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Changes of coagulation parameters during high altitude expedition

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Summary

Principles: Data on changes of haemostatic parameters at altitudes above 5000 m are very limited. So far it is unknown, whether altered coagulation could contribute to the development of acute mountain sickness.

Methods: Thirty four healthy mountaineers were randomised to two acclimatisation protocols and undertook an expedition on Muztagh Ata (7549 m) in China. Tests were performed at five altitudes up to 6865 m. Haemostatic parameters, such as PT, aPTT, D-Dimer, APC-Resistance (APCR), von Willebrand Factor activity (RCo), ADAMTS-13 & C-Natriuretic Peptide (CNP) were assessed together with Lake Louise AMS score.

Results: D-Dimer significantly increased with increasing altitude (median 0.62 to 0.81 µg/L, p <0.0001). During ascent, PT increased (83% to >100%) and APCR decreased significantly from 0.95 to 0.8 (p <0.01). Furthermore, a significant increase of aPTT (38 to 43 sec) was paralleled by significant changes of RCo (102% to 62%) (both p <0.001). There were no significant changes in ADAMTS-13 and CNP. No significant relationship between investigated parameters and AMS scores could be detected. When comparing the participants of the two acclimatisation protocols, there was an overall higher RCo in patients with a faster ascent protocol (p = 0.04). This was accompanied by lower ADAMTS-13 of the coagulation system in these patients (p = 0.04).

Conclusions: Coagulation parameters change significantly during hypobaric hypoxia. Whereas we could detect no association between AMS scores and coagulation parameters, our results do show some parameters to be associated with an acclimatisation protocol and a successful ascent to the summit.

Key words: coagulation; high altitude expedition; ADAMTS-13; von Willebrandt factor; APC-R.

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Introduction

Ascending to a high altitude greater than 8000 feet (2500 m) above sea level is associated with acute mountain sickness (AMS) and more severe conditions such as high altitude cerebral oedema (HACE) and high altitude pulmonary oedema (HAPE). AMS itself is characterised by headache, anorexia, nausea, insomnia and malaise [1, 2].

The prevalence of AMS depends on the rate of ascent, the altitude reached and individual susceptibility [3]. For the diagnosis of AMS the Lake Louise Scoring Consensus Committee has defined the acute mountain sickness score which can be obtained with a questionnaire [4].

To date the detailed pathophysiological mechanisms of AMS, HAPE and HACE are not known. However it is known that hypobaric hypoxia

causes over perfusion of microvascular beds, elevated pulmonary capillary pressure and capillary leakage [5, 6]. Whether capillary leakage results from increased shear stress or is due to reactive oxygen species (ROS) or other as yet unknown mechanisms is subject of further investigation.

In some way all these reactions to hypobaric hypoxia indicate a critical change of interactions within the vascular system. Several of the case reports of venous thromboembolism in high altitude mountaineers triggered scientific interest on clarifying the role of coagulation in high altitude illness [7]. Further, some studies showing evidence of procoagulatory activity under hypobaric hypoxia have been published [8, 9]. Singh and Chohan found increased plasma fibrinogen, platelet adhesiveness, platelet factor 3, factor V, factor VIII in subjects who developed high altitude pulmonary hypertension [10]. Later P. Bärtsch et al. could show that increased fibrinolytic activity did not proceed to HAPE, even though they found an association with procoagulant activity [11]. Andrew et al published data on coagulation following prolonged decompression in a large hypobaric chamber. They found that chronic hypoxia did not affect coagulation factors, whereas factor VIII increased under exercise at all investigated atmospheric pressures [12].

With this present study we aimed to define the role of the coagulation system, von Willebrand Factor (vWF)-System and the vWF-cleaving protease (ADAMTS13) in acclimatisation as these factors have been shown to be involved in microthrombus formation and vessel wall alterations [13, 14]. VWF is synthesized exclusively by endothelial cells and megacaryocytes. It has further been shown that increased concentrations of vWF occur in different vascular diseases such as cerebrovascular diseases, peripheral and pulmonal vascular diseases [15].

