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Case report

A novel case of impaired C-reactive protein response following open-heart surgery: A case report and review of the literature

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ABSTRACT

Background: C-reactive protein (CRP) is expected to increase in response to a range of inflammatory stimuli such as infections or extensive tissue trauma.
Case report: We present a novel case of severely impaired CRP response following NSTEMI, influenza A infection and open-heart surgery in which serum CRP concentrations remained < 1 mg/L during an observational period of 28 days.
Conclusion: To our knowledge, no previous publications exists describing patients with a lack of CRP response following cardiothoracic surgery. We believe this to be a novel finding warranting further investigations regarding the etiology and prevalence of this phenomenon.

1. Introduction

C-reactive protein (CRP) is an important acute phase protein and part of the innate immune response to inflammation, infection and extensive tissue trauma such as major surgical interventions [1-14]. In this report we present a novel case of a severely diminished CRP response following open-heart surgery and provide a review of the available literature on this topic.

2. Case report

During the spring of 2018 a 72-year-old native Norwegian male presented with unprovoked acute onset of retrosternal chest pain. Cardiovascular risk factors included a family history of coronary heart disease and untreated hypercholesterolemia. He had no previous hospital admissions and was without any prescribed medications.

He was emergently admitted to his municipal hospital and a diagnosis of acute non-ST segment elevation myocardial infarction (NSTEMI) was confirmed (troponin I = 1878 ng/L, ref. range < 34 ng/L). The patient was transferred to the regional cardiothoracic center (Haukeland University Hospital), where coronary angiography revealed triple-vessel disease and he was therefore accepted for urgent surgical revascularization during the same hospital stay.

Whilst waiting for cardiac surgery he developed symptoms of influenza consisting of upper respiratory tract symptoms including nasal congestion, sore throat and coughing. He displayed no fever and remained otherwise in good clinical condition. PCR by nasopharyngeal secretion swab confirmed influenza type A virus infection, and antiviral therapy (oseltamivir, Tamiflu®) was administered.

During the following two weeks his respiratory symptoms dissipated and surgery could proceed as planned. The patient underwent coronary artert bypass grafting with five distal anastomoses sewn during cardiopulmonary bypass circulation (CPB) through a midline sternotomy. The duration of aortic cross-clamping, CPB and total skin-to-skin surgical time was 162, 197 and 351 mins, respectively. Following an uncomplicated recovery period, the patient was transferred to his municipal hospital on the fifth postoperative day. Eight days later he was discharged to his home in a state of well-being.

Abbreviations: CABG, coronary aortic bypass graft; CBC, complete blood count; CPB, cardiopulmonary bypass; IL-6, interleukin-6; LoQ, limit of quantification; NSTEMI, non-ST-segment elevation myocardial infarction; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; POCT, point-of-care testing; SAA, serum amyloid A; WBC, white blood cell count.

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Whilst preparing the discharge documentation, the attending surgeon noticed a lack of CRP response during the entire hospital admission of three weeks. This was considered abnormal and initiated further investigations regarding the validity of this finding.

3. Methods

3.1. Blood sampling and analysis

Serum samples were obtained from four separate days following the CABG procedure; on the first, second, third and fifth postoperative days. The samples were aliquoted and stored at −80 °C.

Serum concentrations of CRP were measured on Roche Cobas c702™ by an immunoturbidimetric assay (Roche Diagnostics CRP gen. 3, monoclonal mouse antibodies). At the time of initial admission, CRP (Vario wide range, polyclonal rabbit antibodies) and troponin I were performed on Abbott Architect *ci*16200™ at Haugesund Municipal Hospital. Further measurements of CRP and serum amyloid A were analyzed by immuno matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS Merck Millipore catalogue no. 235752, polyclonal anti-CRP antibodies) on Bruker ultrafleXtreme™ at Bevital AS research laboratory [15]. Haptoglobin, procalcitonin, ferritin and Troponin T were analyzed at Haukeland University Hospital on Roche Cobas c702/e801™, and hematology analysis was performed on Sysmex XN 9100 ™.

3.2. Ethical considerations

The patient has provided written informed consent. The patient has also been given a draft of the manuscript, and had no objections or comments regarding the publication of this case report.

4. Results

Tables 1 and 2 summarizes the patient's laboratory results and clinical features. During this period the patient underwent NSTEMI, respiratory infection (influenza type A) and open-heart surgery. At the time of hospital admission, a serum CRP concentration of < 1 mg/L was reported, and CRP concentrations remained undetectable by immunoturbidimetry during the next 27 days (Table 1). Further analysis of CRP by MALDI-TOF MS revealed a maximum value of 0.36 mg/L during the first five postoperative days.

