Postresuscitation care: entering a new era

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Introduction

- Survival rates following in-hospital and OHCA remain low, but interventions after ROSC significantly influence the chances of survival.
  - Recent advances in the treatment with specific attention to optimizing myocardial and neurological recovery
  - Recent data relating to prognostication in comatose survivors of cardiac arrest

Postcardiac arrest syndrome

- The prolonged period of systemic ischemia during cardiac arrest and the subsequent reperfusion response after ROSC.
- The PCAS comprises
  - postcardiac arrest brain injury
  - postcardiac arrest myocardial dysfunction
  - systemic ischaemia/reperfusion response
  - persistent precipitating disease.

Optimizing myocardial recovery after cardiac arrest

- Primary PCI is the preferred method for restoring coronary perfusion when cardiac arrest has been caused by an STEMI.
- Many cardiac arrest survivors with non-STEMI may also benefit from urgent PCI.
- Arterial hypotension is common, and this was associated with a significantly higher mortality rate.

Optimizing neurological outcome after cardiac arrest

- Postcardiac arrest brain injury is a common cause of morbidity and mortality.
  - Controlled reoxygenation
  - Glucose control
  - Therapeutic hypothermia

Controlled reoxygenation

- Animal data: too much oxygen during the initial stages of reperfusion → free radicals and mitochondrial injury → exacerbates neuronal damage
- During the initial phases of resuscitation, ventilation with the minimum FiO_2 to maintain adequate SaO_2 (94–96%).

Glucose control

- Both high and low glucose values are associated with decreased odds of survival
- Tight blood glucose control (80–110mg/dl) with insulin reduced hospital mortality rates in SICU patients. Losert H, Resuscitation 2008; 76:214–220.
- 90-day mortality was increased among those glucose control in the range from 81–108 mg/dl compared with 180 mg/dl or less

Finfer S, N Engl J Med 2009; 360:1283–1297.

Glucose control

- The rate of hypoglycaemia was higher in the intensive insulin group than the intermediate glucose control group, but the mortality was similar. Preiser JC, Intensive Care Med 2009;35:1738–1748.
- Strict glucose control group : ↑ serum neuron-specific enolase (NSE) between 24~48 h, suggesting more severe brain injury.
  - Strict glucose control may limit the supply of glucose to the brain.

Glucose control

- Padkin
- 'patients successfully resuscitated following cardiac arrest should not be treated with strict glucose control targeting normoglycaemia but that a more moderate blood glucose target range of below 180 mg/dl should be used'. Padkin A. Resuscitation 2009; 80:611–612.

Therapeutic hypothermia

- Therapeutic hypothermia is now generally accepted as part of a standardized treatment for comatose survivors of cardiac arrest

Therapeutic hypothermia

- The mechanisms of mild hypothermia (32~34˚C) improve neurological outcome :
  - ↓ cerebral metabolism (8%/˚C ＜ 37˚C)
  - ↓ apoptosis
  - inhibition of the neuro-excitatory cascade
  - suppression of proinflammatory cytokines
  - ↓ free-radical production
  - ↓ vascular permeability following ischaemia–reperfusion injury
  - improved brain glucose metabolism

Therapeutic hypothermia

- The practical approach to therapeutic hypothermia can be divided into three parts:
  - Induction
  - Maintenance
  - Rewarming

Therapeutic hypothermia

- ***Induction*** can be induced easily and inexpensively with intravenous ice-cold fluids (30 ml/kg of saline 0.9% or Ringer’s lactate) or traditional ice packs, placed in the groins, armpits, and around the neck and head.
  - concomitant neuromuscular blockade with sedation
  - magnesium

Therapeutic hypothermia

- In the ***maintenance*** phase, a cooling method with effective temperature monitoring that avoids temperature fluctuations is preferred.

