UNIVERSITAT DE BARCELONA

Condicionantes fisiológicos en la práctica del alpinismo de alto nivel

Anna Carceller Mallada

TESIS DOCTORAL

CONDICIONANTES FISIOLÓGICOS DEL ALPINISMO DE ALTO NIVEL

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UNIVERSITAT DE BARCELONA

FACULTAD DE BIOLOGÍA

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CONDICIONANTES FISIOLÓGICOS EN LA PRÁCTICA DEL ALPINISMO DE ALTO NIVEL

Memoria presentada por

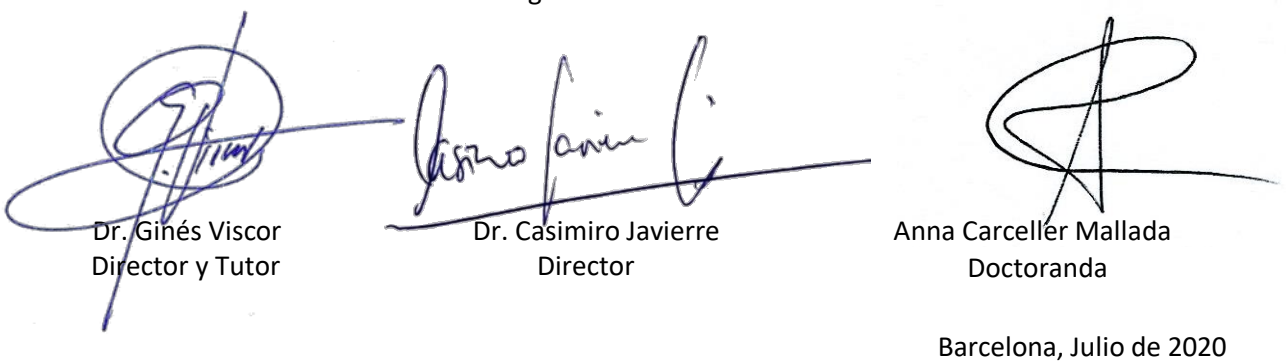
Anna Carceller Mallada

para optar al grado de

Doctora por la Universitat de Barcelona

Tesis realizada bajo la dirección de los doctores Ginés Viscor Carrasco de la Sección de Fisiología del Departamento de Biología Celular, Fisiología e Inmunología de la Facultad de Biología y Casimiro Javierre Garcés del Departamento de Ciencias Fisiológicas de la Facultad de Medicina y Ciencias de la Salud.

Adscrita al Programa de Doctorado de Biomedicina



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Barcelona, Julio de 2020

Para Alex.

ÍNDICE

Agradecimientos

A Ginés Viscor y Casimiro Javierre, directores de esta tesis, por su tiempo, dedicación y paciencia.

A Jordi Corominas, por sus enseñanzas y por acompañarme en la mayor parte de este camino.

A todos los voluntarios que han participado en los test de campo: Jordi Tosas, Oriol Baró, Edurne Toro, Montse Bacardit, Jordi Gavaldà, Oscar Alemán, Alex Castro, Jorge Palop, el Equipo de Esquí de fondo del Ejército de Tierra, Albert Palacín, Dani Ascaso, Lorenzo Ortas, Borja Real, Rogelio Lucas, Xari Adrian, Laura Solaz y Gerard Subirà.

A todos aquellos que participaron en la base de datos de las congelaciones.

A toda mi familia, la que se elige y la que no, y en especial a Alex, Amaia, Alba, Jordi y Pilar.

1. Introducción: El alpinismo como disciplina deportiva

Según el diccionario de la Real Academia Española (RAE):

deporte

1. m. Actividad física, ejercida como juego o competición, cuya práctica supone entrenamiento y sujeción a normas.

2. m. Recreación, pasatiempo, placer, diversión o ejercicio físico, por lo común al aire libre.

deporte de aventura

1. m. deporte que consiste en la práctica de una actividad física, a veces arriesgada, desarrollada en espacios naturales.

deporte de riesgo

1. m. deporte que consiste en la práctica de una actividad física que supone un gran peligro. El montañismo es un deporte de riesgo.

por deporte

1. loc. adv. Por gusto, desinteresadamente. U. t. en sent. irón.

Han pasado cinco años desde la primera vez que, lápiz en mano, nos sentamos a intentar describir objetivamente qué era eso del alpinismo. Con el paso del tiempo, pienso que más que un ejercicio de conceptualización, intentábamos demostrar, en un escenario de récords y premios a actividades alpinísticas, que no todas ellas eran comparables entre sí.

El primer paso fue dilucidar si realmente el alpinismo es un deporte. Concluimos que sí, vistas las definiciones de la RAE y considerando que conlleva actividad física. Mi interlocutor, amante de las letras, puso énfasis en el carácter geográfico de la palabra: "alpinismo" será aquella actividad física que se lleva a cabo en los Alpes, como lo es el "andinismo" en los Andes, el "pirineísmo" en los Pirineos o el "himalayismo" en el Himalaya. Aunque desde luego, en nuestro idioma, cuando nos referimos a alpinismo acostumbramos a querer decir aquella actividad de más o menos dificultad que implica o pretende el ascenso a una cumbre, lo que en inglés se traduciría como "technical climbing" o "alpine climbing". Es decir, a diferencia del "senderismo" o "trekking", el alpinismo conlleva la superación de ciertas dificultades técnicas que pueden requerir más que el mero hecho de andar; y aquí aparecen elementos externos como cuerdas,

anclajes, arneses, crampones, piolets, esquís, ... Bajo este paraguas, podemos considerar que el alpinismo puede ser un "mix" de varias disciplinas que no nos cuesta definir por separado, como son la escalada en roca, la escalada en hielo, el esquí de montaña o la progresión en glaciar.

Fijándonos de nuevo en la definición de la RAE, que curiosamente pone de manifiesto a los deportes de montaña, aparecen las palabras riesgo y peligro. Literalmente: *el montañismo es un deporte de riesgo (supone un gran peligro)*. Quizá este sea uno de los puntos más diferenciales de este deporte: el enfrentar y gestionar los riesgos intrínsecos de la montaña y sus condiciones en cada momento forman parte del juego. Es decir, en la táctica del deporte alpino, la toma de decisiones sobre el terreno (condiciones ambientales, elección de la ruta, estado de la nieve,…) cobra una importancia mayúscula ya no sólo de cara al rendimiento deportivo (que también) sino en cuanto a la dificultad del ascenso y a la seguridad de la propia actividad en sí.

Así, el ascenso a una cumbre determinada será muy diferente si se realiza en verano, en invierno, por una vía desconocida o siguiendo a un guía experimentado.

Para algunos sectores del alpinismo, una actividad será más meritoria cuanto más compromiso suponga; es decir, cuantos menos elementos artificiales sean necesarios (cuerdas fijas, oxígeno suplementario, personal de apoyo, fármacos varios,…) para llevarla a cabo. Además, existe un componente de exploración: se valora la incertidumbre, entendida como el avanzar por un terreno desconocido, que implica tomar decisiones (y asumir sus consecuencias) sobre la marcha, además de rendir físicamente en las diferentes disciplinas que exija la progresión.

El objetivo de esta tesis es intentar abrir una puerta al estudio y análisis de algunas de las variables en la práctica del alpinismo que nos ayuden a profundizar sobre esta disciplina deportiva y la toma de decisiones que lleva intrínseca: la diferencia entre un ascenso a pie por nieve virgen o por terreno pisado; las probabilidades de ser amputado una vez se ha sufrido una congelación a diferentes altitudes; el uso y abuso de fármacos en el alpinismo y la posibilidad de usar fármacos tópicos para prevenir congelaciones en manos y pies.

2. Marco teórico

2.1 El Frío

2.1.1 La termorregulación

El ser humano es un animal homeotermo, de forma que puede mantenerse activo en una gran variedad de ambientes, lo que supone una ventaja frente a los animales que usan otros mecanismos de defensa contra el frío como es la hibernación (1). Este hecho implica el mantener su temperatura corporal central dentro de rangos estrechos para asegurar el óptimo funcionamiento del organismo, pese a grandes oscilaciones en la temperatura ambiental. Desviaciones relativamente pequeñas de la temperatura a nivel celular alteran gran cantidad de propiedades moleculares incluyendo la eficiencia enzimática, la capacidad de difusión y la fluidez de la membrana celular, lo que puede comprometer la disponibilidad energética y los flujos de iones intra y extracelulares y, en definitiva, todas las funciones vitales (2). De esta manera, la capacidad de mantener el cuerpo caliente en ambientes fríos es una de las condiciones fundamentales para nuestra vida, por lo que existen vías especializadas en este fenómeno en nuestro cerebro (3). La zona de "termo-neutralidad" es aquella en la que el organismo no necesita invertir energía para compensar la temperatura ambiente.

Así, el calor corporal es generado por aquellos procesos metabólicos que ocurren en los tejidos corporales, como la grasa o el músculo. Al calor generado por estos procesos se le denomina *termogénesis*.

La *termorregulación* es el proceso mediante el cual el organismo mantiene una temperatura corporal compatible con la vida, independientemente de la temperatura ambiental y a expensas de gasto energético. El principal sensor de la temperatura corporal central está situado en el área preóptica del hipotálamo, que está dotado de neuronas termosensibles. Por otra parte, los sensores de temperatura ambiental se sitúan en la piel, cuyo estímulo es capaz de activar rápidamente las respuestas termorreguladoras frente a cambios de temperatura ambiental antes de que haya una modificación en la temperatura corporal central (4). La piel humana es la interfase entre el organismo y el ambiente, de forma que la termorregulación se basa en gran medida en los fenómenos vasomotores y sudomotores que suceden en ella (5).

Añadida a la termorregulación fisiológica del organismo, existe una termorregulación conductual basada en el estrés emocional que provocan las temperaturas percibidas como desagradables, que sirven como motivación para la búsqueda activa de un ambiente más favorable (2). Las respuestas termorreguladoras vienen condicionadas también por diversos

factores, como el ejercicio físico, los ritmos circadianos, los ciclos menstruales, la edad y el género.

Esther Vives en el campo 4 del Denali (Alaska), protegiéndose del frío junto al equipo femenino Trangoworld

2.1.2 Mecanismos de intercambio de calor entre el organismo y el ambiente

Existen varios fenómenos físicos que regulan la transferencia de calor entre el ambiente y el cuerpo humano, cuyo flujo energético puede medirse a partir de la ecuación de equilibrio térmico. La transferencia de calor siempre ocurre bajo un gradiente térmico (desde el calor al frío).

En un organismo en equilibrio térmico, el resultado de la siguiente ecuación debe ser igual a 0:

$$\text{Equilibrio térmico} =$$

$$\text{metabolismo} - \text{trabajo} - \text{evaporación} \pm \text{radiación} \pm \text{conducción} \pm \text{convección}$$

Si la ecuación no está equilibrada, el organismo gana o pierde calor. La termorregulación se basa, entonces, en alcanzar un balance dinámico entre la producción y la disipación de calor que permita el mantenimiento de la temperatura corporal dentro de unos límites compatibles con la vida.

Conducción

Es la transferencia de calor que sucede cuando dos objetos están en contacto, siendo la dirección del flujo desde el que está más caliente al que está más frío. Un ejemplo típico de este fenómeno es el contacto sin la suficiente protección de una parte del cuerpo sin aislamiento con una superficie metálica en ambientes fríos o la pérdida de calor en una víctima tumbada sobre

la nieve. En ausencia de un aislamiento correcto, la interacción directa entre las moléculas de ambas superficies genera una rápida pérdida de calor del organismo.

$$\boldsymbol{Conducción = kA\,(Tp - Ta)/D}$$

k= conductividad térmica

A= área de contacto

Tp= temperatura de la piel

Ta= Temperatura ambiental

D= distancia entre ambas superficies

La conductividad térmica es variable según las diferentes superficies, siendo la del agua mucho mayor que la del aire, por lo que los tiempos de enfriamiento de una persona sumergida son mucho menores que en ambientes secos. Respecto a los tejidos corporales, la grasa tiene una conductividad mucho menor que la masa muscular, por lo que las acumulaciones de panículo adiposo subcutáneas ejercen como un mecanismo aislante eficaz frente a las bajas temperaturas.

Convección

Se trata de la facilitación de la conducción a través del movimiento de moléculas líquidas o gaseosas sobre una superficie determinada. Este movimiento puede ser causado por una fuerza externa, como el viento o el agua corriente, o interna como consecuencia del cambio de densidad de moléculas adyacentes al cuerpo, que causa su movimiento respecto a la superficie corporal. Por ejemplo, la vasodilatación periférica y el subsecuente aumento en el flujo sanguíneo hacia la piel, sirve para transferir calor por convección del “core” a la superficie cutánea y al ambiente (6).

Radiación

Todos los objetos a más de cero grados absolutos (0°K) emiten radiación electromagnética y pueden recibirla de otros. La radiación es la energía transmitida entre dos cuerpos que no están en contacto pero son visibles entre sí, como en el caso del sol con la tierra o la radiación infrarroja emitida por el cuerpo humano. La cantidad de energía movilizada por este proceso

depende de las temperaturas absolutas, el tipo de superficies implicadas (emisividad de la piel y emisividad del ambiente) y la irradiación solar.

Evaporación

El cambio de estado del agua de gas a líquido o a la inversa implica un gran intercambio energético. Así, la evaporación de 1 gramo de agua a 35 °C requiere el gasto de 0.58 Kcal de energía térmica. En ausencia de ejercicio físico, la evaporación juega un papel menor en la pérdida de temperatura, siendo esta básicamente consecuencia de la evaporación generada en el tracto respiratorio.

La sudoración es el principal fenómeno que implica la pérdida de calor por evaporación en el cuerpo humano. Es uno de los principales mecanismos de regulación cuando la temperatura ambiental excede a la temperatura de la piel y depende de tres factores: 1) la superficie de piel expuesta 2) la temperatura y la humedad relativa en el ambiente 3) corrientes convectivas en el ambiente.

2.1.3 Mecanismos de protección contra el frío

Un sistema de regulación requiere la detección de una variable de control y la capacidad de compararla con un valor ideal, de forma que se pueda producir una respuesta cuando existen diferencias entre ambas.

Las señales captadas por los termorreceptores distribuidos por la piel se integran en el hipotálamo, dando lugar a una respuesta efectora que tiene como objetivo el conservar la temperatura corporal central. En el caso de los receptores del frío, estos se sitúan justo debajo de la epidermis y están activos entre los 10 y los 42 °C (7). Temperaturas más extremas activan otras señales neuronales responsables de la sensación de dolor (8,9). La distribución de estos receptores es irregular a lo largo del cuerpo, de forma que son más numerosos en las zonas cercanas a los labios y más escasos en las extremidades inferiores (10).

Por otra parte, el hipotálamo anterior tiene la capacidad de percibir la temperatura interna, información que integra con las señales de los termoreceptores periféricos, orquestando una respuesta que incluye indicaciones al córtex y la activación de respuestas autonómicas (11).

Los mecanismos de protección resultantes de estos estímulos se basan en la respuesta conductual, la vasoconstricción cutánea, la piloerección, la termogénesis de la grasa parda y el temblor generado en el músculo esquelético.

La vasoconstricción cutánea es un mecanismo de protección contra el frío basado en la redistribución del flujo cutáneo de sangre periférica a zonas centrales, donde se sitúan los órganos fundamentales para el mantenimiento de la vida. Además, se reduce la pérdida de calor por conducción a través de la piel, desplazando la sangre a zonas del organismo con mejor aislamiento térmico. Existen multitud de anastomosis arterio-venosas subcutáneas para llevar a cabo este proceso, a partir de las que se puede controlar el flujo de sangre hacia la superficie corporal en respuesta a un aumento del tono simpático (12). Este es un mecanismo que conlleva menor gasto energético que aquellos que implican la estimulación de la termogénesis, como el temblor en el músculo esquelético o la producción de calor desde el tejido adiposo marrón.

El músculo esquelético es la principal fuente de calor en los humanos expuestos a bajas temperaturas que conservan las reservas energéticas intactas, ya sea con mecanismos de activación voluntarios como el ejercicio físico, o involuntarios en el caso del temblor (13).

El temblor es uno de los últimos procesos en ponerse en marcha durante la exposición al frío, ya que las rápidas y repetidas contracciones musculares entre agonistas y antagonistas implican un gran gasto energético y pueden limitar la respuesta de huida en los animales. En condiciones normales, la fuente energética usada para este mecanismo de defensa son básicamente los carbohidratos, lo que pone de manifiesto la necesidad de evitar su depleción en aquellas personas en riesgo de hipotermia o con hipotermia establecida en grado leve (14).

La piloerección es el fenómeno mediante el cual el músculo erector del pelo se contrae en respuesta a la estimulación simpática y eleva el vello corporal. De esta forma, se crea una capa aislante de aire caliente en contacto con la piel minimizando la pérdida de calor. Este mecanismo tiene una importancia relativa en cuanto a la conservación del calor en los seres humanos, al ir mayormente cubiertos de ropa y disponer de poco pelo cubriendo la piel (12).

El tejido adiposo marrón es capaz de generar calor a partir de la energía contenida en los alimentos a través de la facilitación en el transporte de protones en las mitocondrias. Este mecanismo cobra especial importancia en los primeros estadios de la vida humana y en aquellos mamíferos adaptados crónicamente al frío(15), siendo mediado por el sistema nervioso simpático (16).

Por último, la exposición al frío induce la secreción de hormonas, como la adrenalina, la leptina y la hormona tiroidea, siendo estas responsables del aumento del metabolismo tisular y de la tasa metabólica basal (17).

2.1.4 Hipotermia

Se define la hipotermia como el descenso de la temperatura corporal central por debajo de los 35 °C. La hipotermia puede ser accidental o inducida con intenciones terapéuticas. Clásicamente ha sido una patología asociada a desastres naturales y a conflictos bélicos, convirtiéndose con el tiempo en una patología que afecta a personas que trabajan o pasan su tiempo libre al exterior. Otra causa frecuente se da en aquellas personas con patologías neurológicas, psiquiátricas o que abusan de sustancias tóxicas que quedan inmovilizados al exterior en zonas urbanas, particularmente en invierno.

La incidencia de muerte por hipotermia entre los practicantes de montañismo es alta, justo por detrás de las lesiones traumáticas y de las enfermedades derivadas de la exposición a la altitud (18).

Esta patología puede ser primaria, por enfriamiento directo del organismo, o secundaria a otras eventualidades que provoquen la inmovilización de un sujeto en el ambiente frío (por ejemplo en los eventos traumáticos), lo que conlleva una mayor morbimortalidad.

Tras un primer momento de activación, en general las funciones vitales irán disminuyendo con el enfriamiento hasta desvanecerse. El organismo humano pierde la capacidad de termorregulación por debajo de los 30 °C de temperatura corporal central, cuando se convierte en un animal poiquilotermo y se va enfriando hasta equilibrarse con la temperatura ambiental (3).

Existen diversos factores que pueden impedir los mecanismos fisiológicos de protección frente al frío, como pueden ser las edades extremas de la vida, el tiempo de exposición, la deshidratación, la desnutrición, la fatiga o las enfermedades de base que disminuyan la tasa metabólica (19). Por otra parte, todas aquellas circunstancias que alteren la capacidad de protección conductual frente al frío se presentarán como facilitadoras de la pérdida de calor, ya sean alteraciones cognitivas secundarias a enfermedades neurológicas, intoxicaciones, consumo de fármacos sedantes, etc.

Efectos de la hipotermia sobre los diferentes sistemas

Sistema nervioso

El descenso de más de un grado centígrado de la temperatura neuronal deprime las funciones del sistema nervioso central, lo que se traduce en alteraciones cognitivas, de la memoria y del juicio, enlentecimiento del habla y disminución de la motivación para buscar abrigo. El metabolismo cerebral disminuye entre un 6 y un 10% por cada grado de caída de temperatura entre los 35 y los 25 °C. Esto supone ciertas ventajas respecto a la protección celular, al requerirse menor cantidad de oxígeno y tener menor demanda metabólica, estando descritas múltiples recuperaciones sin secuelas de paros cardíacos prolongados tras haber recibido el tratamiento adecuado (20–22).

Respecto al sistema nervioso periférico, el enfriamiento conduce a un aumento de la tensión muscular, dando lugar al temblor, cuyo control se comparte con el sistema nervioso central.

Sistema cardiovascular

La primera reacción del sistema cardiovascular frente al frío está mediada por el sistema simpático, implicando aumento del consumo miocárdico de oxígeno, taquicardia y vasoconstricción periférica. Si el estímulo continua, y acorde con la disminución de la temperatura corporal central, la frecuencia cardiaca disminuye en ausencia de patologías asociadas como el trauma, la hipoglucemia o la ingesta de fármacos. Progresivamente disminuyen la tensión arterial y el gasto cardíaco, así como la contractilidad miocárdica y el metabolismo cardíaco en general.

El sistema de conducción miocárdico es muy sensible al frío, produciéndose un enlentecimiento del ciclo cardíaco y de los intervalos, que se traducen en un patrón electrocardiográfico característico (23). Este retraso en la conducción puede superar el tiempo refractario, facilitando arritmias fatales como la fibrilación ventricular, desencadenadas por la acidosis, la hipoxia o el movimiento. Por este motivo, la monitorización es un procedimiento prioritario en el manejo de las víctimas hipotérmicas.

Sistema respiratorio

De la misma forma que en otros sistemas, en el respiratorio la respuesta inicial al descenso de la temperatura es una estimulación, seguida por una depresión progresiva acorde a la disminución del metabolismo celular. En hipotermia profunda, la baja frecuencia respiratoria puede dificultar el diagnóstico certero del paro cardíaco en los tiempos contemplados para la

valoración de los pacientes en normotermia (24). La disminución en la frecuencia respiratoria causa, en hipotermia severa, una acidosis respiratoria por la retención del dióxido de carbono.

Sistema renal

La vasoconstricción periférica induce a una hipervolemia relativa central, que estimula la diuresis incluso en presencia de deshidratación leve. Esto conduce a una disminución en el volumen circulante, en especial si se asocia a una hidratación inadecuada (25).

Clasificación de la hipotermia

Durante los primeros estadios de un individuo expuesto al frío sin patología asociada, se activan los mecanismos de respuesta mediados por el sistema nervioso simpático que implican un aumento en la tensión arterial y las frecuencias cardíaca y respiratoria, así como la aparición de temblor que consigue aumentar la tasa metabólica (26). Estos mecanismos de defensa claudican en torno a los 30-32 °C de temperatura corporal central.

La hipotermia puede clasificarse en función de la temperatura corporal central y de la clínica del paciente. En el primer caso, las mediciones certeras de la temperatura corporal central son difíciles de obtener fuera del ambiente hospitalario. Actualmente las guías recomiendan la monitorización de la temperatura corporal central con un termómetro situado en el 1/3 inferior del esófago en el caso de pacientes intubados y con temperatura epitimpánica para aquellos con respiración espontánea. La temperatura epitimpánica indica la temperatura de la arteria carótida interna y refleja de forma bastante precisa la temperatura corporal central siempre y cuando el paciente conserve un correcto gasto cardíaco. Cabe recordar que los termómetros epitimpánicos no están diseñados para ser usados fuera del ambiente hospitalario. Otros recursos como la temperatura oral y rectal no se consideran adecuados para la monitorización de la temperatura corporal central.

Por otra parte, las clasificaciones clínicas de la hipotermia se correlacionan con la viabilidad del sistema de termorregulación, de forma que el grado I se corresponde al momento en que el temblor es funcional y proporcionado al descenso de la temperatura (35-32 °C), el grado II conlleva el compromiso de la capacidad de temblar (32 a 28 °C) y por debajo de los 28 °C la mayor parte de los pacientes están inconscientes y sin capacidad de temblar (27).

La clasificación suiza (28) es una clasificación basada en la clínica y diseñada para orientar el manejo de las víctimas sobre el terreno, fuera del ambiente hospitalario y, en especial, por parte de rescatadores. Se trata de un sistema de clasificación basado en los signos que presenta el

paciente y pueden ser observados por el rescatador; por ello, es susceptible de variar en función de la respuesta fisiológica del organismo intrínseca del individuo y en presencia de otras patologías concomitantes que solapen sus síntomas con los de la hipotermia, como por ejemplo las alteraciones de la consciencia o la incapacidad de temblar del paciente traumático.

• Grado I. Víctima consciente y temblando (35-32°C).

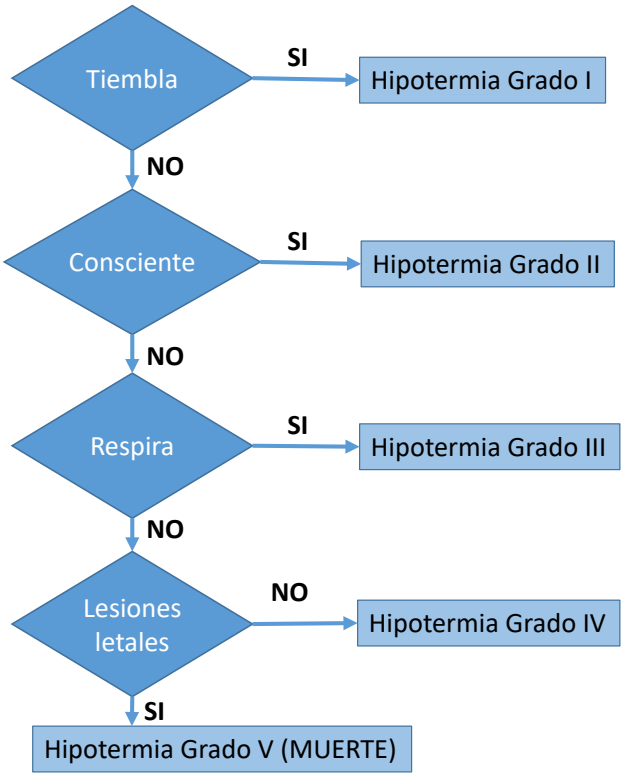
• Grado II. Víctima somnolienta que no tiembla (32-28°C).

• Grado III. Víctima inconsciente pero con signos vitales presentes (28-24°C).

• Grado IV. Ausencia de signos vitales; muerte aparente (24-¿13,7°C?).

• Grado V. Muerte por hipotermia irreversible (temperatura central inferior a 13°C).

Así, los principales aspectos clínicos a valorar en una víctima hipotérmica versan sobre el nivel de conciencia, la capacidad de temblar y la estabilidad cardiovascular.



Tratamiento

Cuando se trata de una asistencia extrahospitalaria, la prioridad inicial es asegurar la seguridad de los rescatadores que van a evaluar y atender a la víctima. Las medidas terapéuticas básicas de la atención al paciente hipotérmico contemplan la adecuada circulación y ventilación, así como la protección al frío. El recalentamiento sobre el terreno es una medida difícil y poco efectiva en la mayor parte de los casos.

Dado el buen pronóstico neurológico de las víctimas hipotérmicas severas en paro cardíaco que reciben tratamiento con circulación extracorpórea, se precisan esfuerzos para cumplir toda la cadena de la supervivencia y alcanzar la atención hospitalaria avanzada en el mínimo tiempo posible.

Colapso del rescate y fenómeno "after-drop"

En una víctima que no está en paro cardio-respiratorio en el momento de la atención, la principal prioridad asistencial es evitar el colapso cardiovascular durante el rescate, prevenir el fenómeno de "after-drop" y empezar a recalentar a la víctima dentro de las posibilidades logísticas.

El fenómeno “after-drop” se define como la bajada progresiva de la temperatura corporal central a pesar de haber retirado a la víctima del ambiente frío o haber iniciado el recalentamiento de forma activa. Se debe a la movilización de la sangre fría de zonas periféricas hacia las zonas centrales al realizar una mala gestión del recalentamiento corporal o del rescate. Cualquier maniobra que produzca la movilización de la sangre periférica en una víctima hipotérmica moderada o severa, como puede ser la deambulación, el recalentamiento de congelaciones, o pasar del rescate en posición vertical a una posición horizontal (camilla), provocará una vasodilatación periférica con un retorno masivo de sangre fría que puede provocar inestabilidad cardiovascular e, incluso, un paro cardíaco.

Por otro lado, el colapso del rescate se define como el empeoramiento clínico de una víctima hipotérmica alrededor del momento de sacarla del agua, pudiéndose manifestar desde un cuadro sincopal hasta el paro cardíaco. La etiología incluye la hipotensión secundaria al cese de secreción de catecolaminas y a las arritmias fatales súbitas, en especial la fibrilación ventricular(26). El proceso patogénico de este fenómeno parece ser el descenso brusco del retorno venoso y de la tensión arterial cuando se elimina el efecto de la presión hidrostática sobre el cuerpo de la víctima. La incapacidad de mitigar la hipotensión con un aumento de gasto cardíaco en las víctimas hipotérmicas puede dar lugar a un síncope o al colapso cardiocirculatorio.

Para intentar mitigar ambos fenómenos, las recomendaciones se basan en un manejo cuidadoso de las víctimas, tanto para evitar el retorno masivo de sangre fría a las zonas centrales como para evitar bajar el umbral arritmogénico del miocardio (25). Se debe evitar el movimiento activo en aquellas víctimas con hipotermia moderada y severa, trasladando en posición horizontal y sin movimiento de las extremidades. En caso de necesidad de retirar la ropa, ésta debe cortarse.

Recalentamiento

La primera medida necesaria en el tratamiento del paciente hipotérmico es prevenir mayores pérdidas de calor. Las medidas de recalentamiento pasivo que incluyen el abrigo, las mantas térmicas no radiantes, colocación de gorros, guantes y demás prendas de abrigo no aportan un aumento significativo de temperatura pero previenen el empeoramiento clínico, a la vez que mejoran el confort de la víctima. El empaquetamiento de las víctimas implica el uso de mantas térmicas, barreras de vapor, barreras térmicas y una última capa "windstopper". La manta aluminizada se mantendrá siempre en contacto con el paciente para mantener el calor que pueda desprender la víctima, siendo adecuada la barrera de vapor inmediatamente por encima de ella si éste está mojado, con objeto de minimizar las pérdidas de calor por evaporación y convección, o más externamente si está seco. Las barreras térmicas pueden ser sacos de dormir, mantas o cualquier material aislante, que evitarán la pérdida de calor por conducción (29,30).

Empaquetamiento de una víctima hipotérmica con barrera de vapor en Benasque (Huesca)

El recalentamiento activo externo implica la aplicación de fuentes de calor radiantes al individuo (bolsas químicas de vapor, mantas radiantes, botellas calientes,…) en los pliegues centrales (cuello, axilas, ingles), para evitar el fenómeno de "after-drop". El incremento de temperatura de estos dispositivos es lento (31) y parecido al que se consigue con el temblor, con la ventaja de que no supone un gasto energético para el paciente. Por este motivo, no se recomienda su

uso en tiempos de traslado cortos (<60 minutos) (32). La aplicación de dispositivos en los que se combinan las medidas pasivas con las activas (barreras de vapor con calor radiante) parecen ser los más efectivos, aunque a día de hoy ninguno ha demostrado ser superior a los demás (33,34).

El recalentamiento activo interno sobre el terreno implica la aplicación intracorporal de fluidos o gases calientes. Esto incluye el oxígeno humedecido caliente y la infusión endovenosa de fluidos calientes. Estas medidas pueden ser poco realistas sobre el terreno a día de hoy por la escasa ventaja en el aumento de temperatura en comparación con los requerimientos logísticos que presentan y deberían ser usados en conjunción con otras medidas de recalentamiento pasivo y activo.

El recalentamiento activo interno hospitalario incluye medidas como los lavados pleurales y peritoneales y la circulación extracorpórea. Esta última ha conseguido unas cifras de supervivencia muy buenas y sin secuelas neurológicas en pacientes en paro cardíaco presenciado, independientemente de si se ha recuperado la circulación espontánea sobre el terreno o no. Así, las recomendaciones son que cualquier paciente con inestabilidad hemodinámica o temperatura corporal central menor a 28°C sea trasladado a un hospital con servicio de cuidados intensivos y soporte vital extracorpóreo (35).

Reanimación cardio-pulmonar

La identificación clínica del paro cardíaco en el paciente hipotérmico puede ser dificultosa (bradicardia, hipopnea, midriasis fija, ausencia de pulso periférico) por lo que se recomienda prolongar el tiempo invertido en la valoración primaria habitual. En el caso de disponer de registro electrocardiográfico, se deberá realizar un registro de al menos un minuto antes de diagnosticar el paro cardíaco.

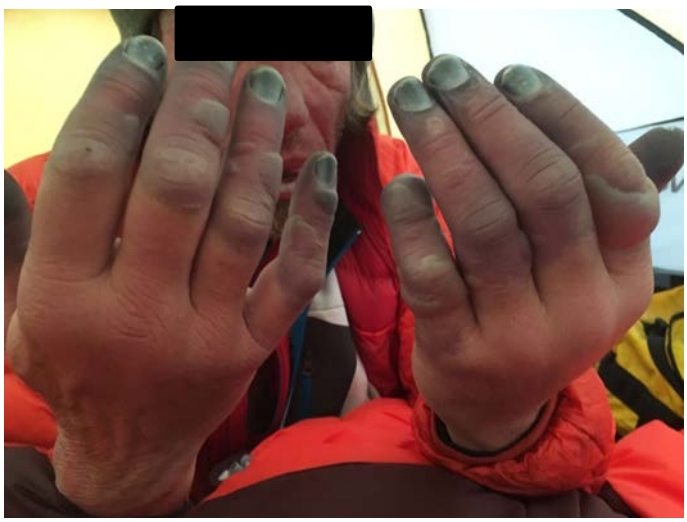
La reanimación cardiopulmonar del paciente hipotérmico difiere de la del normotérmico en cuanto al uso de drogas vasoactivas y la frecuencia de las desfibrilaciones (36). Sobre el terreno, se priorizará el manejo de la reanimación de forma continuada, sea manual o mecánica. Durante rescates en terreno complejo esto puede ser imposible, por lo que se acepta la reanimación cardiopulmonar intermitente en el paciente hipotérmico severo a pesar de la poca experiencia en este manejo, siendo los regímenes recomendados de 5 minutos de reanimación por 5 minutos de traslado si la temperatura corporal central es menor a 28°C, y de 5 minutos de reanimación por 10 minutos de traslado si es menor a 20°C (37).

