WORKSHEET for Evidence-Based Review of Science for Veterinary CPCR

1. Basic Demographics

Worksheet author(s)

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[redacted]	[redacted]

2. Clinical question:

For dogs and cats with ROSC after cardiac arrest (P), does the use of intensive continuous monitoring (e.g. continuous ECG, blood pressure, temperature, pulse oximeter, ± ETCO2) (I) versus standard intermittent monitoring (C) improve outcome (e.g. survival)?

3. Conflict of interest specific to this question:

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? NO

4. Search strategy (including electronic databases searched):

4a. Databases

-MEDLINE Ovid (performed on April 15) – Ovid MEDLINE(R) 1948 to April Week 1 2011
1. exp Cardiopulmonary Resuscitation/ or exp Heart Arrest/ or exp Resuscitation/ 82938 hits
2. return of spontaneous circulation.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 826 hits
3. veterinary.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 39450 hits
4. dogs.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 276843 hits
5. Canine 56600 hits
6. feline.mp. 12621 hits
7. Cats 121987 hits
8. exp Monitoring, Physiologic/ 107122 hits
9.exp Monitoring, Physiologic/ve [Veterinary] 640 hits
10. intensive monitoring.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 560 hits
11. prognosis.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] 88 hits: 6 possible relevant
12. post arrest (87 hits) 4 relevant

1 and 8: limits English and Animals: 1 hit 0 relevant
1 and 9:: 9 hits (0 relevant)
2 and 3: 3 hits (0 relevant)
2 and 4: 35 hits (0 relevant)
2 and 5: 20 hits (0 relevant)
2 and 6: 0 hits (0 relevant)
2 and 7: 4 hits (0 relevant)
2 and 9: 1 hit (0 relevant)
2 and 11: 88 hits: 2 relevant

-CAB (1910 to Feb 2011) April 18:
Return of spontaneous circulation: 10 hits, one additional hit, 0 relevant

4b. Other sources

-GOOGLE SCHOLAR (performed on April 18)
return of spontaneous circulation (exact word in title), 138 hits, 1 additional hit

Expanded search: Key word search: Post cardiac arrest: performed June 13th 2011:

Medline ovid: 118 hits. Limit to English: 113 hits: 3 relevant
Pubmed: 2147 hits, limited to English, clinical trials (any), meta-analysis, randomized controlled, and comparative: 376 hits - 2 relevant

References from retrieved articles: References were also scanned from the following articles:
Nolan JP, Neumar RW, Adrie C et al "Post-cardiac arrest syndrome: Epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anethesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke". Resuscitation 2008 (79): 350-379. 4 additional relevant articles

Peberdy MA, Callaway CW, Neumar RW et al "Post-Cardiac Arrest Care 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care". Circulation 2010 122(suppl 3):S768-S786 2 additional relevant article

Schulman SP, Hartmann TK, Geocadin RG. "Intensive CAre After Resuscitation from Cardiac Arrest: A Focus on Heart and Brain Injury". Neurol Clin 2006 24: 41-59. 4 additional relevant articles

Trzeciak S, Jones AE, Kilgannon JG et al. "Outcome measures utilized in clinical trials of interventions for post-cardiac arrest syndrome: A systemic review". Resuscitation 2009 80: 617-623 3 additional relevant articles.

4c. State inclusion and exclusion criteria for choosing studies and list number of studies excluded per criterion

Inclusion criteria: English, Clinical trials, meta-analysis, randomized controlled and comparative

Exclusion criteria: Non English language, abstracts, reviews

4d. Number of articles/sources meeting criteria for further review: 26

5. Summary of evidence

Evidence Supporting Clinical Question

For dogs and cats with ROSC after cardiac arrest (P), does the use of intensive continuous monitoring (e.g. continuous ECG, blood pressure, temperature, pulse oximeter, ± ETCO2) (I) versus standard intermittent monitoring (C) improve outcome (e.g. survival)?

Good			Balan, oximetry, prospective controlled, 17 dogs			Oksanen, randomized controlled, glucose, 90 patients
Fair						
Poor						Shibata, et al, case series (BIS) 10 patients
						Chen et al,

						Prospective cohort (HRV), 69 patients
						Sideris et al, prospective study, ECG for AMI, 165 patients
						Moon et al, Prospective cohort, Arterial - end tidal CO2, 44 patients
						Losert et al, Retrospective, Blood glucose, 234 patients.
						Mullner, Retrospective, MAP, 136 patients
						Trzeciak, retrospective cohort study, 8736 patients
						Kilgannon, Retrospective cohort, blood pressure, 102 patients
						Kliegel, retrospective, lactate, 394 patients
						Donnino, retrospective, lactate, 79 patients
						Suffoletto, Prospective observational, Body temperature, 3426 patients
						Takasu, retrospective, hyperthermia, 43 patients
						Zeiner, prospective, Hyperthermia, 151 patients
						Mullner et al, Prospective, Blood Glucose, 145 patients
						Skrifvars,

						retrospecitve, survival factors (glucose), 98 patients
						Langhelle, factors effecting survival (seizure, temperature, glucose), retrospective, 459 patients
						Laurent, Myocardial stunning, Prospective, 148 patients
						Brucken, hyperoxemia, retrospective in swine, 15 pigs
						Kilgannon, retrospective, oxygen, 6326 patients
						Nielsen, prospective observational, seizures/outcome, 90 patients
						Gonzalez, prospective, myocardial dysfunction, 84 patients
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

Evidence Neutral to Clinical question

Good						
Fair						
Poor						Gaieski, historical control, Early goal directed therapy, 18 patients
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

Evidence Opposing Clinical Question

Good						
Fair						
Poor						C. Torgersen et al, retrospective, Blood pressure, 153 patients
						Charlotte Chollet-Xémard, et al. prospective observational (BIS) 92 patients
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

6. REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Post arrest patients that have return of spontaneous circulation (ROSC) following CPR have been compared to septic patients in regards to the systemic inflammatory state that has been found in post arrest patients (Chen, Gaieski). As such, some of the early goal directed strategies that have been successful in septic patients have been applied to cardiac arrest patients following ROSC (MAP, CVP, lactate, arterial and central venous oxygen saturation, and cardiac output) (Moon, Donnino, Gaieski). Despite these strategies, there is very little to no evidence in the human or veterinary literature to recommend continuous or intermittent monitoring with regards to outcome in the post arrest phase following (ROSC).

There are a couple of small case series and a prospective observational study looking at continuous bispectral index (BIS) monitoring in people to predict ROSC and cerebral resuscitation following ROSC (Chollet-Xémard, Shabata). The results are conflicting and there are no current recommendation regarding BIS as a marker of cerebral resuscitation or mortality following ROSC in CPR patients. If it is used then BIS values as they correlate to different outcomes will need to be determined.

Electrocardiography (ECG), which can be measured continuously or intermittently, has several indications following ROSC. Arrhythmias are not uncommon following ROSC in people (Neilsen) and continuous ECG monitoring is included in most post arrest monitoring guidelines (Sidiris, 2010 American Heart Association Guidelines, ILCOR Consensus Statement). Given the high incidence of acute myocardial infarction in people that contributes to cardiac arrest, ECG has been used to help detect AMI via ST segment elevation, ST segment depression and QT prolongation (Sideris). In addition, given the incidence of myocardial dysfunction that occurs post cardiac arrest, it has also been used to determine heart rate variability (HRV) measurements (suggestive of autonomic nervous system function) over a 10 minute continuous time period as a predictor of 24 hours mortality in patients with ROSC (Chen). The single study done looking at HRV measurements shows it may be useful as a predictor of outcome following ROSC. There are no veterinary studies looking at the role of ECG following ROSC as it relates to outcome.

A prospective observational study of 44 patients looked at arterial end tidal CO2 difference (P(a-et)CO2) and alveolar dead space ventilation ratio (V_{dA}/V_t) one hour following ROSC in CPR patients and found a significant difference between survivors and non-survivors, with non survivors having elevated (V_{dA}/V_t) and P(a-et)CO2 compared to non-survivors (Moon). Its role in veterinary medicine remains to be determined.