ADAMTS13, a member of the ADAMTS family of metalloproteases, is known to be involved in microvascular diseases such as thrombotic thrombocytopenic purpura (TTP) [16]. VWF is cleaved under shear stress by ADAMTS13 [17]. Shear stress is also seen as a possible factor leading to vessel alteration with consequent capillary leakage and oedema. Finally, it could be demonstrated that oxygen desaturation correlates significantly with multimeric abnormalities of vWF in patients with secondary pulmonary oedema. This is mostly due to loss of larger vWF multimers [18]. To date, however not much is known about coagulation changes during ascent to high altitudes, and whether changes in the coagulation system could be associated with severity of acute mountain sickness scores. We therefore investigated changes in the coagulation system during a research expedition on Mount Muztagh Ata.

Materials and methods

Course of expedition and subjects

This study was a project of the 2005 Swiss Research Expedition on Mount Muztagh Ata (7549 m/24729 ft above sea level) in Western China that took place from 14 June to 8 July 2005. The research expedition was a joint research enterprise with other groups investigating a) the effect of high altitude related hypoxia on cerebral function; b) ventilation, sleep and daytime performance at extreme altitude; and c) pathogenesis of high altitude retinopathy during a high altitude expedition. Our group focused on renal function, [19] coagulation parameters, inflammation and cardiac adaptation to high altitude.

Volunteers were recruited for study inclusion in Swiss newspapers. Inclusion criteria were previous trekking experience and previous sojourns at high altitude. Subjects were excluded when there was evidence of any type of cardiac or respiratory disease or regular intake of any medication. Subjects with a history of high altitude pulmonary oedema, severe acute mountain sickness at altitudes below 3500 m or high altitude cerebral oedema were also included. Thirty four healthy mountaineers participated and gave written informed consent. All of the participants were lowland residents (400–500 m/1310–1638 ft above sea level). The mountaineers were randomised into two groups with different ascent protocols (group 1: 9 days for acclimatisation at altitudes between 3750 to 5533 m; group 2: 13 days for acclimatisation at altitudes between 3750 to 5533 m) to explore a possible role of acclimatisation. The expedition had its base camp at 4497 m / 14731ft above sea level. Further milestones of the expedition were at 5533 m / 18125 ft (camp 1), at 6265 m / 20523 ft (camp 2), at 6865 m / 22488 ft (camp 3) and at 7546 m/24719 ft (Muztagh Ata mountain peak) above sea level. After acclimatisation, the predefined protocol for the final ascent from base camp to the Muztagh Ata mountain peak comprised two nights at camp 1, two nights at camp 2, and one night at camp 3 before reaching the summit of Muztagh Ata. At each camp, several medical tests were conducted. Medical testing was done by researchers (n = 15) none of whom belonged to the group of investigated individuals. The participants were allowed to use pain medication (i.e., paracetamol, aspirin, ibuprofen and mefenaminic acid) as required. If a patient displayed the need for other drugs for altitude related sickness or other medical reasons, the patient was accompanied to a lower location and excluded from further study. A detailed log book regarding the intake of drugs, including painkillers, was kept during the expedition. NSARs, which interfere with platelet function, were the most frequently used medication. We did not expect interaction of the medication used with the study results because endothelial and coagulation factor activation rather than platelet activation was the subject of our research. The study is in accordance with the declaration of Helsinki and has approval of the institutional review board of the University of Zurich. There was no attempt to obtain ethical approval of the study by respective institutions in the host country.

Blood sampling and measurements

In both groups, blood samples were drawn at four altitudes (pre expedition, 450 m/1474 ft above sea level), at base camp (day 6 and 7), at camp 1 (day 9 and 10) and camp 2 (day 16 and 20). In addition, it was possible to obtain blood samples from the mountaineers from group 1 at camp 3 (day 22). The blood specimens were taken after at least one overnight rest after a camp has been reached. The amount of blood we were able to draw at each altitude was limited due to ethical consideration (fatigue) and transport capacity. Venous blood was drawn using 20 gauge butterfly cannulae (Becton Dickinson, Basel, Switzerland) and sterile tubes for collection of serum and citrated plasma (Sarstedt, Sevelen, Switzerland). At each altitude, the samples were centrifugated at 2300 G, aliquoted immediately and kept frozen at ≤–20 °C until analysis. In order to measure haematocrit by a micromethod, capillary blood samples were obtained through puncture, aspiration and immediate centrifugation on site (Hettich, Bäch, Switzerland). Any medication intake was recorded by the expedition physician. Lake Louise acute mountain sickness score was assessed and recorded daily at all levels [20]. Peripheral haemoglobin oxygen saturation (SO_2) was measured using a pulse oxymeter (Onyx 9500, Nonin, Carouge, Switzerland).

