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A Comparison of two methods of heart rate variability assessment at high altitude

Running title: heart rate variability at high altitude

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Abstract

Heart rate variability (HRV) is a useful index of autonomic function and has been linked to the development of high altitude (HA) related illness. However, its assessment at HA has been undermined by the relative expense and limited portability of traditional HRV devices which have mandated at least a five minute heart rate recording. In this study the portable ithlete™ HRV system, which uses a 55 second recording, was compared with a reference method of HRV which utilises a five minute electrocardiograph recording (CheckMyHeart™). The root mean squares of successive R-R intervals (RMSSD) for each device was converted to a validated HRV score ($\ln\text{RMSSD} \times 20$) for comparison. Twelve healthy volunteers were assessed for HRV using the two devices across seven time points at HA over 10 days. There was no significant change in the HRV values with either the ithlete ($P=0.3$) or the CheckMyHeart™ ($p=0.19$) device over the seven altitudes. There was also a strong overall correlation between the ithlete™ and CheckMyHeart™ device ($r=0.86$; 95% confidence interval: 0.79 to 0.91). The HRV was consistently, though non-significantly higher with ithlete™ than with the CheckMyHeart™ device (mean difference [bias] 1.81; 95% CI -12.3 to 8.5). In summary the ithlete™ and CheckMyHeart™ system provide relatively similar results with good overall agreement at HA.

1. Introduction

The autonomic nervous system (ANS) plays a pivotal role in the regulation of a number of physiological processes. ANS control of the heart via both sympathetic and parasympathetic ANS innervation leads to continuous beat to beat deviations in heart rate and RR intervals which can be quantified as changes in heart rate variability (HRV) (Weimer, 2010). Hence, quantification of HRV is an important method of assessing ANS function *in vivo*. It has been shown that a number of factors such as inter-current illness, cardiovascular disease, physical overtraining and even mental stress can lead to increased cardiac sympathetic activation and a reduction in HRV (Lahiri et al., 2008; Kiviniemi AM et al., 2014; Sassi et al., 2015). This has led to a number of useful clinical applications in the field of sport and exercise medicine such as the assessment of physical fitness and overtraining as well as competitive readiness (Da Silva et al., 2015; Routledge et al., 2010; D'Ascenzi F et al., 2014; Kiviniemi AM et al., 2014).

Traditional methods of HRV have required expensive and specialised equipment and processing software with the need to record the cardiac activity for at least five minutes (Task Force 1996). There have been significant recent technological advances with increasing miniaturization of available HRV devices that provide full disclosure single channel ECG recordings with internal software to provide accurate assessment of HRV. Whilst considerably more affordable than traditional methods these devices are still relatively expensive, require the purchase of disposable ECG electrodes and may not be practical for everyday use. There has been a significant expansion in non-invasive HRV devices which utilise either finger sensors or chest straps which can wirelessly link to portable devices and mobile phones for data

analysis. They provide a portable, cheap and more practical method of assessing HRV. One of the key HRV parameters which is well suited to these ultra-portable HRV devices is the root mean square of successive R-R intervals (RMSSD). The RMSSD is a reliable time domain measure of vagally mediated cardiac control and parasympathetic activity (Task Force 2006). It has the advantage over several other HRV outputs in that it can be reliably assessed with ultrashort recordings, (over less ≤ 1 minute), improving its applicability and use compliance in athletes and others (Nussinovitch U et al., 2011; Nakamura et al., 2015; Esco and Flatt 2014; Flatt and Esco 2015). Moreover, the RMSSD appears to be less prone to the influence of respiration than many other HRV parameters and has been shown to be a robust marker of physical and mental stress (Grieco C et al., 2014; Saboul et al., 2013). The ithelte™ (HRV Fit Ltd, Southampton, UK) device is one of best known ultra-portable HRV devices which utilises a 55 second recording to provide a RMSSD derived HRV score. It has been shown to have excellent agreement (correlation coefficient of 0.99) with that obtained from a standard five minute electrocardiographic recording (Flatt and Esco 2013).

