The Heart Surgery Forum #2014-331
17 (3), 2014 [Epub June 2014]
doi: 10.1532/HSF98.2014331

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Associated Factors for Non-Ischemic Serum Myoglobin Release After Cardiac Surgical Procedures

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ABSTRACT

Background: Myoglobin has become established as a serum marker of myocardial injury. However, myoglobin levels can increase exponentially without any correlation to postoperative clinical ischemia symptoms. In this retrospective study, we analyzed the associated factors for a non-ischemic myoglobin release.

Methods: We performed a data analysis from 532 consecutive cardiac surgery patients (2010 to 2011, 73% males; age 65 ± 11 years). Non-ischemic myoglobin elevation was defined as CK-MB <50 U/l and/or the absence of any ischemic clinical events (eg, myocardial infarction, mesenteric vascular occlusion).

Results: Using a multifactorial model, predictive elements and associated factors for non-ischemic myoglobin increase were male sex, ejection fraction < 30%, BMI > 30 and transfusions. Serum myoglobin was not significantly different in patients with high muscle mass.

Conclusions: A non-ischemic serum myoglobin release is rare, but could be associated in subgroups of patients. Further investigations should focus on clinical targets, for example, concomitant medications for which our study was not powered.

INTRODUCTION

Increased myoglobin levels are observed particularly in patients undergoing thoracic and thoracoabdominal surgery. There are a variety of reasons for raised plasma levels during cardiac surgery procedures. Miller et al showed a direct relationship between leg ischemia caused by femoral artery cannulation and plasma myoglobin concentration, as well as postoperative renal failure [Miller 2008]. It is known from operative procedures in bariatric surgery that extremely obese patients in some cases exhibit considerable increases in myoglobin [de Freitas Carvalho 2006; Wigfield 2006]. As Benedetto et al have already established, perioperative myocardial injury is not the only reason for the occurrence of high myoglobin levels. Thus, skeletal muscle injury and necrosis play a vital role in the interpretation of elevated serum myoglobin levels following cardiac surgery [Benedetto 2010]. Increased serum myoglobin levels have been shown to play a major role in the pathogenesis of acute renal failure due to rhabdomyolysis [Huerta-Alardín 2005]. Markedly increased myoglobin levels are associated with a poorer postoperative outcome [Hofmann 2007]. In the diagnosis of ischemia, myoglobin already has a place as a reliable routine parameter in everyday clinical practice. However, there are cases in which increases in myoglobin concentration occur without any evident underlying ischemia. In view of the fact that markers of muscle necrosis increase in association with circulatory shock due to ischemia of striated muscle, it is reasonable to suspect that periods of perioperative hypoperfusion, particularly as a result of the use of a heart-lung machine, also are associated with an increased release of myoglobin. But this has yet to be studied in the field of cardiac surgery. For these reasons, we investigated a retrospective study and analyzed potential associated factors for a non-ischemic increase of serum myoglobin [Munjal 1983].

Received February 26, 2014; accepted May 29, 2014.

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MATERIALS AND METHODS

Study Design

This retrospective, non-randomized, one-arm, single-center study was conducted at the Johann Wolfgang Goethe University Hospital Frankfurt am Main, Germany. Data was anonymized and extracted from the hospital's IT system Orbis (Agfa HealthCare, Bonn, Germany), which is hosted on an on-site server.

General Patient Management

Anesthesiological, surgical, and cardiopulmonary bypass (CPB) management were standardized in all patients by standard operating procedures (SOP). No changes in surgical, anesthetic, or perfusion techniques were made for the purposes of the study.

