Smartphone-enabled Heart Rate Variability and Acute Mountain Sickness

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Introduction

The autonomic system and sympathetic activation appears integral in the pathogenesis of acute mountain sickness (AMS) at high altitude (HA), yet a link between heart rate variability (HRV) and AMS has not been convincingly shown. In this study we investigated the utility of the smartphone-derived HRV score to predict and diagnose AMS at HA.

Methods

Twenty one healthy adults were investigated at baseline at 1400m and over 10 days during a trek to 5140m. HRV was recorded using the ithleteTM HRV device.

Results

AMS occurred in 11 subjects (52.4%) at >2650m. HRV inversely correlated with AMS Scores (r=-0.26; 95% CI -0.38 to -0.13: p<0.001). HRV significantly fell at 3700m, 4100m and 5140m versus low altitude. HRV scores were lower in those with both mild (69.7±14.0) and severe AMS (67.1±13.1) versus those without AMS (77.5±13.1; effect size n_2=0.043: p=0.007). The HRV score was weakly predictive of severe AMS (AUC 0.74; 95% CI 0.58 to 0.89: p=0.006). The change (delta) in the HRV Score (compared with baseline at 1400m) was a moderate diagnostic marker of severe AMS (AUC 0.80; 95% CI 0.70 to 0.90; p=0.0004). A fall in the HRV score of >5 had a sensitivity of 83% and specificity of 60% to identify severe AMS (likelihood ratio 1.9). Baseline HRV at 1400m was not predictive of either AMS at higher altitudes.

Conclusions

The ithlete HRV score can be used to help in the identification of severe AMS, however a baseline score is not predictive of future AMS development at HA

INTRODUCTION

High altitude (HA) illness consists of Acute Mountain Sickness (AMS), which is usually a self-limiting collection of symptoms including headache and lethargy, which can lead to? HA Cerebral Edema (HACE) and HA Pulmonary Edema (HAPE). HACE and HAPE are life-threatening.[1]The incidence of AMS is dependent on a number of factors which include individual susceptibility, the speed of ascent and altitude attained.[2] It is known to affect >50% of persons at ascending to an altitude of 5000m.[1-4]

The mechanism of AMS development is highly complex and is still not fully understood.[1] HA-related hypoxia and changing homeostasis triggers a number of well-established physiological responses which include the adrenal medullary release of epinephrine and an increase in whole body and tissue specific sympathetic nerve activity.[5] This leads to an increase in metabolic, heart and respiratory rate and changes in cerebral blood flow, that act to counteract the effects of hypobaric hypoxia.[5-7] There is accumulating evidence to suggest that the autonomic system and alterations in the sympathetic/parasympathetic balance may play an important pathogenic role in the development of AMS and its susceptibility.[7-11]

Heart rate variability (HRV) represents an increasingly utilised, yet non- invasive method of assessing autonomic function. HRV is quantified by measuring changes in cardiac beat-to-beat (R-R) intervals which are under continuous autonomic control.[12] Conditions that are known to affect the sympathetic/parasympathetic balance such as inter-current illness, cardiovascular disease, physical overtraining ande mental stress have been shown to lead to a reduction in HRV.[13-15] Changes in HRV have been demonstrated on ascent to HA and typified by an increase in measures of sympathetic and a decrease in parasympathetic activity.[16,17] However, a link between alterations in HRV and AMS development at HA has not been convincingly shown.[3,18-21]

Traditional methods of HRV measurement have required relatively large and expensive equipment with a need for at least five minutes of electrocardiographic (ECG) recording.[22] The ithelte™ (HRV Fit Ltd, Southampton, UK) system is a recently available method of non-invasive HRV assessment from only 55 seconds of recording obtained via a chest strap or finger sensor linked to a mobile smartphone. The ithelte™ generates an intuitive 1-100 HRV score which is a logarithmic adaptation of the root mean square of successive R-R intervals (RMSSD) provided by traditional HRV devices.[23] It has been shown that the RMSDD, can be derived from shorter recording times and is less prone to the effects of respiration, which is

advantgeous for the HA environment where hypoxia and hyperventilation is typical.[24-26] The ithlete HRV score has been shown to provide good to excellent agreement with the RMSSD obtained from a standard five minute electrocardiographic recording at sea level and more recently at HA.[25,27]

The aim of this study was to investigate, for the first time, the practical use of the ithlete™ HRV monitor as a way of monitoring acclimatisation to HA and the onset of AMS.

