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Validation of a Score for the Detection of Subjects with High Risk for Severe High-Altitude Illness

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ABSTRACT

RICHALET, J.-P., F. PILLARD, D. LE MOAL, D. RIVIÈRE, P. ORIOL, M. POUSSEL, B. CHENUÉL, S. DOUTRELEAU, S. VERGÈS, S. DEMANEZ, M. VERGNION, J.-M. BOULET, H. DOUARD, M. DUPRÉ, O. MESLAND, R. REMETTER, E. LONSDORFER-WOLF, A. FREY, L. VILCOQ, A. NEDELEC JAFFUEL, D. DEBEAUMONT, G. DUPERREX, F. LECOQ, C. HÉDON, M. HAYOT, G. GIARDINI, and F. J. LHUISSIER. Validation of a Score for the Detection of Subjects with High Risk for Severe High-Altitude Illness. *Med. Sci. Sports Exerc.*, Vol.53, No.6, pp. 00–00, 2021. Purpose: A decision tree based on a clinicophysiological score (severe high-altitude illness (SHAI) score) has been developed to detect subjects susceptible to SHAI. We aimed to validate this decision tree, to rationalize the prescription of acetazolamide (ACZ), and to specify the rule for a progressive acclimatization. Methods: Data were obtained from 641 subjects in 15 European medical centers before and during a sojourn at high altitude. Depending on the value of the SHAI score, advice was given and ACZ was eventually prescribed. The outcome was the occurrence of SHAI at high altitude as a function of the SHAI score, ACZ prescription, and use and fulfillment of the acclimatization rule. Results: The occurrence of SHAI was 22.6%, similar to what was observed 18 yr before (23.7%), whereas life-threatening forms of SHAI (high-altitude pulmonary and cerebral edema) were less frequent (2.6%–0.8%, $P = 0.007$). The negative predictive value of the decision tree based was 81%, suggesting that the procedure is efficient to detect subjects who will not suffer from SHAI.

therefore limiting the use of ACZ. The maximal daily altitude gain that limits the occurrence of SHAI was established at 400 m. The occurrence of SHAI was reduced from 27% to 12% when the recommendations for ACZ use and 400-m daily altitude gain were respected ($P < 0.001$). Conclusions: This multicenter study confirmed the interest of the SHAI score in predicting the individual risk for SHAI. The conditions for an optimized acclimatization (400-m rule) were also specified, and we proposed a rational decision tree for the prescription of ACZ, adapted to each individual tolerance to hypoxia. Key Words: HYPOXIA, ACETAZOLAMIDE, SPEED OF ASCENT, ACUTE MOUNTAIN SICKNESS, EXERCISE, VENTILATORY RESPONSE TO HYPOXIA

An increasing number of sea-level residents visit areas above 4000 m of altitude for leisure, sport-base tourism, or work. They may suffer from severe acute mountain sickness (AMS), high-altitude pulmonary (HAPE) or cerebral (HACE) edema (1). The aforementioned clinical outcomes have been aggregated in a clinical entity called severe high-altitude illness (SHAI), characterized by a serious negative effect on physical activity. A number of studies have proposed various markers of susceptibility to AMS but failed to demonstrate any predictability of these markers, mainly because they were obtained from a limited number of subjects.

From a cohort of 1017 sea-level natives, we developed a risk prediction score of SHAI (SHAI score) combining clinical and physiological factors obtained from a hypoxia submaximal exercise test before their stay at high altitude (HA; Table 1) (2,5). This score was the first to predict the risk of SHAI in a large cohort of sea-level residents visiting HA regions (3,5) and was then used in subsequent studies (6–8). A decision tree was designed to standardize the use of the SHAI score 1) to detect high-risk subjects for SHAI and 2) to prescribe advice for acclimatization and eventually acetazolamide (ACZ) for the prevention of SHAI (Fig. 1) (4). ACZ is the most efficient drug commonly given for the prevention of SHAI but may have some side effects and contraindications (9–11).

Therefore, the main goal of this decision tree was to minimize the risk of SHAI while also minimizing the use of ACZ. A commonly given recommendation is to climb gradually, but the threshold given for the daily altitude gain in the literature varies from 300 to 600 m (1,12). When an advice is given with a lower and an upper range, people have a clear tendency to conform to the upper range, putting them at a higher risk. Moreover, the determination of this daily altitude gain is not clear in the literature.