Another area where HRV has been of increasing relevance has been in the field of high altitude (HA) medicine. There is increasing evidence to suggest that HA exposure leads to altered ANS activity and changes in HRV which may be linked to the development of acute mountain sickness (AMS) (Sevre et al., 2001; Huang et al., 2010; Karinen et al., 2012). The simplicity of the ithelte™ would circumvent many of the challenges faced by studying HRV at HA; however it has never been formally validated in this environment. In this study we sought to assess the ithelte™ HRV

smart phone application in comparison with a reference electrocardiographic HRV device at HA.

2. Materials and Methods

2.1 Subjects

This was a prospective observational study of 12 healthy British military servicemen and women on expedition to the Dhaulagiri region of the Himalayas in Nepal. All Subjects were studied on arrival at Kathmandu (1400m, day 0), at 1045m (day 2), 1600m (day 3), 2050m (day 5), 2500m (day 6), 3100m (day 7) and 3600m (day 9). The study was approved by the Ministry of Defence Research and Medical Ethics. All participants underwent written informed consent. Resting recordings of oxygen saturations (SpO₂) were performed using a Nellcor N-20P pulse oximeter (Nellcor Puritan Bennett, Coventry, UK). Baseline heart rate and blood pressure were measured using an automated blood pressure cuff with the subject sat upright and rested for >10 minutes (M6 Omron Healthcare, Milton Keynes, UK). Symptoms of acute mountain sickness were assessed using the Lake Louise Scoring system. The LLS scores allocates a score of 0–3 (symptom not present to severe) for symptoms of AMS (headache, gastrointestinal symptoms, fatigue/weakness, dizzy/light-headedness, difficulty sleeping). A total score of >3 in the presence of a headache is consistent with AMS.

2.2 Assessment of Heart Rate Variability

Participants were all studied at approximately 0700 in the morning post micturition but prior to breakfast or caffeine. All subjects were seated, wearing warm clothing in

a tent for at least 5 minutes before the HRV recordings were obtained (Flatt et al 2013). HRV variability was obtained using the ithlete™ (HRV Fit Ltd. Southampton, UK) and CheckMyHeart™ (CMH, Daily Care Biomedical, Taiwan) devices.

For the ithlete™ each subject wore an elasticated chest strap heart rate monitor (Cardiosport Bluetooth) that was fastened securely around the upper thorax at the level of the xiphoid process. All ithlete™ HRV data was collected with the ithlete™ ECG receiver and ithlete™ application on the subjects apple smart phone as previously described (Flatt and Esco 2013). Two 55 second recordings were obtained with the ithlete during the first and last minute of a five minute HRV recording obtained by a CheckMyHeart™ device. During these ithlete™ recordings breathing prompts were followed and the average of the two ithlete™ readings were used. This prompt uses an animation to guide a control the overall breathing rate as well as the inspiratory and expiratory phases. The CheckMyHeart™ HRV device is a validated battery powered portable HRV machine that utilises two skin ECG electrodes which were placed at the right sternal edge and over the apex beat to acquire a continuous five minute ECG recording for HRV as previously described (Wen et al 2007). All stored recordings were later exported via USB hook up for full data analysis.

The ithlete™ modifies the acquired RMSSD by taking the natural log transformation and multiplying by twenty ($\ln\text{RMSSD} \times 20$) to provide a more interpretable figure for the user on a ~100 point scale (Wegerif, 2009). Hence this was also undertaken on the RMSSD data obtained from the CheckMyHeart™ device to compare with the ithlete™ as previously described (Flatt et al 2013).