Anesthetic Management

On the evening before surgery, patients were given 20 mg clorazepate dipotassium (Tranxilium, Sanofi-Aventis GmbH, Hoechst, Germany). After routine monitoring, general anesthesia was induced with 0.3 – 1 µg/kg sufentanil (Sufenta, Janssen-Cilag GmbH, Neuss, Germany), 1 – 2.5 mg/kg propofol (Disoprivan, AstraZeneca GmbH, Wedel, Germany), and 0.6 mg/kg rocuronium (Esmeron, Essex GmbH, Munich, Germany). For the maintenance of general anesthesia, all

patients received 1–2 vol % sevoflurane (Sevoran, Abbott, Wiesbaden, Germany) and intermittent bolus administration of sufentanil. Both isotonic crystalloid (Sterofundin, B. Braun GmbH, Melsungen, Germany) and colloid fluids (6% HES 130/0.4, Voluven, Fresenius Kabi, Bad Homburg, Germany) were infused during the operation in line with standard practice within the hospital. Postoperative weaning from mechanical ventilation and timing of extubation were according to our hospital protocols.

Management of Extracorporeal Circulation

The extracorporeal circuit included a membrane oxygenator (Quadrox oxygenator, Maquet Cardiopulmonary AG, Hirrlingen, Germany) and a roller pump system (HL20, Maquet Cardiopulmonary AG, Hirrlingen, Germany) equipped with a heat exchanger (Plegiox, Maquet Cardiopulmonary AG, Hirrlingen, Germany). The circuit was primed with 500 mL crystalloid solution (Sterofundin, B. Braun GmbH, Melsungen, Germany), 500 mL colloid solution (6% HES 130/04, Voluven, Fresenius Kabi, Bad Homburg, Germany), and 250 mL 20% mannitol (Mannitol Baxter, Baxter, Unterschleissheim, Germany). Heparin (Heparin Sodium Braun, B. Braun Melsungen AG, Melsungen, Germany) was administered repeatedly after an initial bolus of 400 IU/kg to maintain an activated clotting time (ACT) of more than 400 seconds. During CPB, a nonpulsatile flow was maintained at 2.6–3 L/min/m^2, and the mean arterial blood pressure was targeted to 50–70 mmHg with the addition of noradrenaline (Arterenol, Sanofi-Aventis GmbH, Hoechst, Germany), if needed. Myocardial protection was achieved with cold blood cardioplegia (20°C). Antifibrinolytic therapy consisted of the administration of 2 g tranexamic acid (Cyclocapron, CC Pharma, Densborn, Germany) after the induction of anesthesia, and another 2 g was added to the priming volume of the heart–lung machine and again during CPB. Extracorporeal circulation was performed in mild hypothermia. When surgery was complete, patients were rewarmed to 36°C and weaned from CPB. To reverse the anticoagulant effects of heparin, protamine sulfate (Protaminsulfat, MEDA Pharma GmbH & Co. KG, Bad Homburg, Germany) was administered, guided by the ACT. If the target ACT was not obtained despite repeated heparin administrations, 500–1,000 IU antithrombin was infused.

Myoglobin

Myoglobin is a cytoplasmic hemoprotein involved in oxygen transport in striated muscle. Following cell injury, myoglobin is released into serum from both types of muscle tissue (smooth and striated myofibrils), where it is detectable within as little as one to four hours. In comparison with the enzyme CK, peak myoglobin concentrations are reached considerably earlier (one to four hours) after the onset of symptoms. Its more rapid increase following reperfusion provides a reliable criterion of the successful postoperative treatment of coronary artery occlusion. Similarly, the infarction size also can be determined by the quantity of myoglobin released. As it has a low molecular weight (17.8 kDa), myoglobin is rapidly eliminated via the kidneys (half-life: 0.25 hours). Its clinical significance therefore is limited, as this purely short-term increase means that ischemic myocardial injury is no longer detectable after 24 hours. The lack of specificity is due to the fact that an intramuscular injection or physical exertion can also produce an increase above the reference range [Munjal 1983]. To determine serum myoglobin concentrations, we used an electrochemiluminescence immunoassay. Reference range was male 18-99 years; 28–72 ng/ml and female 18-99 years; 25–58 ng/ml). Myoglobin was measured at various time points postoperatively (T1= ICU admission, T2 = 12 hours postoperatively, T3 = 24 hours postoperatively, T4 = 36 hours postoperatively).

Non-ischemic myoglobin elevation (> 500 ng/mL) was defined as CK-MB < 50 U/l and/or the absence of any ischemic clinical events (eg, myocardial infarction, mesenteric vascular occlusion).

