ORIGINAL ARTICLE

High altitude trekking after lung transplantation: a prospective study using lung ultrasound to detect comets tails for interstitial pulmonary edema in lung transplant recipients and healthy volunteers

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Clinical trial registration number: NCT03117686 (clinicaltrials.gov).

SUMMARY

The intensity of physical activity which can be tolerated after lung transplantation and the tolerance to prolonged exercise at high altitude are poorly investigated. Lung ultrasound comet tails have been used in the diagnosis of interstitial pulmonary edema and high pulmonary altitude edema. The aim was to assess the number of lung ultrasound comet tails and to monitor changes in the optic nerve sheath diameter (ONSD) during a climb to the top of Mount Kilimanjaro in 10 lung transplant recipients and 10 healthy controls at three different altitude levels: 1360, 3505, 4900 m. Lung transplant recipients showed a constant increase in comet tail scores with altitude, whereas control subjects only showed an increase at the highest measurement point. Differences between groups (transplant versus control) reached significance only after the first ascend: 0.9 (95% CI: −0.41; 2.21) vs. 0.1 (95% CI: −0.12; 0.32) ($P = 0.2$; 1360 m), 2.33 (95% CI: 0.64; 4.02) vs. 0.3 (95% CI: −0.18; 0.78) ($P = 0.04$; 3505 m), and 4.11 (95% CI: 0.13; 0.34) vs. 2.9 (95% CI: 0.49; 5.31) ($P = 0.15$; 4900 m); ONSD increased significantly in both groups from 3.53 (95% CI: 0.34; 0.66) at 1360 m to 4.11 (95% CI: 0.36; 0.71) at 4900 m ($P < 0.05$). Lungs of transplant recipients are able to adapt to altitude and capable of performing prolonged exercise at high altitude after slow ascend.

Transplant International 2018; 31: 1245–1253

Key words
outcome, quality of life

Received: 31 May 2018; Accepted: 15 June 2018; Published online: 9 July 2018

Introduction

Since the first lung transplantation in the 1960s [1], long-term survival, quality of life, and physical possibilities have improved over the decades. Organ function after transplantation is reported to be normal [2], meeting physiological requirements of average daily activities and allowing increased exercise activities over a short period of time [2,3]. However, organ adaption and susceptibility to lung injury with prolonged exercise on high altitude over a long period of several days is unknown.

On high altitude, the reduction in partial inspiratory oxygen pressure causes hypoxic pulmonary vasoconstriction

doi:10.1111/tri.13307

leading to microvascular hydrostatic pressures eventually resulting into interstitial pulmonary edema (iPE) in some individuals [4].

This effect can further be aggravated by the consequences of immunosuppressive medications, that are reported to cause endothelial cell injury increasing capillary permeability and therefore potentially rendering transplant recipients more susceptible to pulmonary complications with increased risk to develop iPE [2,5,6].

Lung ultrasound is a highly sensitive method to detect increases in extravascular lung water and iPE, with comparable sensitivity to computer tomography and even superior to chest radiography [7].

Recent studies conducted in remote areas have shown that lung ultrasound comet tails, or B-lines, can be used to assess the degree of high altitude pulmonary edema (HAPE) in healthy climbers [4,7–10]. HAPE and high altitude cerebral edema (HACE) are life-threatening conditions that are reported to occur with an incidence ranging from 0.2% to 15% when climbing above 2500 m [7,11]. In addition to endothelial injury, the immunosuppressive agent tacrolimus causes extensive cerebral white-matter lesions with an incidence ranging from 7% to 32% and leading to cerebral edema translating into posterior reversible encephalopathy syndrome (PRES) on MRI imaging. Similar to HACE, PRES presents, with clinical signs of cerebral edema such as headache, vomiting, altered mental status, or focal neurological deficits [12]. A noninvasive method in detecting cerebral edema is the ultrasound measurement of the of optic nerve sheath diameter (ONSD), which is increased with raised intracranial pressures [13–15].

The aim of this study was to assess the prevalence rate of iPE and cerebral edema occurring in lung transplant recipients climbing high altitude and to compare them to a group of healthy controls.