The acute phase protein serum amyloid A (SAA) also remained low (0.056–0.169 mg/L, normal range, < 11 mg/L) [16]. Procalcitonin remained low (0.04 μg/L), haptoglobin was undetectable (0.00 g/L) and ferritin (170 μg/L) was within the normal range, 34–300 μg/L on the third postoperative day. The WBC or platelet counts did not increase whilst treated for influenza or postoperatively after open-heart surgery (Table 1). Complete blood counts (CBC) did not reveal any abnormalities of the leucocyte differential or platelets counts.

5. Discussion

We have described a case in which serum CRP concentrations remained <1 mg/L during an observational period of 28 days. During this time the patient underwent NSTEMI followed by a respiratory tract infection with influenza type A and open-heart surgery. These are clinical settings commonly associated with increased serum CRP concentrations [3,10,14,17-20].

5.1. The possibility of a pre-analytical error

We conclude the possibility of a pre-analytical error, e.g. misidentification to be ruled out, as the results remained consistent in all consecutive samples, and other analytes such as troponin T displayed values as one would expect following NSTEMI and CABG. It would be highly unlikely for patient identification procedures to independently fail in such a manner over several weeks.

5.2. The possibility of analytical interference

Interference by exogenous triglycerides has been demonstrated due to phospholipid agglutination of CRP, resulting in fewer CRP-molecules available for binding to the immunoassay [21]. Another mechanism of interference may be due to direct optical effects of the lipid particles on the CRP assay [22]. In a study by Verougstraete et al., measured CRP concentrations were compared to samples in which exogenous triglycerides were added in the form of Intralipid©. A consistent decrease of between −16 to −36% was found on an immunoturbidimetric assay (Abbott Architect i2000R) [23]. On the other hand, in the same study whilst measuring on a point-of-care-test (POCT) assay (Afinion 2, Abbott), the opposite was observed where lipemic samples resulted in increased CRP measurements of up to 117%. The increase was most pronounced when exogenous plasma triglyceride concentrations exceeded 9 mmol/L.

Interference due to exogenous lipids may affect CRP assays due to a net result of the above-mentioned mechanisms, and as Verougstragete et al. have demonstrated postprandial lipemia should be regarded as a possible pre-analytical caveat [23]. However, based on what has been shown in previous studies [23,24], the order of magnitude of such an interference cannot explain the severely impaired measured CRP response as seen in our case on either the immunoturbidimetric or POCT assay. Automatic assessment of hemoglobin (H), icterus (I) and lipemia (L) (HIL indices) on the Roche Cobas 8000 platform were all within normal range (Supplementary Table 1), thus lipemia of the samples can be ruled out. At no point during the hospitalization did the patient receive parenteral lipids or any other form of parenteral nutrition.

The presence of monoclonal immunoglobulin(s) have been reported as an interference [25,26]. However, in our patient, three weeks prior to his hospital admission he had normal protein and immunoglobulin levels. Total protein 73 g/L (ref. range 62–78), IgG 9.7 g/L (5.5–18.2), IgA 1.49 g/L (1.01–6.45) and IgM 0.53 g/L (0.22–2.40). No monoclonal component was detected by serum protein electrophoresis at the same time. Rheumatoid factor interference has been described in immunoassays [27], however rheumatoid factor was negative prior to hospitalization.

Signal interferences of CRP with other plasma compounds in MALDI-TOF MS should always result in an overestimation, and not underestimation of CRP levels because an interfering compound would increase the ion counts for CRP. In addition, mass interferences are highly unlikely due to the immunoaffinity enrichment and the high resolution of the MS instrument [28].

We do not exclude the possibility of an analytical interference, we have however not been able to identify any interference. We believe analytical error is highly unlikely to be the cause of the low CRP concentration, as CRP was analyzed on four different instruments and by three different analytical methods. Both immunoturbidimetry (LoQ = 0.6 mg/L) and MALDI-TOF MS (LoQ = 0.2 μg/L), showed consistent results and are sensitive methods for quantification of CRP. Trace levels of CRP (0.070–0.361 mg/L) were detected by MALDI-TOF, confirming the presence of CRP, although at low levels.

5.3. The possibility of hepatic failure

As both CRP and SAA are synthesized by hepatocytes, hepatic failure could be a possible explanation of a diminished measured acute phase response. However, our patient did not exhibit any clinical or biochemical evidence of hepatic failure. PT-INR, bilirubin, carbamide and albumin were all within the normal reference values preoperatively as well at the time of discharge. We can thus rule out hepatic failure as a possible explanation for the absent CRP response.