The objective of the present study was to validate the decision tree in a large population of subjects explored in a multicenter network (multiSHAI) gathering 15 centers in France, Belgium, and Italy. Our goal was to standardize the use of SHAI score and the advice given to the subjects before their stay at HA. Specific objectives were to propose 1) a validated rule for an optimized prescription of ACZ and 2) a validated rule for the daily altitude gain.

METHODS

The protocol was approved for all centers involved in the study by the “Comité de Protection des Personnes du Sud-Ouest et Outre-Mer IV” Ethics Committee. All participants provided written informed consent before participation.

Subjects

A total of 1216 subjects were recruited during a routine mountain medicine consultation performed before their sojourn at HA (for tourism, trekking, expedition, or work) in 15 medical centers in France, Belgium, and Italy from August 2017 to December 2019. All subjects coming to the routine mountain medicine consultation were invited to participate in the study, as far as their maximal altitude objective was above 4000 m and their minimum duration of stay above 3500 m was 2 d.

Study Protocol

Each subject went through a standard medical consultation and performed a hypoxia exercise test, as previously described (2,6). They were given a field questionnaire to fill out on a daily basis during their stay at HA. Among them, 655 (54%) sent back their questionnaire after their sojourn at HA.

Data Collection

Computation of the SHAI score. The SHAI score was calculated as previously described (3). Items entering the score are shown in Table 1. The value of the score and the threshold to define high-susceptible and low-susceptible subjects were shown to depend on two specific conditions:

- subjects with previous experience at HA (daytime maximal altitude reached ≥ 4000 m, nighttime (sleep) maximal altitude reached ≥ 3500 m) on two occasions
- subjects without such experience

TABLE 1. Computation of the SHAI score to define the individual susceptibility to SHAI.

| Item | Subjects with Previous Experience at High Altitude | Subjects without Previous Experience at High Altitude |
|---|--|---|
| History of SHAI | 2.5 | |
| Planned daily altitude gain (>400 m per night) | 2 | 2 |
| History of migraine | 1.5 | 0 |
| Geographical location (Aconcagua, Ladakh-Zanskar, Mont-Blanc) | 1 | 0.5 |
| Age <46 yr | 0.5 | 0 |
| Female sex | 0 | 0.5 |
| Regular endurance physical activity ^a | 0.5 | 1 |
| HVRe (L·min ⁻¹ ·kg ⁻¹) <0.68 | 3 | 3 |
| HVRe (L·min ⁻¹ ·kg ⁻¹) ≥0.68 and <0.94 | 1 | 1 |
| HCRe (bpm·% ⁻¹) <0.72 | 1 | 1 |
| HCRe (bpm·% ⁻¹) ≥0.72 and <0.95 | 0 | 1 |
| ΔSaO ₂ Exercise (%) ≥24 | 0 | 2 |
| ΔSaO ₂ Exercise (%) ≥19 and <24 | 0 | 1 |
| Threshold to define high susceptibility | >5 | >5.5 |

Numerical values of thresholds for HVRe, HCRe, and ΔSaO₂Exercise were determined in previous publications (2–4).

ΔSaO₂Exercise, decrease in arterial O₂ saturation in hypoxia at exercise; HCRe, cardiac response to hypoxia at exercise; HVRe, ventilatory response to hypoxia at exercise.

^aAt least 40 min of intense aerobic exercise three times a week.

