

### Neuropsychological outcome after cardiac arrest

ERIK BLENNOW NORDSTRÖM, PHD STUDENT, LIC. PSYCHOLOGIST LUND UNIVERSITY, SWEDEN ■ POST CARDIAC ARREST CARE 2019-05-24



## Cardiac arrest and brain injury

- The brain has a constant need of oxygen to meet energy demands
- Oxygen deprivation > 4-8 mins could lead to cerebral infarction/cell death
- Reduced oxygen content in the blood (anoxia/hypoxia) and reduced blood flow to the brain (ischemia)
- Possible hypoxic-ischemic encephalopathy
- Risk of continued reperfusion damage, oxidative stress



## Neuropathology after cardiac arrest

- Cerebral anoxia has historically been identified as the cause of an isolated amnesic syndrome
- The hippocampus, a brain area integral to several learning and memory functions, is extra sensitive to anoxic brain injury
  - The selective vulnerability hypothesis
  - Still debated: Evidence from animal models or autopsies (case studies) and MRI's of anoxic damage from diverse etiologies



## Neuropathology after cardiac arrest

The amnestic syndrome is not that common – rather...

"These observations suggest a widespread pattern of brain damage induced by transient global cerebral ischemia"

Horstmann, Frisch, Schroeter et al (2010). Neurology, 74(4).

Evidence for injuries in hippocampus, but also the basal ganglia, thalamus, cerebellum and watershed cortex



Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 5199

## Cognition and neuroimaging

"Earlier studies overemphasize memory functions"

Overbeck & Schweers (2017). Case Reports in Cardiology, 5.

MRI of long term CA survivors (n = 12, M = 15 months post-arrest) vs matched healthy controls: multiple atrophic areas



Bishop, Lamar, Hurley & Taber (2015). The Journal of Neuropsychiatry and Clinical Neurosciences, 27(2).

## Cognition and neuroimaging

MRI 3 months post-arrest (n = 13) vs matched healthy controls: significantly thinner cortex, reduced memory and fine-motor coordination



Interaction between group and verbal episodic memory recall performance on cortical thickness, adjusted for age and sex.



Ørbo, Aslaksen, Vangberg et al (2019). Neurorehabilitation and Neural Repair, 33(4).

### Measuring cognitive outcome post-arrest

The TTM Trial: > 90 % of survivors had good outcome using the CPC ... but there were other indications of cognitive dysfunction

- Patient reported outcome 18-36 % had problems
- Cognitive performance measures > 50 % had problems
- Informant reported outcome 53 % had problems

Nielsen, Wetterslev, Friberg et al (2013). New England Journal of Medicine, 369(23).
Cronberg, Lilja, Nielsen et al (2015). JAMA Neurology, 72(6).
Lilja, Nielsen, Cronberg et al (2015). Circulation, 131(15).
Blennow Nordström, Lilja, Cronberg et al (2017). Resuscitation, 118.

### Measuring cognitive outcome post-arrest

"Severe cognitive impairments are easily recognized. Mild cognitive impairments are much more difficult to spot."

Boyce & Goossens (2017). Seminars of Neurology, 37(1).



## Cognitive impairment post-arrest

### **Cognitive domains usually impaired:**

- Memory
- Varying degree of impairment, 12-100 %
- Usual deficits: Novel learning, delayed recall
- Unusual: Isolated amnesia
- Attention and processing speed
- Executive functions, such as planning and organisation







## Cognitive impairment post-arrest

### But risk of deficits in other cognitive fuctions as well

- Language (reading, writing, verbal fluency)
- Visuospatial functions
- Insight



Juan, de Lucia, Rossetti et al (2018). *Critical Care Medicine, 46*(4). Dougherty (1994). *American Journal of Critical Care, 3*(2). Roine, Kajaste & Kaste (1993). *JAMA, 269*(2).

## Long-term effects of cognitive impairment

- Steinbusch: The greatest improvement occured 0-3 months post-arrest
- Lilja: Cognitive impairment in half of the survivors 6 months post-arrest, mostly mild
- Buanes: 29 % cognitive impairment 4 years post-arrest (N = 30)
- Drysdale: Moderate-severe memory impairment in an initial assessment
   8 months post-arrest was sustained 3 years post-arrest

Steinbusch, van Heugten, Moulaert et al (2017). *Resuscitation, 120.* Lilja, Nielsen, Cronberg et al (2015). *Circulation, 131*(15). Buanes, Gramstad, Heltne et al. (2015). *Resuscitation, 89.* Drysdale, Grubb, Fox & O'Carroll (2000). *Resuscitation, 49*(1).



