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Could exhaled methane be used as a possible indicator for hemodynamic changes in trauma induced hemorrhagic shock? Scientific basis supported by a case study

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A B S T R A C T

Introduction: Identification of severe blood loss and hemorrhagic shock in polytrauma patients poses a key challenge for trauma teams across the world, as there are just a few objective parameters, on which clinicians can rely. We investigated the relationship between exhaled air methane (CH_4) concentration and blood loss in a polytrauma patient. Decreased blood flow in the superior mesenteric artery (SMA) is one of the first compensatory responses to blood loss. Gases produced by the anaerobic flora of the intestinal segment supplied by the SMA are the primary source of exhaled CH_4, which diffuses through the intestinal microvessels into the circulation and is finally eliminated through the lungs. We hypothesized that diminution of exhaled CH_4 indicates blood loss and tested our theory in a severely injured patient.

Methods: Exhaled CH_4 concentrations of a severely injured patient were measured using a photoacoustic spectroscope (PAS) attached to the exhalation side of the breathing circuit. The primary objective was to investigate the relationship between exhaled CH_4 and conventional indicators of hemorrhage including hemoglobin (Hb) levels, base deficit (BD) values and vital parameters (heart rate and systolic blood pressure) in the early phase of in-hospital care (first 4 h).

Results: A severely injured patient was admitted with unstable hemodynamic parameters and incomplete left lower limb amputation, (Injury Severity Score: 38, 74/36 mmHg, 76 bpm). At the time of arrival, considerably lower CH_4 levels were detected (22,800 PAU) in the exhaled air. During the first 4 h fluid and massive blood resuscitation, the exhaled CH_4 levels were continuously rising in parallel with Htc and Hb values. Corresponding to these changes, BD values displayed a decreasing tendency.

Discussion: Our study was conducted to characterize the changes in exhaled air CH_4 concentration in response to hemorrhagic shock and to provide data on a viable clinical use of an experimental technique. According to our results, the real-time detection of exhaled air CH_4 concentration is an applicable and promising technique for the early detection of bleeding and hemorrhagic shock in severely injured patients. Further research on large sample size and refinement of the PAS technique is required.

Introduction

Hemorrhage is responsible for the majority of potentially preventable mortality in trauma patients [1].Hemorrhagic shock (HS) is often challenging to manage, in many cases due to trauma-induced coagulopathy (TIC), a common accompaniment of HS that may result in death even in case of successful mechanical control of bleeding sites [2–5]. Thus, the best approach to HS and TIC is prevention by early detection and adequate treatment of internal bleeding. Nevertheless, in the lack of promptly accessible, highly sensitive and specific diagnostic

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tools, the late recognition of occult hemorrhage often leads to unfavorable outcomes. To date, the routine hemodynamic assessment of trauma patients relies principally on vital signs (VS) such as heart rate (HR) and blood pressure (BP), laboratory markers including hemoglobin (Hb) and hematocrit (Htc), and blood gas parameters such as base deficit (BD) and lactate [6,7]. However, the reliability of these parameters is a matter of controversy since they may be affected by many factors that are not associated with bleeding, such as age, gender, comorbidities, and hemodilution due to fluid resuscitation and refilling from the interstitium [7–14]. In addition to the difficulties of the detection of impending HS, the prompt evaluation of the patient's response to fluid loading is also challenging. Vital signs alone are suboptimal in guiding resuscitation [5,15,16]. Although increasing urinary output is a reasonably sensitive marker of improving circulatory status, underlying kidney injury, hyperglycemia, or diuretic agents can limit its reliability; furthermore, catheterization is not always a promptly feasible option [6]. Laboratory and blood gas parameters cannot be monitored continuously, thus serial measurements are needed. Invasive monitoring methods such as pulmonary artery catheterization offer reasonable benefits; however, they are hardly applicable directly upon admission due to patient positioning and time factor [17,18]. Therefore, the ascertainment of the patient's response to fluid resuscitation is often time consuming.