METHODS
Subjects
Healthy British Military service personnel aged >18years were included. Health status was confirmed following a detailed baseline health questionnaire. All subjects had to be in date with their fitness assessments including the military fitness standard for a 1.5 mile run. Key exclusion criteria included subjects with any history of cardiac arrhythmias or need for either rate or rhythm controlling medications. All subjects lived at low altitude and none had prior exposure to >1400m terrestrial altitude in the four weeks prior to this study.

Data collection took place during a trek to Dhaulagiri base camp (western Nepal). Subjects were all part of the British Services Dhaulagiri Medical Research Expedition. After arriving at Kathmandu at 1400m, the subjects travelled by road to 890m, then 2650m before commencing the ascent on foot to 5140m (over Dhamphus Pass, 5240m) over 10 days (figure 1).

Recording of Heart Rate variability (HRV)
HRV was recorded at approximately 0700 each morning using a finger sensor and linked smartphone via the ithlete™ app (HRV Fit Ltd. Southampton, UK) as previously described and validated.[25,27] All participants were studied post micturition but prior to breakfast or caffeine. All subjects were seated, wearing warm clothing in either a tent or building. All subjects were encouraged to rest for at least five minutes before the HRV recordings were obtained. The ithlete™ acquires a 55 second recording with visual breathing prompts to regulate the rate of both inspiration and expiration in order to standardise the HRV measurements. The ithlete™ modifies the acquired RMSSD by taking the natural log transformation and multiplying by twenty (lnRMSSD $\times$ 20) to provide a more interpretable HRV score for the user on a ~100 point scale.[23] It has a patented algorithm for the exclusion of both artifacts and ectopic beats whereby R-R (P-P) intervals of <500ms or >2000ms are excluded as are abnormal adjacent R-R intervals whose difference significantly exceeds the mean R-R interval.[28]

Acute mountain sickness (AMS) scores
Measurement of AMS was undertaken at the same time that HRV assessments were performed using the Lake Louis Scoring System (LLS).[29,30] A total score of >3 in the presence of headache was used to diagnose AMS and a score >5was considered consistent with severe AMS.[29-31]

Physiological measurements
Oxygen saturations (SpO_2) and heart rate were measured using a Nonin Onyx (Nonin Medical Inc, Plymouth, Minnesota) pulse oximeter just prior to the assessment of HRV.

Ethics
The study was approved by the Ministry of Defence Research Ethics Committee and complied with the standards set in the Declaration of Helsinki. All subjects gave written informed consent.

Statistical analysis

Statistical calculations and figures were performed using GraphPad Instat and GraphPad Prism version 4.00 for Windows. Normality of continuous data was assessed following inspection and the Kolmogorov-Smirnov statistic. All continuous data are presented as the mean ± standard deviation. Independent two group comparisons of continuous data were analysed using an unpaired t test or Man Whitney test for parametric and non-parametric data respectively. Comparisons of continuous data from >3 groups of parametric and on parametric data were performed using a one-way ANOVA or Kruskal-Wallis test respectively. The effect size (n) for any potential changes in HRV with HA was also calculated as the sum of squares for between-treatment effects divided by the total sum of squares. Correlation analyses were performed using Pearson Correlation and Spearman's rank correlation with 95% confidence intervals depending on data normality. Receiver operating characteristic (ROC) curves were constructed to assess the sensitivity and specificity of the ithlete™ and the area under the curve (AUC) for the HRV score to accurately identify subjects with AMS was determined. A p value of <0.05 was considered significant for all comparisons.

RESULTS
Twenty one subjects (20 men, 1 woman) aged 36.2±6.9 (years were studied over their first 13 days in Nepal (table 1). Seventeen subjects reached 5140m on day 11, two on day 13 and two beyond the study period. There was a significant fall in SpO_2 and increase in resting heart rate with gains in HA (Table 2). There was also an overall increase in LLS at HA (table 2) compared with the values at 890m. Successful ithlete™ recordings were possible in 93% of cases. AMS occurred in 11 subjects (52.4%) and all at an altitude of >2650m. There was a weak but significant correlation between HRV score and SpO_2 r=0.16; 95% CI 0.02 – 0.29: p=0.02). HRV inversely correlated with LLS Scores (r=-0.26; -0.38 to -0.13: p<0.001). There was a moderate inverse correlation between the HRV score and heart rate (r=-0.41; -0.52 to 0.30: p<0.0001).