2.1.5 Las congelaciones

La fisiopatología de las congelaciones se basa en la vasoconstricción periférica extrema a causa del frío y los efectos locales de la baja temperatura sobre los tejidos. Se puede encontrar una revisión del tema aquí (ver publicación 1). Últimamente se realizado esfuerzos por avanzar en dos tratamientos hospitalarios como son la fibrinolisis y los análogos de las prostaciclinas para su uso en congelaciones, así como la posibilidad de trasladar estos tratamientos sobre el terreno. El principal impulsor de este enfoque fue Emmanuel Cauchy, médico y guía de montaña afincado en el hospital de Chamonix donde, a través del IFREMMONT, desarrolló varias líneas de trabajo en este aspecto. Lamentablemente, el Dr. Cauchy falleció en la primavera de 2018 por un alud en los Alpes franceses.

La voluntad de aplicar este tipo de tratamientos sobre el terreno, a pesar de sus particularidades y dificultades logísticas, se basa en el carácter tiempo-dependiente de las congelaciones: el retraso en la primera atención es uno de los principales factores para el desarrollo de congelaciones graves que conllevan amputación quirúrgica (ver publicación 2) y las ventanas terapéuticas de ambos fármacos son pequeñas (24-72 horas).

Así como ya existen propuestas de manejo hospitalario protocolarizadas (38) la aplicabilidad del enfoque práctico extrahospitalario dista todavía de estar claro, aunque parece que las características y perfil de riesgo de los análogos de las prostaciclinas harían más realista su manejo sobre el terreno que en el caso de la fibrinolisis.



Congelaciones grado III al descenso del Makalu (8463m), en un paciente con patología concomitante

2.2 El coste energético del alpinismo

El alpinismo es un deporte que tiene lugar, en general, en un entorno complejo (frío, nieve, viento, hipoxia) que implica la exposición al riesgo (terrenos difíciles, avalanchas, caída de piedras) y la toma de decisiones sobre el terreno.

Debido a la variedad de disciplinas que se engloban dentro del alpinismo invernal (progresión a pie, esquí, escalada en hielo y roca,…) y de su diferente duración en función de las características actividad, resulta difícil establecer con precisión cuales son los requerimientos físicos específicos para su práctica. Además, la mayor parte de las veces, el ejercicio se realiza en condiciones de autosuficiencia de forma que el deportista debe llevar consigo agua, alimento y pertrechos necesarios para cada objetivo en concreto, siendo el peso que acarrea variable en función de las circunstancias. En este sentido, cargar con un peso equivalente al 10% del peso corporal se asocia a un incremento en el coste energético del 10% (39); en concreto, cuando se trata del calzado, su peso implica un aumento en el coste energético entre 1.9 y 4.7 superior que un kilo de masa corporal, dependiendo del género y de la velocidad de la marcha (40). Pero estas estimaciones se refieren al desplazamiento en horizontal, cuando se gana o pierde altura el coste energético es mayor (41,42).

Oriol Baró con su mochila en una aproximación en el Zanskar (India)

Como concepto general, el alpinismo se puede considerar como una actividad de larga duración que conlleva momentos puntuales de alta intensidad; todo ello normalmente en un contexto de

hipoxia moderada o severa, en función de la altitud a la que se realice. Así, el coste energético del alpinismo vendrá condicionado por la duración e intensidad del propio ejercicio, la modalidad que se practique, las condiciones del terreno, las condiciones ambientales (frío, hipoxia, viento), la carga que se transporte, el estado nutricional y de hidratación, el estrés psicológico de la gestión del riesgo y la calidad del sueño en caso de actividades de varios días (43). En cualquier caso, parece clara la necesidad de una buena base aeróbica (potencia aeróbica máxima, VO_2max) para poder llevar a cabo una actividad alpinística con solvencia (44), en especial, si tiene lugar por encima de los 1500 metros de altitud, donde se calcula una disminución del VO_2max entre el 1,5 y el 3% por cada 300 metros de desnivel positivo (45). Estos datos pueden variar en función de la condición física del alpinista y de su estado de aclimatación, en particular si se tiene en cuenta rendimiento a intensidades submáximas (46), pero la estimación es que se requiere un mínimo de 60 $mL/kg^{-1}/min^{-1}$ de consumo máximo de oxígeno a nivel del mar para alcanzar la cumbre del Everest sin el uso de oxígeno suplementario (47).

En un estudio de deportistas profesionales de resistencia, llevando una mochila de 20 Kg, a altitud moderada (3422 metros) en una actividad competitiva que requería escalada invernal y esquí de travesía durante 18 horas repartidas en 2 días, los investigadores concluyeron que el gasto energético del esfuerzo en ascenso fue de 54-57.3 $kJ \cdot min^{-1}$, manteniendo una intensidad del 75% de su frecuencia cardíaca máxima. El balance energético fue negativo con un déficit de 33.5 kJ. Los atletas perdieron 1.5 Kg de peso al finalizar la actividad, básicamente por el mal balance hídrico (43).

Otro estudio llevado a cabo en una expedición de 15 días a un pico de 6170 metros en el Karakorum, el coste energético aproximado fue de 4173±848 $Kcal \cdot d^{-1}$, la mayor parte del tiempo a una intensidad de esfuerzo moderada.

Al contrario de lo que podría parecer, a la vista de los resultados de los estudios realizados hasta el momento, el ejercicio físico en extrema altitud no supone un mayor gasto energético que a altitudes moderadas, probablemente porque el ritmo de aclimatación no permite el ejercicio extenuante y las expediciones a grandes altitudes suponen muchas jornadas seguidas de ejercicio, por lo que la intensidad forzosamente debe de ser menor. En cualquier caso, en ninguno de los estudios hechos a más de 6000 metros se menciona si se ha usado oxígeno suplementario para el ascenso, lo que podría dificultar la interpretación de los datos.

Comparativa de las diferentes publicaciones referentes al gasto energético del alpinismo

Cordillera	**Montaña**	**Altitud** *metros*	**Duración** *días*	**Gasto energético** *Kcal·d^{-1}*
Alpes (43)	Travesía	3422	2	5572,8
Himalaya (48)	Shisha Pangma	5900-8046	7	4636
Himalaya (49)	Everest	8840	7-10	3250
Himalaya (50)	Everest	8840	40	3274 *escaladores* 5394 *porteadores*
Cascade Range(51)	Mt Rainier	2500-3100	7	4558

Por otra parte, cabe tener en cuenta la importancia de las habilidades motrices individuales para llevar a cabo la actividad, sea en ascenso o en descenso. La capacidad aeróbica, si bien es necesaria para evitar retrasos innecesarios que puedan poner en riesgo al deportista, no suple la falta de conocimientos técnicos y tácticos sobre el terreno, ni la eficiencia biomecánica adquirida con la experiencia (39). Además, cabe la posibilidad de que la complejidad del terreno y la demanda muscular limiten las posibilidades de desarrollar plenamente la potencia aeróbica del alpinista si no se ha realizado un trabajo específico previo de extremidades inferiores (52).

2.3 La hipoxia

Efectos de la hipoxia sobre el organismo

Las respuestas fisiológicas a la hipoxia dependen de la altitud de exposición y de la velocidad que se tarda en alcanzarla. Por ello, el organismo reacciona de forma muy diferente en una exposición brusca (por ejemplo, frente a la despresurización repentina de la cabina de una aeronave) que al alcanzar una cumbre de la misma altitud tras semanas de ascenso progresivo. El descenso de la presión atmosférica es la causa por la que, para un mismo porcentaje de oxígeno en el ambiente, la presión parcial de oxígeno disminuya en cada punto de la cascada de transporte de oxígeno. Así, el resultado final es una menor disponibilidad de oxígeno en las mitocondrias de los tejidos (53), lo que desencadena una serie de respuestas fisiológicas en el individuo que, de forma general, ayudan a la aclimatación (54) pero que también pueden generar respuestas maladaptativas.

Efectos de la hipoxia sobre el centro respiratorio

La función de la respiración en los animales es intentar mantener constantes las concentraciones de oxígeno, dióxido de carbono e hidrogeniones en las células del organismo. Por ello, el sistema nervioso central ajusta la ventilación alveolar a la actividad física y a las condiciones ambientales, tendiendo a mantener una presión arterial gaseosa prácticamente constante en condiciones de normoxia.

Uno de los efectos inmediatos de la hipoxia es un aumento en la frecuencia y el volumen respiratorio, resultando en un incremento de la ventilación minuto. Esta respuesta ventilatoria hipóxica es muy variable entre los individuos y resulta favorable a una buena aclimatación (55), confiriendo la ventaja fisiológica de evitar el descenso de la PO_2 alveolar.

Se estima que la hiperventilación debida a la altitud se inicia sobre los 1500 metros en un residente próximo al nivel del mar, y ésta aumenta a medida que la PO_2 arterial va disminuyendo con la altura. Secundariamente a este hecho, se reduce el CO_2 arterial, dando lugar a una alcalosis respiratoria.

El sensor que genera esta respuesta se encuentra en el **centro respiratorio,** y se compone de grupos neuronales situados bilateralmente en el bulbo raquídeo y en la protuberancia. Este conjunto neuronal contiene una zona muy sensible a las concentraciones de dióxido de carbono

e hidrogeniones en sangre, y su estimulación tiene capacidad de activar el resto de zonas del centro respiratorio.

Por otro lado, existe un control químico de la respiración con una sensibilidad específica a la concentración de oxígeno en sangre a través de los denominados quimiorreceptores periféricos, situados fuera del encéfalo. Los quimiorreceptores de mayor interés son los cuerpos carotideos, situados justo encima de la bifurcación de ambas arterias carótidas primitivas; se trata de estructuras extremadamente irrigadas teniendo en cuenta su masa (56).

Estas estructuras contienen un tipo celular que inicia una señal de alarma hacia el sistema nervioso central en caso de disminución de la disponibilidad de oxígeno. Esta respuesta excitatoria frente a la hipoxia se inicia ante la disminución de la presión parcial de oxígeno, pero no es sensible al contenido total de oxígeno en sangre. Así, responde a la hipoxemia pero no a la anemia o al bajo flujo sanguíneo, que por otra parte no serían compensados correctamente con un aumento en la ventilación. Además, la diferencia de presiones entre un lado y otro de la membrana alveolo-capilar es menor por la baja presión de oxígeno alveolar, lo que disminuye la difusión de oxígeno a través suyo.

Cuando un sujeto permanece en bipedestación, la fuerza de la gravedad hace que el flujo sanguíneo en las bases pulmonares sea mayor que en los vértices; por otra parte, la ventilación es mayor en la base que en el vértice, pero no en proporción al aumento de flujo sanguíneo. La traducción funcional de este hecho es que el vértice tiene una ventilación mayor que la base en relación a su flujo sanguíneo. En respuesta a la hipoxia, las arteriolas pulmonares se contraen (vasoconstricción) para aumentar la extracción de oxigeno de los alveolos bien perfundidos (57), mejorar la relación ventilación/perfusión pulmonar y dirigir la sangre predominantemente a zonas mejor ventiladas, contrariamente al funcionamiento vasomotor arteriolar del resto del cuerpo, donde ante la falta de oxígeno a nivel local se tiende al aumento de irrigación (vasodilatación) e incluso a la angiogénesis. Esta vasoconstricción hipóxica pulmonar es reversible en los primeros días de exposición, pero a largo plazo implica cambios anatómicos en la capa muscular arteriolar que impiden su corrección con oxígeno inhalado y causan la denominada cardiopatía de la altitud, que cursa con hipertensión pulmonar e insuficiencia cardiaca derecha.

Efectos de la hipoxia sobre el sistema cardiovascular

Inmediatamente tras la exposición a la hipoxia, el gasto cardíaco aumenta de forma proporcional a la disminución en el contenido arterial de oxígeno, básicamente por un aumento en la

frecuencia cardiaca (58). Ésta aumenta con la altitud, tanto en reposo como durante la actividad física, a pesar de que el gasto cardíaco retorna a valores normales a los pocos días del inicio de la exposición por una disminución en la fracción de eyección ventricular. Si la exposición continúa, la frecuencia cardíaca en reposo y a intensidades submáximas se mantiene ligeramente elevada pero la máxima disminuye, hecho atribuible a un efecto protector cardiaco frente a un elevado consumo de oxigeno miocárdico, con una importante variabilidad individual. Esta limitación de la respuesta cronotropa a ejercicios máximos parece deberse a una desensibilización ante el estímulo adrenérgico pasados unos días de activación de los beta receptores.

El flujo coronario aumenta con la altitud, de forma que hay una mayor capacidad de suministro de oxígeno con una capacidad de extracción mantenida (59), generando una buena tolerancia miocárdica al ambiente hipóxico. De la misma forma, el miocardio tiene la capacidad de limitar su función contráctil durante el ejercicio máximo con objeto de protegerse frente a la hipoxia (60,61).

Efectos de la hipoxia sobre el sistema nervioso central

El cerebro es un órgano muy sensible a los cambios en la concentración de oxígeno, por lo que su función se compromete rápidamente en hipoxia. El suministro de oxígeno depende del flujo cerebral y del contenido arterial de oxígeno. El primero resulta del balance entre la vasodilatación hipóxica y la vasoconstricción hipocápnica, de forma que su regulación se basa en un equilibrio difícil en el ambiente hipóxico. Se ha demostrado que frente exposición aguda a la hipoxia existe cierto grado de edema vasogénico e hipertensión intracraneal, con un aumento de la permeabilidad transmembrana (62) que probablemente sean la causa de los síntomas neurológicos del mal de altura, en especial la cefalea, extremadamente prevalente entre los sujetos expuestos a la altitud. Independientemente de la presencia o no de sintomatología de mal de altura, se han hallado alteraciones en la sustancia blanca y gris de los alpinistas expuestos a extremas altitudes sin oxígeno suplementario (63,64) , lo que sugiere cierto sufrimiento neuronal distribuido de forma heterogénea en el cerebro. La traducción clínica en la exposición aguda se manifiesta como alteraciones en la atención, la memoria a corto y largo plazo y la velocidad de reacción mientras dura la exposición (65), con persistencia de síntomas y hallazgos radiológicos a largo plazo, en especial en zonas del control motor (66).

Efectos de la hipoxia sobre el sistema renal

El riñón es uno de los órganos más resistentes a la hipoxia. La alcalosis respiratoria secundaria a la hiperventilación en altura se compensa (de forma completa sólo hasta los 5000 metros en sujetos aclimatados) aumentando la excreción de bicarbonato por el sistema renal, lo que permite mantener una ventilación intensa en aras de obtener mayor cantidad de oxigeno sin derivar en un aumento excesivo del pH sanguíneo (67).

A extrema altitud esta compensación es lenta e incompleta, y el pH sanguíneo permanece en alcalosis de forma permanente, aunque este hecho no sería del todo perjudicial teniendo en cuenta que la curva de disociación de la hemoglobina se mantendría desplazada hacia la izquierda, incrementando la afinidad del oxígeno hacia la hemoglobina.

Efectos de la hipoxia sobre los parámetros hemáticos

Los bajos niveles de oxígeno ambiental desencadenan una respuesta mediada por el factor inducido por la hipoxia (HIF), que estimula la secreción de eritropoyetina por parte del riñón. Esto conduce a un aumento en la hematopoyesis que, añadida a la disminución del volumen plasmático (deshidratación, secreción inadecuada de ADH y las pérdidas respiratorias por la hiperventilación), conlleva a un aumento del transporte arterial de oxígeno pero a expensas de una viscosidad sanguínea incrementada (68–70).

La hemoglobina sanguínea tiene la capacidad de amortiguar bajas presiones alveolares de oxígeno, permitiendo que hasta alcanzar una altitud de 3000 metros la saturación arterial de oxígeno permanezca en torno al 90%. Esto es así porque la afinidad de la hemoglobina por el oxígeno disminuye en los tejidos periféricos por aumento de la producción de 2,3-DPG, que prevalece sobre la alcalosis respiratoria hasta altitudes más elevadas. Esto permite el desplazamiento de la curva de disociación oxígeno-hemoglobina a la derecha y una mayor cesión de oxígeno a los tejidos oxidativos. Por encima de este punto, la saturación desciende de forma brusca, estimándose entre el 80 - 70% a 6000 metros y con una progresión muy descendente a medida que se alcanzan alturas superiores. A altitudes extremas este fenómeno se invertiría por la profunda hiperventilación, facilitando la unión entre el oxígeno y la hemoglobina en el tejido pulmonar (3). El sueño a gran altitud es desencadenante normalmente del empeoramiento de los síntomas por patología maladaptativa, debido a que las apneas típicas del descanso nocturno a altas cotas generan niveles de hipoxia muy profundos e intermitentes que general un patrón ventilatorio particular conocido como la *respiración periódica* o de *Cheyne Stokes*.

Efectos de la hipoxia sobre el músculo esquelético

El tejido músculo esquelético tiene la particularidad que, añadido a la hipoxia, el ejercicio físico tiene un impacto sobre el balance de oxigenación.

La hipoxia prolongada produce una disminución de la síntesis proteica (71) y aumento del catabolismo proteico (probablemente debido a la disminución de la actividad física por la necesidad de aclimatación, el balance energético negativo y un componente malabsortivo), que se traduce en una pérdida de masa muscular que podría ser más importante en los varones que en las mujeres.

Parece que los efectos del factor inducido por la hipoxia (HIF) en referencia a la angiogénesis y al estrés oxidativo no implican en gran medida al músculo esquelético (72), por lo que el aumento de la densidad capilar se produciría por una disminución del tamaño de las fibras musculares y por tanto de la distancia de difusión del oxígeno a las células, con una reducción de las fibras irrigadas por un mismo capilar. A nivel metabólico, se produce una supresión de la oxidación de ácidos grasos con una estimulación de las vías glucolíticas (73), acorde al mayor coste en términos de consumo de oxígeno de las grasas respecto a los hidratos de carbono.

El factor inducido por la hipoxia

A nivel celular, la respuesta transcripcional a la hipoxia viene producida por el HIF. Éste es un heterodímero compuesto de dos elementos: HIF-1alfa que está regulado por la tensión de oxígeno y HIF-1beta que se expresa de forma constitutiva en casi todos los tejidos de los seres vivos. Cuando el aporte de oxígeno es normal HIF-1alfa es degradado rápidamente en el proteasoma. Pero en condiciones de hipoxia se acumula en el citoplasama, dimeriza con HIF-1beta que es un translocador nuclear (ARNT). Esto permite la entrada al núcleo de la célula del HIF y así iniciar la expresión de genes implicados en la proliferación y la apoptosis, la angiogénesis, la regulación hormonal, el metabolismo energético, la producción de células rojas y la migración celular, todos ellos en gran medida responsables de la aclimatación a la altitud (74).

FRACASO DE LOS MECANISMOS DE ACLIMATACIÓN

Los sujetos no aclimatados que se exponen a más de 2500 metros están en riesgo de desarrollar patologías derivadas de la altitud. Dado que las respuestas a la hipoxia y los ritmos de aclimatación varían entre los individuos, es difícil establecer unas pautas preventivas universales. Se han realizado esfuerzos para identificar el mejor enfoque en cuanto a la prevención mediante la estratificación de los riesgos individuales, pero las estrategias propuestas pueden ser tanto insuficientes en personas susceptibles, como exageradamente lentas para sujetos con buena capacidad de aclimatación y amplia experiencia en altitud, resultando en este último caso en tiempos de exposición al medio montañoso desproporcionadamente largos para sus necesidades (75).

Cuando los mecanismos de aclimatación fisiológicos fracasan, aparece un espectro de sintomatología que comprende desde la cefalea de la altitud al edema pulmonar y cerebral.

Mal agudo de montaña

El mal agudo de montaña es una enfermedad de carácter benigno que aparece en sujetos no aclimatados a la hipoxia. Parece ser que la hipobaria también juega un papel menor en el cuadro clínico, en particular sobre el efecto en la retención de líquidos.

La frecuencia de aparición es variable entre los individuos y depende fundamentalmente de la velocidad que se tarde en alcanzar la altitud, la susceptibilidad intrínseca de cada uno, la cota máxima alcanzada (con especial importancia a la cota donde se duerme), la duración de la exposición y la susceptibilidad genética.

Esta entidad clínica engloba un abanico de sintomatología maladaptativa que, con una buena estrategia de aclimatación, puede resolverse y tomar un carácter anecdótico. El cuadro clínico acostumbra a ser bastante inespecífico, aunque los síntomas más frecuentes son:

- Cefalea holocraneal de carácter pulsátil y predominantemente nocturna.
- Disconfort abdominal, disminución del apetito, náuseas o vómitos.
- Fatiga o agotamiento anormal para la actividad física realizada.
- Trastornos del sueño.

El criterio diagnóstico de mal agudo de montaña se ha consensuado, en ausencia de otra patología orgánica, como cefalea como síntoma cardinal más uno de los demás síntomas descritos en un sujeto que se encuentra a más de 2500 metros de altitud.

La aparición clínica de la sintomatología varía entre las 6 y las 12 primeras horas de exposición, y desaparece entre 1 y 2 días de aclimatación. Se describen como factores de riesgo el antecedente de mal de altura, la velocidad de ascenso mayor a 650 metros de desnivel positivo por día y la ausencia de pre-aclimatación los 5 meses previos (54). Las determinaciones fisiológicas no han resultado útiles en la predicción de aparición de la sintomatología en altura, a pesar de que se baraja la opción de que una pobre respuesta ventilatoria a la hipoxia se podría considerar como factor de riesgo a padecerla.

Riesgo	***Descripción***
Bajo	• Sin antecedentes de enfermedades por altitud a ≤2800 m
	• ≥días para alcanzar la cota 2500–3000 m con incrementos de la altitud nocturna <500 $m \cdot d^{-1}$ y un día extra a 1000 m
Moderado	• Antecedentes de mal de altura en ascensos a 2500–2800 m en1 día
	• Sin antecedentes de mal de altura en ascensos >2800 m en 1 día
	• Todos los individuos ascendiendo >500 $m \cdot d^{-1}$ de cota nocturna a altitudes por encima de los 3000 m pero con un día extra de aclimatación cada 1000 m
Alto	• Antecedentes de mal de altura en ascensos a >2800 metros en un día
	• Todas las personas con antecedentes de ECA o EPA
	• Todas las personas que suban a >3500 m en 1 día
	• Todas los individuos ascendiendo >500 $m \cdot d^{-1}$ de cota nocturna por encima de los 3000 metros sin días extra de aclimatación
	• Ascensos muy rápidos (eg, <7 días en Mt. Kilimanjaro)

EPA= Edema pulmonar de la altitud ECA= Edema cerebral de la altitud

La fisiopatología del mal agudo de montaña se basa en el edema intersticial, la dificultad en el intercambio gaseoso, la retención de líquidos y el aumento en el tono simpático. El agravamiento de este cuadro, cuando incluye aumento de la presión intracraneal, es el origen del edema cerebral, presentándose este como una evolución maligna de un mal de altura no tratado.

De cualquier modo, el mal agudo de montaña es una patología frecuente y que habitualmente se atribuye a otros condicionantes en alta montaña como el bajo nivel físico, la insolación o la falta de sueño.

Métodos diagnósticos

El mal agudo de montaña es una entidad de diagnóstico eminentemente clínico. Para ello, se han usado a lo largo de la historia diferentes escalas de valoración, con una puntuación límite a partir de la cual se considera que el sujeto padece la enfermedad.

El cuestionario de Lake Louise está diseñado para el diagnóstico del mal agudo de montaña (76). Para ser diagnosticado, el paciente debe superar los 3 puntos en el score, uno de los cuales debe corresponderse al dolor de cabeza.

Dolor de cabeza

0—Ausente

1—Leve

2—Moderado

3—Severo, incapacitante

Síntomas gastrointestinales

0—Con apetito

1—Poco apetito o náuseas

2—Náuseas moderadas o vómitos

3—Náuseas severas o vómitos, incapacitantes

Fatiga o debilidad

0—No cansado

1—Fatiga o debilidad leve

2—Fatiga o debilidad moderada

3—Fatiga o debilidad severa, incapacitante

Vértigo/aturdimiento

0—Ausencia

1—Leve

2—Moderado

3—Severo

Tratamiento mal agudo de montaña

El tipo de tratamiento necesario dependerá de la gravedad del cuadro y la logística sobre el terreno, pero habitualmente lo único que es preciso para esta patología es el reposo, la hidratación, y en ocasiones el descenso. En casos graves o muy sintomáticos, está aceptado el uso de acetazolamida y dexametasona por vía oral. Puede ser precisa la administración de tratamiento sintomático para la cefalea y de los síntomas gastrointestinales con los fármacos habituales, teniendo en consideración que enmascararán los síntomas derivados de la mala aclimatación que puedan ser de utilidad para monitorizar el ritmo de ascenso. No se recomiendan los fármacos inductores del sueño ni los sedantes para mejorar el descanso nocturno.

Las recomendaciones terapéuticas se basan en los siguientes puntos:

1) Detener el ascenso, con reposo y aclimatación a la misma altitud.
2) Descender rápidamente si:

- Hay síntomas de mal agudo de montaña severo como alteraciones neurológicas y/o síntomas pulmonares de alarma.

- Los síntomas progresan a la misma altitud durante la aclimatación o con el tratamiento tras 24 horas.

  El descenso de entre 500 y 1000 metros por debajo de donde empezaron los síntomas revierte normalmente el mal agudo de montaña.

3) Medicación específica

- Acetazolamida 250mg cada 12 horas.
- Dexametasona en casos graves o sugestivos de edema cerebral en dosis de choque parenteral de 8mg, seguida de 4 mg cada 6 horas, considerando que es un fármaco que no favorece la aclimatación.

4) Oxigenoterapia si se precisa y es logísticamente posible, para mantener la SaO2>90%
5) Tratamiento hiperbárico: como medida temporal cuando el descenso no es posible.
6) Tratamiento sintomático con antiinflamatorios y antieméticos.
7) Evitar ejercicio extenuante, sedantes y alcohol.

Edema pulmonar de la altitud

Este cuadro clínico es considerado una forma maligna del mal agudo de montaña y la causa más frecuente de muerte dentro de las patologías por altitud, en tanto que en ausencia de tratamiento conduce a una profunda hipoxemia y al fallecimiento en el 44% de los casos. De aparición predominantemente nocturna, se describe como un edema pulmonar no cardiogénico de presentación súbita en individuos susceptibles y mal aclimatados a la altitud. Las bases fisiopatológicas son la hipertensión pulmonar y el aumento de la permeabilidad alveolo-capilar, con el subsecuente fracaso capilar y la aparición de edema alveolar. Los enfermos no tienen por qué haber presentado mal agudo de montaña previamente, aunque normalmente ambas patologías concomitan en un mismo enfermo.

Los signos y síntomas son comunes a un edema pulmonar cardiogénico con algunos matices: disnea como síntoma cardinal con intolerancia al esfuerzo físico, tos seca que sobreviene productiva con expectoración sonrosada, crepitantes húmedos bibasales a la auscultación pulmonar y sibilancias espiratorias por engrosamiento de las paredes bronquiales con espiración alargada; menos frecuentemente, febrícula y dolor torácico opresivo. El cuadro puede evolucionar con taquipnea, crepitantes húmedos, taquicardia, ortopnea y profunda cianosis (77).

Tratamiento del edema pulmonar

El mejor tratamiento para esta patología es el descenso inmediato por lo menos de 1000 metros de desnivel negativo y de la forma más rápida posible, justificándose el uso de helitransporte si hubiera posibilidad. El ejercicio físico debe minimizarse por el riesgo de aumento de la presión pulmonar y de la exacerbación del edema.

El tratamiento farmacológico de elección sobre el terreno es el nifedipino por vía oral, 10 mg de dosis inicial seguida por 20 mg en su formulación retard por vía oral cada 6 horas, aunque estudios recientes no han podido demostrar que en el ambiente hospitalario aporte beneficios al soporte ventilatorio (60). No se recomienda aplicar de forma simultánea otros tratamientos vasodilatadores, aunque fármacos orales alternativos como los inhibidores de la fosfodiesterasa pueden ser de utilidad en ausencia de nifedipino (75).

Edema cerebral de la altitud

El edema cerebral de la altitud es de origen citotóxico (intracelular) por una alteración en el transporte iónico y vasogénico, secundario a múltiples alteraciones moleculares (VEGF, HIF- 1α y radicales libres) que conllevan una disfunción microvascular, con extravasación de líquido y hematíes causantes de microhemorragias difusas (79,80).

Sumado al efecto del edema cerebral, hay otras alteraciones en el balance de los fluidos cerebrales que influyen en la presentación de la clínica, como el aumento del flujo cerebral secundario a la hipoxia y/o la obstrucción venosa, que contribuyen también a la hipertensión intracraneal.

La presentación más habitual es malestar general con cefalea, progresando a confusión, ataxia, agitación, coma y, en ocasiones, la muerte. Puede aparecer de forma insidiosa, con una disminución de las habilidades deportivas e irritabilidad, siendo difícil el determinar en qué punto estos síntomas se pueden deber a un edema cerebral; la aparición de signos apreciables por el observador como la ataxia o la fluctuación del nivel de conciencia son indicativos de la aparición de edema cerebral. En ausencia de tratamiento, los signos y síntomas cada vez se hacen más evidentes, los pacientes no pueden mantener la bipedestación y la muerte es previsible entre pocas horas y dos días.

Oriol Baró precisó evacuación del Huascaran (6768m), en Perú, por edema cerebral

2.4 Uso de fármacos en el alpinismo

Se sabe que ciertos fármacos son usados muy frecuentemente entre los alpinistas, no solo para prevenir los síntomas de mal de altura sino para mejorar el rendimiento físico o psicológico en las montañas (81,82). En un estudio reciente llevado a cabo en los refugios de Goûter y Cosmiques, en el macizo del Montblanc, el 35.8% de las muestras de orina analizadas contenían, al menos, un fármaco relacionado con la paliación de los síntomas de la altitud (diuréticos, hipnóticos, glucocorticoides y estimulantes, por orden de frecuencia) (83). Todas estas sustancias están prohibidas según las directrices de la Agencia Mundial Antidopaje, y algunos de estos fármacos pueden tener efectos secundarios graves reportados en varias publicaciones entre alpinistas, incluyendo desde las alteraciones cognitivas secundarias al uso de acetazolamida a las intoxicaciones corticoideas (84–87).

Iñaki Ochoa de Olza dijo una vez que uno puede ilusionarse con participar en el Tour de Francia pero no estar preparado para ello; los ciclistas del Tour son una ínfima parte de la población que, además de tener unas cualidades excepcionales para el ciclismo, dedican muchas horas de su vida para poder llevarlo a cabo a ese nivel. Sería sorprendente que alguien se presentara en el Tour con una motocicleta y declarara al finalizarlo que ha participado en la competición. Es curioso ver cómo cada uno de nosotros, como profesionales de la salud o como deportistas, tenemos un concepto diferente de lo que es una bicicleta y de lo que es una motocicleta en el mundo del alpinismo: a algunos nos escandalizará el consumo de fármacos preventivos o del oxígeno suplementario en los ascensos y sus consecuencias, pero normalizaremos el uso de las cuerdas fijas o de personal preparando nuestra ruta, y para otros la motivación por un objetivo justificará los medios para alcanzar aquellas (pocas, mínimas) cumbres que quizá deberíamos reservar para esa pequeña parte de la población que tiene el don del alpinismo.

A día de hoy el alpinismo no es un deporte considerado como competitivo, por lo que no está sujeto las regulaciones del código mundial antidopaje. Así, la decisión sobre consumir o no fármacos en el contexto del ejercicio físico en la montaña (en ausencia de patología o accidente) se basa en cuestiones éticas, sobre las que es difícil tener unas directrices claras y universales. Existe un amplio consenso a favor del uso de fármacos como tratamiento de las enfermedades producidas por la hipoxia, en casos de urgencias en la montaña o para rescatadores/trabajadores que deben llevar a cabo un ascenso rápido a la altitud por motivos laborales y durante cortos períodos de tiempo.

Elección de fármacos para el botiquín de ataque en el Ladakh (India)

Desde la Unión Internacional de Asociaciones de Alpinismo se redactó un documento de consenso acerca del uso de fármacos en montaña. El objetivo fue mejorar el conocimiento de los alpinistas y los prescriptores al respecto de los fármacos (profilácticos o terapéuticos) en base a la información científica disponible en el momento: perfiles de seguridad, efectos secundarios, indicaciones, contraindicaciones, riesgos e interacciones. De esta forma, se pretende que la toma de decisiones sobre el consumo de fármacos en montaña sea sobre una base informada (ver publicación 3).

