

Cardiac Intensive Care Research Unit (CICRU) – Update 2023

Clinical heart research with translational aspects focusing on patients with acute ST-elevation myocardial infarction (STEMI) or cardiac arrest admitted to the CICU

Main research projects 2006-2023

GLUMIK- Impaired glucose tolerance in patients with STEMI. Oral glucosetolerance test N=220.

BAMI- Prognostic markers for future adverse cardiovascular event in patients with acute MI. N=2000.

POSTEMI- Randomized interventional study on the effect of ischemic postconditioning in STEMI, N=272.

LEAF- Randomized, placebo controlled study on the effect of levosimendan in patients with acute heart failure complicating STEMI. N=61.

NORCAST- Observational study on post-ROSC patients with out-of- hospital cardiac arrest N=250.

ASSAIL-MI- Randomized, placebo controlled study on the IL-6 receptor inhibitor tocilizumab in patients with STEMI. N=200.

TAME- Randomized, interventional study on the effect of hypercapnia on survival in patients with cardiac arrest. Multicenter trial, N=136 patients included at OUS-Ullevål

TAME-substudy- Hemodynamic effects of permissive hypercapnia in patients with cardiac arrest. N=85

GUT-ACS- Study on microbiota signature and gut-leakage markers in patients with acute coronary syndrome, N=100

More than 3000 patients included in interventional, observational or biobanking studies since start of the research initiative in 2006

MAIN RESULTAS 2022-SPRING 2023:

- **Number of papers published: 11, total number of papers last 5 years: 62**
- **TAME-study published in NEJM 2023**
- PhD student Mathias Melberg with oral presentation at ESC 2023 and finalist in Young investigator award session at ERC 2023. Research from the TAME-substudy
- Ongoing, extensive collaboration on inflammatory biomarkers from thee POSTEMI and LEAF study biobanks

Research objective: Clinical research along the large number of patients submitted to the CICU with acute STEMI or out-of- hospital cardiac arrest. Extensive collaboration with basic research groups. This in line with Oslo University Hospitals research profile on acute emergency medicine including translational aspects and building research networks

Primary objectives:

1. To explore in detail the pathogenesis of acute coronary syndromes ((ACS) including STEMI) and ischemia-reperfusion injury with focus on how systemic and local inflammation may potentially contribute to plaque destabilization and myocardial damage.
2. Interventional studies targeting ischemia/reperfusion injury aiming to reduce infarct size
3. Treatment of acute heart failure and cardiogenic shock complicating STEMI
4. Prognostication, monitoring and treatment of patients with out-of- hospital cardiac arrest in order to improve survival and neurological prognosis
5. Obtain new mechanistic insights on the importance of residual inflammation on patients with ACS, open the way for novel treatment and prevention options

PHD FROM THE CICRU:

- 2011: Eva C, Knudsen –GLUMIK-study
 - Prevalence of abnormal glucose regulation in patients with acute ST-elevation myocardial infarction. An association between glucometabolic disturbances and inflammatory and haemostatic variables
- 2017: Trygve Husebye –LEAF-study
 - Safety and efficacy of levosimendan in patients with acute myocardial infarction complicated by symptomatic heart failure
- 2017: Limal Shanmuganathan –POSTEMI-study
 - Postconditioning in acute ST-elevation myocardial infarction
- 2018: Vibeke Ritschel - BAMI-study
 - Markers of inflammation and haemostasis: Associations with myocardial injury, adverse remodeling and future clinical events in patients with ST-elevation myocardial infarction
- 2019: Anne Bethke (2/3) - POSTEMI-MR study
 - Microvascular perfusion in STEMI patients in infarcted and remote myocardium: Angiographic and CMR findings
- 2019: Henrik Stær-Jenssen – NORCAST-substudy
 - New clinical perspectives in post-resuscitation care after out-of-hospital cardiac arrest
- 2020: Christian Shetelig– POSTEMI-II biobankstudy
 - Inflammation and myocardial injury, remodelling and long-term outcomes in STEMI patients
- 2024: *In preparation* Henning Wimmer, NORCAST long-term follow-up study
 - Prognostication after out-of-hospital cardiac arrest

