Article

Time course of hemoglobin concentrations in the intensive care unit in nonbleeding patients with acute coronary syndrome

PREVISDOMINI, Marco, *et al*.

Abstract

Critically ill patients commonly show a decrease in hemoglobin concentration during their stay in the intensive care unit. The purpose of the present study was to evaluate whether nonbleeding patients with acute coronary syndrome (ACS) show a similar decrease of hemoglobin, and thereby furnish reference values and analyze possible mechanisms. In this retrospective, descriptive study, the charts of all patients with ACS hospitalized between January 2004 and September 2005 were screened with regard to patient characteristics, time course of hemoglobin, as well as clinical parameters, concomitant drug therapy, and fluid balances. One hundred three nonbleeding patients with ACS were analyzed. They showed an average hemoglobin decrease of 1.27 +/- 1.00 g/dl (p

Reference

PREVISDOMINI, Marco, *et al*. Time course of hemoglobin concentrations in the intensive care unit in nonbleeding patients with acute coronary syndrome. *The American journal of cardiology*, 2007, vol. 100, no. 4, p. 579-82

DOI : 10.1016/j.amjcard.2007.03.065
PMID : 17697809

Time Course of Hemoglobin Concentrations in the Intensive Care Unit in Nonbleeding Patients With Acute Coronary Syndrome

Marco Previsdomini, MD[a,*], Reto Stocker, MD[b], Roberto Corti, MD[c], Bernard Cerutti, PhD[d], and Andreas Perren, MD[e]

Critically ill patients commonly show a decrease in hemoglobin concentration during their stay in the intensive care unit. The purpose of the present study was to evaluate whether nonbleeding patients with acute coronary syndrome (ACS) show a similar decrease of hemoglobin, and thereby furnish reference values and analyze possible mechanisms. In this retrospective, descriptive study, the charts of all patients with ACS hospitalized between January 2004 and September 2005 were screened with regard to patient characteristics, time course of hemoglobin, as well as clinical parameters, concomitant drug therapy, and fluid balances. One hundred three nonbleeding patients with ACS were analyzed. They showed an average hemoglobin decrease of 1.27 ± 1.00 g/dl ($p < 0.001$). The decrease in hemoglobin level was observed during the first 12 to 24 hours; thereafter the hemoglobin concentration remained stable. We found a correlation among decrease of hemoglobin, parameters of stress, such as hypertension ($p = 0.019$), tachycardia ($p = 0.004$), pain ($p = 0.043$), and white blood cells ($p = 0.021$), as well as the intravenous administration of nitroglycerin ($p = 0.004$). In conclusion, during the first 24 hours in the intensive care unit the hemoglobin concentration of nonbleeding patients with ACS regularly decreases at 1.27 ± 1.00 g/dl. Any further decrease in hemoglobin level beyond these values should entail early active search of the bleeding source. We hypothesize that this decrease is due to normalization of the previous stress-induced hemoconcentration and "internal hemodilution" by nitroglycerin. **(Am J Cardiol 2007;100:579–582)**

The natural time course of hemoglobin concentration in patients with acute coronary syndrome (ACS) has not yet been studied. We recently became aware of a decrease in hemoglobin concentration in patients with ACS lacking any sign of evident blood loss. The present observational study evaluates this phenomenon and proposes reference values of hemoglobin decrease for nonbleeding patients with ACS.

Methods and Results

This retrospective descriptive study was performed in an interdisciplinary 8-bed intensive care unit (ICU) of a regional teaching hospital in southern Switzerland. The investigation was approved by the local ethics committee. We screened the charts of all patients admitted to our ICU for ACS (*International Classification of Diseases* codes 10: I 20.0, I 21.0 I 21.1, I 21.2, I 21.4) between January 2004 and September 2005. Exclusion criteria were active bleeding (e.g., gastrointestinal bleeding), procedures with possible blood loss such as coronary angiography and surgery, transfusion of red blood cells, hemolysis, hemodialysis, and patients with <2 determinations of hemoglobin. We checked for general patient demographics, total fluid balance (comprehensive of the estimated perspiration), total amount of blood samplings, daily hemoglobin and white blood cells count, cardiac markers of ischemia, and the medication given. We furthermore recorded hemodynamic data and thoracic pain intensity (visual analog scale). The severity of disease was determined by the Simplified Acute Physiology Score II (SAPS II).[1] This scoring system, an analog to Apache II, permits classification of severity of disease and attributes a predicted mortality.