3. Objetivos

Hipótesis

Las actividades realizadas en montaña, tanto recreativas como deportivas o profesionales, han experimentado un aumento en el número de practicantes de muy variado nivel que, entre otras cosas, ha supuesto una mayor incidencia de problemas médicos y deportivos.

Un conocimiento más profundo de las adaptaciones fisiológicas al esfuerzo en montaña y de la incidencia y recuperación de las patologías ambientales derivadas podrá ayudar a prevenir los efectos negativos de la práctica del alpinismo y, al mismo tiempo, a facilitar logros y optimizar sus efectos positivos.

Por eso, el objetivo de esta tesis es analizar diferentes variables del deporte del alpinismo para profundizar en la identificación de los riesgos, en especial considerando los ambientes fríos y el tiempo de exposición en la montaña.

Los objetivos complementarios (secundarios) son:

1) Analizar la probabilidad y condicionantes de amputación tras las congelaciones a diferentes altitudes.
2) Identificar las diferencias en la respuesta cardiovascular y los requerimientos energéticos entre la progresión por nieve virgen y por una traza establecida.
3) Determinar la utilidad de un preparado tópico a base de nifedipino para el tratamiento de las secuelas de las congelaciones y la prevención de nuevas lesiones.

4. Relación de artículos

Artículo 1: Carceller A, Avellanas M, Botella J, Javierre C, Viscor G. "Frostbite: management update". Arch Med Deporte 2017 ; 34(6):345-352
http://archivosdemedicinadeldeporte.com/articulos/upload/rev02_carceller_ingles.pdf

Frostbite: management update

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Received: 14.02.2017
Accepted: 03.07.2017

Summary

The popularity of winter sports is leading to an increase in the number of subjects exposed to environmental pathologies such as frostbite. This is the reason why the patient's profile is changing from the classical descriptions of adults with pre-existing conditions, basically those with cognitive impairment that prevented them from a proper protection against cold or as an occupational illness in working routines related with low temperature exposures. Nowadays these disorders occur mainly in healthy athletic young patients who expose themselves voluntarily to the cold environment, both for professional or amateur aims. Frostbite can occur as a single pathology or can take part in a more complex clinical picture that includes more serious conditions, as hypothermia or trauma. In addition to this fact, it is not uncommon that frostbite appears in exhausted and dehydrated subjects. The likelihood of such injuries taking place in remote areas further complicates its management, primarily because of the delay in diagnosis and definitive treatment. Sequelae after frostbite are common and potentially limiting for the posterior sports career. In recent years, efforts have been made to establish algorithms intended for rescue and expedition doctors to manage mountain medical care based on scientific evidence. Current recommendations include prompt identification and immediate medical care, followed by early hospital treatment if necessary and specific long-term rehabilitation programmes. This review attempts to describe current knowledge of the physiopathology and the clinical aspects of frostbite, in addition to new management perspectives, from in-situ emergency care through to hospital treatment.

Key words:
Frostbite. Rewarming. Iloprost. Amputation.

Actualización en el manejo de las congelaciones

Resumen

La popularidad de los deportes de montaña conlleva que cada vez haya más individuos expuestos a patologías ambientales como son las congelaciones. De esta forma, el perfil de los pacientes está variando respecto a las descripciones clásicas, donde se consideraban lesiones propias del adulto con patología de base, principalmente alteraciones cognitivas que le impedían protegerse adecuadamente del frío, o bien como una enfermedad laboral en profesiones relacionadas con la exposición a las bajas temperaturas. Actualmente esta patología se presenta más frecuentemente en jóvenes sanos y deportistas que se exponen voluntariamente al ambiente frío para la práctica deportiva. Las congelaciones pueden presentarse como una patología aislada o formando parte de un cuadro clínico más complejo, que puede incluir la hipotermia o patología traumática. Añadido a este hecho, es frecuente que se presenten en individuos debilitados por la fatiga y la desnutrición. La posibilidad de que esta patología tenga lugar en entornos remotos añade complejidad a su manejo y empeora el pronóstico debido al retraso del tratamiento definitivo. Las secuelas tras las congelaciones son frecuentes y potencialmente limitantes para la práctica deportiva posterior. En los últimos años se han hecho esfuerzos para basar los algoritmos de actuación de las patologías de montaña en la evidencia científica, destinados tanto al público deportivo como al personal sanitario. En síntesis, estos versan en la identificación y tratamiento inicial tempranos seguidos de tratamientos hospitalarios administrados de forma precoz en caso de ser necesarios y programas de rehabilitación específicos y prolongados. La presente revisión trata de describir las recomendaciones actuales, desde la identificación y clasificación de las congelaciones hasta los nuevos avances en el manejo sobre el terreno, médico inicial y hospitalario de las mismas.

Palabras clave:
Congelación. Recalentamiento. Iloprost. Amputación.

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Definition and background

Frostbite is the most common local injury due to cold and normally occurs when part of the body is exposed to temperatures below the freezing point of intact skin[1], which is estimated to be around -0.55ºC[2], without proper protection and for a sufficiently long period of time[3]. Frostbite has typically been described as an occupational injury (e.g. due to military, mining or industrial tasks), and as characteristic of subjects with permanent or transitory cognitive impairment that prevents them from protecting themselves against the cold[4]. In the last years, the rate among young, healthy adults has increased due to the popularity of winter sports such as skiing, mountaineering, ice climbing and technical climbing/alpinism, at both professional and amateur levels. The incidence among winter mountaineers appears to be very high, as much as 37% in the only study published[5]. Moreover, given that the subjects most frequently affected are aged between 30 and 49 years[6] and usually are physically active, frostbite leads to a substantial interruption in their normal activity. It is worth considering that in most cases it leads to long-term sequelae, particularly if subject's daily activities require exposure to low temperatures to ensure they are carried out safely, or if their job involves constant environmental low temperatures (e.g. ski patrollers, mountain guides, avalanche forecasters and workers involved in cold-chain maintenance).

Frostbite is among the most common consultation causes at Mount Everest medical post (27.5% of traumatic injuries) and Denali medical post (18.1% of total injuries)[7], although these data probably underestimate the actual number of cases, since the number of mild injuries not requiring medical attention is unknown. It is also worth noting that it is the most frequent reason for evacuation from Everest Base Camp[8] and the leading cause of injury at altitude in the Karakoram mountain range[9]. Around 80 cases of frostbite are registered per year at Chamonix Hospital, two thirds of which are diagnosed as superficial.

Risk factors

Since human beings have limited physiological strategies to protect themselves against the cold, any situation that compromises the body's protection capacity in the general population (alcohol abuse, mental illness, very young and very old age, etc.) is considered a risk factor for frostbite. Other intrinsic characteristics of individuals, such as pathologies that affect the vascular bed, neuropathies, Raynaud's syndrome, smoking, genetic predisposition (DD genotype for the angiotensin-converting enzyme) and previous history of frostbite, are predisposing factors that are widely described in the literature[1,4,10]. Other factors include preventable actions such as wearing external body piercing jewellery and constrictive elements (rings, snowboard bindings, elastic clamps, etc.)[11].

It has been suggested that a lack of appropriate clothing and equipment among those who practice sports in cold and high-altitude conditions and the absence of a competent guide can lead to this kind of injury[5], but more investigation is required to confirm this assumption. Any adverse event involving immobilization in a cold environment, including spinal injuries and fractures of large bones, increases the risk of frostbite due to the increased exposure time and the possibility of vascular impairment. With respect to environmental factors, the absolute temperature reached and exposure time are relevant, especially the latter, given that the severity of frostbite is related to the length of time the tissue has been frozen[1,6]. Incidence increases at altitude, particularly from 5100 meters above sea level, due to local factors such as haemoconcentration, a rise in vascular permeability and dehydration, and potential cognitive impairment secondary to hypoxia that can delay or limit self-protection reflexes[9].

Location of injury

Distal areas are the most unprotected from the cold and the most exposed; in addition, the high surface-area-to-volume ratio of fingers makes retaining body heat very difficult, so hands and toes account for up to 90% of frostbite injuries. With respect to alpine climbing, when the terrain verticality is such that crampons and ice axes are required, heat loss by conduction from the distal parts of the extremities is accelerated by contact with snow and ice, which is associated with repetitive trauma during the ascent. Nose, ears and lips cool down more slowly than the extremities[12], but may be affected if the area is not properly protected; other areas may be affected due to exposure in specific situations (e.g. the perineum in subjects sitting on metal surfaces, the penis in Nordic skiers and the knees in prolonged resuscitation manoeuvers)[5,10].

Physiopathology of frostbite

The pathogenesis of frostbite is based on local ischemia, cellular injury and destruction caused by ice crystal formation, and damage resulting from reperfusion after rewarming.

The skin's initial vasomotor response to cold is vasoconstriction, which preserves the core temperature against cutaneous heat loss. The intensity of this phenomenon depends on the severity of the cold and the individual's intrinsic vasomotor response. Secondary ischemia resulting from this process and neuronal cooling cause the initial clinical alterations in sensitivity. If exposure continues, secondary vasodilatation takes place due to the reduction in smooth muscle sensitivity to adrenergic stimuli in five to 10 minute cycles[13]. This process occurs to provide a certain amount of local protection against cold stress. The extent of this phenomenon varies between individuals and increases with exposure, and it has therefore been suggested that there is some grade of acclimatisation to cold[11]. In the context of extremely low temperatures, freeze/thaw cycles result in a thrombotic stage, which causes a progressive local ischemia. This involves cellular death and endothelial destruction, which, in turn, activate a pro-inflammatory response that nourishes the oedema, platelet aggregation and thrombosis cycle[1,4]. If the extremity continues to cool down, arteriovenous shunts may open and generate a non-irrigated distal area that protects the central compartment from further temperature loss, thus sacrificing peripheral zones that are not essential for survival[14].

On the other hand, if the skin continues to cool down, extracellular crystals cause extracellular oncotic pressure to increase, which can lead to dehydration, altered electrolytic balance, lysis and cellular death; if

the reduction in temperature occurs rapidly, intracellular crystals may appear. These may expand and generate mechanical cell destruction by disrupting the organisation of the cellular membrane and intracellular organelles[1].

During the rewarming process, inflammatory changes start taking place, with the appearance of oedema, vasodilation and vascular stasis preceding platelet aggregation and thrombosis, whose clinical manifestations are blisters and severe pain. Prostaglandins and thromboxane appear to play an important role in this process, and these molecules are emerging pharmacological targets for frostbite. After this process, and depending on the grade of the secondary microvascular impairment this sequence can result in two different situations: recovery with blood clot dissolution, resulting in viable tissue, or vascular collapse that results in cellular necrosis and the appearance of dry gangrene[15]. At this point, tissue damage is irreversible.

The consequences of refreezing a previously rewarmed area are devastating because of the massive cellular destruction caused by the formation of crystals in previously damaged tissue[14,16].

Clinical manifestations

In the early stages, alarm symptoms are frequent and often feel unpleasant: a cold sensation and hyperaesthesia or hypoaesthesia are common, though not always present. The affected area becomes numb until frostbite is established, at which point there is a total loss of sensitivity and anaesthesia.

Clinical examination at this point shows a waxy tissue that is yellowish-white or spotted, and differentiating mild from severe injuries is complex.

The rewarming process is painful in most cases and may even require the use of opioid analgesics to control the pain. The tissue at this point is hyperaemic and, depending on the severity, blisters will appear within six to 24 hours; distally located, serum-filled blisters suggest a superficial injury, while proximal, haematic blisters may indicate a deeper injury[1,14]. Blisters can persist for seven to 10 days if not drained. The appearance of any sensation (e.g. paraesthesia, pain or a stinging sensation), oedema and the capacity of skin to warp under local pressure are associated with a better outcome[11], although they do not change its clinical management. Severe frostbite can lead to local infection and systemic involvement. Black eschars are a sign of gangrene in deep tissue.

Classification

There are various proposals for classifying frostbite based on different criteria, including depth of injury, topography and clinical outcome. Given the wide spectrum of injury severity, from reversible changes after rewarming to cellular destruction, it is possible to establish a simple retrospective classification in superficial or deep frostbite based on the preservation or loss of damaged tissue after recovery[16], normally between three weeks and two months after injury. The Wilderness Medical Society guidelines suggest this same classification, but prospectively, after rewarming, based on the probability of tissue loss (Table 1).

Cauchy *et al*. (2001) proposed a predictive scale based on three aspects: topographic extension after first rewarming and, after 48 hours, the presence and aspect of blisters and radiotracer uptake in a bone scan (Table 2).

Table 1. Criteria for Classification of superficial or deep frostbite.

Superficial frostbite	No or minimal anticipated tissue loss, corresponding to 1st- and 2nd-degree injury
Deep frostbite	Deeper injury and anticipated tissue loss, corresponding to 3rd- and 4th-degree injury

According to McIntosh SE, *et al.*, Wilderness Medical Society Practice Guidelines for the Prevention and Treatment of Frostbite, *Wilderness Environ Medicine.* 2014;25:4.

Table 2. Grading score for severity of frostbite injury.

	Grade I	Grade II	Grade III	Grade IV
Extent of initial lesion at day 0 after rapid rewarming	Absence of initial lesion	Initial lesion on distal phalanx	Initial lesion on intermediary (and) proximal phalanx	Initial lesion on carpal/tarsal
Bone scanning at day 2	Useless	Hypofixation of radiotracer uptake area	Absence of radiotracer	Absence of radiotracer uptake area on the carpal/tarsal
Blisters at day 2	Absence of blisters	Clear blisters	Haemorrhagic blisters on the digit	Haemorrhagic blisters over carpal/tarsal
Prognosis at day 2	No amputation	Tissue amputation	Bone amputation of the digit	Bone amputation of the limb +/- systemic involvement+/- sepsis
Sequelae	No sequelae	Fingernail sequelae	Functional sequelae	Functional sequelae

According to Cauchy E, *et al.*, Retrospective study of 70 cases of severe frostbite lesions. A proposed new classification scheme, *Wilderness Environ Med.* 2001;12:248.

This classification, which makes early prognosis possible, was designed in the context of injuries in the French Alps, where there is an effective rescue system that facilitates access to hospitals with the capacity to carry out complex radiological examinations within a short period. In more remote environments, immediate specialised medical attention is not possible within 48 hours of injury, so the outcome is estimated based on clinical examination alone, and the amount of tissue loss is highly unpredictable.

In-situ treatment of frostbite

Emergency treatment should be initiated as soon as frostbite is suspected. General recommendations from the International Commission for Alpine Rescue (CISA-IKAR) and the Medical Commission of the International Climbing and Mountaineering Federation (UIAA MedCom) for immediate treatment must be adapted to each particular situation[17]:

- Move out of the wind.
- Consider turning back.
- Drink fluids (warm if possible).
- Remove boots, but consider that there may be problems replacing them if swelling occurs.
- If wet, replace socks and gloves with dry ones.
- Warm by placing foot/hand in companion's armpit/groin for 10 minutes only.
- Replace boots.
- Give one aspirin or ibuprofen to improve circulation (if available and not contraindicated)
- Do not rub the affected part, since this may cause tissue damage.
- Do not apply direct heat.

If sensation in the affected area returns, it is worth acting on the assumption that previous prevention strategies failed and that continuing to expose the affected body parts under the same conditions is dangerous. If this does not happen, medical treatment may be needed and rewarming in a warm shelter or protected area is recommended.

Treatment of frostbite in base camp, hut or protected area

In the event that transferring the patient to a healthcare centre is difficult or will take too long (over two hours[18]), rewarming must be started in situ, as long as there is no possibility of refreezing and the environment allows for this procedure to be carried out safely[19]. Although walking with established frostbite in the foot is not recommended, self-evacuation in remote areas may be necessary, and the priority is to reach a safe location protected from the cold, rather than remaining immobile in a hostile environment. If an assisted rescue is possible, the extremity should be protected and immobilised with a non-compression bandage. The objective is to reach a safe place, where rapid rewarming can be initiated, considering that the use of heat sources during the transfer should be avoided. Incidentally, frostbite can rewarm spontaneously during attempts to keep the victim warm during transport; in this case, it is not recommended that slow rewarming is actively avoided, but it is imperative to ensure that refreezing does not occur, since this would reduce the possibility of viable tissue[1].

In general, frostbite, as a local injury, must be treated after life-threatening conditions and systemic disorders such as hypothermia and trauma.

Frostbite rewarming

Rewarming must be started as soon as possible and carried out in a water bath (ideally with a diluted antibacterial agent) at a generally accepted temperature of 37ºC-39ºC[20]. Considering that the benefits of faster rewarming are not clear, higher temperatures should be avoided, since they cause more pain and may produce associated burn wounds[19]. Conversely, slow rewarming with lower water temperatures can induce ice crystal fusion, and thus create larger structures that are more damaging to tissue.

Reperfusion criteria are recovery of sensation, normal or red/purple coloration at the distal part of the extremity and pliability of the affected tissue, which occur after 30 minutes to 1 hour of hydrotherapy[11,17]. Active movements inside the heating vessel are beneficial during rewarming[2]. Patients must be informed of the possibility of pain intensification and macroscopic changes of the injury during this process. Early treatment is essential for bone reperfusion and posterior viability[21] and the absence of recovery of sensation after rapid rewarming is a predictive factor for poor prognosis[2].

Water baths should be continued twice a day. The affected area should be kept clean and dry, and the extremity should be elevated above heart level to prevent oedema and venous stasis[4]. Massage and rubbing are not recommended, as mechanical stress on the injured area can cause further damage.

Injuries may present different grades of severity in the same limb, so keeping graphic records can be useful for the clinical monitoring of the evolution of injuries. It can be assumed that if there is loss of tissue, it will be more distal than the damage initially observed[22].

Basic treatment *in situ*

The use of NSAIDs is justified in order to reduce the oedema that can compromise blood flow and local circulation[23]. Acetylsalicylic acid irreversibly inhibits thromboxane-A2 synthesis in platelets, so many authors recommend its use[15,17], although others prefer the administration of ibuprofen[1]. There are no studies that demonstrate the superiority of one treatment over the other.

Oral vasodilators have been recommended on a theoretical basis and because of the low risk associated with their use. The capacity of pentoxifylline to increase erythrocyte deformability may improve blood flow in the damaged area if prescribed as an adjunctive therapy two to six weeks after injury[24]. Buflomedil is an alpha-adrenergic receptor inhibitor with good results in isolated cases that have not been reproducible in subsequent studies[25]. There is currently no scientific evidence to recommend the use of either medication[14,15].

Antibiotic coverage should be reserved in cases of associated cellulitis or potentially contaminated injuries, or where there are septic or traumatic concomitant pathologies that require it, since frostbite itself is not an infectious disease and antibiotic prophylaxis does not prevent secondary infections.

In-situ treatment with heparin has not demonstrated efficacy in modifying the clinical course of frostbite, but it might be recommended to prevent deep vein thrombosis if prolonged immobilization of the patient is needed in the case of frostbite in the lower limbs.

There is consensus in favour of using needles to drain clear blisters if movement is restricted and for conservative management of haemorrhagic blisters, since there is assumed to be deep structural damage underlying them[1,2]. In any case, blisters drain spontaneously within a few days. After treatment of the wound, the area should be cleaned, dried, covered with a topical aloe vera gel[26] and protected with a non-compression bandage that allows oedema to form without restricting blood flow. Dressings should be changed at least every six hours[11], although this depends on the availability of supplies and the specific conditions prior to evacuation.

Frostbite usually occurs in patients who are debilitated by fatigue, dehydration and undernourishment, all of which limit the body's capacity to produce heat[12]. During treatment, it is important to maintain acceptable levels of blood volume, orally if the patient is alert and intravenously if not, especially if clinical signs of dehydration are present, in which case small saline boluses are recommended[14]. In the presence of hypothermia, secondary to the suppression of vasopressin, larger volumes may be necessary, ideally warmed before infusion[2]. Rest and nutrition are essential for recovery, especially for patients in remote locations who face long return journeys.

The use of hyperbaric chambers at high altitude (>3500 m) has been proposed to prevent secondary intense vasoconstriction due to hypoxia and improve the benefits of in-situ treatment and rewarming[27].

Supplementary oxygen is recommended above altitudes of 4500 m[11] or if arterial oxygen saturation is lower than 90%, since tissue recovery depends to a great extent on sufficient tissue oxygenation[14].

Low-molecular weight dextran reduces blood viscosity and prevents microthrombi formation and could be a good therapeutic tool in the future considering their low anaphylactic risk and for those patients who are not good candidates for iloprost or thrombolytic therapy.

Advanced medical treatment in the field

Recent publications of isolated cases suggest that emerging therapies reserved for hospital treatment, such as iloprost and rt-PA (human recombinant tissue plasminogen activator), could be used in the field in the future for severe frostbite through resource-limited treatment strategies[22], although there are no randomised trials that justify this procedure at present. It would be particularly useful to develop optimal in-situ medical care, particularly for patients with severe frostbite who are not close to a hospital, and since the therapeutic window of these drugs is the first 12-48 hours.

Need for evacuation

If frostbite is considered the only reason to assess the possibility of evacuation, mild frostbite (grade I) does not justify ending the activity, but prevention strategies should be improved and the potential risk for refreezing assessed. Grade II frostbite does not require urgent evacuation, but the need for medical care on the field requires the activity to be discontinued for treatment and the regular application of dressings. Severe frostbite (grades III/IV) is a medical emergency in which a delay in treatment worsens prognosis, increases the risk of amputation and risks further systemic involvement.

Hospital management

The anamnesis of a patient admitted to hospital with frostbite should include the time the injury occurred (although this can be difficult to define), the moment in which first rewarming took place, and the type and frequency of any medical treatment received.

Complementary examinations are not required as routine in mild frostbite. For severe frostbite with a risk of tissue loss, angiography can show residual vascular occlusions after rewarming, thus allowing local thrombolytic treatment to be carried out and its effectiveness monitored[28]. The tendency to use Doppler ultrasounds to evaluate blood flow is becoming more popular these days, with angiography being reserved for when vascular interventions are required.

Scintigraphy with Tc99 can predict surgical indication and the extent of tissue loss after 48 hours of injury in 84% of cases[29]. While the application of this technique makes it possible for the patient to find out the extent of their injury and their prognosis at an early stage, waiting for the natural demarcation of necrosis is still recommended before surgery is carried out.

Nuclear magnetic resonance makes it possible to view soft tissues, vessels and ischemic areas clearly and noninvasively[29], although there is little experience of its use in frostbite.

Patients with severe frostbite who are attended within the first 12-24 hours in a hospital with intensive-monitoring capacity are candidates for thrombolytic treatment with rt-PA, either intravenous or intra-arterial with catheter guidance in the absence of contraindications. The aim is to restore arterial flow by eliminating thrombotic residues when distal tissues are still viable, and thus significantly reduce the number of amputations[30,31]. Although there are published dosage recommendations[2], no comparative studies have been made to strongly support an specific infusion titration. In addition to the possibility of bleeding, the most relevant secondary effect is the appearance of post-reperfusion oedema that can lead to compartment syndrome by raising interstitial pressure[10].

Infusion of vasodilators prior to rt-PA reverts the vasospasm associated with frostbite without any aditional adverse effects[32,33]. An open-label study showed that coadministration of heparin and rt-PA, both in intravenous or intra-artery delivery, appears to be a safe and effective practice for reducing vascular microthrombi formation[34]. Treatment with rt-PA should end when blood flow is restored in the distal vessels (observed with angiography) or after 48 or 72 hours in the absence of recovery[31,33]. Those patients at risk of tissue loss with a complete angiographic response have a very good prognosis[35].

Given the good results of this intervention in several case reports and published studies, it seems that patients with severe frostbite should be rapidly evacuated to hospital in order to take advantage of the therapeutic window, although there is a shortage of randomised trials to support these measures[28,34,36].

Table 3. Comparison between different thrombolytic management regimes.

Reference	Cases (n)	Grade of injury	Initial treatment	Type of administration	Drug	Dosage	Study type	Amputation rate
Wexler *et al.* 2017[41]	6	No data	Rapid rewarming	Intra-venous	tPA+/-aspirin+/-warfarin+/-heparin	initial bolus dose followed by a 6-hour infusion of tPA	Retrospective case review	24.6%
Jones *et al.* 2017[42]	7	No data	No data	Intra-venous	tPA + heparin +/-coumarin +/-antiplatelet	tPA at 0.15mg/kg IV bolus+ tPA. IV infusion (0.15 mg/kg) over 6h up to a total dose of 100mg. After: heparin+/-coumarin+/-antiplatelet agent	Retrospective case review	27.5%
Tavri *et al.* 2016[35]	13	At risk of tissue loss	?	Intra-arterial	t-PA	27,5 mg (12-48 mg) during 34h (12-72h)	Retrospective review	20,5%
Cauchy *et al.* 2016[43]	20	Severe	Rapid rewarming+ 250 mg aspirin +buflomedil 400 mg for 1 hour.	Intra-venous	Aspirin + tPA + ilosprost	tPA 100 mg, single dose + iloprost 2 ng/6 h+ Aspirin 250 mg	Retrospective case review	27.3% for grade 3, 44.4% for grade 4
	41	Severe	Rapid rewarming+ 250 mg aspirin +buflomedil 400 mg for 1 hour.		Aspirin + buflomedil	After, daily treatment of aspirin and buflomedil		62.5% for grade 3, 100% for grade 4
	58	Severe	Rapid rewarming+ 250 mg aspirin +buflomedil 400 mg for 1 hour.		Aspirin + iloprost	Aspirin and IV iloprost 2 ng/6 h		4.9% for grade 3, 66.7% for grade 4
Ibrahim *et al.* 2015[28]	3	Severe	Rapid rewarming+fluid replacement	Intra-arterial	tPA + heparin	tPA 4 mg bolus+infusion 1mg/hr+ heparin until PTT 50-70 s for maximum 48 h	Retrospective case review	0%
Handford *et al.* 2014[2]	-	Severe	-	Intra- arterial	tPA + heparin	tPA 3 mg over 15 min followed by constant infusion of 1 mg/h. Maximum 48h of no improvement + 500 units/hr heparin for 4 hours	Review	No data
Cauchy *et al.* 2011[21]	16	Severe frostbite (grade3/4)	Rapid rewarming of the areas with frostbite plus 250 mg of aspirin and IV administration of buflomedil (400 mg)	Intra -venous	Aspirin + iloprost + tPA	250 mg of aspirin + iloprost (2 ng per kilogram per minute for 6 hours per day) for 8 + tPA (100 mg) for the first day	Prospective, randomized, open-label Controlled trial	19%
	15	Severe frostbite (grade3/4)	Rapid rewarming of the areas with frostbite plus 250 mg of aspirin and IV administration of buflomedil (400 mg)		Aspirin + buflomedil	250 mg of aspirin and buflomedil (400 mg for 1 hour per day) for 8 days		60%
	16	Severe frostbite (grade 3/4)	Rapid rewarming of the areas with frostbite plus 250 mg of aspirin and IV administration of buflomedil (400 mg)		Aspirin + iloprost	250 mg of aspirin plus a prostacyclin (0.5 - 2 ng of loprost per kilogram of body weight per minute for 6 hours per day)		0%
Johnson *et al.* 2011[36]	11	Severe	No data	Intra-venous	tPA + heparin	0.15mg/kg bolus + 0.15mg/kg/h6h to a maximum of 100mg. Followed with heparin to PTT 2X control for 3–5 days	Retrospective case review	59%
Bruen *et al.* 2007[31]	6	Patients with perfusion defects	Immediate rewarming and fluid resuscitation as appropriate	Intra-arterial	tPA + heparin	tPA initial rate of 0.5 to 1.0 mg/h + Heparin at 500 U/h until normal perfusion or maximum 48 h	Retrospective case review	10%
	26	Varying degrees of injury severity. Not treated with thrombolytic therapy	Immediate rewarming and fluid resuscitation as appropriate	-	-	-		41.5%
Twomey *et al.* 2005[34]	13	No data	Rapid rewarming	Intra- venous	tPA + heparin	0.15 mg/kg bolus + 0.15 mg/kg/h6h to a maximum of 100 mg. Followed by IV heparin to PTT 2 control for 3–5 days, then Coumadin 4 weeks	2 Groups Arterial Venous Prospective, open label, unblinded	19% (not reported by route of administration)
	6	No data	Rapid rewarming	Intra -arterial	tPA + heparin	0.075 mg/kg/h 6 h. Repeated additional 6 h if repeat scan abnormal		19% (not reported by route of administration)

On the other hand, iloprost is a prostacyclin analogue with vasodilator and antiplatelet properties that has been associated with reductions in digital amputations in severe frostbite, so many authors recommend its intravenous administration as a first-line treatment[22,29]. Dose titration in published clinical experiences is based on the appearance of adverse effects within the therapeutic range (starting at 0,5-2 ng/kg/min, with 0,5 ng/kg/min increases every 30 minutes until the maximal toleration rate is achieved and maintaining its infusion 6 hours/day for 5-8 days), with consideration for the fact that the patient must be maintained in the supine position to prevent orthostatic hypotension[21]. The effect of its association with rt-PA is not well known, although in accordance with a recent randomized trial it seems to be optimal in grade IV frostbite within the first 12 hours[21]. Contraindications of its use include unstable angina, recent cardio-vascular events and increased risk of bleeding. The advantages of iloprost over rt-PA are that it does not require interventionist procedures, the therapeutic window is larger, it can be administered in patients with trauma and intensive monitoring, other than blood pressure monitoring, is not required.

Tetanus vaccination is recommended, according to the usual schedule.

If amputation is required, surgical intervention must be delayed until viable tissue can be demarcated accurately, provided that an emergency justification for proceeding (e.g. gangrene, sepsis and compartment syndrome). This measure is justified by the possibility that tissue initially considered non-viable is restored[37] and the risk of surgical trauma interfering with the healing of proximal tissues[4,6]. This is not carried out in normal conditions until at least four to six weeks after injury, including in patients receiving thrombolytic therapy, which can imply the need for psychological support.

Sequelae

Sequelae after frostbite are common and occur independently of its severity. In a study of 30 patients with grade II frostbite, 63% were found to have sequelae after four to 11 years from injury (cold sensitivity 53%, digital numbness 40%, reduction in touch sensitivity 33%)[38]. It is estimated that sensitivity disturbances are present for at least four years in nearly all those who have suffered from frostbite[11].

Chronic pain secondary to frostbite is very common and is usually refractory to conventional analgesics. It sometimes responds to drugs designed for neuropathic pain (e.g. amitriptyline and gabapentin). Despite efforts to treat later symptoms (e.g. pain, paraesthesia and numbness) with chemical and surgical sympathectomies, there is no clear indication for their use.

Other common problems include hyperhidrosis, secondary to an abnormal response of the sympathetic system, trophic alterations in skin and fanerae, digital flexor retraction and high susceptibility to future cold-related injuries. Alterations of skin colouration, ranging from depigmentation to local cyanosis, are not uncommon.

Long-term sequelae include osteoporosis, and where the frostbite affected the joints, osteoarthrosis with damaged joint surfaces and a decline in joint mobility with tendinous retractions of the flexor musculature[39].

Digital amputations (partial or total) involve functional limitations to daily life and sporting activities, given the alteration in the normal biomechanics of the limb. Gait will be severely impaired if frostbite affects the metacarpophalangeal joint in the foot. Risk factors related to amputation include duration of exposure to cold, absence of proper equipment, exposure to cold in remote areas, presence of infection and delay in treatment.

There is a broad consensus on the need to prioritise an early multidisciplinary rehabilitation programme for patients who have undergone amputation, including prompt controlled mobilisation to prevent tendinous retraction and reach optimal levels of functional recovery[10,15], and long-term, non-aggressive treatment[40] (Table 3).

Conclusions

Frostbite is no longer primarily an occupational pathology or characteristic of subjects with cognitive impairment. It has become a common cause of morbidity among healthy young adults who voluntarily expose themselves to cold, usually while practising winter sports. Knowledge of activity planning, survival skills and cold protection is strongly recommended as basic prevention tools. Early recognition of frostbite is essential to ensure prompt diagnosis and early initial treatment, since a delay in first rewarming is associated with a worse prognosis. At present, in-field treatments are relatively basic and can be initiated by non-qualified subjects with the proper training. New perspectives are focusing on improving initial care by applying advanced treatments under medical supervision. For superficial frostbite, there is no need for further complementary tests beyond the clinical monitoring of the injury. For severe frostbite, scintigraphy with Tc99 is a good prognosis predictor after 48 hours of injury. Angiography is both an imaging and a therapeutic tool, but less invasive options such as MRI and ultrasound appear to be good alternatives when direct thrombolysis is not required. Emerging hospital treatments have a therapeutic window that needs to be known to take fast and optimal decisions regarding patient evacuation, considering the rescue time lapses and the hospital resources of each mountain area and country. Surgical interventions must be delayed until there is a clear demarcation of the necrotic area. Long-term sequelae are prevalent among subjects with frostbite, even in non-severe injuries. A multidisciplinary approach to caring for patients with frostbite is needed in the management of long-term functional sequelae.