2.3 Statistical Analysis

Data were analysed using GraphPad InStat version 3.05 and with all graphical figures presented using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, CA, USA; www.graphpad.com). The Kolmogorov-Smirnov test was undertaken to assess normality of all continuous data. The results were presented as mean \pm standard deviation (SD). As the HRV data for both ithlete™ and CheckMyHeart™ were normally distributed paired comparisons of HRV measures were performed with a paired T test and correlations were quantified using the Pearson correlation coefficient \pm 95% confidence interval (CI). Time dependent changes of continuous data within each group were assessed using repeated measures ANOVA and Tukey post-hoc test and the Friedman Test with the Dunn post-test for parametric and non-parametric data respectively. Comparison of HRV scores with increasing LLS Scores were assessed using the Kruskal-Wallis (nonparametric ANOVA) Test. Agreement in the paired sampling of the ithlete™ at the end of the first and fifth minute were assessed using the coefficient of variation and Pearson Correlation coefficient. Agreements in HRV measurement between ithlete™ and CheckMyHeart™ were assessed using Bland-Altman plots (Bland and Altman., 1986) in which the difference between the two values were compared with the average values from the comparative two readings. The bias was defined as the mean \pm SD of the difference between the readings. Reasonable agreement was defined as <5% of readings being within 1.96SD (95% CI) from the mean. A p value of <0.05 was considered significant for all comparisons.

3. Results

The study group consisted of 12 volunteers with an average age of 26.0 ± 2.3 (range 23-32) years (9 men and 3 women). Their body weight was 71.60 ± 6.8 kg with a height of 172.8 ± 5.6 cm and body mass index of 24.0 ± 1.6 kg/m². There were no smokers in the study group and no subjects took any regular medications other than the oral contraceptive pill. There was no significant change in the LLS scores with increasing HA ($p=0.16$) and no cases of acute mountain sickness, although increasing altitude did lead to a significant fall in oxygen saturations ($97.9 \pm 0.7\%$ at baseline vs $92.9 \pm 1.2\%$ at 3600m) and heart rate (62.3 ± 9.4 at baseline vs 74.8 ± 12.3 /minute at 3600m) (table 1). There were only two subjects with a LLS score of 3 and no LLS scores >3 . There was no change in the HRV score with increasing LLS (figure 1; $p=0.52$)

There was no significant change in the RMSSD-derived HRV values across all the seven altitudes with either the ithlete™ ($P=0.3$) or the CheckMyHeart™ Device ($p=0.19$) (figure 2). Further, there were no significant differences in RMSSD-derived HRV between the ithelte™™ and CheckMyHeart™ Device at any of the seven altitudes ($p=0.47$).

There was a significant correlation between the first and second readings of the Ithlete™ taken at the end of one and five minutes ($r=0.89$; $0.82-0.93$; coefficient of variation 5.5%). The first ($r=0.80$; $0.70-0.87$; $p<0.0001$) and second ($r=0.83$ 95% confidence interval: $0.74-0.89$) ithlete™ HRV readings both strongly correlated with the five minute acquired CheckMyHeart™ HRV scores. However, the strongest correlation between the ithlete™ with the CheckMyHeart™ was obtained when the average of the two ithlete™ readings were used ($r=0.86$; 0.79 to 0.91) (figure 3).

On Bland-Altman comparisons of the two methods of HRV assessment the values for RMSSD derived HRV were consistently but non-significantly higher with averaged ithlete™ than with the CheckMyHeart™ device (mean difference [bias] 1.8l; 95% limit of agreement -12.3 to 8.5) (figure 4).

4. Discussion and Conclusions

To the authors knowledge this is the first study to evaluate HRV at HA using two differing methods of HRV assessment. In this study the ithlete™ smart phone HRV application using a chest-borne heart rate sensor was compared with that of the CheckMyHeart™ electrocardiograph derived system over 55 second and five minute recordings respectively. The overall agreement between methods was reasonably good across the differing altitudes. HRV readings were consistently, though non-significantly higher with the ithlete™ than with the CheckMyHeart™ System.