HRV and acute Mountain Sickness
There was a non-significant trend to reducing HRV score with increasing HA (n_2 0.042; p=0.09) (table 2 and figure 2). However, this fall was significant at 3700m, 4100m and 5140m versus 890m. The HRV score fell with increasing AMS Scores (ANOVA n_2=0.043; p=0.007) (figure 3), but this difference was only significant on post-test between those with a LLS of 0 versus those with a LLS >5. HRV scores were significantly lower in those with AMS (mild and severe combined) 67.9±13.1 vs those without AMS 77.5±13.1 (p=0.002). HRV scores significantly fell from 77.5±13.1 for those with no AMS to 69.7±14.0 with mild AMS and 67.1±13.1 with severe AMS (p=0.007, figure 4), however the difference was only significant between those without AMS and those with severe (not mild) AMS on post-test.

The HRV score was very marginally better at distinguishing severe AMS versus those without severe AMS (ROC curve 0.74; 95% CI 0.58 to 0.89: p=0.006) than differentiating all AMS (mild and severe combined) from no AMS (area under the curve [AUC] 0.71: 95% CI 0.58 to 0.84; p=0.002) (figure 5). An HRV score of <76 had a sensitivity of 83% and a specificity of 53% for the correct identification of severe AMS at a likelihood ration of 1.80 (figure 5). However, the change (delta) in the ithlete™ HRV Score (compared with baseline at 1400m) was a better predictor of severe AMS (AUC 0.80; 95% CI 0.70 to 0.90; p=0.0004) (figure 6). A fall in the HRV score of >6 points compared had a sensitivity of 83% and specificity of 60% to identify severe AMS (likelihood ration 1.9) (figure 6). There was no difference in the HRV

scores at 1400m between those who did or did not develop severe or any AMS at higher altitudes.

DISCUSSION

This is the first study, to the author's knowledge, to investigate the link between AMS and HRV at HA to 5140m using a portable smart phone HRV device (ithlete™). The ithlete™ HRV Score inversely correlated with the LLS but was a relatively weak discriminator for the identification of AMS and its severity. However, a fall in the HRV score, at HA versus baseline, of >6 versus baseline was a moderate *albeit* non-specific marker of severe AMS.

There is an increasing body of research that has shown that HA exposure leads to a reduction in HRV. This is thought to relate to a significant increase in sympathetic and a decrease in parasympathetic tone.[17,18,22] With acclimatization there appears to be progressive shift toward a higher parasympathetic tone.[31] Much less is known about the link between HRV and AMS. There is data to suggest that changes in HRV are linked to the AMS susceptibility and development.[19,22] but also data to the contrary challenging refuting this the link.[20,21] This conflicting data may be partly explained by the marked differences in the design, ascent profile and the methods of HRV recording across the studies. Karinen et al studied 36 climbers on four different expeditions and three differing ascents. The authors found that those with a lower HRV (RMSSD[2min] and HF [high frequency] [2min] from a five minute HRV recording) at 2400m predicted those who later developed AMS at moderate altitudes (3000-4300m).[22] Huang et al study 32 patients over a progressive HA trek to 3440m. They noted that those with both (high frequency) HF% < 20% (suggesting reduced parasympathetic tone) and low frequency: high frequency (LF:HF) ratio > 1.3 (increased sympathetic balance) measured at 1317 m had an odds ratios of 7.00 (p = 0.047) for the subsequent development of develop AMS at 3440m (Huang 2013).[19] The authors did not report data on the RMSSD. In our study whilst we did observe significantly lower ithlete™ HRV (RMSSD) scores in those with AMS and more severe AMS, lower altitude HRV scores failed to predict AMS development at HA. Furthermore the effect size for change in HRV with worsening AMS severity was modest.