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Artículo 2: Carceller, A, Javierre C, Ríos M, Viscor G. "Amputation Risk Factors in Severely Frostbitten Patients ". Int J Environ Res Public Health. 2019; 16(8): 1351

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6517929/?report=classic

International Journal of
Environmental Research and Public Health

MDPI

Article

Amputation Risk Factors in Severely Frostbitten Patients

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Received: 11 March 2019; Accepted: 10 April 2019; Published: 15 April 2019

Abstract: In recent years, the incidence of frostbite has increased among healthy young adults who practice winter sports (skiing, mountaineering, ice climbing and technical climbing/alpinism) at both the professional and amateur levels. Moreover, given that the population most frequently affected is healthy and active, frostbite supposes a substantial interruption of their normal activity and in most cases is associated with long-term sequelae. It particularly has a higher impact when the affected person's daily activities require exposure to cold environments, as either sports practices or work activities in which low temperatures are a constant (ski patrols, mountain guides, avalanche forecasters, workers in the cold chain, etc.). Clinical experience with humans shows a limited reversibility of injuries via potential tissue regeneration, which can be fostered with optimal medical management. Data were collected from 92 frostbitten patients in order to evaluate factors that represent a risk of amputation after severe frostbite. Mountain range, years of expertise in winter mountaineering, time elapsed before rewarming and especially altitude were the most important factors for a poor prognosis.

Keywords: frostbite; risk factors; amputation; winter sports

1. Introduction

Frostbite is a type of cold-related injury caused by the exposure of a part of the body to temperatures below the freezing point of the tissue, which is estimated to be −0.55 °C. Frostbite has increasing incidence as a non-occupational affliction in young healthy adults, linked to the increase in the popularity of winter mountain sports [1]. Cutaneous circulation plays an important role in thermoregulation by varying blood flow through peripheral structures in order to maintain core body temperature, which is essential for survival. In a cold environment, maximal vasoconstriction in hands and feet is reached when their temperature drops to 15 °C. This is followed by local protective cycles of vasodilation if cooling persists [2], but leads to progressive local ischaemia if exposure continues. Meanwhile, direct cellular injury caused by cold includes intra- and extracellular ice formation, structural alterations of cells and their components, and osmotic changes. The length of cold exposure and rapidity of freezing determine the magnitude and importance of these different pathological processes [3]. Frostbite is an injury that involves local ischaemia, cell injury and both local oedema and thrombotic events related to reperfusion of tissue damaged due to cold [4,5]. The microvascular impairment determines the

potentially hypoxic tissues that can lead to necrotic areas [3]. According to the depth of the skin damage, necrosis can be so severe that it results in spontaneous or surgical amputation. Amputation is related to the severity of the injury, with the most severe injuries being more likely to result in non-viable tissue [6].

Numbness and coldness of the injured part count as secondary clinical signs and symptoms, after vasoconstriction and ischaemia, and are usually of little help for predicting prognosis before rewarming.

Thawing restores blood flow and induces congestion, inflammation and thrombosis in the injured endothelium [7,8], which may prompt erythrocyte extravasation due to failure of the vessel wall. Clinical manifestations include severe pain and macroscopic changes that can help to predict the extent of the injury [6].

Efforts have been made to establish risk factors for frostbite [9–11], as well as risk factors for amputation once the patient has reached in-hospital care [12,13]. However, little is known of the possibility of reducing amputation rates and improving the quality of injury management in the field once frostbite has already occurred. In this study, we aimed to determine which factors influence prognosis in established frostbite secondary to cold exposure in mountaineers, and what strategies to recommend in immediate care in order to achieve better injury outcomes.

2. Materials and Methods

We performed a retrospective study of data from 92 patients (74 men, 18 women) aged 33.1 ± 8.5 years, with 12.3 ± 9.5 years of mountaineering experience in winter conditions, who had recovered from acute frostbite injury regardless of the presence or absence of long-term sequelae. Patients (75% amateurs and 25% professionals) from different countries anonymously completed a survey once they had restarted their normal working or sporting activities. We collected the following data: gender, age, smoking habits, professional affiliation (if one existed), years of experience at activities over 3000 m in altitude, existence of previous preparation one year and five years before the accident, frostbite date, location (mountain and range), altitude, maximal altitude reached in the expedition, awareness of frostbite, modification of objectives, acute mountain sickness incidence, perception of fatigue previous to frostbite, affectation of decision making, specific causes of frostbite, time to reach first aid and first-aid post location. We also recorded details concerning the nature of the therapeutic measures received, recovery and rehabilitation and changes in habits or equipment; and on the existence of sensitivity alterations, sequelae and amputation. The single patient who suffered frostbite during a mountain rescue was excluded from the analysis, leaving a total of 91 subjects in the study. None of them did refreeze after rewarming. Chi-square, ANOVA with normality variables, Kruskal–Wallis and U-Mann–Whitney for non-parametric variables, and stepwise regression tests were performed to study interactions between variables and to check for risk factors. Data are presented as mean value and standard deviation. Statistical significance was considered when $p < 0.05$. After approval of the study by the local ethics committee, all the participants were informed of the objective of the study and freely gave their consent to participate.

3. Results

No differences were found with regard to age, gender, smoking habits or occupation between frostbitten patients needing surgical amputation (A = 68) and those who did not (NA = 23). The perception of fatigue prior to the frostbite incident was recorded on a scale ranging from 0 (absence) to 10 (maximal), suggesting a tendency towards correlation with the amputation group, although this did not reach statistical significance (6.9 ± 2.4 (A) vs. 6.0 ± 2.3 (NA); $p = 0.083$).

We found statistically significant differences in the number of years of experience in winter mountaineering activities (10.8 ± 9.2 years for NA, 16.7 ± 9.5 years for A group; $p < 0.001$). The average altitude at which the frostbite occurred was 4850 ± 2400 m, with considerable differences between the

groups (4210 ± 2210 m (NA) vs. 6760 ± 1910 m (A); $p < 0.001$), as well as in the maximum altitude reached during the ascent (4920 ± 3130 m (NA) vs 7190 ± 1860 m (A); $p < 0.001$).

The time lapse between injury and first attention showed significant differences (23.5 ± 27.3 h for NA vs. 42.1 ± 31.6 h for A group; $p = 0.003$) as well as the mountain range in which the frostbite occurred (Figure 1), with the Himalayas and Karakoram showing the greatest incidences ($p < 0.001$). Only one case (Mt. Cook, New Zealand) of frostbite resulting in amputation was recorded outside of the Earth's highest ranges.

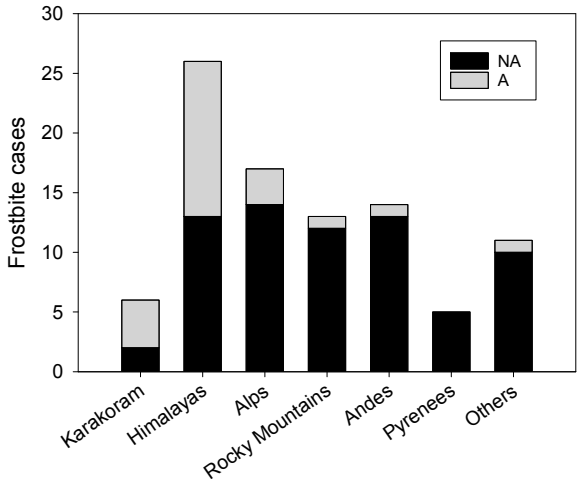

Figure 1. Occurrence of frostbite according to the main mountain ranges in our sample. Cases requiring amputation represented as grey bars stacked over those not requiring amputation denoted in black. The "Others" group of ranges include several mountains over 2000 m and Antarctica.

Capacity to make correct decisions seemed to be impaired in both frostbitten groups, 6.8 ± 2.5, although non-significant statistical differences were found.

We developed a stepwise regression model [14] to establish the main risk factors for surgical amputation once severe frostbite occurs, considering the different variables that were included in the survey. We found that altitude had a very strong weight in our model, to the extent that the rest of the variables considered (including mountain range, years of experience and delay before first attention) were far less relevant for amputation prognosis as independent factors. However, these other variables are also strongly related to altitude, andafter maximum likelihood estimation regression analysis, altitude alone was a good predictor of amputation incidence. The probability of amputation after frostbite for any specific altitude, as yielded by this simplified mathematical model, is depicted in Figure 2.

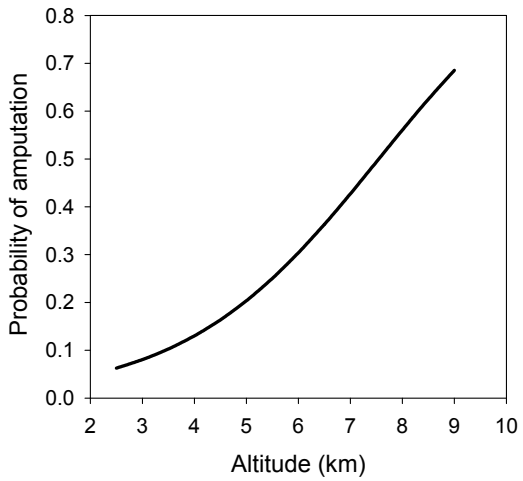

Figure 2. Relationship between probability of amputation after frostbite and altitude.

In Table 1 we have listed the cut-off points of the above regression function with their corresponding values for the probability of error for prediction of amputation risk after frostbite occurrence.

Table 1. Results for the prediction of amputation probability if frostbite occurs.

Cut-Off Point	True (%)	False (%)
0	100	0
0.05	100	15.09
0.1	90.48	39.62
0.15	80.95	58.49
0.2	80.95	58.49
0.25	80.95	62.26
0.3	80.95	64.15
0.35	80.95	64.15
0.4	71.43	75.47
0.45	61.9	84.91
0.5	52.38	88.68
0.55	**47.62**	**92.45**
0.6	9.52	100
0.65	0	100
0.7	0	100
0.75	0	100
0.8	0	100
0.85	0	100
0.9	0	100
0.95	0	100
1	0	100

Taking 0.55 as the index value for the prediction of amputation probability (in bold in Table 1), there is a 47.62% probability of making a correct prediction for amputation and a 92.45% probability of making a correct prediction for patients who will not undergo amputation. This is the cut-off point that suits to make the least error in what is most important for medical advice. Thus, we obtained the following formula, termed the amputation index:

$$(\mathrm{AI}) = -4.04446 + 0.000535925 \times \text{altitude (expressed in metres)}. \quad (1)$$

The results of this index can be interpreted as the 0 value representing a 50% probability of amputation if frostbite occurs, which corresponds to an altitude of 7547 m. As has been shown, the maximal value of our sample corresponds to an AI of 0.55, which corresponds to a 100% probability of amputation if severe frostbite occurs at altitudes over 8573 m (Figure 3).

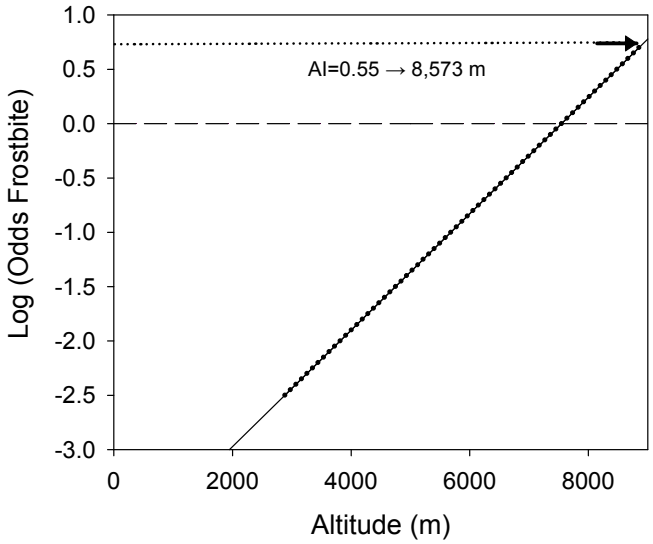

Figure 3. Amputation index in relation to altitude.

4. Discussion

According to our results, altitude is the most relevant amputation risk factor. This could be expected from the well-known lapse rate of a drop of approximately 1 °C every 150 metres of ascent (about 6.5 °C/1000 m), and the predisposition of individuals to experience peripheral vasoconstriction to maintain core temperaturein the cold environements. Haemoconcentration, dehydration, small vessel blockage and hypercoagulability resulting from a hypobaric environment may also play an important role [5,15]. Recent publications indicate that the additional effect of hypoxia on top of cold exposure results in a greater damage to microcirculation in animal models [16]. Acute hypoxia itself does not seem to have any relevant effect on tissue temperature [17]. The effects of acclimatization to altitude on this phenomenon are yet to be established, although laboratory observations suggest that it could worsen frostbite injuries due to the altered haemorheological behaviour [16]. In addition to this, hypoxia impairs rewarming responses of injured tissue [18]. Whether the causal mechanism of this finding is the additional effect of hypoxia on the severity of the injury due to vasoconstriction, the impairment of rewarming mechanisms, the increased difficulty for the subject to reach medical assistance and protection, or a combination of all factors is still unknown. It is worth noting that altitude was the strongest risk factor of the analysed variables, but the influence on altitude of other confounding factors in the field remain to be revealed.

An increased number of years of experience at winter activities appeared to be a risk factor in our sample population. This is contrary to what could be expected, considering that experience in winter mountaineering may lead to an increase in knowledge of protection and prevention strategies against cold. It is worth noting that frostbitten patients in this study showed a high degree of expertise in mountaineering in winter conditions, averaging 12.3 years of preceding practice. Prior observations regarding risk and mountaineering experience indicate that climbing experience at high altitude does not have a positive influence on mortality. Furthermore, there is a positive association between mortality and the number of expeditions at high altitude [19,20]. In the case of avalanche accidents, an increase in mortality due to the repeated exposure to the hostile environment has been observed among more experienced and skilled subjects [21]. Our results suggest that experience per se should be considered a strong risk factor for suffering deep frostbite. This observation can be explained by the fact that experience may enable subjects to take part in activities that are more technical and performed at higher altitude. These may occur in more remote areas and may therefore have lower probability of receiving prompt medical attention. Finally, years of experience in winter mountaineering might imply a prior history of frostbite or alterations on distal peripheral circulation that have not been considered in the survey and might have an unknown influence on our results.

Delay before receiving first medical attention for the frostbite injury after it was already produced was another strong risk factor for posterior amputation. This may be related to limitations in reaching medical installations in some mountain ranges (the Himalayas and Karakorum between them saw most of the severe frostbite leading to amputation in our study) and the lack of knowledge of frostbite first aid of the subjects involved. The average time until rewarming the injury was 23.6 h for those not requiring amputation, whereas this increased to 42 h for those who did require amputation. This observation is consistent with previous publications that suggest that the length of time for which tissue is exposed to cold is more damaging than the absolute temperature reached [4,22]. Different durations of freezing had different influences on blood circulation in frostbitten tissues, with the longest being the most harmful [16]. According to our results, time before first rapid rewarming of frostbite is a crucial factor for the risk of amputation, especially during the first 24 hours after frostbite occurs. The time to reach a clinical setting in order to receive advanced treatments (e.g., intravenous vasodilators or thrombolytic agents) was not considered in this study as none of the subjects received them. However, evidence suggests that reducing the time lapse before reaching an advanced medical post with possibilities of receiving more complex treatments such as thrombolytic factors and/or vasodilator iloprost in an adequate time frame may decrease the risk of amputation [12,23,24]. Nonetheless, more research is needed to evaluate the real impact of these therapies on frostbite sequelae.

The rate of perceived exertion was higher in those patients who later underwent amputation. Although our results did not reach statistical significance, they match prior observations which considered that fatigue may predispose subjects to greater heat loss when exposed to cold [25].

Regarding the last, this theoretical prediction model for amputation risk presumes that below 7547 metres, the probability of amputation is lower than the possibility of preserving the affected appendages, as these values correspond to the negative values of the AI index. We must remark that our mathematical model has a certain specificity and sensibility that is dependent on our database content, and it is susceptible to improvement through the inclusion of more cases.

The practical application of this mathematical model involves considering, in the medical advice previous to participation in an alpine expedition, which risks the alpinists face regarding sequelae from frostbite injuries at certain high altitudes. Taking into consideration that risk 0 does not exist, there are some points that can be considered as part of optimal management and prevention of sequelae from cold injuries at altitude (Table 2).

Table 2. Suggested guidelines for the optimal management of high-altitude frostbite and the prevention of sequelae.

Guideline	Procedure	Evidence
(1) Evaluate risk for severe frostbite injuries with regard to ascent and team characteristics:	Consider the possibility of frostbite in spite of a high degree of expertise in winter mountaineering, regarding the level of exposure to the cold environment as a risk in itself.	Present study
	Consider the strong influence of altitude on amputation and sequelae (see Equation (1) AI in previous lines) if frostbite occurs.	Present study
	Consider the influence of the mountain range on amputation and sequelae, considering rescue timing to reference hospitals (Pyrenees/Alps < Himalayas < Karakoram).	Present study
	Consider the influence of logistics and the characteristics of each ascent (mountain, range, climbing style, etc.) leading to different complexities in providing prompt and adequate field treatment.	Present study
(2) Minimize risks of amputation and sequelae if frostbite occurs	Consider first-aid training for frostbite injuries as a must among all members of the expedition.	Hubell [26]
	Include in your fist aid kits those medications and resources needed in cases of frostbite.	Tek [27]
	Design and be aware of an evacuation schedule to first aid field installations, intermediate medical points (if they exist) and hospital or clinical settings, considering weather and local limitations for rescue.	Bowman and Kummerfeldt [28]
	Try to have effective communication with an expert in case you need advice or no medical staff are included in your expedition.	State of Alaska CIG [29]
(3) Act correctly if frostbite occurs	Learn to make correct and prompt identification of frostbite.	Zafren [5]
	Enact rapid rewarming if there is no reasonable possibility of secondary exposure to cold.	Syme [30]
	Provide optimal care for injuries and later treatment.	State of Alaska CIG [29]
(4) Minimize time course before receiving advanced treatments and medical advice if required	Provide the shortest evacuation time for severe injuries.	Linford et al. [31]
	Evacuate to a hospital where proper treatments can be administered.	State of Alaska CIG [29]
	Try to ensure correct management during rescue and transport.	State of Alaska CIG [29]

5. Conclusions

According to our observations, among all the considered variables, altitude is the best predictor of amputation rates after severe frostbite. Delays in rewarming the initial injury appeared to worsen prognosis, with a clear window of improved outcome opportunity during the first few hours. On the other hand, experience in winter mountaineering seems to be also a risk factor, probably due to the increased likelihood of taking part in more complex, technically demanding activities and at higher altitude, as well as the potential likelihood to assume more risks than less-experienced subjects. Altitude may be influenced by factors related to remoteness, because in most high-altitude expeditions the rescue times are prolonged and on-site or nearby medical assistance is usually limited.

Expedition members considering high- or extreme-altitude routes should consider carrying adequate and accessible supplies for easy and rapid rewarming and first aid of frostbite, in light of the importance of immediate management for the posterior evolution of frostbite. They should not rely only on their own experience, as simple exposure to cold seems to play a superlative role in the possibility of suffering frostbite. Regarding actual knowledge of advanced medical treatments, therapeutic time windows to hospital settings are short (<48 h) so the approximate rescue timing based on local and expedition resources should be known before travelling in order to facilitate decision making in the field and thereby to optimize prognosis.

Author Contributions: Conceptualization and data curation, A.C.; methodology and formal analysis, A.C., C.J., M.R., and G.V.; writing—original draft preparation, A.C. and G.V.; all the authors participated in writing, review and editing, and approved the final version of this manuscript.

Funding: This research received no external funding.

Acknowledgments: Authors are grateful to Cristopher Evans *(Servei d'Assessorament Lingüístic i Terminologia de la Universitat de Barcelona)* for his help editing the text.

Conflicts of Interest: The authors declare no conflict of interest.

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Artículo 3: Donegani E, Paal P, KüpperT, Hefti U, Basnyat B, Carceller A, Bouzat P,van der Spek R, Hillebrandt D. “Drug use and Misuse in the Mountains; a UIAA MedCom Consensus Guide for Medical Professionals”. High Alt Med Biol. 2016 Sep;17(3):157-184

https://www.liebertpub.com/doi/abs/10.1089/ham.2016.0080

HIGH ALTITUDE MEDICINE & BIOLOGY
Volume 17, Number 3, 2016

DOI: 10.1089/ham.2016.0080

Recommendation

Drug Use and Misuse in the Mountains: A UIAA MedCom Consensus Guide for Medical Professionals

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Abstract

Donegani, Enrico, Peter Paal, Thomas Küpper, Urs Hefti, Buddha Basnyat, Anna Carceller, Pierre Bouzat, Rianne van der Spek, and David Hillebrandt. Drug use and misuse in the mountains: a UIAA MedCom consensus guide for medical professionals. *High Alt Med Biol.* 17:157–184, 2016.—***Aims:*** The aim of this review is to inform mountaineers about drugs commonly used in mountains. For many years, drugs have been used to enhance performance in mountaineering. It is the UIAA (International Climbing and Mountaineering Federation–Union International des Associations d'Alpinisme) Medcom's duty to protect mountaineers from possible harm caused by uninformed drug use. The UIAA Medcom assessed relevant articles in scientific literature and peer-reviewed studies, trials, observational studies, and case series to provide information for physicians on drugs commonly used in the mountain environment. Recommendations were graded according to criteria set by the American College of Chest Physicians. ***Results:*** Prophylactic, therapeutic, and recreational uses of drugs relevant to mountaineering are presented with an assessment of their risks and benefits. ***Conclusions:*** If using drugs not regulated by the World Anti-Doping Agency (WADA), individuals have to determine their own personal standards for enjoyment, challenge, acceptable risk, and ethics. No system of drug testing could ever, or should ever, be policed for recreational climbers. Sponsored climbers or those who climb for status need to carefully consider both the medical and ethical implications if using drugs to aid performance. In some countries (e.g., Switzerland and Germany), administrative systems for mountaineering or medication control dictate a specific stance, but for most recreational mountaineers, any rules would be unenforceable and have to be a personal decision, but should take into account the current best evidence for risk, benefit, and sporting ethics.

Keywords: acclimatization; acute mountain sickness; altitude; doping; exercise; mountain medicine; prevention; sports; training; treatment

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Introduction

SINCE THE EARLIEST DAYS of recreational mountaineering, climbers have tried various drugs to enhance their experiences. Whisky has been used at the end of a hard Scottish mountain day (Ogilvie, 1976), supplementary oxygen at altitude for Everest expeditions since 1922 (Bruce, 1923), methamphetamine to aid endurance (Buhl, 1998), cannabis and psychostimulants on big wall bivouacs (Mortimer and Rosen, 2014), cocaine for solo climbing (Perrin, 1978), drug cocktails to aid acclimatization (Freer, 2015), acetazolamide to facilitate fast ascents of Kilimanjaro to minimize the daily mountain fee, despite the risks involved (Küpper et al., 2010), and drug use on Mont Blanc (Robach et al., 2016).

In 2004, the topic of drug use in the mountains was informally discussed at the International Climbing and Mountaineering Federation (UIAA) Medical Commission (MedCom) meeting in Teheran, and at the Aachen meeting in 2005, it was formally acknowledged that the Management committee of the UIAA agreed that the topic fell under the remit of the UIAA MedCom. The UIAA MedCom has over 50 members from over 25 countries representing views, which cross all geographical, political, cultural, religious, and historical boundaries. Achieving a consensus is not easy, especially when it involves the ethics of our sport, so it was not until our meeting in Sweden in 2011 that we agreed that an advice article was needed and should be based on the following principles:

(1) World Anti-Doping Agency (WADA) regulation was fully accepted for all formal competitive climbing or mountaineering (competitive sport climbing either indoor or outdoor, ice climbing competitions, and ski mountaineering competitions).
(2) Formal regulation of all recreational mountaineers is impossible.
(3) A policy of encouraging honesty with one's peers regarding use of any artificial aids on climbs should be encouraged. This includes drug use as much as bolts and fixed ropes.
(4) With much misinformation available on drug use, our aim must be to protect climbers and mountaineers from harm caused by ill-advised drug use. This is best achieved by supplying evidence-based guidance.

This agreement paved the way for our first advice article on drug use and misuse in the mountains, which was written for a lay audience and, after some controversy, was adopted by the UIAA and published on their website in 2014 with its more detailed introduction and history (UIAA, 2016). It immediately became apparent that a more technical version of the article was needed for medical professionals advising mountaineers and work on this article has taken a further 2 years.

Methods

The UIAA MedCom convened an expert group to develop evidence-based guidelines for drug use and misuse in mountains. Drugs included in this work were selected according to their importance in mountain medicine due to their action on general health, preventing and treating acute altitude illness, or physical and psychological performance-enhancing effects.

A literature review was performed using PubMed, Current Contents, Embase (DIMDI) Medline, and bibliographies of retrieved articles. Search terms, including (1) the pharmacological agent alone or (2) in combination with the search keywords (i.e., ''acute mountain sickness,'' ''altitude,'' ''doping,'' ''exercise,'' ''mountain medicine,'' ''sport''), were used. Randomized controlled trials, observational studies, case series, and case reports limited to humans were included in this work. The article was compiled by one author (E.D.) and revised by the coauthors. Recommendations were developed by consensus and graded based on available evidence strength and quality using the grading system of the American College of Chest Physicians (Table 1) (Guyatt et al., 2006).

The reference list was last updated with PubMed on May 15, 2016, and references were included based on the pertinence to this article. When no studies existed to provide evidence, the recommendations were based on experience and knowledge of the expert group. Finally, the article was discussed and approved by the UIAA MedCom, using a consensus approach to develop recommendations. Conclusions of the authors were considered in the formulation of our conclusions to provide a substratum of information on the various problems and their management. Any discrepancy or heterogeneity between results from different studies on the same drug or inconclusive studies was evaluated and discussed and resolved by UIAA MedCom.

Results

Several hundred articles, including randomized controlled trials, review articles, observational studies, case series, and single reports, were identified, and 321 were deemed relevant and included in this study. The primary purpose of this analysis was to determine the medical efficacy and the level of evidence of each drug commonly used for (1) the prevention and (2) treatment of high-altitude illness, assessing risks and benefits. The secondary purpose was to determine the state of knowledge on the effects of peculiar drugs generally used on improving physical and cognitive performance in the mountains.

TABLE 1. CLASSIFICATION SCHEME FOR GRADING EVIDENCE (GUYATT ET AL., 2006)

Grade 1A	Strong recommendation, high-quality evidence benefits clearly outweigh risks and burden or vice versa
Grade 1B	Strong recommendation, moderate-quality evidence benefits clearly outweigh risks and burdens or vice versa
Grade 1C	Strong recommendation, low-quality or very low-quality evidence benefits clearly outweigh risks and burdens or vice versa
Grade 2A	Weak recommendation, high-quality evidence benefits closely balanced with risks and burdens
Grade 2B	Weak recommendation, moderate-quality evidence benefits closely balanced with risks and burdens
Grade 2C	Weak recommendation, low-quality or very low-quality evidence, uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced

Discussion

Alcohol

Ethanol (ethyl alcohol) is an intoxicating ingredient found in many beverages. Its toxicity is largely caused by its primary metabolite, acetaldehyde (systematic name ethanal), and secondary metabolite, acetic acid (Caballeria, 2003). Ethanol diminishes muscular performance by inhibiting sarcolemmal calcium channel actions, thereby impairing excitation–contraction coupling (Cofan et al., 2000).

Alcohol has detrimental effects on exercise performance, depending on dose, individual characteristics (e.g., sex, age, metabolic activity, consumption habits), and on the sort of physical activity undertaken (Pesta et al., 2013). While light drinking the night before will not significantly influence physical activity the following morning, heavier drinking severely affects aerobic capacity, increasing heart rate and reducing maximal oxygen consumption (VO_2max) (Bond et al., 1983; Vella and Cameron-Smith, 2010). The detrimental effects on aerobic performance are dose dependent with a threshold of 20 mmol/L, upon which the effects become substantial (Bond et al., 1983).

Alcohol intoxication impairs the myocardium, resulting in a decreased end-systolic pressure-dimension slope and reduced velocity of myocardial fiber shortening (Barnes et al., 2010b). Alcohol also impairs recovery following exercise by compromising glycogen resynthesis after prolonged effort, most likely by suppressing the mammalian target of rapamycin (mTOR) pathway, a serine/threonine protein kinase that regulates cell growth (Pesta et al., 2013).

Alcohol consumption is associated with the deterioration of psychomotor skills and delayed recovery after strenuous exercise (Barnes et al., 2010a). Athletes who consume alcohol at least once a week almost double their risk of injury compared with nondrinkers, but the exact mechanisms are unknown (O'Brien and Lyons, 2000). It also interferes with the body's ability to recover from injury: 1g/kg body weight alcohol consumption significantly decreases isokinetic torque production (40%–44%) in quadriceps 36 hours into recovery (Gutgesell and Canterbury, 1999; O'Brien and Lyons, 2000; Barnes et al., 2010b).

At altitude. The theoretical benefit of the glass of red wine before or during the ascent to ameliorate physical performance may be related to the inhibition of release of the potent pulmonary artery vasoconstrictor, endothelin-1 (ET-1), and increased generation of reactive oxygen species (superoxide anion, O_2–) by wine polyphenols, especially resveratrol, whose total content is greater in red wines than in white, rose, and distilled spirits. The ingestion of one glass (100 mL) of standard dry red wine ($\sim$12% alcohol) provides 12 grams of ethanol. This low-dose ethanol may inhibit increased vasoconstricting ET-1 synthesis and superoxide anion generation in response to altitude hypoxia. The effect of red wine may be both through ethanol itself and by many of the polyphenols such as resveratrol that it also contains. Especially red wine is a rich source of polyphenols and their ability to enhance endothelial-type nitric oxide (NO) synthase (eNOS) expression in humans has been demonstrated (Wallerath et al., 2005).

Low concentrations of alcohol induce increased release of NO from the human endothelial cells due to activation of eNOS, which exerts important effects in physiological blood flow and blood pressure, with vasoprotective effects preventing pathological vascular damage (Toda and Ayajiki, 2010). Perhaps this explains the preference of some mountain climbers for that glass of red wine that makes them feel better (Schafer and Bauersachs, 2002).

The effects of excessive intake of alcohol may be exacerbated by other altitude-related factors such as dehydration, sleep disorders, fatigue, and cold and, in turn, its diuretic effect may worsen dehydration. Alcohol has marked effects on judgment and decision-making. It also reduces reflex times, interferes with balance motor control and coordination, and also impairs the ability to assess and manage risk. Its slow degradation means that the effects persist well beyond a traditional alpine start: also small amounts of blood alcohol concentration of 0.03 g/L can persist for a substantial period of time after the acute effects of alcohol impairment disappear (Roeggla et al., 1995).

Doping. Alcohol (ethanol) is only prohibited *in-competition* in some sports (e.g., air sports, archery, automobile, karate, motorcycling, and powerboating). Detection is conducted by blood or breath gas analysis. The doping violation threshold is 0.10 g/L on blood samples (WADA, 2016b).

Conclusions. The American College of Sports Medicine concludes that acute alcohol consumption adversely affects psychomotor skills and exercise performance depending on dose, age, and metabolic activity (American Heart Association Nutrition Committee et al., 2006). Ethanol may slow postexercise recovery by inhibiting protein synthesis and increases the risk of injury during exercise by reducing decision-making capability, reflex times, and balance (Barnes et al., 2010a; Pesta et al., 2013; Haugvad et al., 2014). A possible theoretical beneficial effect of moderate consumption of red wine at altitude is that it may help to prevent or ameliorate symptoms of high altitude pulmonary edema (HAPE) by inhibition of ET-1synthesis (Fellermeier et al., 2001).

Recommendations. Excessive intake of alcohol should be avoided before and during medium- to high-grade exercise in mountains as it will exacerbate fitness debilitating factors (e.g., dehydration, hypothermia), reduce exercise performance, delay recovery, and increase the risk of injury. Recommendation Grade: 1A.

Anabolic agents: androgenic steroids

Anabolic steroids, technically known as anabolic–androgenic steroids, are drugs structurally related to the cyclic steroid ring system and synthetic derivatives of the male hormone, testosterone.

Generic names include Androstenedione, Clostebol, Methasterone, Nandrolone, and 1-Testosterone.

Anabolic–androgenic steroids have two different, but overlapping, effects. First, they are *anabolic*, which means they increase protein synthesis from amino acids, appetite, bone remodeling, and growth. The anabolic effect also stimulates erythropoiesis by increasing renal production of erythropoietin and by exerting an effect on bone marrow stem cell division. Second, these steroids are *androgenic*, affecting the development and maintenance of masculine characteristics (Thein et al., 1995). Anabolic–androgenic steroids are used therapeutically to stimulate bone marrow growth in

aplastic anemia, in children with growth failure, to stimulate muscle growth, to treat chronic wasting conditions, such as with cancer and AIDS, and to treat gender dysmorphia by producing secondary male characteristics. They are also given to boys with extreme puberty delay and to men with low levels of testosterone as a replacement therapy (Anonymous, 1990; Shahidi, 2001).

Short- and long-term anabolic–androgenic steroid abuse can lead to aggression, violence, and irrational behavior, which may persist for months after withdrawal. Cardiovascular risk factors include elevation of blood pressure, depression of serum high density lipoprotein (HDL), and an increase in cholesterol levels. Cardiac hypertrophy is associated with secondary changes in cardiac metabolism, which contribute to cardiac dysfunction, and can progress to heart failure. Alterations in connective tissue structure induced by anabolic–androgenic steroid therapy have been associated with weakening of tendon strength. Mood disturbances (e.g., depression, hypomania, psychotic features) are likely to be dose and drug dependent (Shahidi, 2001; Kutscher et al., 2002; Maravelias et al., 2005).

