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Catalytic iron in acute myocardial infarction complicated by cardiogenic shock — A biomarker substudy of the IABP-SHOCK II-trial

Georg Fuernau [a,b,c,*,1], Florian Traeder [c,1], Suhas S. Lele [d,1], Mohan M. Rajapurkar [e,1], Banibrata Mukhopadhyay [f,1], Suzanne de Waha [a,b,1], Steffen Desch [a,b,1], Ingo Eitel [a,b,1], Gerhard Schuler [c,1], Volker Adams [c,1], Holger Thiele [a,b,1]

[a] Department of Internal Medicine II, Cardiology/Angiology/Intensive Care Medicine, University Heart Center Lübeck, Lübeck, Germany
[b] German Center for Cardiovascular Research (DZHK), partner site Hamburg/Kiel/Lübeck, Lübeck, Germany
[c] Department of Internal Medicine/Cardiology, University of Leipzig — Heart Center, Leipzig, Germany
[d] Department of Cardiology, Bhailal Amin General Hospital, Baroda, Gujarat, India
[e] Department of Nephrology, Muljibhai Patel Society for Research in Nephro-Urology, Nadiad, India
[f] Department of Biochemistry, Muljibhai Patel Urological Hospital, Nadiad, India

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ABSTRACT

Background: Catalytic iron (CI) is unbound ferric iron with the potential to generate reactive oxygen species with further deleterious vascular effects. In acute coronary syndromes, high levels of CI are linked to all-cause mortality. The prognostic impact of CI and iron metabolism in cardiogenic shock (CS) is currently undetermined. Aims of this study were to investigate the prognostic impact of CI and to identify predictors of high CI levels in patients with CS complicating acute myocardial infarction.

Methods: The Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial randomized 600 patients with CS to either therapy with intraaortic balloon pump or control. In 185 of these patients, blood samples were systematically collected at baseline and day 3. CI levels were measured using a modified bleomycin detectable iron assay. Furthermore, levels of free hemoglobin, total serum iron, transferrin, total iron binding capacity, ferritin, hepcidin, and transferrin saturation were assessed.

Results: Patients with baseline CI levels in the highest quartile had a worse outcome in comparison to patients with lower CI (day 1: HR 1.91 [1.11–3.31], p = 0.005; day 3: HR 2.15 [1.06–4.34], p = 0.01). In multivariable Cox-regression analysis baseline CI remained an independent predictor of 30-day mortality (HR per 10LOG 2.08 [1.25–3.47], p = 0.005). Predictors of CI levels on day 3 were baseline CI, bleeding events, and baseline troponin T.

Conclusions: CI levels were associated with increased short-term mortality in CS complicating acute myocardial infarction. High levels of CI at day 3 were associated with bleeding and high troponin levels.

1. Introduction

Catalytic iron (CI) is the non-transferrin, non-ferritin bound free circulating oxidized ferric iron which is a powerful catalyst for production of reactive oxygen species by participating in the metal catalyzed Haber–Weiss and Fenton reactions [1]. Elevations in catalytic iron levels trigger the release of free hydroxyl radicals leading to vascular injury mediated by endothelial apoptosis [2]. In acute myocardial infarction (AMI) elevated CI levels are associated with impaired clinical outcome [3,4]. Similar findings were observed in critically ill patients, where an association of elevated CI levels with mortality and renal failure was observed [5]. Up to date, there are no data on CI in AMI complicated by cardiogenic shock (CS).

The aim of the present study was thus to assess a possible association between CI levels and clinical outcome in patients with CS and AMI. Furthermore, factors associated with high CI levels were investigated together with possible physiological protective mechanisms against elevated CI levels including upregulation of ferritin and hepcidin.

Abbreviations: AMI, acute myocardial infarction; CI, catalytic iron; CS, cardiogenic shock; ELISA, enzyme-linked immunosorbent assay; HR, hazard ratio; IABP, intraaortic balloon counterpulsation; IQR, interquartile range; PCI, percutaneous coronary intervention.

* Corresponding author at: University Heart Center Lübeck, University Hospital Schleswig-Holstein, Medical Clinic II Cardiology/Angiology/Intensive Care Medicine, Ratzeburger Allee 160, 23538 Lübeck, Germany.
E-mail address: georg.fuernau@uksh.de (G. Fuernau).