The therapeutic regimen of our patients was adapted to the clinical situation. At arrival they received 250 mg of acetylsalicylic acid intravenously, followed by 100 mg/day by mouth. Clopidogrel was given with a loading dose of 300 mg by mouth, followed by 75 mg/day. Four patients were enrolled in the Electrocardiogram Clarity-Thrombolysis In Myocardiol Infarction (TIMI) 28 study and received the study drug.[2] The dose of unfractioned heparin was tailored to augment the activated partial thromboplastin time value to 1.5 to 2.3 times the control value. Patients treated with low- molecular-weight heparins received nadroparin 2 × 86 IU/kg body weight subcutaneously. Tirofiban and thrombolytic agents were applied according to the body weight, following the recommendations of the manufacturers.

The analysis was retrospective and the sample size was not defined on the basis of power consideration. Continuous data are reported as means ± SDs. Categorical data are described as absolute values and percentages. A paired Student's *t* test was used to compare the values of a continuous variable at 2 different time points. A linear fitting was used to check the strength of the linear correlation between 2 continuous variables. All the analyses were done with S-Plus 7.0 for Win-

Divisions of [a]Medical Intensive Care and [b]Surgical Intensive Care and [c]Department of Cardiology, University Hospital, Zurich; [d]Department of Public Health and Social Welfare; and [e]Intensive Care Unit, Ospedale Regionale Bellinzona e Valli, Bellinzona, Switzerland. Manuscript received January 3, 2007; revised manuscript received and accepted March 14, 2007.

*Corresponding author: Tel: 41-44-255-22-52; fax: 41-44-255-31-81.
E-mail address: marconico@hispeed.ch (M. Previsdomini).

0002-9149/07/$ – see front matter
doi:10.1016/j.amjcard.2007.03.065

Table 1
Demographic data (n = 103 patients)

Variable	Number
Men/women	64/39
Age (yrs)	71 ± 13
SAPS II	28 ± 13
Length of intensive care unit stay (hs)	49 ± 28
Intensive care unit mortality	4 (4%)
In-hospital mortality	15 (15%)
Primary diagnosis	
ACS	16 (16%)
Acute non–ST-segment elevation myocardial infarction	49 (48%)
Acute ST-segment elevation myocardial infarction	17 (17%)
Myocardial infarction with cardiac arrest	6 (6%)
Subacute myocardial infarction	15 (15%)

Continuous data are presented as mean ± SD.

dows, Enterprise Developer (Insightful Corporation, Seattle, Washington).

We examined the charts of 172 patients with ACS. Sixty-nine patients were excluded from final evaluation because of insufficient hemoglobin assessments (n = 48), too short length of stay (n = 8), previous procedures with unknown blood loss (n = 4), preexistent anemia requiring blood transfusions (n = 5), gastric ulcer disease with active bleeding (n = 2), hemolysis (n = 1), and chronic intermittent hemodialysis (n = 1). Thus, the analysis concerned 103 white nonbleeding patients with ACS, 6 of whom with cardiac arrest, who met the inclusion criteria. General patient demographics are listed in Table 1.

The mean hemoglobin concentration at ICU admission was 13.90 ± 1.62 g/dl and decreased during the ICU stay for 88% of patients. After a decrease of 1.29 ± 0.79 g/dl during the first 12 to 24 hours (95% confidence interval 1.12 to 1.46 g/dl, $p < 0.001$), it remained stable (mean reduction for the complete ICU stay of 1.27 ± 1.00 g/dl; Figure 1). The average fluid balance during the entire ICU stay was −616 ± 1,465 ml, + 771 ml in the subgroup of patients who died ($p < 0.001$), and blood samplings accounted for 52 ± 18 ml. We found a positive correlation between the height of the SAPS II score and the global fluid balance (correlation coefficient 0.325, $p < 0.001$), but there was no evidence of correlation between the fluid balance and the hemoglobin decline ($p = 0.150$). The decrease in hemoglobin was more important in patients with a higher SAPS II score (+0.02 g/dl per unit of SAPS II, $p < 0.001$). In contrast, it was less for patients who died during the hospitalization (difference of 0.95 g/dl, $p < 0.001$).