Use in sport. Anabolic–androgenic steroids can benefit athletic performance. Short-term administration can increase strength and body weight, attributed to an increase of the lean body mass. Although anabolic–androgenic steroid administration may affect erythropoiesis and hemoglobin concentration, no effect on endurance performance was observed (Anonymous, 1990; Urhausen et al., 2003; Powers, 2005). The serious adverse effects of anabolic–androgenic steroids are dependant on dose, duration of use, and individual genetic factors (Friedl, 2000; Hartgens and Kuipers, 2004; Wilson, 2008; Luijkx et al., 2013).

At altitude. The psychological side effects reported by studies include sleeplessness, increased irritability, depression, change in mental attitude, psychotic symptoms, and feelings of euphoria and grandiosity (Tabin and McIntosh, 2001) and these can have fatal consequences. No governing body monitors recreational climbers for drug use, although anabolic–androgenic steroids have been and are being used in the preparation of expeditions and hard rock climbs. Several famous rock climbers admit to using anabolic–androgenic steroids to speed their recovery from injury or to improve performance (Tabin and McIntosh, 2001).

Doping. Anabolic–androgenic steroids are banned by virtually every sporting organization. The WADA includes all anabolic–androgenic steroids and precursors and all hormones and related substances at all times, both *in-* and *out-competition* (WADA, 2016b).

Conclusions. The multiple adverse effects seen at sea level may be even more pronounced at altitude and interfere with the diagnosis of high altitude cerebral edema (HACE). Their use is contraindicated.

Recommendations. Anabolic–androgenic steroids should not be used at any time by any mountaineer. Recommendation Grade: 1B.

β_2-Adrenergic agonists

Inhaled β_2-agonists and sport. A review performed by Kindermann in 2006 on the use of inhaled β_2-agonists (studies using Salmeterol, Formoterol, Orterbutaline, and Salbutamol) in nonasthmatic competitive athletes revealed that there are no performance-enhancing effects and no ergogenic potential of these agents in normoxia (Kindermann and Meyer, 2006). No data exist about possible ergogenic effects in hypoxia. A number of factors can induce an acute asthmatic attack in predisposed athletes, including exposure to pollen, dust, chemical particles, viral infections, and psychological stress (Pierson et al., 1986; Helenius et al., 1998). Physical exercise may give rise to specific exercise-induced asthma (Tikkanen and Helenius, 1994).

Inhalation of large volumes of cold dry air with resultant bronchial edema adds to the problem, so athletes participating in winter sports are at increased risk (Heir and Oseid, 1994). Currently, all β_2-agonists are prohibited by WADA *in-* and *out-competition*, with the exception of Formoterol, Salbutamol, Salmeterol, and Terbutaline when inhaled to prevent and treat asthma and exercise-induced asthma. Some β_2-agonists (i.e., Salmeterol and Salbutamol) have received interest in the prevention and treatment of HAPE due to their ability to enhance alveolar clearing of the fluid.

Generic name: Salmeterol

At altitude. Clinical experience with Salmeterol at high altitude is limited. In one randomized placebo-controlled study, the inhaled long-acting β_2-adrenergic agonist, Salmeterol, at 2.5 times the normal dosing decreased the incidence of HAPE by 50% in *susceptible* individuals (Sartori et al., 2002; Luks et al., 2014). The theoretical benefit proposed by Sartori et al. (2002) occurs through changes in pulmonary transepithelial sodium transport. The tightening of the alveolo-capillary barrier, the direct lowering of pulmonary artery pressure, the indirect hypoxic ventilatory stimulation, and increased NO production may also explain the beneficial effects in the reduction in the incidence of HAPE (Vivona et al., 2001; Bartsch and Mairbaurl, 2002; Basnyat, 2002). Although this finding requires confirmation, this agent is considered useful and convenient in the prevention of HAPE and, by extension possibly, for treatment as well (Hackett and Roach, 2001; Sartori et al., 2002; Dunin-Bell and Boyle, 2009).

Wilderness Medical Society (WMS) Consensus Guidelines now suggest that Salmeterol used in high doses close to the toxic level may help in the prevention of HAPE in susceptible individuals if combined with Nifedipine (Luks et al., 2014). At high doses, the drug may present important side effects (headache, hypertension, tachycardia, muscular cramps, nasal congestion, tremor) (Hackett and Roach, 2001) and it remains unclear whether its possible benefits outweigh the risks compared with Nifedipine alone.

Doping. Salmeterol is not prohibited by the antidoping WADA Code when taken by inhalation in accordance with the manufacturers' recommended therapeutic regime (WADA, 2016b).

Conclusions. Salmeterol can be used as a second-line therapy in the prevention of HAPE. With no scientific evidence, some mountaineers have assumed that Salmeterol

may also increase physical performance, but evidence of improved performance is lacking (Carlsen et al., 1997; Sue-Chu et al., 1999).

Generic name: Salbutamol (Albuterol)

Salbutamol improves muscle weight in animals, and anecdotal reports hypothesize that it might be an alternative to Clenbuterol for the purpose of fat burning and muscle gain, but other studies contradict these findings (Caruso et al., 2005).

At altitude. Salbutamol has not been studied for the prevention or treatment of HAPE. Only anecdotal experiences in the Himalayas using Salbutamol inhalers or nebulizers for the treatment of patients with HAPE indicate an increase in the pulse oximeter reading after administration of the drug (Basnyat, 2002). As Salbutamol should function similarly to Salmeterol, this agent could be considered for the prevention and treatment of HAPE (Hackett and Roach, 2001)

Debilitating dry cough is a frequent problem in subjects traveling to high altitude. Bakewell et al. (1999) showed that inhaled Salbutamol twice daily may prevent high altitude cough.

Doping. Salbutamol is not prohibited by the antidoping WADA Code. When taken by inhalation in accordance with the manufacturers' recommended therapeutic regime (maximum 1600 μg over 24 hours) (Berges et al., 2000; Nichols, 2004), overall performance is not improved (Koch et al., 2015).

Conclusions. Because of contradictory results and limited experience at altitude, its use is not recommended by UIAA MedCom.

Generic name: Clenbuterol

Clenbuterol induces skeletal muscle growth through mTOR-dependent protein synthesis, with an increase in size of muscle fiber cells (Wong et al., 1998). In terminal heart failure patients, left ventricular assist device support combined with high-dose Clenbuterol therapy produces maximal reverse remodeling by the induction of physiological cardiac hypertrophy (Hon and Yacoub, 2003).

As a β_2 sympathomimetic, Clenbuterol increases aerobic capacity, central nervous system (CNS) stimulation, blood pressure, and oxygen transportation in animals (e.g., horses, rats), but its use as a performance-enhancing drug in humans is not proven (Kuiper et al., 1998). By increasing the rate at which body fat is metabolized while increasing the body's basal metabolic rate (i.e., thermogenic and lipolytic effects), Clenbuterol is used by body builders for cutting off all the extra body fat that has been gained while on the bulking cycle (i.e., cut period) (Kuiper et al., 1998). More recently, it has become known for its off-label use for weight loss and to increase lean mass, despite the lack of any clinical evidence (Waldman and Terzic, 2012).

At altitude. No studies have been performed at altitude for acute mountain sickness (AMS) prevention or treatment.

Doping. Clenbuterol is included by WADA in the prohibited list of performance-enhancing drugs, banned *in-* and *out-competition* (WADA, 2016b).

Conclusion. Its use at altitude or in any aspect of mountaineering is not recommended.

Recommendations. In general, the use of inhaled β_2-agonists in nonasthmatic mountaineers is not recommended. Salmeterol at the dose of 125 μg twice/day could be used for HAPE prevention or treatment, but only in conjunction with other medications. Recommendation Grade: 2B.

β-*Blocking agents*

Generic names inlcude Atenolol, Acebutolol, Carvedilol, Labetalol, Metoprolol, Nebivolol, Pindolol, and Propanolol.

β-Blockers block the action of endogenous catecholamines such as epinephrine (adrenaline) and norepinephrine (noradrenaline), in particular on adrenergic β-receptors, of the sympathetic nervous system (American Pharmacists Association, 2012). Some agents block all β-adrenergic receptors (first-generation nonselective combined $\beta_1\beta_2$-blockers), while others are selective (second-generation cardio β_1-selective agents) (Opie and Gersh, 2009). Third-generation agents, Nebivolol and Carvedilol, also have added vasodilating properties (mediated by release of NO) or by adding α-adrenergic blockade as in Labetalol and Carvedilol or acting through β_2-intrinsic sympathomimetic activity, as in Pindolol and Acebutolol (Opie and Gersh, 2009).

β-Blockers and sport. Bradycardia and the negative inotropic effects are of special importance when these drugs are used in sport since these changes decrease the myocardial oxygen demand (Tesch, 1985). Exercise-induced β-adrenergic stimulation leads to β-mediated coronary vasodilation. Thus, during exercise, the heart pumps faster and more forcefully, while the coronary flow is increased. Conversely, β-blockade should have a coronary vasoconstrictive effect with a rise in coronary vascular resistance. However, the longer diastolic filling time, resulting from the decreased heart rate in exercise, leads to better diastolic myocardial perfusion to give an overall positive benefit (Tesch, 1985).

Bronchospasm occurs in susceptible individuals due to blockade of β_2-receptors, which mediate dilation in the bronchi. Asthma is a contraindication for β-blockers (American Pharmacists Association, 2012). Peripheral vasoconstriction may result in cold hands and feet due to reduced cardiac output and possibly blockade of β_2-receptors, which promote vasodilation in blood vessels supplying skeletal muscles. Tiredness and fatigue may be due to reduced cardiac output exacerbated by blockade of β_2-receptors in skeletal muscle and associated with increased muscle activity (American Pharmacists Association, 2012).

At altitude. The high prevalence of hypertension in the general population means that it is also common among skiers, hikers, and visitors to moderate and high altitude. β-blockers are used for blood pressure regulation because they decrease sympathetic activity, but the frequency of therapeutic β-blocker use in mountaineers is unknown (Bouissou et al., 1989; Berg et al., 2004; Tissot van Patot et al., 2005; Luks, 2009; Dehnert and Bartsch, 2010; American Pharmacists Association, 2012). As expected, β-blockers limit the cardiac response to hypoxia, but do not impair the ventilatory response and do not modify the susceptibility to high-altitude-related illness (Richalet et al., 2013). Regular

β-blocker intake in hypertensive elderly persons can provoke oxygen desaturation during submaximal exercise, leading to reduced exercise tolerance in people taking β-blockers at acute high altitude (Faulhaber et al., 2003).

In a study performed to evaluate the effects of different β-blockers (selective and nonselective) on cardiopulmonary response to exercise at high altitude, Valentini et al. (2012) found that Nebivolol may be preferred due to better preserved peak oxygen consumption (VO_2), increased peak minute ventilation, and peripheral vasodilation. β-Blockers may induce bronchospasm in susceptible individuals with exercise and cold air-induced asthma (Van Wijck et al., 2012). β-Blockers may interfere with thermoregulation in response to heat or cold (Mieske et al., 2010). β-Blockers are contraindicated in individuals with Raynaud's phenomenon (American Pharmacists Association, 2012). Frostbite may be a risk at high altitude (Luks, 2009).

Doping. β-Blockers are prohibited *in-competition* in specific sports. In archery and shooting, they are also prohibited *out-competition.* Currently, β-blockers are accepted for competition climbing (WADA, 2016b).

Generic name: Ivabradine

Ivabradine is a cardiotonic agent, approved by the European Medicines Agency in 2005 (American Pharmacists Association, 2012). It is a pure heart rate-lowering agent, with no negative inotropic effect or blood pressure reduction, as with β-blockers, nor any rebound on cessation of therapy (DiFrancesco, 2004). Ivabradine provides an effective and significant dose-dependent reduction in heart rate, which is also reflected in a reduction in the rate pressure product leading to a reduction in myocardial oxygen consumption (Yusuf and Camm, 2003). So far, no studies at altitude exist.

Conclusions. β-Blockers may be helpful for blood pressure regulation at high altitude because of increased sympathetic activity, but they reduce the maximum pulse rate and therefore limit maximal workload in healthy subjects, and can decrease circulation to the extremities, potentially putting the person at a higher risk of frostbite. Patients with coronary heart disease may benefit by the use of β-blockers because the work of their myocardium will be optimized and the oxygen demand lowered. β-Blockers have been used to reduce the physical symptoms of stress and anxiety and consequently might be considered by sport climbers.

Recommendations. The use of β-blockers may be recommended for patients who are already established on chronic antihypertensive β-blocker medication. The use of β-blockers at high altitude limits the cardiac response to hypoxia, does not impair the respiratory response, and does not modify susceptibility to high-altitude-related illnesses. Recommendation Grade: 1B.

Diuretics

At altitude. Dehydration due to exertion, low humidity, vomiting, or diarrhea may be exaggerated in those taking diuretics. Electrolyte disturbances, particularly hypokalemia, can develop and predispose subjects to life-threatening consequences. Rehydration salts and dried fruit (especially apricots and bananas) may resolve the problem (West et al., 2012).

Doping. According to the WADA Prohibited List, diuretics belong to the group of masking agents. Drugs in this category are prohibited at *all times* (WADA, 2016b).

Generic name: Acetazolamide

Acetazolamide is a carbonic anhydrase inhibitor and its predominant site of action is the luminal membrane of the proximal convoluted renal tubule where it catalyzes the dehydration of H_2CO_3. By blocking carbonic anhydrase, inhibitors block $NaHCO_3$ reabsorption, causing diuresis, significant HCO_3^- losses, and hyperchloremic metabolic acidosis, resulting in better arterial oxygenation. More recently, it has been speculated that carbonic anhydrase inhibitors may act on the brain and the lungs as well, reducing aquaporin-mediated transmembrane water transport, and with antioxidant actions, vasodilation, and anti-inflammatory effects (Swenson, 2016).

Drowsiness, dizziness, fatigue, headache, malaise, taste alteration (it makes fizzy drinks taste flat), and paresthesia are common side effects. Acetazolamide may enhance the hypotensive effect of other antihypertensive drugs (Katzung et al., 2012; Waldman and Terzic, 2012). Acetazolamide (250 mg) mitigates an acute hypoxia-induced rise in cerebral blood flow; it reduces an elevated cerebral aerobic metabolism, thereby improving cerebral tissue oxygenation (Wang et al., 2015; Swenson, 2016).

At altitude

Prevention of AMS and HACE. Acetazolamide is commonly used in individuals with a history of AMS or when a graded ascent and acclimatization are not possible (e.g., when rapid ascent is necessary for rescue purposes or when flight into a high-altitude location). Acetazolamide minimizes the symptoms of AMS as one acclimatizes, but it does not mask the symptoms of altitude illness (Ritchie et al., 2012). Acetazolamide (125–250 mg twice a day) should be started either the day before (preferred) or on the day of ascent and may be discontinued after staying at the same elevation for 2–3 days (i.e., after acclimatization is achieved) or when the highest elevation is reached and descent initiated (Aldashev et al., 2005; Beaumont et al., 2007). Higher doses are not usually required (Hackett and Roach, 2001; Basnyat et al., 2003, 2006; Carlsten et al., 2004; van Patot et al., 2008). For children, the dosage is 2.3 mg/kg every 12 hours.

In a systematic review, Kayser et al. (2012) concluded that the degree of efficacy of acetazolamide for the prevention of AMS is limited when the baseline risk is low, there is some evidence of dose responsiveness, the risk of paresthesia is increased with all doses, and the risk of polyuria and taste disturbance is increased at 500 and 750 mg/day. When a rapid ascent is unavoidable, the use of Acetazolamide to aid acclimatization might be warranted. People with known previous susceptibility to AMS may benefit from prophylaxis to aid in acclimatization. Side effects do occur with Acetazolamide, such as paresthesia, skin rashes, dyspepsia, lassitude, fatigue, and possible dehydration in 30%–40% of subjects, but generally are well tolerated. The most important risks are severe acidosis, respiratory failure, and encephalopathy in subjects with renal, pulmonary, and hepatic

diseases (Swenson, 2014). Some authorities recommend trial doses at sea level before a high altitude trip.

Sulfa allergy is generally considered a contraindication to Acetazolamide use (Hackett and Roach, 2001; Pollard et al., 2001). Acetazolamide is a nonantibiotic sulfonamide and many allergies are caused by sulfonamide antibiotics. The absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics (Strom et al., 2003) implies that individuals with a history of allergy do not necessarily have to avoid the use of Acetazolamide (Kelly and Hackett, 2010)

Treatment of AMS. Acetazolamide is used as a treatment for mild AMS (Goldstein et al., 2010) and combined with Dexamethasone for severe AMS (Luks et al., 2014) where, combined with supplemental oxygen and a portable hyperbaric chamber, it can buy time for the vital descent. The dose recommended is 250 mg twice daily (Luks et al., 2014). There are no studies of treatment of acute altitude illness in children with Acetazolamide (Pollard et al., 2001).

Prevention of HAPE. Acetazolamide decreases pH in fluid compartments and has been shown to blunt hypoxic pulmonary vasoconstriction. As a result, Acetazolamide reduces pulmonary artery systolic pressure, ventilation increases, and oxygenation improves (Grissom et al., 1992; Jonk et al., 2007; Ke et al., 2013). Research studies in animals (Hohne et al., 2004; Shimoda et al., 2007) and in humans (Teppema et al., 2007; Ke et al., 2013) showed that this mechanism may play a role preventing HAPE, while another study could not draw any conclusions about its efficacy in preventing HAPE (Basnyat et al., 2008b). Acetazolamide seems to be a rational choice for HAPE prevention supported by clinical experience, but definitive data are lacking (Luks et al., 2014).

A randomized, double-blind placebo-controlled study was conducted to evaluate the effects of Theophylline and Acetazolamide in the treatment of sleep-disordered breathing (SDB) after fast ascent to high altitude (3454 m) and the authors concluded that both oral slow-release drugs are effective (Fischer et al., 2004). Medical research on Acetazolamide has only been undertaken at an altitude of 6300 m (Hackett et al., 1985). It is not proven whether any benefit is conferred at higher altitude. Acetazolamide is now licensed for high altitude use by US FDA (American Pharmacists Association, 2012), but since its use is still off-license in many other countries, some doctors are reluctant to prescribe it. In many countries, Acetazolamide is freely available without a prescription.

At altitude, Acetazolamide seems to affect performance by at least two mechanisms: (1) feeling better with few symptoms of AMS and (2) a direct increase of the hypoxic ventilatory response by the induced metabolic acidosis, thereby increasing O_2 uptake (Leaf and Goldfarb, 2007). Fulco et al. (2006) showed that endurance performance was impaired with Acetazolamide only at sea level, but not at altitude, probably due to offsetting secondary effects resulting from acidosis, which resulted in an increased oxygen pressure gradient from capillary to exercising muscle. On the contrary, Garske et al. (2003) reported that Acetazolamide reduces exercise capacity and increases leg fatigue under hypoxic conditions.

McLellan et al. (1988) reported a decrease of exercise performance of only 37% with Acetazolamide versus 45% in the placebo group. More recently, Bradwell et al. assessed the effect of Acetazolamide on exercise performance evaluated by bicycle ergometer during early acclimatization, followed by rapid ascent to 3459 m in 20 healthy subjects (placebo or Acetazolamide 250 mg twice daily). In a study assessing the effects of Acetazolamide on exercise at altitude, performance was reduced in subjects on Acetazolamide in terms of perceived difficulty and the failure to complete the test ($p < 0.01$) and SpO_2 decreased more during exercise ($p < 0.005$), particularly in older subjects, despite a higher resting SpO_2 ($p < 0.001$) and fewer AMS symptoms before the test (Bradwell et al., 2014).

Doping. Acetazolamide is listed by WADA because it can camouflage doping tests, but not because it has any effect on performance (WADA, 2016b).

Conclusions. Acetazolamide is currently the gold standard if drugs must be used for the prevention of AMS and probably HACE (Severinghaus, 2001; Luks et al., 2014). Acetazolamide does not protect against worsening AMS with continued ascent (Luks et al., 2014).

Recommendations

AMS-HACE prevention. Gradual ascent with natural acclimatization must be the gold standard for any high altitude venture, but if drug use is required for a specific clinical reason, then Acetazolamide (125 mg twice daily) should be started either the day before (preferred) or on the day of ascent and may be discontinued after staying at the same elevation for 2–3 days (i.e., after acclimatization is achieved) or when the highest elevation is reached and descent initiated. Recommendation Grade: 1A.

AMS treatment. Acetazolamide (250 mg twice daily) alone for mild AMS or in severe AMS combined with Dexamethasone, supplemental oxygen, a portable hyperbaric chamber, and descent is recommended. Recommendation Grade: 1B.

HAPE prevention. Acetazolamide may be useful for HAPE prevention. Recommendation Grade: 2C.

Erythropoietin

Erythropoietin (EPO), hematopoietin or hemopoietin, is a glycoprotein hormone that controls erythropoiesis. While liver production predominates in the fetal and perinatal period, renal production is predominant during adulthood. Exogenous EPO is produced by recombinant DNA technology in cell culture. Several different pharmaceutical agents are available with a variety of glycosylation patterns (epoetin, darbepoetin) and are collectively called erythropoiesis-stimulating agents (ESAs) (Jelkmann, 2007; American Pharmacists Association, 2012).

US boxed warning. ESAs increase the risk of serious cardiovascular events, stroke, thromboembolic events, mortality, and tumor progression when administered to target hemoglobin levels >12 g/dL (American Pharmacists Association, 2012).

At altitude. Drugs such as EPO, ESAs, or other erythropoietic products aim to stimulate erythropoiesis at altitude. It

should be stressed that all low oxygen states, including hypoxia of high altitude, cause physiological EPO release. By increasing oxygen-carrying capacity, EPO increases aerobic capacity and performance in endurance sports, including mountaineering, but at higher risk of thrombosis due to dehydration (Tabin and McIntosh, 2001). Other studies using simulated altitude conditions and oxygen deprivation (e.g., acute exposure to 12.6% O_2) have shown that ESA treatment causes hemoglobin and accordingly arterial oxygen content to increase both in normoxia and hypoxia, but at maximal exercise in hypoxia, maximal oxygen uptake (VO_2max) is not increased (Lundby and Damsgaard, 2006).

Prolonged administration of recombinant human EPO increases submaximal performance more than maximal aerobic capacity (Thomsen et al., 2007). A study performed at Annapurna base camp (4130 m) (Heo et al., 2014) showed that epoetin α pretreatment decreased AMS incidence in those requiring immediate descent with no adverse effects. The fact that EPO or ESAs have contradictory effects on performance illustrates that their use is based on theory rather than medical evidence. This increase of red blood cells and thickening of blood come with the risk of serious cardiovascular events, stroke, and other thromboembolic events. High altitude exposure initially causes rapid plasma and extracellular volume losses, while erythrocyte volume is unaffected, thus viscosity increases. Diluting blood to reduce viscosity with a plasma volume expander administrated simultaneously with EPO will probably increase exercise capabilities more than augmenting the total red cell volume alone (Sawka et al., 2000). In reality, this increased viscosity of blood results in reduced cardiac output and in less oxygen-carrying capacity in the blood (Young et al., 1996).

Doping. Blood doping is defined as the use of illicit erythropoietic products (EPO, ESAs, peginesatide, hypoxia-inducible factor stabilizers) and increasing aerobic capacity methods (blood transfusions, blood substitutes as hemoglobin-based oxygen carriers, and perfluorocarbons) used to maximize the uptake of O_2 and to enhance O_2 transport to the muscles, thus improving athlete's aerobic capacity (VO_2 max) and endurance (Robach et al., 2008). According to the WADA Prohibited List, all these products and methods are prohibited at *all times* (WADA, 2016b).

Conclusions. EPO and ESAs aim to increase erythropoiesis and by this VO_2max, resulting in little improvement in athletic performance. The side effects may be very dangerous at high altitude. Combining the unpredictable effects of EPO on each climber's individual physiology associated with the possibility of dehydration, malnourishment, and altitude sickness (all possible events when living at high altitude) makes EPO use risky for mountaineers.

Recommendations. Avoid the use of EPO. It is better to rely on sophisticated changes in blood, with natural acclimatization that has evolved over millions of years. Recommendation Grade: 1C.

Glucocorticosteroids

Glucocorticosteroids (glucocorticoids) are a class of steroid hormones present in almost every vertebrate animal cell.

Generic name: Dexamethasone. Dexamethasone is a synthetic steroid medication (Blue and Lombardo, 1999) with a variety of therapeutic actions. It suppresses inflammation by stimulating neutrophil migration, reversing capillary permeability, and decreasing production of inflammatory mediators and it acts as an immunosuppressant agent. It may be used in management of cerebral edema associated with brain tumor. Unlicensed use includes prevention and treatment of AMS and HACE (Ferrazzini et al., 1987; American Pharmacists Association, 2012).

Corticosteroids represent one of the most important drug classes for prevention and treatment of AMS and their benefits include their anti-inflammatory and antiedema effects. More recently, it has been speculated that corticosteroids may protect against increase in vascular endothelial and blood–brain barrier permeability, suppress inflammatory cytokines, reduce ROS formation upregulating endogenous antioxidant enzyme synthesis, and with a potent sympatholytic action for suppression of adrenergic tone (Swenson, 2016)

Patients receiving Dexamethasone report moderate–severe problems with insomnia (45%), indigestion and epigastric discomfort (27%), agitation (27%), increased appetite (19%), weight gain (16%), and acne (15%). Side effects encompassing cardiocirculatory function, lungs, gastrointestinal system, skin, and hair are also reported (American Pharmacists Association, 2012).

At least 853 drugs are known to interact with Dexamethasone. For instance, if combined with Acetylsalicylic acid, it increases its antiplatelet effects increasing the risk of internal bleeding from stomach and gut, brain, retina, and respiratory system. Dexamethasone should be taken with meals to decrease gastrointestinal upset. Salt in the diet should be reduced to avoid fluid retention. Ethanol or Acetylsalicylic acid, which may enhance gastric mucosal irritation, should be avoided (American Pharmacists Association, 2012).

At altitude

Medical efficacy for the prevention and treatment of high-altitude illness. Dexamethasone is effective in reducing the incidence of AMS during rapid ascent (Dumont et al., 2000; O'Hara et al., 2014). Possible mechanisms include improvement in microcirculatory integrity and reduction in cerebral blood flow by vasoconstriction. It has also the ability to stimulate sodium and water reabsorption while also increasing the release of NO with overall pulmonary vasodilation (Maggiorini et al., 2006). Comparing Dexamethasone with Acetazolamide or placebo, the use of Dexamethasone significantly reduced the incidence of AMS and the severity of symptoms, without affecting physical or mental aspects ($p < 0.05$) (Ellsworth et al., 1987, 1991). A study showed a decrease of cognitive deficits in asymptomatic subjects caused by subclinical cerebral edema (Lafleur et al., 2003).

Dexamethasone is effective in the prevention of AMS and HACE (2 mg every 6 hours or 4 mg every 12 hours) and HAPE in *susceptible* individuals (4 mg every 6 hours). The duration of use should not exceed an absolute maximum of 10 days with gradual dose reduction to minimize serious side effects (Dunin-Bell and Boyle, 2009; Luks, 2009; Subedi et al., 2010; Tang et al., 2014). Dexamethasone does not facilitate physiological acclimatization, so individuals using this drug prophylactically are not physiologically protected

against the hypoxic environment. If it is suddenly stopped at altitude, expect a rebound effect with rapid onset of altitude-related symptoms. If used as a prophylactic drug for AMS, it may eventually trigger symptoms mimicking AMS (e.g., sleep disorders, fatigue, mania, edema, muscle weakness) (Subedi et al., 2010). Some authorities consider Dexamethasone a second option for AMS prevention in cases of Acetazolamide intolerance (West et al., 2012).

Dexamethasone is very effective in the treatment of severe AMS (4 mg every 6 hours) and is the first-line drug for HACE treatment (8 mg once, then 4 mg every 6 hours) (Levine et al., 1989; Luks et al., 2014). If Dexamethasone is used for treatment, it should only be done to buy time for the essential descent or when descent is impossible (Schoene, 2005).

Rumor has circulated that inhaled steroids may prevent AMS. Two recent double-blind, randomized controlled trials demonstrated the efficacy of inhaled Budesonide for the prevention of AMS (Zheng et al., 2014; Chen et al., 2015), but clinical experience with this medication at high altitude is very limited. No other inhaled steroids have been tested at high altitude.

Ability to maintain physical performance at high altitude. Many studies suggest that Dexamethasone may be useful in improving physical performance, increasing maximal aerobic capacity and oxygen uptake kinetics, reducing pulmonary arterial resistance, increasing alveolar fluid clearance, and also improving cognitive ability (Peacock, 1998; Fischler et al., 2009; Siebenmann et al., 2011). Deaths have occurred when Dexamethasone is taken as an aid to going higher faster. Overconfidence in the drug's properties can lead to poor risk assessment when planning high-altitude climbs (Subedi et al., 2010).

Doping. The WADA prohibits all glucocorticosteroids used *in-competition* whether administered by oral, intravenous, intramuscular, or rectal routes (WADA, 2016b). Athletes who are prescribed glucocorticoids may take these medications *out-competition* without submitting a therapeutic use exemption (TUE) as long as the prohibited substance has cleared their system before the time defined as *in-competition*. If athletes need to use these drugs shortly before or during competition, they must obtain a TUE. Inhalation of glucocorticoids (e.g., for asthma) is permitted. Injections of glucocorticoids around tendons, into joints, and epidural (into the spine) are permitted, but an injection into a muscle is prohibited.

Conclusions. The use of corticosteroids has to be a personal decision for mountaineers. These agents can cause significant side effects and the risk/benefit equation is very different from that for Acetazolamide (Basnyat, 2002). Dexamethasone should be available on any high altitude expedition for treatment of HACE and HAPE to buy time for rapid descent or when the descent is impossible (Levine et al., 1989; O'Hara et al., 2014). It can be lifesaving and use in short courses for emergency treatment will avoid many of the potential long-term side effects.

Recommendations

AMS prevention. Gradual ascent with natural acclimatization must be the gold standard for any high altitude venture, but if drug use is required for a specific clinical reason and Acetazolamide is contraindicated, Dexamethasone can be considered for prevention of AMS and HACE (2 mg every 6 hours or 4 mg every 12 hours). Recommendation Grade: 1B.

Dexamethasone can be used in preventing HAPE in susceptible individuals (4 mg every 6 hours). Recommendation Grade: 1B.

Inhaled Budesonide seems to be effective in the prevention of AMS. Recommendation Grade: 1B.

AMS treatment. Dexamethasone can be used in the treatment of severe AMS (4 mg every 6 hours) and is the first-line drug for HACE (8 mg once then 4 mg every 6 hours). Recommendation Grade: 1B.

Dexamethasone should be available on any high altitude expedition for treatment of HACE and HAPE to buy time for rapid descent (Recommendation Grade: 2B).

Oxygen

Oxygen is widely available and commonly prescribed by medical and paramedical staff. When administered correctly, it may be lifesaving, but oxygen is often given without careful evaluation of its potential side effects. Like any drug, there are clear indications for treatment with oxygen and appropriate methods of delivery. Inappropriate dose and failure to monitor treatment can have serious consequences (Bateman and Leach, 1998).

Oxygen at high altitude. Although the percentage of oxygen in inspired air is constant at different altitudes, the fall in atmospheric pressure with ascent decreases the partial pressure of inspired oxygen and hence the driving pressure for gas exchange in the lungs. The weight of air above us is responsible for the atmospheric pressure, which is about 760 mmHg (101 kPa) at sea level, and as oxygen is 20.9% of dry air, the inspired oxygen pressure is 149.6 mmHg (20 kPa) (Peacock, 1998). Atmospheric pressure and inspired oxygen pressure fall with altitude to be 50% of the sea level value at 5500 m and only 30% of the sea level value at 8848 m (summit of Mt. Everest) (Peacock, 1998). The first line of O_2 transport from the environment to the blood is the ventilatory air convection. West (1982, 1990b) has pointed out that this function is the most important adaptive parameter during ascent to high altitude and that it allows some acclimatized humans to reach the top of Mt. Everest.

Hyperventilation is one of the most important features of acclimatization to high altitude. Resting ventilation at extreme altitudes increases up to fourfold and exercise ventilation for a given work level increases to the same extent. Hypoxic stimulation of peripheral chemoreceptors is the chief mechanism for hyperventilation, but there is also evidence that central sensitization of the respiratory centers occurs. Cardiac output increases in responses to acute hypoxia, but returns to normal in acclimatized lowlanders. Oxygen uptake at extreme altitudes is markedly limited by the diffusion properties of the blood–gas barrier. As a consequence, the maximal oxygen consumption of a climber near the summit of Mt. Everest is near his basal oxygen requirements. Maximal oxygen consumption is so sensitive to barometric pressure that it may be that seasonal or day-to-day variations will affect the chances of a climber reaching the summit without supplementary oxygen (West, 1999; West et al., 2012).

Oxygen transport by red blood cells is regulated by erythropoiesis and Hb-O_2 affinity. The O_2-carrying capacity is characterized by changes in hematocrit, red blood cell count, or the mass of circulating red blood cells. Erythropoiesis is controlled by the hormone, EPO, which induces slow changes of the O_2 transport capacity. The Hb-O_2 affinity is modified mainly by pH and 2,3-DPG. In hypoxia at high altitude, despite their apparently diverse effects, a compromise seems to be adopted, optimizing both arterial O_2 loading and peripheral O_2 unloading. In contrast to erythropoiesis, adjustments of Hb-O_2 affinity occur quickly and allow rapid adjustments of O_2 binding and release. In severe hypoxia, adjustments of both, hematocrit and Hb-O_2 affinity, are insufficient to maintain tissue O_2 supply (Lenfant et al., 1968; Mairbaurl, 1994).