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2. Methods

This study is a predefined monocentric substudy of the Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial (ClinicalTrials.gov Identifier: NCT00491036). The design and outcomes of the IABP-SHOCK II trial have been reported previously [6–8]. IABP-SHOCK II was a randomized study evaluating the role of intraaortic balloon counterpulsation (IABP) on mortality in the setting of AMI complicated by CS. In brief, 600 patients were enrolled in 37 centers in Germany and were randomized to either IABP or to a control group in a 1:1 fashion. The definition of CS included hypotension, pulmonary congestion, and signs of end-organ hypoperfusion. Exclusion criteria were onset of CS >12 h before randomization, cardiopulmonary resuscitation >30 min, severe cerebral deficit, mechanical causes of CS, age > 90 years, absolute contraindications against IABP insertion, shock of other cause, or severe concomitant disease with life expectancy <6 months. All patients underwent cardiac catheterization immediately after hospital admission. In resuscitated patients, cooling was initiated after percutaneous coronary intervention (PCI) and baseline blood sample drawing. All-cause mortality at 30 days was defined as primary endpoint.

Two hundred eighteen patients were randomized at the University of Leipzig - Heart Center with a prospectively planned serial blood sampling [9]. In 185 of these patients, blood samples were available for the present analysis.

The study was conducted according to the Declaration of Helsinki, has been approved by the local ethics committee, and all patients or their legal representatives gave written informed consent.

2.1. Laboratory measurements

Blood samples were collected under standardized conditions at different predefined time points (day 1 [day of admission during primary PCI] and day 3). The samples were immediately centrifuged at 2400 *g* for 10 min at room temperature. The ethylenediaminetetraacetic acid plasma was stored in aliquots at −80 °C.

CI was measured using a modified bleomycin detectable CI assay at Muljibhai Patel Society for Research in Nephro-Urology in Nadiad, India. The assay is based on the principal that bleomycin, which is an antitumor antibiotic, binds to and degrades DNA leading to the formation of a chromogen by reacting with thiobarbituric acid in the presence of ferric iron and a suitable reducing agent. The amount of chromogen formed is measured as color intensity in a spectrophotometer (DU 800; Beckman Coulter, Brea, CA, USA) at 532 nm against a blank sample. The assay hence measures ferric iron complexes that can catalyze free radical reactions in biological systems and is expressed in μmol/L. The assay used is a modification of the original assay, which enables accurate measurement of CI across a wide range of CI levels at a stable pH. All reactions were carried out in polypropylene tubes to avoid iron contamination. All reagents were treated with chelex (Bio-Rad Laboratories, Inc. Hercules, CA, USA) at 300 mg for 10 ml solution to remove any iron contamination. At a CI concentration of 0.045–3.15/L the intra-assay coefficient of variation was 0.58% and the inter-assay coefficient of variation was 3.4%.

Standard parameters of iron metabolism also measured in addition to CI included plasma total iron, transferrin, transferrin saturation, and total iron binding capacity. In addition, plasma free hemoglobin and the two iron regulatory parameters ferritin and hepcidin were determined. Plasma free hemoglobin was assessed by a highly sensitive quantitative enzyme-linked immunosorbent assay (ELISA) kit (Bio Rad ELISA reader PR4100, My BioSource Inc., San Diego, CA, USA, intra-assay coefficient of variation 0.28%, inter-assay coefficient of variation 5.1%). Plasma hepcidin levels were measured using ELISA (My BioSource Inc., San Diego, CA, USA). The hepcidin detection range in the ELISA kit is 1.17–300 ng/mL. The intra- and inter-assay precision of the kit are <8% and <10%.

2.2. Statistical analysis

As most continuous variables were not normally distributed, all continuous variables are presented as medians with interquartile range (IQR) for reasons of uniformity. Categorical data are presented as counts or proportions with the corresponding percentages. For comparison of continuous variables, student's t-test or Mann–Whitney test were used, for comparison of categorical variables Fisher's exact- or Chi^2-test were used, as appropriate. For outcome analysis, all-cause mortality at 30 days was assessed. Patients were stratified into two groups by baseline CI levels with comparison of quartile 1–3 versus quartile 4. The rationale for this comparison was that patients with CI levels in the highest quartile demonstrated worse outcome in a prior acute coronary syndrome study [3].

Kaplan–Meier analysis with log-rank-testing and corresponding hazard ratios (HR) was used for outcome assessment. Stepwise logistic regression analysis was performed to identify predictors of mortality at 30 days. All baseline variables with an association (p-value <0.1) to mortality in univariable analysis entered a multivariable model.