Data concerning the therapeutic regimen are reported in Table 2. There was no significant relation between the administration of clopidogrel ($p = 0.600$) or tirofiban ($p = 0.646$) and the hemoglobin decrease. In contrast, hemoglobin significantly decreased after systemic thrombolysis (−0.58 g/dl, $p = 0.008$). Patients receiving nitrates had a mean hemoglobin decrease of 1.43 g/dl during the first 12 to 24 hours, whereas those not receiving nitrates had a hemoglobin decrease of 0.89 g/dl ($p = 0.004$). The relation between the administration of β blockers and the degree of hemoglobin decrease did not reach a significant level ($p = 0.070$). Data concerning hemodynamic parameters, white blood cells, and thoracic pain intensity are reported in Table 3. There was an association between the hemoglobin course, the decrease of arterial pressure during the ICU stay (0.01 g/dl by decrease of 1 mm Hg, $p = 0.019$), the decrease in heart rate (0.01 g/dl by decrease of 1 beat/min, $p = 0.004$), the lessening of pain intensity (0.06 g/dl per unit on the visual analog scale, $p = 0.043$), and the decrease of white blood cells during the hospitalization (0.06 g/dl by decrease of $10^3/\mu l$, $p = 0.021$).

Discussion

The present observational study evaluates the time course of blood hemoglobin concentrations in a population of nonbleeding patients with ACS with the additional purpose of providing reference values and evaluating possible affecting factors, considering that these patients are exposed to many drugs that can promote bleeding. Our data indicate that the hemoglobin level decreases 1.29 ± 0.79 g/dl during the first 12 to 24 hours and then remains constant during the remaining stay in the ICU. Theoretically, this might be due to the many blood samples taken at beginning of the hospitalization. As described in the past, blood samplings can contribute to a reduction of hemoglobin concentration, a phenomenon referred to as nosocomial or iatrogenic anemia.[3,4] However, the total amount of blood needed for laboratory testing has decreased over the years with improvement in techniques and equipment, and in our study it was rather limited, with an average of 52 ml during the entire ICU stay. In relation to the assumed mean weight of our patients[5] this would imply a hemoglobin decrease of 0.13 to 0.15 g/dl (estimated blood volume 7% of body weight),[6] which is far from the value observed in our study. The fluid balance was constant or negative with only 8 exceptions, therefore hemodilution after correction of fluid deficits can be discarded as a reason for the hemoglobin reduction. The mean ICU stay was too short for nutritional, endocrine, renal, or hepatic insufficiency to influence the course of hemoglobin level.

Our statistical analysis could not demonstrate a relation between the number and type of platelet-inhibiting and anticoagulating drugs and the course of hemoglobin concentration. This might be due in part to the limited sample size and the presence of very similar treatment protocols among the patients. The only significant correlation was found between the application of systemic thrombolysis and the degree of hemoglobin decrease, but this is in the absence of a visible blood loss.

About 3/4 of our patients received nitroglycerin intravenously during the first hours of hospitalization. Brugger et al[7] and Arend et al[8] described an effect called internal hemodilution after the administration of nitrates. The latter reported an average hemoglobin decrease after administration of intravenous nitroglycerin for 24 hours of 1.48 g/dl, a value close to our results.

