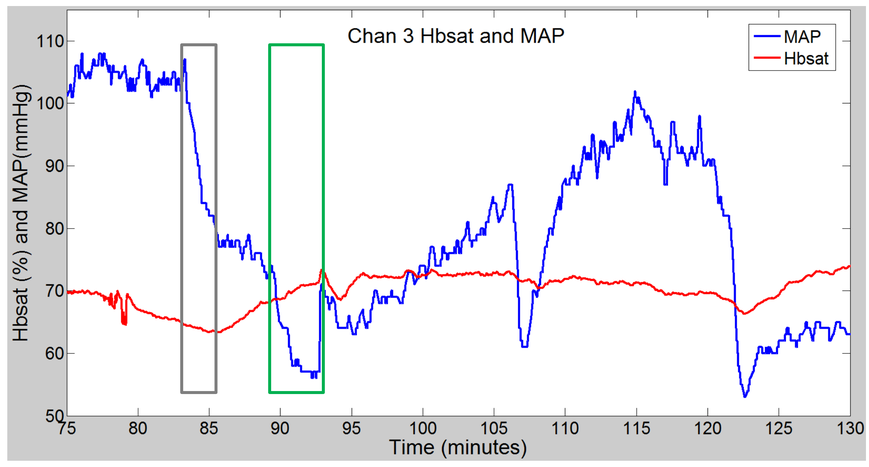

Figure 4: Time series showing both MAP and one channel of Hbsat data. The gray box shows a period when autoregulation fails while MAP is high. The green box shows a time period when autoregulation is maintained while MAP < 60mmHg.

Marker	POCD	No POCD	P-value
Age	76.0	58.8	0.0173
Surg. Length (min)	291.0	238.1	0.0519
Autoreg – global	103.1	71.0	0.0173
Autoreg – 12 good	114.8	80.4	0.0303
Autoreg – forehead	122.1	84.4	0.0087
Autoreg – INVOS mimic	113.1	82.8	0.0303
Tot-MAP – global	74.3	66.7	0.4286
Tot-MAP – forehead	102.4	72.9	0.0519
Sat < 65% – global	5127	2387	0.1775
Sat <65% – forehead	4777	994	0.3463
Tot <20% BL – global	7281	7170	0.9307
Tot <20% BL – forehead	4247	3076	0.7100
Autoreg * Age	9242	5029	0.0043
Corrected - forehead	77.0	55.6	0.1775
Corrected - INVOS	49.8	46.3	0.9307

Table 1: Biomarker values and p values for differences between the patient groups (rank-sum testing).

Repeated Measures ANCOVA

- Performed using each partial array as a repeated measure, with patient age or duration of surgery as a covariate
- p-values are reported for one-tailed tests; *a priori* hypothesis is that number of autoregulatory failures cannot be higher in patients who do not develop POCD.
- Autoregulatory marker of the forehead array after adjusting for age has a large effect ($\eta_p^2 = 0.36$); compare to the small effect for age ($\eta_p^2 = 0.02$)

Autoregulatory marker covaried with age (d.f. = 1,11)		
Global	F = 3.02	p = 0.06
Forehead	F = 4.46	p = 0.034
INVOS-mimic	F = 0.69	p = 0.22
Autoregulatory marker covaried with surgery duration (d.f. = 1,11)		
Global	F = 3.97	p = 0.04
Forehead	F = 6.39	p = 0.018
INVOS-mimic	F = 0.43	p = 0.12

Table 2: Output from the repeated measures ANCOVA, using age or surgery duration as a covariate.

Conclusions

- *Correlation-based autoregulatory markers* are easy to obtain and can differentiate those with and without POCD
- *Superficial correction methods are not needed*

- RM ANCOVA analysis:
  - Forehead array demonstrated significant results after covarying for age and surgery duration
  - Only a small inter-group effect due to age or surgery duration

- Small, but high-density forehead array may provide best balance between ease-of-use and data quantity
- Autoregulation may be dependent on rate of change of MAP as well as its absolute level
  - More study needed

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