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ORIGINAL RESEARCH

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Femoral blood gas analysis, another tool to assess hemorrhage severity following trauma: an exploratory prospective study

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Abstract

Background Veno-arterial carbon dioxide tension difference (ΔPCO_2) and mixed venous oxygen saturation (SvO_2) have been shown to be markers of the adequacy between cardiac output and metabolic needs in critical care patients. However, they have hardly been assessed in trauma patients. We hypothesized that femoral ΔPCO_2 ($\Delta PCO_{2\,fem}$) and SvO_2 ($SvO_{2\,fem}$) could predict the need for red blood cell (RBC) transfusion following severe trauma.

Methods We conducted a prospective and observational study in a French level I trauma center. Patients admitted to the trauma room following severe trauma with an Injury Severity Score (ISS) > 15, who had arterial and venous femoral catheters inserted were included. $\Delta PCO_{2\,fem}$, $SvO_{2\,fem}$ and arterial blood lactate were measured over the first 24 h of admission. Their abilities to predict the transfusion of at least one pack of RBC ($pRBC_{H6}$) or hemostatic procedure during the first six hours of admission were assessed using receiver operating characteristics curve.

Results 59 trauma patients were included in the study. Median ISS was 26 (22–32). 28 patients (47%) received at least one $pRBC_{H6}$ and 21 patients (35,6%) had a hemostatic procedure performed during the first six hours of admission. At admission, $\Delta PCO_{2\,fem}$ was 9.1 ± 6.0 mmHg, $SvO_{2\,fem}$ 61.5 ± 21.6% and blood lactate was 2.7 ± 1.9 mmol/l. $\Delta PCO_{2\,fem}$ was significantly higher (11.6 ± 7.1 mmHg vs. 6.8 ± 3.7 mmHg, $P = 0.003$) and $SvO_{2\,fem}$ was significantly lower (50 ± 23 mmHg vs. 71.8 ± 14.1 mmHg, $P < 0.001$) in patients who were transfused than in those who were not transfused. Best thresholds to predict $pRBC_{H6}$ were 8.1 mmHg for $\Delta PCO_{2\,fem}$ and 63% for $SvO_{2\,fem}$. Best thresholds to predict the need for a hemostatic procedure were 5.9 mmHg for $\Delta PCO_{2\,fem}$ and 63% for $SvO_{2\,fem}$. Blood lactate was not predictive of $pRBC_{H6}$ or the need for a hemostatic procedure.

Conclusion In severe trauma patients, $\Delta PCO_{2\,fem}$ and $SvO_{2\,fem}$ at admission were predictive for the need of RBC transfusion and hemostatic procedures during the first six hours of management while admission lactate was not. $\Delta PCO_{2\,fem}$ and $SvO_{2\,fem}$ appear thus to be more sensitive to blood loss than blood lactate in trauma patients, which might be of importance to early assess the adequation of tissue blood flow with metabolic needs.

Keywords Veno-arterial carbon dioxide tension difference, Venous oxygen saturation, Lactate, Tissue hypoxia, Severe trauma, Hemorrhagic shock

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Background

Severe trauma remains the leading cause of death before the age of 50 [1]. Approximately 40% of trauma deaths involve hemorrhagic shock and are possibly preventable through damage control resuscitation and early bleeding control [2, 3]. Hemorrhage-induced hypovolemia leads to a drop in cardiac output (CO) responsible for tissue hypoperfusion and impaired oxygen delivery to the organs. When the adaptive mechanisms to hypovolemia are overwhelmed and can no longer compensate for the decrease in oxygen delivery, alterations of cellular homeostasis may ultimately lead to refractory shock and multiorgan dysfunction [4]. It is therefore necessary to identify patients with severe blood loss as early as possible in order to quickly start appropriate resuscitation.

At the initial phase of severe trauma management, CO monitoring is not readily available. Several biomarkers have been proposed to assess the adequacy between oxygen delivery and demand in these conditions. Thus, admission lactate has been shown to be predictive of severe hemorrhage associated with massive transfusion [5]. However, during hemorrhage, blood lactate increases only beyond a critical threshold of oxygen delivery when cell anaerobic metabolism is triggered to maintain ATP production. Lactate production therefore only rises when blood loss gets significant [6]. Other metabolic parameters have been proposed to assess the adequacy between oxygen demand and supply in different critical conditions such as sepsis and major surgery. These parameters include the venous to arterial carbon dioxide gradient (ΔPCO_2) [7, 8] and venous oxygen saturation (SvO_2) [9, 10] but none of them has been studied in severe trauma patients. A drop in CO is responsible for a decrease in tissue blood flow leading to venous carbon dioxide accumulation and an increase in the fraction of extracted oxygen that cause an increase in ΔPCO_2 [11] and a decrease in SvO_2 respectively [12].

Femoral arterial and central venous catheters are commonly inserted during initial management of severe trauma patients in the trauma bay [13]. They make venous and arterial blood gas available to appraise the venous to arterial difference in CO_2 ($\Delta PCO_{2\ fem}$) as well as femoral venous oxygen saturation ($SvO_{2\ fem}$).

The aim of the present study was to assess the ability of $\Delta PCO_{2\ fem}$, $SvO_{2\ fem}$ and arterial blood lactate to predict transfusion of red blood cells (RBC) over the first hours following severe trauma.

Methods

Study design

This observational, prospective and single-centre study was conducted in the surgical Intensive Care Unit of Bicêtre Hospital, an academic level-1 trauma center, from September 2015 to May 2020. This hospital provides 24-h availability of all essential trauma specialties, staff and equipment for trauma patient care. This study was approved by the ethics committee ("Comité de Protection des Personnes") of the hospital (SC13-014 RCB: 2013-A01171-44) with waiver of participant consent. Patients or relatives were informed and we obtained confirmation of non-objection to data use.

Study population

Patients over 18, admitted from the trauma scene, with an Injury Severity Score (ISS) greater than 15, and for whom initial management in the trauma room required the insertion of an arterial and a venous catheter at the femoral site, were included.

Pregnant women, patients with NYHA III or IV heart failure or chronic kidney disease (clearance < 30 ml/min) and patients with lower limb amputation or severe crush injury on the same side the femoral catheters were inserted were not included in the study.

