Mont Blanc: where red meets white: The effect of altitude on thrombin generation

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Primary Objective: The primary objective is to investigate the effect of hypoxia on blood coagulation using different techniques, among others the very sensitive TG assay in whole blood and plasma.Secondary Objective: The secondary objective is to...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON38743

Source
ToetsingOnline

Brief title
The Mont Blanc study

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

Synonym
bloodcoagulation / disturbed coagulation

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W,Synapse bv,Synapse bv (30.000¤);Diagnostica Stago (30.000);Beverzwerfsport (60.000)

Intervention

Keyword: coagulation, hypoxia, thrombine generatie

Outcome measures

Primary outcome

• TG in whole blood (peak height, ETP, lagtime, time-to-peak, velocity index)

• TG in plasma (peak height, ETP, lagtime, time-to-peak, velocity index)

• Rotem (MCF, CFT, CT, alpha-angle, ML with intem, extem, fibtem and aptem)

• Routine coagulation tests (APTT, PT, INR, platelet count, haematocrit,

fibrinolysis assay, dRVVT-X)

• Measurements of coagulations factor levels (II, V, VII, VIII, IX, X, XI, XII,

protein S and C, ADAMTS-13)

Secondary outcome

• Blood pressure, heart frequency, body temperature, electrocardiogram, blood

oxygen level.

Study description

Background summary

Thrombin generation (TG) is increasingly being recognized as a versatile diagnostic tool in the field of thrombosis and haemostasis. Many groups established that measuring TG is more sensitive to detect conditions of hyper- and hypocoagulabilty, compared to the routine coagulation tests performed in the hospital (e.g. aptt and INR). In plasma TG is most accurately measured with the Calibrated Automated Thrombogram assay (CAT) as developed by Prof. Dr. Hemker and co-workers. This method has been designed for application to platelet free and platelet rich plasma. However, application of this method to samples of whole blood leads to highly erratic signals, due to variable quenching of the fluorescent signal by haemoglobin and red cells that sediment, cluster and retract with in the clot. At Synapse b.v. we found that the problems caused by the presence of red blood cells can be overcome by

dispersing the blood in a porous matrix and by using a new substrate that is not quenched by erythrocytes. By these modifications of the plasma CAT assay, quenching and problems related to unequal distribution of red blood cells were acceptably reduced. The method can be applied in a 96 well flat bottom plate like the original CAT method. The technical validation of the method revealed that the assay is of sufficient precision to enable measurement of TG and a study the contribution of blood cells (i.e. platelets, leukocytes and red blood cells) to thrombin generation. We also developed a transportable point-of-care (POC) test able of measuring TG in a drop of blood. A reliable TG assay in whole blood is of importance because it enables to go one step closer to physiology than present practice is. Apart from this conceptual advantage there is the practical advantage that no centrifugation step is required. In the past many studies have been executed to study the effect of oxygen deprivation due to altitude on hemostasis. Contrasting results were found though most of the studies found a prothrombotic effect on hemostasis. Two major conceptual errors were made with studies performed in the past. The first error is that on altitude the change in barometric pressure has an effect on blood drawing as less blood will be in the tube although the anticoagulant will be the same. With other words, the ratio blood:anticoagulant is no longer correct and thereby induces an artificial anticoagulant effect. Another conceptual error often made is that exercise, e.g. due to climbing or walking to a different height induces an increase in Von Willebrand Factor and thereby in factor VIII. This will introduce an exercise-increased hemostatic response not related to altitude. Both influences have blurred the studies performed till now. We have designed a study in which the exercise-induced increased hemostatic response is isolated and we make use of a point of-care machine using capillary blood without the need for vena-puncture. In fact, this will be the first *clean study* to performed in the field of altitude induced hemostatic changes. The primary goal of this study is to investigate the effect of hypoxia due to high altitude on coagulation and haemostatic parameters.

Study objective

Primary Objective: The primary objective is to investigate the effect of hypoxia on blood coagulation using different techniques, among others the very sensitive TG assay in whole blood and plasma.
Secondary Objective: The secondary objective is to look at the effect of physical activity during hypoxia on coagulation parameters between two groups: the physically inactive *cable car group*, who will climb the Mont Blanc by cable car, and the physically active *climbing group*, who will climb the Mont Blanc by walking.

Study design

This study is a comparative case-control study, in which we compare the effect of oxygen deprivation on coagulation. For this study we will travel to the Mont

Blanc area where two groups will be formed. One group existing of 15 healthy volunteers will actively climb the Mont Blanc by walking, while the other group of 15 healthy volunteers will use the cable car. Blood will be taken every other day by experienced researchers at different heights (at sea level, at 1000m, at 2000m, at 3100m and at 3850m) via venapuncture in the control group (non-exercise group). In the exercise group blood will be drawn at sea level, at 1000m, at 2000m, at approximately 3000 meter and at approximately 4000m. In total 90ml of blood will be taken (5 times 18ml). Blood will also be taken 5 times with a fingerstick (two times 15µl, in total 150µl). The duration of the study will last 11 days.
All blood drawing procedures will be done by certified persons holding at least a nursing degree. Each group will be accompanied by at least 3 experienced medical doctors.
All medical equipment will be delivered to the mountain refuges via helicopter where needed. During the 11 day experiment, a helicopter will be stand by for any needs.

Intervention

Due to the climbing there will be reduced oxygen in the air, so the volunteers will experience hypoxia.

Study burden and risks

Serious precaution is taken to prevent any other discomfort/burden: Experienced guides (With E. Bekker as leader) will be hired to escort both groups to the indicated areas. In case of symptoms preceding acute mountain illness or other discomfort, the subject will be withdrawn immediately. The subject will be escorted immediately to the basic camp at 1000m (Finhaut, Swiss) with a helicopter and there he/she will receive the proper attention and transported back to the Netherlands. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. Both groups will be escorted by at least 2 experienced medical doctors (cardiologists, haematologists, aneasthologists).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Healthy subjects (not having any morbidity and without obvious sign of illness and not taking any medication interfering with coagulation) living in the Netherlands and willing to travel to the Mont Blanc area for 11 days and to donate 18ml blood 5 times during this trip.
• All healthy volunteers will undergo a physical check-up in April by an authorized medical doctor. During this physical check-up the doctor will look at the ECG before and after exercise (cycling), the blood pressure, the heart rate and blood oxygen level.
• Between 18 and 50 years of age. We take 50 year as a maximal age to prevent any co-morbidity that could have an influence on coagulation (like diabetes, atherosclerosis, peripheral arterial disease, *).
• Although only walking through snow will be done, requirement for joining this study: any mountain experience on the level of C1 (see website NKBV),
• Etnicity will not be included as an inclusion or exclusion criteria.

Exclusion criteria

• Subjects taking any medication interfering with coagulation.
• Subjects having a cardiovascular disease or any other serious medical problem.
• Subjects with a mobility impairment (not being able of walking by themselves or on a normal manner without discomfort for the subject).
• Subjects below 18 years of age.
• Subject that did not pass the physical check-up.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-06-2013
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	17-04-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL43244.068.13

Study results

Date completed: 10-11-2013

Actual enrolment: 30

Summary results
Trial is onging in other countries