

Clinical paper

Neurologic prognostication and bispectral index monitoring after resuscitation from cardiac arrest[☆]

Marion Leary^a, David A. Fried^a, David F. Gaieski^a, Raina M. Merchant^a, Barry D. Fuchs^b, Daniel M. Kolansky^c, Dana P. Edelson^d, Benjamin S. Abella^{a,b,*}

^a Center for Resuscitation Science and Department of Emergency Medicine, University of Pennsylvania, Philadelphia, USA

^b Section of Pulmonary, Allergy and Critical Care, University of Pennsylvania, Philadelphia, USA

^c Section of Cardiology, University of Pennsylvania, Philadelphia, USA

^d Section of Hospital Medicine, University of Chicago, Chicago, USA

ARTICLE INFO

Article history:

Received 8 December 2009

Received in revised form 13 April 2010

Accepted 23 April 2010

Keywords:

Cardiopulmonary resuscitation

Heart arrest

Sudden death

ABSTRACT

Objective: While the use of therapeutic hypothermia (TH) has improved outcomes after resuscitation from cardiac arrest, prognostication of survival and neurologic function remains difficult during the post-arrest time period. Bispectral index (BIS) monitoring, a non-invasive measurement of simplified electroencephalographic data, is increasingly being considered for post-arrest neurologic assessment and outcomes prediction, although data supporting the technique are limited. We hypothesized that BIS values within 24 h after resuscitation would correlate with neurologic outcomes at discharge.

Methods: We prospectively collected BIS data in consecutive patients initially resuscitated from cardiac arrest and treated with TH in one academic medical center. We assessed BIS values in context of cerebral performance category (CPC) assessment on the day of discharge.

Results: Data were collected in 62 post-arrest patients, of whom 26/62 (42%) survived to hospital discharge. Mean BIS values at 24 h post-resuscitation were significantly different in the survivors with CPC 1–2 (“good” outcome) vs those with CPC 3–5 (“poor” outcome) or death during hospitalization (49 ± 13 vs 30 ± 20 ; $p < 0.001$). Receiver operator characteristic analysis suggested that 24 h BIS was most predictive of CPC 1–2 outcome compared to the other timepoints; a BIS cutpoint of 45 exhibited a sensitivity of 63% and a specificity of 86%, with a positive likelihood ratio of 4.67. Sixteen patients exhibited a BIS of zero during at least one timepoint; all of these patients died during hospitalization.

Conclusions: BIS monitoring values at 24 h post-resuscitation are correlated with neurologic outcomes in patients undergoing TH treatment. In 16/62 patients, a BIS of zero at any timepoint was observed, which was uniformly correlated with poor outcome after resuscitation from cardiac arrest; however, a non-zero BIS is insufficient as a sole predictor of good neurologic survival.

© 2010 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Therapeutic hypothermia (TH) improves both the probability of survival and neurologic recovery after resuscitation from cardiac arrest.^{1–4} Patient selection for post-arrest TH remains problematic, as there are no clinically validated tools to determine who might benefit from the therapy.^{5,6} Furthermore, current neurologic assessment techniques during the early post-arrest timeframe are

considered unreliable in the resuscitated patient undergoing TH treatment, making prognostication of survival and neurologic outcomes difficult.^{7–9}

Bispectral index (BIS) monitoring, which represents a calculated summary of raw electroencephalographic (EEG) data including frequency and amplitude, is routinely used to assess the level of consciousness during anesthesia and critical care sedation.^{10,11} BIS is currently being investigated as a diagnostic method to monitor brain activity in patients resuscitated from cardiac arrest.^{12,13} Although BIS monitoring is attractive due to its relative simplicity and non-invasive nature, its role in prognostication remains unclear. We sought to determine if BIS monitoring during the initial 24 h after cardiac arrest resuscitation, and during TH application, could predict survival outcomes and neurologic function at hospital discharge.

[☆] A Spanish translated version of the summary of this article appears as Appendix in the final online version at doi:10.1016/j.resuscitation.2010.04.021.

