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

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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. © 2007 Elsevier Inc. All rights reserved. (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). 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 Myocardial Infarction (TIMI) 28 study and received the study drug. 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-
The present observational study evaluates the time course of blood hemoglobin concentrations in a population of non-bleeding 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 the 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. 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 this would imply a hemoglobin decrease of 0.13 to 0.15 g/dl (estimated blood volume 7% of body weight), 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. and Arend et al. 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. on 29 healthy men, acute psychological stress can produce a significant hemococoncentration, probably through a fluid shift from the
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. Most clinical trials were conducted on patients undergoing coronary artery bypass. For elderly patients with acute myocardial infarction, Wu and al 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. However, there are ≥2 arguments that make this hypothesis rather improbable: (1) a hemoglobin decrease 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.