STATISTICAL ANALYSIS

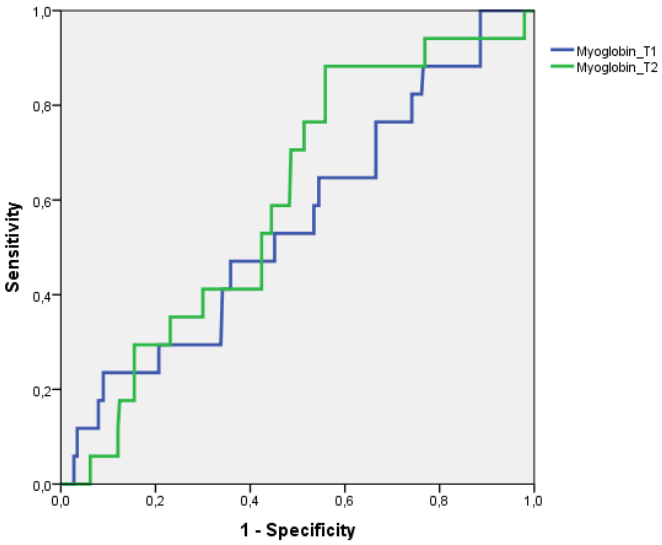
Continuous variables with normal distribution were evaluated using the unpaired t-test, and variables with non-normal distribution were evaluated using the Wilcoxon signed-rank test. Categorical variables were measured with a chi-squared test and Fisher's exact test. Myoglobin and all other blood samples were compared at each measurement time point with the two-way analysis of variance (ANOVA) and the Bonferroni post hoc test. Receiver operating characteristic (ROC) analysis was calculated in order to describe the correlation of myoglobin. The area under the curve (AUC) with an associated 95% confidence interval (CI) was used as a measurement for the discriminating capacity of myoglobin to predict a high muscle mass. An ROC AUC value of 0.60–0.69 demonstrates a poor predictive value, 0.70–0.79 a moderate predictive value, 0.80–0.89 a good predictive value, and 0.90–0.99 an excellent predictive value. Multiple regressions are also performed for the validation of risk variables. Twenty-five preoperative, eight intraoperative, and 25 postoperative variables were included for the calculation in the overall logistic regression model. The risk variables are evaluated in a univariate model for the endpoints "myoglobin high = >500 ng/mL)" and were finally included stepwise in multivariable, logistic models (cut-off: *P* value < .05).

All analyses were calculated using IBM SPSS version 21.0 (New York, USA). A two-sided *P* value of < .05 was considered to be statistically significant.

This work builds on that previously presented by the authors as an abstract during the meeting of the German Society of Thoracic and Cardiovascular Surgery [Kiessling 2013].

RESULTS

To calculate a predictive item for an early postoperative increase in myoglobin (>500 ng/mL) in patients without evidence of ischemia, pre- and intraoperative data were incorporated in a logistic regression model. The following predictive parameters at time T1 were then identified in the univariate analysis and subsequently in the multivariate analysis: Male sex (*P* = .008), BMI > 28 kg/m^2 (*P* = .0001), NYHA



Serum myoglobin concentration in patients with a high muscle mass presented in a receiver operating characteristics (ROC) curve. The area under the ROC curve is for T1 = 0.552 and for T2 = 0.601.