The primary outcome was the occurrence of B-lines with prolonged exercise on high altitude between lung transplant recipients and healthy volunteers. Secondary outcome was the incidence of cerebral edema, measured by ONSD as surrogate marker, between the two groups during the climb.

Materials and methods

The study was approved by the local Ethics committee (Ref: 1236/2017), and registered prior to enrolment at clinicaltrials.gov (NCT03117686, date of registration: 18th April 2017). This manuscript adheres to the applicable CONSORT guidelines. Written informed consent was obtained from all subjects. The study was conducted during an expedition to the summit of Mount Kilimanjaro (5895 m), Tanzania, in June 2017. In this prospective, controlled, observational study, we included 10 patients more than 2 years after lung transplantation and 10 healthy volunteers. Patients were recruited and invited at a university teaching hospital with more than 100 lung transplantations per year. Members of the accompanying medical team served as a healthy control group. Both groups had to meet the following inclusion criteria: age above 18 years, maximal oxygen consumption capacity (VO_2max) of more than 25 ml/min/kg, and an active lifestyle and the ability to perform more than 8 METs (metabolic equivalent of task).

Six months prior to the start of the expedition, all subjects had to complete a physical examination including a complete medical history, cardio pulmonary exercise testing on a cycle ergometer to measure VO_2max, and follow an individual training schedule based on the results of the exercise test. Known risk factors for HAPE such as history of migraine, female sex, age under 46 years, and regular endurance physical activity were noted in each participant before start of the expedition [16,17]. All subjects received vaccination according to the current recommendations. None of the subjects received prophylactic medication for acute mountain sickness. Transplant patients continued their usual immunosuppressant medication regimen: all patients received tacrolimus and two of them received additional everolimus.

The climb started at Londorossi gate at 2360 m and covered 71 km in 8 days along the Lemosho route to the summit (Table 1).

We performed ultrasound scanning with a portable pocket ultrasound device (Vscan extend™; GE Vingmed Ultrasound, Horten, Norway) of the chest and the optic nerve sheath diameter at baseline in Arusha (day 0) at 1360 m, day 2 at Shira I camp (3505 m) and day 6 at Kosovo camp (4900 m). Ultrasonography was performed in supine or near-supine position using a 8–12 MHz linear probe for both measurements. For lung sonography, we performed an 8-zone examination as recommended for out-of-hospital use [7,18]. According to this, the chest wall was divided into eight areas, one scan for each area was obtained. The areas were two anterior and two lateral per side. The anterior chest wall was delineated from the sternum to the anterior axillary line and was subdivided into upper and lower halves. The lateral zone was delineated from the anterior to the posterior axillary line and was subdivided into upper and basal halves [15]. In each intercostal space, the number of comet tail signs was recorded. The total number of comet tails yielded the "comet score" [19]. The presence of 3 or more CTs per

Table 1. Description of the climb and success rate.

Day	Camp	Altitude (m)	Distance covered (km)	Duration of climb (h)	Success rate transplant (%)	Success rate control (%)
Baseline 0	Arusha	1360	6	3	10/10 (100)	10/10 (100)
1	Mti Mkubwa	2650	8	6	10/10 (100)	10/10 (100)
2	Shira I camp	3505	11	5	9/10 (90)	10/10 (100)
3	Moir hut	4200	7	4	8/10 (80)	10/10
4	Barranco camp	3980	8	4	8/10 (80)	10/10 (100)
5	Karanga camp	4030	4	4	8/10 (80)	10/10 (100)
6	Kosovo camp	4900	5	7	8/10 (80)	10/10 (100)
	Uhuru peak	5895	12	6	8/10 (80)	10/10 (100)
7	Mweka camp	3100	10	4	8/10 (80)	10/10 (100)

intercostal space is evidence of extravascular lung water (EVLW), and if seen diffusely in more than one intercostal space, it is indicative of interstitial pulmonary edema and called a positive B-pattern [7,10,11]. A lung comet tail is defined as an echogenic, coherent, wedge-shaped signal with narrow origin from the hyper-echoic pleural line [9,18,19].