Therapeutic hypothermia

- The ***rewarming*** phase can be achieved with either external or internal cooling devices, or with other heating systems.
- The optimal rate of rewarming is not known, but the consensus is currently about 0.25°C of warming per hour

Table 1 Complications associated with therapeutic hypothermia

Shivering (particularly during the induction phase)	
Increased systemic vascular resistance	
Dysrhythmias	Bradycardia (most common)
Diuresis	May cause hypovolaemia and electrolyte abnormalities
Electrolyte abnormalities	Hypophosphataemia
	Hypokalaemia
	Hypomagnesaemia
	Hypocalcaemia
Decreased insulin sensitivity and insulin secretion	Hyperglycaemia
Impaired coagulation and increased bleeding	
Impairment of the immune system	Increased infection rates, e.g. pneumonia
Hyperamylasaemia	
Reduced drug clearance	For example, clearance of sedative drugs and neuromuscular blockers is reduced by up to 30% at a temperature of 34°C

Prognostication

- Predicting the eventual outcome of those remaining comatose after initial resuscitation from cardiac arrest remains problematic
- Neurological examination does not reliably prognosticate futility in the first 24 h after ROSC

Prognostication

- Poor outcome :
  - Absent pupillary light responses at day 3 after ROSC
  - Absence of a corneal reflex or motor response to painful stimuli at day 3 after ROSC
  - Myoclonic status epilepticus at 24 h after ROSC
  - EEG: burst suppression or generalized epileptiform discharges
  - Bilateral absence of the N20 component of the somatosensory- evoked potential (SSEP) with median nerve stimulation

Prognostication

- The effect of therapeutic hypothermia on the predicative tests for prognostication is uncertain.
- There is an emerging consensus that after hypothermia therapy, prognostication (particularly when based on the motor response) should probably be delayed until at least 3 days after normothermia has been restored.

Organ donation

- Up to 16% of patients who achieve sustained ROSC after cardiac arrest develop clinical brain death and can be considered for organ donation.

Outcome after admission to ICU

- Considerable variation
- There was lower mortality among those admitted to ICUs that treated a high volume of postcardiac arrest patients.

Conclusion

- Survivors from cardiac arrest develop postcardiac arrest syndrome.
- A postresuscitation care bundle (therapeutic hypothermia, primary PCI, control of blood sugar) improves survival and neurological outcome in cardiac arrest survivors.
- Predicting outcome in comatose survivors of cardiac arrest requires caution because the effect of therapeutic hypothermia on the tests used for prognostication is uncertain.

Meta-analysis: Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema

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Annals of Internal Medicine, 2010;152:590-600.

Introduction

- Noninvasive ventilation (NIV) is commonly used to treat patients with acute cardiogenic pulmonary edema (ACPE)
- Previous trials showed reduced in-hospital mortality and intubation rates associated with NIV, but the findings of a recent large clinical trial (3CPO) suggest that NIV may be less effective for ACPE than previously thought.

Introduction

- To provide an estimate of the effect of NIV on clinical outcomes in patients with ACPE that incorporates recent trial evidence and explore ways to interpret that evidence in the context of preceding evidence that favors NIV.

Methods

- **Search Strategy:**
  - PubMed and EMBASE from 1966 to December 2009
  - Cochrane Central Register of Controlled Trials and conference proceedings through December 2009
  - Reference lists
  - without language restriction

Methods

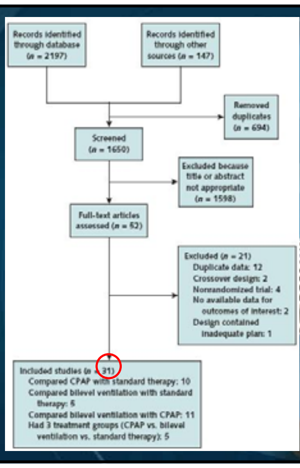
- **Study Selection:**
  - Randomized trials that compared continuous positive airway pressure and bilevel ventilation with standard therapy or each other.