For prediction of CI levels at baseline and day 3 a multiple stepwise regression model was built including all parameters with an association ($p < 0.1$) with CI levels at the specific timepoint. To analyze differences between CI levels at day 1 and day 3 in patients with or with prior cardiopulmonary resuscitation and with or without bleeding repeated measures ANOVA with log-transformation were performed. The within-subject-effect was assessed by an interaction test using Huynh and Feldt-correction [10].

Statistical analysis was performed using commercially available software (MedCalc for Windows, version 15.8.0; MedCalc Software, Ostend, Belgium). A two-tailed p-value <0.05 was considered statistically significant.

3. Results

In 185 of 218 patients (85%) baseline blood samples were available. Patients with day 1 CI levels in the highest quartile were younger, had higher baseline serum lactate, lower rates of known hypertension, showed a trend to higher hemoglobin levels, and were more often resuscitated prior to randomization (Table 1).

3.1. CI and clinical outcome

Levels of CI were significantly higher in non-survivors than in on day 1 as well as on day 3 (Table 2). Patients in the highest quartile of CI levels at day 1 and day 3 were more likely to die until day 30 (Fig. 1A + B). In multivariable Cox-regression analysis, baseline CI and serum lactate as well as age and reperfusion success remained independent predictors of 30-daymortality (Table 3).

3.2. Predictors of CI levels at admission and on day 3

In univariable regression modeling cardiopulmonary resuscitation prior to randomization ($\beta = 0.16$; $p = 0.03$) and mechanical ventilation at admission ($\beta = 0.14$; $p = 0.052$) showed an association to CI levels at baseline. In multivariable testing only cardiopulmonary resuscitation prior to randomization remained significant ($\beta = 0.16$; $p = 0.03$).

Baseline CI levels, bleeding complications and/or need for blood transfusions, baseline troponin T levels, the development of acute kidney injury, mechanical ventilation at admission and early hemodynamic stabilization at day 1 were associated with CI levels on day 3 (all $p < 0.1$). After multivariable testing baseline CI levels ($\beta = 0.25$; $p = 0.009$), bleeding and/or blood transfusions ($\beta = 0.50$; $p < 0.001$), and baseline troponin T levels ($\beta = 0.44$; $p < 0.001$) remained independent predictors of CI levels at day 3.

Table 1
Baseline and procedural characteristics.

		Catalytic iron		
	Overall n = 185	Quartile 1–3 n = 139	Quartile 4 n = 46	p
Age, years	70 (58;79)	72 (60;80)	63 (54;73)	0.002
Male sex, n (%)	129 (70)	99 (71)	30 (65)	0.56
Body mass index, kg/m^2	27.3 (24.7;29.4)	26.9 (24.5;29.4)	27.8 (26.1;29.4)	0.23
Baseline serum creatine, μmol/L	117 (95;163)	116 (94;154)	119 (95;182)	0.50
Baseline serum lactate, mmol/L	3.7 (2.3;7.4)	3.2 (2.2;5.5)	7.6 (3.7;10.6)	<0.001
Baseline serum creatine kinase, μmol/L	9.4 (3.4;22.7)	8.1 (3.4;20.1)	13.5 (3.0;34.5)	0.25
Baseline troponin T, μg/L	0.86 (0.26;3.02)	0.82 (0.26;2.35)	1.08 (0.33;0.54)	0.32
Heartrate at admission, n/min	91 (77;110)	90 (72;110)	100 (80;110)	0.23
Systolic blood pressure at admission, mmHg	85 (78;106)	85 (79;103)	89 (75;110)	0.65
Baseline hemoglobin, mmol/L	8.1 (7.1;8.9)	7.9 (6.7;8.9)	8.3 (7.5; 9.0)	0.06
Hypertension, n (%)	129 (70)	103 (74)	26 (57)	0.04
Hypercholesterolemia, n (%)	57 (31)	43 (31)	14 (30)	0.90
Diabetes mellitus, n (%)	66 (36)	54 (39)	12 (26)	0.16
Known peripheral artery disease, n (%)	23 (12)	19 (14)	4 (9)	0.53
Prior myocardial infarction, n (%)	40 (22)	33 (24)	7 (15)	0.31
Prior PCI[a], n (%)	35 (19)	30 (22)	5 (11)	0.16
Prior coronary artery bypass grafting, n (%)	10 (5)	9 (7)	1 (2)	0.46
Coronary 3-vessel disease, n (%)	91 (49)	71 (51)	20 (44)	0.47
Resuscitation prior admission, n (%)	69 (37)	38 (27)	31 (67)	<0.001
TIMI[b] flow <3 after PCI, n (%)	46 (25)	34 (25)	12 (27)	0.90
Randomized to balloon pump, n (%)	92 (50)	66 (48)	26 (57)	0.37
Bleeding events Day 1 and 2, n (%)	15 (8)	11 (8)	4 (9)	0.87

Continuous data are presented as median and interquartile range.
[a] PCI = percutaneous coronary intervention.
[b] TIMI = Thrombolysis in Myocardial Infarction.