Table 1
Laboratory tests during hospitalization. Analytes are shown horizontally in chronological order (x-axis), and vertically grouped by type of analyte (y-axis).

Analyte	Assay	Material, Unit	Reference range	28. Feb	1. March	2. March	6. March	19. March	22. March	23. March	24. March	25. March	27. March
Comment	–	–	–	–	–	Clinical diagnosis of influenza. Positive influenza virus A (PCR)	–	–	**CABG performed**	Postoperative day 1.	Postoperative day 2.	Postoperative day 3.	Postoperative day 5. (discharged to municipal hospital)
Acute phase proteins													
CRP	Immunoturbidimetry	Serum, mg/L	< 5	0.2[*]	< 1	< 1	< 1	< 1	< 1	< 1	< 1 (<5[**])	< 1	< 1
CRP	MALDI-TOF MS	Serum, mg/L	< 5	–	–	–	–	–	–	0.361	0.153	0.074	0.070
SAA	MALDI-TOF MS	Serum, mg/L	< 11.0	–	–	–	–	–	–	0.169	0.109	0.059	0.056
Procalcitonin	Electrochemiluminescence immunoassay (ECLIA)	Serum, µg/L	< 0.10	–	–	–	–	–	–	–	–	0.04	–
Haptoglobin	Immunoturbidimetry	Serum, g/L	0.50–2.10	–	–	–	–	–	–	–	–	0.00	–
Ferritin	Electrochemiluminescence immunoassay (ECLIA)	Serum, µg/L	34–300	–	–	–	–	–	–	–	–	170	–
Hematology/ cardiac biomarkers													
Hemoglobin	Sysmex XN-9100	EDTA, g/dL	13.4–17.0	15.2	16.1	15.2	15.3	–	10.5[†]	10.0[†]	11.0	12.0	11.2
Platelet count	Sysmex XN-9100	EDTA, 10^9/L	145–348	147	158	–	121	–	150	121	–	132	145
WBC	Sysmex XN-9100	EDTA, 10^9/L	3.5–11.0	5.3	5.3	–	–	4.9	–	4.8	3.9	5.2	4.6
Troponin T	Electrochemiluminescence immunoassay (ECLIA)	Serum, ng/L	≤ 14 / ≤ 34[‡]	1878[‡]	202	132	105	16	–	1169	445	547	346

[*] Haugesund municipal hospital, immunoturbidimetry (Abbott Architect ci16200™).
[**] Point-of-care instrument, Afinion, solid phase immunochemical cassette. Limit of quantification (LoQ) = 5 mg/L.
[†] Point-of-care blood gas analyzer. Radiometer, ABL 800 Flex. (spectrophotometry).
[‡] Troponin I performed at Haugesund Municipal Hospital.

Table 2
Clinical features during hospitalization at Haukeland University Hospital, Bergen, Norway.

	1. March	11. March	15. March	19. March	20. March	22. March	23. March	27. March
Pulse (BPM)	91	–	58	59	55	64	76	59
Temperature, ear. (°C)	36.7, 36.3	36.7	36.1	36.5	36.6	36.4	37.6	37.3
Clinical signs of infection / comments	No obvious signs	Nasal congestion and sore throat	Coughing, sore throat and 'runny nose'. General fatigue, muscle aches.	Light coughing and light symptoms of upper respiratory tract infection.	Extended isolation precautions discontinued. Displays no clinical signs or symptoms of influenza last 12 h.	**CABG performed**	Mild fatigue. No fever present. Patient is oriented for time and place.	No fever. Drinking and eating well. Postoperative recovery uncomplicated.

5.4. Relevant historical clinical and laboratory health records for the patient

We collected relevant historical clinical records and laboratory results for the patient. The patient's general practitioner noted that he did not exhibit an increased CRP during any of his visits to their practice. CRP on a POCT instrument had been taken two times reporting findings of < 5 mg/L. Although on the first occasion a large acute phase reaction was not expected due to clinical findings (mild rubor, dolor and calor of the knee). The second relevant consultation (symptoms of a mild upper respiratory tract infection) also provided a CRP of < 5 mg/L on the POCT instrument.