Laboratory methods

Both aPTT [reference range 25–38 sec, interassay variance 2.3–3.3%] and PT [reference range 14–20 sec, interassay variance 1.9–3.1%] measurements were done on citrated plasma using Platelin FS (Endotell, Basel, Switzerland) and Inovin (Siemens, Düdingen, Switzerland). Both clotting times were measured on a CA-7000 (Sysmex, Horgen, Switzerland). Concentration of D-Dimer [reference range <0.5 mg/l, interassay variance 2.7–5.8%] was measured in citrated plasma samples with a latex-enhanced turbidimetric test for quantitative determination of cross-linked fibrin degradation products (Behring Coagulation System, Dade Behring, Düdingen, Germany) [21]. vWF-RCo [reference range 56–150%, interassay variance 6.6%] was determined by an automated system (BCS, Dade Behring, Marburg, Germany) which utilises an agglutination of stabilised platelets in presence of vWF. This induces a change in optical density that is quantified by the coagulation analyser (Behring Coagulation System, Dade Behring, Düdingen, Germany). Activated protein C resistance (APC-R) was measured by coagulation analyser [reference range >0.9, interassay variance 5.7–7.9%] (BCS, Dade Behring, Düdingen, Germany). All participants were genotyped for the presence of Factor V Leiden and Prothrombin G20210A mutation of the coagulation system. We also measured levels of C-natriuretic peptide (CNP) [<10 µmol/l, interassay variance 9%] as an endothelial marker. NT-proCNP, as the most stable fragment, was detected by a sandwich immunoassay using antibodies directed against specific amino acids sequence [interassay variance 6.9–8.2%] [22]. BNP [<33 ng/l, interassay variance 3.3–5.0%] and measured on an Advia Centaur (Siemens Diagnostics, Zürich, Switzerland). ADAMTS 13 [>50%, interassay variance 7.5%] was measured as described elsewhere [23]. A brief overview of the investigated coagulation parameters is summarised in table 1.

Statistical methods

Firstly, we investigated changes of the measured parameters during ascent. We then analysed whether the ascent protocol and the fact that the mountaineer reached the mountain peak resulted in differences of the investigated coagulation parameters. Finally, we investigated whether there was an association between Lake Louise AMS scores and the coagulation parameters. Changes in all the different parameters at each altitude were investigated using Friedman's statistic followed by Dunn's test. Comparison between the two groups was done with the Mann Whitney U-test. Correlations were calculated by the nonparametric Spearman rank method. Calculation of statistics and graphs were constructed by means of GRAPHPAD PRISM, Version 4.03 (GraphPad Software, San Diego, CA, USA) and SPSS 11.0.1 (Chicago, IL, USA). Two-sided P-values <0.05 were assumed significant.

Table 1
Overview of the investigated coagulation parameters.

Parameter	Description
aPTT	Screening test measuring the intrinsic system of coagulation
PT	Screening test measuring the extrinsic coagulation system
D Dimer	Fibrin degradation product. Indirect measure of activated coagulation system
APC-R	Anticoagulant response to activated Protein C may be diminished due to congenital (Factor V Leiden) or acquired factors. Activated Protein C, together with Protein S inactivates procoagulant Factors V and VIII. Increased APC-resistance (APC-R) leads to an increased risk for venous thromboembolic diseases
vWF Rco	Measures activity of procoagulant von Willebrand factor (vWF). Indicates qualitative or quantitative defects of vWF
ADAMTS 13 activity	Metalloprotease distributed by vessel wall, Degrades procoagulant von Willebrand factor (vWF) multimers, thereby reducing multimer activity

Results

Baseline characteristics and changes during expedition

Thirty four volunteers were included in the study, 18 of whom were assigned to the group with the faster acclimatisation period (group 1), whereas 16 were assigned to the group with a longer ascent (group 2). The baseline participant characteristics obtained prior to the expedition are given in table 2.