There is evidence associated with induced hypothermia and favorable outcomes following CPR, however, there is also evidence to suggest worse outcomes following hyperthermia in post CPR patients. Ischemic neuronal damage is exacerbated in the face of hyperthermia and worse neurologic outcomes and increased mortality have been demonstrated in ROSC patients that have experienced episodes of hyperthermia (Takasu, Suffoletto, Zeiner, Langehelle). A large prospective observational study intermittently monitored temperature in 3426 patients for 24 hours following ROSC for episodes of hypothermia or hyperthermia and compared them to patients that maintained normothermia (Suffoletto). The study found that each degree Centigrade increase above normal body temperature resulted in a decreased odds ratio of survival to hospital discharge. In addition, an episode of passive hypothermia resulted in a decreased odds of survival to hospital discharge. A smaller prospective study showed similar results with an odds ratio of 2.26 for risk of an unfavorable neurolgic recovery for every degree Centigrade above 37°C (Zeiner). The cause and effect is still uncertain, as many additional factors including epinephrine administration, GI bacterial translocation, aspiration, infection, and anterior hypothalamic necrosis have been suggested as possible etiologies for hyperthermia (Zeiner, Suffoletto, Takasu).

Despite the association of poor outcome with high blood glucose at time of admission following cardiac arrest (Longstreth), optimum blood glucose values in people have not been determined for patients with ROSC (Losert). Three studies (two prospective studies of 145 and 765 patients respectively and and two retrospective studies of 98 and 459 patients respectively) found that hyperglycemia occurring in the first 24-72 hours after ROSC was associated with a worse outcome (Mullner, Nielsen, Skrifvars, Langhelle,). A retrospective study of 234 patients looked at the association of a single blood glucose at 12 hours post ROSC and outcome at 6 months (Losert). The study found patients with high glucose levels did poorly, however, a moderate increase in glucose was found to have a similar outcome to normal glucose values. A prospective randomised study of 90 patients found no difference between moderate glucose control and strict glucose control (Oksanan). Further prospective studies are needed to determine the optimum blood glucose and need for intensive insulin therapy in patients with ROSC following cardiac arrest.

Maintaining mean arterial blood pressure (MAP) following ROSC is an area that has received considerable attention in the human literature although a MAP goal for different time points following ROSC has not been determined. Some studies have demonstrated a poorer outcome with episodes of hypotension occurring in the first 1-6 hours after ROSC (Moon, Kilgannon, Trzeciak), while others looking at blood pressure over a longer time period (24 hours) failed to show an association with outcome (Torgersen). Target values for MAP vary between studies and range from 65-100 mmHg. The ideal pressure following ROSC has not been conclusively determined.

Lactate clearance has been looked at as a marker of tissue perfusion following ROSC and early effective lactate clearance does appear to be associated with improved mortality (Donnino, Moon, Kliegel).

Myocardial dysfunction has been documented in animals and people following ROSC and has been associated with lower survival rates (Laurent). It is characterized by decreased CI, tachycardia, elevated left ventricular end-diastolic pressures, and low filling pressures (Laurent). It tends to be reversible and appears to respond to therapy (Laurent). A prospective study in 87 people found the left ventricular ejection fraction decreases 25% in the post arrest phase when compared to pre-arrest values (Gonzales).

Seizures: There are reports in the human literature that seizures are common during the post arrest phase and that patients experiencing seizures in the first 24 hours post arrest phase have a worse long term outcome (Langhelle, Neilsen).

Oxygen therapy is recommended during CPR, to be continued into the ROSC phase. However, hyperoxemia has been associated with brain injury and worse neurologic outcomes and increased mortality in swine, dogs and people (Brucken, Balan, Kilagnnon). Oximetry-guided reoxygenation following ROSC has been associated with improved neurological outcomes in dogs (Balan). A prospective randomized study in 17 dogs, using continuous oximetry followed by blood gas analysis, demonstrated improved neurologic scores and less histologic brain injury in dogs maintained at a lower arterial O_2 saturation (between 94 and 96%) within 12 minutes of ROSC, when compared to dogs maintained on 100% O_2 following ROSC (Balan).

7. Conclusion

Veterinary studies looking at monitoring as it relates to outcome following ROSC are lacking and therefore any recommendations for intermittent or continuous monitoring following ROSC must be drawn from the human literature. In the human literature most studies looking at monitoring following ROSC as it relates to outcome are primarily based on a small number of retrospective or uncontrolled prospective studies, often involving only a few patients with cardiac causes of cardiac arrest. Very little has been proven and recommendations for monitoring after ROSC in the human literature tend to be extrapolated from studies in other shock states or based on expert opinion (Trzeciak). It is safe to say that further studies are needed before it can be determined which parameters in veterinary patients are associated with outcome and therefore which parameters should be monitored continuously or intermittently.

Albeit not proven, given the preliminary results of what has been published in the human profession, it seems reasonable to establish some guidelines to follow for monitoring after ROSC, at least until further human and veterinary studies can be completed. It should be kept in mind that extrapolation from human studies needs to be considered carefully given differences between out of hospital and in hospital arrests and underlying arrhythmias and causes of arrest.

Treatment

Although not supported by prospective research, there is a current trend towards early goal directed therapy in post arrest patients following ROSC, similar to what has been established for septic patients. Given the similarities in the pathophysiology demonstrated between SIRS, sepsis and post cardiac arrest syndrome, this seems reasonable. Early goal directed therapy, which tries to establish early hemodynamic stability relies on serial lactate measurements, central venous pressure measurements, arterial blood pressure measurements, urine output, mixed venous and arterial oxygen saturation. If hemodynamic stability is also the goal in veterinary patients these parameters should be followed whenever possible although end targets have yet to be established. Most human studies target urine output greater than 0.5 ml/kg/hour, central venous pressures > 8 mmHg and mixed venous oxygen saturation > 70%, although there are no prospective clinical trials to support these targets. Values in veterinary patients also need to be determined.

Given there is evidence to suggest episodes of hypotension correlate with a poorer outcome in people, and that blood pressure can vary at different times during ROSC, it would be reasonable to measure blood pressure continuously whenever possible. Target values for blood pressure (MAP and SAP) in the veterinary profession following ROSC have yet to be determined (similar to the human profession).

Glucose should be monitored serially to detect hypoglycemia and hyperglycemia. Although there is insufficient evidence to make recommendations regarding insulin therapy for treatment of hyperglycemia in veterinary patients, it seems prudent to avoid iatrogenic hyper or hypoglycemia. This recommendation is based on the preliminary evidence in people that suggests marked hyperglycemia in the post arrest phase is associated with a worse outcome and that the brain is dependent on glucose for energy.

Although induced hypothermia in veterinary patients remains controversial, given the association of a poorer outcome in people that have episodes of hyperthermia or passive hypothermia following ROSC, it seems reasonable to serially monitor rectal or core temperature in veterinary patients. Whether active interventions to avoid or treat hyperthermia will affect outcome remains to be determined.

There appears to be some evidence that arterial - end tidal CO_2 difference may be associated with outcomes in people following ROSC and measuring blood gasses and $ETCO_2$ would be reasonable in veterinary patients whenever possible. The effects of hypercapnia or hypocapnia on intracranial pressures and cerebral blood flow, and risk of hypoventilation due to decreased mental status of many patients in the post-arrest period, would also support the serial measurement of $ETCO_2$ and/or arterial/venous partial pressures of CO_2.

There is controversy in the human profession as to the appropriate inspired oxygen concentrations to use following ROSC, with some studies suggesting hyperoxemia may be detrimental. Continuous oximetry has proven useful when used to guide titration of inspired oxygen concentrations in experimental studies in dogs, and seems reasonable to measure in veterinary patients with ROSC. The actual targets for arterial oxygenation remain to be elucidated. Regardless of the desired inspired oxygen concentration to be used, complications such as pulmonary edema, pneumonia and pulmonary contusions are not uncommon following CPR and veterinary patients should be monitored for hypoxemia via the use of pulse oximetry and/or arterial blood gasses. This is especially true for patients placed on positive pressure ventilation.