* Corresponding author at: Center for Resuscitation Science and Department of Emergency Medicine, University of Pennsylvania, 3400 Spruce Street, Ground Ravidin, Philadelphia, PA 19104, USA. Tel.: +1 215 279 3452; fax: +1 215 662 3953.

E-mail address: benjamin.abella@uphs.upenn.edu (B.S. Abella).

2. Methods

This observational study, performed prospectively on patients during their post-arrest care at one hospital site, was approved by the University of Pennsylvania Institutional Review Board. All data were collected in a manner compliant with the Health Insurance Portability and Accountability Act of 1996 regulations.

Patients were evaluated at the Hospital of the University of Pennsylvania (HUP) from June 2007 to November 2009. HUP is a 700-bed tertiary-care academic medical center, and has utilized a TH post-arrest protocol since 2006.^{14,15} All adult patients who achieved return of spontaneous circulation (ROSC) after resuscitation from cardiac arrest and were treated with TH at our facility were considered eligible for this study. Patients were included regardless of initial arrest location (out-of-hospital or in-hospital). The decision to employ TH in post-arrest patients who achieved ROSC was made by staff physicians irrespective of this study. Given our goal of assessing BIS monitoring during TH, we excluded patients who did not receive hypothermia treatment. Given that our patient sample represented an observational cohort without differing interventions, our enrollment was not established by power calculation but rather by an *a priori* defined time period for enrollment.

2.1. Therapeutic hypothermia protocol

Post-arrest patients at HUP are generally considered eligible for TH regardless of initial arrest rhythm or location of arrest. Patients suffering traumatic arrest or exhibiting clinically significant bleeding are excluded, as are patients resuscitated from arrest within 48 h of major operative intervention. Patients selected for TH are cooled to a target temperature of 32–34 °C, via both an intravenous bolus of chilled (approx. 4 °C) saline of up to 2 L and a commercially available cooling system with external pads (Gaymar III 7800, Gaymar Industries, Orchard Park, NY). Target temperature is then maintained for 24 h via the external pad system, using either an indwelling bladder or esophageal temperature monitoring probe. BIS monitoring (Aspect Medical Systems, Norwood, MA) is applied immediately after resuscitation and the initiation of sedation and neuromuscular blockade. In the HUP TH protocol, neuromuscular paralysis is induced before cooling and then continued for at least 24–36 h, until rewarming is complete. The BIS monitoring sensor is applied to the patient's forehead and the device is checked by the RN for signal accuracy prior to recording. After completion of the 24 h TH maintenance period, rewarming to 37 °C is performed. BIS monitoring is discontinued after completion of both this process and the discontinuation of neuromuscular blockade.

2.2. Data collection

BIS values are derived by incorporating multiple features of the EEG signal, including frequency, amplitude and morphologic features (burst suppression, delta waves, etc.). The output from BIS monitoring reflects the predominant EEG feature that is being detected at the time of monitoring and transforms that feature into a dimensionless single integer from 0 to 100, with a zero value representative of a "flatline" EEG and values approaching 100 representative of the normal awake state. In the neurologically intact patient undergoing operative sedation, BIS values of 40–60 are considered reflective of adequate "depth" of anesthesia.¹⁰

In the HUP post-arrest protocol, numeric output from the BIS device is continuously available until the device is removed. For the purposes of this investigation, BIS values were recorded at a "zero" timepoint (immediately upon initiation of BIS recording) and subsequently at timepoints of 12 and 24 h post-resuscitation. BIS was started during the initiation phase of TH; the 12 and 24 h timepoints

Table 1

Subject demographics and clinical data (n=62).