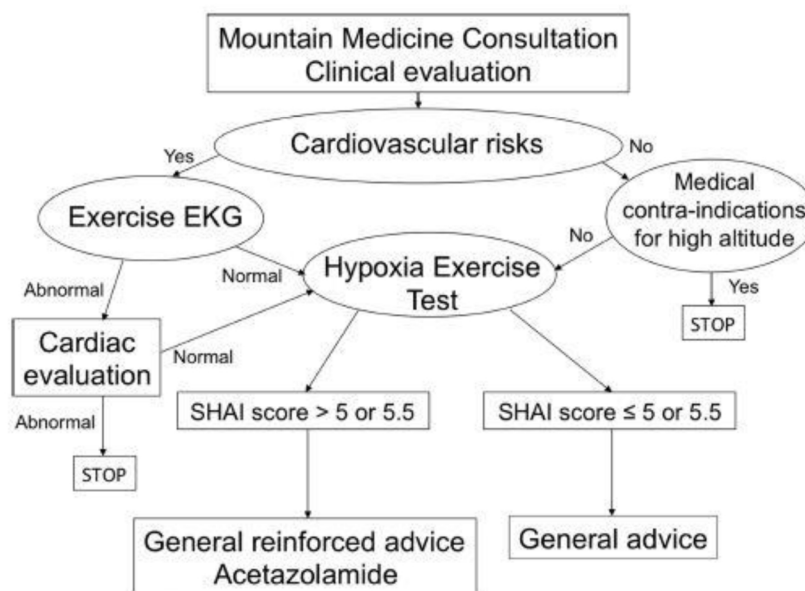


FIGURE 1—Decisional tree used during the mountain medicine consultation. In case of the absence of cardiovascular disease or any other medical contra-indication for HA, the hypoxia exercise test is performed and the SHAI score calculated (see text for details). When the score is below the threshold (5 for subjects who have a previous experience at high altitude, 5.5 for those who do not), general advice for prevention of acute altitude illness is given: limit intense exercise, good hydration, respect the 400-m rule of acclimatization, avoid hypnotics, and so on. When the score is above the threshold, 1) advice are reinforced, insisting on the potential risk of severe manifestations if these advices are not followed, and 2) ACZ is given for a preventive use: 125 mg B.I.D. (morning and midday), starting the day before reaching 3000 m and continuing until the day when the maximal altitude is reached, but not longer than 7 d.

medical consultation. From the analysis of the questionnaire, the following information was derived:

-highest altitude reached

-highest daily altitude gain in the first 2 wk of the stay over 3000 m (after 2 wk, the acclimatization process is supposed to be completed). It was calculated as the maximal difference of sleeping altitudes between two consecutive nights, considering the mean of two successive daily intervals. For example, the following calculation was done for two given profiles of ascent:

Night 1: 3000 m – Night 2: 3800 m – Night 3: 3900 m. Calculated gain: 450 m/night
Night 1: 3000 m – Night 2: 3800 m – Night 3: 3400 m. Calculated gain: 200 m/night

If the night before the first night above 3000 m (i.e., 3800 m) is lower than 3000 m (i.e., 2500 m), the value for this night is taken as 3000 m, assuming that up to 3000 m, the climb does not need a progressive acclimatization. The 400-m rule is considered fulfilled if the daily altitude gain is equal or lower than 400 m.

-The Lake Louise score (LLS) to define AMS (13). LLS was calculated from five items (headache, digestive symptoms, fatigue, dizziness, sleep disturbances) quoted from 0 to 3. The total score is the sum of the five items and allows to define three levels of outcome: 0–2, no or mild AMS; 3–5, moderate AMS; and 6 and above, severe AMS. The functional item (0–3) is used to evaluate the impact of the symptoms on the activity of the subject.

-HAPE was defined by the presence of clinical signs of respiratory distress (dyspnea, cyanosis, rales), confirmed by a thorax x-ray upon descent to low altitude. HACE was defined by clinical signs of neurological deficit (ataxia, mental confusion). The diagnosis of HAPE or HACE was always confirmed by an expert, either on the spot where the disorder occurred or later on when hospitalized.

-The presence of localized peripheral edema -The preventive use of ACZ during the stay -The personal feeling of the subject if he or she significantly suffered from intolerance to HA and if his/her symptoms led him/her to seek medical advice

SHAI outcome was defined if the subject had a maximal LLS of 6 and above or HAPE or HACE.

Quality Control

Independently, the clinical and physiological database as well as the field questionnaires was analyzed for quality control, identifying missing or uninterpretable data and incorrect values for physiological variables. Data from 14 subjects were rejected, and therefore, 641 subjects were included in the analysis.