Seizures are not uncommon in people following ROSC and may be associated with a worse outcome. It is therefore reasonable to include monitoring for seizures in veterinary patients with ROSC.

Given the role myocardial dysfunction plays in human post arrest syndrome and it's potentially reversible and treatable state, it seems reasonable to serially monitor veterinary cardiac arrest patients with echocardiography following ROSC, when ultrasonography is available.

At the very least, there is evidence for continuous monitoring of ECG, arterial oxygenation, body temperature, blood glucose, and blood pressure following ROSC, in addition to serial exams and neurologic monitoring. There is not clear evidence to delineate between recommendations for continuous monitoring versus intermittent monitoring of these variables, and this should be tailored to individual patients and circumstances, especially when determining the intervals for intermittent monitoring.

8. Acknowledgement

9. Citation list

C. Torgersen, C. A. Schmittinger, J. Takala, S.M. Jakob and M. W. Dunser. 2010 "The association between early hemodynamic variables and outcome in normothermic comatose patients following cardiac arrest". Acta Anaesthesiol Scand 54: 1027–1035

Background: Currently, few data exist on the association between post-cardiac arrest hemodynamic function and outcome. In this explorative, retrospective analysis, the association between hemodynamic variables during the first 24 h after intensive care unit admission and functional outcome at day 28 was evaluated in 153 normothermic comatose patients following a cardiac arrest.
Methods: Medical records of a multidisciplinary intensive care unit were reviewed for comatose patients (Glasgow Coma Scale 9) admitted to the intensive care unit after successful resuscitation from an in- or an out-of-hospital cardiac arrest. The hourly variable time integral of hemodynamic variables during the first 24 h after admission was calculated. At day 28, outcome was assessed as favorable or adverse based on a Cerebral Performance Category of 1–2 and 3–5, respectively. Bi- and multivariate regression models adjusted for relevant confounding variables were used to evaluate the association between hemodynamic variables and functional outcome.
Results: One hundred and fifty-three normothermic comatose patients were admitted after a cardiac arrest, of whom 64 (42%) experienced a favorable outcome. Neither in the adjusted bivariate models (r2, 0.61–0.78) nor in the adjusted multivariate model (r2, 0.62–0.73) was the hourly variable time integral of any hemodynamic variable during the first 24 h after intensive care unit admission associated with functional patient outcome at day 28 in all patients as well as in patients after an in- or an out-ofhospital cardiac arrest.

Conclusion: Commonly measured hemodynamic variables during the first 24 h following intensive care unit admission due to a cardiac arrest do not appear to be associated with the functional outcome at day 28.
NOTES: Arterial (100% of patients), central (70 %) and pulmonary (24%) catheters placed at discretion of attending physician. Heart rate, central venous pressure, cardiac index, central/mixed venous oxygen saturation measured.

Donnino MW, Miller J, Goyal N, et al. 2007 " Effective lactate clearance is associated with improved outcome in post-cardiac arrest patients". Resuscitation 75: 229-234.

Summary
Introduction: Early, effective lactate clearance has been shown to be associated with improved mortality in patients with trauma, burns, and sepsis. We investigated whether early, high lactate clearance was associated with reduced mortality in postcardiac arrest patients.
Methods: We performed a retrospective analysis of post-cardiac arrest patients in an urban emergency department. Inclusion criteria included pre-hospital cardiac arrest patients over the age of 18. Exclusion criteria were traumatic arrest, successful resuscitation prior to the arrival of emergency medical services, and cardiac arrest in the presence of pre-hospital providers. Primary endpoints consisted of survival to 24 h and survival to hospital discharge.
Results: A total of 79 patients were analyzed with a mean age of 64±17 and mean APACHE II score of 37.7±5. Of the 79 patients, 27 (34%) died within 24 h and 66 (84%) died during the hospital course. The mean initial lactate level for the overall group was 15±5.2 mmol/dl with a mean lactate of 14.4±5.1 mmol/dl in the survivors and 16±5.3 mmol/dl in the non-survivors ($p > 0.05$). Lactate clearance at both 6 and 12 h was significantly higher for both 24-h and overall in-hospital survival ($p < 0.05$). A multivariable analysis showed that high lactate clearance at 12 h was predictive of 24-h survival ($p < 0.05$).
Conclusions: Early, effective lactate clearance is associated with decreased early and overall in-hospital mortality in post-cardiac arrest patients. These findings suggest that post-arrest tissue hypo-perfusion plays in an important role in early as well as overall mortality.

Kilgannon JH, Roberts BW, Reihl LR, Chanskya ME, Jones AE, Dellinger RP, Parrillo JE, Trzeciaka, S. 2008 " Early arterial hypotension is common in the post-cardiac arrest syndrome and associated with increased in-hospital mortality". Resuscitation 79: 410-416

Aim: After return of spontaneous circulation (ROSC) from cardiac arrest, profound myocardial stunning and systemic inflammation may cause hemodynamic alterations; however, the prevalence of post-ROSC hemodynamic instability and the strength of association with outcome have not been established. We tested the hypothesis that exposure to arterial hypotension after ROSC occurs commonly (>50%) and is an independent predictor of death.
Methods: Single-center retrospective cohort study of all post-cardiac arrest patients over 1 year. Inclusion criteria: (1) age >17; (2) non-trauma; (3) sustained ROSC after cardiac arrest. Using the Jones criteria, subjects were assigned to one of two groups based on the presence of hypotension within 6 h after ROSC: (1) exposures—–two or more systolic blood pressures (SBPs) <100mmHg or (2) non-exposures—–less than two SBP <100mmHg. The primary outcome was inhospital mortality. We compared mortality rates between groups and used multivariate logistic regression to determine if post-ROSC hypotension independently predicted death.
Results: 102 subjects met inclusion criteria. In-hospital mortality was 75%. Exposure to hypotension occurred in 66/102 (65%) and was associated with significantly higher mortality (83%) compared to non-exposures (58%, $p = 0.01$). In a model controlling for common confounding variables (age, pre-arrest functional status,

arrest rhythm, and provision of therapeutic hypothermia (HT)), early exposure to hypotension was a strong independent predictor of death (OR 3.5 [95% CI 1.3—9.6]).

Trzeciak S, Jones AE, Kilgannon JH, Milcarek B, Hunter K, Shapiro NI, Hollenberg SM, Dellinger RP, Parrillo JE. 2009 " Significance of arterial hypotension after resuscitation from cardiac arrest" Crit Care Med 37 (11): 2895-2903

Objective: Expert guidelines advocate hemodynamic optimization after return of spontaneous circulation (ROSC) from cardiac arrest despite a lack of empirical data on prevalence of post- ROSC hemodynamic abnormalities and their relationship with outcome. Our objective was to determine whether post-ROSC arterial hypotension predicts outcome among postcardiac arrest patients who survive to intensive care unit admission.
Design: Cohort study utilizing the Project IMPACT database (intensive care unit admissions from 120 U.S. hospitals) from 2001–2005.
Setting: One hundred twenty intensive care units.
Patients: Inclusion criteria were: 1) age >18 yrs; 2) nontrauma; and 3) received cardiopulmonary resuscitation before intensive care unit arrival.
Interventions: None.
Measurements and Main Results: Subjects were divided into two groups: 1) Hypotension Present—one or more documented systolic blood pressure <90 mm Hg within 1 hr of intensive care unit arrival; or 2) Hypotension Absent—all systolic blood pressure >90 mm Hg. The primary outcome was in-hospital mortality. The secondary outcome was functional status at hospital discharge among survivors. A total of 8736 subjects met the inclusion criteria. Overall mortality was 50%. Post-ROSC hypotension was present in 47% and was associated with significantly higher rates of mortality (65% vs. 37%) and diminished discharge functional status among survivors (49% vs. 38%), p < .001 for both. On multivariable analysis, post-ROSC hypotension had an odds ratio for death of 2.7 (95% confidence interval, 2.5–3.0).
Conclusions: Half of postcardiac arrest patients who survive to intensive care unit admission die in the hospital. Post-ROSC hypotension is common, is a predictor of in-hospital death, and is associated with diminished functional status among survivors. These associations indicate that arterial hypotension after ROSC may represent a potentially treatable target to improve outcomes from cardiac arrest.