Patient age (years), mean ± SD	55 ± 16
Gender, n (%)	
Female	26 (42%)
Male	36 (58%)
Location, n (%)	
OHCA	32 (52%)
In-hospital	17 (27%)
ICU	4 (6%)
Ward	58 (93%)
Outside hospital transfer	13 (21%)
Initial rhythm, n (%)	
VF/VT	25 (40%)
Asystole	12 (19%)
PEA	21 (34%)
Other	4 (7%)
Outcomes	
Survival to discharge	26 (42%)
Survival with CPC 1 or 2	20 (32%)

SD, standard deviation; OHCA, out-of-hospital cardiac arrest; ICU, intensive care unit; VF/VT, ventricular fibrillation/ventricular tachycardia; PEA, pulseless electrical activity; CPC, cerebral performance category.

occurred during the TH maintenance phase before rewarming was begun. Paralytics were routinely discontinued once the rewarming process was initiated, after the 24 h timepoint. Therefore, given the possible confounding of neuromuscular activity on BIS values, we chose to evaluate BIS up until the 24 h timepoint to maintain reliability of our measurements. Given that BIS may be sensitive to other factors such as temperature or dosing of anesthetic agents, we collected patient temperature at each timepoint as well as types and doses of sedatives given. Other clinical data were abstracted from patient medical records. Global neurologic assessment was classified by cerebral performance category (CPC)¹⁶ in concordance with prior investigations of BIS in the post-arrest state.^{12,13} For study purposes, these outcome assessments were dichotomized, with a CPC of 1–2 considered a "good" outcome and a CPC of 3–5 reflective of "poor" outcome. Our primary outcome in the current study was survival to hospital discharge with good neurologic outcome (CPC 1–2).

2.3. Statistical analysis

Descriptive statistics were utilized for demographics and were compiled using a spreadsheet application (Excel, Microsoft Corp, Redmond, WA). Two-sided Student's *t*-tests were used to compare BIS values at each of the timepoints by outcome. Receiver operator characteristics (ROC) curves were constructed and the area under the curve (AUC) compared across timepoints in the same patients using paired Chi-squared statistics. In addition, sensitivity, specificity and positive likelihood ratios at various BIS cutpoints were calculated based on ROC analysis. An alpha of <0.05 was considered statistically significant. All analyses were conducted using a statistics application (STATA 10, Statacorp, College Station, TX).

3. Results

During the time period of the study, 66 post-arrest patients were treated at our institution with TH according to the hospital's post-arrest/TH protocol. Of those cooled, 62 were included in our analysis (see Table 1). Three patients were excluded as TH treatment was conducted without paralytic use, and one additional patient was excluded due to missing clinical records. Mean age of patients in this study cohort was 55 ± 16 years; 26/62 (42%) were female. Out-of-hospital arrest accounted for 32/62 (52%) of the subjects. Initial arrest rhythms were VF in 25/62 (40%) patients, PEA in

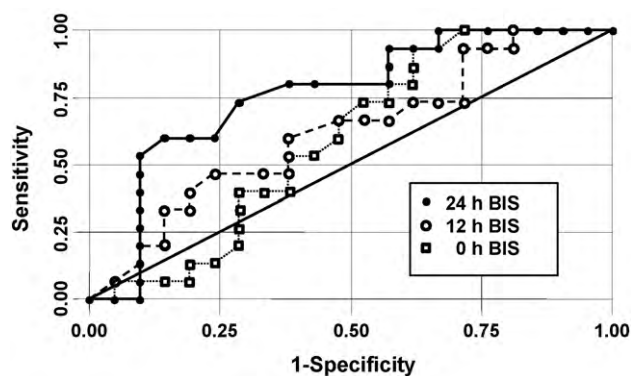


Fig. 1. Receiver-operator characteristic (ROC) curves for the three BIS timepoints analyzed in this study cohort. The ROC with the greatest area under the curve (AUC) was the 24 h timepoint (closed circles), with an AUC = 0.785 (95% CI 0.654–0.916).