Decision Tree

From our 20-yr experience of mountain medicine consultation and hypoxia exercise test, we designed a decision tree adapted for people aiming to visit HA regions (4). This algorithm is presented in Figure 1. The first part of the tree is the standard medical consultation aiming at identifying cardiovascular risk factors and for medical contraindications for HA, as proposed by various authors (14,15). Then, the hypoxia exercise test is performed and the SHAI score is calculated for each individual, integrating the estimated possibility to respect the 400-m rule for daily altitude gain. If the SHAI score is higher than the susceptibility threshold, ACZ is prescribed (twice 125 mg·d⁻¹—morning and midday—starting the day before reaching 3000 m and continuing until the day when the highest altitude is reached but not longer than 7 d). The threshold has been previously defined as 5.5 for subjects without previous experience of stay at HA (day altitude ≥4000 m, night altitude ≥3500 m, on two occasions) and 5 for subjects who have such experience (6). Whatever the score, standard recommendations are given to all subjects: respect of the 400-m rule, reducing physical activity at the beginning of the stay over 3000 m, good hydration, and avoid hypnotics. Patients with a history of allergy for ACZ or any sulfonamide are not given ACZ. Caution is taken with pregnant women, patients on diuretics, patients with recurrent kidney stones, and those at risk for retinal detachment. Altogether, when both the decision tree (ACZ use if high susceptible) and the 400-m rule were respected, only 12% of the subjects suffered from SHAI as compared with 27% if the recommendations were not respected ($P < 0.001$; Fig. 3).

As expected, subjective appreciation of tolerance to HA was associated with the occurrence of SHAI: difficulties for acclimatization were reported in 55% of subjects who suffered from SHAI compared with only 14% in subjects without SHAI (Table 3). Among subjects with SHAI, 13% had a field medical consultation, whereas only 2% of SHAI-free subjects did (Table 3).

Justification of the threshold for the daily altitude gain rule. The highest daily altitude gain in the first 2 wk at HA was recorded for each subject, and the relative frequency is reported in Figure 4A for subjects who suffered (SHAI+) or not (SHAI-) from SHAI. The number of SHAI+ subjects exceeds the number of

SHAI- subjects above 400 m (Fig. 4A). This threshold was confirmed by the calculation of the cutoff value of the daily altitude gain by maximizing the Youden index (Fig. 4B). A clear cutoff for daily altitude gain is therefore 400 m.

Compliance markers. Compliance of the physician with the SHAI score to prescribe ACZ was 75%. Compliance of the subject with the prescription of ACZ by the physician was 73%. Among subjects who were prescribed ACZ, 17% did not use it, whereas 9% of subjects who were not prescribed ACZ effectively took it ($P < 0.001$). Altogether, the use of ACZ was in accordance with the SHAI score for 70% of all subjects. Compliances to SHAI score and to prescription were not influenced by the occurrence of SHAI. Compliance of the physician to SHAI score was higher when subjects took ACZ ($P = 0.013$), whereas compliance of the subject to the prescription was higher when ACZ was used ($P = 0.009$). Among high-susceptible subjects

TABLE 2. General characteristics of the population.

| | Female | Male | <i>P</i> |
|-------------------------------------|-------------|-------------|----------|
| No. subjects | 292 | 349 | |
| Age, yr | 48.8 ± 14.6 | 51.8 ± 13.9 | 0.008 |
| Body mass index, kg·m ⁻² | 22.2 ± 3.0 | 24.4 ± 2.9 | <0.001 |
| Coronary diseases | 1 | 6 | 0.13 |
| Systemic hypertension | 15 (5.1) | 42 (12.0) | 0.002 |
| Raynaud syndrome | 28 (9.6) | 3 (0.9) | <0.001 |
| Hypercholesterolemia | 16 (5.5) | 41 (11.7) | 0.005 |
| Asthma | 14 (4.8) | 20 (5.7) | 0.59 |
| Bronchopulmonary diseases | 7 (2.4) | 6 (1.7) | 0.54 |
| Allergy | 90 (30.9) | 93 (26.6) | 0.23 |
| Perinatal events | 2 (0.8) | 8 (2.6) | 0.11 |
| Migraine | 35 (12.0) | 25 (7.2) | 0.037 |
| Menopause | 148 (53.4) | | |
| Smoking | 28 (9.6) | 29 (8.3) | 0.57 |
| Sleep apneas syndrome | 6 (2.1) | 14 (4.0) | 0.16 |
| Snoring | 40 (13.7) | 106 (30.4) | <0.001 |
| Regular endurance training | 94 (32.2) | 154 (44.1) | 0.002 |
| Previous stay at HA | 106 (36) | 157 (45) | 0.026 |
| Previous SHAI if previous stay | 21 (20) | 24 (15) | 0.34 |
| Planned altitude, m | 5250 ± 753 | 5366 ± 777 | 0.06 |
| SHAI score | 5.1 ± 2.3 | 4.7 ± 2.0 | 0.03 |
| LLS | 4.0 ± 2.5 | 3.8 ± 2.6 | 0.42 |
| Presence of SHAI | 64 (22.0) | 81 (23.0) | 0.70 |
| Peripheral edema | 59 (20.2) | 34 (9.7) | <0.001 |
| Subjective feeling of intolerance | 71 (24.3) | 80 (22.9) | 0.68 |
| Medical consultation | 9 (3.1) | 20 (5.7) | 0.11 |
| Highest altitude reached | 5178 ± 738 | 5223 ± 744 | 0.46 |
| Highest daily altitude gain | 420 ± 163 | 418 ± 182 | 0.88 |
| Preventive use of ACZ | 141 (48) | 138 (40) | 0.026 |
| Compliance to prescription | 217 (74) | 253 (73) | 0.60 |