For measuring the ONSD, the ultrasound probe was placed lightly over each closed eyelid using an aqueous contact gel. Eye structures were imaged in order to align the optic nerve directly opposite the probe. This was achieved by ensuring that the posterior aspect of the lens was visible in the scan. A continuous recording of the scan was made (typically 5 s). ONSD was measured 3 mm behind the globe in each eye, and the average of three measurements was recorded to reduce intra-observer variability [20]. A distance of 3 mm was used because changes in ONSD with intracranial pressure are greatest at this level [2,4,12,21,33]. An ONSD of more than 5.8 mm was defined as increased intracranial pressure (ICP) and equivalent of more than 20 mmHg [24].

All examinations were performed by the same physician. The images were digitized and stored on an USB storage device. To evaluate intra- and inter-observer reliability a secondary analysis of the stored images was performed. The analysis was performed 4 weeks after the expedition by the examining physician and an independent observer, both experienced in the application of lung ultrasound as a diagnostic tool.

In addition, a clinical lung examination was performed by auscultation for crackles, wheeze, or other pathological lung sounds using a stethoscope.

Transcutaneous oxygen saturation, heart rate (Nonin GO2; Nonin Medical Inc., Plymouth, MN, USA), manual blood pressure, and Lake Louise Acute Mountain Sickness Score (LLAMS) were recorded daily. The LLAMS score allows to determine the severity of acute mountain sickness if headache and one or more symptoms (anorexia, nausea or vomiting, fatigue or weakness, dizziness or light-headedness, difficulty sleeping) are present. Each symptom can be rated on a scale from 0 to 3. It is defined as mild (score 2–4), moderate (score 5–10), or severe (score >11) [9,22]. We evaluated perceived exertion using the Borg scale [23] at baseline, 1 day before summit and on summit day. Additional medications for acute mountain sickness (AMS) were also recorded.

Outcomes

The primary outcome of the study was the difference in total number of lung ultrasound comet tails at different altitude levels between the two groups. The secondary outcome was the difference of the ONSD at different altitude levels between the two groups.

Statistical analysis

Demographic and clinical baseline data were summarized by mean, 95% confidence intervals and minimum and maximum for metric variables or absolute frequencies for categorical variables. Differences between groups were analyzed using Student's *t*-test, for continuous variables, chi^2 test for categorical variables.

Due to the observational study design, there were only a limited number of subjects available and no sample size calculation was feasible. We included transplant recipients willing to climb the top of Mount Kilimanjaro and a matching number of healthy control subjects. We performed a *post hoc* analysis and reached a power of 0.36 with an alpha of 0.05 retrospectively.

To test inter- and intraobserver reliability, we calculated Cohen's κ (κ < 0: poor agreement; κ 0–0.2: slight agreement; κ 0.21–0.4: fair agreement, κ 0.41–0.6: moderate agreement; κ 0.61–0.8: substantial agreement; κ