Clinical management

Following the emergency call, a physician-staffed mobile intensive care unit was sent to the trauma scene. After clinical assessment and medical care adjusted to trauma severity, patients were transported to the study center. Upon arrival in the trauma room, the insertion of femoral catheters was decided based on the patient's history, clinical examination, and FAST ultrasound results, at the discretion of the clinician in charge as detailed elsewhere [13]. Briefly, the catheter lines were prepared in a sterile manner before patients' arrival. Arterial (5 Fr, 11 cm) and venous femoral catheters (7 Fr, 20 cm) were simultaneously inserted by a trained resident under supervision of the trauma leader (consultant). The decision to transfuse was made by the physician in charge, based on his evaluation of the patient's clinical situation using standard parameters (including clinical signs of shock, positive FAST ultrasound or obvious external hemorrhage and bed-side measurement of hemoglobin level) and blinded to the $\Delta PCO_{2\ fem}$, $SvO_{2\ fem}$ results.

Data collection

For each patient, demographics, past medical history, trauma characteristics, pre-hospital management data such as time to hospital admission, initial Glasgow Coma Scale (GCS) score, minimum systolic blood pressure, peripheral oxygen saturation, maximum heart rate, need for mechanical ventilation, volume of fluid resuscitation, catecholamines use were collected. We also reported the following scores: Injury Severity Score (ISS) [14], details of injuries for each organ (Abbreviated Injury Scale 2015, AIS) [15] and simplified acute physiology score (SAPS

II) [16]. Severe organ injury was defined by an AIS for the correspondent organ over 2. On hospital admission, mean arterial blood pressure, heart rate, peripheral oxygen saturation, laboratory parameters (hemoglobin, prothrombin time, fibrinogen, myoglobin) were reported. Fluid administration, dose of catecholamines, transfusion therapy (type of product and amount) and hemostatic procedures were collected during the first 6 h of admission. The following outcome variables were also reported: length of mechanical ventilation, length of intensive care unit (ICU) stay and hospital mortality.

Blood gas measurement

Venous and arterial blood gas were sampled from femoral catheters at insertion and regularly during the first 24 h, between 4 and 8 h from ICU admission (H6), 10 and 14 h from ICU admission (H12) 20 and 26 h from ICU admission (H24). pH, arterial ($PaCO_{2fem}$) and femoral venous carbon dioxide partial pressure ($PvCO_{2fem}$), arterial oxygen partial pressure (PaO_2), venous oxygen saturation (SvO_{2fem}), arterial oxygen saturation (SaO_2), hemoglobin concentration and blood lactate were measured on both samples using a point-of-care blood gases analyzer (ABL 800, Radiometer). The femoral venous to arterial difference in carbon dioxide pressure ($\Delta PCO_{2\ fem}$) was calculated as femoral $PvCO_2$–$PaCO_2$.

Outcome

The primary outcome of interest was the transfusion of at least one pack of RBC during the first six hours of admission ($pRBC_{H6}$). The secondary outcome was the need for an emergency hemostatic procedure. It was defined as performing angioembolization or hemostatic surgery within the first six hours of management from admission. Orthopedic surgery for fracture osteosynthesis was not considered as a hemostatic procedure.

There is no data regarding $\Delta PCO_{2\ fem}$ and SvO_{2fem} in trauma patients. Since trauma patients present a wide variety of traumatic injuries, we considered that a sample of 60 patients would be representative for this exploratory study.

Statistical analysis

Qualitative variables were expressed as counts (proportions). Quantitative variables were expressed as mean (SD) or median (25th–75th interquartile range) according to their distributions. Correlations between blood lactate, $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ at admission were analyzed by Pearson correlation.

In the overall population, volumes of $pRBC_{H6}$ transfused were reported according to quartile distribution of blood lactate, $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$. Then, patients were separated into two groups according to whether they had been transfused with $pRBC_{H6}$ or not. Their characteristics were compared by a Student t-test or a Mann–Whitney test for quantitative variables (according to data distribution) and by a Chi-square test for qualitative variables. Evolution of lactate, $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ during the 24 first hours of admission were compared over time and between the two groups with a mixed-effect model. Time, group (transfusion, no transfusion) and interaction (time x group) were set as fixed effect and patient as random effect.

To evaluate the ability of admission lactate, $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ to predict the need for $pRBC_{H6}$ transfusion or an emergency hemostatic procedure, receiver operating characteristic curves (ROCs) were built and their areas under the curve (AUC) were calculated. The best threshold for the prediction of $pRBC_{H6}$ transfusion or to predict the need for an emergency hemostatic procedure was defined as the value maximizing the Youden index (Y = Sensitivity + Specificity-1). Sensitivity, specificity, positive and negative predictive values (PPV and NPV), were reported for each variable. Two-sided level of significance was fixed at $P = 0.05$. Data were analyzed using Prism (GraphPad Software, San Diego, California, USA).

Results

Population characteristics

Seventy patients were enrolled in the study. Eleven patients were secondarily excluded because their ISS was less than 15, leaving 59 patients in the final analysis (Additional file 1). Patients were 46 ± 20 years old and one third were women (17(29%)). Patients experienced predominantly blunt trauma (87%) with a median ISS of 26 (22–32). Median ICU length of stay was 10 (5–15.5) days and the overall hospital mortality was 26%. Two patients died in the first 24 h. The main characteristics of the population are presented in Table 1.

Incidence of transfusion

Over the first six hours of admission, 28 patients (47%) received at least one pack of RBC. The characteristics of transfused and non-transfused patients are shown in Table 1. Transfused and non-transfused patients were similar with regard to age, gender, SAPSII, type of trauma and on-scene hemodynamic parameters. Transfused patients presented more severe abdominal (43% vs. 10%, $P = 0.006$) and pelvic trauma (54% vs. 29%, $P = 0.020$), but they had significantly less traumatic head injuries (28.6% vs. 64.5%, $P = 0.006$) than non-transfused patients.

Mean blood pressure at hospital admission was significantly lower in the transfused group ($P = 0.020$). The given volume of crystalloids ($P < 0.001$) and colloids ($P = 0.020$) over the first six hours of management were significantly greater in patients who got transfused.