CICRU research group

- Senior Cardiologists, Ph.D.: Geir Øystein Andersen (head), Eirik Qvigstad, Arnljot Flaa, Christian Shetelig, Ingvil Tøllefsen, Trygve Husebye
- PhD students: Mathias Melberg (TAME-substudy), co-supervision of Henning Wimmer (NORCAST substudy), Andraz Nendl (Microbiota project)

Collaboration

Oslo University Hospital (OUS) Ullevål

- Oslo Center for Clinical Heart Research professor Ida Gjervold Lunde
- Professor Kjetil Sunde and Theresa Olasveengen, Emergency department
- Professor Sigrun Halvorsen, head of Dept of Cardiology
- Pavel Hoffman, Eigil Fossum, Anders Opdahl, Cardiac Intervention Unit
- Professor Nils-Einar Kløw, Dept of Radiology
- Espen Nakstad, Dept of Acute Medicine, Bård Waldum, Dept of nephrology
- Post-doc. Maria Vistnes, Ayodeji Awoyemi and Ragnhild Helseth, Dept of Cardiology
- Professor Ivar Sjøstad, Institute for Experimental Medical Research

External collaboration:

- Professor em. Pål Aukrust, Bente Halvorsen, Tom Erik Mollnes, Thor Ueland, Research Institute for Internal Medicine, OUS Rikshospitalet
- Professor Lars Gullestad em., Kaspar Broch, Dept of Cardiology, OUS Rikshospitalet.
- Professor Rune Wiseth, St.Olavs hospital, Trondheim
- Professor Charlotte Bjørk Ingul, Department of Circulation and Medical Imaging, NTNU
- Professor Erik Øie, Diakonhjemmet Hospital
- Marius Trøseid, Dept of Infectious disease. OUS Rikshospitalet
- Professor Christofer Lundqvist, Dept of Neurology. AHUS.
- Professor Finn-Olav Levy, Dept of Pharmacology, UiO.

International collaboration: Professor Eric Biessen, Lieve Temmerman, Cardiovascular Research Institute Maastrich, Nederland

Study protocol synopsis

Background: Acute coronary syndromes (ACS), including ST-elevation (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) account for approximately 15% of deaths in Europe, and patients remain at significant risk of poor prognosis due to re-admission for recurrent ACS, development of heart failure (HF) and death. Infarct size is a major determinant of mortality following MI, and while the most effective way to limit infarct size is to reperfuse the myocardium through percutaneous coronary intervention (PCI), the abrupt restoration of blood flow may cause ischemia/reperfusion (I/R) injury and account for up to 50% of the myocardial damage following MI. Thus, morbidity and mortality of MI patients remains significant and there is need for deeper insight into the pathogenesis of ACS and myocardial I/R injury. Such studies could contribute to the development of biomarker-based tools for early risk prediction following ACS and open the way for novel treatment and prevention options.

Inflammation plays a crucial role in atherosclerotic disease and both local and systemic inflammation may potentially contribute to plaque destabilization and myocardial damage. I/R injury also triggers a local and systemic inflammatory response that could promote cellular injury and organ failure during post-operative recovery.

Survival rates after out-of-hospital cardiac arrest remains low and there are important uncertainties regarding optimal post-ROSC (return of spontaneous circulation) treatment and prognostication in patients that remain comatose after admission with ROSC. Local and systemic inflammation may play an important role in the development of anoxic brain injury. The cardiac and hemodynamic effects of treatment options such as therapeutic hypothermia and permissive hypercapnia are largely unknown and optimal monitoring of cardiac arrest patients in the post-ROSC period is not clear.