Delivery systems. Providing supplemental oxygen in adverse conditions at 8000 m is not simple. Frozen valves, deformed masks, ice formation in the tubing, and other problems can prevent the delivery of the right amount of oxygen at the right time. Too much and there is waste of gas, too little and the climber may die. Modern, light reliable systems are now available (Windsor et al., 2005, 2008).

Supplemental oxygen and mountaineering

Ethics. The ethics of oxygen use have been extensively debated since the 1920s and will continue to be debated for many years to come (UIAA Tyrol Declaration, 2002). There is no doubt that oxygen is a drug, in many countries available only on prescription, and that it improves exercise tolerance at altitude. Depending on the oxygen flow, 8000-m peaks will be physiologically reduced to 6500–7400-m summits (Küpper et al., 2010). Some say that any drug or artificial aid, which increases performance, is not acceptable, and every mountaineer will express respect for the very few climbers who have summited 8000-m peaks without using supplementary oxygen. Most people can acclimatize to 5000 m, so they can climb peaks of over 6000 m from a high camp. It is only well above 7000 m where the oxygen debate is relevant.

Medics. Reaching the summit of 8000-m peaks is dangerous, and many mountaineers are unaware of the dangers of hypoxia at extreme altitude when they overcome the unpleasantness of acclimatization at lower altitude (4000–5000 m). Few individuals have the physiological and mental capacity to reach extreme altitudes (>8000 m) and return safely without using supplemental oxygen. There is no doubt that the use of oxygen at extreme altitude reduces the risks of death, especially during descent when mountaineers are often near exhaustion and vulnerable to accident, poor decision-making, storm, or illness (Pollard and Clarke, 1988).

Supplementary oxygen provides the human body with the one substance it really lacks at extreme altitude. Oxygen does not affect performance at sea level because neither the amount of available oxygen nor its partial pressure is the limiting factor for maximal performance. This changes dramatically at extreme altitude, where the oxygen cascade from the atmosphere to the mitochondria is limited by decreased inspiratory PO_2 and capillary–mitochondrial ΔPO_2 (West, 1990a). Supplemental oxygen improves exercise tolerance (West, 1993), allows a significant improvement in maximal steady-state power output (Morris et al., 2000), benefits climbers subjectively, and improves SaO_2 in the resting state and during exercise (West, 1995; Huey and Eguskitza, 2000a; Windsor et al., 2007; Grocott et al., 2009). Climbers who reach extreme altitudes without using supplemental oxygen may have more effective respiratory acclimatization than others and have therefore a higher PaO_2 when breathing ambient air. If supplemental oxygen is withdrawn in the hypoxic environment (Grocott et al., 2009), there is a high risk from the sudden onset of HACE and HAPE (Pollard and Clarke, 1988). Supplemental oxygen enhances climbing speed and performance (Huey and Eguskitza, 2000a), thereby decreasing time spent at extreme altitude and reducing physical deterioration (Pollard and Clarke, 1988; Huey and Eguskitza, 2001). It not only reduces cognitive impairment but also lures less experienced climbers onto extreme objectives (Pollard and Clarke, 1988; Huey and Eguskitza, 2000b).

Significant improvements are expected when using oxygen at extreme altitude. Few studies have attempted to analyze factors that influence death rate, but data about risk and mortality while using oxygen or not are scant and difficult to analyze in this extreme environment. Limited data are given for the most popular peaks and the cause of death is analyzed by different categories: peak altitude, geographical region, climbing season, age, gender, and experience. Ascents are also analyzed by team composition, member and hired personnel, and if commercial or noncommercial expeditions. These populations are difficult to compare as those not using supplementary oxygen are often more experienced, fitter, and climb in a lighter style on more technically difficult ground.

The risk of death during ascent and descent from the summit of Mt. Everest or K2 is increased for climbers without supplemental oxygen: 8.3% versus 3.0% on Mt. Everest and 18.8% versus 0% on K2 (Huey and Eguskitza, 2000a, 2000b; Huey et al., 2001). These raw data do not indicate the primary cause of death or contributing factors. According to the Himalayan Database, differences in death rates only reached statistical significance on Mt. Everest (Salisbury and Hawley, 2011).

Across all altitudes, lethal falls during descent are three times higher than during ascent, and hypoxia can contribute to accidents through disorientation, misjudgments, or exhaustion (Salisbury and Hawley, 2011). Another study shows that while 70% of deaths at altitude over 6500 m reflect the hazardous mountain terrain (e.g., crevasse, avalanches, and storm), altitude hypoxia contributes to the 30% of deaths ascribed to HACE, HAPE, or neurological damage impairing motor and cognitive activities. Supplemental oxygen could reduce these medical deaths (Pollard and Clarke, 1988).

The brains of mountaineers operating at extreme altitude demonstrate significant long-term deficit involving motor (West, 1990b; Di Paola et al., 2008) and cognitive activities (e.g., impaired concentration, short-term memory, and ability to shift concepts and control errors) (Hornbein et al., 1989; Richalet et al., 1999; Virues-Ortega et al., 2004; Firth et al., 2008; Grocott et al., 2009; Yan, 2014; Turner et al., 2015), sometimes persisting after return to sea level (West, 1990b) with structural neurologic damage (e.g., frontal subcortical lesions, cortical atrophy) (Garrido et al., 1993, 1995). Amateur climbers are at higher risk than professionals (Fayed et al., 2006). Repeated extreme altitude exposure can cause mild but persistent cognitive impairment (Regard et al., 1989), while one article shows no significant deficit in acclimatized individuals climbing to 7500 m (Merz et al.,

2013). Death due to acute hypoxia during ascent or descent following failure of supplemental oxygen circuits is not unusual (e.g., 2 deaths of 62 during 1978–2006 on Mt. Everest) (Firth et al., 2008).

Recent improvements in open-circuit systems for mountaineers have reduced weight, while increasing comfort and reliability (Windsor et al., 2005, 2008). Room oxygen enrichment (e.g., to 24%) may improve sleep and subsequent daytime performance at high altitude (Luks et al., 1998; Barash et al., 2001; West, 2016).

Doping. No formal competitions take place at extreme altitude, so WADA has made no judgment on oxygen use.

Conclusions. It is for the individual climber to make their own ethical and tactical decisions. Supplemental oxygen should be available on climbing expeditions to 8000-m peaks for optimal treatment of HACE and HAPE. Supplemental oxygen is recommended for rescues at high altitude (>6500 m). Medically, UIAA Medcom recommends the use of supplementary oxygen on peaks above 7500 m. Being active mountaineers, the UIAA Medcom members do admire those mountaineers with the experience, skill, fitness, and physiology to climb safely above this altitude without supplementary oxygen while being aware of the risks involved.

Recommendations. Supplemental oxygen should be available on climbing expeditions to 8000-m peaks for optimal treatment of HACE and HAPE. Recommendation Grade: 1A.

Supplemental oxygen should be provided in rescues at high altitude (>6000 m). Recommendation Grade: 1A.

Sleep medication

Sleeping difficulty is very common with acute high altitude exposure and can prove very uncomfortable and impair daytime activities. Sleep disturbances were reported by more than 70% of participants in AMS treatment trials (Ainslie et al., 2013). These complaints are associated with frequent brief arousals. The main concern when considering the use of sleep medications (hypnotics) at high altitude is whether the sleep disruption is an environmental effect or a physiological one related to poor acclimatization or an overactive respiratory response to high altitude, leading to periodic breathing (Küpper et al., 2008a; Tseng et al., 2015).

Up to 3500 m, periodic breathing may be of advantage because it stabilizes oxygen saturation at a relatively high level, but at higher altitudes, disadvantages predominate and frequent arousals cause total sleep deprivation and exhaustion (Zielinski et al., 2000). Recent research has shown that direct hypoxia has a far greater effect upon sleep at altitude than previously thought (Eichenberger et al., 1996; Windsor and Rodway, 2012). If the individual is well acclimatized with no other signs or symptoms of AMS, it is not unreasonable to consider sleep medications to prevent the dangers of sleep deprivation (Taylor et al., 2016). Sleep medication, not hitherto included in the 2016 WADA list, used in conjunction with energy drinks and alcohol may result in intoxication, similarly to the effects of some recreationally abused drugs, which are WADA prohibited (Taylor et al., 2016).

Theophylline–Acetazolamide (see also respective chapters). Insomnia at altitude is associated with increased waking and periodic breathing or apnea due to effect of hypoxemia and poor acclimatization. Acetazolamide has been shown to have beneficial effects on sleep disturbances (Wickramasinghe and Anholm, 1999; Rodway et al., 2011; Windsor and Rodway, 2012; Richalet, 2013). A randomized, double-blind placebo-controlled study was conducted to evaluate the effects of both Theophylline and Acetazolamide in the treatment of SDB after fast ascent to high altitude (3454 m), showing that both drugs are effective in normalizing high-altitude sleep disorders.

Both Theophylline (250 mg × 2 daily) and Acetazolamide (250 mg × 2 daily) reduced oxyhemoglobin desaturation during sleep, with a reduction in obstructive events during sleep compared with the incidence of central apnea of controls (Küpper et al., 2008b). Acetazolamide also significantly improved basal oxyhemoglobin saturation during sleep compared with Theophylline (86.2% vs. 81%) (Fischer et al., 2004). In addition to the established side effects of Acetazolamide, if taken at night, its diuretic effect can interrupt sleep.

Recommendations. Theophylline and Acetazolamide should be considered for reducing the occurrence and intensity of sleeping disorders. Recommendation Grade: 1B.

Hypnotics. Insufficient data exist to determine which agent is most effective at altitude, nor is it known whether combination therapy with Acetazolamide and a hypnotic agent offers any benefits over monotherapy (Luks, 2008).

Benzodiazepines. Hypnotic benzodiazepine side effects are related to CNS depression, including somnolence, dizziness, fatigue, ataxia, headache, lethargy, impairment of memory and learning, longer reaction time and impairment of motor functions (including coordination problems), slurred speech, decreased physical performance, numbed emotions, reduced alertness, muscle weakness, blurred vision (in higher doses), and inattention (American Pharmacists Association, 2012; Katzung et al., 2012). All are potentially dangerous in the event of a standard 3 a.m. alpine start.

Generic name: Loprazolam. Some studies demonstrated that benzodiazepines improve sleep quality and do not aggravate periodic breathing (Duff and Gormly, 2012; Richalet, 2013). Goldenberg et al. (1988, 1992) showed that Loprazolam (1 mg) did not worsen either slow-wave sleep (SWS) depression or apnea and allowed normal sleep reappearance after acclimatization. On the contrary, other limited evidence suggests that it may cause hypoventilation at high altitude (Roggla et al., 1994). Benzodiazepines with a long half-life such as diazepam risk cause accumulative impairment of reasoning.

Benzodiazepine use in this environment should be discouraged especially when combined with alcohol.

Generic name: Temazepam. Temazepam, a short-acting benzodiazepine, has been shown to improve sleep quality, but to only cause a small decrease in mean oxygenation in unacclimatized climbers (Dubowitz, 1998).

The addition of Theophylline or Aminophylline has been shown to reduce the sedative effects of Temazepam and other benzodiazepines (Katzunget al., 2012).

At altitude. During a Himalayan expedition, both Acetazolamide (250 mg × 2) and Temazepam (10 mg) were used between 4100 and 4846 m. Compared with placebo (only Acetazolamide 250 mg × 2), there were no prolonged sleep latencies, less wakefulness and drowsy sleep, and increased sleep duration in the first 6 hours after ingestion (290 and 231 minutes, respectively), and sleep quality evaluated by visual analog scale was at sea level values (Nicholson et al., 1987).

In a randomized, blinded, crossover placebo-controlled trial at base camp of Mt. Everest (5300 m), participants taking Temazepam (10 mg) showed no significant drop in mean oxygen saturation during sleep. The quality of sleep improved as a result of a reduction in the number of awakenings, a greater respiratory stability, and fewer episodes of periodic breathings (Dubowitz, 1998). In another double-blind, randomized crossover trial at 5000 m, Temazepam (10 mg) was effective in reducing periodic breathing, safe to use, and without any adverse effect on next-day performance (Nickol et al., 2006).

Short-acting benzodiazepine Temazepam (10 mg) given with Acetazolamide (500 mg slow release) improved sleep and maintained SaO_2%, counteracting a 20% decrease in SaO_2% when Temazepam was given alone (Manang, Nepal, at 3540 m) (Bledsoe et al., 2009).

Last, the first comparative, randomized double-blind trial of Temazepam (7.5 mg) versus Acetazolamide (125 mg) taken at bedtime for one night at an altitude of 3540 m showed no difference with regard to mean nocturnal oxygen saturation, proportion of the night spent in periodic breathing, relative desaturations, sleep onset latency, awakenings, wake after sleep onset, sleep efficiency, daytime drowsiness, or change in self-reported Lake Louise Score. The Acetazolamide group reported significantly more awakenings to urinate (Tanner et al., 2013).

Conclusions. Benzodiazepines are controversial. As a general rule, the use of drugs such as Diazepam should be discouraged as they decrease the respiratory drive causing hypoventilation, especially if combined with alcohol. Studies would suggest that Temazepam may have a useful role in management of altitude insomnia.

Recommendations. Benzodiazepines should not be used at high altitude. Alcohol will increase benzodiazepine-related adverse effects, for example, nocturnal hypoventilation and desaturation and day sedation. Recommendation Grade: 2B.

Between 4000 and 5000 m, coingestion of Acetazolamide (500 mg) and Temazepam (10 mg) may result in a sleep quality comparable with sea level values. Recommendation Grade: 1B.

Temazepam (10 mg) taken up to 5300 m may improve sleep quality by reducing awakening and providing a greater respiratory stability and fewer episodes of periodic breathing, without any negative side effects during night or detrimental effects on next day's performance. Recommendation Grade: 1A.

Nonbenzodiazepines. Generic names: Zolpidem, Zaleplon. The new-generation hypnotic drugs, Zolpidem and Zaleplon, are at least as efficacious as benzodiazepines and may offer advantages in terms of safety due to their very short half-life. Frequency of side effects may be dosage and age dependent, and include headache, somnolence, dizziness, hypertension, rash and urticaria, and arthralgia (Muller et al., 1987; American Pharmacists Association, 2012).

At altitude. Zolpidem improved sleep characteristics at 4000 m, inducing a decrease in sleep onset latency (placebo, 22 ± 12 minutes vs. Zolpidem, 10 ± 6 minutes), an increase in SWS (stage three of non-rapid-eye-movement [non-REM] sleep) duration (placebo, 46 ± 28 minutes vs. Zolpidem, 69 ± 28 minutes), and a reduction in the arousal index during SWS (placebo, 7.4 ± 4.1/h vs. Zolpidem: 2.4 ± 1.0/h) (Beaumont et al., 1996).

A 2007 double-blind, randomized, placebo-controlled crossover trial at 3613 m to assess the effects of Zolpidem and Zaleplon on nocturnal sleep as well as on daytime attention, fatigue, and sleepiness showed no adverse effect on nighttime SpO_2, daytime attention levels, alertness, or mood (Beaumont et al., 1996, 2007; Jouanin et al., 2009).

Conclusions. Hypnotic nonbenzodiazepine drugs treat both physiological and environmental causes and seem to work without affecting respiratory drive, so sleep quality and structure were improved. With no studies describing the effects of high doses of hypnotic drugs at altitude, common sense and experience suggest high doses are inadvisable and should definitely be avoided if AMS is identified (Luks, 2008).

Recommendations. Up to 3600–5000 m, Temazepam (7.5–10 mg at bedtime), Zolpidem (10 mg), and Zaleplon (10 mg) are often taken for night rest without proven effects on ventilation, attention, or performance, but great care should be exercised in their use when combined with an early alpine start for an ascent. Recommendation Grade: 1A.

Hypnotic nonbenzodiazepines should be avoided in AMS. Recommendation Grade: 1B.

Stimulants

Stimulants are psychoactive drugs that induce temporary improvements in either or both mental or physical functions (Ambrose, 2004). The US Anti-Doping Agency defines a stimulant as a chemical agent that temporarily arouses or accelerates physiological or organic activity (The National Institute on Drug Abuse [NIDA], 2015). Many stimulants have a significant potential to cause drug dependency.

Generic name: Amphetamines. Amphetamines act primarily by enhancing the brain activity of noradrenaline and dopamine, intensifying psychological sensations of alertness, concentration, and self-confidence (Sulzer et al., 2005; Cruickshank and Dyer, 2009). Amphetamines are indicated for the treatment of attention-deficit–hyperactivity disorder and narcolepsy. The effects of amphetamine include an increase in physical energy, mental aptitude, talkativeness, restlessness, excitement, and good humor. Subjects taking amphetamine also report that they feel confident, efficient, ambitious, and that their food intake is reduced (Heal et al., 2013). Some negative effects of amphetamine (that can be dose dependent) are anxiety, indifference, slow reasoning, irresponsible behavior, irritability, dry mouth, tremors, insomnia, and, following withdrawal, depression (Heal et al., 2013). The role of sympathomimetic drugs in the pulmonary arterial pressure response to hypoxia is well known. Amphetamines may lead to pulmonary artery hypertension due to the release of synaptic

dopamine, norepinephrine, and serotonin, which may cause pulmonary vasoconstriction, enhancing the risk of HAPE at altitude (van Wolferen et al., 2005).

Use in sport. Amphetamines enhance anaerobic performance, while having little or no effect on aerobic performance. They enhance sports performance with a supplemental mental stimulus as well as effects on physical power derived from the ATP-CP, lactic acid, and aerobic energy systems (glycolysis and Krebs Cycle). Their use can carry substantial health risks of heatstroke and cardiac arrest, which have resulted in several fatalities among competitive cyclists (Logan, 2002). Amphetamines obscure pain from injuries and have enabled athletes to continue to compete while exacerbating injuries (Logan, 2002).

Generic name: Cocaine. Cocaine is an extract from the leaves of the coca bush (*Erythroxylum coca*) native to South America (Biondich and Joslin, 2015). Coca tea has often been recommended for travelers in the Andes. Cocaine is the most potent stimulant of natural origin (Casikar et al., 2010). Cocaine modifies the action of dopamine in the brain and this increased activation of the dopaminergic reward pathway leads to a feeling of euphoria (Barnett et al., 1981; Kuhar, 1992). Physical effects of cocaine use include constricted blood vessels, dilated pupils, and increased temperature, heart rate, and blood pressure. It also increases motor activity (Cone et al., 1998). Complications associated with cocaine use include disturbances in heart rhythm and heart attacks (risk of cardiac sudden death increased more than 20-fold), chest pain and respiratory failure, strokes, seizures, headaches, and gastrointestinal complications (abdominal pain and nausea). Cocaine misuse is strongly associated with cerebrovascular accidents arising either from rupture or spasm of cerebral blood vessels (Barnett et al., 1981; Pomara et al., 2012).

Use in sport. Cocaine does not enhance performance, whether in the workplace, in sports, at school, or during sex (Braiden et al., 1994). At all doses, cocaine significantly increases glycogen degradation while increasing plasma lactate concentration without producing consistent changes in plasma catecholamine levels (Docherty, 2008). A number of dramatic fatalities associated with coronary occlusion have occurred in athletes misusing cocaine who have been exercising intensely following drug administration (Kloner and Rezkalla, 2003; Sordo et al., 2014). Many athletes who misuse cocaine complain of negative central effects such as perceptual misjudgments and time disorientation that reduces their athletic performance (Kloner and Rezkalla, 2003; Sordo et al., 2014).

Generic name: Cannabinoids. Cannabinoids are a class of diverse chemical compounds that act on cannabinoid receptors on cells that repress neurotransmitter release in the brain. The most notable cannabinoid is the tetrahydrocannabinol, the primary psychoactive compound of cannabis (Fellermeier et al., 2001). The dried leaves and flowers of the cannabis plant are known as *marihuana*, which can be smoked or taken orally with food (baked in cookies). The resinous secretions of the plant are known as *hashish*, which can be smoked or eaten.

Use in sport. Performance-enhancing effect of cannabis is questionable. Cannabis increases resting heart rate and blood pressure, and this chronotropic effect leads to achievement of maximum heart rate at reduced workloads, decline of cardiac output, and reduced psychomotor activity that have been demonstrated in many studies (Avakian et al., 1979; Lach and Schachter, 1979; Renaud and Cormier, 1986). On the other hand, cannabis may reduce an athlete's precompetition stress and anxiety as a result of the euphoric effect it may produce. It has relaxing and sedative properties and improves sleep quality (Pesta et al., 2013). Its hemodynamic effects and negative psychomotor effects reduce any positive potential effects in sports (Lorente et al., 2005; Pesta et al., 2013).

Generic name: Mescaline. Mescaline or 3,4,5-trimethoxyphenethylamine is a naturally occurring psychedelic alkaloid of the phenethylamine class, known for its hallucinogenic effects similar to those of Lysergic acid diethylamide (LSD) and psilocybin. It shares strong structural similarities with the catecholamine, dopamine (Nichols, 2004). Users typically experience visual hallucinations and radically altered states of consciousness, often experienced as pleasurable and illuminating, but occasionally with feelings of anxiety or revulsion. Other effects include open- and closed-eye visualizations, euphoria, dream-like state, laughter, and a psychedelic experience (Monte et al., 1997). Side effects of mescaline use may include anxiety, tachycardia, dizziness, diarrhea, vomiting, and headache (Monte et al., 1997).

Stimulants at altitude. Stimulant drugs have a long story in the mountains. Anecdotal accounts suggest that many ascents of 8000-m peaks in the 1950s were done with the use of amphetamines (Pervitin = methylamphetamine). A 1993 study in the Austrian Alps found amphetamines in the urine of 7.1% of mountaineers going above 3300 m (Roggla et al., 1993). WADA has reported international top class competition climbers testing positive for both amphetamines and cocaine (Boghosian et al., 2011). At high altitude, central effects of stimulants such as perceptual misjudgments and time disorientation may cause life-threatening risks for a mountaineer (Roggla et al., 1993). Coca-derived products are commonly recommended for prophylaxis for travelers in the Andes, and anecdotal reports suggest they are now also being used by trekkers in Asia and Africa. Their use in prevention of AMS has never been systematically studied, and they should not be substituted for other established preventive measures (Luks et al., 2014). Only one small study suggests that chewing coca leaves may be beneficial during exercise and that the effects are felt over a prolonged period of sustained physical activity (Braiden et al., 1994).

Stimulants and doping. A total of 62 stimulants (from 61 chemical entities) are listed in the WADA list. Many of these compounds are old agents, with research going back to the 1950s and 1960s, long before modern techniques and knowledge of receptor subtypes were studied in detail (Boghosian et al., 2011; WADA, 2016b). All stimulants are prohibited, except substances included in the 2016 Monitoring Program (caffeine, nicotine, etc.). Due to the transient advantage they give in nature, stimulants are prohibited *in-competition* only; this means that an athlete who is not

competing does not need to obtain a TUE to use these drugs (WADA, 2016b).

Conclusions. The risk of overexertion is high when using stimulants. This may result in exhaustion, hypothermia, collapse, and death. Euphoric effects of stimulants may lead to poor decision-making, resulting in mountain accidents.

Recommendations. Stimulants should not be used during mountaineering as they reduce attention and may increase the chances of risk-taking and exhaustion. Recommendation Grade: 1B.

Benefits for acclimatization are unproven. Recommendation Grade: 1C.

Analgesics

There are many painkillers available, some of them are suitable for use by a lay person in the wilderness and, when taken alone or in combination, they will safely treat nearly all painful conditions (e.g., Acetylsalicylic acid [ASA], Ibuprofen, Acetaminophen). The strongest painkillers (opioids) need specific training for their use.

Nonopioid analgesics

Headache is known to be the predominant symptom in AMS, which is also frequently accompanied by nausea, vomiting, and insomnia. At altitudes between 2500 and 5000 m, about 20%–90% of those who are not acclimatized will experience this problem. Headache is an essential symptom in the current diagnosis of AMS (Richalet et al., 1991; Roach et al., 2011), but West (2011) argues that there are some people who suffer from acute altitude-related symptoms, but do not have a headache. High altitude headache is a different entity (Gertsch et al., 2010). The differential diagnosis of headache at high altitude is complex (Küpper et al., 2012). Both AMS and high altitude headache can be simulated by other conditions such as migraine that are not necessarily related to altitude exposure (Young et al., 1996). Analgesics, for example, Acetylsalicylic acid and Ibuprofen, are frequently used by subjects suffering from migraine (Broome et al., 1994; Burtscher et al., 1998). Consequently, serotonin receptor agonists, specifically effective for treatment of migraine (Sumatriptan), or drugs normally used to control neuropathic pain, epilepsy, and as an unlicensed drug for migraine control (Gabapentin) have been studied for treatment of AMS headache.

Generic name: Acetylsalicylic acid. Acetylsalicylic acid irreversibly inhibits cyclooxygenase-1 and -2 (COX-1 and -2) enzymes, through acetylation, which results in decreased formation of prostaglandin precursors; this inhibits formation of prostaglandin derivate, thromboxane A_2, through acetylation of platelet COX, thus inhibiting platelet aggregation (Vane and Botting, 2003). Many adverse effects are dose related and dependent on patient susceptibility. Extensive side effects encompassing cardio-circulatory function, lungs, gastrointestinal system (6%–31%), skin, and hair are reported (American Pharmacists Association, 2012).

At altitude. Burtscher showed the efficacy of Acetylsalicylic acid as prophylaxis against headache when mostly resting during acute high-altitude exposure (320 mg Acetylsalicylic acid, one tablet every 4 hours, starting 1 hour before arrival at 3480 m altitude and then after 3 and 7 hours after arrival) (Burtscher et al., 1998). Acetylsalicylic acid probably prevented high altitude headache since acute hypoxia augments prostaglandin concentration and prostaglandins increase. In a second study (Burtscher et al., 2001) using the same drug protocol, Acetylsalicylic acid reduced the incidence of headache when exercising during acute altitude exposure: climbers were transported to an altitude of 3000 m and then climbed up to 3800 m. Afterward, they descended to a mountain hut at 3480 m and spent two nights there. Its antiplatelet effect increases the risk of internal bleeding, which could be further increased if combined with Dexamethasone (i.e., gastrointestinal bleeding) (Vane and Botting, 2003; Wu and Liu, 2006; Wu et al., 2007). The potential benefit in reducing clotting at high altitude to prevent the risk of venous thrombosis is negligible (Stovitz and Johnson, 2003).

Generic name: Ibuprofen. Ibuprofen reversibly inhibits COX-1 and –2 enzymes, which results in decreased formation of prostaglandin precursors (American Pharmacists Association, 2012).

At altitude. Two prospective, double-blind placebo-controlled studies (Gertsch et al., 2012; Lipman et al., 2012) have evaluated the use of Ibuprofen for prevention of AMS. The authors of both studies cite the importance of inflammation in the pathophysiology of AMS (Olesen, 1994; Tissot van Patot et al., 2005; Julian et al., 2011) as supporting evidence that a nonsteroidal anti-inflammatory drug should be of benefit in preventing AMS. As the authors point out, this favors the conclusion that Ibuprofen acts to prevent the constellation of symptoms rather than just treating the headache. Another study comparing Acetaminophen (i.e., acetaminophen 1000 mg) with Ibuprofen (400 mg) for the prevention of AMS might shed light on the relative importance of antiheadache and anti-inflammatory effects because Acetaminophen has no significant anti-inflammatory effect, but is effective against headache (Harris et al., 2003).

Ibuprofen does carry potentially serious risks such as gastrointestinal hemorrhage (Van Wijck et al., 2012), but tends to have fewer overall side effects than Acetazolamide. Unlike Dexamethasone, it does not cause euphoria or decrease nausea. Its analgesic and antiheadache properties are limited and unlikely to mask significant symptoms (Broome et al., 1994). The fact that it is widely available without a prescription makes it an attractive option for prevention of AMS. Current evidence suggests that Ibuprofen is effective in the prevention of AMS and that its benefit is not limited to preventing headache. It is likely that ibuprofen acts by decreasing inflammatory responses to hypoxia (Zafren, 2012). Ibuprofen is used to mask soft tissue pain in endurance mountain marathon runners and sport climbers (Stovitz and Johnson, 2003; Nieman et al., 2006), but it aggravates exercise-induced small intestinal injury in 20% of healthy endurance athletes (Van Wijck et al., 2012).

Generic name: Sumatriptan. Selective agonist of serotonin (5-HT_{1B} and 5-HT_{1D} receptors) in cerebral arteries, Sumatriptan, causes vasoconstriction and reduces neurogenic inflammation associated with antidromic neuronal

transmission correlating with relief of migraine (American Pharmacists Association, 2012).

At altitude. Three reports suggest the efficacy of Sumatriptan for the treatment of high altitude headache (Bartsch et al., 1994; Utiger et al., 2002; Jafarian et al., 2007b). A randomized, placebo-controlled double-blind trial performed at 4559 m on 29 mountaineers, receiving 100 mg orally, noted a significant decrease of headache scores one and 3 hours after administration, but not after 12 hours, concluding its possible use only for a transient amelioration of headache (Utiger et al., 2002). Jafarian et al. conducted a prospective, double-blind, randomized, placebo-controlled clinical trial, in 102 subjects at 3500 m within 24 hours of ascent. Sumatriptan 50 mg was effective to prevent AMS development (Jafarian et al., 2007b). In nine subjects at 4559 m, 100 mg of Sumatriptan reduced the headache score from mean 2.8 to 0.8 ($p < 0.01$, Wilcoxon signed rank test) (Bartsch et al., 1994).

Burtscher et al. (1995), in a randomized double-blind trial (33 subjects at 3480 m, Sumatriptan 100 mg or Ibuprofen 600 mg), showed that Ibuprofen, but not Sumatriptan, was effective for high-altitude headache (nearly complete relief in the Ibuprofen group, no decrease of the score in the other group).

Generic name: Gabapentin. Gabapentin is structurally related to *gamma*-Aminobutyric acid (GABA). Gabapentin modulates the action of glutamate decarboxylase and branched-chain aminotransferase, two enzymes involved in GABA biosynthesis. In human and rat studies, Gabapentin was found to increase GABA biosynthesis and to increase nonsynaptic GABA neurotransmission *in vitro* (Petrucci et al., 2016).

At altitude. Two studies were performed at 3500 m to evaluate the treatment of Gabapentin on altitude headache (Jafarian et al., 2007a, 2008). The first was on 12 subjects at an altitude of 3500 m receiving 300 mg of Gabapentin and 12 placebos. Nine subjects of the placebo group asked for additional analgesia. The mean headache-free period in the Gabapentin group was 17.1 hours, significantly longer than in the placebo group (10.1 hours). The second study was on 204 unacclimatized subjects aged 15–65 years, at the same altitude, assigned randomly to 600 mg single dose of Gabapentin or placebo. The incidence of headache was the same, but the severity of headache was lower in the Gabapentin group with acceptable tolerability. The drug's side effect profile would put most climbers off using it (including dizziness, somnolence, fatigue, and paresthesia) (American Pharmacists Association, 2012)

Doping. The four mentioned analgesics are not included in the WADA list of prohibited agents.

Conclusions. There are several ways to prevent AMS when going to high altitude. The most reliable and safest method is gradual ascent to allow time for acclimatization. In an extensive evidence based medicine (EBM) review from 2000 to 2011 (Seupaul et al., 2012), different studies have reported reduction in the incidence of AMS with the use of Gabapentin or Sumatriptan and have showed that Ibuprofen is effective in the prevention of AMS and not limited to preventing headache. It is likely that the primary effect of Acetylsalicylic acid may simply be on headache control rather than true prevention of AMS. A greater beneficial effect may be achieved by the combined application of Acetazolamide and Acetylsalicylic acid (Basnyat et al., 2008a). This combination increases oxygenation and reduces prostaglandin synthesis, but the adverse effects of Acetylsalicylic acid should not be underestimated.

Recommendations. Acetylsalicylic acid (320 mg every 4 hours for a total of three doses) or Ibuprofen (400 or 600 mg once, may be repeated) may be used in the prevention and in the treatment of high altitude AMS-related headache. Recommendation Grade: 1A.

Side effects of nonopioid analgesics should be considered (e.g., internal bleeding). Gastrointestinal bleeding risks are higher when combined with Dexamethasone or simply when at high altitude. Recommendation Grade: 1B.

Gabapentin (300 mg) and Sumatriptan (50–100 mg before ascent) may help prevent AMS, Recommendation Grade: 2B.

Opioids

Opioids are a group of drugs that are used for treating pain. They are derived from opium, which comes from the poppy plant (*Papaver somniferum*).

Generic name: Morphine. Morphine binds to opioid receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain, and producing generalized CNS depression (Busch-Dienstfertig and Stein, 2010; American Pharmacists Association, 2012).

Generic name: Codeine. Codeine or 3-methylmorphine is a naturally occurring methylated morphine, with the same mechanism of action (Busch-Dienstfertig and Stein, 2010).

Generic name: Tramadol. Tramadol and its active metabolite (M1) bind to μ-opiate receptors in the CNS causing inhibition of ascending pain pathways, altering the perception of and response to pain. It also inhibits the reuptake of norepinephrine and serotonin, which also modifies the ascending pain pathway (American Pharmacists Association, 2012).