One of the major additional confounders in all of these studies examining the relationship of HRV to symptom of AMS has been in the definition of AMS itself. The diagnosis of AMS is made using a self-reported questionnaire based assessment, most notably the LLS and is highly subjective and therefore likely to be influenced by a subjects' expectations or aspirations and it can be a relatively poor predictor of illness.[33,34] For example, in a previous study of 248 healthy adults travelling to 3200m Bartsch has noted that only 61% of the mountaineers reporting a LLS>5 actually said they felt ill.[35] Hence, a more reproducible and objective measure of HA- related illness would be welcome. The rational for using HRV to improve the detection of AMS is strong. Whilst the underlying pathophysiology of AMS is still poorly understood current evidence suggests that it involves vasogenic cerebral oedema secondary to hypoxia-induced sympathetic activation.[1] The normal physiological diuresis at HA, which acts to reduce plasma volume and increase in haematocrit (to improve tissue oxygenation) , is also affected leading to a reduced water clearance and a positive net water balance.[36] Changes in plasma volume which is integral to the HA acclimatisation and AMS development are strongly influenced by alterations in parasympathetic tone.[37] HRV is also heavily afeected by a number of other autonomic stressors such as fitness levels, physical fatigue, cold and exertion which important factors at HA and are known to be contributory factors to AMS development and progression.[38]

One of the greatest clinical applications of the ithleteTM and other HRV measures is in the detection of overtraining which shares many features in common with AMS. Hence further studies examining the utility of HRV to monitor recovery from exercise at HA and to tailor individuals' acclimatisation, rather than relying on guidelines such as 300m ascent per day, would be welcome. The ithleteTM is currently marketed with a visual display of other domains such as sleep, fatigue, irritability and muscle soreness which could be potentially adapted to give a scale related to the LLS and is an area worthy of further research.

This study has a number of limitations and strengths that need to be acknowledged. The ambient temperature varied throughout the study and the HRV measurements were performed in tents above 1400m. It is well known that change in both environment and temperature can influence HRV and due to the nature of this study it was not possible to adjust for these factors.38 In this study we used a finger probe rather than a blue tooth chest strap sensor to acquire heart beat data and successful data recording was not possible in 7% which could have influenced the findings. The ithleteTM only provides a single measure of HRV from a very short recording time. Hence, we do not know whether our findings would be different if another HRV platform and a five-minute recording period with a wider array of HRV data outputs include frequency domain analyses were used. The ithleteTM HRV score is related the RMSSD and is considered a marker of relative parasympathetic activity and does not assess sympathetic tone or the sympathetic/parasympathetic balance provided by more sophisticated devices. However, the aim of this study was to assess the utility of a simple, inexpensive, portable and user friendly deice that is widely available to potentially predict HA related illness and hence maximising the clinical impact of a potentially strongly positive finding. The key strengths of this study was that all subjects underwent the same exercise, diet and acclimatisation protocol and the altitude achieved was significant and greater than the majority of published HRV studies at HA.

In summary this is the first paper to show a practical application of a simple measure of HRV to provide an objective measure of severe AMS. A fall in the ithleteTM HRV score of >6 points from baseline had moderate precision for the detection of severe AMS.

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Table 1: Baseline Demographics

Demographic	Result
Number	21
Age, years (range)	36..2±6.5 (26-48)
Males n, %	20 (95.2%)
Height, cm	177.3±7.9
Weight, kg/m^2	76.2±8.7
Heart rate/ minute	59.7±12.0
Systolic blood pressure	134.3±12.3
Diastolic blood pressure	80.0±8.4
Body mass index kg/m^2	24.2±2.0
Ethnicity, %	
- Caucasian	100%
Smoking status (N, %)	
- Current	9.5%
- Ex	33.3%
- Never	57.2%

Table 1. Effect of High Altitude on Physiological measurements, Lake Louise Scores for Acute Mountain Sickness and Heart Rate Variability

	1400m	890m	2650m	3700m	4100m	5140m	P Value
SpO₂, %	96.6±1.4	96.9±1.7	94.3±2.2	88.8±3.4	88.0±3.4	79.3±5.7	<0.001[bcd]
Heart rate, beats/min	62.3±10.5	60.9±9.6	64.1±11.4	70.8±10.7	76.0±10.4	79.5±11.6	<0.001[bcd]
LLS (range)	0.4±0.7 (0-2)	0.3±0.7 (0-2)	2.2±5.5 (0-23)	1.3±2.1 (0-9)	1.1±2.5 (0-16)	1.8±2.9 (0-15)	0.04b
HRV Score	79.6±14.5	82.8±13.0	78.7±13.1	74.3±14.6*	74.5±12.4*	76.0±12.5*	0.09