Table 1 General characteristics in the overall population and in both transfused and non-transfused patients

	All **n = 59**	**Non-transfused** **n = 31**	**Transfused[ε]** **n = 28**	***P*[#]**
Characteristics				
Age-years	46 ± 20	47 ± 21	45 ± 19	0.7
Women-n (%)	17 (29)	10 (32)	7 (25)	0.6
Type of trauma-n (%)				0.4
Road accident	35 (59.3)	18 (58)	17 (61)	
Fall from height	19 (32.2)	11 (35.5)	8 (28.5)	
Penetrating trauma	2 (3.4)	0 (0)	2 (7)	
Other	3 (5.1)	2 (6.5)	1 (3.5)	
ISS	26 (22–32)	27 (25–35)	25 (21–30)	0.1
AIS[φ] Head or neck-n (%)	28 (47)	20 (64.5)	8 (28.6)	0.006*
AIS Chest-n (%)	32 (54)	20 (64.5)	12 (42.9)	0.1
AIS Abdomen-n (%)	15 (25)	3 (9.6)	12 (42.9)	0.003*
AIS Pelvis and extremities-n (%)	24 (41)	9 (29)	15 (53.6)	0.02*
AIS External-n (%)	2 (1)	0 (0)	1 (4)	0.3
SAPS II	43 (20)	45 (20)	40 (20)	0.4
On scene parameters				
Time from trauma to hospital admission-min	98 (67–120)	105 (74–122)	95 (57–113)	0.3
GCS	14 (8–15)	13 (6–15)	15 (13–15)	0.03*
Minimum SBP-mmHg	106 ± 33	104 ± 39	107 ± 24	0.7
Maximum HR-bpm	106 ± 25	102 ± 27	108 ± 23	0.4
Minimum SpO_2-%	98 (94–98)	97 (90–98)	99 (95–100)	0.02*
Intubation-n(%)	32 (54.2)	20 (64.5)	12 (42.9)	0.09
Fluid administration-ml	800 (500–1250)	1000 (500–1250)	750 (500–1038)	0.2
Catecholamines-mg/h	0 (0–0.4)	0 (0–0.5)	0 (0–0.25)	0.9
Parameters on admission to resuscitation room				
MBP H0-mmHg	80 ± 19	85 ± 16	73 ± 19	0.02*
HR H0-bpm	98 ± 26	93 ± 23	102.6 ± 27	0.2
Ht-%	0.34 ± 0.06	0.37 ± 0.04	0.31 ± 0.6	< 0.001*
Hb-g/dl	11.5 ± 2.1	12.6 ± 1.5	10.3 ± 2	< 0.001*
PT-%	70 ± 17	75 ± 14	64 ± 18	0.01*
Fibrinogen-g/l	2 ± 1	2.4 ± 0.8	2.0 ± 1.0	0.1
Myoglobin-IU	945 (386–2597)	910 (425–1762)	1151 (350–2722)	0.8
Outcome during hospital stay				
Crystalloids H6-ml	1750 (875–3500)	1000 (500–1870)	3125 (1575–4137)	< 0.001*
Colloids H6-ml	0 (0–500)	0 (0–0)	0 (0–500)	0.02*
RBC H6-ml	0 (0–892)	0	900 (505–1243)	< 0.001*
Catecholamines H6-mg/hour	1.0 (0.3–2.5)	0.6 (0.25–2.5)	1 (0–2.6)	0.8
RBC H6-H12-ml	0 (0–0)	0 (0–0)	0 (0–70)	0.004*
Hemostatic procedure-n	21 (35.6)	2 (6.5)	19 (67.8)	< 0.001*
Mortality-n	15 (25.9)	11 (35.5)	4 (14.8)	0.06

AIS[φ] is the number of patients with an AIS > 2. Hemostatic procedure was defined as performing angioembolization or hemostatic surgery within the first six hours of management from admission

Data are reported as mean ± SD or median [Q1–Q3]

GCS glasgow coma scale, *Hb* hemoglobin, *HR* heart rate, *Ht* hematocrit, *H6* Over the first 6 h after admission, *H6-H12* between H6 and H12 after admission, *ICU* intensive care unit, *ISS* injury severity score, *MBP* mean blood pressure, *PT* prothrombin time, *RBC* red blood cells, *SAPS* simplified acute physiology score, *SD* standard deviation, *SBP* systolic blood pressure, SpO_2 pulse oximeter oxygen saturation

[ε] Patient transfused with red blood cells over the first six hours of admission

[#] Non-transfused patients were compared with transfused patients

[*] Two-sided level of significance was fixed at 5%

Nineteen patients (67.8%) required an emergency hemostatic procedure in the transfused group and only 2 (6.5%) in the non-transfused group ($P<0.001$). Mortality was not different between the two groups ($P=0.060$) (Table 1).

Blood gas analysis

In the whole cohort, blood lactate was 2.7 ± 1.9 mmol/l, $\Delta PCO_{2\ fem}$ was 9.1 ± 6.0 mmHg and $SvO_{2\ fem}$ was 61.5 ± 21.6% on admission. As shown in Fig. 1, volume of $pRBC_{H6}$ was associated with a greater $\Delta PCO_{2\ fem}$ or blood lactate level and a lower $SvO_{2\ fem}$. Volume of $pRBC_{H6}$ transfused was larger when $\Delta PCO_{2\ fem}$ was greater than 13 mmHg, $SvO_{2\ fem}$ was less than 50% or blood lactate was greater than 3.5 mmol/l (Fig. 1).

At admission, in the overall population $\Delta PCO_{2\ fem}$ was at its highest level and then decreased to a mean minimal value at H24 of 5.4 ± 3.5 mmHg. $SvO_{2\ fem}$ was the lowest at admission and then plateaued from H6 with a mean value of 68.5 ± 16.8%. Maximum lactate was reached at H6 (2.8 ± 2.1 mmol/) and then decreased with a mean value of 2.0 ± 1.9 mmol/l at H24 (Additional file 1). At admission, $\Delta PCO_{2\ fem}$ (r = 0.48; $P<0.001$) and $SvO_{2\ fem}$ (r = 0.40; $P<0.004$) were correlated with lactate and they were correlated together (r = 0.63; $P<0.001$).