In case of hemorrhage, the centralization of circulation is initiated prior to the derangements of conventional markers of blood loss such as BP, BD and Hb. Thus, being able to detect early circulatory redistribution would reduce the time needed to diagnose occult bleeding [19]. The diminution of mesenteric perfusion is one of the earliest responses to blood loss. The particular sensitivity of intestinal perfusion has been demonstrated by studies on large animal models, where the superior mesenteric artery (SMA) flow displayed a significant drop already at 5 % loss of total blood volume [20]. Several direct methods for detecting microcirculation are known to be in use, [21] however they do not seem to be applicable while examining the small intestinal tissue in humans. Although reliable noninvasive methods for the bedside monitoring of intestinal perfusion have not been elaborated to date, recent animal experiments suggest that methane (CH_4) concentration of the exhaled air corresponds to the SMA blood flow [20,22,23]; moreover, it follows hemodynamic changes during fluid resuscitation.

Methane is the smallest hydrocarbon molecule known as a biologically inert gas, produced in humans exclusively by methanogenic Archaea as part of the small intestinal microbiome. Once produced, CH_4 is either simply eliminated with intestinal gases or absorbed into the small intestinal microvessels, then transported into the bloodstream and excreted in unchanged form through the alveoli of the lung. A rapid change in CH_4 excretion concomitant with blood loss has been demonstrated in a porcine model of haemorrhagic shock, but has not yet been studied in humans [20].

Based on these findings, our research team hypothesized that the amount of exhaled CH_4 varies proportionally with the rate of blood loss in humans due to redistribution of the intestinal circulation, and thus may be suitable for monitoring the rate of blood loss [19]. To investigate this, we have initiated a prospective observational clinical trial, of which this comprehensively documented case report is part [23]. Our aim is to examine the changes in exhaled CH_4 concentration during continuous monitoring of a severely injured bleeding trauma patient for 4 h. We further aim to investigate the suitability of exhaled CH_4 concentration for monitoring blood loss by comparison with conventional markers of blood loss.

Methods

Case presentation

Patient information and prehospital care

A 45-year-old caucasian male motorcyclist was transported to the Emergency Department of the University of Szeged, Hungary, by helicopter-based emergency medical services (HEMS), following a frontal collision with a car in October 2021.The motorcyclist suffered multiple injuries including the incomplete amputation of the left lower limb at the femoral level. The arriving HEMS detected profound bleeding with hemodynamic instability and a Glasgow Coma Scale (GCS) score of 3 at the scene. Intravenous crystalloid solution (2500 ml Isolyte solution), epinephrine (9×1 mg), tranexamic acid (1 g), and fibrinogen (2 g) were administered, endotracheal intubation and bilateral thoracostomy was perfomed and a tourniquet was placed on the bleeding left leg just above the level of the incomplete femoral amputation.

Diagnostic assessment

The patient reached our trauma center at 10 AM, with a BP of 74/36 mmHg, HR of 76 beats per minute (bpm), and he was taken over by the trauma team on duty. Close hemodynamic monitoring, and continuous norepinephrine infusion were initiated, and chest tubes were placed into the pleural space through the thoracostomy openings on both sides. Based on the ATLS hemorrhage classification the patient was treated for a Class IV (Severe) hemorrhage, so the massive blood transfusion (MBT) protocol was applied. The initial focused assessment with sonography for trauma (FAST) was negative. Whole-body computed tomography (CT) revealed a small pneumothorax ($\leq$20 mm) on both sides; non-displaced fracture of the body of the CII. cervical vertebra; subcutaneous hematoma in the inguinal region; dislocated, comminuted, closed fracture in the distal third of the left humerus shaft; and confirmed the subtotal amputation of the left lower limb at the border of the proximal and medial thirds of the femur. Signs of intracranial bleeding, hemothorax, hemopericardium, free intraperitoneal fluid or air were not detected. The list of injuries sustained by the patient is demonstrated in Table 1.