At altitude. Opioids should be avoided during acute altitude exposure or illness due to their respiratory depressant effects (Teichtahl and Wang, 2007). Respiratory side effects are exacerbated with alcohol, sedatives, sleeping pills, sedating antihistamines, or prochlorperazine (Gudin et al., 2013). Tramadol has a less depressant effect on respiration than the other opioids (Rojas-Corrales et al., 1998). The theoretical possibility of developing HAPE as a result of a hypoxic increased pulmonary capillary hydrostatic pressure and an increased pulmonary capillary permeability due to hypoxemia, potent histamine release, and respiratory acidosis caused by depression of medullary respiratory centers must be taken in account (Radke et al., 2014). There is no HAPE recorded in FDA reports in 38,699 people who have side effects while taking Tramadol (eHealthMe, 2016).

Central sleep apnea is induced by the use of opioids. In 2007, a study conducted at an elevation of 1500 m showed a dose-dependent relationship between chronic opioid use and

the development of specific central sleep apnea and ataxic breathing (Gudin et al., 2013). Constipation is a common side effect of opioids, so a laxative must be given if more than a few doses are taken. Only consider opioids for abdominal pain if constipation has been excluded and the victim is moving his bowels normally due to the risk for paralytic ileus (Dubowitz, 1998; Duff and Gormly, 2012). In a 1969 comparison, Carson showed that codeine 132 mg was less efficacious than a placebo in the prevention of AMS (Dumont et al., 2000). Opioids should be used with extreme caution in patients with head injury (American Pharmacists Association, 2012).

High altitude dry cough is associated with inflamed mucous membranes in the respiratory tract. Codeine-containing preparations may be of some limited value as a cough suppressant (Duff and Gormly, 2012).

Doping. All opioids are included in the list of WADA substances and methods prohibited *in-competition* (WADA, 2016b).

Conclusions. At altitude >2500 m, any medication that depresses respiration may make AMS, HACE, and HAPE more likely or worse. Most reviews conclude that opioids produce impairment of human performance on tests of sensory, motor, or attention abilities and can bring excessive risks, with very little advantage. The only ethical medical use is for treatment of severe pain (Tramadol 50 mg tablets one–two every 4 hours, up to maximum 400 mg/24 h or Codeine 30 mg one–two tablets every 4 hours as needed) (Duff and Gormly, 2012).

Note. Opioids are illegal in many countries, even in transit. Carry appropriate Customs forms. Check country requirements with relevant government departments.

Recommendations. Opioids should not be used for exertional purposes. Recommendation Grade: 1B.

Opioids should be considered in the treatment of severe pain. Recommendation Grade: 1A.

Vasodilators

Generic name: Nifedipine. Nifedipine is a dihydropyridine calcium channel blocker (CCB) that primarily blocks L-type calcium channels. It works by affecting the movement of calcium into the cells of the heart and blood vessels. Nifedipine inhibits the spasm of the coronary artery and dilates the systemic arteries, resulting in increase of myocardial oxygen supply reducing its workload. The vasodilatory effects of Nifedipine result in an overall decrease in blood pressure. It is also used for the small subset of pulmonary hypertension patients whose symptoms respond to CCBs. Headache (10%–23%), peripheral edema (7%–30%), dizziness (10%–27%), flushing (10%–25%), nausea, and heartburn (10%) are the most important side effects. Symptoms of overdose include dizziness, drowsiness, nausea, severe drop in blood pressure, slurred speech, and weakness.

The rapid reduction in blood pressure may precipitate adverse cardiovascular events and peripheral edema may lead to an increased risk of frostbite. Alcohol may increase CNS depression and may increase the effects of Nifedipine. Natural licorice and grapefruit in all forms (e.g., whole fruit, juice, or rind) can significantly increase levels of Nifedipine, may cause toxicity, and should be avoided (Kulhmann et al., 1986; Ramsch et al., 1986; American Pharmacists Association, 2012).

At altitude. Nifedipine effectively lowers hypoxic pulmonary hypertension and improves gas exchange in patients with HAPE. These result in regression of alveolar and interstitial edema (Simonneau et al., 1981). For its arterial pulmonary vasodilatory effect, Nifedipine is cheap, effective, lifesaving, and the drug of choice in the treatment of HAPE (Oelz et al., 1989, 1991, 1992; Luks and Swenson, 2008; Maggiorini, 2010; Luks et al., 2014). In mountaineers with HAPE at 4559 m, treatment with 20 mg slow-release Nifedipine taken every 6 hours led to a persistent relief of symptoms, improvement of gas exchange, and radiographic clearance over an observational period of 34 hours. In this study, Nifedipine therapy was not associated with hypotension (Maggiorini, 2006).

Being effective in the treatment of increased pulmonary artery pressure during acute high altitude exposure, Nifedipine may have a role in the prevention of HAPE in susceptible individuals (Bartsch et al., 1991). Twenty milligrams of Nifedipine of the slow-release formulation taken every 8 hours starting 24 hours before ascent to 4559 m and continued until descent decreased the incidence of HAPE from 63% to 10% (Maggiorini, 2006).

If symptoms are present despite Nifedipine prevention, prophylaxis with Acetazolamide is recommended (Greene et al., 1981; Basnyat et al., 2003). Whether Acetazolamide prophylaxis prevents HAPE is yet unknown, although Acetazolamide inhibited hypoxic pulmonary vasoconstriction in animals (Berg et al., 2004; Hohne et al., 2004), but failed to do the same in a large study of partially acclimatized humans in the Everest region (Basnyat et al., 2008b).

Nifedipine does not treat or prevent AMS. Many studies demonstrated that lowering pulmonary artery pressure has no beneficial effects on gas exchange and symptoms of AMS (Hohenhaus et al., 1994; Maggiorini et al., 2006). Its use in high altitude medicine should be limited to prevention and treatment of HAPE and, if used for prevention, it cannot then be used for treatment (Hohenhaus et al., 1994). For treatment, first check that the patient is not already on hypertension therapy with a CCB. Marked hypotension may be precipitated if used in very dehydrated patients or those receiving other antihypertensive drugs (phosphodiesterases [PDE]-5I, β-blockers, α-blockers, other CCBs) (Donegani et al., 2014). At altitude, slow-release preparations should be preferably used. If the patient is semiconscious, but swallowing, the Nifedipine capsule (10 mg) may be pierced and the liquid squirted into his mouth (use with caution); blood pressure lowering should be done at a rate appropriate for the patient's conditions (Luks and Swenson, 2008). Note: Although often stated to the contrary, the patient must be able to swallow, otherwise the drug will have no effect (van Harten et al., 1987).

Note. Management of pulmonary hypertension, prevention and treatment of HAPE, is an off-license use (Kulhmann et al., 1986; American Pharmacists Association, 2012).

Doping. Nifedipine is not included in the WADA prohibited list.

Conclusions. Nifedipine can be used specifically for treatment of severe HAPE to buy time for vital lifesaving descent. In specific cases, it may be used for prevention to minimize the risk of HAPE developing.

Phosphodiesterases

The two major PDE5 inhibitors (PDE5-Is) for mountain sport purposes are Sildenafil and Tadalafil.

Generic name: Sildenafil, Tadalafil. Both Sildenafil and Tadalafil are not only primarily used to treat erectile dysfunction but are also effective in the treatment of pulmonary arterial hypertension. They relax the arterial wall, leading to decreased pulmonary arterial resistance and pressure. This, in turn, reduces the workload of the right ventricle of the heart and improves symptoms of right-sided heart failure (Jeon et al., 2005; Kirsch et al., 2008; Sakuma and Shirato, 2008; Wang et al., 2012). Side effects include headache (16%–46%), epistaxis (9%–13%), dyspepsia (7%–17%), flushing (10%), insomnia (7%), myalgia (7%), exacerbated dyspnea (7%), abnormal vision (color changes, blurred vision, or increased sensitivity to light) (3%–11%), diarrhea (3–9%), and erythema (6%) (American Pharmacists Association, 2012). In the same trial, several participants reported feeling subjectively more fatigued and unable to mentally focus during exercise while on active drug treatment (Hsu et al., 2006). Blood pressure may drop due to vasodilator effects (Cheitlin et al., 1999; Chrysant, 2013). Concurrent use with alpha-adrenergic antagonist therapy or substantial alcohol consumption may cause symptomatic hypotension. Avoid concomitant use with organic nitrate vasodilators and be careful if combined with CCBs. Substantial consumption of ethanol may increase the risk of hypotension and grapefruit may increase serum levels to toxic levels (American Pharmacists Association, 2012).

At altitude. A limited number of studies have evaluated the use of the PDE5-I as preventive/therapeutic agents for mountain sickness (Kleinsasser and Loeckinger, 2002; Maggiorini et al., 2006; Fagenholz et al., 2007; Jouanin et al., 2009). PDE5-I is not effective in preventing AMS (Maggiorini, 2006; Jouanin et al., 2009). In some susceptible individuals, PDE5-I may possibly exacerbate AMS by an unknown mechanism (Ghofrani et al., 2004).

Prevention of HAPE. Prevention of HAPE in individuals with a positive history of HAPE could be obtained using 10 mg Tadalafil bid: the incidence of HAPE was 74% in the placebo and 10% in the Tadalafil group (randomized placebo-controlled trial, at 4559 m, eight subjects, $p < 0.007$ vs. placebo) (Maggiorini et al., 2006). The number of individuals in the study was small and extensive clinical experience with the medication is lacking when compared with Nifedipine. Regardless, in the WMS guidelines for the prevention and treatment of altitude illness, Sildenafil and Tadalafil, with longer half-life, are recommended only for HAPE prevention (Luks et al., 2014).

Treatment of HAPE. By virtue of their ability to cause pulmonary vasodilation and decrease pulmonary artery pressure, there is a strong rationale for using PDE5-Is in HAPE treatment (Kirsch et al., 2008; Jin et al., 2010), but to date there are no clinical trials on the use of more selective pulmonary vasodilators such as Sildenafil or other phosphodiesterase-5 inhibitors for HAPE treatment (Maggiorini, 2006). In one small study (Fagenholz et al., 2007), 11 patients were treated for HAPE at 4240 m in Nepal using concomitant drugs (Nifedipine and Acetazolamide in all, Sildenafil in most).

Altitude-induced hypoxia can cause severe decrements in submaximal and maximal exercise performance. These decrements can be attributed, in part, to a ventilation–perfusion mismatch. Strategies to reduce pulmonary hypertension in hypoxia would be predicted to improve oxygen diffusion and arterial oxygen saturation (SaO_2), cardiac output, and exercise performance (Salisbury and Hawley, 2011). Richalet et al. (2005) and Faoro et al. (2007) observed an increase of exercise SaO_2 after 3 days of treatment. Bates et al. (2011) showed a trend toward higher SaO_2 at day 1, but any difference between treatment and control groups for up to 7 days. On the contrary, Xu et al. (2014) showed that short-term treatment attenuated the pulmonary systolic arterial pressure, but had no significant beneficial effects on SaO_2, heart rate, and AMS. Other studies have investigated the effects of PDE5-I on exercise performance at altitude (Zhao et al., 2001; Ghofrani et al., 2004; Aldashev et al., 2005; Perimenis, 2005; Ricart et al., 2005; Richalet et al., 2005; Hsu et al., 2006; Reichenberger et al., 2007) and these studies showed that certain individuals can benefit from Sildenafil use during acute hypoxia, but not normoxia, in terms of cardiac output, arterial saturation, and exercise performance (Di Luigi et al., 2008).

Doping. Sildenafil and Tadalafil (PDE5-I) are not included in WADA prohibited list.

Conclusions. Currently, limited data and experience at altitude with side effects could be potentially dangerous at altitude. PDE5-Is should be used with caution at altitude.

Recommendations

Prevention of AMS. Both Nifedipine and Tadalafil are not effective in preventing AMS.

Prevention of HAPE. Nifedipine: 30 mg of slow release twice daily or 20 mg of slow release every 8 hours, without loading dose (Bartsch et al., 1991; Luks et al., 2014). Recommendation Grade: 1B.

Sildenafil: 50 mg every 8 hours or Tadalafil: 10 mg twice daily. Recommendation Grade: 1C.

Adding Acetazolamide (125 mg twice daily) may further increase HAPE prophylaxis. Recommendation Grade: 2C.

Treatment of HAPE. Nifedipine: 30 mg of slow release every 12 hours or 20 mg of slow release every 6–8 hours (Oelz et al., 1989). Recommendation Grade: 1B (in adjunct to vital descent).

Do not use PDE5-I for treatment of HAPE. Recommendation Grade: 1B.

Xanthine alkaloids

Xanthine (3,7-dihydro-purine-2,6-dione) is a purine base found in many living tissues. A number of stimulants are derived from xanthine, including theophylline, caffeine (also

known as theine, found in coffee beans and tea leaves) and theobromine (found in cocoa and derivatives) (Rall, 1980). Derivatives of xanthine (known collectively as xanthines) are a group of alkaloids commonly used for their effects as mild stimulants and as bronchodilators (Rall, 1980; Fredholm, 1985). Methylated xanthines (i.e., methylxanthines) affect not only the airways but also stimulate heart rate, force of contraction causing cardiac arrhythmias at high concentrations. Toxicity can also lead to convulsions that are resistant to anticonvulsants. Methylxanthines induce acid and pepsin secretion in the gastrointestinal tract. Methylxanthines are metabolized in the liver (Fredholm, 1985).

Generic name: Caffeine. Caffeine is a psychoactive drug whose stimulant properties depend on its ability to block adenosine transmission in the brain. Caffeine has vasoconstriction properties, antagonizing adenosine receptors in the blood vessels and reducing adenosine-mediated vasodilatation, thereby decreasing cerebral blood flow, myocardial blood flow, and exercise-induced myocardial flow reserve (Namdar et al., 2006; Umemura et al., 2006). Caffeine stimulates ventilation, increasing hypoxic ventilatory response, hypercapnic ventilatory response, and thus ventilatory response to exercise. Additionally, caffeine increases resting ventilation and metabolic rate (Fisone et al., 2004; Lorino et al., 2006; Chapman and Stager, 2008; American Pharmacists Association, 2012).

Caffeine can improve exercise performance at low altitudes (An et al., 2014; Fernandez-Elias et al., 2015; Diaz-Laraet al., 2016; Richardson and Clarke, 2016). The mechanism is both central with reduced perceived exertion and peripheral with increased muscular force from changes in calcium utilization, stimulating the release of calcium ions from the sarcoplasmic reticulum (Graham, 2001; Paluska, 2003; Burke, 2008; Woolf et al., 2008; Davis and Green, 2009; Goldstein et al., 2010). Side effects include palpitations, sinus and supraventricular tachycardia, arrhythmias, angina, and flushing; agitation, dizziness, delirium, hallucinations, insomnia, irritability, restlessness, and psychosis; urticaria; esophageal sphincter tone decreased, gastritis; fasciculations; and intraocular pressure increase, miosis. Diuresis is increased (American Pharmacists Association, 2012; WADA, 2016b).

Typical caffeine contents of commonly consumed beverages (Hackett, 2010) are as follows: instant coffee (8oz [1oz = 30 mL] cup) 40–110 mg, coffee espresso (2oz cup) 100 mg, black tea (8oz cup) 50 mg, green tea (8oz cup) 30 mg, Coca Cola (12oz can) 34 mg, Pepsi Cola (12oz can) 38 mg, and Red Bull (8oz can) 80 mg.

Caffeine and theine are chemically identical; the only thing that sets them apart is the concentration, lesser in a cup of tea than in a cup of coffee. Tea is the most widely consumed beverage in the world after water. Tea is known to be a rich source of caffeine, flavonoid antioxidants (oxidized polyphenols), and also contains a unique amino acid, L-theanine, which may modulate aspects of brain function in humans. One randomized, placebo-controlled, double-blind, balanced crossover study investigated the acute cognitive and mood effects of L-theanine (250 mg) and caffeine (150 mg), in isolation and in combination. The results suggest that beverages containing L-theanine and caffeine show a significant positive interaction and may have more pronounced cognitive effects to those containing caffeine alone (faster simple reaction time, faster numeric working memory reaction time, and improved sentence verification accuracy) (Haskell et al., 2008).

In addition, other data indicate that L-theanine has a significant positive effect on the general state of mental alertness or arousal (Scott et al., 2004; Bryan, 2008; Nobre et al., 2008; Camfield et al., 2014).

At altitude. Because of its capacity to reduce cerebral vasodilation in response to hypoxia owing to its vasoconstriction properties, caffeine will help prevent or treat altitude headaches and therefore AMS. In addition, at high altitude, it may improve sleep by reducing episodes of oxygen desaturation. Caffeine reduces cerebral blood flow and the ratio of cerebral blood flow to cerebral metabolic rate for oxygen. Caffeine stimulates ventilation and this effect could be more pronounced where ventilation is already markedly increased and therefore at high altitude this may be helpful. Studies of caffeine and exercise are limited, but they suggest that caffeine might confer more benefit to performance at high altitude than at sea level and do not suggest that it might impair exercise.

Caffeine does have diuretic effects, but with normal consumption, even in an environment of cold and altitude where diuresis is stimulated, caffeine did not increase diuresis with no risk for dehydration (Hackett, 2010). A study performed by Scott et al. (2004) showed that there is no evidence that tea acts as a diuretic when drunk by regular tea drinkers at altitude, but it does have a positive effect on mood. It also did not increase the altitude-induced increase of heart rate significantly.

Caffeine may interfere with sleep and promotes wakefulness, so it is recommended avoiding caffeine in the late afternoon or evening, especially in nonhabitual users, to avoid caffeine-induced insomnia, which could aggravate altitude-associated insomnia (Hackett, 2010). Habitual caffeine users should not discontinue it because of travel to altitude since withdrawal symptoms are very similar to those of AMS (Hackett, 2010).

Doping. Caffeine was removed from the WADA Prohibited List in January 2004 since it is present in a wide range of popular foods, metabolized at very different rates in individuals with different urinary concentrations, which do not always correlate with the dose ingested. In 2012, following concerns raised by some sport physiologists, WADA included caffeine in the 2012 Monitoring Program to monitor potential misuse in sport, keeping the situation under review (WADA, 2016b).

Conclusions. Even at physiological doses (3–6 mg/kg), caffeine provides an ergogenic aid especially in endurance events. It has a peripheral effect targeting muscle metabolism as well as a central effect on the brain to enhance performance, which is also relevant for anaerobic performance. Postexercise caffeine intake seems to benefit recovery by increasing rates of glycogen resynthesis.

Recommendations. Caffeine (1.5–3 mg/kg) may help exercise performance at altitude. Recommendation Grade: 1B.

Generic name: Theophylline. Theophylline is a drug used for respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma. As a xanthine, it

bears structural and pharmacological similarity to caffeine and theobromine (Scott et al., 2004). Theophylline is naturally found in cocoa beans. Trace amounts are also found in brewed tea. Theophylline causes bronchodilation, diuresis, CNS and cardiac stimulation, and increased gastric acid secretion (Schultze-Werninghaus and Meier-Sydow, 1982; Essayan, 2001). The metabolic effect of theophylline was studied (Greer et al., 2000), demonstrating that this substance is ergogenic independent of muscle glycogen (Pigozzi et al., 2003). Adverse effects observed at therapeutic serum levels include tachycardia and flutter, hyperactivity, insomnia, restlessness, seizures, tremor, hypocalcemia (with concomitant hyperthyroidism), nausea, vomiting, gastric reflux, difficulty urinating (elderly males with prostatism), and increased diuresis (American Pharmacists Association, 2012).

At altitude. Theophylline at low dose (300 mg daily) is known to significantly reduce AMS symptoms at altitude (Küpper et al., 2008b). The mechanism found for the beneficial effect is most likely related to stimulation of respiratory drive reducing the frequency of oxygen desaturation during sleep (Fischer et al., 2004; Küpper et al., 2008b). Additional effects of theophylline on AMS symptoms may include a decrease in adenosine-mediated cerebral blood flow or a reduction in inflammatory responses and vascular permeability as a result of its phosphodiesterase inhibitor activity. There is also no evidence that theophylline increases significantly the heart rate at altitude (Küpper et al., 2008b).

If combined with dehydration, alcohol, smoking, or even viral illness, even a low dose of Theophylline (250 mg slow release) can lead to potentially dangerous toxicity (Fischer et al., 2000), although such problems were never observed at altitude so far (Fischer et al., 2004; Küpper et al., 2008b). This drug has multiple interactions with other drugs and a narrow therapeutic range. With Acetazolamide, Theophylline can decrease the potassium level in blood and if combined with Azithromycin, which is often used to treat traveler's diarrhea, it can easily reach toxic levels (American Pharmacists Association, 2012).

Doping. Theophylline has been discussed at WADA since 2003, but it is not prohibited, although it increases performance at sea level (WADA, 2016b).

Conclusions. Theophylline could be considered an alternative to reduce AMS symptoms in those intolerant of Acetazolamide, but it has potential side effects, many drug interactions, and a narrow therapeutic range.

Recommendations. Low-dose slow-release theophylline (300 mg) may be used to reduce symptoms of AMS in association with alleviation of events of periodic breathing and oxygen desaturations. Recommendation Grade: 1B.

Meldonium

Meldonium, also known as *Quaterine*, *MET-88*, and *THP*, is a limited-market pharmaceutical, developed in 1970. It is distributed in Eastern European countries as an anti-ischemia medication. It is not approved in most Western countries. Meldonium is used to treat angina and myocardial infarction (Hayashi et al., 2000; Sesti et al., 2006; Dzerve et al., 2010, Zhu et al., 2013). It acts by reducing damage to cells that can be caused by some products of carnitine. It reduces, presumably by inhibiting, the enzyme γ-butyrobetaine hydroxylase in the carnitine biosynthetic pathway. γ-Butyrobetaine hydroxylase belongs to the 2-oxoglutarate oxygenase superfamily and catalyzes the formation of L-carnitine from γ-butyrobetaine (Liepinsh et al., 2006; Jaudzems et al., 2009). Recent studies argued that Meldonium demonstrates an increase in endurance performance of athletes, improved rehabilitation after exercise, protection against stress, and enhanced activation of CNS functions (Dzintare and Kalvins, 2012; Gorgens et al., 2015). Ninety-day administration of Meldonium improved sexual performance and sperm motility of boars and it also increased concentration of testosterone in blood serum (Bruveris et al., 2013).

At altitude. No data available.

Doping. Since January 1, 2016, Meldonium has been on the WADA list of substances banned from use by athletes. WADA classes the drug as a metabolic modulator, just as it does insulin (WADA, 2016b). However, there are debates over its use as an athletic performance enhancer. Some athletes are known to have been using it before its ban. In March 2016, WADA made a partial retraction on Meldonium (WADA, 2016a). WADA admitted that there are only limited data on how quickly the drug is cleared from the human body. It was found that low levels of the drug could show up in an athlete's urine for a few months, meaning some positives could have been the result of the athlete using the drug before it was banned. Based on preliminary data and awaiting ongoing studies, WADA stated that if the urine level of the drug was <1 μg/mL, the result is compatible with an intake before January 2016, and the responsible antidoping agency could clear the athlete. Other levels were adjusted to allow for a potentially long washout period.

Conclusion. No data exist on whether this substance might be of benefit or harm or how it might work in hypoxia.

Recommendations. Meldonium should not be used at any time by any mountaineer. Recommendation Grade: Expert opinion.

Conclusions

Drugs have been and are being used in the mountaineering community. Some essential drugs can be lifesaving in a medical emergency. There is also good evidence that some drugs can be beneficial at altitude or even for low altitude climbing, but many drugs are used by climbers to enhance performance based on very poor evidence and unverified rumor. In many cases, the drug itself is unproven, its effects at physiological extremes are untested, and there is a risk of side effects or interactions. Even with proven drugs, the small size of most high altitude studies results in poor quality evidence. We hope that this review will help people make informed decisions when working with their mountain medicine physician. Although the ethics of drug use in the mountains are a personal decision, we believe that all mountaineers should be open about any artificial aids, including drugs, used for any ascent.

Author Disclosure Statement

No competing financial interests exist.

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Received July 9, 2016;
accepted in final form July 13, 2016

Artículo 4: Carceller A, Javierre C, Corominas J, Viscor G. "Differences in Cardiorespiratory Responses in Winter Mountaineering According to the Pathway Snow Conditions". High Alt Med Biol. 2019; (20): 89-93.

https://www.liebertpub.com/doi/10.1089/ham.2018.0096

HIGH ALTITUDE MEDICINE & BIOLOGY
Volume 20, Number 1, 2019

DOI: 10.1089/ham.2018.0096

Differences in Cardiorespiratory Responses in Winter Mountaineering According to the Pathway Snow Conditions

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Abstract

Carceller, Anna, Casimiro Javierre, Jordi Corominas, and Ginés Viscor. Differences in cardiorespiratory responses in winter mountaineering according to the pathway snow conditions. *High Alt Med Biol.* 20:89–93, 2019.—Locomotion during ascent requires higher energy consumption than on flat terrain. Locomotion efficiency decreases in snowy terrain, with changes in the biomechanical pattern of walking. This study aims to evaluate differences in both cardiorespiratory responses and energy expenditure between locomotion over snowy terrain with an established footstep pathway (FP) and fresh snow (FS) that has not previously been compacted. Fifteen volunteers with experience in mountain activities at a competition level and a regular training schedule of up to 10 hours a week participated in the study. Estimated maximal theoretical oxygen consumption showed a mild increase (2.6%, 95% confidence interval: 0.9%–4.5%, $t = 3.2$, $p = 0.005$) when subjects followed the FP compared with FS. More time was necessary to complete locomotion in FS (256 ± 30 seconds) than FP (225 ± 29 seconds; $p = 0.01$). Uphill walking velocity increased by 0.43 ± 0.11 km/h ($t = 4.2$, $p = 0.01$) in FP compared with FS; and the FS respiratory rate was higher (by 2.3 ± 2.4 beats/min, $t = 4.0$, $p = 0.001$). For a same itinerary, locomotion in snow that has not been compacted before requires more time and represents a higher energetic cost, either at maximal or submaximal intensities. This should be considered in scheduling mountain ascents as part of the safety strategies. Climbing on virgin snow impedes developing maximal aerobic power, so athletes must regard the value of strength work of lower limbs to improve performance. Indirect calculation of maximal oxygen consumption based on time to complete locomotion in FP can have practical application as a field test.

Keywords: cardiopulmonary function; exercise; maximal oxygen uptake; perception of effort; work capacity

Introduction

Winter mountaineering is a challenging sport that has gained popularity in recent years at recreational, competitive, and commercial levels (Ainslie et al., 2005). Even though the most popular mountains usually have an established ascent route, it is not uncommon for technical mountaineers to climb on virgin snow. In addition to this, within certain mountaineering styles and philosophies, first ascents are considered meritorious and, by definition, they have to take place through routes that have not previously been trodden (International Climbing and Mountaineering Federation, 2002). Locomotion in ascent requires higher energy expenditure than over flat terrain (Billat et al., 2010), and the most efficient mountain path gradient is 25% if there are no performance limitations impeding the subject from reaching maximal power (Minetti, 1995). Efficiency in locomotion decreases in snowy terrain, especially in individuals with little experience (Billat et al., 2010), presumably because of changes in biomechanical patterns of walking (Ramaswamy et al., 1966). Considering this, fitness is described as an additional strategy to increase mountain safety (Burtscher et al., 2015), especially if ascents are performed at altitude or in adverse meteorological conditions, but little is known of its influence on technical mountaineering performance and additional energy demands. Our working hypothesis was that walking on fresh snow (FS) is more expensive in terms of the need for power and energy expenditure as ascents along nontraced routes usually appear to be slower and more fatiguing. Moreover, among professional

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mountain guides, it is well known that being the first climber in a group is usually more exhausting than not leading the climb. However, to the best of our knowledge, there are no controlled intrasubject comparisons that confirm this statement or elucidate the metabolic reason for this widespread subjective feeling, neither have specific repercussions on training programs been assessed.

Therefore, the main objective of this study was to evaluate differences in cardiorespiratory responses and the energetic cost of locomotion between an exercise performed in snowy terrain that had been previously compacted and walking on FS. Our findings may contribute to decision-making not only when planning an ascent but also during training for this specific mode of sport and when facing unexpected events on a mountain.

Materials and Methods

Subjects

The subjects recruited for this study were 15 healthy and physically active volunteers (13 males and 2 females), who were 35.4 ± 5.3 years old. All were highly experienced in winter mountain activities at a competitive level and followed a training regime of up to 10 hours per week. The anthropometric characteristics of the subjects were as follows: height 1.72 ± 0.07 m, weight 67.1 ± 8.5 kg, and body–mass index 22.8 ± 2.6 kg/m^2. Their maximal peak oxygen consumption was 66.4 ± 7.7 mL/(kg·min). After approval by the local ethics committee, all of them were informed of the objective of the study and signed an informed consent form to accept participation in the study. The protocol was conducted according to the principles of the Declaration of Helsinki.

A group of 15 subjects shows statistical power higher than 80%. The sample size calculated to evaluate the differences in performance in a maximal test, with α error = 0.05, β error = 0.20, and an expected dropout of 15%, was of 11.

Laboratory test

The laboratory test was performed in the exercise laboratory of the Physiological Sciences Department of the Universitat de Barcelona at an ambient temperature of 22°C–24°C and relative humidity between 55% and 66%. Each test took place in the morning after a light breakfast.

Participants performed the laboratory test on a precalibrated treadmill (Quasar; HP Cosmos Sports & Medical GmbH, Nussdorf-Traunstein, Germany) at a constant speed of 9 km/h, starting at 0% slope, which increased 1% every minute until exhaustion. Oxygen consumption and CO_2 production were recorded by means of an automatic gas analyzer (Metasys TR-plus; Brainware SA, La Valette, France), equipped with a pneumotachograph using a double way mask (Hans Rudolph, Shawnee Mission, KS). Before each test, calibration was performed, including volume and gas composition, according to the manufacturer's recommendations. The heart rate was continuously monitored during the test (CardioScan v.4.0; DM Software, Stateline, NV).

Field test

The field test took place on a northeastern slope, from a starting altitude of 2043 m to a final altitude of 2104 m, resulting in a positive ascent of 61 m. The total distance covered was 211 lineal meters. The ascent profile exhibited an initial gradient of 15% with a progressive increase in inclination, reaching a maximum gradient of 59%.

The snowpack was homogeneous, of ~ 60 cm depth. With altitude gain, stiffness and cohesion of the surface crust varied, becoming weaker, thus allowing a deeper descent of the footstep, varying from 1–3 to 10–12 cm depth.

Experimental design

A crossover study was designed to compare the different variables, with subjects being their own controls.

Before the start of the field test, a homogeneous pathway 50 cm wide was traced, which permitted comfortable locomotion. The depth of the pathway varied depending on characteristics of the snowpack previously described. The test took place between 12:00 and 16:00 hours.

For each subject, four ascents were performed: locomotion inside the pathway (footstep pathway [FP]) at 100% (FP100) and 70% (FP70) of individual maximal capacity and locomotion outside the pathway (FS) at 100% (FS100) and 70% (FS70) of individual maximal capacity. Assignment of the sequence of ascents was random among the participants. The ascents in virgin snow (FS) took place in parallel to the pathway (FP), without modifying the ascent conditions.

Every participant was equipped with a GPS watch, including a heart rate monitor (Sunnto Ambit3 Peak, Vantaa, Finland). Only the ascending phase was considered for data collection. The participants wore rigid mountaineering footwear and dressed with the innermost of the three layers of clothing that are considered the gold standard in mountaineering apparel. The participants were allowed to cover up with warmer layers between ascents, but all ascents had to be performed with the same clothing. At each ascent finish, monitoring was interrupted and a Borg test (rate of perceived exertion scale; 6–20) was performed (Borg and Kaijser, 2006). The variables reported by the GPS watch were heart rate, respiratory rate, oxygen consumption (calculated from heart rate), and time elapsed. Participants were allowed to descend slowly and recovery was at the base of the slope.

Resting time between ascents was 12–15 minutes, checking that subjects had reached their basal heart rate.

Atmospheric conditions

On the day of the test, the average temperature at a local meteorological station was −6.7°C, with a maximum temperature of 0.8°C, which minimized the risk of snow transformation. Relative humidity was 73%, with moderate winds and no precipitation.

Statistical analyses

The Kolmogorov–Smirnov test was used to establish normal distribution of different samples. Student's *t*-test was used to evaluate differences between outdoor ascent trials. Correlations between the different cardiorespiratory responses and performance indicators during outdoor tests were analyzed using Pearson's bivariate correlation test. Statistical significance was set at $p < 0.05$ for all analyses, which were performed using SPSS, v.15 (SPSS, Inc., Chicago, IL).

Results

Field test

Maximal exercise. As can be observed in Table 1, the maximal calculated oxygen consumption showed a moderate but statistically significant increase (2.6% 95% confidence interval: 0.9%–4.5%, $t=3.22$, $p=0.005$) when subjects followed the previously traced pathway (FP) compared with the virgin snow (FS). The time necessary to complete the FS100 route was clearly longer than for the FP100 pathway. Thus, compacted snow allowed locomotion speed to increase by 0.43 ± 0.11 km/h ($t=4.21$, $p=0.01$). Meanwhile, the respiratory rate was significantly higher during FS100 ascent conditions (an increase of 2.3 ± 2.4 beats/min, $t=4.00$, $p=0.001$) than for FP100. No statistically significant differences were found between FS100 and FP100 when considering Borg scores for declared perception of effort, heart rate, or oxygen consumption (Table 1).