The rationale for this study was clear. HRV has evolved as an increasingly useful tool to assess physical and mental fitness (da Silva et al., 2015). However, traditional HRV assessments require at least five minutes of data recording, are more expensive and provide a plethora of highly complex time and frequency domain derived data undermining their applicability for everyday use. The ithlete™ circumvents these issues by providing an easy to understand intuitive RMSSD derived HRV reading obtained over 55 seconds which can be recorded to a mobile phone or portable tablet (Flatt and Esco., 2013). In the only previous comparative study to compare the ithlete™ to a reference HRV device a near perfect correlation between the ithlete™ and a five minute electrocardiography HRV device was observed in 25 healthy

subjects at sea level ($r = 0.99$, $p < 0.001$) (Flatt and Esco 2013). On Bland Altman analysis the level of agreement was -2.57 to 2.63 above the constant bias (constant error) of -0.03 . This is clearly much higher level of agreement than that obtained in our study. However, we believe this difference relates to the environmental and methodological differences between the two studies. The previous *ithlete*TM validation study was performed in a temperature controlled laboratory at sea level. Conversely, our study was performed across several different time points and altitudes under very remote and challenging field conditions at HA. Secondly, the breathing prompts were only followed during the *ithlete*TM recordings within the five minute *CheckMyHeart*TM recording and not during the entire five minutes. This was because the *CheckMyHeart*TM device does not provide breathing prompts which were only available during the *ithlete*TM recording. This could explain the consistent, but marginally higher, HRV values for the *ithlete*TM. Whilst we could have maintained the breathing prompts for the non-*ithlete*TM recording periods we were eager to assess the comparative differences in the two devices under their directed use. The subjects were instructed to undertake slow relaxed breathing during the non-*ithlete*TM *CheckMyHeart*TM recording periods.

In this study we aimed to assess the utility and validity of a more simplified measure of HRV at HA as there has been accumulating data to suggest that hypoxia and HA lead to a reduction in HRV with a reduction in parasympathetic activity and a relative increase in sympathetic activity (Chen et al., 2008; Botek et al., 2015). In these previous studies the ascents were far more dramatic and rapid than in our current study which more closely reflects a real life HA trek. For example, in a previous study of 27 volunteers Chen et al noted significant changes in several time and

frequency domain measures of HRV but their ascent was from 555 to 3180m in a cable car in <3 hours (Chen et al., 2008). And in another study Botek et al noted significant changes in HRV following abrupt exposure to normobaric hypoxia (FiO₂=9.6%) which is a degree of hypoxia akin to that of >4000m (Botek et al.; 2015). There is some data to suggest that changes in HRV may be linked or even predictive of AMS though this still remains controversial (Lanfranchi et al., 2005; Chen et al., 2008; Koehle et al., 2010; Willie et al., 2012; Song et al., 2013; Karinen et al., 2012). This has important clinical implications as travel to HA has significantly increased in the last 10 years and AMS affects $\geq 35\%$ of persons traveling to altitudes $\geq 3000\text{m}$ (Crougns et al., 2014). Previous studies assessing HRV and its links to HA have been partly undermined by the relatively small sample size. Hence, the ability to utilise more portable HRV devices such as the ithlete™ or the CheckMyheart™ device may have competitive value over several other HRV platforms. Given the sensitivity of the RMSSD to changes in parasympathetic activity and its recognised alterations at HA this created another persuasive reason to further explore the validity of the ithlete™ at HA. RMSSD is just one of the many time domain measures of HRV (eg SDNN, SDANN, pNN50). However, all of these measurements of short-term variation estimate high frequency variations in heart rate and have been shown to be highly correlated (Task Force., 1996).

