N-Terminal Pro-Brain Natriuretic Peptide, Cardiac and Vascular Function in Patients with Type 1 Diabetes Mellitus during the Ascent of Mt. Kilimanjaro

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Abstract

Aim: Hypobaric hypoxia during high altitude mountaineering and trekking triggers physiological changes in the cardiovascular and pulmonary systems that optimize the delivery of oxygen to tissues. As Type 1 Diabetes Mellitus (T1DM) is associated with increased cardiovascular risk, our goal was to investigate any disproportionately adverse effects of hypobaric hypoxia on cardiac and vascular parameters in patients with T1DM during an expedition to the summit of Mt. Kilimanjaro.

Methods: Sixteen well-trained subjects, 8 with T1DM and 8 non-diabetic controls, climbed Mt Kilimanjaro (5,895 m) over a 7-day period. Cardiac function was evaluated by echocardiography and measurement of NTproBNP levels both at Sea Level (SL) and at 4000 m. Vascular measurements were performed at 1300 m and 4000 m, and included assessment of blood pressure (Dinamap), derived central aortic systolic pressure (B-PRO) and pulse wave velocity (VICORDER). Oxygen saturation (SatO₂) was assessed at 4000 m. The Lake Louise Acute Mountain Sickness (AMS) score was obtained daily.

Results: All participants reached the summit. At 4000 m SatO₂ was reduced in both groups. NTproBNP levels were significantly higher in the total group at 4000 m compared to SL. Left ventricular function and right ventricular diameter did not change. However, tricuspid annular plane systolic excursion decreased significantly. High altitude increased both systolic and diastolic peripheral Blood Pressure (BP) in the total group (SBP: 116.4 ± 8.9 vs. 121.4 ± 10.5, p < 0.05; DBP: 70.7 ± 6.3 vs 74.7 ± 8.2, p < 0.05), but not the pulse wave velocity.

AMS scores remained modest except for a significantly higher score on the summit day. No significant differences were observed between T1DM subjects and controls in all parameters measured.

Conclusion: Well-trained subjects with T1DM showed similar adaptation of the cardiopulmonary system compared to non-diabetic controls, with increased NTproBNP levels and peripheral blood pressure at high altitude up to 4000 m in both groups.

Keywords: NTproBNP; RV function; Pulse wave velocity; Diabetes; High altitude

Introduction

Hypobaric conditions at high altitude result in hypoxia, which in turn triggers physiological changes in the cardiovascular and pulmonary systems to allow adequate delivery of oxygen to tissues despite the reduced partial pressure of inspired oxygen. Exposure to acute hypoxia leads to mild pulmonary hypertension, increased heart rate, activation of the sympathetic nervous system, and altered vascular resistance [1,2]. Additionally, increases in diastolic blood pressure have also been described to be an adaptation to high altitude [3].

Early signs of pulmonary hypertension include an increase in the diameter of the Right Ventricle (RV) and a decrease in the Tricuspid Annular Plane Systolic Excursion (TAPSE), which is an echocardiographic measure of the RV ejection fraction. Additionally, dilation of the RV can lead to a leftward shift of the interventricular septum which could result in impairment of Left Ventricular (LV) diastolic function. A decrease in RV function may occur as well. Plasma levels of cardiac natriuretic peptides such as Brain Natriuretic Peptide (BNP) and its inactive amino terminal fragment, NTproBNP, serve as biomarkers for cardiac dysfunction. Ventricular wall stress, due to volume expansion and pressure overload, results in an increased synthesis and secretion of BNP and NTproBNP by both ventricles. As such the measurement of cardiac natriuretic peptides, such as BNP and its inactive amino-terminal fragment NTproBNP, is used increasingly in the clinical routine to identify patients with pulmonary hypertension and patients with (suspected) heart failure and RV- and LV dysfunction [2]. When NTproBNP < 50 pg/ml, heart failure is highly unlikely; when NTproBNP > 450 pg/ml, heart failure is likely.