21/62 (34%), and asystole in 12/62 (19%). Post-arrest care and TH treatment was delivered to 61/62 (98%) patients in either the medical or cardiac intensive care unit at HUP, with one patient receiving treatment in the surgical intensive care unit. Patients were treated with sedatives and paralytics according to a uniform hospital protocol, that included the use of fentanyl/lorazepam for sedation, and either cisatracurium and pancuronium for neuromuscular blockade. Survival to discharge was attained in 26/62 (42%) patients; at discharge, 20/62 (32%) had a CPC 1–2 and 6/62 (10%) had a CPC 3–5. These survival statistics are similar to prior published reports from hospitals employing post-arrest TH.^{17,18}

BIS data from initial and subsequent timepoints are shown in Table 2 along with corresponding temperature values. Initial BIS values demonstrated differences between survival to hospital discharge with CPC 1–2 vs CPC 3–5 or non-survival, although these differences became more pronounced at both 12 and 24 h after resuscitation at which points there were statistically significant differences between the two groups (12 h BIS: 45 ± 16 vs 34 ± 21 , $p = 0.038$; 24 h BIS: 49 ± 13 vs 30 ± 20 ; $p < 0.001$). Interestingly, 16/16 (100%) of subjects who exhibited a BIS value of zero during at least one timepoint expired during hospitalization, although 11/16 (69%) of these patients had care withdrawn due to clinical perception of moribund condition. Temperature variations were modest at the 12 and 24 h timepoints and reflected implementation of the thermostatically-controlled TH protocol. Dosing of sedation medications varied widely but no statistically significant differences were found across the three timepoints for the overall patient cohort (see Table 3).

The ROC curves for each of the timepoints are shown in Fig. 1, demonstrating a significantly higher area under the curve (AUC) at 24 h compared with the other timepoints, AUC = 0.785 (95% CI 0.654–0.916). We therefore utilized this timepoint to generate sensitivity and specificity values for the various BIS cutpoints, which are shown in Tables 4A and 4B. The cutpoint that maximizes the percentage of correctly classified patients was a BIS of 45, which predicted CPC 1–2 survival to discharge with a sensitivity of 63%, a specificity of 86%, and a positive likelihood ratio of 4.67 (see Table 4A). These analyses were repeated for the ability of BIS to predict survival independent of neurologic function, with similar results (see Table 4B).

4. Discussion

In this prospective evaluation of post-arrest BIS monitoring at one U.S. hospital, significant differences were found in mean BIS values between survivors to hospital discharge with good neurologic function (CPC 1–2) and those patients who died or survived

with poor neurologic outcomes. Receiver operator characteristic analysis suggested that the 24 h BIS timepoint was most predictive of CPC 1–2 survival, with a cutpoint of BIS ≥ 45 yielding the highest positive likelihood ratio. At this cutpoint, however, sensitivity and specificity for good outcomes are still somewhat modest. Distinct from this finding, we determined that a BIS value of zero at any point up to 24 h after resuscitation was associated uniformly with death, although this patient subset is admittedly small (16 patients). Our work adds to the small clinical literature on neuroprognostication after resuscitation from cardiac arrest with concomitant TH, and specifically addresses the role of non-invasive brain monitoring.

Our observation of 100% sensitivity for predicting death with a BIS of zero is a finding largely consistent with prior work by Stammet et al., who found that a BIS of zero predicted poor outcome in 14/14 (100%) of cases in their series, although 3/14 (21%) were alive at 6 months with a CPC of 3–5. In their work, they found a modest correlation between non-zero BIS values and clinical outcomes. Stammet et al.¹² compared patients at highest and lowest BIS values throughout a 72 h timecourse, which may be less clinically practical than comparison of BIS measurements at a fixed point after resuscitation. When we compared BIS values at a fixed point of 24 h, significant differences existed between survivors and non-survivors. Although individual values overlapped, it raises the possibility that a 24 h BIS measurement could be combined with another assessment method at 24 h, such as somatosensory evoked potentials, to derive a robust prognostication scoring system. This is further suggested by the work of Seder et al.,¹³ who combined assessment of both BIS and electroencephalographic suppression ratios in a single site investigation and found that this combination was an early predictor of outcome. However, it must be stressed that BIS measurement alone is unlikely to serve as a reliable sole predictor of outcome, in very similar fashion to EEG analysis in this patient population.