This study has several limitations that need to be acknowledged. The sample size of this study was small however as the subjects were studied at seven different altitudes this significantly increased the data which is larger than the vast majority of HA HRV studies to date. The altitude achieved was moderate (with no reported cases of AMS) and hence the results cannot necessarily apply to much higher altitudes though the

consistency of the data and good agreement across all seven altitudes is encouraging. Despite its obvious portability and simplicity, the ithlete™ only records one parameter of HRV. Whereas the CheckMyHeart™ and other electrocardiograph HRV devices which use five minute recordings are able to provide detailed frequency domain and power spectral analysis allowing a more in depth assessment of changes in autonomic tone and sympatho/vagal balance.

In conclusion the ithlete™ HRV system is a ultraportable HRV assessment system utilising a 55 second recording that has shown a good correlation with a reference method of HRV using a five minute recording from a surface ECG. It has potential clinical applicability for the study of HRV at HA and comparative data from larger studies would be helpful.

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Conflict of Interest

All authors have read and approved the manuscript and that there is no conflict of interest to declare.

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Table 1 Changes in Key physiological variables with changing altitude

Altitude	1400m	1100m	1600m	2000m	2500m	3110m	3600m	
Heart rate/minute	62.3±9.4	62.8±12.7	64.9±14.1	64.6±13.9	67.6±13.1	69.8±12.1	74.8±12.3*	0.002
Systolic blood pressure, mmHg	131.6±13.2	122.8±11.2	121.8±10.8*	130.3±13.2	128.8±13.1	131.3±14.1	129.1±16.0	0.006
Diastolic blood pressure, mmHg	79.5±7.5	73.9±10.8	73.4±9.0	78.8±9.9	76.3±8.3	81.2±9.0	79.8±9.3	0.03
LLS	0.1±0.3	0.6±0.9	0.6±0.5	0.5±0.7	0.3±0.7	0.9±1.0	0.6±0.8	0.16
SpO ₂ ,%	97.9±0.7	98.0±1.0	96.8±1.2	97.0±1.3	95.4±1.2*	93.0±1.7*	92.9±1.2*	<0.001

SpO₂, oxygen saturations; LLS, lake Louise Scores; * significance vs baseline 1400m on post hoc test.

Legend for Figures

Figure 1 Changes in the Heart Variability Score with increasing Lake Louise Scores.

Figure 2 Paired changes in heart Rate Variability for the ithlete™ versus CheckMyHeart™ at high altitude

Figure 3 Correlation between ithlete™ and CheckMyHeart™ Heart Variability Score at high altitude

Figure 4 Bland-Altman plots comparing ithlete™ and CheckMyHeart™ Heart Variability Scores at high altitude. The mean bias and the 95% confidence interval of the bias (2 standard deviations) are shown.

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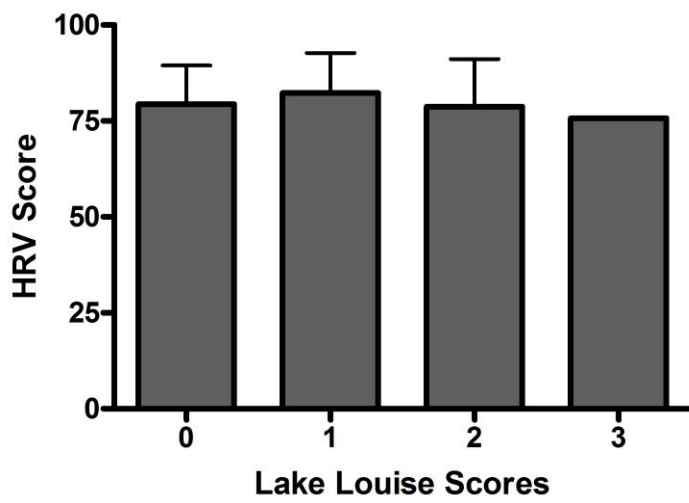


Figure 1 Changes in the Heart Variability Score with increasing Lake Louise Scores.