LLS, Lake Louis Score for Acute Mountain Sickness; HRV Heart Rate Variability; * significant (p<0.05) differences in unpaired test vs 890m.; a 1400m vs 890m, b 2650m vs 890m, c 3700m vs 890m, d 4100m vs 890m, e 5140m vs 890m
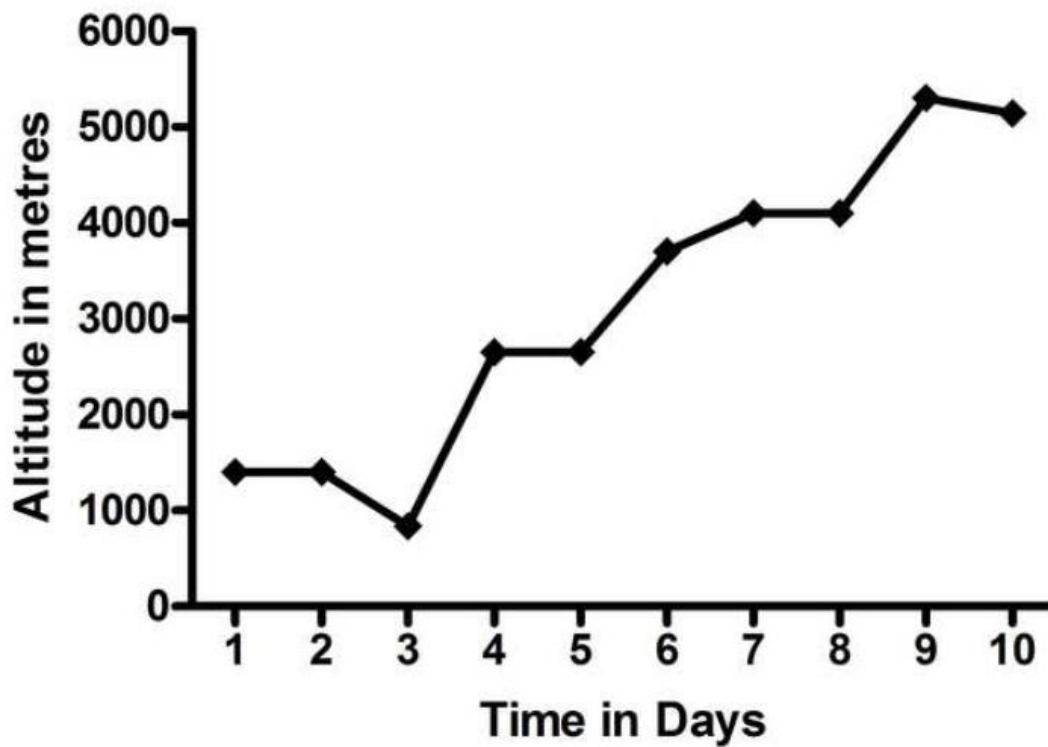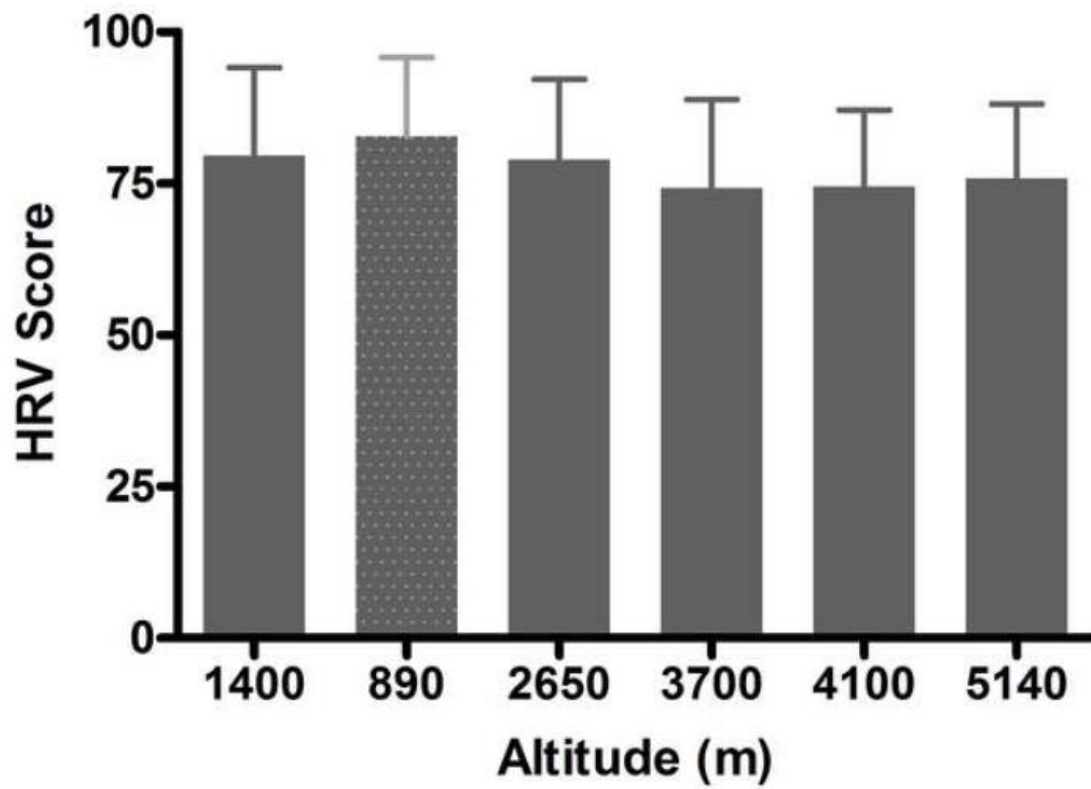