Alongside the routine blood tests, new type modified viscoelastic ClotPro coagulation tests (enicor GmbH, Munich, Germany; Haemonetics Corporation) were performed to assess TIC and to guide MBT. ClotPro tests are based on the principle of rotational thromboelastometry. EX-Test and FIB-Test clotting times and clot formation time in FIB-Test (CFT) were significantly prolonged and maximum clot firmness (MCF) was significantly reduced in both tests, showing the presence of severe TIC.

In-hospital therapeutic interventions

Following the patient's arrival at the emergency department the trauma team started the initial fluid resuscitation with the administration of 1000 ml Gelofusine, 500 ml Ringer's lactate and 1000 ml Isolyte solution. MBT was started parallel, which was controlled with POCT blood gas and laboratory tests and viscoelastic measurements. The initial Hb was less then 4 g/dl, the Htc 11.8 %, and BD 20.8 mmol/l. As MBT 6 units of pRBC, 6 units FFP and 6 units platelets were administered on account of balanced resuscitation. To aid the MBT 3 g fibrinogen and 1000 IU prothrombin complex concentrate was given. To avoid hypotension, epinephrine was administered continuously. The torniquet was released every 60–70 min for 10–15 min periods while steady pressure was applied with sterile dressing. The surgical completion of the amputation of the left leg was performed in the trauma operating room, and the patient was relocated to the intensive care unit (ICU).

Follow-up and patient outcomes

Under ongoing massive transfusion protocol (8 units pRBC, 8 units FFP and 8 units platelet) and vasopressor administration, the patient's circulatory status showed improvements, Hb became normalized, and BD displayed decreasing tendency. After hours of temporary hemodynamic stability, deteriorating circulatory and neurological status were detected at 7 PM, anisocoria occurred, then the patient's pupils became maximally dilated and unresponsive to light. Free intraperitoneal fluid could not be depicted with abdominal sonography thus a whole-body CT

Table 1
Sustained injuries and their severity.

	Minor	Moderate	Serious	Severe	Critical	Untreatable
Head and neck		X				
- nondisplaced fracture of the body of the II. cervical vertebra						
Face	X					
- facial contusions						
Chest	X					
- small pneumothorax on both sides ≤20mm						
Abdomen and pelvic organs	X					
- subcutaneous hematoma in the left inguinal region (25 mm)						
Extremities and pelvic girdle						X
- subtotal amputation of the left lower limb at the border of the proximal and medial thirds of the femur, with severe hemorrhage resulting in untreatable TIC						
- dislocated, comminuted, closed fracture in the distal third of the left humerus shaft						
External		X				
- extensive skin lacerations on the back affecting 5 % of the body surface						

Injuries of a 45-year-old motorcyclist after frontal collision with a car. Although only minor and moderate injuries occurred in the regions of the neck, face, chest, abdomen and external region; the left lower limb was immensely damaged, resulting in profound blood loss, hemorrhagic shock, and trauma-induced coagulopathy (TIC).

was performed to assess intracranial status and potential sources of bleeding. Computer tomography showed bilateral pleural effusion with a maximal width of 4 cm, perihepatic fluid with a maximal width of 2 cm, and free fluid in the pelvis, all equaling the density of blood. Intracranially, diffuse cerebral oedema and tonsillar herniation were depicted. At that time, brainstem reflexes were absent, thus the physical and radiological findings were consistent. The patient went into cardiac arrest, and he was declared dead at 10:42 PM.

Measurement of exhaled CH_4 levels

In addition to conventional diagnostic tools (VS, laboratory tests, blood gas analyses, sonography, CT imaging) exhaled CH_4 concentrations of the patient were measured continuously during the first 4 h of resuscitation. A near-infrared laser technique-based photoacoustic spectroscopy (PAS) apparatus was attached to the exhalation outlet of the ventilator, thereby allowing the continuous monitoring of exhaled CH_4 [24]. Photoacoustic spectroscopy is a subclass of optical absorption spectroscopy measuring optical absorption indirectly through the conversion of absorbed light energy into acoustic waves due to the thermal expansion of absorbing gas samples. The amplitude of the generated sound is directly proportional to the concentration of the absorbing gas component. The gas sample passes through the photoacoustic cell generating a photoacoustic signal, which is detected by a microphone [25]. The CH_4 concentration of the background air was measured with the same technique.