An increasing number of people with a chronic condition, such as patients with Type 1 Diabetes Mellitus (T1DM), ascend...
to high altitudes and expose themselves to hypoxia. During high altitude trekking, the physiological and metabolic adjustments to hypobaric hypoxia are even more pronounced due to the strenuous physical activity involved. Exposure to high altitude conditions is also associated with Acute Mountain Sickness (AMS), which presents as a constellation of signs and symptoms including nausea, fatigue, dizziness, and sleep disturbance which are exacerbated by strenuous activity. Thus, counselling of such patients is now more important than ever [3]. In general, patients with T1DM have an increased cardiovascular mortality and morbidity risk compared to non-diabetic subjects. Many complications in T1DM have a cardiovascular background [4,5].

Methods

Echocardiography

Echocardiography assessment was performed at Sea Level (SL) before the expedition and at an altitude of 4,000 m (2 days prior to the summit ascent) after 10 days acclimatization. All acquisitions were made by an experienced cardiac sonographer using a portable Vivid 1 ultrasound system (GE Ultrasound) equipped with Tissue Doppler technology (TDI). Care was taken to ensure that the position of the subjects and the transducer were similar in all examinations. The echocardiographic evaluation, according protocol, systematically included Wall Motion Score Index (WMSI, a measure of global LV function), LV systolic and diastolic diameter, septum and posterior wall diameter. These measurements were obtained in the apical four chamber view. LV systolic and diastolic diameter, septum and posterior wall diameter were measured in the parasternal long axis view.

Assessment of NTproBNP

NTproBNP at SL was analyzed with an electrochemiluminescence immunoassay (Elecsys, Roche Diagnostics, Almere, The Netherlands). All blood samples were analyzed immediately after collection. The Elecsys NTproBNP method is unavailable at high altitude, therefore the Cobas h232 (Roche Diagnostics) Point-of-Care (POC) system was used at 4,000 m. The validity of results obtained using this POC system has been evaluated against the Elecsys system and a diagnostic concordance of 93% was found between the two assays [12]. In analyses of results obtained with the POC assay, values < 60 pg/ml were replaced by 60 pg/ml as has been previously reported in the comparison of the two methods [12]. All blood samples were analyzed immediately after being drawn with the subject in supine position.

Vascular measurements

Vascular measurements were performed in patients with T1DM and control subjects during the expedition at an altitude without prior mountaineering experience can safely participate in high altitude climbing. The expedition started with a 4-day acclimatization climb of Mount Meru (4,566 m), one day of rest at 1,300 m, followed by a 7-day climb of Mount Kilimanjaro (5,895 m). Exclusion criteria were the presence of complications (retinopathy, neuropathy, nephropathy), uncontrolled hypertension (systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 90 mmHg), severe hypoglycemia unawareness, cardiac disease (abnormal ECG, ICD or pacemaker, cardio-myopathy, coronary or valvular disease), peripheral arterial insufficiency, smoking or use of illicit drugs. All subjects were well trained. A symptom limited cardiopulmonary exercise test was performed in all subjects at sea level and all participants received an individualized training schedule to further improve their fitness. During the time of training, there were multiple training weekends to check the improvement of the participants. Another exercise test was taken shortly before the expedition took place. All participants were informed of the possible risks and gave their voluntary written consent. The study was approved by the medical ethics committee of the Isala Clinics in Zwolle, The Netherlands.
of 1,300 m and 4,000 m. The subjects were measured in a supine position after a 15 minutes resting period. Five blood pressure measurements were taken with a 2 minute interval using a Dinamap (Mobil-0-Graph®NG). In order to derive the central aortic pressure, pulse wave analysis was performed using a B-PRO, a radial Pulse Wave Acquisition device with possibility to obtain a 24 hr macroscopic view of blood pressure, heart rate, mean arterial pressure and pulse pressure. Pulse wave velocity was assessed three times using a VICORDER [13]. The mean of these 3 measurements was taken as the pulse wave velocity.