As shown in figure 1a, D-Dimer concentrations gradually increased with altitude, indicating incrementing activation of coagulation whilst reaching higher altitudes ($p < 0.001$). The increase of D-Dimer also remains significant when cor-

recting D-Dimer concentrations for haem dilution, as assessed with the haematocrit (p <0.001). During ascent, PT increased (p <0.001; fig. 1b) and APCR decreased significantly from 0.95 to 0.8 (p <0.001; fig. 1c), indicating procoagulant changes in the protein C inactivation with increasing altitude. Interestingly, a significant increase of aPTT (p <0.001; fig. 1d) was paralleled by significant decreases of von Willebrand factor (RCo) (p <0.001), possibly indicating increased consumption of von Willebrand Factor. The correlation of the relative changes of RCo with the relative changes in PTT was significant (r = –0.26; 95% CI –0.44 to –0.07; p = 0.006). There were no significant changes in ADAMTS-13 activity (p = 0.28) and CNP concentrations (p = 0.35).

Lake Louise AMS Score and influence of different ascent protocols

When relating the investigated coagulation parameters to AMS scores (table 3), no significant correlation could be detected with any parameter.

Table 2

Baseline characteristics of the two groups. All subjects have been checked for thrombophilia, such as Factor V Leiden Mutation and G20210A prothrombin mutation. Two subjects were found with a heterozygote Faktor V Leiden mutation.

	Group 1 (shorter acclimatization period)	Group 2 (longer acclimatization period)	p-value
N	18	16	
Gender (female/male)	(3/15)	(4/12)	n.s.
Age, years (mean ± SD)	46 [31, 56]	46 [37, 51]	n.s.
Reaching Muztagh Ata Peak	11/18	8/16	n.s.
Haematocrit	43 [41, 44]	43 [42, 45]	n.s
PT, %	80 [77, 85]	87 [74, 100]	n.s
aPTT, sec.	32.5 [30, 34]	33 [31.5, 36.5]	n.s.
D-Dimer, mg/L	0.54 [0.35, 0.74]	0.62 [0.46, 0.71]	n.s.
vWF-RCo, %	105 [74, 125]	100 [65, 129]	n.s.
ADAMTS-13	61 [54, 73]	71 [54, 85]	n.s.
CNP	2.18 [1.76, 5.18]	2.96 [1.73, 4.22]	n.s.
APC-R, Index	0.84 [0.79, 0.87]	0.83 [0.72, 0.89]	n.s.

Data are given as median and interquartile range [IQR].