Outcomes and statistical analyses

Our goal was to disclose if concentrations of CH_4 in the exhaled air could reflect the changes in the circulatory status of the patient. For this purpose, we investigated the relation between exhaled CH_4 and conventional indicators of hemorrhage including Hb and BD in the early phase of in-hospital care (first 4 h). The above-mentioned parameters were designated as outcomes based on their ability to indicate blood loss, and they were recorded every 20 min in the first 4 h. Hemoglobin is one of the most widely used markers of blood loss and it is the most emphasized objective guide for transfusion protocols [12,26–28]. Regarding BD, the current ATLS guidance on HS highlights its importance by associating explicit BD values with explicit percentages of blood loss, whilst the alterations of VS are only described subjectively, without quantification [6].

In this study, we presumed linear association between exhaled CH_4 levels and Hb and BD (respectively) for our hypothesis. Scatter plots were constructed, and Pearson's correlation analyses (r) were performed with SPSS 25.0 (IBM Corporation, Chicago, IL, USA). P-values $P < 0.05$ were considered as statistically significant.

Results

Hemorrhage control and MBT resulted in normalized Hb values and decreasing tendency in BD. In line with these findings, exhaled CH_4 levels displayed an increasing trend. The initial Hb was less then 4 g/dl, BD was 20.8 mmol/l and the exhaled CH_4 concentration was 22,800 PAU (2840 PAU equals 1 ppm, background methane levels is about 1912 ppb). At the end of the first 4 h Hb increased to 13 g/dl, CH_4 concentration to 31,800 PAU and BD decreased to 8.5 mmol/l. Hb and BD are presented together with exhaled CH_4 concentrations in Table 2. Fig. 1 demonstrates the changes in the investigated parameters to the given blood transfusion and in result of that, the simultaneous increase of Hb and continuously rising exhaled CH_4 concentration, The study found significant correlation between the changes in Htc and CH_4 concentration, Hb and CH_4 concentration and in BD and CH_4 concentration. Fig. 2 shows the correlation of Hb (A), Hct (B), and BD (C) with exhaled CH_4 levels. $EtCO_2$ levels were registered ranging from 27 to 40 mmHg, these values show the lack of significant ventilatory impairment that could influence exhaled CH_4 concentrations.

Discussion

Although the link of breath composition to gastrointestinal pathologies such as peptic ulcer disease or lactose intolerance is already well known and utilized in clinical practice [29,30], using breath analysis as a hemodynamic monitoring tool is a completely new approach which recognizes the relationship between components of exhaled gas, mesenteric perfusion, and systemic circulatory status. In other words, our hypothesis is based on the realization that mesenteric perfusion is a sensitive indicator of the circulatory status and a significant influencer

Table 2
Indicators of blood loss, end-tidal carbon-dioxide levels and exhaled methane concentrations in the first 4 in-hospital hours.

Time	Hb (g/dl)	BD (mmol/L)	Exhaled CH_4 (PAU)
10:00	4.1	20.8	22,800
10:20	5.2	22.1	22,412
10:40	6.0	20.8	19,808
11:00	9.5	20.3	23,184
11:20	8.3	10.9	25,341
11:40	7.2	14.9	22,405
12:00	8.7	12.0	25,900
12:20	9.5	10.8	26,829
12:40	12.3	9.7	29,779
13:00	12.4	8.8	28,400
13:20	11.0	7.6	28,956
13:40	12.5	10.9	28,220
14:00	13.0	8.5	31,800