Suffoletto B, Peberdy MA, van der Hoek T, Callaway C. 2009 " Body temperature changes are associated with outcomes following in-hospital cardiac arrest and return of spontaneous circulation" Resuscitation 80: 1365-1370

Introduction: Spontaneous changes in body temperature after return of circulation (ROSC) from cardiac arrest are common, but the association of these changes with outcomes in hospitalized patients who survive to 24 h post-ROSC is not known. We tested the hypothesis that adults who experience temperature lability in the first 24 h have worse outcomes compared with those who maintain normothermia.
Materials and methods: A prospective observational study from a multicenter registry of cardiac arrests (National Registry of Cardiopulmonary Resuscitation) from 355 US and Canadian hospitals. 14,729 adults with return of circulation from a pulseless cardiac arrest.Weexcluded those who died or were discharged before 24 h post-event, those made Do-Not-Resuscitate (DNR) within 24 h of event, those that had a preceding trauma, and those with multiple cardiac arrests. Finally, we included only subjects that had both a lowest (Tmin) and highest (Tmax) body temperature value recorded during the first 24-h after ROSC, resulting in a study sample of 3426 patients.
Results: After adjustment for potential covariates, there was a lower odds of survival in those having an episode of hypothermia (adjusted odds ratio [OR], 0.62; 95% confidence interval [CI], 0.48–0.80), those having an episode of hyperthermia (OR, 0.67; 95% CI, 0.48–0.80), and those having an episode of both (OR,

0.59; 95% CI, 0.39–0.91). Among those who survived to discharge, there was also a lower odds of favorable neurologic performance in those who had an episode of hyperthermia (OR, 0.71; 95% CI, 0.51–0.98). Conclusions: Episodes of temperature lability following in-hospital resuscitation from cardiac arrest are associated with lower odds of surviving to discharge. Hyperthermia is also associated with fewer patients leaving the hospital with favorable neurologic performance. Further studies should identify whether therapeutic control over changes in body temperature after in-hospital cardiac arrest improves outcomes.

Chollet-Xémard C, Combes X, Soupizet F, Jabre P, Penet C, Bertrand C, Margenet A, Marty J. 2009 " Bispectral index monitoring is useless during cardiac arrest patients' resuscitation" Resuscitation 80: 213-216

Aim: It has been suggested that out-of-hospital bispectral (BIS) index monitoring during advanced cardiac life support (ACLS) might provide an indication of cerebral resuscitation. The aims of our study were to establish whether BIS values during ACLS might predict return to spontaneous circulation, and whether BIS values on hospital admission might predict survival.
Materials and methods: This was a prospective observational study in 92 patients with cardiac arrest who received basic life support from a fire-fighter squad and ACLS on arrival of an emergency medical team on the scene. BIS values, electromyographic activity, and signal quality index were recorded throughout resuscitation and out-of-hospital management.
Results: Seven patients had recovered spontaneous cardiac activity by the time the medical team arrived on scene. Of the 92 patients, 62 patients died on scene and 30 patients returned to spontaneous cardiac activity and were admitted to hospital. The correlation between BIS values and end-tidal CO_2 during the first minutes of ACLS was poor ($r^2 = 0.02$, $P = 0.19$). Of the 30 admitted patients, 27 died. Three were discharged with no disabilities. There was no significant difference in BIS values on admission between the group of patients who died and the group who survived ($P = 0.78$).
Conclusions: Although BIS monitoring during resuscitation was not difficult, it did not predict return to spontaneous cardiac activity, nor survival after admission to intensive care. Its use to monitor cerebral function during ACLS is therefore pointless.

Shibata S, Imota T, Shigeomi S, Sato W, Enzan K. 2005 " Use of the bispectral index during the early postresuscitative phase after out-of-hospital cardiac arrest" J Anesth 19:243-246

Non-invasive and real-time measures of neurological status after cardiac arrest are needed to be able to make an early determination of the postresuscitative outcome. We investigated whether the bispectral index (BIS) predicts the postresuscitative outcome in 10 patients with out-of-hospital cardiac arrest. We measured the BIS after return of spontaneous circulation (ROSC) in the emergency room and on admission to the intensive care unit (ICU). We determined the Glasgow Coma Scale (GCS) on admission to the emergency room and the ICU and the Glasgow Outcome Scale (GOS) on discharge from the ICU. The BIS increased after about 30min of ROSC or reached a plateau in patients rated as achieving a good recovery or moderate disability, but it did not increase to >80 in patients rated as being in a permanent vegetative state/ dead. The GCS on admission to the ICU was the same as that on admission to the emergency room. The BIS values were significantly lower in the nonsurviving group than in the surviving group. There was a positive correlation between the BIS on admission to the ICU and the GOS on discharge from the ICU. The BIS can thus be used to predict the postresuscitative outcome of patients with out-of-hospital cardiac arrest. tients. A recent study reported that the brain-derived proteins S-100 and NSE and electroencephalography (EEG) results predict the long-term outcome after cardiac arrest [4]. Although these measures are useful clinically, we wanted to find simpler, noninvasive, reproducible, and quantifiable monitoring methods for therapeutic strategies. The bispectral index (BIS) is a novel EEG-derived parameter that is based on a combination of time domain, frequency domain, and second-order spectral subparameters. The BIS ranges from 100 (awake) to 0 (isometric EEG) and has been shown to correlate well with the level of hypnosis or depth of sedation produced by volatile agents, propofol, midazolam, and opioids [5]. Because BIS is a noninvasive tool and a real-time indicator, it may be more useful than other measures (e.g., EEG or the S-100 or NSE assay) as a clinical monitoring tool for predicting the prognosis of postcardiac arrest outcomes from brain damage caused by cardiac arrest. In addition, because the relation between BIS and outcome is not well studied, we investigated whether BIS could be used as an early predictive tool for the neurological prognosis of postresuscitation in out-of-hospital cardiac arrest patients.

Moon SW, Lee SW, Choi SH, Hong YS, Kim SJ, Kim NH. 2007 "Arterial minus end-tidal CO2 as a prognostic factor of hospital survival in patientsresuscitated from cardiac arrest". Resuscitation 72: 219-225

Aims: The purpose of this study was to determine the clinical value of arterial minus end-tidal CO2 [P(a—et)CO2] and alveolar dead space ventilation ratio (VdA/Vt) as indicators of hospital mortality in patients that have been resuscitated from cardiac arrest at emergency department.
Materials and methods: Forty-four patients with a return of spontaneous circulation (ROSC) after cardiac arrest were studied in the emergency department of a university teaching hospital from March 2004 to February 2006. Mean arterial pressure (MAP), serum lactate, arterial blood gas studies, end-tidal CO2 (EtCO2), P(a—et)CO2, and VdA/Vt were evaluated at 1 h after ROSC. We compared these variables between hospital survivors and non-survivors.
Results: The rates of ventricular fibrillation and pulseless ventricular tachycardia in hospital survivors were higher than those of non-survivors (53.0 and 9.7%, respectively, $p = 0.002$). Hospital survivors had significantly higher MAP, lower serum lactate, lower P(a—et)CO2, and lower VdA/Vt value than non-survivors. Receiver operator characteristic (ROC) curves of serum lactate, P(a—et)CO2, and VdA/Vt showed significant sensitivity and specificity for hospital mortality. Specifically, lactate ≥10.0 mmol/L, P(a—et)CO2 ≥12.5 mmHg, and VdA/Vt ≥0.348 were all associated with high hospital mortality ($p = 0.000$, 0.001 and 0.000, respectively).
Conclusions: This study showed that high serum lactate, high P(a—et)CO2 and high VdA/Vt during early ROSC in cardiac arrest patients suggest high hospital mortality. If future studies validate this model, the P(a—et)CO2 and VdA/Vt may provide useful guidelines for the early post-resuscitation care of cardiac arrest patients in emergency departments.

