CRP apheresis in myocardial infarction - a therapeutic option?

C-reactive protein apheresis as anti-inflammatory therapy in acute myocardial infarction: Results of the CAMI-1 study.

Ries W, Torzewski J, Heigl F, Pfluecke C, Kelle S, Darius H, Ince H, Mitzner S, Nordbeck P, et al. Front Cardiovasc Med 202; 8:591714

Open questions in myocardial infarction therapy

The most effective treatment of acute myocardial infarction is reopening of the occluded coronary vessel as soon as possible. Despite well-organized prehospital logistics, sophisticated revascularization techniques and standardized post-interventional intensive care, the mortality rate of infarcted patients is still about 10%, and in the case of infarct-related cardiogenic shock it is as high as about 40%.

On sober reflection, it must be assumed that this treatment concept of the earliest possible revascularization cannot be further optimized in terms of quality and thus the high mortality rate cannot be further reduced. What else contributes to the high mortality of the infarct patient besides infarct necrosis? One candidate is inflammation. It is a double-edged sword: on the one hand, it helps the body heal wounds and fight infections; on the other hand, excessive inflammation also increases the risk of atherosclerosis, diabetes, and age-related diseases (Sheriff A; Front Immunol 2021; 12:630430).

We now know that inflammation plays a role in numerous heart diseases, including acute myocardial infarction. TNF-a, IL-1 and IL-6 are frequently named as causative cytokines. As expected, these pathophysiological findings were quickly followed by therapeutic approaches using cytokine antibodies/antagonists and other anti-inflammatory agents such as colchicine and methotrexate. Probably the most convincing evidence currently supports therapeutic approaches with the IL-1β antibody canakinumab and the anti-inflammatory colchicine in patients following myocardial infarction. Nevertheless, the place of inflammation in acute and chronic coronary syndromes is currently the subject of sometimes controversial debate (Newby LK; N Engl J Med 2019; 381:2562).

C-Reactive Protein - Marker and also Mediator?

TNF-a, IL-1 and IL-6 are inflammatory biomarkers as well as potentially harmful mediators. In contrast, C-reactive protein (CRP) is primarily considered a very sensitive inflammatory marker with rapid onset and decay kinetics. In daily practice in the intensive care unit, it is indispensable as a progression marker.

In coronary patients it has been used to estimate the residual cardiovascular risk under statin therapy (Ridker PM; Eur Heart J 2020; 41:2952; Ridker PM; N Engl J Med 2005; 352:20) to

prove the anti-inflammatory efficacy of a rehabilitation program (Milani RV; JACC 2004;43: 1056), to demonstrate the anti-inflammatory and prognostic efficacy of an IL-1β antibody (canakinumab) in post-infarction patients (Ridker PM; N Engl J Med 2017; 377:1119), and to show which patient might benefit from canakinumab therapy (Ridker PM; Lancet 2018; 391:319).

CRP is synthesized in the liver in an IL-6-mediated manner; it detects and opsonizes invading bacteria by binding to specific structures of the bacterial membrane. However, CRP binds not only to bacterial membranes, but also - due to damaged cell membranes - to dead, dying, damaged or hypoxic/ischemic cells, but not to the cell membrane of healthy cells (Sheriff A; Front Immunol 2021; 12:630430). The cells that have bound CRP are subsequently cleared via complement activation. However, CRP appears to be not only an inflammatory marker but also a potentially damaging mediator: In rabbits, intravenous injection of human CRP to achieve a CRP level of 50 mg/L results in a pronounced drop in blood pressure lasting approximately 20 minutes without a compensatory increase in heart rate, a phenomenon that may also play a role in the hypotension seen in sepsis (Bock C; Front Immunol 2020; 11:1978).