Methods

- **Data Extraction:**
  - Two independent reviewers extracted data.
  - Outcomes examined were mortality, intubation rate, and incidence of new myocardial infarction (MI)

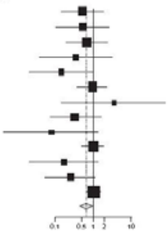
Results

- **Study characteristics:**
  - 2887 patients
  - most were elderly (aged 51~92 y/o)
  - 49.6% were male



Results

- In-hospital mortality (CPAP vs. standard therapy)



Study, Year (Reference)	CPAP Events, n	CPAP Patients, n	Standard Therapy Events, n	Standard Therapy Patients, n	RR (95% CI)	W (random), %
Räsänen et al, 1985 (24)	3	20	6	20	0.50 (0.14–1.73)	7.2
Bersten et al, 1991 (26)	2	19	4	20	0.53 (0.11–2.55)	4.7
Lin et al, 1995 (26)	4	60	6	60	0.67 (0.20–2.22)	7.6
Takeda et al, 1997 (27)	1	15	3	15	0.33 (0.04–2.85)	2.7
Takeda et al, 1998 (28)	1	11	7	11	0.14 (0.02–0.98)	3.3
Delclaux et al, 2000 (29)	7	22	7	20	0.91 (0.39–2.14)	12.9
Park et al, 2001 (43)	1	9	0	10	3.32 (0.15–72.00)	1.3
Kelly et al, 2002 (30)	2	27	7	31	0.33 (0.07–1.45)	5.3
Crane et al, 2004 (44)	0	20	6	20	0.08 (0.00–1.28)	1.6
L'Her et al, 2004 (32)	12	43	14	46	0.92 (0.48–1.76)	18.5
Park et al, 2004 (45)	1	27	6	26	0.16 (0.02–1.24)	2.9
Plaisance et al, 2007 (17)	2	63	8	61	0.24 (0.05–1.09)	5.1
Gray et al, 2009 (12)	33	346	36	367	0.97 (0.62–1.52)	26.8
Random-effects model	69	672	110	697	0.64 (0.44–0.92)	100

Results

- Need for intubation (CPAP vs. standard therapy)

Study, Year (Reference)	CPAP Events, n	CPAP Patients, n	Standard Therapy Events, n	Standard Therapy Patients, n	RR (95% CI)	W (random), %
Räsänen et al, 1985 (24)	6	20	12	20	0.50 (0.23–1.07)	17.1
Bersten et al, 1991 (25)	0	19	7	20	0.07 (0.00–1.16)	1.3
Lin et al, 1995 (26)	8	50	18	50	0.44 (0.21–0.93)	18.3
Takeda et al, 1997 (27)	1	15	6	15	0.17 (0.02–1.22)	2.5
Takeda et al, 1998 (28)	2	11	8	11	0.25 (0.07–0.92)	5.8
Delclaux et al, 2000 (29)	6	22	6	20	0.91 (0.35–2.36)	10.8
Park et al, 2001 (43)	3	9	4	10	0.83 (0.25–2.76)	6.9
Kelly et al, 2002 (30)	0	27	0	31		0
Hao et al, 2002 (31)	1	25	9	26	0.12 (0.02–0.85)	2.5
Crane et al, 2004 (44)	1	20	0	20	3.00 (0.13–69.42)	1
L'Her et al, 2004 (32)	2	43	4	46	0.53 (0.10–2.77)	3.6
Park et al, 2004 (45)	2	27	11	26	0.18 (0.04–0.72)	5
Plaisance et al, 2007 (17)	6	63	16	61	0.36 (0.15–0.87)	13.1
Gray et al, 2009 (12)	1	346	3	367	0.35 (0.04–3.38)	1.9
Ghanem et al, 2009 (19)	5	44	10	41	0.47 (0.17–1.25)	10.2
Random-effects model	44	741	114	764	0.44 (0.32–0.60)	100

Results

- Incidence of new MI (CPAP vs. standard therapy)