### Associations with other factors of life

- Cognitive impairment post-arrest due to brain injury: Higher risk of psychological distress
- Self-reported emotional symptoms in 75 % of survivors
  - Depressive symptoms 14-45 %
  - Symptoms of anxiety 13-61 %
  - Symptoms of PTSD 19-27 %
- Self-reported symptoms of fatigue ≈ 69 %
- Cognitive impairment, symptoms of fatigue, depression and restricted mobility are predictive variables associated with restricted participation

### Knowledge gap in cognition post-arrest

Lack of detailed, longitudinal follow-up

- Larger *N*, smaller numbers of examined cognitive functions
- Smaller *N*, larger numbers of examined cognitive functions

Highlighted articles of interest	Included participants	Neurocognitive assessment time-point	Neurocognitive assessments
Blennow Nordström et al.	268	6 months	Iqcode-ca; mmse; rbmt
Evald <i>et al.</i>	79 (36+43)	6 months	WAIS-IV Digit Span, Vocabulary; RAVLT; RCFT; TMT A and B; D-KEFS Verbal Fluency
Juan et al.	42	6 months	WAIS-IV Digit Span forward, Digit Symbol; WMS-III Spatial Span forward; Lexis Naming; CVLT; Doors And People Test; Five-Points Test; Test Battery For Attentional Performance Alert, Divided Attention; Verbal Fluency; TMT A and B, Stroop
Koller et al.	38/50/114	Discharge from the ICU	CAMCI; MoCA; 41 Cent Test
Lilja et al.	270	6 months	RBMT; SDMT; FAB
Ørbo et al.	33	3 months, 12 months	WASI Matrix Reasoning, Vocabulary; CVLT-II; RCFT; D-KEFS TMT 4–5, Verbal Fluency; Grooved Pegboard
Steinbusch <i>et al.</i>	140/120/110	2 weeks, 3 months, 6 months	CogLog; Adult Memory and Information Processing Task A; Verbal Fluency; TMT A and B; Paragraph Recall Test
Verberne <i>et al.</i>	141/120/110	2 weeks	CogLog

CAMCI, Computer Assessment of Mild Cognitive Impairment; CogLog, Cognitive Log; CVLT, California Verbal Learning Test; D-KEFS, Delis-Kaplan Executive Function System; FAB, Frontal Assessment Battery; IQCODE-CA, Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; RAVLT, Rey Auditory Verbal Learning Test; RBMT, Rivermead Behavioural Memory Test; RCFT, Rey Complex Figure Test and Recognition Trial; SDMT, Symbol Digit Modalities Test; TMT, Trail Making Test; WAIS-IV, Wechsler Adult Intelligence Scale – Fourth Edition; WASI, Wechsler Abbreviated Scale of Intelligence; WMS-III, Wechsler Memory Scale – Third Edition.

#### Blennow Nordström & Lilja (2019). Current Opinion of Critical Care, 25(3).

## Knowledge gap in cognition post-arrest

- Does TTM protect against cognitive disabilities?
- Cognitive impairment due to acute anoxic injury or slower cardiovascular degeneration?
  - Lilja: Cognitive impairment was common post-arrest, but also in a cohort of matched ST-elevated myocardial infarction patients
- Are our screening instruments accurate enough to identify cognitive decline?

#### **Circulation**

#### ILCOR ADVISORY STATEMENT

COSCA (Core Outcome Set for Cardiac Arrest) in Adults An Advisory Statement From the International Liaison Committee on Resuscitation