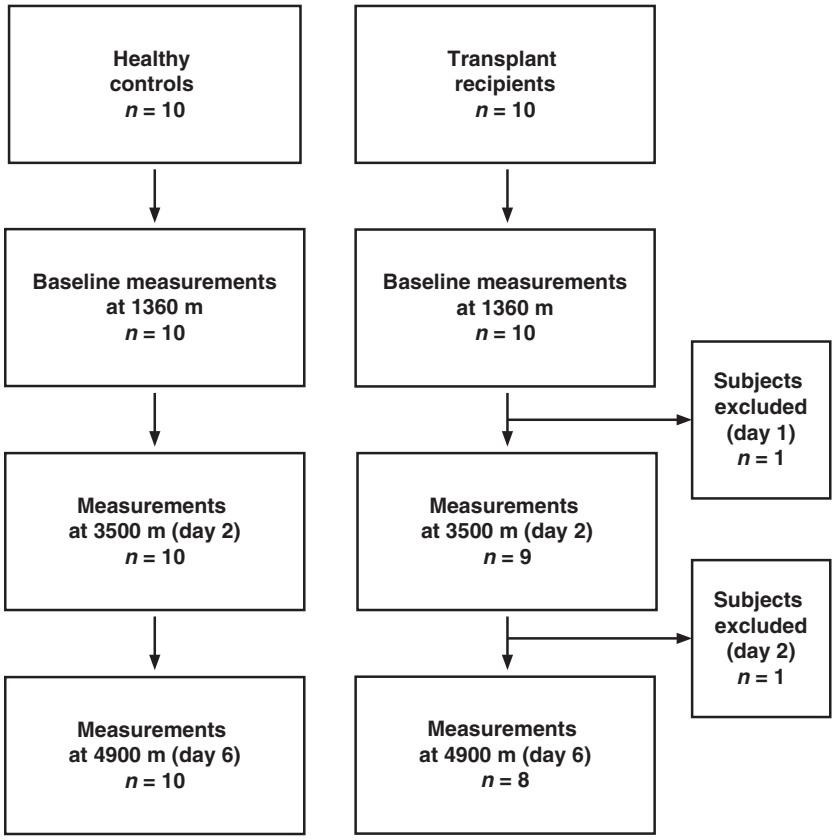

Figure 1 Flowchart. Number of participants included in each group.

0.81–1.0: almost perfect agreement). *P*-values of <0.05 were considered significant. All statistics were performed using the statistical environment R version 3.4.1.

Results

Eighteen of 20 (90%) subjects reached the summit of Mount Kilimanjaro. Two transplant recipients quit on day 1 and on day 2, both because of physical exhaustion and muscle pain (Fig. 1). They had no signs of headache, shortness of breath, or crackles on physical examination. Their peripheral oxygen saturation values were above 95%. Demographic parameters and baseline characteristics of all participants are presented in Table 2.

We recorded the following risk factors for HAPE: none of the participants had history of migraine, all participants performed regular endurance physical activity (more than 2 h per week), 15 participants were under 46 years (seven in the transplant and eight in the control group) and four participants were female (one in the transplant and three in the control group). The transplant recipients received mainly gender and age matching organs, only one male patient received a female organ. The mean age of the donor organs was 37.3 (95% CI: 26.8; 47.8) years.

The number of lung comet tails increased significantly with altitude in both groups. Lung ultrasound showed comet tails in five of 20 subjects (25%) at 1360 m, in nine of 19 subjects (47%) at 3505 m, and in 17 of 18 (94%) subjects at 4900 m. Lung transplant recipients developed a significantly higher mean number of B-lines detected by ultrasound at 3500 m ($P = 0.03591$), although no transplant recipient developed positive B-pattern or iPE (Fig. 2 and 3). Table 3 shows the mean and range of the total number of B-lines counted. Only one healthy volunteer had a positive b-pattern with ≥3 lung comet tails in more than one zone and also developed signs of acute mountain sickness during physical examination with a LLAMS Score of 7 (headache, fatigue, poor appetite, difficulty sleeping) on summit day. Of the 18 subjects reaching the top of Mount Kilimanjaro, none had crackles on physical lung examination.

Optic nerve sheath diameter also augmented significantly with altitude (Table 4). None of the subjects had values of more than 5.8 mm. Peripheral oxygen saturation decreased with altitude, whereas heart rate and blood pressure increased (Fig. 2a–c). Oxygen saturation values were 96.56 ± 0.92% at day 0 and 84.44 ± 5.11% at 4900 m at day 6 ($P < 0.05$), heart rates increased

Table 2. Baseline demographics and characteristics of transplant recipients and control subjects.

	Transplant (n = 10)	Control (n = 10)
Age	46.6 (38.8; 54.4) (24–62)	38 (28.6; 47.4) (29–68)
Gender (m/f)	9/1	7/3
BMI (kg/m^2)	21.4 (19.5; 23.3) (16.9–26.8)	22.7 (20.6; 24.8) (17.5–29.6)
VO_2max (ml/min/kg)	33.63 (30.68; 36.59) (27.7–38.6)	38.47 (35.22; 41.72) (34.6–49.7)
Time since Tx (years)	7.6 (4.4; 10.8) (2–15)	
Reason for Tx		
Cystic fibrosis	5	
Pulmonary fibrosis	2	
Alpha-1 antitrypsin deficiency	2	
CTEPH	1	

BMI, body mass index; CTEPH, chronic thromboembolic pulmonary hypertension; Tx, transplantation; VO_2max, maximal oxygen consumption capacity.