Study, Year (Reference)	CPAP Events, n	CPAP Patients, n	Standard Therapy Events, n	Standard Therapy Patients, n	RR (95% CI)	W (random), %
Park et al, 2001 (43)	1	9	0	10	3.32 (0.15–72.00)	0.6
Crane et al, 2004 (44)	3	20	6	20	0.50 (0.14–1.73)	3.9
Park et al, 2004 (45)	0	27	0	26		0
Gray et al, 2009 (12)	94	346	91	367	1.10 (0.86–1.40)	95.5
Random-effects model	98	402	97	423	1.07 (0.84–1.37)	100

- The effect was more prominent in trials in which myocardial ischemia or infarction caused ACPE in higher proportions of patients (RR=0.92 when 10% of patients had ischemia or MI vs. 0.43 when 50% had ischemia or MI).

Results

- In-hospital mortality (Bilevel vs. standard therapy)

Study, Year (Reference)	Bilevel Ventilation Events, n	Bilevel Ventilation Patients, n	Standard Therapy Events, n	Standard Therapy Patients, n	RR (95% CI)	W (random), %
Masip et al, 2000 (33)	0	19	2	18	0.19 (0.01–3.69)	1.3
Levitt, 2001 (34)	3	21	3	17	0.81 (0.19–3.51)	5.5
Park et al, 2001 (43)	0	7	0	10		0
Nava et al, 2003 (35)	6	65	9	65	0.67 (0.25–1.77)	12.5
Ferrer et al, 2003 (36)	1	15	2	15	0.50 (0.05–4.94)	2.3
Crane et al, 2004 (44)	5	20	6	20	0.83 (0.30–2.29)	11.6
Park et al, 2004 (45)	2	27	6	26	0.32 (0.07–1.45)	5.2
Weitz et al, 2007 (13)	1	13	1	10	0.77 (0.05–10.85)	1.7
Gray et al, 2009 (12)	34	356	36	367	0.97 (0.62–1.52)	59.8
Random-effects model	52	543	65	548	0.82 (0.58–1.15)	100

Results

- Need for intubation (Bilevel vs. standard therapy)

Study, Year (Reference)	Bilevel Ventilation Events, n	Bilevel Ventilation Patients, n	Standard Therapy Events, n	Standard Therapy Patients, n	RR (95% CI)	W (random), %
Masip et al, 2000 (33)	1	19	6	18	0.16 (0.02–1.19)	5.2
Levitt, 2001 (34)	5	21	7	17	0.58 (0.22–1.50)	18.9
Park et al, 2001 (43)	0	7	4	10	0.16 (0.01–2.48)	2.8
Nava et al, 2003 (35)	13	65	16	65	0.81 (0.43–1.55)	32.3
Ferrer et al, 2003 (36)	1	15	2	15	0.50 (0.05–4.94)	4.1
Crane et al, 2004 (44)	1	20	0	20	3.00 (0.13–69.42)	2.2
Park et al, 2004 (45)	2	27	11	26	0.18 (0.04–0.72)	10
Gray et al, 2009 (12)	4	356	3	367	1.37 (0.31–6.10)	9
Ghanem et al, 2009 (19)	4	44	10	41	0.37 (0.13–1.10)	15.6
Random-effects model	31	574	59	579	0.54 (0.33–0.86)	100

Results

- Incidence of new MI (Bilevel vs. standard therapy)

Study, Year (Reference)	Bilevel Ventilation Events, n	Bilevel Ventilation Patients, n	Standard Therapy Events, n	Standard Therapy Patients, n	RR (95% CI)	W (random), %
Levitt, 2001 (34)	4	21	5	17	0.65 (0.21–2.04)	3.9
Park et al, 2001 (43)	0	7	0	10		0
Nava et al, 2003 (35)	7	65	5	65	1.40 (0.47–4.18)	4.3
Crane et al, 2004 (44)	9	20	6	20	1.50 (0.66–3.43)	7.6
Park et al, 2004 (45)	0	27	0	26		0
Gray et al, 2009 (12)	95	356	91	367	1.08 (0.84–1.38)	84.2
Random-effects model	115	496	107	505	1.09 (0.87–1.37)	100