3.3. Bleeding events and CI levels

Bleeding or need for blood transfusion at day 1 and 2 occurred in 15 of 185 (8.1%) patients. These patients had a significantly higher 30-day-mortality (80 vs. 38%; Central Illustration). No significant differences in baseline CI levels between patients with or without bleeding were present (0.34 [IQR 0.30;1.05] vs. 0.43 [IQR 0.31;0.67] μmol/L; p = 0.74). In contrast, significant differences were observed at day 3 (0.71 [IQR 0.44;2.87] vs. 0.35 [IQR 0.30;0.42] μmol/L; p < 0.001). In repeated measures ANOVA a significant difference between the two groups as well as a significant group-factor interaction was observed (Fig. 2A). To probe the link between bleeding and CI elevations free hemoglobin levels amongst those with or without bleeding at day 1 and day 3 were analyzed. The free hemoglobin levels were similar in both groups at day 1 (bleeding vs. no bleeding 5.4 [IQR 1.8;16.0] vs. 5.5 [IQR 2.8;17.0] mg/dl; p = 0.91), but there was a trend to higher free hemoglobin levels in those with bleeding compared to those without bleeding at day 3 (8.7 [IQR 3.7;21.1] vs. 3.8 [IQR 1.9;7.5] mg/dl; p = 0.09).

3.4. Cardiopulmonary resuscitation and CI levels

In patients undergoing cardiopulmonary resuscitation prior to randomization CI levels were significantly higher at baseline (0.57 [IQR 0.38;1.24] vs. 0.37 [IQR 0.30;0.48] μmol/L; p < 0.001), but not at day 3 (0.37 [IQR 0.31;0.49] vs. 0.34 [IQR 0.29;0.42] μmol/L; p = 0.15). Repeated measures ANOVA showed a significant difference between the two groups and a significant group-factor interaction (Fig. 2B).

3.5. Association of CI levels with other markers of iron metabolism and regulation at baseline

Moderate correlations of baseline CI levels with ferritin, free hemoglobin, and hepcidin were observed (r = 0.48, p < 0.001; r = 0.42, p < 0.001 and r = 0.34; p < 0.001, respectively). For total iron binding capacity, transferrin saturation, transferrin, and total iron levels nearly no correlation could be observed (r = −0.16, p = 0.03; r = 0.18, p = 0.01 and r = −0.15; p = 0.04, respectively). There was no correlation with total iron levels (r = 0.08; p = 0.29). Absolute values of markers of iron metabolism are presented in Table 2.

4. Discussion

The current first analysis of CI in AMI-related CS observed a strong independent prognostic impact of high levels of CI on mortality. Furthermore, a strong association of high CI with bleeding events could be demonstrated. This implicates a possible role of CI as mediator of morbidity and mortality after bleeding events in CS (Central Illustration).

Table 2
Iron status and physiological chelation responses to elevations in CI Levels amongst 30-day survivors versus non-survivors.

	Day 1			Day 3		
	Survivors n = 109	Non-survivors n = 76	p	Survivors n = 104	Non-survivors n = 43	p
Catalytic iron, μmol/L	0.37 (0.30;0.58)	0.48 (0.35;1.18)	0.007	0.35 (0.30;0.41)	0.41 (0.31;0.62)	0.03
Serum iron, mg/dL	74 (65;86)	71 (63;83)	0.23	71 (62;81)	68 (61;75)	0.13
Ferritin, mg/mL	257 (107;722)	776 (304;1333)	<0.001	258 (119;566)	463 (230;958)	0.02
Hepcidin, ng/mL	28 (16;60)	47 (27;83)	<0.001	22 (9;49)	34 (17;56)	0.03
Transferrin, mg/dL	176 (141;212)	143 (90;184)	<0.001	287 (114;202)	104 (79;136)	<0.001
TIBC[a], μg/dL	241 (194;291)	196 (123;245)	<0.001	208 (151;278)	143 (109;187)	<0.001
Transferrin saturation, %	32 (24;41)	40 (30;53)	<0.001	33 (28;47)	44 (35;70)	<0.001

Continuous data are presented as median and interquartile range.
[a] TIBC = total iron binding capacity.