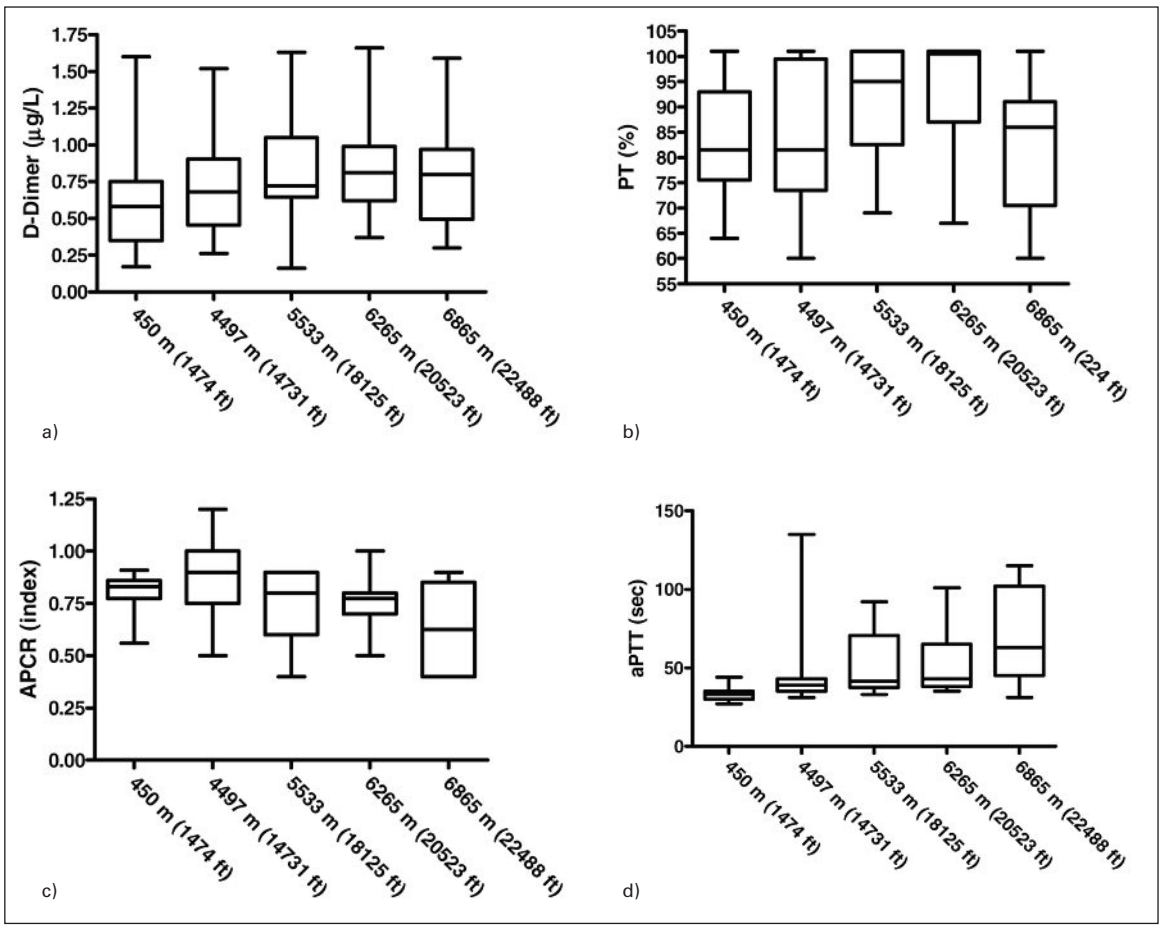

Figure 1

Course of coagulation parameters during high altitude expedition. First sample taken pre expedition (450 m above sea level; 1474 ft), other samples taken consecutively at base camp (4497 m; 14731 ft), camp 1 (5533 m; 18125 ft), camp 2 (6625 m; 20523 ft) and camp 3 (6885 m; 22488 ft). Measurements were compared using the Friedman repeated measures ANOVA on ranks test. The levels of a) D-Dimer concentrations (p <0.001), b) prothrombin time (PT) (p <0.001), c) APC-resistance (p <0.001), and d) activated partial thromboplastin time (p <0.001) exhibited significant changes and are shown at the different altitudes. At base camp, there was a measurement with substantially prolonged aPTT. The reason for this finding remains unclear, a review of pre-analytical and analytical procedures reveal no causes for such prolongation.

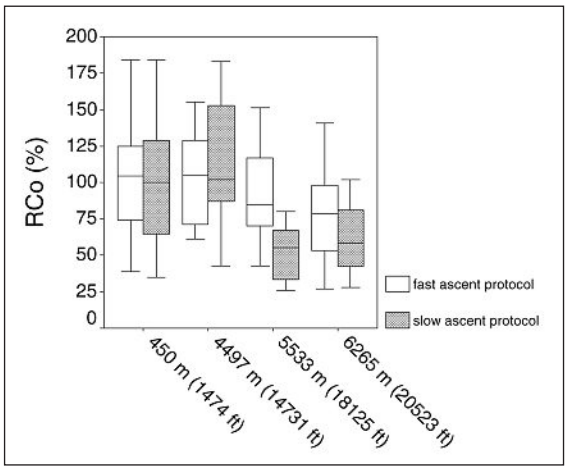

Figure 2

Course of von Willebrand factor activity (RCo) during high altitude expedition according to ascent protocol. There was a significant decrease with increasing altitude (p <0.001). Mountaineers with fast ascent protocol overall had lower RCo than mountaineers with fast ascent protocol (p = 0.04).