The aims of the CICRU initiative in 2006 were to take advantage of the large number of patients admitted yearly to the CICU. There is a lack of clinical research on patients with emergency admission due to logistic challenges and patients that lack capacity to give informed consent.

We have performed several investigator- initiated randomized interventional studies on patients with STEMI, acute heart failure or cardiac arrest during the last 15 years and have extensive collaboration with excellent imaging and basic research units using cardiac MRI, echocardiography and extensive biobanking. During the last 5 years we have published the ASSAIL- MI study in JACC, a three-center study with OUS-RH and St. Olav. We were able to demonstrate as a proof-of- concept study that administration of the interleukin-6 receptor inhibitor tocilizumab at the time of PCI resulted in improved myocardial salvage in patients with STEMI. Furthermore, we delivered 139 (number two contributor among 62 ICU-centers world-wide) patients with cardiac arrest to the TAME-study. Patients surviving cardiac arrest were randomized to permissive hypercapnia or normocapnia in the first 24 hours after admission. The results were neutral and the study was published in NEJM in July 2023. A total of 86 (of 139) of these patients were included in a substudy at our Department. The aim of this substudy is to use a pulmonary artery catheter together with echocardiography to elucidate the cardiac and hemodynamic effects of hypercapnia.

We are currently investigating in detail the possible contribution of inflammation to I/R-injury in patients with acute STEMI (infarct size) and survivors of cardiac arrest (anoxic brain injury). Whereas a balanced inflammatory response may facilitate scar healing, a persistent pro-inflammatory activation promotes adverse post-MI left ventricular remodeling and further plaque destabilization and progression of coronary atherosclerosis. Furthermore, local and systemic inflammation may contribute to enhanced anoxic brain injury and the development of post-cardiac arrest syndrome (PCAS). PCAS is an inflammatory state of pathophysiology often associated with multi-organ failure and high mortality.

The standard operating procedure (SOP) for post-ROSC care of out-of-hospital cardiac arrest patients that remains comatose at admission has changed recently. Due to recent publications of clinical trials, we have changed the target for temperature control during the first 24 hours from 33°C to avoid fever (<37.7°C). We have also restricted acute coronary angiography in patients with cardiac arrest with suspect cardiac etiology, to patients with ST-elevation on post-ROSC ECG. It is important to evaluate outcome in our patients when major treatment changes are implicated. Quality indicators including mortality should be monitored in observational studies.

Specific goals 2023-24:

1. Take advantage of the large number of patients with STEMI, acute heart failure or cardiac arrest admitted to the CICU with a goal of inclusion of the majority of patients in investigator-initiated clinical trials or observational studies including biobanks
2. To provide new insight into prognostication of patients obtaining return-of-spontaneous-circulation (ROSC) after cardiac arrest and to improve post-ROSC treatment
3. To evaluate different monitoring tools used to perform hemodynamic measurements in cardiac arrest survivors
4. Pharmacogenetic profiling of 1000 patients with STEMI. Elucidate possible effects of homozygote mutations in CYP2D6 for future cardiovascular events in patients with STEMI discharged on metoprolol
5. Observational study comparing quality indicators including mortality, on patients admitted comatose after out-of-hospital cardiac arrest. Comparison before (NORCAST study) and after (new observational study implementation of new SOP)

6. Explore in detail the importance of the innate immune systems for the development of STEMI/ACS, reperfusion injury as well as adverse remodeling after PCI treatment.
7. Study goal-directed therapy against inflammation and unwanted cytokine release in patients with STEMI of cardiac arrest. The IL-6/IL-1beta/CRP axis is of special interest
8. Elucidate the potential importance of gut microbiota and gut leakage markers in patients with ACS including STEM
9. Rescue-Doppler project: Participate in a multi-center study on transcutaneous measurement of blood flow during CPR in patients in-hospital cardiac arrest using Doppler methodology. Multi-center study
10. Prepare for a pilot study on IL-1 inhibition in patients with cardiac arrest using anakinra. Primary endpoint: Reduction in neuron-specific enolase (NSE)