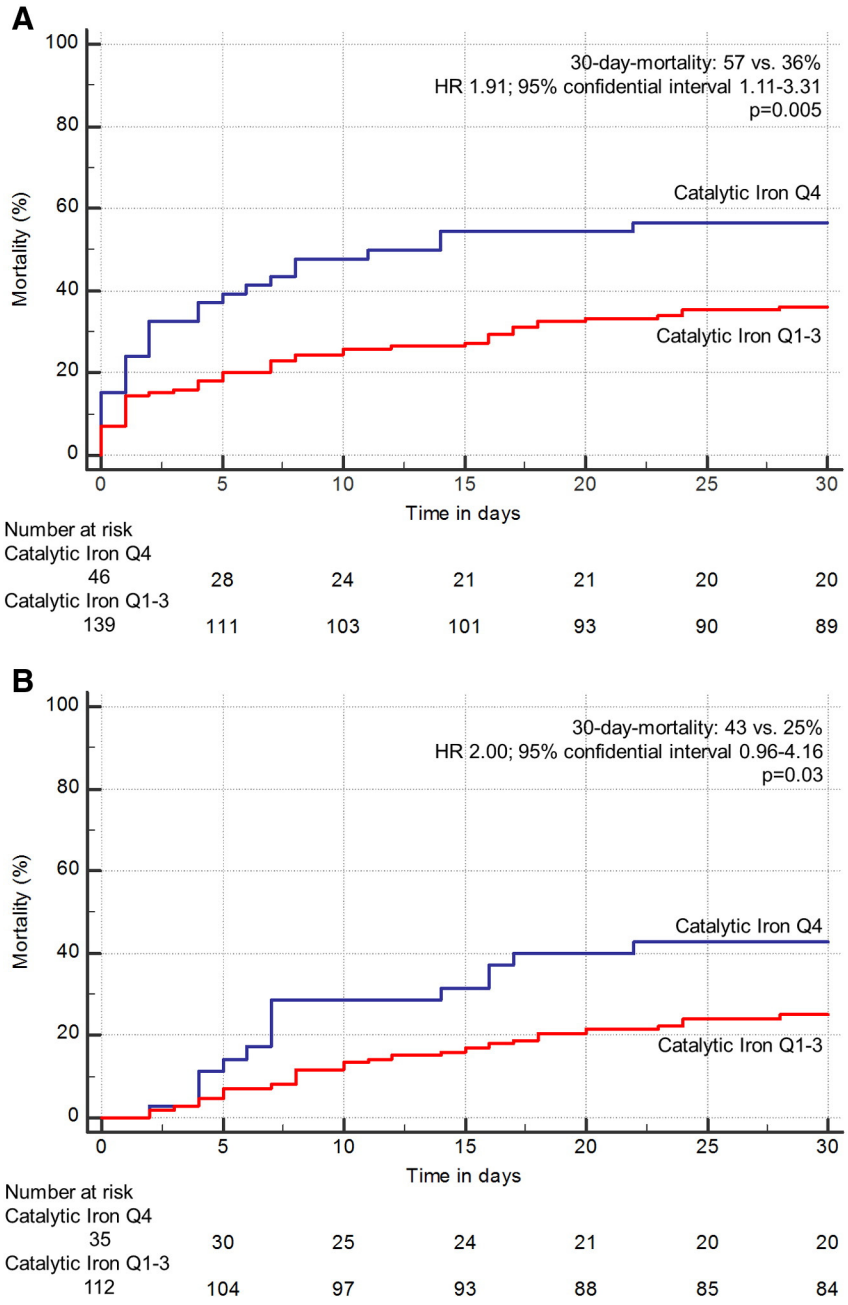

Fig. 1. Kaplan–Meier curves and log-rank-test for baseline catalytic iron (A) and on day 3 (B) stratified by highest vs. lowest three quartiles.