Our work attempts to address the difficulty with prognostication during the immediate post-arrest time period. Standard neurologic physical examination, for example, is largely insensitive to outcomes. We have not included neurologic examination data from our cohort, as patients included for treatment with TH exhibit coma or marked neurologic impairment, and then are paralyzed during TH treatment rendering neurologic examination insensitive. In fact, a 2006 consensus statement from the American Academy of Neurology suggested that clinicians should refrain from prognostication for the first 72 h after resuscitation from cardiac arrest, especially based on clinical neurologic exam,⁸ given that severe encephalopathy during this time may not be reflective of eventual outcomes.

A number of alternative assessment methods have been recently evaluated for the purposes of prognostication, with mixed results. These have included measurement of injury biomarkers such as S100B and nerve-specific enolase,¹⁹ or tests of neurophysiology such as somatosensory evoked potentials.²⁰ In addition, continuous EEG recording is performed as part of TH protocols at a number of hospitals; the use of EEG for prognostication remains poorly characterized. Further investigation will be required to establish which techniques provide adequate discriminatory power to enter clinical practice during TH application. Development of a useful prognostication system will be an important step towards broader comfort with, and acceptance of, TH by a range of practitioners.²¹ In addition, further elucidation of the mechanisms of post-arrest brain injury will help guide prognostication efforts. For example, the mechanism for BIS values correlating with outcomes are unclear, with possibilities ranging from BIS assessment correlated with lessening of cerebral edema and improvement of cerebral blood flow, to improved BIS reflecting improved neuronal function as diffuse inflammatory processes are attenuated.

Table 2
Mean BIS values for those who survived to discharge with CPC 1–2 vs CPC 3–5.

Timepoint	T (°C)	BIS values			p value
		CPC 1–2	CPC 3–5	All patients	
Initial	34.6 ± 2.0	57 ± 24	41 ± 32	46 ± 30	0.069
12 h	33.3 ± 0.8	45 ± 16	34 ± 21	38 ± 20	0.038
24 h	33.1 ± 0.6	49 ± 13	30 ± 20	37 ± 20	<0.001

The CPC 3–5 category includes patients who either experienced brain death or expired. Temperature and BIS values are shown ±SD. BIS, bispectral index; CPC, cerebral performance category; SD, standard deviation.

Table 3
Doses of sedative medications given during post-arrest care.

Timepoint	Temp	Fentanyl	Lorazepam	Propofol	Midazolam
Initial	34.5 ± 2.0				
n		36	19	6	1
Dose		96.7 ± 84.5	1.8 ± 0.7	35.8 ± 22.9	2.0 ^a
12 h	33.3 ± 0.8				
n		50	25	7	2
Dose		135.3 ± 84.0	2.0 ± 0.8	26.4 ± 11.4	2.0 ^a
24 h	33.1 ± 0.6				
n		51	26	7	1
Dose		146.5 ± 105.3	2.4 ± 1.2	26.0 ± 16.4	2.0 ^a
p value across timepoints		p = NS	p = NS	p = NS	p = NS

Fentanyl dosing is given as mcg/h, lorazepam as mg/h, propofol as mcg/kg/min, and midazolam as mg/h. p values were calculated for each pairwise comparison within medication type; no comparison was found to be statistically significant.

^a No SD given due to small sample size. ±SD, standard deviation.

Given that TH alters the pathophysiology of post-resuscitation injury, it is likely that prognostication may be different in patients who receive TH vs those who do not. Further complicating this, the timing of TH induction may also affect the ability of different techniques to predict outcome. Recent work in both laboratory investigations and the clinical arena have suggested that TH induction before the restoration of circulation may provide the most clinical benefit.^{22,23} It remains to be seen whether patients treated with TH before reperfusion exhibit markedly different characteristics when monitored via BIS or EEG, for example.