Publications last 5 years (antall 63) 2018-2023 - Forskningsenheten HIO, Oslo universitetssykehus Ullevål:

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Selection of abstract from international scientific session last 5 years

2023:

1. European Society of Cardiology (Eur Heart) Scientific session:

Shetelig C. et al: Systemic inflammation and elevated cytokines in the acute phase after cardiac arrest is associated with poor neurological outcome and all-cause mortality – the prospective Norwegian Cardio-Respiratory Arrest Study (NORCAST)

2. European Resuscitation Council (ERC) Scientific session:

Melberg M et al: Targeted therapeutic mild hypercapnia after acute myocardial infarction and out-of-hospital cardiac arrest may have cardioprotective effects. A substudy of the TAME cardiac arrest trial.

2022: European Society of Cardiology (Eur Heart) Scientific session:

1. Ayodeji A et al: Circulating endotoxin levels are associated with acute inflammation and BNP-levels in patients with acute heart failure.
2. Andrup S et al: Detecting changes in the cardiac extracellular matrix after STEMI: association between novel biomarkers and adverse outcomes

2021 European Society of Cardiology (Eur Heart) Scientific session:

1. Tøllefsen I et al: The role of IL-6 receptor trans-signalling in ischemia-reperfusion injury, infarct healing and future major adverse clinical events in patients with ST-Elevation Myocardial Infarction
2. Kluge K et al: Complement activation is associated with neutrophil extracellular traps and all-cause mortality in ST-elevation myocardial infarction

2019: European Society of Cardiology (Eur Heart) Scientific session 2019:

Shetelig C et al. Circulating levels of ST2 are associated with myocardial injury, left ventricular function and future adverse clinical events in patients with ST-elevation myocardial infarction. **(Oral presentasjon)**

2018: European Society of Cardiology (Eur Heart) Scientific session 2018:

1. Shetelig C et al. Neutrophil extracellular traps are associated with myocardial injury, left ventricular function and future adverse clinical events in patients with ST-elevation myocardial infarction.
2. Helseth R et al. Neutrophil extracellular traps (NETs) assessed by dsDNA and PAD4 mRNA in patients with ST-elevation myocardial infarction are associated with plasma glucose.
3. Langseth MS et al. Markers of neutrophil extracellular traps as related to mortality in patients with ST-elevation myocardial infarction.

European Society of Radiology Scientific session 2018:

Bethke A et al. Microvascular perfusion in infarcted and remote myocardium after successful primary PCI: Coronary angiography and CMR findings

European Society of Intensive Care medicine (ESICM) 2018:

1. Wimmer H et al. Changes in quality of life in the following years after out-of-hospital cardiac arrest
2. Reichenbach AS et al. Transcranial doppler flow pattern during and after targeted temperature management for outcome prediction after out-of-hospital cardiac arrest

Eurothrombosis 2018:

Helseth R et al. Glucose associated NETosis in patients with ST-elevation myocardial infarction

Other publications 2016-20:

1. Qvigstad E: Akutt høyre ventrikkelsvikt. **Hjerteforum 2023. nr 2. 36-45.**
2. Andersen GØ: Akutt hjertesvikt og kardiogent sjokk. En oversikt med vekt på nye momenter knyttet til patofysiologi og behandling. **Hjerteforum 2018. nr 3. vol. 31. 10-23.**
3. Andersen GØ, Levy FO: Legemidler ved hjerte- og karsykdommer. **Norsk Legemiddelhåndbok 2016; L8:10591143.**
4. Andersen GØ: Medforfatter, Hjerterytmier. Klinikk, EKG og behandling. Red. Finn Hegbom, Torkel Steen. 2016. ISBN 978-82-303-3254-2.