Values presented are mean ± SD or number (percentage). *P* value is calculated via unpaired Student's *t*-test for continuous variables and via χ^2 or Fisher's exact test for categorical variable.

TABLE 3. Outcomes in the four groups of subjects according to ACZ use and occurrence of SHAI.

| | No Preventive Use of ACZ | | Preventive Use of ACZ | | P ACZ Effect | P SHAI Effect |
|----------------------------------|--------------------------|------------------|-----------------------|------------------|-----------------|------------------|
| | No SHAI | Presence of SHAI | No SHAI | Presence of SHAI | | |
| No. subjects | 282 | 80 | 214 | 65 | | 0.72 |
| SHAI score | 3.84 ± 1.92 | 4.64 ± 2.18 | 5.83 ± 1.90 | 6.36 ± 1.67*** | <0.001 | <0.001 |
| LLS | 2.92 ± 1.58 | 7.69 ± 1.54 | 2.70 ± 1.52 | 7.40 ± 1.93*** | 0.075 | <0.001 |
| Functional item | 0.37 ± 0.65 | 1.43 ± 1.00 | 0.52 ± 0.77 | 1.80 ± 1.06*** | 0.001 | <0.001 |
| No or mild AMS | 107 (38) | 0 (0) | 103 (48) | 0 (0) | | NA |
| Moderate AMS | 175 (62) | 0 (0) | 111 (52) | 0 (0) | | NA |
| Severe AMS | 0 | 80 | 0 | 65 | | NA |
| HAPE | 0 (0) | 2 (2.4) | 0 (0) | 3 (4.7) | | NA |
| HACE | 0 (0) | 0 (0) | 0 (0) | 0 (0) | | NA |
| Peripheral edema | 32 (11) | 19 (24) | 25 (12) | 17 (26)** | 0.73 | <0.001 |
| Subjective feeling of severe AMS | 39 (14) | 45 (56) | 32 (15) | 35 (54)*** | 0.81 | <0.001 |
| Medical consultation | 6 (2) | 8 (10) | 5 (2) | 10 (15)*** | 0.36 | <0.001 |
| Maximal altitude reached, m | 5097 ± 747 | 5424 ± 678 | 5212 ± 749 | 5352 ± 688** | 0.21 | 0.001 |
| Maximal daily altitude gain, m | 388 ± 184 | 493 ± 170 | 413 ± 152 | 478 ± 160*** | 0.26 | <0.001 |
| Compliance to SHAI score | 217 (77) | 67 (84) | 146 (68) | 49 (75) | 0.013 | 0.10 |
| Compliance to prescription | 197 (70) | 54 (68) | 171 (80) | 48 (74) | 0.009 | 0.36 |

Values presented are mean ± SD or number (percentage). P value is calculated as indicated in the Statistical Analysis section (ANOVA or χ^2 test when appropriate).

**P < 0.01, SHAI with ACZ vs no SHAI without ACZ.

***P < 0.001, SHAI with ACZ vs no SHAI without ACZ.

AMS, acute mountain sickness (no or mild, LLS <3; moderate, LLS 3–5; severe, LLS >5); Compliance to prescription, use of ACZ by the subject conforms to the prescription by the physician; Compliance to SHAI score, prescription of ACZ by the physician conforms to SHAI score vs threshold; Functional item, functional item (0–3) of the LLS; NA, not applicable.

(SHAI score > threshold), 16% did not have a prescription of ACZ, and finally 33% did not take ACZ. Among low-susceptible subjects (SHAI score ≤ threshold), 31% had a prescription ACZ, whereas 29% effectively took ACZ.

