DPP3 levels in out of hospital cardiac arrest patients admitted to the intensive care unit: an explorative study

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In this explorative-study, we aim to investigate the relation between cDPP3 release kinetics and clinical outcome parameters in OHCA patients after ICU admission. This could lead to the identification of a new predictive marker, a potential...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Observational invasive

Summary

ID

NL-OMON50128

Source
ToetsingOnline

Brief title
DPP3inOHCA

Condition

- Heart failures
- Decreased and nonspecific blood pressure disorders and shock

Synonym
'cardiac arrest', 'heart-attack', 'out of hospital cardiac arrest'

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: cardiac arrest, DPP3, post cardiac arrest syndrome, vasodilatory shock

Outcome measures

Primary outcome

Plasma DPP3 levels and DPP3 enzyme activity. Correlation with development of post-cardiac arrest syndrome, 28 day mortality.

Secondary outcome

Development of vasodilatory shock with concurrent vasopressor dosage necessity, plasma cytokine concentrations, development of other complications related to disease/treatment, vital parameters, kidney function, blood gas values, age, body mass index, cause of cardiac arrest, sequential organ failure assessment (SOFA) score, use of medication, survival

Study description

Background summary

Despite marked advancements in post-resuscitation care, with different strategies to prevent secondary organ damage, patients admitted to the ICU department after an out of hospital cardiac arrest (OHCA) still have an in-hospital mortality as high as 60-70% [1].

More than half of OHCA-patients in whom return of spontaneous circulation (ROSC) is achieved will develop post cardiac-arrest syndrome (PCAS) [2]. In PCAS, generalized ischemia-reperfusion after circulatory arrest causes a sepsis like-inflammatory response, leading to vasodilatory shock, which often requires high dose vasopressor therapy despite adequate fluid resuscitation [3, 4]. Approximately half of all patients developing PCAS die as a consequence of multi-organ failure caused by refractory shock [2]. This sequence of events takes place in the first 3 days after admission, often before any neurological assessment is possible. The pathogenesis of PCAS is incompletely understood and treatment is lacking [2].

Dipeptidyl peptidase 3 (DPP3) is a zinc-dependent metallopeptidase capable of hydrolyzing a broad spectrum of oligopeptides between 3 and 10 amino-acids in length [5]. DPP3 has been implicated in blood pressure regulation [6], inflammation [7], and pain regulation [8, 9] through its capability to hydrolyze and thus inactivate bioactive peptides like angiotensin II, enkephalins and endorphins. Recently, specific assays for the detection of DPP3 concentration and enzyme activity in plasma have been developed [10]. Whereas plasma levels of DPP3 are low in healthy volunteers [10], high levels of plasma DPP3 (also known as circulating (c)DPP3) were predictive for outcome of septic and cardiogenic shock patients [10-12]. Furthermore, normalization of cDPP3 following the first 24 hours of treatment was associated with reduced 3 0 day-mortality [11].

Based on these negative clinical associations, it was hypothesized that persistent elevation of cDPP3 despite adequate supportive treatment represents a state of ongoing cell death (necrosis) compared to patients with normalizing cDPP3 values [11]. Since OHCA patients are known to exhibit marked ischemia reperfusion-induced cell damage [13, 14], increased cDPP3 levels are to be expected and could represent a novel prognostic marker for subsequent development of PCAS and mortality.
Next to its value as a prognostic marker, therapeutic effects of cDPP3 modulation were recently evaluated in an animal study [12]. In healthy mice, intravenous DPP3 injections provoked a rapid decrease in left ventricular function, while in a murine heart-failure model, inhibition of cDPP3 function rapidly improved left ventricular function [12]. Interestingly, DPP3 inhibitors are currently developed for clinical use. Therefore, if OHCA patients indeed exhibit elevated cDPP3 levels, it could represent a therapeutic target to combat refractory shock caused by PCAS.

Study objective

In this explorative-study, we aim to investigate the relation between cDPP3 release kinetics and clinical outcome parameters in OHCA patients after ICU admission. This could lead to the identification of a new predictive marker, a potential therapeutic target for post cardiac arrest syndrome, and a timeframe for therapeutic intervention.

Study design

Prospective observational study.

Blood will be sampled at time-points:
- Immediately after admission to the Intensive Care department (timepoint T0)
- 12 hours after admission (T12)
- 24 hours after admission (T24)
- 48 hours after admission (T48)

- 72 hours after admission (T72)

When possible, an existent arterial line or intravenous line will be used to sample blood. A venapuncture will only be performed when necessary. Informed consent will be asked if a venapuncture is necessary to obtain blood.

Study burden and risks

The burden of the study will be neglectable in these patients, because blood can be drawn from the arterial line, central venous line or during standard lab rounds no vena puncture will be necessary in the majority of cases.

If vena puncture should be necessary, it carries a small risk on development of a local hematoma. This risk is reduced by applying adequate pressure for a long enough time after puncture. If a local hematoma develops nonetheless, it spontaneously resolves within days to weeks after the injury, and is generally regarded as a mild adverse event.

This study will (partly) be conducted in incapacitated persons, since cardiac arrest patients are often sedated during the first days following circulatory arrest. The conduct of the study in this specific group of patients does not result in additional risks associated with participation in this study.

This research may be considered group-related, since scientific knowledge on DPP3 release kinetics after out of hospital cardiac arrest can only be obtained by studying this specific group of patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Out of hospital cardiac arrest
- Intensive Care admission (this applies to all out-of-hospital cardiac arrest patients who required endotracheal intubation because they did not regain consciousness within 20 minutes of onset of cardiac arrest)

Exclusion criteria

- Necessity for extracorporeal membrane oxygenation, intra-aortic balloon pumps
- Patients admitted with an already proposed withdrawal of life-sustaining treatment because of diagnosed irreversible neurological injury or because of treatment limitations expressed by the patient before the event.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-11-2020
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO

Date:	17-06-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL73150.091.20