Mean (95% confidence intervals) (minimum—maximum).

from 76.38 ± 10.02 bpm at day 0 to 90.44 ± 12.87 bpm at day 6 ($P < 0.05$).

Mean values for LLAMS scores were 0 in both groups at baseline, 0.44 (95% CI: 0.11; 0.78) (range 0–2) in the transplant and 0.3 (95% CI: 0.07; 0.08) (range 0–1) in the control group at 3500 m, 0.88 (95% CI: 0.25; 1.5) (range 0–4) in the transplant and 0.8 (95% CI: 0.12; 0.4) (range 0–4) in the control group at 4900 m and 3.75 (95% CI: 2.83; 4.67) (range 2–7) in the transplant versus 3.3 (95% CI: 2.09; 4.51) (range 1–7) in the control group at the peak of Mount Kilimanjaro. Mean values on the Borg scale were 0 in both groups at baseline, 0.13 (95% CI: 0.04; 0.29) (range 0–1) in the transplant and 0 in the control group at 4900 m and 1.13 (95% CI: 0.5; 1.75) (range 0–3) in the transplant and 0.1 (95% CI: 0.05; 0.25) (range 0–1) in the control group at the peak. None of the participants had headache at baseline, nine participants developed headache at 4900 m and 10 on summit day. Only one healthy control subject needed to take medication for AMS (Mefenamic acid) at 4900 m, but seven participants took medication for AMS (Mefenamic acid, Ibuprofen, Paracetamol) on summit day.

Postexpedition analysis of the stored ultrasound videos showed an almost perfect agreement of intra- and interobserver reliability of $\kappa = 0.985$ and $\kappa = 0.935$.

Discussion

The principal finding of this study was that lung transplant recipients start to develop interstitial pulmonary edema in lung ultrasound at lower altitude levels than healthy ones. Both groups showed an increase in comet tail scores with altitude, with a significant difference at the second measurement point at 3500 m, but with no clinical signs of AMS.

Although ONSD increased with altitude in both groups, diameters remained below a cutoff reported to be associated with increased ICP.

Studies investigating healthy volunteers at high altitude also demonstrated that the number of comet tails rose with altitude and decreasing oxygen saturation [4,8–10,27,28]. However, the comparison of transplant recipients with healthy subjects in our study revealed significantly more B-lines compared to healthy subjects at 3500 m, but a similar number of B-lines at 4900 m in both groups. One key difference between the groups is that the transplanted lung is denervated. As it is not solely dependent on autonomic input, hypoxic pulmonary vasoconstriction is still present in the denervated, transplanted lung, similarly as in a normal lung [29]. However, it is not clear whether denervation has an effect on the time course of hypoxic pulmonary vasoconstriction or how other chemoreceptor responses are affecting hypoxic pulmonary vasoconstriction. Therefore, it could be possible that lung transplant recipients have different chemoreceptor sensitivity and response to hypoxia. Further, several medications can affect hypoxic pulmonary vasoconstriction including aspirin and immunosuppressive medications such as calcineurin inhibitors and glucocorticoids [5,6,30]. Seven participants were taking pain medication for AMS on summit day (Mefenaminacid, Paracetamol, Ibuprofen), but none of them at 3500 m. Transplant recipients were taking their usual immunosuppressant medication regimen consisting of tacrolimus and two of them received additional everolimus. Furthermore, during lung transplant surgery, the pulmonary lymphatic vessel continuum is completely disrupted, and,