Figure 1 Ascent profile

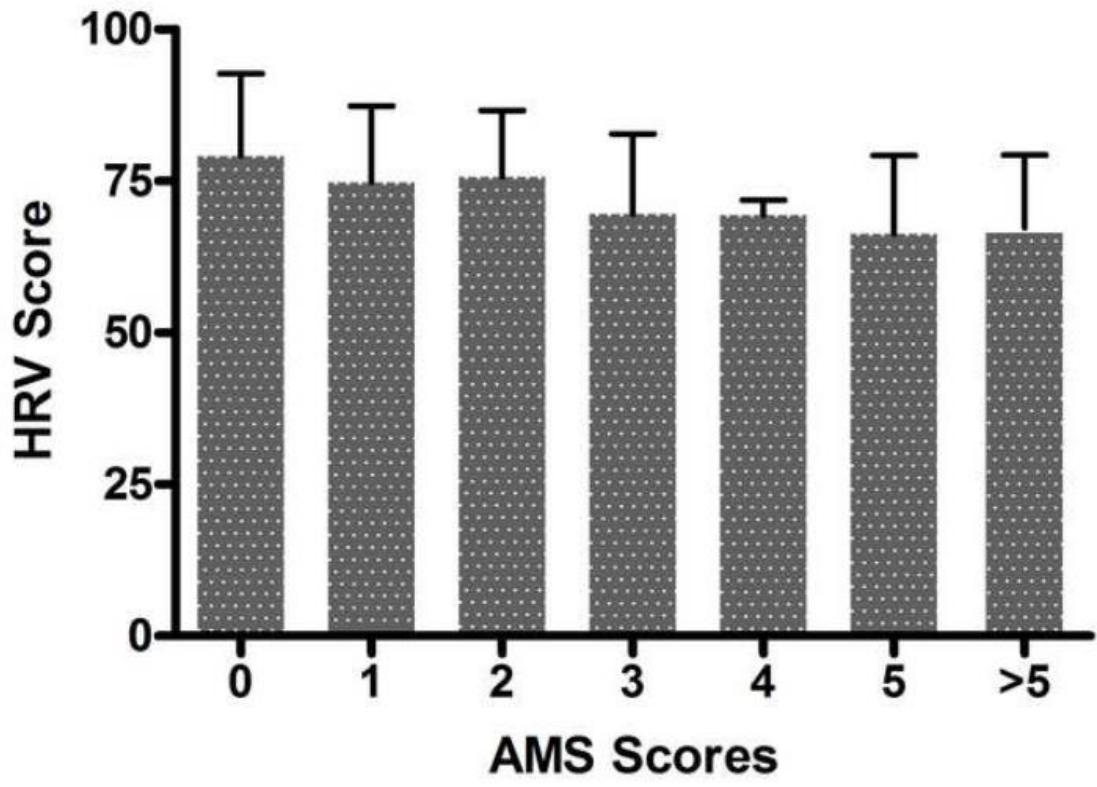**Figure 2** Changes in ithlete™ Heart Rate Variability Score with increases in altitude