Measurement of oxygen saturation

Oxygen saturation (SatO₂) was assessed at 4,000 m by pulse oximetry using Apena Link with oximetry (Res Med Corp, USA). The oximeter itself stored the measured values and created an average. The average SatO₂, was calculated during 30 minutes of rest in an upright position.

Assessment of Acute Mountain Sickness (AMS)

Participants were required to fill out a daily self-report questionnaire on symptoms associated with development of AMS during the 7-day Kilimanjaro expedition. An AMS score based on the Lake Louise scoring system was calculated. Acetazolamide (250 mg orally) was provided above an altitude of 3,000 m in order to prevent the onset and/or progression of AMS. The 3,000 m was chosen after the acclimatization period. Medication, besides insulin, was provided only after consultation with one of the doctors and consisted of Paracetamol and Loperamide.

Statistical analyses

All data are expressed as the mean value ± SD. The data were analyzed using SPSS software. We used the paired t-test for comparison between values at SL and 4,000 m and the Mann Whitney U test for comparison between the two groups. A p-value of < 0.05 was considered statistically significant. An ANOVA (GLM repeated measures) analysis was not performed as the power of the test for normality for such a small sample size would be far too low.

Results

Sixteen subjects, 8 with T1DM (5 male, 3 female) and 8 non-diabetic controls (4 male, 4 female) participated in the study. All participants live at SL and had normal renal function. The T1DM cohort had a mean age of 31.5 ± 5.3 yrs, diabetes duration of 10.4 ± 8.1 yrs, BMI of 23.5 ± 1.5 kg/m² with a height of 182 ± 10 cm and weight of 74 ± 10 kg. They were free from long-term diabetes complications and exhibited good glycemic control (HbA1C 6.8 ± 0.6%). Mean insulin use per day was 45.8 IU/24h (HbA1C 6.8 ± 0.6%). Mean insulin use per day was 45.8 IU/24h at om. Ascending M. Kilimanjaro mean insulin use per day was < 0.05 was considered statistically significant. An ANOVA (GLM repeated measures) analysis was not performed as the power of the test for normality for such a small sample size would be far too low.

Acute mountain sickness

Fifteen participants completed their daily AMS score form. AMS scores were modestly elevated at high altitude except for a significantly higher score on day 7 when all participants climbed to the summit of Mt. Kilimanjaro (5,895 m) (p < 0.05) (Figure 1A). There were no significant differences in AMS scores between the T1DM and control subjects (Figure 1A). 5/8 T1DM and 4/8 control subjects used acetazolamide (250 mg/day) given that acetazolamide relieves symptoms of AMS and may therefore impact the reported AMS score, we performed a separate analysis excluding the reported AMS scores of those subjects who had taken acetazolamide (Figure 1B). With these low sample numbers (3 T1DM, 4 control) no differences could be observed between T1DM and control subjects (p = 0.4). At 4000 m, resting oxygen saturation (SpO₂) was 87 ± 3% in the T1DM group and 89 ± 2% in the control subjects (p = 0.2).

Figure 1: Acute mountain sickness (AMS) scores based on the Lake Louise scoring system were obtained daily from 15/16 participants (8 control, 7 type 1 diabetes mellitus, T1DM). (A) AMS scores of all participants. (B) The AMS scores of the acetazolamide non-users only (4 control, 3 T1DM) were plotted and analyzed to exclude and impact of acetazolamide on the differences in AMS score between the two groups.
Echocardiography

There were no significant changes in WMSI and RV diameter at high altitude compared to SL in both groups (Table 1). TAPSE decreased significantly in both groups compared to the values obtained at SL (22.8 ± 3.8 at SL vs 20.9 ± 2.1 at 4,000 m, p < 0.05), with no significant differences between T1DM and non-diabetic controls. Six subjects (2 T1DM and 4 controls) developed an increase in tricuspid regurgitation at 4,000 m. Estimates of pulmonary artery pressures could not be obtained in all subjects due to technical difficulties.