DISCUSSION

This study is the first multicenter attempt to validate the subjects preventive measures for high-altitude illness in a large cohort ACZ, (N = 641) of persons planning to visit HA (>4000 m) regions.

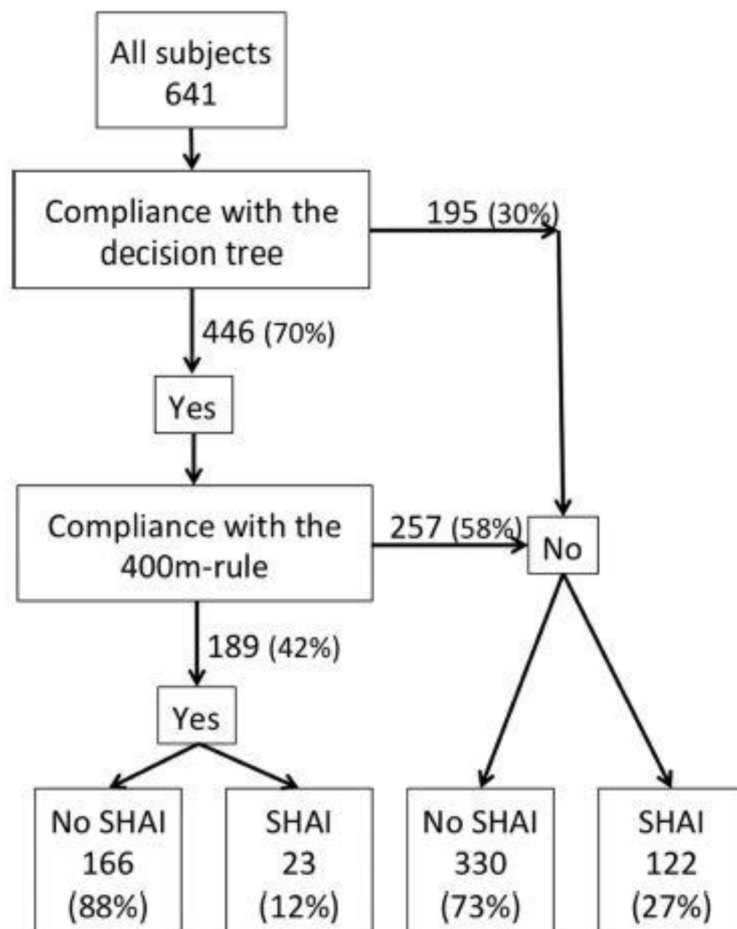


FIGURE 3—Classification of subjects following the compliance with the decision tree and the 400-m rule. In each block is the number of subjects (percentage of above population size).

General characteristics of the population studied did not evidence obvious differences when compared

with a general population. We compared the main characteristics of our population who returned their questionnaire (n=641) with the overall population initially included in the study (n= 1216). There was no difference in age (50 ± 14 vs 46 ± 15 yr), in sex ratio (male/female) (1.2 vs 1.3), in the proportion of subjects with previous SHAI (7% vs 8%), or in the proportion of high-susceptible subjects (39% vs 36%). Therefore, there was no a priori bias in the analysis of the subgroup that returned the questionnaire. No significant sex effect was found for the occurrence of severe AMS, as found in some studies (3,17) but not in others (2,18,19). All five subjects who presented HAPE were men; however, this limited number did not allow us to draw any conclusion. Peripheral edema was approximately two times more frequent in women than in men, as previously demonstrated (8). When comparing the occurrence of high-altitude illness in the present study with data previously obtained with the same methodology between 1992 and 2008 (2), the occurrence of SHAI was insignificantly reduced (23.7%–22.6%), whereas the occurrence of HAPE (1.7%–0.8%) and HACE (1%–0%) was drastically reduced. The overall decrease in life-threatening forms of altitude sickness in these two large cohorts (2.7%–0.8%, $P=0.007$) is encouraging, although the small number of affected subjects makes it difficult to attribute to the mountain medicine consultation (i.e., better information about susceptibility given during this medical visit).