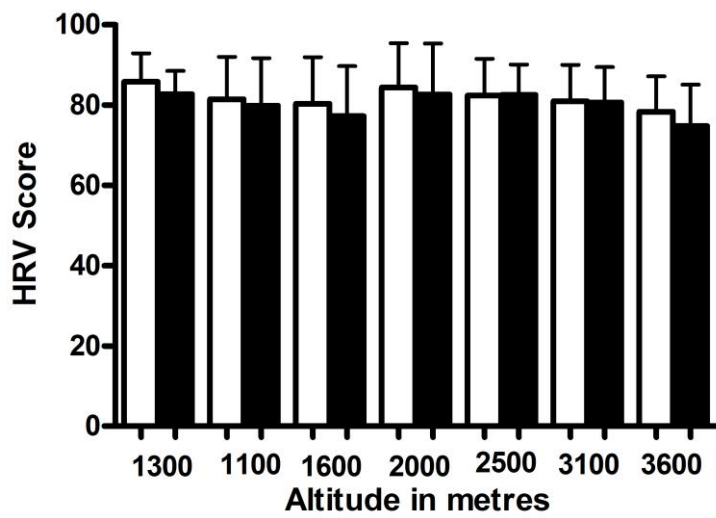


Figure 2 Paired changes in heart Rate Variability for the ithlete™ versus CheckMyHeart™ at high altitude

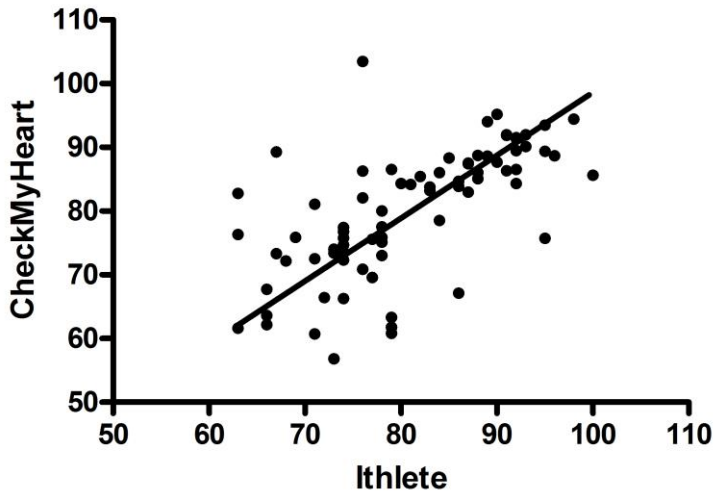


Figure 3 Correlation between ithlete™ and CheckMyHeart™ Heart Variability Score at high altitude

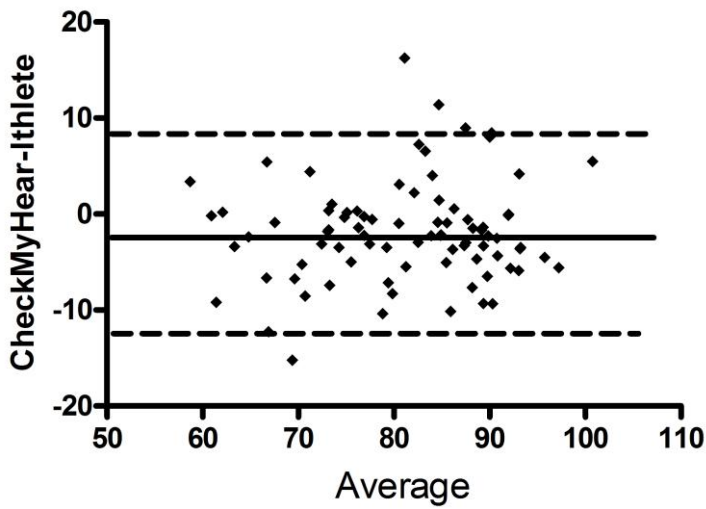


Figure 4 Bland-Altman plots comparing ithlete™ and CheckMyHeart™ Heart Variability Scores at high altitude. The mean bias and the 95% confidence interval of the bias (2 standard deviations) are shown.