class ≥ III (P = .015), a reduced ejection fraction < 30% (P = .008), mitral valve surgery (P = .0001), and receipt of blood/blood products at time T1 (P = .001). In a subanalysis, we focused on patients with a high muscle mass. Consistent myoglobin levels were found at the different measurement time points, T1 through T4, in 24 out of 26 of the muscular patients, and in 493 out of 532 patients. These patients were included in the analysis. Mean serum levels in these patients were 460.60 ± 296.44 ng/mL. The t-test for equality of means revealed a significance level of P = .252 in the group comparison (T1). Similarly, no significance was found at any of the subsequent measurement time points T2 through T4 either. The mean levels did not differ in muscular patients. In the ROC curve, an AUC value of 0.527 was found (Figure). Consequently, a direct relationship between increased myoglobin levels and a high proportion of muscle in tall, muscular patients cannot be inferred. Although no significant differences were detectable in terms of myoglobin kinetics, the two groups differ in some pre- and postoperative items (Tables 1 and 2). As a result of the selection and definition of muscle mass, the groups understandably differ in terms of height, weight, and sex. All other preoperative parameters are identical. This also applies to postoperative outcome and clinical course. Only the type of surgery (CABG 51%/19% P = .003) accounts for the increased use of compression bandages following saphenectomy. As a result of this selection bias, significantly prolonged surgery, CPB, and cross-clamp times are found in the group of patients with a high muscle mass (Table 1). This is explained by the fact that more complex combined surgical procedures were undertaken in the high muscle mass group. In terms of laboratory analyses at five different time points, there is no tendency for patients with increased muscle mass to have a different course from patients with a lower muscle mass and/or increased proportion of fat

Table 1. Clinical and procedural Characteristics of Patients According to a Low or High Muscle Mass (BMI < 28 and Height > 185cm)

	Low muscle mass	High muscle mass	*P*
	N = 509	N = 26	
Demographics			
Age in years (mean ± sd)	65 ± 11	61 ± 15	.06
Weight kg (mean ± sd)	82 ± 16	92 ± 11	.001
Height m (mean ± sd)	1.71 ± 0.08	1.90 ± 0.02	.001
Body Mass Index (mean ± sd)	27.7 ± 4.5	25.4 ± 2.8	.001
Male (%)	77	100	.002
Clinical Factor			
Peripheral vascular disease (%)	7.5	7.7	1.0
New York Heart Association Class ≥ III (%)	50	39	.68
Ejection fraction < 30% (%)	2	3.8	.64
Prior cardiac procedure (%)	4.3	0	.32
Diabetes mellitus Type II (%)	25	8	.04
Hypertension (%)	92	88	.44
Procedural characteristics			
Operation time (minutes) (mean ± sd)	255 ± 70	312 ± 78	.001
Cardiopulmonary bypass time (minutes) (mean ± sd)	121 ± 46	166 ± 57	.001
Cross-clamp time (minutes) (mean ± sd)	77 ± 35	110 ± 44	.001
Coronary artery bypass graft isolated (%)	51	19	.003
Postoperative outcome			
Hospital stay (days) (mean ± sd)	12.4 ± 6.3	13 ± 8.7	
ICU stay (days) (mean ± sd)	1.8 ± 2.2	1.5 ± 0.8	.48
Leg compression tape (%)	48	19	.004
Red blood cells transfusion T1 (%)	77	73	.38
Intra-aortic balloon pump (%)	0.8	3.8	.22
Prolonged resp. weaning (%)	9.8	18.2	.3

(Table 2). Isolated significance values at various time points had disappeared again after 12 hours or 24 hours, at the latest.

In summary, it can be remarked that age, weight, height, all of the named pre-existing diseases (chronic obstructive pulmonary disease, diabetes mellitus, and hypertension), duration of stay in ICU or hospital, or prior cardiac surgery have no effect on increased serum myoglobin levels immediately following cardiac surgery. Conversely, a direct correlation with a postoperative increase in myoglobin levels was