NTproBNP

The levels of NTproBNP of each participant measured at SL and at 4,000 m are plotted in Figure 2. NTproBNP levels at rest were significantly higher at an altitude of 4,000 m compared to sea level (157 ± 129 vs 51 ± 35 pg/ml, p < 0.01). There were no significant differences between subjects with (148 ± 145 pg/ml) and without (166 ± 121 pg/ml) T1DM (p = 0.3) (Table 1). The mean change in NTproBNP levels (NTproBNP_4000m - NTproBNP_SL) was similar between acetazolamide users (107.4 ± 139.2 pg/ml) and non-users (105.4 ± 115.4 pg/ml).

Pulse wave analysis

High altitude resulted in a significant increase of Systolic Blood Pressure (SBP) in the control group. This group also had a significantly higher Central Aortic Systolic Pressure (CASP) at 4,000 m than the subjects with T1DM. Pulse wave velocity did not change in either group during this stay at high altitude (Table 1).

Discussion

In this observational study, all participants with T1DM reached the summit of Mt. Kilimanjaro at an altitude of 5,895 m with similar degrees of arterial hypoxemia compared to the control subjects, thus allowing comparison of cardiovascular parameters between these two groups. The main results of our cardiovascular investigation show that subjects with T1DM who are well trained and exhibit good glycemic control can safely perform high altitude trekking and have a similar cardiac adaptation to hypobaric hypoxia up to 4,000 m compared to equally well trained subjects without diabetes. Our echocardiographic examinations revealed no significant changes in gross cardiac morphology in either the T1DM or non-diabetic subjects. The only significant changes observed were in the TAPSE. TAPSE is a reliable marker of global RV function, and correlates with right ventricular ejection fraction [15]. We found a modest but significant TAPSE decrease in the total group which is indicative of an increase of pulmonary arterial pressure. Indeed, the development of or increase in tricuspid regurgitation in 6 subjects also suggests this. Patients with T1DM were comparable to controls with regard to TAPSE or tricuspid regurgitation.

Both type 1 and type 2 diabetes mellitus may develop increased stiffness of the large arteries which likely contributes to the increased risk of the development of cardiovascular disease in subjects with diabetes. Decreased distensibility results in an increase of the Pulse Wave Velocity (PWV) [6]. Exposure to high altitude is also associated with changes in the cardiovascular function, including altered vascular resistance [1]. Since in theory, subjects with diabetes mellitus would be prone to such changes, we considered it likely that ascending to high altitude might induce an earlier increase in arterial stiffness. However, PWV did not change significantly during this relatively short stay at 4,000 m. High altitude was associated with higher blood pressure, which was more prominent in the control group. Blood pressure is an important contributor to arterial stiffness [4] and may influence PWV. Few studies have been done on vascular measurements at high altitude. Schneider et al. [16] investigated the differences in PWV between recently acclimatized individuals and Himalayan high altitude natives. At baseline there were no differences in PWV at high altitude, however blood flow velocity was higher in the high-altitude native-group following muscular ischemia induced by leg occlusion [16]. Other research at M. Kilimanjaro showed a greater increase in systolic blood pressure in the legs versus the arms of healthy volunteers at an altitude of 4,100m probably caused by a higher adrenergic stimulus.
Feddersen et al. [19] also reported a correlation between NTproBNP levels and severity of AMS. We could not observe such a correlation between NTproBNP and AMS scores in our study (data not shown). The Lake Louise Scoring system of AMS symptoms revealed that all participants had a similar susceptibility to AMS symptoms and showed no significant differences in the average daily AMS score reported between T1DM and control subjects, also when corrected for acetazolamide use. However, due to the small numbers of acetazolamide non-users in each group, there was likely insufficient statistical power to detect any differences in this analysis. Acetazolamide was used by several subjects in both groups. Basnyat et al. [22] showed no differences in mean pulmonary artery pressure between groups using acetazolamide and placebo at high altitude. However, the drug was efficacious against AMS. While it is unlikely that the use of acetazolamide had an effect on echocardiographic parameters or NTproBNP concentrations, there is insufficient data at high altitude to completely exclude this possibility.