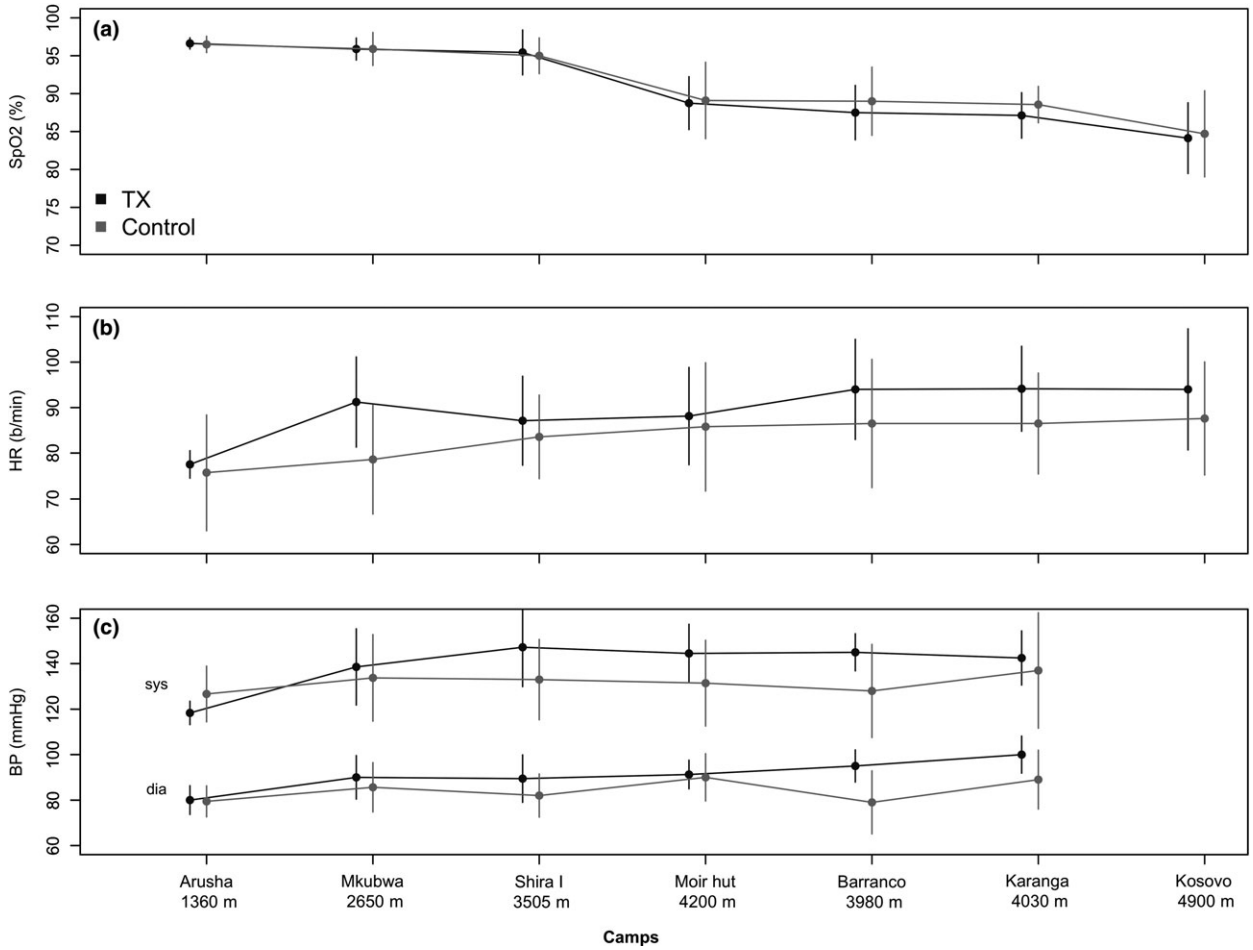

Figure 2 Mean values with standard deviation for peripheral oxygen saturation, heart rate, and blood pressure values for transplant recipients and control subjects at all camp sites. *P*-values for the comparison between groups were calculated using the Student *t* test.

as a result, lymphatic drainage function is severely compromised. After transplantation, the regeneration of an effective lymphatic drainage system plays a crucial role in maintaining interstitial fluid balance in the lung allograft, which could also contribute to the observed difference in B-lines at 3500 m [31].