Results

- In-hospital mortality (Bilevel vs. CPAP)

Study, Year (Reference)	Bilevel Ventilation Events, n	Bilevel Ventilation Patients, n	CPAP Events, n	CPAP Patients, n	RR (95% CI)	W (random), %
Mehta et al, 1997 (37)	1	14	2	13	0.46 (0.05–4.53)	2.8
Park et al, 2001 (43)	0	7	1	9	0.42 (0.02–8.95)	1.6
Bollaert et al, 2002 (38)	4	17	4	19	1.12 (0.33–3.79)	8.8
Martin-Bermudez et al, 2002 (39)	2	41	5	39	0.38 (0.08–1.85)	5.5
Cross et al, 2003 (41)	3	35	5	36	0.62 (0.16–2.39)	7.3
Crane et al, 2004 (44)	5	20	0	20	11.00 (0.65–186.32)	1.8
Bellone et al, 2004 (4)	0	24	2	22	0.18 (0.01–3.62)	1.7
Park et al, 2004 (45)	2	27	1	27	2.00 (0.19–20.77)	2.6
Bellone et al, 2006 (42)	0	18	1	18	0.33 (0.01–7.66)	1.6
Ferrari et al, 2006 (14)	11	53	4	53	2.75 (0.93–8.09)	10.8
Moritz et al, 2007 (15)	4	50	8	59	0.59 (0.19–1.84)	9.9
Ferrari et al, 2007 (16)	3	25	2	27	1.62 (0.29–8.91)	4.8
Gray et al, 2009 (12)	34	356	33	346	1.00 (0.63–1.58)	34.9
Ferrari et al, 2009 (18)	7	40	2	40	3.50 (0.77–15.83)	6
Random-effects model	76	727	70	728	1.06 (0.72–1.57)	100

Results

- Need for intubation (Bilevel vs. CPAP)

Study, Year (Reference)	Bilevel Ventilation Events, n	Bilevel Ventilation Patients, n	CPAP Events, n	CPAP Patients, n	RR (95% CI)	W (random), %
Mehta et al, 1997 (37)	1	14	1	13	0.93 (0.06–13.37)	4
Park et al, 2001 (43)	0	7	3	9	0.18 (0.01–2.99)	3.6
Bollaert et al, 2002 (38)	5	17	4	19	1.40 (0.45–4.37)	21.9
Liesching et al, 2003 (40)	0	13	1	14	0.36 (0.02–8.06)	2.9
Cross et al, 2003 (41)	1	35	4	36	0.26 (0.03–2.19)	6.2
Crane et al, 2004 (44)	1	20	1	20	1.00 (0.07–14.90)	3.9
Bellone et al, 2004 (4)	2	24	1	22	1.83 (0.18–18.84)	6.2
Park et al, 2004 (45)	2	27	2	27	1.00 (0.15–6.59)	8
Bellone et al, 2005 (42)	2	18	1	18	2.00 (0.20–20.15)	6.3
Ferrari et al, 2006 (14)	3	53	0	53	7.00 (0.37–132.26)	3.3
Moritz et al, 2007 (15)	2	50	1	59	2.36 (0.22–25.26)	5.1
Ferrari et al, 2007 (16)	1	25	0	27	3.24 (0.14–75.87)	2.9
Gray et al, 2009 (12)	4	356	1	346	3.89 (0.44–34.61)	6
Ferrari et al, 2009 (18)	3	40	0	40	7.00 (0.37–131.22)	3.3
Ghanem et al, 2009 (19)	4	44	5	44	0.80 (0.23–2.78)	18.3
Random-effects model	31	743	25	747	1.23 (0.72–2.10)	100

Results

- Incidence of new MI (Bilevel vs. CPAP)