At admission, $\Delta PCO_{2\ fem}$ (11.6 ± 7.1 mmHg vs. 6.8 ± 3.7 mmHg; $P=0.003$), $SvO_{2\ fem}$ (50.0 ± 23.0% vs. 71.8 ± 14.1%; $P<0.001$) and lactate (3.3 ± 2.4 mmol/l vs. 2.2 ± 1.3 mmol/l; $P=0.04$) were significantly different in transfused compared to non-transfused patients (Table 2).

Over the first 24 h, $\Delta PCO_{2\ fem}$ decreased significantly and was statistically different between transfused and non-transfused groups without interaction between time and groups (time effect, $P=0.002$; transfusion effect, $P=0.008$; time x transfusion effect, $P=0.1$). $SvO_{2\ fem}$ remained stable in the non-transfused group, over the first 24 h, while it significantly increased over time

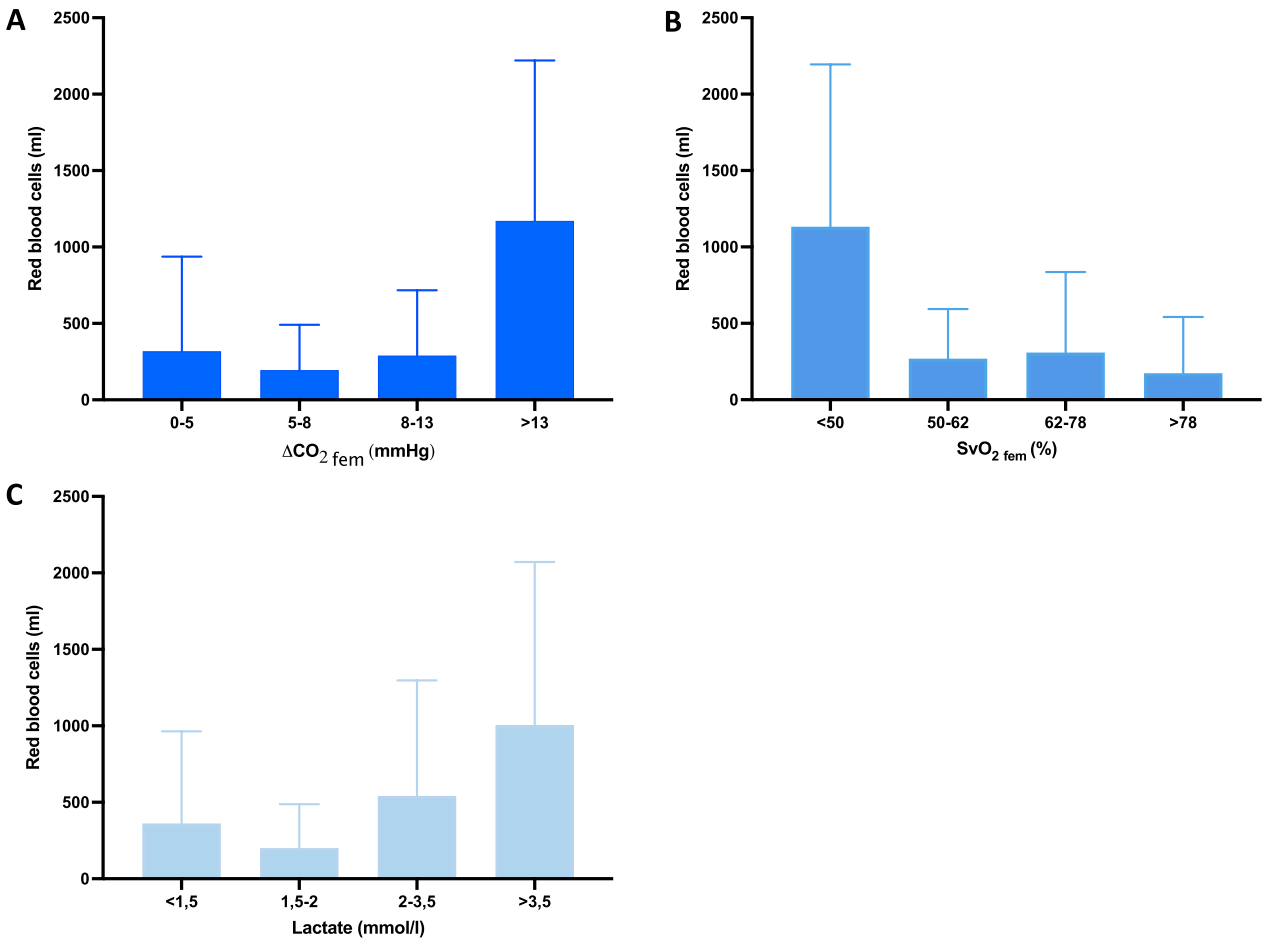

Fig. 1 Volumes of red blood cells transfused during the first six hours of admission. Volumes are shown according to quartile distribution of **A** $\Delta PCO_{2\ fem}$. **B** $SvO_{2\ fem}$ and **C** lactate. All data are reported as mean ± SD. $\Delta PCO_{2\ fem}$ femoral venous-arterial difference in carbon dioxide pressure. $SvO_{2\ fem}$ femoral venous oxygen saturation

Table 2 Hemodynamic variables in the overall population and in transfused and non-transfused patients

	All n = 59	Not transfused n = 31	Transfused n = 28	*P*
Lactate—mmol/L	2.7 ± 1.9	2.5 ± 1.9	3.1 ± 2.1	0.036
$\Delta PCO_{2\ fem}$—mmHg	9.1 ± 6.0	6.8 ± 3.7	11.6 ± 7.1	0.003
$SvO_{2\ fem}$—%	61.5 ± 21.6	71.8 ± 14.1	50.0 ± 23.0	< 0.001

$\Delta PCO_{2\ fem}$ femoral venous-arterial difference in carbon dioxide pressure. $SvO_{2\ fem}$ femoral venous oxygen saturation. Data are reported as mean ± SD

in the transfused group (time effect, $P=0.04$; transfusion effect, $P=0.02$; time x transfusion effect, $P<0.001$). In the transfused group, blood lactate peaked at H6 and then decreased over the first 24 h while it decreased, from admission to H24, in the non-transfused group. Blood lactate was different between non-transfused and transfused patients without interaction between time and groups (time effect, $P=0.01$; transfusion effect, $P=0.007$; time x transfusion effect, $P=0.7$) (Fig. 2 and Additional files 2 and 3).