We found a statistical correlation between the amount of hemoglobin decrease, the difference of blood pressure, heart rate, pain acuity, and white blood cells between admission and discharge. As reported by Patterson et al[9] on 29 healthy men, acute psychological stress can produce a significant hemoconcentration, probably through a fluid shift from the

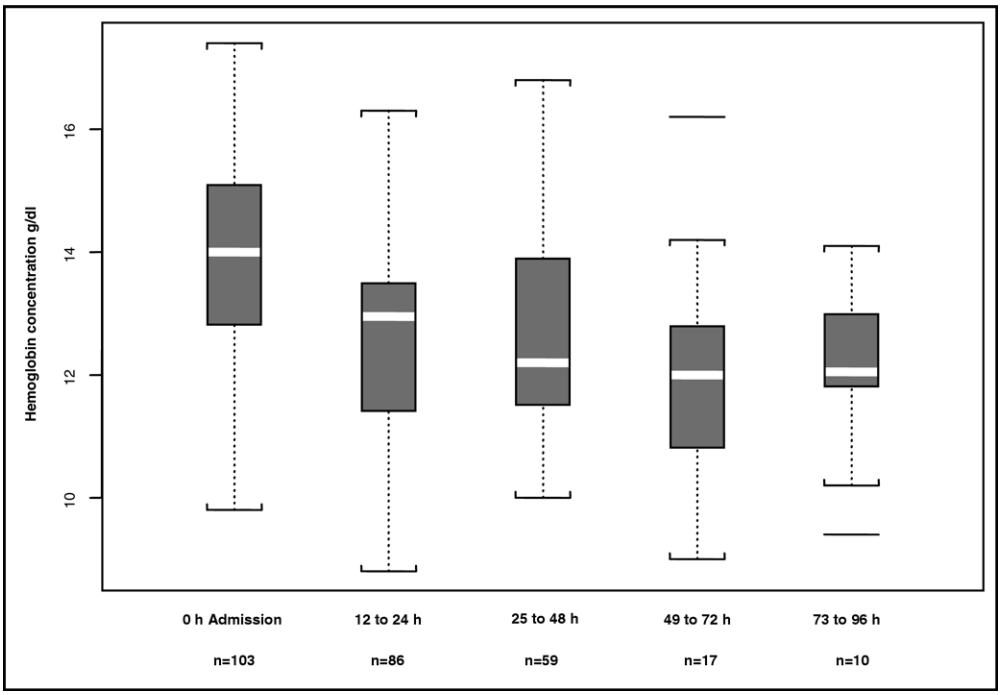

Figure 1. Time course of hemoglobin concentrations in 103 patients with acute coronary syndrome. The mean hemoglobin concentration at ICU admission was 13.90 ± 1.62 g/dl. After a decrease of 1.29 ± 0.79 g/dl during the first 12 to 24 hours (95% confidence interval 1.12 to 1.46 g/dl, $p < 0.001$) it remained stable (mean reduction for the complete ICU stay of 1.27 ± 1.00 g/dl). The *white lines* represent the medians of the observations, whereas the *lower and upper extremities of the box* represent the first and the third quartiles. The maximum length of each whisker is 1.5 times the interquartile range. Any data value larger than this range is drawn with a *horizontal line*.

Table 2
Therapeutic regimens of the study population (n = 103)

Variable	Number
Acetylsalicylic acid	96 (93%)
Clopidogrel	48 (47%)
Electrocardiogram clarity-TIMI 28 Study drug	4 (4%)
Heparin	101 (98%)
Unfractioned heparin	13 (13%)
Low weight molecular heparin	84 (82%)
Tirofiban	13 (13%)
Systemic thrombolysis	17 (17%)
Tenecteplase	11 (11%)
Alteplase	1 (1%)
Streptokinase	5 (5%)
Nitroglycerin	79 (77%)
β Blocker	70 (68%)

Table 3
Hemodynamic data, white blood cells and thoracic pain intensity

Variable	Admission	Discharge
Mean arterial pressure (mm Hg)	98 ± 24	84 ± 14
Heart rate (beats/min)	84 ± 22	71 ± 14
White blood cells ($10^3/\mu l$)	10.1 ± 3.5	8.9 ± 3.1
Thoracic pain intensity (visual analog scale)	2.2 ± 2.9	0.0 ± 0.3

Data are presented as mean ± SD.

vascular to the interstitial space secondary to vasoconstriction. After fading of stress, the fluid backflow from the interstitial space to the vascular bed may explain the decrease in hemoglobin level. Patients with a higher SAPS II score, being more acutely ill at admission, showed more hemoglobin decline, probably due to the same mechanism. The reason why patients who died experienced less hemoglobin decrease, is not completely clear, as their mean positive fluid balance would imply the contrary. On one hand they received less nitrates. On the other, their reduced decrease in hemoglobin level could represent a sign of ongoing instability and stress. Considering the small sample size, these results might also be due to chance.