Study, Year (Reference)	Bilevel Ventilation Events, n	Bilevel Ventilation Patients, n	CPAP Events, n	CPAP Patients, n	RR (95% CI)	W (random), %
Mehta et al, 1997 (37)	10	14	4	13	2.32 (0.96–5.60)	9.7
Park et al, 2001 (43)	0	7	1	9	0.42 (0.02–8.95)	0.9
Bollaert et al, 2002 (38)	3	17	4	19	0.84 (0.22–3.22)	4.4
Martin-Bermudez et al, 2002 (39)	7	41	7	39	0.95 (0.37–2.46)	8.5
Liesching et al, 2003 (40)	1	13	0	14	3.22 (0.14–72.51)	0.9
Crane et al, 2004 (44)	9	20	3	20	3.00 (0.95–9.48)	6
Bellone et al, 2004 (4)	2	24	3	22	0.61 (0.11–3.32)	2.8
Park et al, 2004 (45)	0	27	0	27		0
Moritz et al, 2007 (15)	3	50	2	59	1.77 (0.31–10.18)	2.7
Ferrari et al, 2007 (16)	4	25	8	27	0.54 (0.19–1.57)	6.8
Gray et al, 2009 (12)	95	356	94	346	0.98 (0.77–1.25)	57.4
Random-effects model	134	594	126	595	1.09 (0.82–1.46)	100

Weighting the 3CPO Trial

- The weight assigned to the 3CPO trial didn't affect findings of effect for any of the other trial comparisons and outcomes.
- Exception:
  - comparison of CPAP and standard therapy on need for intubation
  - comparison of bilevel ventilation with standard therapy on need for intubation

Subgroup Analyses

Appendix Table 6. **Results of Subgroup Meta-analysis, by Allocation Concealment**

Comparison	Allocation Concealment	Studies, *n*	Relative Risk (95% CI)
Mortality			
CPAP vs. standard therapy	Yes	8	0.45 (0.25–0.82)
	No	5	0.88 (0.59–1.31)
Bilevel ventilation vs. standard therapy	Yes	3	0.57 (0.25–1.27)
	No	5	0.89 (0.61–1.30)
Bilevel ventilation vs. CPAP	Yes	8	1.24 (0.62–2.47)
	No	4	0.92 (0.60–1.39)
	NA	2	1.12 (0.16–7.71)
Intubation rate			
CPAP vs. standard therapy	Yes	8	0.46 (0.29–0.71)
	No	6	0.37 (0.19–0.70)
	NA	1	0.47 (0.17–1.25)
Bilevel ventilation vs. standard therapy	Yes	3	0.27 (0.07–1.08)
	No	5	0.73 (0.45–1.19)
	NA	1	0.37 (0.13–1.10)
Bilevel ventilation vs. CPAP	Yes	8	1.66 (0.81–3.40)
	No	5	0.69 (0.17–2.87)
	NA	2	1.59 (0.21–12.26)

Discussion

- CPAP was associated with a statistically significant reduction in inhospital mortality and need for intubation, but not incidence of new MI.
- The effect was especially prominent among patients in whom myocardial ischemia or infarction was a cause of pulmonary edema.

Discussion

- Bilevel ventilation was associated with a statistically significant reduction in the need for intubation, but not in mortality or incidence of new MI.
- Bilevel ventilation and CPAP did not significantly differ on any clinical outcome in which they were directly compared.

Discussion

- 3CPO trial differ from preceding evidence:
  - The study samples were different
  - 3CPO trial had considerable crossover among treatment groups
  - Standard monitoring and therapy for ACPE may have improved since the first trials of NIV
  - Our estimated effect of NIV is derived from calculations that assign different importance (weight) to the individual studies

Limitations

- The quality of the evidence base was limited
- No trial met all standard quality criteria
- Only small differences in size when analyzing trials by quality and date of publication
- Criteria for diagnosis of ACPE are not well established, and the definitions, causes, and severity of ACPE differed among the trials
- The evidence base was heterogeneous
- The possibility of publication bias

Conclusion

- Although a recent large trial contradicts results from previous studies, the evidence in aggregate still supports the use of NIV for patients with ACPE.
- CPAP reduces mortality more in patients with ACPE secondary to acute myocardial ischemia or infarction.

Thank you for your attention !