Transfusion prediction

The abilities of admission $\Delta PCO_{2\ fem}$, $SvO_{2\ fem}$ and blood lactate to predict the need for $pRBC_{H6}$ transfusion and the need for a hemostatic procedure during the first six hours of admission are presented in Fig. 3 and Additional file 4.

Admission $\Delta PCO_{2\ fem}$ significantly predicted $pRBC_{H6}$ transfusion with an AUC of 0.71 (CI95% 0.57–0.86; $P=0.008$) and $SvO_{2\ fem}$ significantly predicted $pRBC_{H6}$ transfusion with an AUC of 0.77 (CI95% 0.64–0.91; $P<0.001$). At admission, the optimal thresholds of $\Delta PCO_{2\ fem}$ to predict the need for $pRBC_{H6}$ transfusion was 8.1 mmHg and the optimal threshold of $SvO_{2\ fem}$ to predict the need for $pRBC_{H6}$ transfusion was 63%. The predictive performances of $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ are given in Table 3.

Admission $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ significantly predicted the need for an emergency hemostatic procedure with respective AUCs of 0.74 (CI95% 0.58–0.90, $P=0.02$) and 0.72 (CI95% 0.57–0.87, $P=0.01$). A threshold of 5.9 mmHg for $\Delta PCO_{2\ fem}$ and 63% for $SvO_{2\ fem}$ at

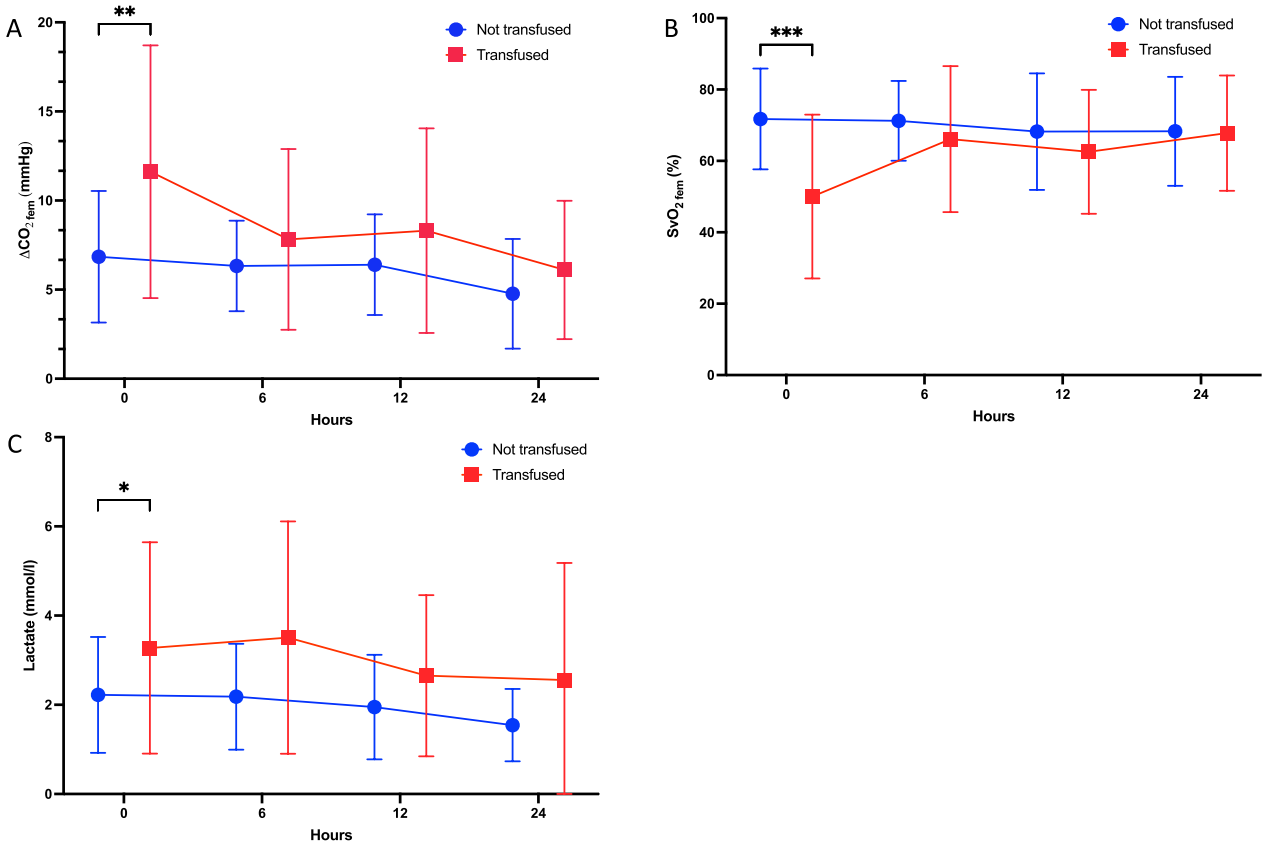

Fig. 2 Evolution during the first 24 h of hemodynamic variables in transfused and non-transfused patients. **A** $\Delta PCO_{2\ fem}$. **B** $SvO_{2\ fem}$ and **C** lactate. All data are reported as mean ± SD. *$P<0.05$; **$P<0.005$; ***$P<0.001$. Parameters were measured at hospital admission and over the first 24 h. $\Delta PCO_{2\ fem}$ femoral venous-arterial difference in carbon dioxide pressure. $SvO_{2\ fem}$ femoral venous oxygen saturation