Table 2. Blood Samples at 5 Different Time Points

	Muscle mass	T0	T1	T2	T3	T4
Lactate mg/dl	low	8.4 ± 3.9	15.5 ± 8.6	16.5 ± 14.2	16.1 ± 8.6	13.1 ± 6.3
	high	7.3 ± 3.5	13.8 ± 6.1	20.8 ± 17.7	14.7 ± 5.5	12.0 ± 2.4
CRP mg/dl	low	0.9 ± 2.0	0.6 ± 1.4	4.9 ± 4.1	12.6 ± 6.1	18.3 ± 7.3
	high	1.1 ± 2.4	1.0 ± 1.9	5.7 ± 5.1	14.6 ± 6.2	20.3 ± 7.0
Creatinine mg/dL	low	0.96 ± 0.24	0.92 ± 0.24	0.99* ± 0.34	0.97 ± 0.35	1.08 ± 0.44
	high	1.03 ± 0.18	1.05 ± 0.19	1.11* ± 0.39	0.97 ± 0.33	1.14 ± 0.60
BUN mg/dL	low	39 ± 16	36 ± 13	38 ± 15	41 ± 17	47 ± 20
	high	39 ± 27	39 ± 15	40 ± 16	39 ± 18	47 ± 23
AST U/L	low	32 ± 19	52 ± 47	74 ± 64	82 ± 73	77 ± 77
	high	28 ± 11	55 ± 28	84 ± 66	95 ± 55	85 ± 53
ALT U/L	low	32 ± 24	27 ± 25	31 ± 26	34 ± 33	37 ± 45
	high	28 ± 11	22 ± 8	24 ± 9	26 ± 10	28 ± 11
CK U/L	low	105 ± 92	357* ± 238	768 ± 922	967 ± 1572	863 ± 173
	high	91 ± 79	486* ± 262	887 ± 583	853 ± 580	817 ± 742
CKMB U/L	low	15 ± 12	40* ± 33	43 ± 41	42 ± 44	33 ± 43
	high	13 ± 5	56* ± 43	55 ± 33	49 ± 36	34 ± 23
Troponin_T pg/mL	low	±	0.5 ± 0.7	0.6 ± 0.6	0.7 ± 0.9	0.8 ± 0.9
	high	±	0.6 ± 0.4	0.7 ± 0.4	0.6 ± 0.2	0.9 ± 1.0
Myoglobin ng/mL	low	±	398 ± 261	632 ± 966	540 ± 706	1096 ± 232
	high	±	461 ± 296	606 ± 534	300 ± 164	364 ± 137
Procalcitonin ng/mL	low	0.1 ± 0.1	0.2 ± 0.3	1.1 ± 2.0	1.1 ± 3.0	1.4 ± 2.7
	high	0.0 ± 0.1	0.3 ± 0.2	1.0 ± 1.3	0.5 ± 0.3	0.6 ± 0.3
Leukocytes/nL	low	7.8 ± 2.9	11.6 ± 5.6	11.1 ± 5.3	11.9 ± 5.8	12.5 ± 6.0
	high	6.8 ± 1.5	11.2 ± 3.9	9.7 ± 3.2	10.8 ± 3.9	11.0 ± 3.8
Platelets/nL	low	232* ± 66	141 ± 49	165 ± 54	164 ± 52	158* ± 49
	high	205* ± 53	125 ± 44	149 ± 56	144 ± 57	132* ± 54
PTT sec	low	36 ± 9	46 ± 15	41 ± 11	41 ± 8	42 ± 7
	high	37 ± 6	46 ± 9	43 ± 9	42 ± 5	42 ± 6
HCO3 mmol/L	low	25.1 ± 1.8	22.7 ± 1.8	23.1 ± 1.8	23.4 ± 1.8	24.1 ± 2.5
	high	24.5 ± 1.7	22.0 ± 1.5	23.3 ± 1.7	24.4 ± 2.3	25.9 ± 2.8
Hemoglobin g/dL	low	12.7 ± 1.8	9.2* ± 1.1	10.3 ± 1.1	10.3 ± 1.2	9.9 ± 1.1
	high	13.2 ± 1.8	9.9* ± 1.2	10.8 ± 1.2	10.4 ± 1.0	9.6 ± 1.0
Hematocrit %	low	39 ± 5	28* ± 3	32 ± 5	32 ± 4	31 ± 3
	high	40 ± 5	31* ± 4	33 ± 4	32 ± 3	30 ± 3
pH	low	7.42 ± 0.1	7.38 ± 0.1	7.36 ± 0.0	7.37 ± 0.0	7.38 ± 0.1
	high	7.40 ± 0.1	7.36 ± 0.1	7.35 ± 0.1	7.39 ± 0.0	7.43 ± 0.0

*T0 = preoperative, T1 = Arrival ICU, T2 = 12 hours postoperative, T3 = 24 hours postoperative, T4 = 36 hours postoperative
† T2 = significant differences ($P < .05$) are marked by *

found for the variables sex, BMI, NYHA classification, ejection fraction, surgical procedure, and administration of blood and/or blood products.