ABSTRACT: Cardiac arrest effectiveness trials have traditionally reported Kirstle Haywood, DPhil, outcomes that focus on survival. A lack of consistency in outcome BSc(Hons), PGCertHE aura Whitehead, PhD etween trials limits the opportunities to pool results for meta-BModSc(Hons) analysis The COSCA initiative (Core Outcome Set for Cardiac Arrest) Vinay M. Nadkarni, MD, MS a partnership between patients, their partners, clinicians, research FAHA, Co-Chair Feltx Adhana, PhD o develop a consensus core outcome set for cardiac arrest Stefanle Beesems, Ph rials. Core outcome sets are primarily intended fo Sernd W. Böttiger, MD, ML Anne Brook randomized clinical effectiveness trials (sometimes referred to Maaret Castrén, MD, PhD prnatic trials or phase IIIIIV trials) rather than for pilot or efficace Marcus EH Ong, MBBS, MPI view of the literature combined with qualitati Mary Fran Hazinski, MSN nterviews among cardiac arrest survivors was used to generate a list o RN. FAHA udolph W. Koster, MD, PhD isela Ulta, PhD process, which involved clinicians, patients, and their relatives/par advisory panel narrowed these down to 3 core loanraad G. Monsi Peter T. Morley Laurie Morrison, MD, MSc Graham Nichol, MD, MPH that a core outcome set for reporting on effectiveness studies of cardiac alentino Oriolo, RGN, MS arrest (COSCA) in adults should include survival, neurological function. alth-related quality of life. This should be reported as survival status and modified Rankin scale score at hospital discharge, at 30 days, Michael Smyth, BSc (Hons Health-related quality of life should be measured with ≥1 tools MSc ties Index version 3. Short-Form 36-Item Health Survey. Ken Spearpoint, MSc PGCortHE, BSc, RN and EuroOol 5D-5L at 90 days and at periodic intervals up to 1 year arry Williams, LLB after cardiac arrest. If resources allow avin D. Perkins, MB Ch MMEd. MD. Co-Chall

On behalf of the COSCA

 The MoCA was recently supported by the ILCOR to use in a Core Outcome Set for Cardiac Arrest trials (COSCA)

Lilja, Nielsen, Cronberg et al (2015). *Circulation, 131*(15). Haywood, Whitehead, Perkins et al (2018). *Circulation, 137*(22).

## The TTM2 Trial

- Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest
- Clinical Trials identifier: NCT02908308
- Primary outcome: *All-cause mortality at 180 days*
- Secondary outcomes: Functional outcome at 180 days (dichotomized mRS), patient reported health related quality of life (EQ5D-5L), days alive and outside hospital within the first 180 days, survival analysis (time to event)
- Tertiary/exploratory outcomes, e.g.: Detailed functional outcome at 180 days (ordinal mRS, GOSE), cognitive screening battery (MoCA, SDMT), self and observer reported cognitive disability (TSQ, IQCODE-CA)

ttm2trial.org



# The TTM2 neuropsychological sub-study

Clinical Trials identifier: NCT03543371

### Aims:

- Provide detailed and longitudinal information on cognition after out-of-hospital cardiac arrest and its relationship to associated factors as emotional function, fatigue and sleep
- Validate the the main TTM2 Trial cognitive screening battery (MoCA, SDMT) used at 180 days



# The TTM2 neuropsychological sub-study

### **Patients:**

 All patients on participating sites 18-80 years without dementia diagnosis, active drug abuse ( $n \approx 100$ )

### Intervention:

Neuropsychological examination

7 and 24 months post-arrest (performance-based tests of cognition, questionnaires of behavioral and emotional function, fatigue and insomnia)

### **Comparison:**

- Matched myocardial infarction controls ( $n \approx 100$ ) and comparison over time

Cognitive domain	Test	
Manhal	WAIS-IV Vocabulary	
verbai	D-KEFS Verbal Fluency	
	WAIS-IV Block Design	
visual/constructive	WAIS-IV Matrix Reasoning	
	WAIS-IV Digit Span	
working memory	WMS-III Spatial Span	
	Rey Auditory Verbal Learning Test	
Episodic memory	WMS-III Logical Memory	
	Brief Visuospatial Memory Test-Revised	
Description	Trail Making Test A	
Processing speed	D-KEFS Color Word Interference Test 1-2	
	Trail Making Test B	
Executive functions	D-KEFS Color Word Interference Test 3	



Should be combined with the TTM2 sub-study of Physical Activity

# The TTM2 neuropsychological sub-study

### **Outcome:**

- Composite z-score per cognitive domain at 7 and 24 months (7 months reported separately)
- Comparison TTM2 cognitive screening battery and neuropsych sub-study results at 7 months time

### **Current situation:**

- Approximately **25 OHCA patients** and **25 MI patients** have completed the 7 months examination
- Recruiting at sites in Sweden. Centers in the UK and Denmark soon to be recruiting?



### Conclusion

### To consider

- Cognitive impairment is common, and is associated with other factors of life
- Increasing amount of survivors, thus an increasing need for systematic organized follow-up of hidden disabilities such as cognitive impairment, psychological distress and fatigue
- Call for valid and reliable outcome measures and screenings to capture cognitive impairment, psychological distress and fatigue
- Future research on interdisciplinary rehabilitation interventions focusing on support, psychoeducation and treatment of patients, families and caregivers



UNIVERSITY

erik.blennow\_nordstrom@med.lu.se www.med.lu.se/cardiacarrest