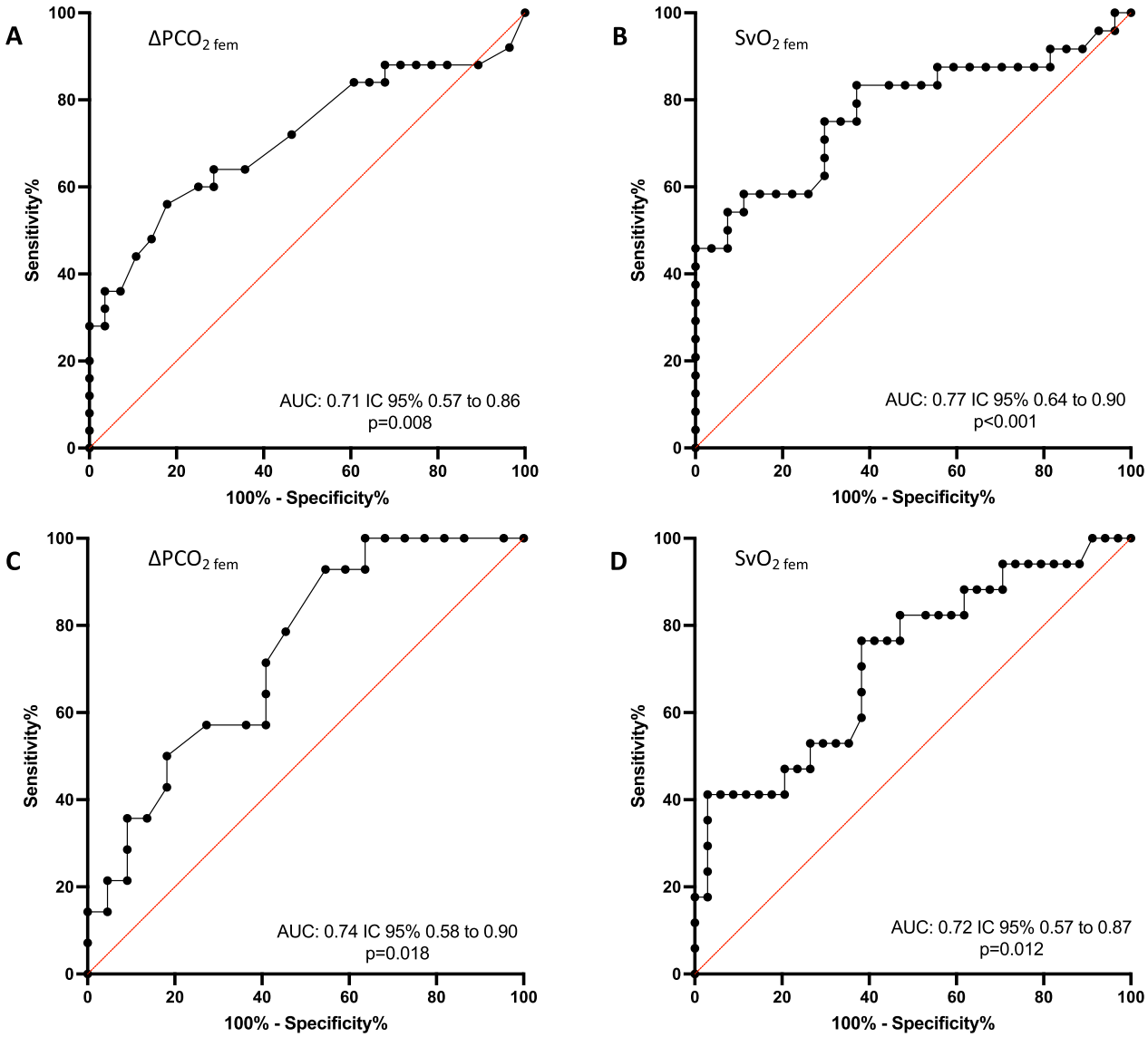

Fig. 3 ROC curves for prediction of RBC transfusion and hemostatic procedure by ΔPCO_{2fem} and SvO_{2fem}. **A** ROC curve for prediction of $pRBC_{H6}$ by $\Delta PCO_{2\,fem}$ at admission. **B** ROC curve for prediction of $pRBC_{H6}$ by $SvO_{2\,fem}$ at admission. **C** ROC curve for prediction of hemostatic procedure during the first 6 h of admission by $\Delta PCO_{2\,fem}$ at admission. **D** ROC curve for prediction of hemostatic procedure during the first 6 h of admission by $SvO_{2\,fem}$ at admission. AUC area under the curve. $\Delta PCO_{2\,fem}$ femoral venous-arterial difference in carbon dioxide pressure. $pRBC_{H6}$ transfusion of at least 1 pack of red blood cell during the first 6 h of admission. ROC Receiver operating characteristics. $SvO_{2\,fem}$ femoral venous oxygen saturation

Table 3 Predictive performances of hemodynamic variables for transfusion of red blood cells during the first six hours of admission

	AUC (95% CI)	*P*	Cutt-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Lactate	0.64 (0.5–0.79)	0.07	1.9 mmol/l	78.6	58.1	62.4	75.3
$\Delta PCO_{2\,fem}$	0.71 (0.57–0.96)	0.008	8.1 mmHg	64	71.4	66.2	68.4
$SvO_{2\,fem}$	0.77 (0.64–0.9)	< 0.001	63%	75	70.4	69.7	75.7

$\Delta PCO_{2\,fem}$ femoral venous-arterial difference in carbon dioxide pressure. $SvO_{2\,fem}$ femoral venous oxygen saturation

NPV negative predictive value. *PPV* positive predictive value of parameters

admission were the optimal values to predict the need for an emergency hemostatic procedure.

Admission blood lactate did not significantly predict the need for $pRBC_{H6}$ transfusion (AUC = 0.64 CI95% 0.49–0.79; $P = 0.07$) or the need for a hemostatic procedure (AUC = 0.60 CI95% 0.42–0.78; $P = 0.3$) in the first six hours of admission.