The association of high CI levels with adverse outcome has recently been shown in two observational studies consisting of 1701 and 806 patients with acute coronary syndromes [3,4]. Patients with high CI levels were at higher risk for death in comparison to patients with low CI levels. Differences with respect to the rate of myocardial re-infarction were not observed. Both of these studies included low risk cohorts (10 month mortality of ~2% in the study by Steen et al. and 1 month mortality of 1.6% in the study by Lele et al.). In both studies, no information was given if and how many patients presented in CS. The current study is the first to confirm these findings in a cohort of patients with CS. In addition, due to serial blood sampling, we were able to investigate dynamic changes of CI levels. There was an acute elevation in baseline values for patients undergoing resuscitation, which was no longer evident 2 days later. In contrast, patients with bleeding complications displayed similar CI levels at baseline with a significant rise of CI at day 3 in comparison to patients without bleeding. This implicates CI to be a marker with rapid rise and decline and suggests a correlation of CI with bleeding. The only independent predictor of high baseline CI was cardiopulmonary resuscitation. This may be explained by the fact that mechanical resuscitation is often associated with multiple traumas like rib or sternum fractures as cause of at least minor bleedings up to major bleeding events like hemoperitoneum and retroperitoneal hemorrhage [11]. The association of CI with bleeding is further underlined by the significant correlation of CI to plasma free hemoglobin levels.

4.1. Pathophysiological mechanism in bleeding, myocardial injury, and CI metabolism

Following the destruction of red blood cells in hematoma hemoglobin and iron are set free. Reactive oxygen species alone have a rather low cellular toxicity, but together with CI they have the ability to catalyze Haber–Weiss and Fenton reactions. This leads to enhanced production of hydroxyl radicals and endothelial cell apoptosis [1,12,13]. The exact cause for the release of CI in acute coronary syndromes still

Table 3
Cox-regression analysis for 30-day-mortality.a, b, c, d, e

	Univariable			Multivariable stepwise			
	HR[a]	95%CI[b]	p	Wald	HR	95%CI	p
Catalytic iron day 1 per 10Log	2.01	1.33–3.03	<0.001	9.2	1.97	1.27–3.04	0.003
Baseline serum lactate per 10Log	6.00	2.81–12.80	<0.001	17.9	6.45	2.73–15.25	<0.001
Baseline serum creatinine per 10Log	6.00	2.10–17.18	<0.001	-	-	-	-
Troponin T per 10Log	1.26	0.89–1.79	0.19				
Age per 10 years	1.25	1.03–1.51	0.03	11.7	1.44	1.17–1.77	<0.001
TIMI[c] flow <3 after PCI[d]	1.82	1.12–2.94	0.02	8.2	2.06	1.26–3.57	0.004
Female sex	1.42	0.89–2.26	0.15				
Body mass index per kg/m^2	1.02	0.97–1.06	0.48				
Baseline hemoglobin per mmol/L	0.98	0.85–1.12	0.75				
Known chronic renal failure	1.23	0.86–2.01	0.40				
Hypertension	1.04	0.63–1.70	0.88				
Prior stroke	1.75	0.87–3.49	0.12				
Hypercholesterolemia	0.85	0.52–1.40	0.53				
Diabetes mellitus	1.14	0.72–1.81	0.57				
Prior peripheral artery disease	1.19	0.63–2.25	0.60				
Presence of coronary 3-vessel disease	1.45	0.93–2.28	0.11				
Resuscitation before admission	1.26	0.80–1.98	0.33				
Mechanical ventilation at admission	1.44	0.92–2.28	0.12				
Randomized to IABP[e]	0.88	0.56–1.37	0.56				

[a] HR = hazard ratio.
[b] CI = confidence interval.
[c] TIMI = Thrombolysis in Myocardial Infarction.
[d] PCI = percutaneous coronary intervention.
[e] IABP = intraaortic balloon counterpulsation.