The small sample size due to the logistic and financial aspects of such a climbing expedition involving subjects with T1DM and no previous climbing experience is a limitation of our study. The non-randomized use of acetazolamide, additionally limits the statistical power of the comparison between the two groups. There is also a significant age difference between both groups. This limits the statistical power of the comparison between the two groups.

We demonstrate that NTproBNP levels are increased in both healthy and T1DM subjects at 4,000 m despite an acclimatization to high altitude (1,800-4,500 m) for 10 days. The increase in NTproBNP could be expected since we found a significant decrease in TAPSE and tricuspid regurgitation developed in several subjects. While our results are congruent with a report by Feddersen et al. [19] who observed an increase in BNP levels with strenuous activity on NTproBNP levels. [17]. A longer stay at high altitude might contribute to further stiffening of the arteries resulting in an increase in PWV, but this phenomenon is not only necessarily associated with the presence of diabetes mellitus. The more prominent increase in blood pressure in control subjects might be explained by the age difference. The mean age of this group was significantly higher than the T1DM group. There is a progressive stiffening of the large arteries with age, which can contribute to the development of systolic hypertension [18].

Table 1: Echocardiographic and NTproBNP results and Pulse Wave Analysis according to group.

<table>
<thead>
<tr>
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<th>T1DM (N = 8)</th>
<th>Control (N = 8)</th>
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<tbody>
<tr>
<td></td>
<td>4,000 m</td>
<td>4,000 m</td>
</tr>
<tr>
<td>WMSI</td>
<td>1.0 ± 0.0</td>
<td>1.0 ± 0.0</td>
</tr>
<tr>
<td>RV</td>
<td>43.8 ± 3.9</td>
<td>42.9 ± 5.7</td>
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<tr>
<td>TAPSE</td>
<td>22.9 ± 5.2</td>
<td>20.8 ± 2.8</td>
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<tr>
<td>LVES (mm)</td>
<td>48.4 ± 5.7</td>
<td>47 ± 11.2</td>
</tr>
<tr>
<td>LVES (mm)</td>
<td>34.6 ± 4.7</td>
<td>31.8 ± 8</td>
</tr>
<tr>
<td>Septum (mm)</td>
<td>63 ± 0.7</td>
<td>6.9 ± 1.6</td>
</tr>
<tr>
<td>Posterior (mm)</td>
<td>8.9 ± 1.6</td>
<td>7.5 ± 2.1</td>
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<tr>
<td>NTproBNP (pg/ml)</td>
<td>49 ± 31***</td>
<td>148 ± 145***</td>
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<tr>
<td></td>
<td>1,300 m</td>
<td>1,300 m</td>
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<tr>
<td>CAPS (mmHg)</td>
<td>106.9 ± 4.8</td>
<td>103.7 ± 6.6#</td>
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<tr>
<td>SBP (mmHg)</td>
<td>117.1 ± 6</td>
<td>119.8 ± 8.4</td>
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<tr>
<td>DBP (mmHg)</td>
<td>68.3 ± 3.5</td>
<td>71.8 ± 5.6</td>
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<tr>
<td>Mean PWV (m/s)</td>
<td>5.5 ± 0.42</td>
<td>5.5 ± 0.48 (n = 7)</td>
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</table>

WMSI: Wall Motion Core Index; RV: Right Ventricle Diameter; TAPSE: Tricuspid Annular Plane Systolic Excursion; LVES: Left Ventricle End Systolic Diameter; PWV: Pulse Wave Velocity; CAPS: Central Aortic Pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

*p = p < 0.05, ** = p < 0.01, *** = p = 0.07  SL vs 4,000 m or 1,300 m vs 4,000 m

# = p < 0.05 T1DM vs controls

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