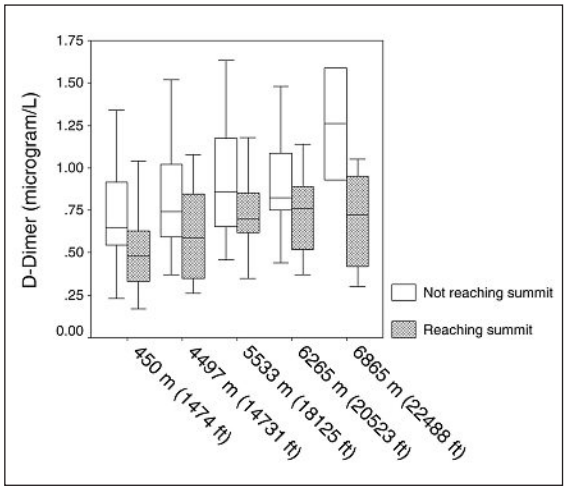

Figure 3

Course of von D-Dimer concentrations during high altitude expedition according to whether a mountaineer reached Muztagh Ata mountain peak. There was a significant increase with increasing altitude (p <0.001). Mountaineers reaching the mountain peak had significantly lower D-Dimer concentrations than mountaineers having to stop ascent, both at baseline before the expedition (p = 0.04) and overall (p <0.01).

When further comparing the participants of the two acclimatisation protocols, there was an overall higher RCo activity in mountaineers with a faster ascent protocol (88%, interquartile range, IQR, 64–121%, vs 65%, IQR 43–106%, p = 0.04; fig. 2). This might be partly explained by the fact that overall ADAMTS-13 activity was lower in those with a faster ascent protocol (62%, IQR 50–79%, vs 72%, IQR 51–94%, p = 0.04). With regard to the ascent protocol none of other investigated parameters exhibited significant overall differences.

Difference between mountaineers who reached the summit and those who did not

Finally, we investigated whether levels of coagulation parameters were associated with the fact that a mountaineer was able to successfully reach the mountain peak. Interestingly, overall, mountaineers reaching Muztagh Ata mountain peak had significantly lower D-Dimer concentrations at baseline (0.48 μg/L, IQR 0.31–0.63 μg/L vs 0.65 μg/L, IQR 0.53–0.95 μg/L; p = 0.04) and overall (0.71 μg/L, IQR 0.46–0.89 μg/L vs 0.82 μg/L, IQR 0.66–1.17 μg/L; p <0.01) (fig. 3). Further, mountaineers reaching Muztagh Ata mountain peak overall had longer aPTT (44s, IQR 38-71s, vs 41s, IQR 36-56s; p = 0.06) and lower ADAMTS-13 activity (59%, IQR 48–78% vs 72%, IQR 60–92%; p <0.01) than mountaineers, who had to stop ascent due to different reasons. Neither aPTT nor ADAMTS-13 activity exhibited significant differences at baseline. In regard to whether a mountaineer reached the mountain peak, none of the other investigated parameters exhibited significant overall differences.

Table 3

Lake Louise AMS score, oxygen saturation (SaO_2) and haematocrit during expedition.

	Lake Louise AMS score	SaO_2	Haematocrit
Base camp, 4497 m / 14731 ft	2 [1, 2.5]	85 [83, 86] %	44 [43, 47] %
Camp 1, 5533 m / 18125 ft	2 [1, 3]	76 [71, 79] %	45 [44, 48] %
Camp 2, 6265 m / 20523 ft	1 [1, 3]	75 [68, 76] %	49 [48, 53] %
Camp 3, 6865 m / 22488 ft	1 [1, 2]	74 [70, 79] %	–

Haematocrit could not be measured at Camp 3.

Discussion

The present study could demonstrate an activation of coagulation while ascending to high altitude, as D-Dimer concentrations, PT and APC-resistance exhibited procoagulatory changes. Further, an association of rapidity of ascent with levels of ADAMTS 13 activity and Ristocetin Cofactor activity could be detected. Finally, we could identify coagulation parameters which were associated with the fact that a mountaineer reached the mountain peak.