We note a number of important limitations to our study. We only obtained BIS data during the early phase (0–24 h) of post-resuscitation care, as the technique is limited when paralytics are discontinued due to muscular activity artifact. In addition to paralytics, variations in sedation medications might also play a role in BIS measurements, although we did not find marked changes in sedation dosing across the initial 24 h of care. Given that our

purpose was to assess BIS monitoring for practical hospital-based prognostication, we limited our outcomes to hospital discharge and did not perform longer term follow-up assessments. It is possible that some of the patients classified as CPC 3–5 improved over several months after discharge, although prior studies suggest that this would only occur in a minority of patients, if at all. We are also limited by a small sample size at one hospital. It is unclear whether inter-hospital differences, either in details of pharmacologic paralysis or other aspects of post-arrest care, might affect the interaction of BIS measurement and outcomes. Future work with larger patient populations will be required, and additional investigations might benefit from the study of multiple assessment techniques in concert, with the goal of developing a clinically useful “bundle” of prognostic tools.

A final limitation is reflected in the fact that BIS monitoring was originally developed and validated to assess the level of sedation during procedures requiring anesthetics. Other investigations that

Table 4A
Sensitivity and specificity values at illustrative BIS cutpoints to predict CPC 1–2 survival, using the 24 h BIS timepoint receiver-operator characteristic curve.

BIS cutpoint	Sensitivity (%)	Specificity (%)	Positive likelihood ratio
30	95	41	1.59
40	79	68	2.43
45	63	86	4.67
50	53	89	4.38
60	21	92	2.60

BIS, bispectral index; CPC, cerebral performance category; SD, standard deviation.

Table 4B
Sensitivity and specificity values at illustrative BIS cutpoints to predict overall survival, using the 24 h BIS timepoint receiver-operator characteristic curve.

BIS cutpoint	Sensitivity (%)	Specificity (%)	Positive likelihood ratio
30	100	48	1.94
40	81	71	2.78
45	62	94	9.54
50	54	97	16.69
60	19	100	–

No positive likelihood ratio is given for the final cutpoint, as specificity is 100%. BIS, bispectral index; CPC, cerebral performance category; SD, standard deviation.

have evaluated BIS in the context of sedation have found that interpretation of BIS values is complex, and it may not be a reliable indicator of appropriate sedation in all cases; other factors such as temperature may play a role in BIS interpretation.^{24,25} Furthermore, some studies have even suggested a limited or negative role for BIS during cardiac arrest resuscitation.²⁶ Additional work will be required to characterize the value of BIS monitoring in a variety of settings including the care of patients after resuscitation from cardiac arrest.

5. Conclusions

BIS monitoring during the immediate post-arrest care period (0–24 h) may be a useful component of prognostication, with a BIS measurement at 24 h providing the highest clinically predictive value for good neurologic outcome at discharge. In addition, consistent with the work of others, a BIS of zero in our investigation correlated with poor outcomes in 100% of this subset (16/62) of patients. Further investigation will be required to establish the most reliable method to prognosticate these complex critically ill patients.

Conflict of interest statement

No author has received honoraria or research support from the manufacturers of BIS technology. Ms. Leary has received an honorarium from Philips Healthcare; Dr. Abella has received honoraria from Medivance Corporation, Gaymar Industries and Philips Healthcare and research support from Philips Healthcare; Dr. Gaieski has received honoraria and research support from Gaymar Industries. Drs. Kolansky, Merchant and Fuchs have received honoraria from Gaymar Industries. Dr. Edelson has received honoraria and research support from Philips Healthcare.

Acknowledgements

We would like to thank the staff of the Emergency Department and the Intensive Care Units at the Hospital of the University of Pennsylvania for their help and support in the conduct of this work, as well as their excellent care of patients resuscitated from cardiac arrest. We thank Emily Esposito and Raghu Seethala for critical review of this manuscript.