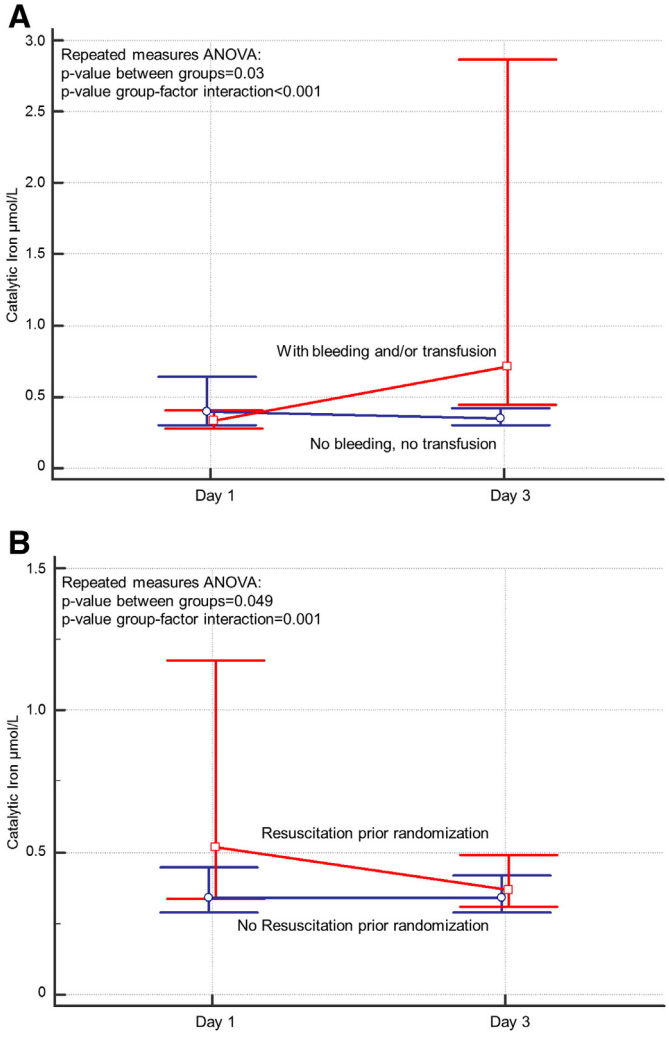

Fig. 2. Levels of catalytic iron over time stratified by bleeding events on day 1 and 2 (A) and cardiopulmonary resuscitation prior randomization (B).

remains unclear. In response to myocardial ischemia and necrosis, CI can be released from intracellular stores such as lysosomes or microsomes as shown in acute kidney injury [14,15]. Local acidosis can also trigger dissociation of circulating iron from transferrin and hemorrhage within the infarct zone could be yet another source for the release of free iron [16]. In CS also kidney hypo-perfusion is common and acute kidney injury is prognostically relevant [17]. Therefore some of the released CI may be of renal origin [5,18], although acute renal failure was not associated with CI levels after multivariable adjustment in our study. This may lead to local and systemic elevated levels of CI as suggested by our findings with its association of troponin T levels as marker of the amount of myocardial necrosis at day 3 CI levels. CI may also influence reperfusion injury; similar effects were described in intracerebral hemorrhage with good evidence from experimental as well as human data that bleeding causes inflammatory reactions and iron being a major factor causing brain injury after intracerebral bleeding [19].

4.2. Possible impact on therapy

We observed a significant correlation of CI levels to ferritin and hepcidin, which are iron regulatory hormones secreted by hepatocytes into the circulation. Their functions are mediated via effects on iron absorption from the gastrointestinal tract and inhibition of free iron release from hemoglobin degradation by blocking the action of macrophages [20]. This physiological chelation response to elevation in CI levels highlights its significance and role in adversely affecting mortality in this setting. The strong physiological "chelation" response evident in this study in response to rising CI levels gives a hint of CI as a player rather than a bystander in CS. Yet, due to the observational design of the current analysis we are not able to clarify the roles of bystander versus player. The association between CI and mortality raises the issue of whether therapeutic "chelation" may have a role in reducing mortality in the setting of AMI and CS. In intracerebral hemorrhage such therapies were already tested positively in experimental trials with a demonstrated reduction of secondary brain injury [21]. This implicates the possibility that chelatic agents may also help to reduce myocardial damage in AMI due to intramyocardial hemorrhage. Furthermore, given the fact that a systemic inflammatory response syndrome is evident in CS [22] such a therapy may also be helpful in these patients.

This needs further evaluation in experimental and adequately powered human studies.

4.3. Study limitations

First, an observational study is not able to prove causal associations. Second, given the relatively small number of patients with early bleeding events our findings may be a play of chance. Yet, this appears to be not plausible due to the strong association of CI with bleeding and mechanical cardiopulmonary resuscitation.

5. Conclusions

Levels of CI are associated with short-term mortality in CS complicating AMI. Bleeding events as well as the amount of myocardial necrosis and mechanical resuscitation may contribute to high CI. Further investigations are needed targeting a hypothetic therapeutic effect of chelating CI to improve outcomes.

Disclosures

S.S.L. and M.M.R. hold patents on catalytic iron assays in US and Europe (US 7,927,880 B2; US 8,192,997 B2 and EU 2250500), all other authors declare that they have no conflicts of interest concerning the specific subject of this study.