Patients receiving blood transfusions were excluded from our study. There are few clinical data about the hemoglobin threshold for transfusion in patients with cardiac disease.[10] Most clinical trials were conducted on patients undergoing coronary artery bypass.[11] For elderly patients with acute myocardial infarction, Wu and al[12] reported that blood transfusion was associated with lesser short-term mortality if the hematocrit at admission was ≤30.0% and may still be effective with a hematocrit as high as 33.0% on admission. Based on these data, the hemoglobin threshold for transfusion in patients with ACS is set at most institutions between 8.5 and 10 g/dl.

Our study has several limits. The retrospective observational design implies possible selection bias. For instance, 28% of the screened patients were discarded from the study population because of insufficient hemoglobin assessments. In contrast, the scattered measurement of hemoglobin level could also potentially influence the data. One difficulty with such an analysis is the unavoidable decrease in the number of patients over time, as patients are discharged early, are transferred to other institutions, or die. Although patients discharged or transferred could be followed up for a prede-

termined time interval, we did not collect these data considering the bias caused by the different laboratory techniques. Although no occult blood losses were recognized, one cannot entirely exclude unrecognized gastrointestinal bleeding as a contributing factor.[13] However, there are ≥2 arguments that make this hypothesis rather improbable: (1) a hemoglobin decease could be noted in as much as 88% of the examined patients and (2) the rapid onset of hemoglobin decrease with consequently stable values despite continuing the previously described therapy.

1. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993;270:2957–2963.
2. Scirica BM, Sabatine MS, Morrow DA, Gibson CM, Murphy SA, Wiviott SD, Giugliano RP, McCabe CH, Cannon CP, Braunwald E. The role of clopidogrel in early and sustained arterial patency after fibrinolysis for ST-segment elevation myocardial infarction: the ECG CLARITY–TIMI 28 Study. *J Am Coll Cardiol* 2006;48:37–42.
3. Eyster E. Nosocomial anemia. *JAMA* 1973;223:73–74.
4. Henry ML. Iatrogenic anemia. *Am J Surg* 1986;151:362–363.
5. Anonymous. Bundesamt für Statistik (2003c), Schweizerische Gesundheitsbefragung 2002, Thema 4: Gesundheitszustand. Neuenburg. Sektion Gesundheit des Bundesamt für Statistik.
6. Weiss C, Jelkmann W. Funktionen des Blutes. In: Schmidt und Thews, ed. Physiologie des Menschen. Berlin: Springer Verlag, 1990:422–460.
7. Brugger W, Imhof P, Müller P, Moser P, Reubi F. Effect of nitroglycerin on blood rheology in healthy subjects. *Eur J Clinical Pharmacol* 1985;29:331–336.
8. Arend SM, Bax JJ, Hermans J, van der Wall EE, Sedney MI. The short-term effect of intravenous nitroglycerin on haematocrit; an additional benefit in patients with myocardial ischaemia? *Eur Heart J* 1994;15:114–119.
9. Patterson SM, Marsland AL, Manuck SB, Kameneva M, Muldoon MF. Acute hemoconcentration during psychological stress: assessment of hemorheologic factors. *Int J Behav Med* 1998;5:204–212.
10. Hébert CP, Yetisir E, Martin C, Blajchman MA, Wells G, Marshall J, Tweeddale M, Pagliarello G, Schweitzer I. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? *Crit Care Med* 2001;29:227–234.
11. Johnson RG, Thurer RL, Kruskall MS, Sirois C, Gervino EG, Critchlow J, Weintraub RM. Comparison of two transfusion strategies after elective operations for myocardial revascularization. *J Thorac Cardiovasc Surg* 1992;104:307–314.
12. Wu W-C, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001;345:1230–1236.
13. Von Ahsen N, Müller C, Serke S. Important role of non diagnostic blood loss and blunted erythropoietic response in the anemia of medical intensive care patients. *Crit Care Med* 1999;27:2630–2639.