Chen WL, Tsai TH, Huanga CC, Chena JH, Kuoe CD. 2009 " Heart rate variability predicts short-term outcome for successfully resuscitated patients with out-of-hospital cardiac arrest". Resuscitation 80: 1114-1118

Objective: To assess the possibility of heart rate variability (HRV) measures as predictors of 24-h mortality in successfully resuscitated patients with out-of-hospital cardiac arrest (OHCA).
Methods: This prospective cohort study was conducted at a 40-bed emergency department (ED) of a university-affiliated medical centre. Adult patients with OHCA who were successfully resuscitated were consecutively enrolled over an 18-month period. A 10-min electrocardiogramwas recorded for retrospective off-line HRV analysis 30–60 min after the return of spontaneous circulation and further correlated with 24-h mortality of the patients.
Results: Sixty-nine patients aged 31–82 years who met the inclusion criteria were enrolled. According to the 24-h mortality, the patients were categorised into non-survivors ($n = 28$) and survivors ($n=41$) groups. The HRV measures were compared between these two groups. The low-frequency power (LFP), normalized LFP (nLFP) and low-/high-frequency power ratio in the non-survivorswere significantly lower than those of the survivors, whereas root mean square successive difference, high-frequency power (HFP), HFP/tidal volume, normalized HFP (nHFP), and nHFP/tidal volume in the non-survivorswere significantly higher than those of

the survivors. Multiple logistic regression model identified nLFP as the independent variable to predict 24-h mortality (odds ratio, 1.354; 95% confidence interval [CI], 1.124–1.632; $p = 0.001$). Receiver operating characteristic area for nLFP in the prediction of 24-h mortality was 0.946 (95% CI, 0.897–0.995; $p < 0.001$).
Conclusions: HRV measures, especially the nLFP, may be used as predictors of 24-h mortality for successfully resuscitated patients with OHCA in the ED

Losert H, Sterz F, Roine RO, Holzer M, Martens P, Cerchiari E, Tiainen M, Mullner M, Laggner AN, Herkner H, Bischof MG. 2008 " Strict normoglycaemic blood glucose levels in the therapeutic management of patients within 12 h after cardiac arrest might not be necessary " Resuscitation 76: 214-220

Aim of the study: The admission blood glucose level after cardiac arrest is predictive of outcome. However the blood glucose levels in the post-resuscitation period, that are optimal remains a matter of debate. We wanted to assess an association between bloodglucose levels at 12 h after restoration of spontaneous circulation and neurological recovery over 6 months.
Materials and methods: A total of 234 patients from a multi-centre trial examining the effect of mild hypothermia on neurological outcome were included. According to the serum glucose level at 12 h after restoration of spontaneous circulation, quartiles (Q) were generated: Median (range) glucose concentrations were for QI 100 (67—115 mg/dl), QII 130 (116—143 mg/dl), QIII 162 (144—193 mg/dl) and QIV 265 (194—464 mg/dl).
Results: In univariate analysis there was a strong non-linear association between blood glucose and good neurological outcome (odds ratio compared to QIV): QI 8.05 (3.03—21.4), QII 13.41 (4.9—36.67), QIII 1.88 (0.67—5.26). After adjustment for sex, age, ‘‘no-flow’’ and ‘‘low-flow’’ time, adrenaline (epinephrine) dose, history of coronary artery disease and myocardial infarction, and therapeutic hypothermia, this association still remained strong: QI 4.55 (1.28—16.12), QII 13.02 (3.29—49.9), QIII 1.37 (0.38—5.64).
Conclusion: There is a strong non-linear association of survival with good neurological outcome and blood glucose levels 12 h after cardiac arrest even after adjusting for potential confounders.

Müllner M, Sterz F, Binder M, Hellwagner K, Meron G, Herkner H, Laggner AN. 1996 " Arterial Blood Pressure After Human Cardiac Arrest and Neurological Recovery". Stroke 27: 59-62

Abstract
Background and Purpose In animal cardiac arrest studies, outcome has been improved by inducing arterial hypertension early after return of spontaneous circulation. The aim of our study was to evaluate whether arterial blood pressure within the first minutes and hours after return of spontaneous circulation influences neurological recovery in human cardiac arrest survivors.
Methods Of 136 retrospectively evaluated patients after sudden cardiac death, two groups were defined: group 1, mean arterial blood pressure (MABP) within 5 minutes after return of spontaneous circulation above 100 mm Hg; group 2, MABP of 100 mm Hg or less. Thereafter MABP was measured every 5 minutes until 2 hours after return of spontaneous circulation. The groups were compared in regard to age, sex, in/out of hospital, witnessed/not witnessed, first electrocardiographic rhythm, time from cardiac arrest to beginning of life support and to return of spontaneous circulation, cumulative epinephrine dose administered, and best neurological outcome within 6 months.
Results In group 1 (n=54) good neurological recovery was observed in 63% and in group 2 (n=82) in 55% (χ^2=0.87, P=NS). Both groups exhibited comparable baseline values except that time intervals from beginning of life support to return of spontaneous circulation were shorter in group 1. After we controlled for this difference with Spearman's partial rank correlation (rs), there was no association between MABP measured

within the first 5 minutes and outcome (rs=-.023; P=NS). Good neurological recovery was independently and directly related to MABP measured during 2 hours after return of spontaneous circulation (rs=.26; P<.01). Conclusions In human cardiac arrest survivors, good functional neurological recovery was independently and positively associated with arterial blood pressure during the first 2 hours after human cardiac arrest but not with hypertensive reperfusion within the first minutes after return of spontaneous circulation.

Kliegel A, Losert H, Sterz F, Holzer M, Zeiner A, Havel C, Laggner AN. 2004 "Serial Lactate Determinations for Prediction of Outcome After Cardiac Arrest" Medicine 83(5): 274-279

Abstract: We investigated the relationship between lactate clearance and outcome in patients surviving the first 48 hours after cardiac arrest. We conducted the study in the emergency department of an urban tertiary care hospital. We analyzed the data for all 48-hour survivors after successful resuscitation from cardiac arrest during a 10-year period. Serial lactate measurements, demographic data, and key cardiac arrest data were correlated to survival and best neurologic outcome within 6 months after cardiac arrest. Parameters showing significant results in univariate analysis were tested for significance in a logistic regression model. Of 1502 screened patients, 394 were analyzed. Survivors (n = 194, 49%) had lower lactate levels on admission (median, 7.8 [interquartile range, 5.4–10.8] vs 9 [6.6–11.9] mmol/L), after 24 hours (1.4 [1–2.5] vs 1.7 [1.1–3] mmol/L), and after 48 hours (1.2 [0.9–1.6] vs 1.5 [1.1–2.3] mmol/L). Patients with favorable neurologic outcome (n = 186, 47%) showed lower levels on admission (7.6 [5.4–10.3] vs 9.2 [6.7–12.1] mmol/L) and after 48 hours (1.2 [0.9– 1.6] vs 1.5 [1–2.2] mmol/L). In multivariate analysis, lactate levels at 48 hours were an independent predictor for mortality (odds ratio [OR]: 1.49 increase per mmol/L, 95% confidence interval [CI]: 1.17–1.89) and unfavorable neurologic outcome (OR: 1.28 increase per mmol/L, 95% CI: 1.08–1.51). Lactate levels higher than 2 mmol/L after 48 hours predicted mortality with a specificity of 86% and poor neurologic outcome with a specificity of 87%. Sensitivity for both end points was 31%. Lactate at 48 hours after cardiac arrest is an independent predictor of mortality and unfavorable neurologic outcome. Persisting hyperlactatemia over 48 hours predicts a poor prognosis.