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References

[1] D.B. Kell, Iron behaving badly: inappropriate iron chelation as a major contributor to the aetiology of vascular and other progressive inflammatory and degenerative diseases, BMC Med. Genet. 2 (2009) 2.
[2] A.K. Jacob, R.S. Hotchkiss, S.L. DeMeester, et al., Endothelial cell apoptosis is accelerated by inorganic iron and heat via an oxygen radical dependent mechanism, Surgery 122 (1997) 243–253 (discussion 54).
[3] D.L. Steen, C.P. Cannon, S.S. Lele, et al., Prognostic evaluation of catalytic iron in patients with acute coronary syndromes, Clin. Cardiol. 36 (2013) 139–145.
[4] S.S. Lele, B.N. Mukhopadhyay, M.M. Mardikar, et al., Impact of catalytic iron on mortality in patients with acute coronary syndrome exposed to iodinated radiocontrast—the Iscom study, Am. Heart J. 165 (2013) 744–751.
[5] D.E. Leaf, M. Rajapurkar, S.S. Lele, B. Mukhopadhyay, S.S. Waikar, Plasma catalytic iron, AKI, and death among critically ill patients, Clin. J. Am. Soc. Nephrol. 9 (2014) 1849–1856.
[6] H. Thiele, G. Schuler, F.J. Neumann, et al., Intraaortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock: design and rationale of the Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial, Am. Heart J. 163 (2012) 938–945.
[7] H. Thiele, U. Zeymer, F.J. Neumann, et al., Intraaortic balloon support for myocardial infarction with cardiogenic shock, N. Engl. J. Med. 367 (2012) 1287–1296.
[8] H. Thiele, U. Zeymer, F.J. Neumann, et al., Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial, Lancet 382 (2013) 1638–1645.
[9] G. Fuernau, C. Poenisch, I. Eitel, et al., Growth-differentiation factor 15 and osteoprotegerin in acute myocardial infarction complicated by cardiogenic shock: a biomarker substudy of the IABP-SHOCK II-trial, Eur. J. Heart Fail. 16 (2014) 880–887.
[10] B. Lecoutre, A correction for the $\tilde{\varepsilon}$ approximate test in repeated measures designs with two or more independent groups, J. Educ. Stat. 16 (1991) 371–372.
[11] Y. Koga, M. Fujita, T. Yagi, et al., Effects of mechanical chest compression device with a load-distributing band on post-resuscitation injuries identified by post-mortem computed tomography, Resuscitation 96 (2015) 226–231.
[12] R.E. Williams, J.L. Zweier, J.T. Flaherty, Treatment with deferoxamine during ischemia improves functional and metabolic recovery and reduces reperfusion-induced oxygen radical generation in rabbit hearts, Circulation 83 (1991) 1006–1014.
[13] B. Halliwell, J.M. Gutteridge, Role of free radicals and catalytic metal ions in human disease: an overview, Methods Enzymol. 186 (1990) 1–85.
[14] R. Baliga, Z. Zhang, M. Baliga, S.V. Shah, Evidence for cytochrome P-450 as a source of catalytic iron in myoglobinuric acute renal failure, Kidney Int. 49 (1996) 362–369.
[15] M.S. Paller, H.S. Jacob, Cytochrome P-450 mediates tissue-damaging hydroxyl radical formation during reoxygenation of the kidney, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 7002–7006.
[16] C. Cannan, I. Eitel, J. Hare, A. Kumar, M. Friedrich, Hemorrhage in the myocardium following infarction, JACC Cardiovasc. Imaging 3 (2010) 665–668.
[17] G. Fuernau, C. Poenisch, I. Eitel, et al., Prognostic impact of established and novel renal function biomarkers in myocardial infarction with cardiogenic shock: a biomarker substudy of the IABP-SHOCK II-trial, Int. J. Cardiol. 191 (2015) 159–166.
[18] D.E. Leaf, M. Rajapurkar, S.S. Lele, et al., Increased plasma catalytic iron in patients may mediate acute kidney injury and death following cardiac surgery, Kidney Int. 87 (2015) 1046–1054.
[19] Y. Hua, R.F. Keep, J.T. Hoff, G. Xi, Brain injury after intracerebral hemorrhage: the role of thrombin and iron, Stroke 38 (2007) 759–762.
[20] G. Rishi, D.F. Wallace, V.N. Subramaniam, Hepcidin: regulation of the master iron regulator, Biosci. Rep. 35 (2015).
[21] P.K. Belur, J.J. Chang, S. He, B.A. Emanuel, W.J. Mack, Emerging experimental therapies for intracerebral hemorrhage: targeting mechanisms of secondary brain injury, Neurosurg. Focus. 34 (2013), E9.
[22] J.S. Hochman, Cardiogenic shock complicating acute myocardial infarction: expanding the paradigm, Circulation 107 (2003) 2998–3002.