Although oxygen saturation decreased and the number of comet tails increased with altitude in the whole cohort, we could only observe a small difference in oxygen saturation values and also in LLAMS and Borg scores with higher values in the transplant group. We performed a very slow ascend to the top of Mount Kilimanjaro (7 days) and our measurements at 4900 m were performed at day 6. Study subjects had more time to adapt to altitude, and this might add to the fact that we did not observe any severe cases of AMS and HAPE or a significant difference in the number of comet tails at the highest measurement point.

At baseline we observed comet tails in 5 of 20 subjects (25%), mainly at the lower zones. One transplant recipient even showed a total number of six comet tails at baseline. The number of comet tails increased with altitude in this subject and reached a total number of 12 at the highest point at 4900 m without any symptoms. Occasional B-lines can be seen in normal lungs, especially at the bases. Up to two between two adjacent ribs can be considered normal [9,17]. A number of ≤ 5 CTs is considered a normal echo-graphic chest pattern in a 28 zone examination; healthy athletes may have a small number of CTs, especially when confined laterally to the last intercostal spaces above the diaphragm [9].

Optic nerve sheath diameter increased continuously from baseline with altitude, but never reached values above 5.8 mm in any subject which is defined as equivalent with an intracranial pressure (ICP) of more than 20 mmHg [8]. Also we did not observe any severe cases of AMS.

Ultrasonography studies have shown that ONSD correlates with ICP in critical care patients [24], and that a

Table 3. Lung ultrasound comet tail score.

Time point	CTS transplant	CTS control	*P* value	CTS all	Positive B-pattern
Baseline: 1360 m (day 0)	0.9 (−0.41; 2.21) (0–6)	0.1 (−0.12; 0.32) (0–1)	0.2095	0.5 (−0.14; 1.14) (0–6)	0/20
Total number of comet tails	9	1		10	
Shira I: 3505 m (day 2)	2.33 (0.64; 4.02) (0–8)	0.3 (−0.18; 0.78) (0–2)	**0.03591**	1.26 (0.34; 2.18) (0–8)	0/19
Total number of comet tails	21	3		24	
Kosovo camp: 4900 m (day 6)	5.38 (2.94; 7.81) (2–12)	2.9 (0.49; 5.31) (0–12)	0.1501	4 (2.33; 5.67) (0–12)	1/18
Total number of comet tails	43	29		72	
P value* (day 0 versus day 6)	**0.0006**	**0.0307**		**0.0001**	

Mean (95% confidence intervals) (minimum—maximum) of the total number of CTs in the chest. Positive B-pattern: the presence of 3 or more CTs per intercostal space seen diffusely in more than one intercostal space it is indicative of interstitial pulmonary edema [6,14,15].

**P*-values for the comparison between groups were calculated using the Student *t* test.

Table 4. Optic nerve sheath diameter.

Time point	ONSD transplant	ONSD control	*P* value* (transplant versus control)	ONSD all
Baseline: 1360 m (day 0)	3.62 (0.27; 0.7) (3–4.7)	3.44 (0.28; 0.73) (2.3–4.2)	0.246	3.53 (0.34; 0.66) (2.3–4.7)
Shira I: 3505 m (day 2)	3.69 (0.24; 0.61) (2.9–4.5)	3.69 (0.2; 0.52) (3–4.4)	0.973	3.69 (0.26; 0.52) (2.9–4.5)
Kosovo camp: 4900 m (day 6)	4.11 (0.13; 0.34) (3.7–4.5)	4.11 (0.29; 1) (2.4–5.1)	0.982	4.11 (0.36; 0.71) (2.9–5.1)
P value* day 0 versus day 6)	**0.0005**	**0.0013**		**0.000006**

Mean (95% confidence intervals) (minimum—maximum).

**P*-values for the comparison between groups were calculated using the Student *t* test.

variation in ONSD is detectable within minutes of increase in ICP [19,32].