Sideris G, Voicua, S Dillinger JG, Stratiev V, et al. 2011 " Value of post-resuscitation electrocardiogram in the diagnosis of acute myocardial infarction in out-of-hospital cardiac arrest patients" Resuscitation : in press on line

Abstract
BACKGROUND:Diagnosis of acute myocardial infarction (AMI) in out-of-hospital cardiac arrest (OHCA) patients is important because immediate coronary angiography with coronary angioplasty could improve outcome in this setting. However, the value of acute post-resuscitation electrocardiographic (ECG) data for the detection of AMI is debatable.
METHODS:We assessed the diagnostic characteristics of post-resuscitation ECG changes in a retrospective single centre study evaluating several ECG criteria of selection of patients undergoing AMI, in order to improve sensitivity, even at the expense of specificity. Immediate post resuscitation coronary angiogram was performed in all patients. AMI was defined angiographically using coronary flow and plaque morphology criteria.
RESULTS: We included 165 consecutive patients aged 56 (IQR 48-67) with sustained return of spontaneous circulation after OHCA between 2002 and 2008. 84 patients had shockable, 73 non-shockable and 8 unknown initial rhythm; 36% of the patients had an AMI. ST-segment elevation predicted AMI with 88% sensitivity and

84% specificity. The criterion including ST-segment elevation and/or depression had 95% sensitivity and 62% specificity. The combined criterion including ST-segment elevation and/or depression, and/or non-specific wide QRS complex and/or left bundle branch block provided a sensitivity and negative predictive value of 100%, a specificity of 46% and a positive predictive value of 52%.
CONCLUSION:In patients with OHCA without obvious non-cardiac causes, selection for coronary angiogram based on the combined criterion would detect all AMI and avoid the performance of the procedure in 30% of the patients, in whom coronary angiogram did not have a therapeutic role.

Zeiner A, Holzer M, Sterz F et al 2001 "Hyperthermia After Cardiac Arrest Is Associated With an Unfavorable Neurologic Outcome" Arch Intern Med 161: 2007-2012

Background: Moderate elevation of brain temperature, when present during or after ischemia, may markedly worsen the resulting injury.
Objective: To evaluate the impact of body temperature on neurologic outcome after successful cardiopulmonary resuscitation.
Methods: In patients who experienced a witnessed cardiac arrest of presumed cardiac cause, the temperature was recorded on admission to the emergency department and after 2, 4, 6, 12, 18, 24, 36, and 48 hours. The lowest temperature within 4 hours and the highest temperature during the first 48 hours after restoration of spontaneous circulation were recorded and correlated to the best-achieved cerebral performance categories' score within 6 months.
Results: Over 43 months, of 698 patients, 151 were included. The median age was 60 years (interquartile range, 53-69 years); the estimated median no-flow duration was 5 minutes (interquartile range, 0-10 minutes), and the estimated median low-flow duration was 14.5 minutes (interquartile range, 3-25 minutes). Forty-two patients (28%) underwent bystander-administered basic life support. Within 6 months, 74 patients (49%) had a favorable functional neurologic recovery, and a total of 86 patients (57%) survived until 6 months after the event. The temperature on admission showed no statistically significant difference (*P*=.39). Patients with a favorable neurologic recovery showed a higher lowest temperature within 4 hours (35.8°C [35.0°C-36.1°C] vs 35.2°C [34.5°C-35.7°C]; *P*=.002) and a lower highest temperature during the first 48 hours after restoration of spontaneous circulation (37.7°C [36.9°C-38.6°C] vs 38.3°C [37.8°C-38.9°C]; *P*,.001) (data are given as the median [interquartile range]). For each degree Celsius higher than 37°C, the risk of an unfavorable neurologic recovery increases, with an odds ratio of 2.26 (95% confidence interval, 1.24-4.12).
Conclusion: Hyperthermia is a potential factor for an unfavorable functional neurologic recovery after successful cardiopulmonary resuscitation.

Mullner M, Sterz F, Binder M, Schreiber W, Deimel A, Laggner AN. 1997 " Blood Glucose Concentration After Cardiopulmonary Resuscitation Influences Functional Neurological Recovery in Human Cardiac Arrest Survivors" J Cereb Blood Flow Metab 17: 430-436

Summary: Experimental data suggest that postischemic blood glucose concentration plays an important role in modulating both ischemic cerebral infarction and selective neuronal necrosis. This study investigated the association between functional neurological recovery and blood glucose concentrations in human cardiac arrest survivors. A group of 145 nondiabetic patients were evaluated after witnessed ventricular fibrillation cardiac arrest. Data regarding cardiac arrest were collected according to an internationally accepted protocol immediately after arrival. Blood glucose was measured on admission and 6, 12, and 24 h thereafter. To control for duration of cardiac arrest and cardiogenic shock, both known to influence outcome as well as blood glucose, levels, Spearman rank partial correlation was used. In this multivariate analysis, a high admission blood glucose level tended to be associated with poor neurological outcome (rs = -0.16,n = 142,P = 0.06). The association between high median blood glucose levels over 24 h and poor neurological outcome was strong and statistically significant (rs = -0.2, n = 145, P = 0.015). High blood glucose concentrations occurring over the first 24 h after cardiac arrest have deleterious effects on functional neurological recovery. Whether cardiac arrest survivors might benefit from reduction of blood glucose levels needs further investigation.

Skrifvars MB, Pettila V, Rosenberg PH, Castren M. 2003 " A multiple logistic regression analysis of in-hospital factors related to survival at six months in patients resuscitated from out-of-hospital ventricular fibrillation" Resuscitaiton 59: 319-328.

Introduction: The impact of the immediate in-hospital post-resuscitation care after out-hospital cardiac arrest is not well known. Based on treatment variables and laboratory findings a multiple logistic regression model was created for the prediction of survival at 6 months from the event. Materials and methods: A retrospective study of the hospital charts of patients successfully resuscitated and treated in one of three community hospitals from 1998 to 2000. In addition to several pre-hospital variables, the mean 72 h values of clinical features such as blood pressure, blood glucose concentration and initiated treatment used, were included in a forward multiple logistic regression model predicting survival at 6 months from the event. Results: The charts of 98 out of a total of 102 patients were sufficiently complete and included in the analysis. Variables independently associated with survival were age, delay before a return of spontaneous circulation, mean blood glucose and serum potassium, and the use of beta-blocking agents during post-resuscitation care. When those patients who were assigned a 'do not attempt to resuscitate' (DNAR) order during the first 72 h of treatment were excluded from the analysis blood glucose, blood potassium and the use beta-blocking agents remained independently associated with survival. Conclusion: This study suggests that in-hospital factors are associated with survival from out-of-hospital cardiac arrest. The mean blood glucose and serum potassium during the first 72 h of treatment and the use of betablocking agents were significantly and independently associated with survival.

Langhelle A, Tyvold SS, Lexow K, Hapnes SA, Sunde K, Steen PA. 2003 " In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest. A comparison between four regions in Norway". Resuscitation 56: 247-263

Introduction: While pre-hospital factors related to outcome after out-of-hospital cardiac arrest (OHCA) are well known, little is known about possible in-hospitals factors related to outcome. Hypothesis: Some in-hospital factors are associated with outcome in terms of survival. Material and methods: An historical cohort observational study of all patients admitted to hospital with a spontaneous circulation after OHCA due to a cardiac cause in four different regions in Norway 1995_/1999: Oslo, Akershus, Østfold and Stavanger. Results: In Oslo, Akershus, Østfold and Stavanger 98, 84, 91 and 186 patients were included, respectively. Hospital mortality was higher in Oslo (66%) and Akershus (64%) than in Østfold (56%) and Stavanger (44%), P_/0.002. By multivariate analysis the following pre-arrest and pre-hospital factors were associated with in-hospital survival: age 5/71 years, better pre-arrest overall performance, a call-receipt-start CPR interval 5/1 min, and no use of adrenaline (epinephrine). The in-hospital factors associated with survival were: no seizures, base excess _/_/3.5 mmol l_1, body temperature 5/37.8 8C, and serum glucose 5/10.6 mmol l_1 1_/24 h after admittance with OR (95% CI) 2.72 (1.09_/8.82, P_/0.033), 1.12 (1.02_/1.23, P_/0.016), 2.67 (1.17_/6.20, P_/0.019) and 2.50 (1.11_/5.65, P_/0.028), respectively. Pre-arrest overall function, whether adrenaline was used, body temperature, the occurrence of hypotensive episodes, and the degree of metabolic acidosis differed between the four regions in parallel with the inhospital survival rates. Conclusion: Both pre-arrest, pre- and in-hospital factors were associated with in-hospital survival after OCHA. It seems important also to report in-hospital factors in outcome studies of OCHA. The design of the study precludes a conclusion on causability.