Discussion

We performed this prospective and observational study to assess the ability of $\Delta PCO_{2\ fem}$, $SvO_{2\ fem}$ and arterial blood lactate to predict transfusion of red blood cells over the first six hours ($pRBC_{H6}$) following severe trauma. We found that the difference in femoral venous to arterial PCO_2 ($\Delta PCO_{2\ fem}$) and venous oxygen saturation ($SvO_{2\ fem}$) at admission were predictive of RBC transfusion within the first six hours of admission, with respective optimal thresholds of 8.1 mmHg and 63%. Second, we also found that $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ were predictive of an emergency hemostatic procedure. Third, though admission blood lactate correlated with the volume of transfused RBC over the first 6 h, it was neither predictive of $pRBC_{H6}$ transfusion nor predictive of an emergency hemostatic procedure. Fourth, $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ normalized earlier than lactate after transfusion.

Relationship with previous studies

Venous to arterial PCO_2 difference and venous O_2 saturation have hardly been studied in the setting of severe trauma. We found that admission $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ were predictive of $pRBC_{H6}$ transfusion. These results are consistent with studies carried out on animal models of hemorrhagic shock [17, 18] where incremental blood loss led to a progressive increase in ΔPCO_2 and decrease in SvO_2. According to Fick equation, generated CO_2 (VCO_2) equals the product of CO by the difference between mixed venous and arterial CO_2 contents ($Cv\text{-}aCO_2$) and is constant in aerobic and anaerobic conditions. ΔPCO_2 has been shown to be linearly related to $Cv\text{-}aCO_2$. Thus, increase in ΔPCO_2 during hemorrhage results from a drop in CO leading to CO_2 stagnation at tissue level with an increase in venous CO_2. During hemorrhage, an increase in ΔPCO_2 thus reflects the inadequacy between CO and metabolic activity. Hemorrhage also results in a decrease in oxygen transport to tissues responsible for an increase in oxygen extraction ratio and therefore a decrease in SvO_2. Thus, increased $\Delta PCO_{2\ fem}$ and decreased $SvO_{2\ fem}$ likely reflect the decrease in tissue blood flow to the lower limbs related to the magnitude of blood loss in trauma patients.

We measured femoral ΔPCO_2 and SvO_2 ($\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$) while most clinical and experimental studies reported about central ΔPCO_2 and $ScvO_2$. Normal central ΔPCO_2 ranges from 2 to 5 mmHg [19]. In a study conducted in 14 healthy volunteers, $\Delta PCO_{2\ fem}$ ranged from 2 to 4 mmHg while volunteers were passively cycling [20]. Several studies reported conflicting differences between $ScvO_2$ and $SvO_{2\ fem}$ with bias of $2.7 \pm 7.9\%$ in patients undergoing elective right heart catheterization [21] to bias of 2 to 8% in critical care patients [22, 23]. However, though $SvO_{2\ fem}$ is not a reliable surrogate of $ScvO_2$, we found it to be more predictive of $pRBC_{H6}$ transfusion than admission $\Delta PCO_{2\ fem}$ or blood lactate.

Although there is a significant correlation between blood lactate, $\Delta PCO_{2\ fem}$, $SvO_{2\ fem}$, these measurements are not interchangeable. Unlike what Régnier et al. reported, admission lactate was not found as a predictive marker of $pRBC_{H6}$ transfusion [5]. However, we used a lower threshold (one $pRBC_{H6}$ as compared to massive transfusion defined by 6 pack of RBC in 24 h). $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ appeared thus to be more sensitive than blood lactate to predict hemorrhage requiring RBC transfusion. A hypothesis is that these two parameters are a direct reflection of tissue blood flow to the lower limbs while aerobic metabolism is still present [24], whereas blood lactate increases at a later stage of hemorrhage, when patient blood loss is more pronounced with concomitant triggering of anaerobic metabolism [6, 25]. Consistently with what has been shown in animals [6], following an active hemorrhage, it would seem that the drop in CO, responsible for peripheral vasoconstriction and a drop in blood flow to the lower limbs can be more rapidly detected by an elevation of $\Delta PCO_{2\ fem}$ and a decrease of $SvO_{2\ fem}$ than using blood lactate level. Blood flow is indeed early reduced in musculo-cutaneous tissue (i.e. lower limbs) to preserve flow to the noble organs (i.e. heart, brain) [26], which may explain the early increase in $\Delta PCO_{2\ fem}$ and decrease in SvO_{2fem}.

It is interesting to note that patients did not present with the same injuries in the two groups. The transfused group presented mainly abdominal and pelvic injuries, more often responsible for hemorrhage, while the non-transfused group presented mainly intracranial injuries. Although mean $\Delta PCO_{2\ fem}$ was higher in the transfused group compared to the non-transfused group (11.6 vs. 6.8 mmHg), some patients had a high $\Delta PCO_{2\ fem}$ in the non-transfused group. These patients presented a severe head injury with an AIS head greater than 3, or had bowel perforation without hemorrhage and others had severe thoracic injuries with a hemo- or pneumothorax. In patients with no clinical or CT evidence of hemorrhage, the presence of a high $\Delta PCO_{2\ fem}$ should therefore lead to the search for another cause of cardiovascular dysfunction. Severely injured trauma patients can indeed present causes of shock other than hemorrhage like tamponade, peritonitis associated with bowel perforation, spinal cord

injury but also neurogenic cardiovascular dysfunction reported in several studies in patients with severe head injury [27].

Consistent with what has been observed in animals, $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ corrected more rapidly than lactate, which increased until H6 in the transfused group [25]. $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ are likely corrected in parallel with the improvement of tissue blood flow following transfusion, whereas hyperlactatemia is an unreliable marker of hypoxia and hypoperfusion. Indeed, lactate production is also a consequence of cellular dysoxia secondary to injury-induced inflammation and microcirculation alterations, frequently observed after severe trauma, despite tissue perfusion improvement [28]. Unrelated to tissue dysoxia, hyperlactatemia is also frequently observed in shock state, following aerobic glycolysis activation through catecholamine-dependent ß2-receptor stimulation [29].