Figure 3 Changes in Heart Rate Variability with Acute Mountain Sickness Scores (LLS)

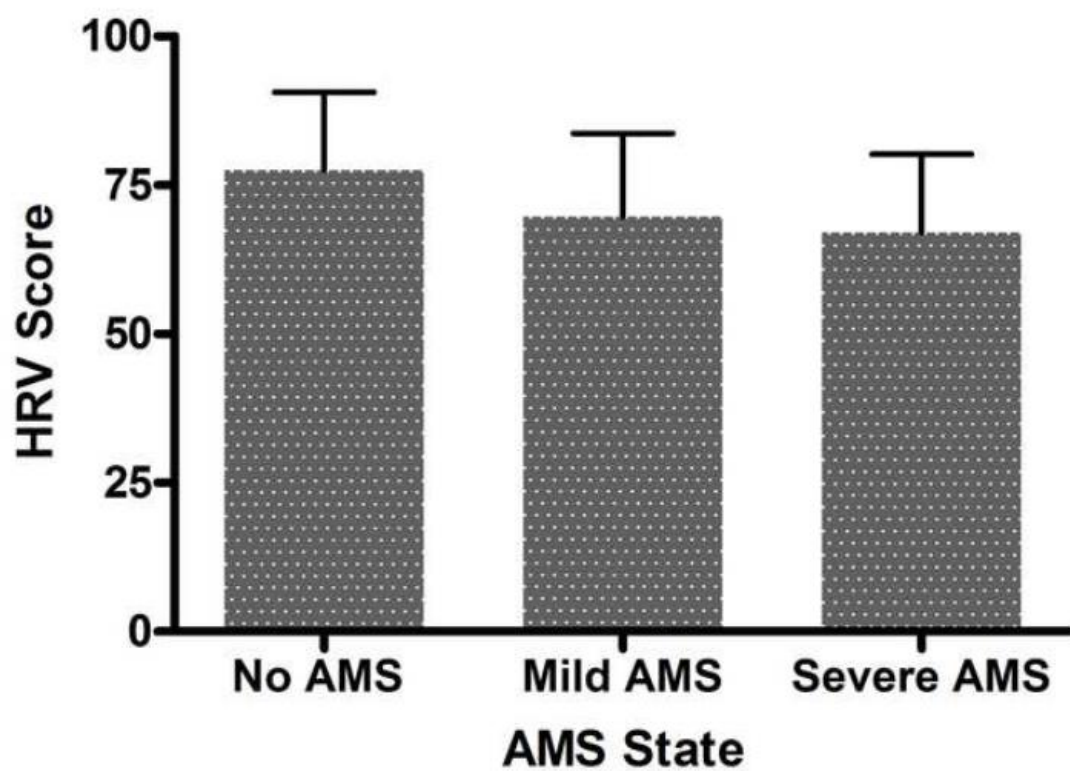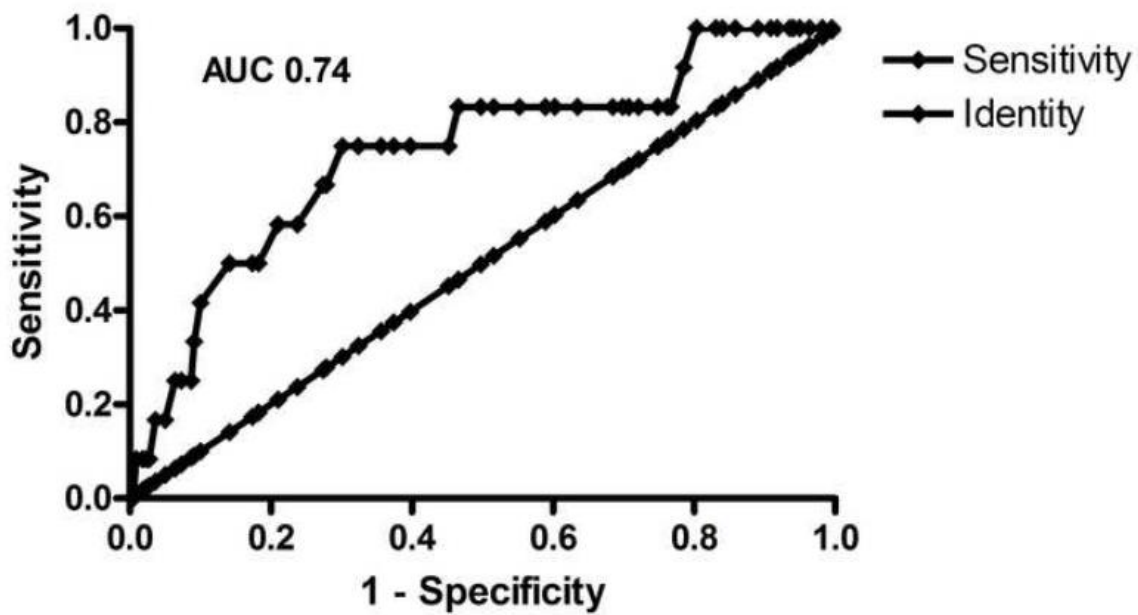**Figure 4** Acute Mountain Sickness Severity and ithleteᴛᴍ Heart Rate Variability Scores