The decision tree and the prescription of ACZ. We propose a decision tree based on the individual SHAI score, which had already been proven to detect persons susceptible to severe high-altitude illness (3). The efficiency of the decision tree cannot be evaluated by standard indices used in binary classification tests because it includes a main intervention (prescription of ACZ depending on the SHAI score) aiming at decreasing the occurrence of the outcome (SHAI at HA). As it was not ethical to compare a treated group (recommendations including ACZ) with an untreated group (no recommendation), the effectiveness of the decision tree was evaluated by studying the occurrence of SHAI in subjects who complied with the protocol. Our main result is that the SHAI score obtained during the pre-sojourn visit is in good agreement with the occurrence of SHAI during the sojourn at HA. Participants who suffered from SHAI in spite of preventive use of ACZ showed a much higher SHAI score (6.36) than those who did not suffer from SHAI without taking ACZ (3.84). The low positive predictive value (29%) is expected because subjects detected as high susceptible will be given particular advice to limit their risk of SHAI during their stay at HA. Furthermore, these subjects who have identified themselves as being at high risk will probably be more cautious. The high negative predictive value (81%) confirms that low-risk subjects have a low probability to develop SHAI and that the procedure is efficient to detect subjects who will not suffer from SHAI, therefore limiting the use of ACZ.

Precise value of maximal daily altitude gain. The daily altitude gain is a well-established determinant factor for the occurrence of SHAI (20–22), although the precise rule to be respected has not been well defined (23). The gap between 300 and 600 m given in the literature seems much too large if we consider that the great majority of observed altitude gains lie between these values. As shown in Figure 4A, the relative frequency of SHAI is reduced only in the strict range 0 to 400 m, confirming that the threshold for the golden rule “Do not go too high too fast” should be 400 m. This was confirmed by the Youden index (Fig. 4B). In fact, from our first study about risk factors for high-altitude sickness in 1988 and in the following studies, we used a strict threshold of 400 m (2–4,8,24). Thus, we propose the following rule: “Daily altitude gain should not be higher than 400 m above 3000 m, at the beginning of the stay at HA. This daily altitude gain is computed as the mean between two consecutive day-intervals. In other words, the two-day (three-night) altitude gain should not exceed 800 m.” The limited effect observed in high-susceptible subjects respecting the 400-m rule suggests that in this high-risk category, respecting the 400-m rule cannot fully counterbalance individual susceptibility.

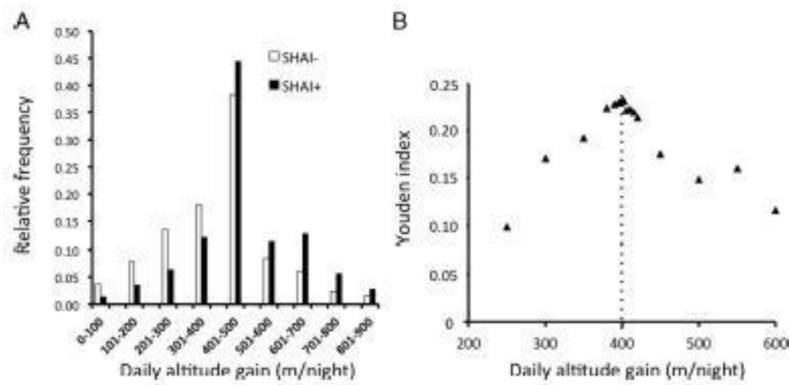


FIGURE 4—A, Histogram of observed daily altitude gains in subjects who suffered (SHAI+) or not (SHAI-) from SHAI. SHAI is more frequent above 400 m of daily altitude gain. See text for the exact calculation of daily altitude gain. B, Computation of the Youden index ($- \text{Sensitivity} + \text{Specificity} - 1$) as a function of the threshold for daily altitude gain. The maximal value of the index is observed for a 400-m threshold.

Compliance with decision tree and with prescription. The compliance of the physicians with the decision tree was not perfect because 25% of ACZ prescription was not in accordance with the SHAI score. Some physicians had a clear tendency to prescribe ACZ, whereas the score did not warrant prescription. Similarly, 27% of the subjects did not follow the physician’s prescription. Altogether, the use of ACZ did not conform to the value of the SHAI score in 30% of all subjects. Physicians seem to overprescribe ACZ, probably because they think it will reduce the risk even in low-risk subjects. Subjects seem to underuse ACZ when prescribed, either for ethical reasons or because they fear side effects.