References

- Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;346:549–56.
- Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346:557–63.
- Holzer M, Bernard SA, Hachimi-Idrissi S, Roine RO, et al. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. *Crit Care Med* 2005;33:414–8.
- Sugerman NT, Abella BS. Hospital-based use of therapeutic hypothermia after cardiac arrest in adults. *J Neurotrauma* 2009;26:371–6.
- Bernard S. Hypothermia after cardiac arrest: expanding the therapeutic scope. *Crit Care Med* 2009;37:S227–33.
- Sagalyn E, Band RA, Gaieski DF, Abella BS. Therapeutic hypothermia after cardiac arrest in clinical practice: review and compilation of recent experiences. *Crit Care Med* 2009;37:S223–6.
- Geocadin RG. Understanding and enhancing functional outcomes after cardiac arrest: the need for a multidisciplinary approach to refocus on the brain. *Resuscitation* 2009;80:153–4.
- Wijdicks EF, Hijdra A, Young GB, et al. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006;67:203–10.
- Nolan JP, Neumar RW, Adrie C, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. *Resuscitation* 2008;79:350–79.
- LeBlanc JM, Dasta JF, Kane-Gill SL. Role of the bispectral index in sedation monitoring in the ICU. *Ann Pharmacother* 2006;40:490–500.
- Rosow C, Manberg PJ. Bispectral index monitoring. *Anesthesiol Clin N Am* 2001;19:947–66.
- Stammet P, Werer C, Mertens L, et al. Bispectral index (BIS) helps predicting bad neurological outcome in comatose survivors after cardiac arrest and induced therapeutic hypothermia. *Resuscitation* 2009;80:437–42.
- Seder DB, Fraser GL, Robbins T, Libby L, Riker RR. The bispectral index and suppression ratio are very early predictors of neurological outcome during therapeutic hypothermia after cardiac arrest. *Intensive Care Med* 2009 [October 22, epub ahead of print].
- Gaieski DF, Band RA, Abella BS, et al. Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Resuscitation* 2009;80:418–24.
- Gaieski DF, Fuchs B, Carr BG, et al. Practical implementation of therapeutic hypothermia after cardiac arrest. *Hosp Pract*;43:1–13.
- Booth CM, Boone RH, Tomlinson G, Detsky AS. Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. *JAMA* 2004;291:870–9.
- Rittenberger JC, Guyette FX, Tisherman SA, et al. Outcomes of a hospital-wide plan to improve care of comatose survivors of cardiac arrest. *Resuscitation* 2008;79:198–204.
- Oddo M, Schaller MD, Feihl F, et al. From evidence to clinical practice: effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. *Crit Care Med* 2006;34:1865–73.
- Ekmektzoglou KA, Xanthos T, Papadimitriou L. Biochemical markers (NSE, S-100, IL-8) as predictors of neurological outcome in patients after cardiac arrest and return of spontaneous circulation. *Resuscitation* 2007;75:219–28.
- Tiainen M, Kovala TT, Takkunen OS, Roine RO. Somatosensory and brainstem auditory evoked potentials in cardiac arrest patients treated with hypothermia. *Crit Care Med* 2005;33:1736–40.
- Merchant RM, Soar J, Skrifvars MB. Therapeutic hypothermia utilization among physicians after resuscitation from cardiac arrest. *Crit Care Med* 2006;34:1935–40.
- Abella BS, Zhao D, Alvarado J, Hamann K, Vanden Hoek TL, Becker LB. Intra-arrest cooling improves outcomes in a murine cardiac arrest model. *Circulation* 2004;109:2786–91.
- Castrén M, PRINCE investigators. Intra-arrest trans-nasal evaporative cooling: a randomized pre-hospital multicenter trial: PRINCE (Pre-ROSC intranasal cooling effectiveness). *Circulation* 2009. Resuscitation Science Symposium abstract O13.
- Avidan MS, Zhang L, Burnside BA, et al. Anesthesia awareness and the bispectral index. *NEJM* 2008;358:1097–108.
- Honan D, Doherty D, Frizelle H. A comparison of the effects on bispectral index of mild vs. moderate hypothermia during cardiopulmonary bypass. *Eur J Anaesthesiol* 2006;23:385–90.
- Chollet-Xémard C, Combes X, Soupizet F, et al. Bispectral index monitoring is useless during cardiac arrest patients' resuscitation. *Resuscitation* 2009;80:213–6.