Figure 5 Receiver operating characteristic (ROC) Curve for Heart Rate Variability score for Detection of severe Acute Mountain Sickness
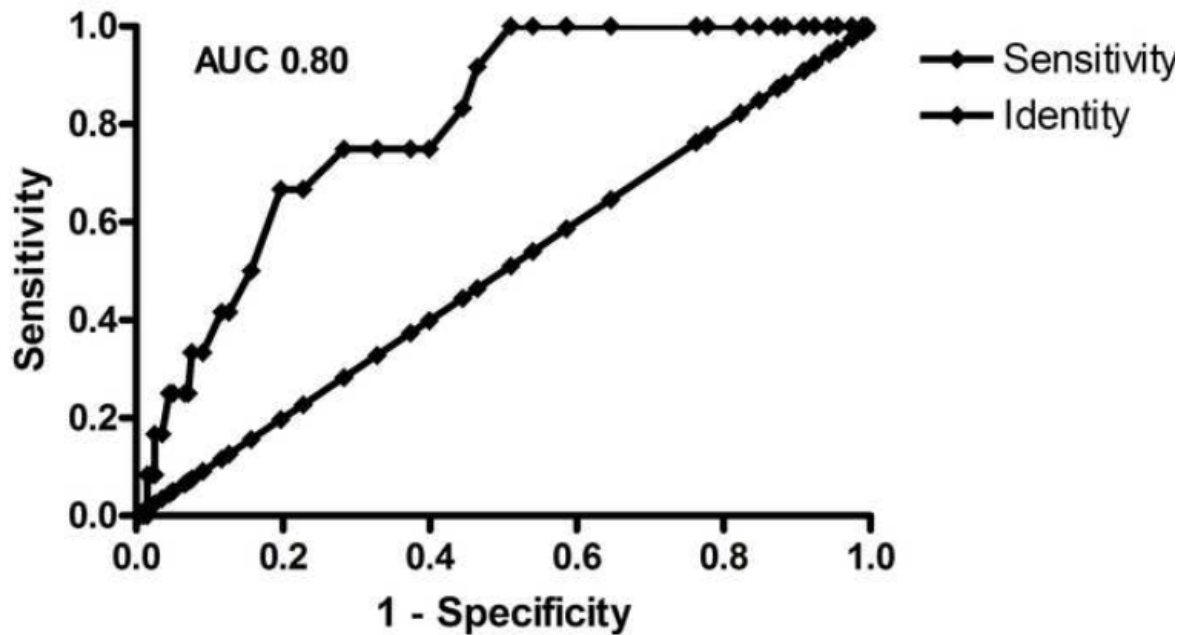

Figure 6 Receiver operating characteristic (ROC) Curve for change in Heart Rate Variability score and identification of severe Acute Mountain Sickness