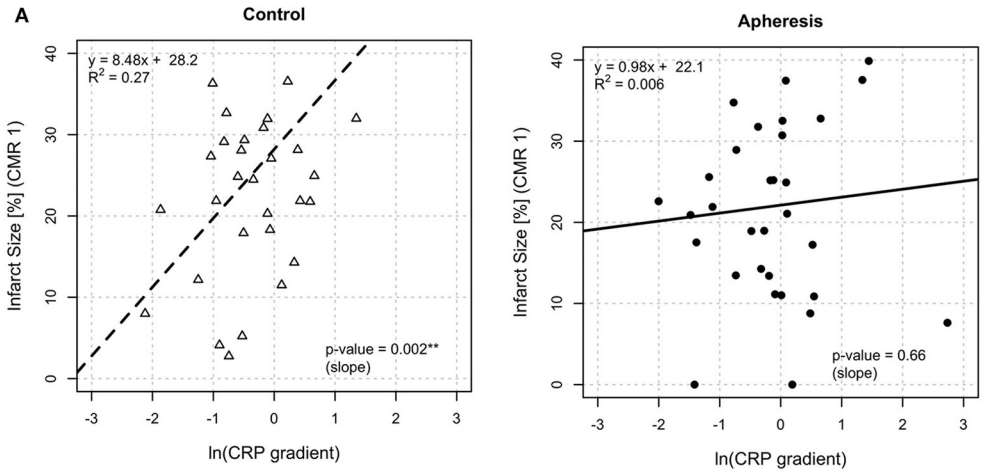

Figure: Correlation of myocardial infarct size measured by cardiac magnetic resonance (CMR) (day 2-9) and CRP gradient.

ln (CRP gradient) = natural logarithm of the CRP gradient. Left figure: patients in the control group; right figure: patients in the CRP apheresis group. (modified after Ries W; Front Cardiovasc Med 2021; 8:591714)

In rats with myocardial infarction, administration of human CRP leads to an increase in infarct size (Griselli M; J Exp Med 1999; 190:1733).

CRP apheresis as a therapeutic concept?

If, accordingly, CRP should not only have a biomarker function but also a mediator effect that damages the cardiovascular system, the question naturally arises whether a therapeutic effect can be achieved by blocking (Sheriff A; Front Immunol 2021; 12:630430) or eliminating CRP in the form of CRP apheresis (Mattecka S; Ther Apheresis Dialysis 2019; 23:474; Ries W; Ther Apher Dial 2019; 23:570).

The CAMI-1 study

■ Study Design:

In the exploratory, multicenter (8 centers in Germany), controlled, nonrandomized CAMI-1 pilot study ("CRP apheresis in Acute Myocardial Infarction study"), patients with acute ST-segment elevation myocardial infarction (STEMI) with a Killip class ≤ 2 (study inclusion: n = 83; in final analysis: n = 66) received either only the standard myocardial infarction therapy (primary percutaneous coronary intervention (PCI) plus adjunctive therapy with TIMI grade III coronary flow after PCI) (n = 38) or additionally CRP apheresis treatment (n = 45) (Ries W; Front Cardiovasc Med 2021; 8:591714). The primary end point was a reduction in infarct size as determined by cardio-magnetic resonance imaging (CMR1: day 2-9; CMR2: week 12±2). During the 12-month follow-up, three adverse cardiac events (death, need for coronary revascularization, need for pacemaker implantation) occurred in the control group and none in the verum group.

■ Neutral primary endpoint:

To put it in a nutshell: The primary end point was not met. As shown in Supplementary Table 1, infarct size was 26.3±13.4% (CMR1) and 18.0±7.9% (CMR2) in patients in the control group and 22.0±11.4% (CMR1) and 18.6±8.8% (CMR2) in patients in the CRP apheresis group and was thus not significantly different.

And yet, despite this neutral primary result, it is worthwhile to take a closer look at this study, because it provides us with important information, both with regard to CRP as a biomarker and as a possible mediator, and also with regard to what we could potentially expect from CRP apheresis in myocardial infarction patients.

■ Infarct size correlates with CRP:

A compelling finding is the significant correlation of infarct size with the amount of CRP measurable in plasma in control patients (Fig. left). This is an important finding, but it is not suitable as a practical, easy-to-survey indicator because the so-called CRP gradient (initial increase in plasma CRP within 20 hours) must be determined to establish this correlation.

This suggests that the more CRP is produced and released by the liver, the greater and thus prognostically less favorable the myocardial infarction.

■ CRP apheresis in STEMI patients - effective and safe:

The PentraSorb® system (Pentracor GmbH, Germany) can eliminate up to 94% of circulating CRP in blood plasma (Mattecka S; Ther Apher Dial 2019; 23:474). Patients in the CAMI-1 trial received the first CRP apheresis 24±12 hours after symptom onset-at a median serum CRP concentration of 23.0 mg/L (range 9-279)-and the second 48±12 hours after symptom onset. A third CRP apheresis was performed if the serum CRP level had risen again to levels above 30 mg/L approximately 12 hours after the end of the second.