Laurent I, Monchi M, Chiche JD et al. 2002 " Reversible Myocardial Dysfunction in Survivors of Out-of-Hospital Cardiac Arrest" J Am Coll Cardiol 40(12): 2110-2116

OBJECTIVES The aim of the study was to assess the hemodynamic status of survivors of out-of-hospital cardiac arrest (OHCA).
BACKGROUND The global prognosis after successfully resuscitated patients with OHCA remains poor. Clinical studies describing the hemodynamic status of survivors of OHCA and its impact on prognosis are lacking.
METHODS Among 165 consecutive patients admitted after successful resuscitation from OHCA, 73 required invasive monitoring because of hemodynamic instability, defined as hypotension requiring vasoactive drugs, during the first 72 h. Clinical features and data from invasive monitoring were analyzed.
RESULTS Hemodynamic instability occurred at a median time of 6.8 h (range 4.3 to 7.3) after OHCA. The initial cardiac index (CI) and filling pressures were low. Then, the CI rapidly increased 24 h after the onset of OHCA, independent of filling pressures and inotropic agents (2.05 [1.43 to 2.90] 8 h vs. 3.19 l/min per m2 [2.67 to 4.20] 24 h after OHCA; p _ 0.001). Despite a significant improvement in CI at 24 h, a superimposed vasodilation delayed the discontinuation of vasoactive drugs. No improvement in CI at 24 h was noted in 14 patients who subsequently died of multiorgan failure. Hemodynamic status was not predictive of the neurologic outcome.
CONCLUSIONS In survivors of OHCA, hemodynamic instability requiring administration of vasoactive drugs is frequent and appears several hours after hospital admission. It is characterized by a low CI that is reversible in most cases within 24 h, suggesting post-resuscitation myocardial dysfunction. Early death by multiorgan failure is associated with a persistent low CI at 24 h.

Gonzalez M, Berg RA, Nadkarni VM et al. 2008 " Left Ventricular Systolic Function and Outcome After In-Hospital Cardiac Arrest " 117:1864-1872

Background—The effect of prearrest left ventricular ejection fraction (LVEF) on outcome after cardiac arrest is unknown.
Methods and Results—During a 26-month period, Utstein-style data were prospectively collected on 800 consecutive inpatient adult index cardiac arrests in an observational, single-center study at a tertiary cardiac care hospital. Prearrest echocardiograms were performed on 613 patients (77%) at 11_14 days before the cardiac arrest. Outcomes among patients with normal or nearly normal prearrest LVEF (_45%) were compared with those of patients with moderate or severe dysfunction (LVEF _45%) by _2 and logistic regression analyses. Survival to discharge was 19% in patients with normal or nearly normal LVEF compared with 8% in those with moderate or severe dysfunction (adjusted odds ratio, 4.8; 95% confidence interval, 2.3 to 9.9; *P*_0.001) but did not differ with regard to sustained return of spontaneous circulation (59% versus 56%; *P*_0.468) or 24-hour survival (39% versus 36%; *P*_0.550). Postarrest echocardiograms were performed on 84 patients within 72 hours after the index cardiac arrest; the LVEF decreased 25% in those with normal or nearly normal prearrest LVEF (60_9% to 45_14%; *P*_0.001) and decreased 26% in those with moderate or severe dysfunction (31_7% to 23_6%,

*P*_0.001). For all patients, prearrest _-blocker treatment was associated with higher survival to discharge (33% versus 8%; adjusted odds ratio, 3.9; 95% confidence interval, 1.8 to 8.2; *P*_0.001).
Conclusions—Moderate and severe prearrest left ventricular systolic dysfunction was associated with substantially lower rates of survival to hospital discharge compared with normal or nearly normal function.

Gaieskia DF, Band RA, Abella BS et al. 2009 " Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest". Resuscitation 80: 418-424

Background: Comatose survivors of out-of-hospital cardiac arrest (OHCA) have high in-hospital mortality due to a complex pathophysiology that includes cardiovascular dysfunction, inflammation, coagulopathy, brain injury and persistence of the precipitating pathology. Therapeutic hypothermia (TH) is the only intervention that has been shown to improve outcomes in this patient population. Due to the similarities between the post-cardiac arrest state and severe sepsis, it has been postulated that early goal-directed hemodyamic optimization (EGDHO) combined with TH would improve outcome of comatose cardiac arrest survivors.
Objective: We examined the feasibility of establishing an integrated post-cardiac arrest resuscitation (PCAR) algorithm combining TH and EGDHO within 6 h of emergency department (ED) presentation.
Methods: In May, 2005 we began prospectively identifying comatose (Glasgow Motor Score < 6) survivors of OHCA treated with our PCAR protocol. The PCAR patients were compared to matched historic controls from a cardiac arrest database maintained at our institution.
Results: Between May, 2005 and January, 2008, 18/20 (90%) eligible patients were enrolled in the PCAR protocol. They were compared to historic controls from 2001 to 2005, during which time 18 patientsmet inclusion criteria for the PCAR protocol. Mean time from initiation of TH to target temperature (33 ◦C) was 2.8 h (range 0.8–23.2; SD = h); 78% (14/18) had interventions based upon EGDHO parameters; 72% (13/18) of patients achieved their EGDHO goals within 6 h of return of spontaneous circulation (ROSC). Mortality for historic controls who qualified for the PCAR protocol was 78% (14/18); mortality for those treated with the PCAR protocol was 50% (9/18) (p = 0.15).
Conclusions: In patients with ROSC after OHCA, EGDHO and TH can be implemented simultaneously.

Takusa A, Kaneko N, Sakamoto T, Y Okada. 2001 " Hyperthermia: is it an ominous sign after cardiac arrest"? Resuscitation 49: 273-277

Objective: To clarify the clinical characteristics of hyperthermia at an early stage after resuscitation from cardiac arrest (CA).
Materials and methods: We reviewed the medical records of 43 adult patients with non-traumatic out-of hospital CA, who survived for longer than 24 h after admission to our intensive care unit (ICU) between January, 1995, and December, 1998. The patients were divided into two groups: a clinical brain death (CBD) group (n=23) and a non-CBD group (n=20), and various factors relating to hyperthermia were compared between the two groups.
Results: The mean value of peak axillary temperatures within 72 h of admission was 39.8_0.9°C for the CBD group, which was significantly greater than 38.3_0.6°C for the non-CBD group (P_0.0001). The time of occurrence of the peak axillary temperature was at 19_16 h of admission in the CBD group and 20_18 h in the non-CBD group (not significantly different). There were no significant differences in risk factors relating to the occurrence of hyperthermia between the two groups, except for the number of patients who received epinephrine at ICU. In 23 patients with a peak axillary temperature of _39°C during the first 72 h of

hospitalization, brain death was diagnosed in 20 patients, whereas only 3 of 20 patients having a peak axillary temperature of _39°C developed brain death (odds ratio, 37.8; 95% confidence interval, 6.72–212.2). Conclusion: Hyperthermia at an early stage after resuscitation from CA may be associated with the outcome of brain death.

Balan IS, Fiskum G, Hazelton J, Cotto-Cumba C, Rosenthal RE. 2006 " Oximetry-Guided Reoxygenation Improves Neurological Outcome After Experimental Cardiac Arrest" Stroke 37(12): 3008-3013

Background and Purpose—Current guidelines suggest that cardiac arrest (CA) survivors should be ventilated with 100% O2 after resuscitation. Breathing 100% O2 may worsen neurological outcome after experimental CA. This study tested the hypothesis that graded reoxygenation, with oximetry guidance, can safely reduce FiO2 after resuscitation, avoiding hypoxia while promoting neurological recovery.
Methods—Mature dogs underwent 10 minutes of CA and restoration of spontaneous circulation with100% O2. Animals were randomized to 1-hour additional ventilation on 100% FiO2 or to rapid lowering of arterial O2 saturation to <96% but >94% with pulse oximeter guidance. Animals were awakened at hour 23, and the neurological deficit score (0=normal; 100=brain-dead) was measured. Reanesthetized animals were perfusion-fixed and the brains removed for histopathology.
Results—The neurological deficit score was significantly better in oximetry (O) dogs. O dogs appeared aware of their surroundings, whereas most hyperoxic (H) animals were stuporous (neurological deficit score=43.0±5.9 [O] versus 61.0±4.2 [H]; n=8, $P<0.05$). Stereological analysis revealed fewer injured CA1 neurons in O animals (cresyl violet: 35.5±4.3% [O] versus 60.5±3.3% [H]; $P<0.05$). There were also fewer fluoro-Jade B-stained degenerating CA1 neurons in O animals (3320±267 [O] versus 6633±356 [H] per 0.1 mm3; $P<0.001$).
Conclusions—A clinically applicable protocol designed to reduce postresuscitative hyperoxia after CA results in significant neuroprotection. Clinical trials of controlled normoxia after CA/restoration of spontaneous circulation should strongly be considered.