Recent studies also reported an increase in ONSD at high altitude compared to baseline values [13–15,32,33].

In the literature, only two studies have been published who investigated transplant function at high altitude and comparing cardiopulmonary parameters to healthy control subjects [25,26]. One of them studied six liver transplant recipients [25] the other two lung, two heart, two kidney, four liver, one small bowel, and one allogenic stem cell recipients [26]. Both evaluated cardiopulmonary parameters and acute mountain sickness scores only, but none of them used ultrasound to monitor high altitude lung or cerebral edema.

In previous trials in remote areas, the detection of ultrasound comet tails was performed using laptop sized devices that were dependent on electricity [4,7–10,27]. This is the first study using a handheld pocket ultrasound device (Vscan extend™, GE Healthcare) weighing less than 500 g at high altitude. Despite its size, our ultrasound device provides sufficient resolution and accuracy to detect lung comet tails and measure ONSD. Postexpedition

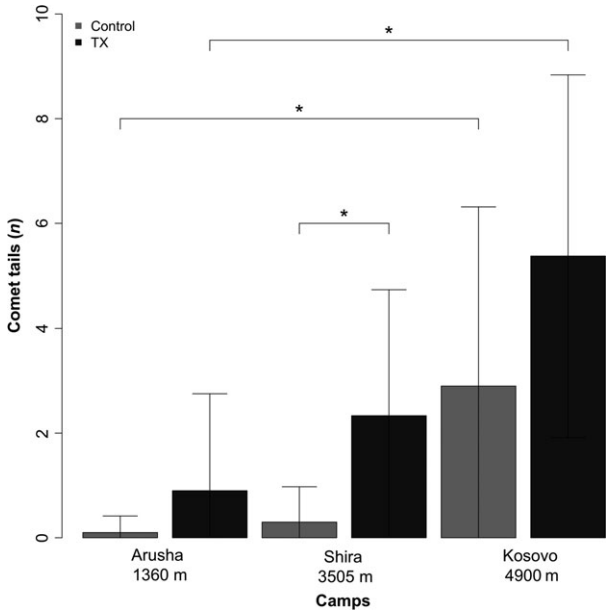

Figure 3 Mean values with standard deviation for the total number of comet tails at baseline (1350 m), 3505 and 4900 m are presented. *P*-values for the comparison between groups were calculated using the Student *t*-test. Significant *P*-values are marked with *.

analysis of stored ultrasound videos showed an almost perfect agreement of intra- and interobserver reliability.

Limitations

We were not able to perform a sample size calculation because in this prospective controlled observational study, only a limited number of subjects were available like in the majority of prospective field studies in high altitude [4,8–10,25–28]. Moreover, we observed a 20% drop out rate in the transplantation group which resulted in low power (0.36, $\alpha = 0.05$).

Furthermore, our population of transplant patients was not representative for the average transplant recipient and subjects enrolled were heterogeneous according age, gender, altitude of residence, and history of acute mountain illness, which renders the responses highly variable.

Another technical limitation of our study is that we performed a shorter 8-zone examination instead of the 28-zone examination. The 8-zone examination does not include a check of every intercostal space in each area like the 28-zone examination, but can be preferred for out-of-hospital clinical use as it has been shown to be effective in detecting extravascular lung water and avoids the need for undressing [4,7,18].

We were not able to perform ultrasound measurements at the peak of Mount Kilimanjaro at 5900 m. Because of the cold environment of minus 10 degrees Celsius, participants refused to have lung ultrasound.

Conclusion

Our study showed that the lungs of transplant recipients are able to adapt to altitude and capable of performing prolonged exercise at high altitude after a slow ascend.

Further, ultrasound seems to be a reliable and practical tool to assess interstitial lung edema and cerebral edema by optic nerve sheath diameter in extreme sports in remote areas.

Authorship

UW: designed research/study, performed research/study, collected data, wrote the manuscript. JS and JM: performed research/study and collected data. MB: analyzed data. CO: designed research/study and wrote the manuscript. PJ: performed and designed research/study.

Funding

The authors have declared no funding.

Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

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