DISCUSSION

Increased serum myoglobin levels already are known to increase mortality. This applies in particular to patients with

renal failure [Slater 1998]. Hofmann et al also have shown that myoglobin levels were more than 10 times higher in their group of patients who died in the intensive care unit than in the group of survivors [Hofmann 2007]. The postoperative finding of increased myoglobin levels due to muscle injury is prognostic for the occurrence of acute kidney injury and renal replacement therapy [Ramarapu 2011]. As a prognostic marker of acute kidney injury, myoglobin provides greater accuracy than creatine kinase (CK) [Huerta-Alardín 2005; Hofmann 2007], among other reasons because there is an earlier increase in the muscle protein than in CK [Janssen 2000]. Perioperative myocardial injury alone, however, cannot entirely explain the occurrence of increased blood myoglobin levels. These markers indicate the important role of skeletal muscle disintegration and necrosis in interpreting the origin of such large quantities of muscle protein [Hofmann 2007]. Benedetto et al provided evidence of this in a subanalysis of their study, in which patients with perioperative myocardial injury were excluded and myoglobin concentrations were still increased [Benedetto 2010]. This subgroup is highly comparable to that in our own analysis: In contrast to Benedetto, we divided our study population into "ischemic" and "non-ischemic" subgroups using CK-MB. This enabled us to exclude a cause of cardiac origin for the increased myoglobin levels.

A major problem of this retrospective study design was to be found in the categorization of patients as "muscular" or "normal to obese" [Janssen 2000]. On the basis of the available data, we had to resort to using height and BMI as assessment criteria as to whether the patient did or did not have a high proportion of muscle. A more detailed method for assessing muscle mass would be a radiological visualization of the body composition. Cruz et al used computed tomography scans for this purpose [Cruz 2013]. Other, albeit more demanding, assessment methods are dual-energy X-ray absorptiometry and bioelectrical impedance analysis [Böhm 2013]. Alternatively, if a retrospective estimate of muscle mass cannot be deduced from normal patient records, in the future a crude determination of body fat could also be performed through simple measurements of abdominal circumference or abdominal skinfold thickness, from which conclusions could be drawn about muscle mass [Jackson 2010]. In that respect, we undertook a corresponding subanalysis of myoglobin at time T1 and like Benedetto et al, we came to the conclusion that the BMI value exhibits a high correlation with increased myoglobin levels [Benedetto 2010]. In an overall consideration of the subject of rhabdomyolysis, pharmacological causes must not be overlooked. As far as the question of unexplained increases in myoglobin is concerned, statins in particular are suspected of playing a crucial role [Cziraky 2013]. However, other anesthetic and cardiac medications are also known to exhibit this side effect profile. The muscle relaxant suxamethonium, the antifibrinolytic tranexamic acid, and the antiarrhythmic agent amiodarone and mannitol in particular should be mentioned in this respect [Ramarapu 2011]. The combination of statins and amiodarone especially is associated with a particular risk of rhabdomyolysis, and a dose limitation of 20 mg simvastatin has been set accordingly by the US Food and Drug Administration [Karimi 2010]. However, our data analysis, with its retrospective approach and high numbers of patients with these groups of pharmacological active substances, is not designed to provide an assessment of the pharmacovigilance of amiodarone and lipid-lowering medication. Before the reason for a non-ischemic increase in myoglobin and the possibility of rhabdomyolysis can be confirmed in future studies in cardiac surgery, preoperative and in-patient concomitant medication must be held in suspicion.

CONCLUSION

A non-ischemic serum myoglobin release is rare. Potential associated factors are sex, ejection fraction, BMI, and red blood cell transfusion. In our definition, a high muscle mass is not associated with a postoperative myoglobin increase. Further investigations should focus on concomitant medications, for which our study was not powered.

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