Apheresis was accessed via the cubital vein. With 12 cycles of 500 mL each, a plasma volume of up to 6,000 mL was cleared of CRP per five-hour apheresis, with a halving of serum CRP levels and a 62.5% reduction in the amount of CRP detectable in serum over 72 h after symptom onset ("area under the curve," AUC). Severe side effects did not occur, but only those typical for extracorporeal apheresis procedures; in five of the 45 apheresis patients, only incomplete performance was possible.

■ Abstract statement: "CRP apheresis has the potential to interfere with deleterious aspects of STEMI":

This very cautious statement by the authors already shows that the primary endpoint, reduction in STEMI infarct size determined by cardiac MRI, was not achieved by CRP apheresis.

Instead of the primary study results - which are only shown in Supplementary Table 1 (see above) - we find figures in the original publication (see Fig.), which should make the reader aware that in the patients of the control group the infarct size correlates with the CRP gradient (Fig. left, "Control"), but not in the patients of the CRP apheresis group (Fig. right, "Apheresis").

This is interpreted in the publication in a comprehensible way as a favorable effect of CRP elimination on infarct size. With a total of 24 such individual figures, the authors present the described differences - correlation in the control group, no correlation in the CRP apheresis group - as favorable effects on both infarct size and left ventricular ejection fraction as well as longitudinal and circumferential strain. Considering the subgroups of STEMI patients with a relatively high CRP gradient of > 0.6 (ln gradient -0.5; maximum CRP concentration ~ 22 mg/L), the mean infarct size was 31% in the control group (20/34) and 22.5% in the CRP apheresis group (23/32) ($p = 0.03$). This is interpreted by the authors as an indication that in patients with more pronounced inflammatory response - more than half - infarct size reduction could be achieved with CRP apheresis.

CRP apheresis in infarct-related cardiogenic shock?

In the CAMI-1 study, 24 hours after the onset of infarct pain, CRP plasma levels averaged 16.1 mg/L (2.5-150) in patients in the control group and 15.0 mg/L (5.2-102) in the CRP apheresis group. Substantially higher CRP levels than in uncomplicated STEMI are found in patients with infarct-related cardiogenic shock (ICS), with reported peak CRP levels in the CardShock trial of 137 mg/L (median; 59-247); however, CRP levels do not correlate with lethality (Kataja A; Int J Cardiol 2021; 322:191).

In the CAMI-1 trial, infarct-related cardiogenic shock was an exclusion criterion for safety reasons; left ventricular ejection fraction averaged 50-55% in CAMI-1 trial patients (Supplementary Table 1). However, it is well known that a massive inflammatory response occurs in ICS patients, with documented prognostic relevance for IL-6, 7, 8, and 10 (Prondzinsky R; Clin Res Cardiol 2012; 101:375). Perhaps CRP apheresis or mediator apheresis in general would be worthwhile especially in this patient population?

What does the CAMI-1 study tell us?

If you take the time to read this article, which is not easy to read, the first thing you notice is that the primary endpoint - the reduction of infarct size by CRP apheresis - was not achieved. However, to note only this information would not do justice to this study, because it also provides important "positive" results: Convincingly, in uncomplicated STEMI, CRP production correlates with infarct size. Also comprehensible are the indirect, hypothesis-generating indications that CRP apheresis in STEMI could both reduce infarct size and improve impaired pump function.

Consequently, the next step-which the authors also encourage-would be a sufficiently large randomized trial of CRP apheresis therapy in uncomplicated STEMI with the end point of "infarct size reduction," with patients with higher peak CRP levels (>20 mg/L) likely to benefit most. Such a study is currently under development at the Medical University of Innsbruck.

And a study in patients with infarct-related cardiogenic shock might seem even more worthwhile, as the authors also note. That RCTs are also possible in these critically ill patients has been shown by the IABP-SHOCK-II study (Thiele H; N Engl J Med 2021; 367:1287).

Conflicts of interest: K. Werdan is Chairman of the Novartis Heart Failure Think Tank.

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