Brücken A, Kaab AB, Kottmann K, Rossaint R, et al. 2010 " Reducing the duration of 100% oxygen ventilation in the early reperfusion period after cardiopulmonary resuscitation decreases striatal brain damage". Resuscitation 81:1698 - 1703

Purpose: Previous data indicate that 100% O2 ventilation during early reperfusion after cardiac arrest (CA) and cardiopulmonary resuscitation (CPR) increases neuronal death. However, current guidelines encourage the use of 100% O2 during resuscitation and for an undefined period thereafter. We retrospectively analyzed data from a porcine CA model and hypothesized that prolonged hyperoxic reperfusion would be associated with increased neurohistopathological damage and impaired neurological recovery.
Methods: Fifteen male pigs underwent 8 min of CA and 5 min of CPR. After resuscitation animals were ventilated with either 100% oxygen for 60 min (hyperoxia; n = 8) or 10 min (normoxia; n = 7). Physiological variables were obtained at baseline and 10, 60 and 240 min after resuscitation. Daily functional performance was assessed using an established neurocognitive test in parallel to a neurological deficit score (NDS). On day 5, brains of the re-anaesthetized pigs were harvested for neurohistopathological analyses.
Results: At baseline there were no differences in hemodynamics and neurological status between groups. Post-arrest only PaO2, as a result of the different inspired oxygen fractions, was significantly higher in the hyperoxia group.
There was a numerical trend towards improved clinical recovery in both the NDS and the neurocognitive

testing for animals exposed to 10 min of 100% oxygen. However, hyperoxic animals showed a significantly greater degree of necrotic neurons and perivascular inflammation in the striatum in comparison to normoxic animals.
Conclusion: In this retrospective analysis prolonged hyperoxia after CA aggravated necrotic brain damage and perivascular inflammation in the striatum of pigs.

Kilgannon JH, Jones AE, Shapiro NI et al. 2010 " Association Between Arterial Hyperoxia Following Resuscitation From Cardiac Arrest and In-Hospital Mortality" JAMA. 303(21):2165-2171

Context Laboratory investigations suggest that exposure to hyperoxia after resuscitation from cardiac arrest may worsen anoxic brain injury; however, clinical data are lacking.
Objective To test the hypothesis that postresuscitation hyperoxia is associated with increased mortality.
Design, Setting, and Patients Multicenter cohort study using the Project IMPACT critical care database of intensive care units (ICUs) at 120 US hospitals between 2001 and 2005. Patient inclusion criteria were age older than 17 years, nontraumatic cardiac arrest, cardiopulmonary resuscitation within 24 hours prior to ICU arrival, and arterial blood gas analysis performed within 24 hours following ICU arrival. Patients were divided into 3 groups defined a priori based on PaO2 on the first arterial blood gas values obtained in the ICU. Hyperoxia was defined as PaO2 of 300 mm Hg or greater; hypoxia, PaO2 of less than 60 mm Hg (or ratio of PaO2 to fraction of inspired oxygen _300); and normoxia, not classified as hyperoxia or hypoxia.
Main Outcome Measure In-hospital mortality.
Results Of 6326 patients, 1156 had hyperoxia (18%), 3999 had hypoxia (63%), and 1171 had normoxia (19%). The hyperoxia group had significantly higher inhospital mortality (732/1156 [63%; 95% confidence interval {CI}, 60%-66%]) compared with the normoxia group (532/1171 [45%; 95% CI, 43%-48%]; proportion difference, 18% [95% CI, 14%-22%]) and the hypoxia group (2297/3999 [57%; 95% CI, 56%-59%]; proportion difference, 6% [95% CI, 3%-9%]). In a model controlling for potential confounders (eg, age, preadmission functional status, comorbid conditions, vital signs, and other physiological indices), hyperoxia exposure had an odds ratio for death of 1.8 (95% CI, 1.5-2.2).
Conclusion Among patients admitted to the ICU following resuscitation from cardiac arrest, arterial hyperoxia was independently associated with increased in-hospital mortality compared with either hypoxia or normoxia

Oksanen T, Skrifvars MB, Varpula T et al. 2007 " Strict versus moderate glucose control after resuscitation from ventricular fibrillation" Intensive Care Med 33: 2093-2100

Abstract *Objective:* Elevated blood glucose is associated with poor outcome in patients resuscitated from out-of-hospital cardiac arrest (OHCA). Our aim was to determine whether strict glucose control with intensive insulin treatment improves outcome of OHCA patients.
Design: A randomized, controlled trial.
Setting: Two university hospital intensive care units.
Patients: Ninety patients resuscitated from OHCA with ventricular fibrillation detected as the initial rhythm were treated with therapeutic hypothermia.
Interventions: Patients were randomized into two treatment groups: a strict glucose control group (SGC group),

with a blood glucose target of 4–6 mmol/l, or a moderate glucose control group (MGC group), with a blood glucose target of 6–8 mmol/l. Both groups were treated with insulin infusion for 48 h, because a control group with no treatment was considered unethical.
Measurements and results: Baseline data were similar in both groups. In the SGC group 71% of the glucose measurements were within the target range compared with 41% in the MGC group. Median glucose was 5.0 mmol/l in the SGC group and 6.4 mmol/l in the MGC group. The occurrence of moderate hypoglycemic episodes was 18% in the SGC group and 2% in the MGC group ($p = 0.008$). No episodes of severe hypoglycemia occurred. Mortality by day 30 was 33% in the SGC group and 35% in the MGC group ($p = 0.846$); the difference was 2% (95% CI –18% to +22%). *Conclusions:* We found no additional survival benefit from strict glucose control compared with moderate glucose control with a target between 6 and 8 mmol/l in OHCA patients.

Nielsen N, Sunde K, Hovdenes J, et al. 2011 " Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia" Crit Care Med 39: 57-64

Objectives: To investigate the association between adverse events recorded during critical care and mortality in out-ofhospital cardiac arrest patients treated with therapeutic hypothermia.
Design: Prospective, observational, registry-based study.
Setting: Twenty-two hospitals in Europe and the United States.
Patients: Between October 2004 and October 2008, 765 patients were included.
Interventions: None.
Measurements and Main Results: Arrhythmias (7%–14%), pneumonia (48%), metabolic and electrolyte disorders (5%–37%), and seizures (24%) were common adverse events in the critical care period in cardiac arrest patients treated with therapeutic hypothermia, whereas sepsis (4%) and bleeding (6%) were less frequent. Sustained hyperglycemia (blood glucose >8 mmol/L for >4 hrs; odds ratio 2.3, 95% confidence interval 1.6 –3.6, $p < .001$) and seizures treated with anticonvulsants (odds ratio 4.8, 95% confidence interval 2.9–8.1, $p < .001$) were associated with increased mortality in a multivariate model. An increased frequency of bleeding and sepsis occurred after invasive procedures (coronary angiography, intravascular devices for cooling, intraaortic balloon pump), but bleeding and sepsis were not associated with increased mortality (odds ratio 1.0, 95% confidence interval 0.46 –2.2, *p* _ .91, and odds ratio 0.30, 95% confidence interval 0.12– 0.79, *p* _ .01, respectively).
Conclusions: Adverse events were common after out-of-hospital cardiac arrest. Sustained hyperglycemia and seizures treated with anticonvulsants were associated with increased mortality. Bleeding and infection were more common after invasive procedures, but these adverse events were not associated with increased motallity in our study.