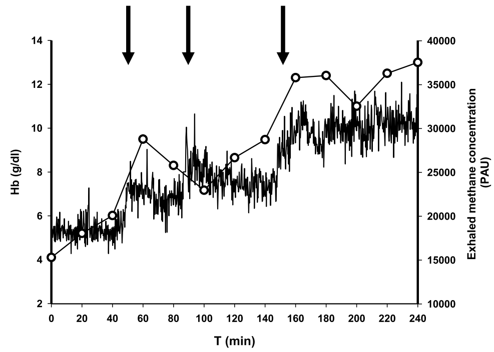

Fig. 1. Representative photoacoustic spectroscopy (PAS) record of the severely injured patient. The arrows indicate administrations of 2 units of pRBCs. Each transfusion is followed by an increase of exhaled CH_4.

of breath composition at the same time. Although the potential of breath analysis for monitoring mesenteric perfusion is still elusive, attempts have been made to identify volatile markers that correspond to intestinal blood flow. Of these, CH_4 may be the most promising one. CH_4 is an intrinsically non-toxic, combustible gas [31,32] originating mainly from anaerobic methanogenic intestinal microorganisms in the human gut [33]. Due to its physicochemical properties, it can enter freely to the mesenteric and systemic circulation, and as a gas with low solubility in blood, it becomes rapidly excreted by the lungs [34]. The significance of this for trauma surgeons lies in the following: blood loss due to hemorrhage initiates circulatory redistribution through various mechanisms such as the baroreceptor reflex, sympathetic activation, release of catecholamines, and mobilization of blood from venous reservoirs. Mesenteric perfusion diminishes rapidly, causing a prompt decrease in the activity of methanogenic gut bacteria, resulting in lowered CH_4 production, which can easily be identified and monitored in breath. Supporting this, a recent study on large animal model (Vietnamese minipigs, $n = 6$) found that exhaled CH_4 levels correspond to ileal microcirculation and the blood flow of the SMA which displayed a significant drop already at 5 % loss of total blood volume and continued to diminish in line with ongoing hemorrhage [20,34]. Consequently, CH_4 may carry substantial benefits for clinicians in the initial hemodynamic assessment and monitoring of patients with bleeding, especially in case of occult hemorrhage. In contrast to conventional markers such as Hb and BD, serial measurements are not needed since real-time monitoring is feasible with a near-infrared laser technique-based PAS apparatus. In comparison with monitoring delta-pulse pressure, measuring exhaled CH_4 does not require an arterial line and intubation, it is completely non-invasive and it can be performed on people of all ages and conditions without posing a risk to the patients. Nevertheless, there are limitations that need to be discussed. Although CH_4 measurements can also be performed in the prehospital setting, baseline CH_4 values can hardly be obtained. Thus, the benefit of the method lies in dynamic, constant monitoring instead of detection of static values at a given time. Additionally, CH_4 production may be affected by several factors including alcohol consumption and differences in gut microbiome. In trauma patients, thoracal injuries and their influence on respiration may further complicate the issue. Nonetheless, our current knowledge is limited to animal experiments. Although the porcine cardiovascular system closely resembles human anatomy and physiology [35], it is important to note that the intestinal vascular anatomy of pigs is considerably different [36]. Thus, human studies are essential to clarify the relevance and feasibility of this method in clinical practice.