Of greater interest, following his NSTEMI the patient was during the winter of 2019 operated electively by endarterectomy for a carotid artery stenosis at Stavanger University Hospital. During this hospital admission, multiple CRP measurements also remained < 1 mg/L (Immunoturbimetry, Abbott Architect^{TM}, CRP Vario wide-range method, polyclonal antibodies. LoQ = 0.2 mg/L)

5.5. Reports of an incomplete or absent CRP response in the literature.

A substantial increase in serum CRP concentrations have been widely reported following conventional CABG procedures [4,19,29–42]. An 83-fold rise in serum CRP concentration, from a preoperative baseline level of 2 mg/L to a postoperative peak of 167 mg/L, was seen 72 h after heart surgery [10], and previous studies have reported median CRP concentrations ranging from 209 to 293 mg/L on the second and third days following open-heart surgery [3,13].

Skuladottir et al. found postoperative CRP concentrations peaking on the third day after CABG, with a median CRP of 217 mg/L (range 36–416 mg/L) in patients who developed postoperative atrial fibrillation and median CRP of 97 mg/L (range 34–370 mg/L) in patients who did not [19]. In a large study (n = 6 711) Olesen et al. report a *minimum* postoperative CRP of approximately 10 mg/L on the second postoperative day and 15 mg/L on the third postoperative day. Average CRP values were 175 and 190 mg/L on the second and third days, respectively. On the fourth postoperative day mean CRP was 138.3 mg/L (SD 64.9 mg/L), with a minimum level as low as 2.0 mg/L and maximum level as high as 453.5 mg/L [14].

Reports of an absent or severely diminished CRP response following stimuli expected to increase serum CRP are remarkably scarce, and we have only been able to identify a single publication discussing this phenomenon in relation to major surgery. In a study of 74 patients admitted with open fracture of the lower limb and treated by surgical osteosynthesis, Bourguignat et al. described seven patients exhibiting an incomplete or absent CRP response (prevalence 9%) [43]. However, the lower limit of quantification (LoQ) was 5 mg/L. Thus, we do not know if these patienets actually displayed postoperative CRP concentrations in the range of 0 to 5 mg/L.

5.6. The possibility of a disturbance of the interleukin pathway

In our case, CRP postoperatively was quantifiable at trace levels (0.070–0.361 mg/L) by method of MALDI-TOF (LoQ = 0.2 μg/L). We would consider this a severely reduced CRP-response, and to our knowledge no such a case has previously been published and confirmed by multiple independent methods of measurement. The etiology or possible pathophysiology however remains obscure and warrants further investigations.

One possible explanation may be a deficiency of interleukin 6 (IL-6) as IL-6 is an important inducer of increased CRP and SAA production during the acute phase [11,44-46]. The simultaneous lack of both CRP and SAA responses could support a hypothesis of a disturbance of the interleukin pathway and support the case that the patient in fact exhibits an abnormal acute phase response. Unfortunately, in our case it was not possible to measure IL-6 due to surpassed sample storage stability [47,48].

6. Conclusion

As few studies provide an exact range of the CRP response after major surgical heart procedures, the prevalence of small or absent CRP responses remains largely unknown. The reported standard deviations in the literature are generally large, indicating that there is a substantial between-subject variation in postoperative CRP responses [10,14,19]. This case report and cited publications might however implicate that a diminished or low CRP response may in fact not be uncommon. As physicians commonly rely on the CRP response for decision making, the prevalence of CRP non-responders after major inflammatory stimuli should be further investigated.

7. Authorship contributions

Erik W. Vinnes and Paul Kjetel S. Lillemoen wrote the manuscript with support of Anne Lise Bjørke-Monsen. All authors have performed literature search. Erik W. Vinnes and Anne Lise Bjørke-Monsen procured and aliquoted the patient's initial serum samples during hospitalization. Klaus Meyer performed analysis utilizing MALDI-TOF MS. Robert M. Persson and Erik W. Vinnes initiated investigations upon discharge of the patient. Anne Lise Bjørke-Monsen and Rune Haaverstad has provided guidance and advice as senior scientists and consultants in clinical chemistry and cardiothoracic surgery, respectively. All authors have reviewed and provided revisions to the final draft of the manuscript.

8. Search strategies

We have searched for articles published in English or with an abstract in English, between January 1971 through March 2021 in PubMed, EMBASE, Cochrane Library and Google Scholar. The following search terms were used: "absent C-reactive protein response", "absent CRP response", "lack of C-reactive protein acute phase", "non-responder CRP acute phase", "CRP deficiency in acute phase", "hereditary C-reactive protein deficiency", "hereditary CRP deficiency", "congenital C-reactive protein deficiency", "congenital CRP deficiency", "defective acute phase response", "defective c reactive protein response". "false negative CRP", "CRP assay interference". "incomplete CRP response",

"incomplete acute phase response", "impaired acute phase response", "impaired CRP response"

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.cca.2021.06.007.

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