Limitations. The outcome in field conditions is evaluated through the LLS, which is a combination of nonspecific symptoms. A recent proposal was made to remove the “sleep” item from the total score, but major methodological flaws (absence of control of medications) do not allow for the validation of this reduced score for field studies (25,26). Moreover, digestive symptoms and fatigue are nonspecific symptoms that can be provoked by many other conditions such as gastrointestinal infections or intense exercise. It was recently shown that dizziness and neurological manifestations can be linked to a ventilatory hyperresponse to hypoxia and thus considered as a good marker of acclimatization (27). Therefore, we should accept the LLS in its original version for field studies, with all its imperfections and subjective drawbacks. No case of HACE was reported. However, several subjects reported symptoms that may account for starting cerebral edema, such as drowsiness, slurred speech, and confusion, but these symptoms rapidly disappeared on descent and no participant reported loss of consciousness. One may argue that the presence of a subgroup of subjects with previous experience of SHAI may have had an effect on our results. However, the proportion of these subjects in our cohort is limited (7%) and comparable to a general population (8%). By reanalyzing our data, it seems that the overall results are not modified after excluding this subgroup. For ex-ample, the incidence rates of SHAI are 19% in low-susceptible subjects and 27% in high susceptible subjects, and the difference is still significant ($P = 0.023$). If we now consider the specific subgroup with previous episodes of SHAI, when both decision tree and 400-m rule were respected, 27% suffered de novo from SHAI, whereas 64% were sick if they did not respect the rules ($P = 0.04$), suggesting that the consultation is even more important for subjects with previous episodes of SHAI.

Another limitation is that the compliance of the physician to follow the decision tree and of the subject to follow the prescription (based on the decision tree) was not perfect, with a tendency for an overprescription of ACZ by the physician. One of the objectives of this study was to give an objective tool to limit this prescription to those who would really need it, knowing that ACZ may have some side effects (polyuria, dehydration, paresthesias, digestive symptoms, fatigue) (11) and could interfere with current medications, as seen in trekkers in Nepal (28). In spite of this probable slight overuse of ACZ, a great majority (80%) of persons who were low susceptible and did not take ACZ did not suffer from SHAI.

Preacclimatization (in normobaric or hypobaric conditions) before trekking or expedition has been recently developed to “prepare” the subject to the hypoxic stress and limit the occurrence of SHAI (21,29–31). In the present study, no subject had preacclimatized, so we cannot evaluate the efficiency of this hypoxic training method. However, based on previous data, it could be suggested as a countermeasure to reduce the risk of SHAI in high-susceptible subjects (30,31).

In 10 yr from 2008 to 2018, there is clear tendency for a decrease in the incidence of life-threatening

forms of altitude sickness (HAPE, HACE). The incidence of HAPE in our cohort (0.8%) is lower than what is currently observed in the literature (2.5%–4% in trekkers) (1,20). However, severe AMS is still observed in around one quarter of the population. The advice for a progressive altitude gain (400-m rule) has been rationalized and documented. Detecting low-susceptible subjects seemed useful to limit and rationalize the prescription of ACZ. Moreover, it allows for the detection of high-susceptible subjects for whom in addition to ACZ prescription, preventive advice (limitation of exercise intensity, proper hydration, respect of the acclimatization rule, avoidance of hypnotics, eventual preacclimatization) is particularly important. However, it is clear that the 400-m rule is sometimes impossible to fulfill because of geographical and practical constraints, such as during the Kilimandjaro climb or when the arrival at HA is abrupt, by flight or by car (Ladakh, Lhassa, La Paz, etc.).

An important aspect of the decision tree based on the SHAI score is that it allows for an individualization of the prescription and advice given to the subject, by taking into account his/her personal physiological response to hypoxia (32) as opposed to a simple interview and general advice proposed by others (33). Altogether, the main result comforting the interest of a prealtitude medical consultation with a hypoxic exercise test leading to the computation of the SHAI score is that the occurrence of SHAI is reduced by more than half (27%–12%) when the recommendations, in accordance with the SHAI score and the 400-m rule, are respected by the subjects. The limited cost of the consultation (100–120 €) encourages people with no previous experience of high altitude (59% of our cohort) to perform a hypoxia exercise test and evaluate their personal tolerance to hypoxia.

CONCLUSIONS

The present observations obtained in a large multicenter cohort confirmed the interest of the SHAI score in predicting the individual risk for SHAI, allowed to determine the precise conditions for an optimized acclimatization (400-m rule) and proposed a rational decision tree for the prescription of ACZ.

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