Implication of study findings

Our findings imply that $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ are more sensitive than blood lactate to predict the need for early blood transfusion or hemostatic procedure, on admission of severe trauma patients. Seven patients (25%) who were transfused with RBC during the first six hours of management had indeed a high $\Delta PCO_{2\ fem}$ and/or a low $SvO_{2\ fem}$ but a normal blood lactate. Moreover, the evolution of $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ over time may help to assess transfusion effectiveness to restore adequate tissue perfusion. Cardiac output monitoring using standard tools such as cardiac ultrasound or thermodilution are not available in the trauma bay during the initial phase, and macro-hemodynamic parameters such as heart rate and mean blood pressure are poorly correlated with CO during hemorrhagic shock states. Thus, in this study, we showed that $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ could be easily used to assess the adequation of tissue blood flow (i.e. to the lower limbs) with metabolic needs following severe trauma.

Strengths and limitations

This study has several strengths. To our knowledge, this is the first study evaluating ΔPCO_2 and $SvO_{2\ fem}$ in severe trauma patients and their capacities to predict early transfusion. Moreover, we provided new data on the level of $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ values in such patients. These results allowed us to propose alternative markers to assess the adequacy between tissue blood flow and metabolic needs in trauma patients.

This study also has several limitations. First, it is a single-centre study with a small sample-size, in patients who required the insertion of an arterial and a venous catheter at the femoral site which prevents generalization of these results. Indeed, only patients which ICU clinician judged, severe at hospital admission [13], were included which make this study applicable only to these patients. Second, we studied ΔPCO_2 and SvO_2 at the femoral site which are not good surrogates of central ΔPCO_2 and $ScvO_2$, considered as standards. However, we were able to report cut-off values for these markers at femoral site for transfusion prediction. Third we do not know the normal values for $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ at baseline but we highlighted significant differences in $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ according to the need for transfusion, reflecting the hemorrhage-induced drop in tissue blood flow and allowing to assess resuscitation efficacy over time. Nevertheless, additional studies will be necessary to determine the range of normal value of $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ at the femoral level. Finally, since SvO_2 is dependent on hemoglobin, its predictive value for red blood cell transfusion may have been overestimated by the effect of anemia in patients with severe hemorrage [30]. Moreover, due to the Haldane effect, it is possible that in the most severe patients with low hemoglobin level and significant metabolic acidosis, the $\Delta PCO_{2\ fem}$ may have been overestimated compared to veno-arterial CO_2 content ($Cv\text{-}aCO_2$). Indeed, for the same level of $Cv\text{-}aCO_2$, ΔPCO_2 increases in case of metabolic acidosis and anemia [31] making the relationship between the two values no longer linear. This was however observed at the late phase of hemorrhage, when bloodloss was major [17] and, in a way, reflect the seriousness of hemorrhage which is consistent with what we expected to predict.

Conclusion

In severe trauma patients, ΔPCO_2 and SvO_2 measured at the femoral level at admission were predictive for the need of RBC transfusion and hemostatic procedures during the first six hours of management while admission lactate was not. In this study, $\Delta PCO_{2\ fem}$ and $SvO_{2\ fem}$ appear thus to be more sensitive to blood loss than lactate in patients requiring femoral venous and arterial catheters insertion, which might be of importance to assess the adequation of tissue blood flow with metabolic needs following severe trauma.

Abbreviations

ΔPCO_2	Veno-arterial carbon dioxide tension difference
$\Delta PCO_{2\ fem}$	Femoral veno-arterial carbon dioxide tension difference
AIS	Abbreviated Injury Scale 2015
CO	Cardiac output
GCS	Glasgow Coma Scale
Hb	Hemoglobin
HR	Heart rate
Ht	Hematocrit
ICU	Intensive care unit
ISS	Injury severity score
MBP	Mean blood pressure

$PaCO_2$	Arterial carbon dioxide partial pressure
PaO_2	Arterial oxygen partial pressure (PaO_2)
$pRBC_{H6}$	Pack of red blood cell transfused over the first 6 h of admission
$PvCO_2$	Venous carbon dioxide partial pressure
PT	Prothrombin time
RBC	Red blood cells
ROC	Receiver operating characteristics
SAPS	Simplified Acute Physiology Score
SD	Standard deviation
SBP	Systolic blood pressure
SaO_2	Arterial oxygen saturation
SpO_2	Pulse oximeter oxygen saturation
SvO_2	Venous oxygen saturation
$SvO_{2\ fem}$	Femoral venous oxygen saturation

Supplementary Information

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Additional file 1. Flow-chart of study participants.

Additional file 2. Evolution of $\Delta PCO_{2\ fem}$, $SvO_{2\ fem}$ and lactate during the first 24 hours in the overall population. All data are reported as mean ± SD. Parameters were measured at hospital admission and over the first 24 hours. $\Delta PCO_{2\ fem}$ femoral venous-arterial difference in carbon dioxide pressure. $SvO_{2\ fem}$ femoral venous oxygen saturation.

Additional file 3. Evolution of blood gas parameters during the 24 first hours of admission. Data are shown in the overall population in non-transfused and transfused patients. All data are reported as mean ± SD. Art pH arterial pH. H0 measurement at admission. H_6 measurement 6 hours after admission. H12 measurement 12 hours after admission. H_24 measurement 24 hours after admission. ΔPCO_2 fem femoral venous-arterial difference in carbon dioxide pressure. SvO_2 fem femoral venous oxygen saturation.

Additional file 4. ROC curves for prediction of red blood cell transfusion and hemostatic procedure by lactate. **a** ROC curve for prediction of pRBCH6 by lactate at admission. **b** ROC curve for prediction of hemostatic procedure during the first 6 hours of admission by lactate at admission. AUC area under the curve. pRBCH6 transfusion of at least 1 pack of red blood cell during the first 6 hours of admission. ROC Receiver operating characteristics.

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Author contributions
MW, BV and AH concepted and designed the study. MW performed the statistical data analysis, designed the figures and wrote the manuscript. MW and AH interpreted the data. AH revised the article critically. All authors were involved in collection of data, revised the article for important intellectual content and approved the version to be published.

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Declarations

Ethic approval and consent to participate
This study was approved by the ethics committee ("Comité de Protection des Personnes") of the hospital (SC13-014 RCB: 2013-A01171-44) with waiver of participant consent. Patients or relatives were informed and we obtained confirmation of non-objection to data use.

Consent for publication
All authors read and approved the manuscript for publication.

Competing interests
The authors declare that they have no competing interests.

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