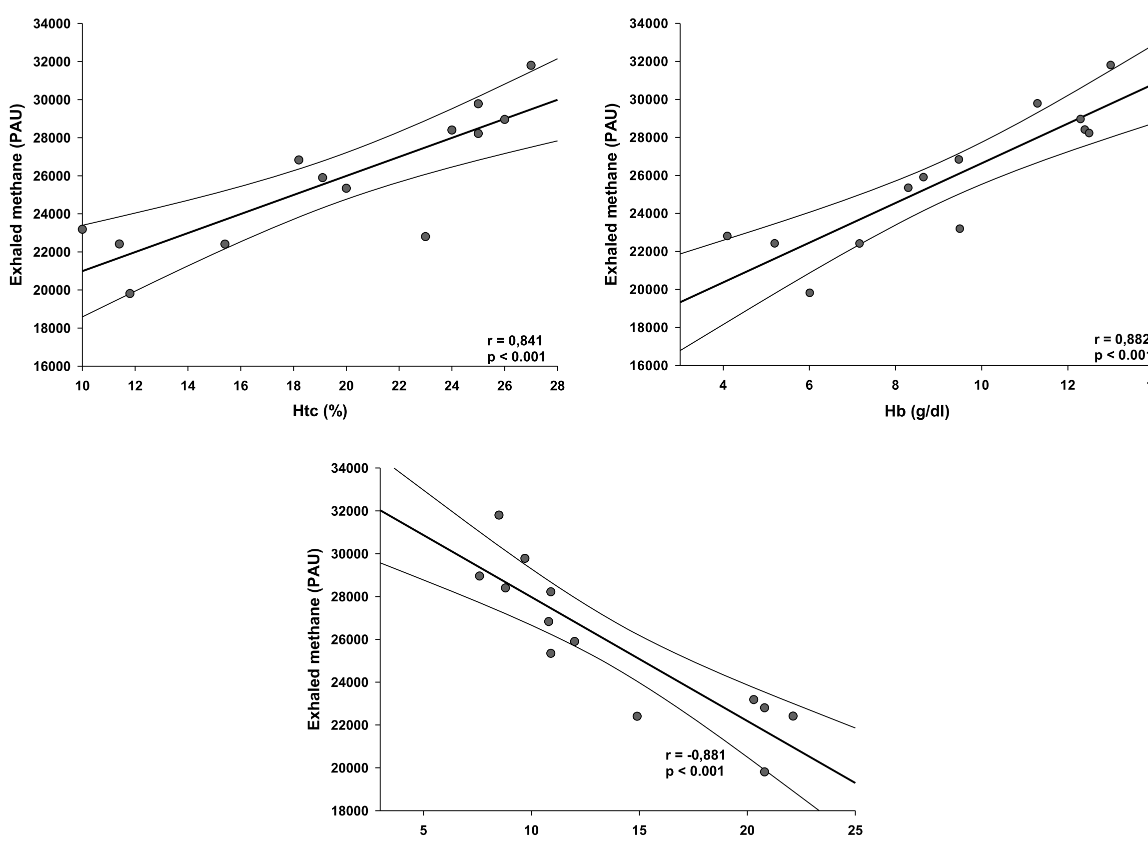

Fig. 2. Association between Htc values, Hb levels, BD levels and exhaled CH_4 concentrations of the severely injured patient. Black scatters show individual data. The plots demonstrates regression lines (straight black line) and the corresponding r values as an indicator of the strength of linear associations, and the p values of significance.

Our present study investigated associations between exhaled CH_4 concentrations and conventional indicators of hemorrhage via presenting a case of a severely injured patient. In the first 4 h of in-hospital care, CH_4 levels in breath displayed significant association with Htc, Hb and BD values. We also saw in the registered graph that CH_4 concentration changes were immediate to given blood supplements.

PAS CH_4 analysis may be a suitable method for the initial assessment of blood loss and continuous monitoring, which could be utilized in emergency and trauma care. However, further research is needed to confirm this statement. In our trauma center, a prospective observational study investigating the clinical value of measuring exhaled CH_4 concentrations in trauma patients is already in progress (ClinicalTrials.gov identifier: NCT04987411) [23] .

Conclusion

In conclusion, alterations in CH_4 concentration in breath may promptly indicate internal bleeding and allow the real-time, indirect monitoring of intestinal perfusion during resuscitation. Thus, monitoring exhaled CH_4 levels may serve as a useful adjunct to the initial hemodynamic assessment of trauma patients with potential hemorrhage; however, further human studies are needed.

CRediT authorship contribution statement

Péter Jávor: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Tibor Donka:** Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Hanne Sofie Solli:** Formal analysis. **Lilla Sándor:** Formal analysis, Investigation, Project administration, Visualization. **Bálint Baráth:** Formal analysis, Investigation, Visualization. **Domonkos Perényi:** Formal analysis, Investigation. **Árpád Mohácsi:** Methodology, Project administration, Software, Validation. **László Török:** Resources, Supervision, Validation. **Petra Hartmann:** Conceptualization, Data curation, Formal analysis, Methodology, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.injury.2024.111456.

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