The fact that significant increase of aPTT is accompanied by significant decrease of RCo during ascent might suggest consumption of vWF. Therefore we assumed an activation or disruption of the endothelial structure. Interestingly, CNP, an endothelial marker, did not show significant change during ascent. Further, ADAMTS13 activity did not show significant changes during the expedition. In short, whereas von Willebrand factor activity is associated with changes in altitude, no such relationship was found regarding CNP and ADAMTS-13 levels.

We could identify a procoagulatory state with increasing altitude, as reflected with increasing D-

Dimer concentrations and APC-resistance (as indicated by a decreased APC-R test result). Both increasing D-Dimer concentrations and APC-Resistance have been shown to increase the risk for venous thromboembolism [24]. Our study design was not able to differentiate whether hypoxia or exercise contributes to the procoagulant changes. A study by De Loughery et al. investigated the interaction between hypoxia and exercise and their influence on coagulation tests [25]. It was found that exercise induced a procoagulant change in coagulation factors which was reduced by hypoxia. In our study, we could have supplied participants with oxygen, in order to study the effect of prolonged hypoxia on exercise induced procoagulant changes during mountain expeditions. However, this was not done as supplying oxygen is not common practice on mountain expeditions to heights of about 7000 m above sea level.

One might argue that since D-Dimer was measured over a period of several weeks, it could be possible that sea level D-Dimer shows day to day fluctuations which are not associated with a prothrombotic state. Higher within-person variability would bias research findings to the null hypothesis of no association [26]. Sakkinen et al. found the intraindividual variability statistics to be similar to those of an emerging cardiovascular disease risk marker, high-sensitivity C-reactive protein or somewhat higher than those of the widely used total cholesterol measurement [27]. We think that intraindividual variability of D-Dimer concentrations does not invalidate our findings.

The fact that increasing altitude leads to a procoagulatory state raises the question of whether persons with pre-existing thrombophilic disorders such as Factor V Leiden mutation, the G20210A prothrombin promoter polymorphism or deficiencies of protein S or protein C levels might have an increased risk for venous thromboembolism during high altitude expedition. In high altitude expeditions, additional factors that may raise the risk of thrombotic event are common (diarrhoea, bad weather with immobilisation, long travel). For mountaineers in whom thrombophilic disorders might be a problem due to a positive family history, we suggest examination for the common thrombophilic conditions.

When looking at the impact of ascent protocol and differences among the investigated coagulation parameters, there were different levels of RCo and ADAMTS-13 activity, with higher RCo and lower ADAMTS-13 activity in mountaineers with a faster ascent protocol. Surprisingly, there was no relationship between the investigated parameters and the AMS scores. Even though we found some association in changes of coagulation parameters with reaching the summit, causality is hard to evaluate because of too many other factors are involved (e.g., physical fitness, psychological factors). Nevertheless, the fact that participants reaching the summit had significantly lower D-Dimer levels pre-expedition than those participants who were forced to stop ascent was very surprising. This finding is difficult to interpret, but could also be due to type 1 error.

In our view, the present study has two limitations. Firstly, we could not draw enough blood from the mountaineers to assess more factors of the systems for coagulation and fibrinolysis. As a consequence, the conclusions are limited to the investigated parameters. Secondly, the study has a relatively low number of study participants in whom changes in coagulation parameters were assessed and is much too underpowered to assess the frequency of clinically manifest venous thromboembolism during high altitude expedition. As a result of this, our reasoning on prophylactic measures for patients with pre-existing thrombophilic defects remains speculative.

Despite this we could demonstrate significant changes in the investigated coagulation parameters during high altitude expedition. We can also demonstrate that newer markers of the coagulation system such as ADAMTS-13 or APCR are involved in high altitude pathophysiology. It remains unclear whether these changes are causative or merely reflective of the decreased fitness to reach a mountain peak. It might be possible that high altitude expedition confers a procoagulatory state that could pose an additional risk for venous thromboembolism in people with pre-existing thrombophilic disorders.

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