Submaximal exercise. Similarly to the maximal test, more time was necessary to complete FS70 than FP70 (Table 2), with this difference (36 ± 25 seconds) being statistically significant ($t=6.33$, $p<0.001$). The calculated mean oxygen consumption during the FS70 test was higher than for FP70 and this difference also reached statistical significance (1.2 ± 2.3 [mL/(kg·min)], $p=0.048$). In line with this, the respiratory rate was faster during FS70 by 2.9 ± 4.4 beats/min ($p=0.02$). We also detected statistical differences in the subjective perception of effort, according to the Borg scale: it was higher for FS70 than for FP70 (FS70: 14.6 ± 0.7; FP70: 14.0 ± 0.2; $p=0.04$). Remarkably, the average score was around 14, which corresponds to a moderate effort equivalent to 70% of maximal individual capacity. As in the maximal test, the average heart rate did not show a statistically significant difference between FS70 and FP70 (Table 2).

Laboratory test

Maximal exercise. In the laboratory test, we observed that the maximal respiratory parameters (oxygen consumption and respiratory rate) as well as the maximum heart rate were higher than those observed in the maximal field test (Table 3). When comparing the maximal performance observed in the field test with maximal parameters obtained in the laboratory, we observed a correlation between individual maximal O_2 consumption and the time elapsed during the maximal test inside the pathway (FP100; $r=0.763$, $p=0.002$). When studying values observed at the aerobic threshold (ATh1) of the laboratory test, we observed correlations between time for the field test inside the pathway (FP70) and oxygen consumption (VO_2) in the laboratory ($r=0.539$, $p=0.047$), fraction of O_2 in expired air (FeO_2; $r=-0.634$, $p=0.002$), fraction of CO_2 in expired air ($FeCO_2$; $r=0.604$, $p=0.029$), oxygen uptake per heart beat (O_2 pulse; $r=0.626$, $p=0.022$), and end-tidal P_{CO_2} (P_{ETCO_2}; $r=0.622$, $p=0.023$). Conversely, there was no relationship between submaximal virgin snow performance (FS70) and cardiorespiratory data observed in laboratory conditions at ATh1, except for the heart rate. When correlating values observed at the anaerobic threshold (AnTh2) of the laboratory test with data for the submaximal effort field test, we observed a relationship between performance in the field test of FP70 and tidal volume (V_T; $r=-0.736$, $p=0.004$). When considering performance in FS70 and laboratory cardiorespiratory data, we also observed a positive relationship with FeO_2 ($r=0.579$, $p=0.038$), respiratory equivalent for O_2 (ERO_2; $r=0.585$, $p=0.036$), respiratory equivalent for CO_2 ($ERCO_2$; $r=0.566$, $p=0.044$), end-tidal PO_2 ($PETO_2$; $r=0.596$, $p=0.031$), and P_{ETCO_2} ($r=-0.575$, $p=0.04$).

Table 1. Data for Outdoor Tests Performed at Maximal Individual Capacity

Variables	*FS100*	*FP100*	p
Time (seconds)	256 ± 30	225 ± 29	<0.001
Speed (km/h)	3.14 ± 0.36	3.56 ± 0.52	0.001
Heart rate (beats/min)	164.0 ± 9.6	163.6 ± 8.0	0.521
Respiratory rate (breaths/min)	38.1 ± 5.5	35.8 ± 5.8	0.001
Calculated VO_{2max} [mL/(kg·min)]	33.5 ± 4.4	34.4 ± 4.3	0.007
Calculated VO_{2mean} [mL/(kg·min)]	29.9 ± 4.0	29.7 ± 3.9	0.631
Borg score	20 ± 0	20 ± 0	-

Mean values ± standard deviations.
FP100, locomotion along the pathway at 100%; FS100, locomotion off the pathway at 100%.

Discussion

In this study, we show the differences between training and performing a real ascent on an FS surface or a previously trodden route (FP), which have different repercussions for energy expenditure and imply the use of different metabolic substrates. This can have significant technical, biomechanical, and tactical (in competition) repercussions. The applicability of our results includes the fields of competition and sports events as well as mountain safety strategies affecting the workload that can be assumed by mountain rescue teams, mountain border patrols, and other emergency service operatives in snowy terrain. Moreover, there is the possibility of applying field CT100 tests to obtain an estimated maximal oxygen consumption value for athletes.

The time to complete the same route was higher in virgin snow (FS): 12% at maximal intensity and 11% in submaximal efforts. The power developed, considering time spent for moving the same weight, was higher when following the route inside an established pathway (FP) in both series. Given that alpinism is a sport where intensities are usually mild or moderate, but sustained for a long period of time (Burtscher et al., 2015), our data suggest that when planning activities in snowy terrain not previously traced out, slower ascents can be expected. This is common knowledge among experienced mountaineers, but our study allows for a more accurate quantification of this extra effort to be developed.

The lack of significant differences in values of heart rates for different routes in the field test reflects similar intensity during ascents and consequently our FP and FS data are comparable, in either maximal or submaximal efforts.

It is known that for an equal load, walking on snow implies a higher maximal oxygen consumption than on a treadmill at the same intensity along flat terrain (Smolander et al., 1989) and that the increase in energy expenditure is proportional to the depth of the footprint in the snow (Heinonex et al., 1959). The value of maximal oxygen consumption observed in maximal ascents in this study was 2.6% higher when locomotion was performed in FP than in FS due to the higher

Table 2. Data from Submaximal Outdoor Tests

Variables	*FS70*	*FP70*	p
Time (seconds)	326 ± 30	290 ± 24	<0.001
Speed (km/h)	3.1 ± 0.4	3.6 ± 0.5	0.001
Heart rate (beats/min)	148.6 ± 11.5	144.3 ± 11.7	0.084
Respiratory rate (breaths/min)	31.8 ± 5.8	28.9 ± 4.6	0.02
Calculated VO_{2mean} [mL/(kg·min)]	25.2 ± 3.3	24.0 ± 3.8	0.048
Borg score	14.6 ± 0.7	14.0 ± 0.2	0.004

Mean values ± standard deviations.

capacity to develop speed and aerobic power. In the maximal effort outside the pathway (FS), there probably exists a greater anaerobic component, reflected in an increase of the respiratory rate of 2.3 cycles/min in maximal effort and 2.9 in submaximal effort. This could be related to additional biomechanical requirements for locomotion in virgin snow, due to the loss of the elastic rebound component of walking on a solid surface and greater peripheral energy requirements of lower limb muscles (Minetti, 1995), as more effort is necessary to overcome the obstacle that the thickness of the snow represents (Ramaswamy et al., 1966); this leads to less efficient body postures and increased difficulties in maintaining balance (Pandolf et al., 1976). All of this could be modulated according to individual experience as well as acquisition of locomotor abilities through training (Billat et al., 2010; Burtscher et al., 2015).

The difference in respiratory data between field tests and laboratory tests is higher in submaximal efforts than in maximal efforts. This finding can be justified by considering that at maximal load, there is an intrinsic anaerobic component due to the high intensity, which could reduce differences between respiratory cycles observed in FP and FS. In contrast, at submaximal load and when locomotion is performed in FP, this component is reduced due to the lower intensity; consequently, there is no need for such a degree of anaerobic metabolism to be involved.

Finally, speed was significantly greater in maximal efforts (13%) and in the submaximal series (16%) in FP, suggesting that even at low intensities and at the depth of snow footprint assessed in this study, alterations to normal walking gestures

Table 3. Performance-Related Parameters Measured During Maximal Laboratory Tests

Variables	*ATh1*	*AnTh2*	*Maximal*
Respiratory rate (breaths/min)	30.7 ± 5.7	41.6 ± 8.2	51.4 ± 9.0
V_E (L/min)	67.8 ± 9.6	108.0 ± 19.2	135.7 ± 27.3
V_T (L/min)	2.01 ± 0.33	2.38 ± 0.32	2.41 ± 0.38
VO_2 [mL/(kg·min)]	44.4 ± 12.6	58.1 ± 6.1	66.4 ± 7.7
VO_2 (L/min)	2.75 ± 0.56	3.88 ± 0.70	4.44 ± 0.84
VCO_2 (L/min)	2.40 ± 0.44	3.94 ± 0.70	4.90 ± 1.01
Heart rate (beats/min)	141.7 ± 35.9	171.7 ± 10.3	178.2 ± 10.6
O_2 pulse (mL/beat)	17.2 ± 5.8	22.5 ± 3.7	24.8 ± 4.3

Mean values ± standard deviations.

AnTh2, anaerobic threshold; ATh1, aerobic threshold; O_2 pulse, oxygen uptake per heart beat; VCO_2, CO_2 production; V_E, ventilation; VO_2, oxygen consumption; VO_2/kg, oxygen uptake relative to body weight; V_T, tidal volume.

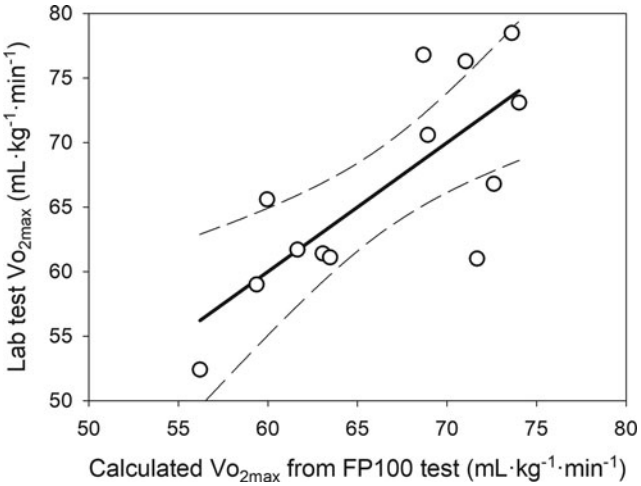

FIG. 1. Relationship between real maximal oxygen consumption during the laboratory test and estimated oxygen consumption during outdoor ascent at individual maximal capacity. *Circles* represent individual values, the *solid line* is the fitted regression function and *dashed lines* represent upper and lower limits of a 95% confidence interval for the predicted values.

can be a limiting factor when it comes to maintaining an appropriate locomotion speed. This finding is not in agreement with previous reports that the maximum depth of the footprint in snow suitable to maintain constant locomotion is 20 cm (Pandolf et al., 1976).

When analyzing correlations among data in submaximal effort in the field test and in the laboratory test, we observed that respiratory parameters during effort intensity below the aerobic threshold in the laboratory are related to performance results of the field test in the FP trials. Conversely, performance on FS did not correlate with data obtained at the aerobic threshold in the laboratory test. Thus, the hypothesis that development of aerobic power is not limited in FP is reinforced.

Maximal values of heart rate and respiratory parameters in the laboratory test were higher than those obtained in the field test, challenging the equivalence of data observed in a laboratory stress test and real performance in the field in spite of using a laboratory stress test adapted to mountaineering requirements. Even so, it was possible to establish a relationship between time in the maximal test FP100 and maximal aerobic power registered in the laboratory. This opens up a possibility for a valid field test to estimate maximal oxygen consumption based on time to complete FP100 ($VO_2max = 110.9 - 11.73 \times t$). The results of this correlate fairly well with those of the laboratory test (Fig. 1). However, despite there being a correlation, maximal oxygen uptake results are lower in the field than in the maximal laboratory test. This, added to the lower tachycardization for the same workload when performing in the field, either at maximal or submaximal efforts, suggests that limitation of individual performance when walking uphill remains, even if there is a trodden pace, but the limiting factor does not seem to be the cardiorespiratory system. Peripheral muscular demands appear be higher in the field, and even adapting the laboratory test by increasing the specificity for alpine needs, the results yield an acceptable data correlation, but the test is not capable of faithfully reproducing mountaineering requirements of other components of fatigue, such as muscular fatigue of the lower limbs. Differences in intensity measurements between

laboratory tests and field tests may also influence different results.

These observations lead us to consider that for the design of both a field test and a laboratory test oriented to assessing the physical performance in a mountaineer whose sporting objective includes progression in snow, inclusion of peripheral strength requirements when designing the treadmill protocol might be considered. This would potentially improve the specificity of the test in addition to the usual assessment of aerobic power and oxygen uptake capacity. Technical and lower limb strength training to achieve more efficient locomotion in snow seems to be an important element that would permit mountain athletes to develop their aerobic power in the field.

Limitations

Backpack weight and altitude effects were not considered during the field tests. The reduced number of participants did not permit us to have strong statistical power. Although mountaineering experience was one of the inclusion criteria of the study, individual ability to walk in snow is difficult to control for, as is the influence of footwear. We tried to solve these limitations by taking the subjects as their own controls. Sex differences were not analyzed because of the small number of female participants included in the study.

Conclusions

Whether locomotion on snowy terrain is conducted on a previously trodden pathway or breaking a trail through virgin snow, it has demonstrable consequences. The latter requires more time and has an increased energy cost for a given route either at maximal or submaximal intensities.

During submaximal efforts, at an exercise intensity equivalent to that usually adopted in mountaineering climbing activity, locomotion on virgin snow involves greater average oxygen consumption, an increase of the workload, a higher energy cost, with a higher anaerobic component, and higher subjective fatigue perception than following a previously trodden path. This limitation for locomotion due to the characteristics of the terrain impedes development of maximal aerobic power, especially on FS, so peak oxygen consumption is higher when walking inside an established pathway. Consistent with this, respiratory data observed in the laboratory below the anaerobic threshold correlate with performance in the submaximal test on the terrain; and these laboratory data at the anaerobic threshold are fairly well related with field tests performed on virgin snow. Our results should be interesting for mountain safety as they objectively describe limitations to ascents, depending on the pathway. This knowledge could lead to different strategies when climbing with a group to limit individual fatigue, such as changing the leader regularly, assuming longer ascent times along virgin snow routes, and considering lower limb strength and specific training for snowy terrain as important requirements when confronting the ascent. These data may also be useful to design field tests for performance assessment in mountaineering and other snow sports, which allow aerobic power to be estimated.

In the same way, knowing if an ascent has been performed on a previously established pathway or on FS can be a differential factor when comparing different activities, especially if time of ascent is assessed as a sports merit or if ascents of the same mountain are performed through different routes under a range of snow conditions.

Acknowledgments

The authors are grateful to the participants in this study for their enthusiasm and commitment. They would also like to thank the members of the ACNA (Asociació pel Coneixement de la Neu i Allaus) for their collaboration in obtaining the snow cuts reported in this article. The authors also want to thank Dr. Christopher Evans at the SAL (Servei d'Assessorament Lingüístic) of the University of Barcelona for help with editing the text.

Author Disclosure Statement

No competing financial interests exist.

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Received July 26, 2018;
accepted in final form January 7, 2019.

Artículo 5: Carceller A, González JP, Viscor G. "Topical Nifedipine Administration for Secondary Prevention in Frostbitten Patients". 2020 (in press). https://www.frontiersin.org/articles/10.3389/fphys.2020.00695/abstract

frontiers in Physiology

ORIGINAL RESEARCH
published: 19 June 2020
doi: 10.3389/fphys.2020.00695

Topical Nifedipine Administration for Secondary Prevention in Frostbitten Patients

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Frostbite is a cold-related injury with a growing incidence among healthy subjects. Sequelae after frostbite are frequent and vary among individuals. Here, we studied the thermal response in the digits of hands and feet of five subjects who had recovered from previous frostbite, except for their lasting sequelae. We considered three different conditions: digits unaffected by frostbite nor sequelae (healthy), those affected but which did not suffer amputation (frostbitten without amputation), and the remainder/stumps of digits that underwent partial amputation (frostbitten with amputation). Three consecutive immersions in cold water (8°C; 3 min) interspersed by 1 minute of thermal recovery were performed. After 30 min, a topical 10% nifedipine preparation was applied to hands and feet, and the same cold exposure protocol to evaluate its effect was followed. In basal condition and immediately after each immersion, the temperature of individual digits was assessed using thermography. We observed different thermal responses among the different digits of hands and feet, even without the nifedipine treatment. Nifedipine had a cooling effect on healthy and post-amputated tissue without thermal stress. In cold conditions, topic nifedipine application improved the cold response in healthy fingers but had a negative effect on those from which parts had been amputated. The topical nifedipine had detrimental effects on toes in all conditions. Topical nifedipine can help to the preservation of healthy fingers exposed to cold, with adequate thermal insulation; but it is necessary to remark its potentially harmful effects on previously frostbitten tissue. Because of the differences observed on individual regional response to cold, thermography can be a useful tool in the frostbite prevention for subjects habitually exposed to cold environment.

Keywords: frostbite, topical nifedipine, secondary prevention, amputation, cold injuries

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Environmental, Aviation and Space Physiology, a section of the journal Frontiers in Physiology

Received: *04 March 2020*
Accepted: *27 May 2020*
Published: *19 June 2020*

Citation:
Carceller A, González Torcal JP and Viscor G (2020) Topical Nifedipine Administration for Secondary Prevention in Frostbitten Patients. Front. Physiol. 11:695. doi: 10.3389/fphys.2020.00695

INTRODUCTION

Frostbite is a local injury caused by exposure to environmental temperatures that are low enough to reach freezing point for a part of the body. The digits on hands (fingers) and feet (toes) are most affected by frostbite due to their peripheral location (Imray et al., 2009). Severity is related to the depth of tissue cooling, with a high incidence of digit total or partial amputation if the injury affects

microvasculature and bone (Murphy et al., 2000). Sequelae after mild frostbite are frequent and can be debilitating, involving pain and hypersensitivity to cold that frequently persist for at least 4 years after the initial injury and can last for life (Ervasti et al., 2000; Hassi and Makinen, 2000; Carlsson et al., 2014). Severe frostbite, especially if acute treatment is delayed, can result in cell death and amputation, with functional sequelae.

Although a wide range of frostbite sequelae exists, for professional or personal reasons, some people previously affected by frostbite stay active in mountains or cold environments. These people face different degrees of symptoms in affected tissues on new exposure to low temperatures and a relative risk of a new frostbite incident. Nifedipine is an arterial specific vasodilator used in a variety of systemic pathologies in oral preparations, as well as topically for local symptoms in pathologies as Raynaud syndrome or chilblains. To our knowledge, no studies are available regarding its effect on tissue temperatures of frostbitten digits in the pathological spectrum (amputated and non-amputated). This study aims to elucidate whether a topical preparation based on nifedipine can relieve, or even reverse, cold-related symptoms in previously frostbitten extremities. This would have implications for those working in or exposing themselves to cold environments, and could minimize symptoms via a formulation that is easy to self-apply.

MATERIALS AND METHODS

Subjects

Five subjects who had suffered moderate to severe frostbite (grades II, III, and IV) in recent years participated in the study, regardless of having undergone amputation of one or more digits or not. All of them suffered frostbite while practicing alpine activities, and after recovery, they continued regular activity in the cold for professional or sport reasons. Inclusion criteria were (1) healed from frostbite at least 1 year before data collection, (2) not have suffered any acute cold injury in the past year (including non-freezing injuries), (3) no local vasomotor alterations, such as Raynaud syndrome, and (4) no previous chronic illnesses. All of the recruited subjects described some degree of sequelae, from cold hypersensitivity to total intolerance to the exposure of the affected parts to extremely low environmental temperature. After approval by the local ethics committee, all of them were informed of the objective of the study and signed an informed consent form whereby they accepted to participate in the study. The protocol was conducted according to the principles of the Declaration of Helsinki.

Thermography

An infrared thermography camera was used to assess surface skin temperature (NEC® H2640, Avio Infrared Technologies Co., Tokyo, Japan), with a thermal sensitivity of 0.03°C. All measurements were performed using low-infrared-emission foam as a background. The test was performed in a room at a constant temperature of 23°C, with no direct sunlight so as not to alter the precision of the measurements. Infrared data from the images were processed using the thermographic image analyzer Image Processer Pro II. A trained observer checked the delimitation of the perimeter of the fingers, and the software automatically computed the average, maximal and minimal temperature for the selected areas of each digit in all the images. **Figure 1** contains representative images showing the delimited areas for the calculation of average, maximal and minimal temperatures of each digit.

Protocol

After 30 min of thermal acclimatization to room temperature, basal temperature image was taken, and immediately followed by 3 immersions of 3 min each in a tank filled with cold water at a constant temperature of 8°C (Keramidas et al., 2015). The time elapsed between these consecutive immersions was 1 minute. After the third immersion, a Vaseline-based cream containing 10% nifedipine was applied to the hands and feet of each participant. After a further 30 min at ambient temperature rewarming, 3 new immersions of 3 min each, again interspersed by 1 min of incomplete recovery, were performed in the cold water (8°C). Thermographic images of the extremities were taken immediately after each immersion. The subjects were asked not to move their limbs, while their hands and feet were dried without rubbing.

Statistics

Because maximal and minimal temperatures offered considerable statistical dispersion, average local temperatures for each of the twenty digits (hands and feet) were assessed separately for statistical calculations, with the exception of one of the subjects who only participated with upper limbs, because of recent frostbitten injuries sustained to the feet. Thus, we studied a total number of 90 digits. We considered healthy (HD, $n = 47$), frostbitten non-amputated (FNA, $n = 35$) and frostbitten amputated (FA, $n = 8$) digits separately, in order to elucidate possible differences in their patterns of response. The total of healthy ($n = 47$) and affected ($n = 43$) digits are balanced. In order to minimize possible inter-subject and intra-subject vasomotor response variability, each subject was considered as his or her own control in basal condition. Statistical analysis was performed by comparing the difference in the decay from basal temperature along consecutive immersions for each digit in each participant, instead of the absolute temperature measured, to avoid the effect of different basal thermal conditions between subjects. A three way RM-ANOVA was applied. By comparing the effect of the treatment in the same subject and under the same conditions, changes in the thermal response can be attributed only to nifedipine application thus minimizing other possible confounding factors. *Post hoc* analysis (Student's *t*-test for repeated measures) was performed considering step changes for individual digits into the three above mentioned categories (HD, FNA, FA), thus allowing to contrast the thermal responses of each clinical condition. Statistical significance was set at $p < 0.05$ for all the analysis, which we performed using SPSS v.15 (SPSS Inc., Chicago, United States).

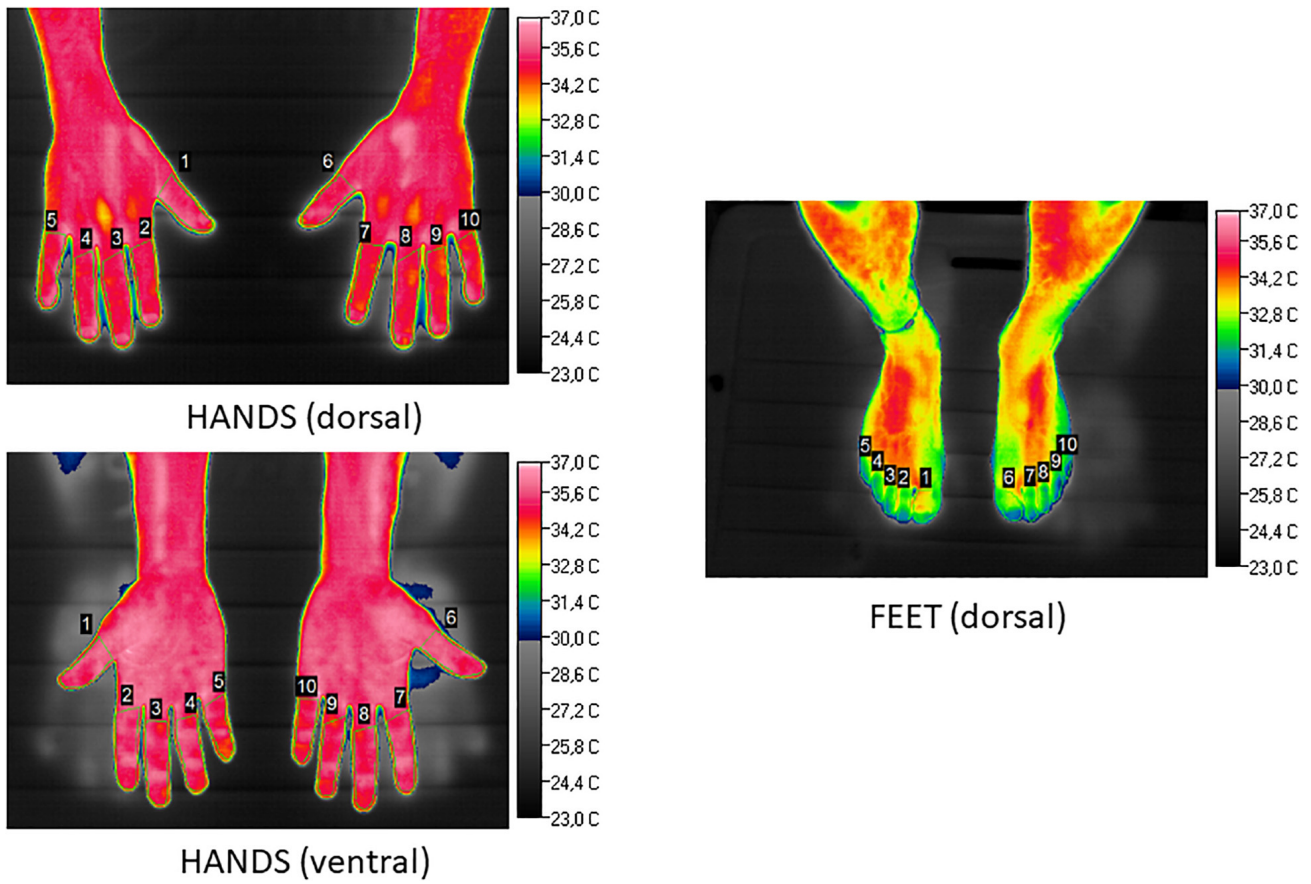

FIGURE 1 | Illustration (basal conditions, Subject 2) of selected areas for calculation of minimal, maximal and average temperature of each finger (dorsal and ventral surfaces) and the dorsal surface of feet. Temperature scale (°C) is to the **right** of each picture.

RESULTS

Temperatures were computed from thermographies for each finger and toe to check the local thermal response (**Figure 1**), from basal conditions, during the cooling protocol, with and without nifedipine treatment. This yielded a total of n = 1,130 processed values.

The average basal temperature before the cooling protocol was 30.7°C ± 0.2°C (CI: 95%). Average temperatures for all measurements after first, second and third immersion, regardless of the presence or not of the nifedipine treatment, were 17°C ± 0.17°C, 14.8°C ± 0.17°C, and 13.8°C ± 0.17°C, respectively (CI: 95%).

Regarding the global response of fingers and toes, we found, as expected, due to their lower surface to volume ratio, that thumbs were the digits that maintained the highest average temperatures (21.3°C ± 0.3°C right and 21.5°C ± 0.3°C left hand, respectively), with statistically significant differences when compared to all the other fingers and toes. The coldest digit was the middle finger, with global values of 19.8°C ± 0.3°C for both hands, although differences when comparing with the rest of the digits did not reach statistical significance. Toes showed globally cooler temperatures than hands. **Figure 2** illustrates the effect of the nifedipine treatment under basal conditions on Subject 5. Meanwhile, **Figure 3** presents the comparative effect of nifedipine treatment on the temperature of the fingers and toes of Subject 3 after the third immersion.

Comparison Between Hands and Feet

The anatomical thermal pattern of the hands was not the same as in the feet: the big toe showed greater temperatures than the others, averaging 18.6°C ± 0.4°C on the right foot and 18.7°C ± 0.4°C on the left. The coolest toe was the second one (2 and 7 in **Figure 1**), with average temperatures of 17.3°C ± 0.4°C for the right foot and 17.1°C ± 0.4°C for the left.

Considering only the hand measurements, average finger basal temperature was 32.1°C ± 0.2°C and average temperature after first, second and third immersions was: 17.5°C ± 0.2°C, 15.5°C ± 0.2°C, and 14.4°C ± 0.2°C, respectively. Computing all the data for all the conditions, healthy digits (HD) showed an average temperature of 18.9°C ± 0.1°C, frostbitten non-amputated fingers (FNA), 20.3°C ± 0.1°C and frostbitten amputated (FA), 20.4°C ± 0.6°C. The difference of temperature between healthy and frostbitten digits reached statistical significance (p < 0.05), regardless of having undergone amputation or not.

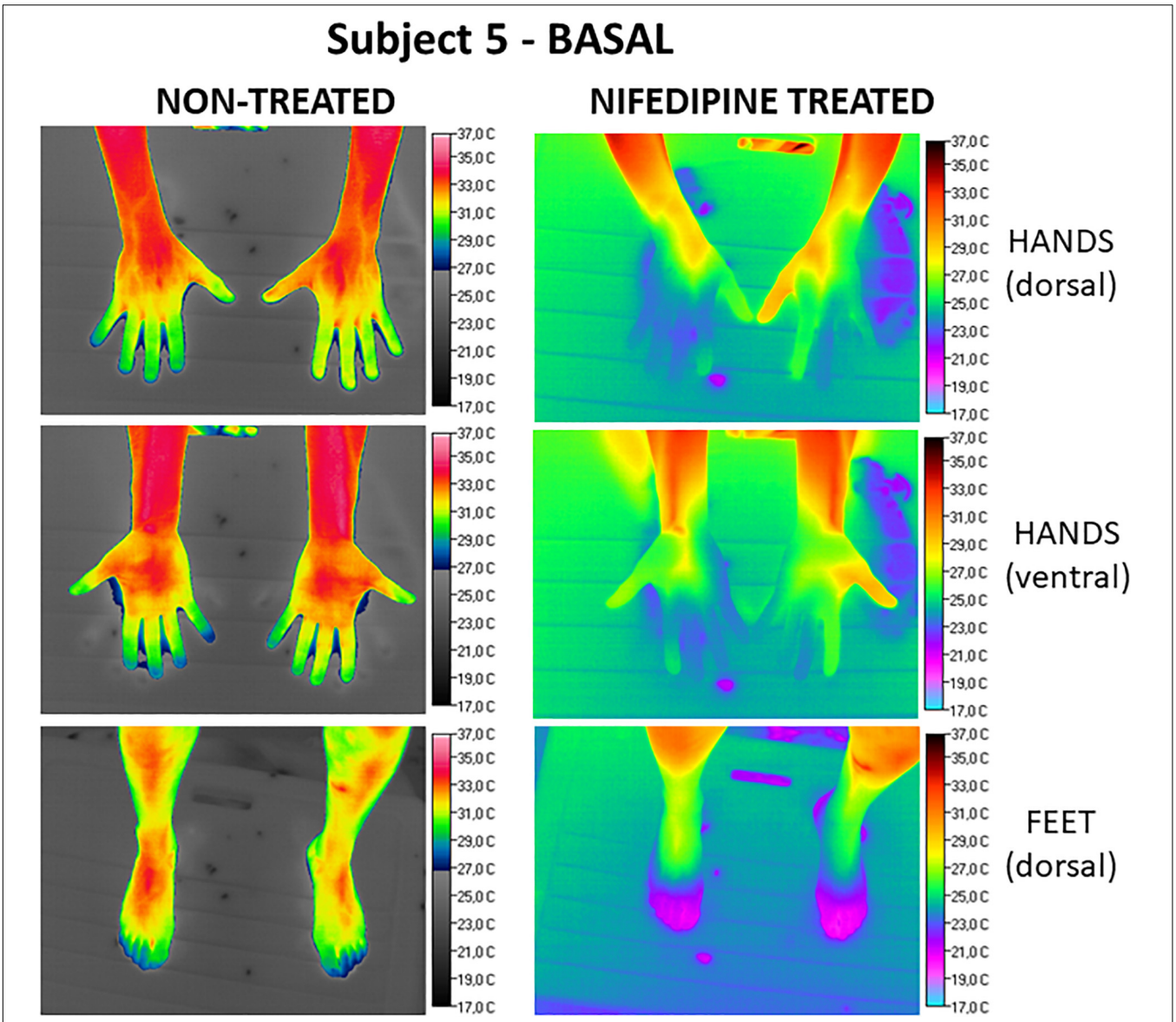

FIGURE 2 | Comparative effect under basal conditions (Subject 5) of nifedipine on the surface temperature of hands (dorsal and ventral view) and feet. Images obtained without nifedipine treatment are on the **left**. The **right** panel shows the images registered after nifedipine treatment. Temperature scale (°C) is to the **right** of each picture.

Comparison of Digit Conditions

When classifying according to the condition of the digits, average temperature of HD was of 17.9°C ± 0.1°C. Regarding frostbitten parts, FA digits presented an average temperature of 20.4°C ± 0.3°C and FNA 18.9°C ± 0.1°C (CI 95%).

When comparing the response to cold of healthy digits versus frostbitten digits, there were no significant differences in basal temperatures, although significant differences were reached when comparing frostbitten digits with healthy ones after maximal cooling (third immersion), with frostbitten ones being warmer than healthy digits (**Table 1**). When considering the interaction between response to cold and nifedipine treatment for HD, FA and FNA, statistically significant differences were only found in amputated toes, where treatment with nifedipine showed lower temperatures than when no treatment was applied (**Table 1**).

Comparison Between Condition and Treatment

When the effects of treatment were assessed by pooling measurements for all conditions, average temperature without nifedipine was of 19.9°C ± 0.1°C and with nifedipine, 18.3°C ± 0.14°C (CI: 95%).

Significant differences were found when comparing previously frostbitten fingers without amputation under basal conditions, which were warmer after nifedipine administration. In contrast,

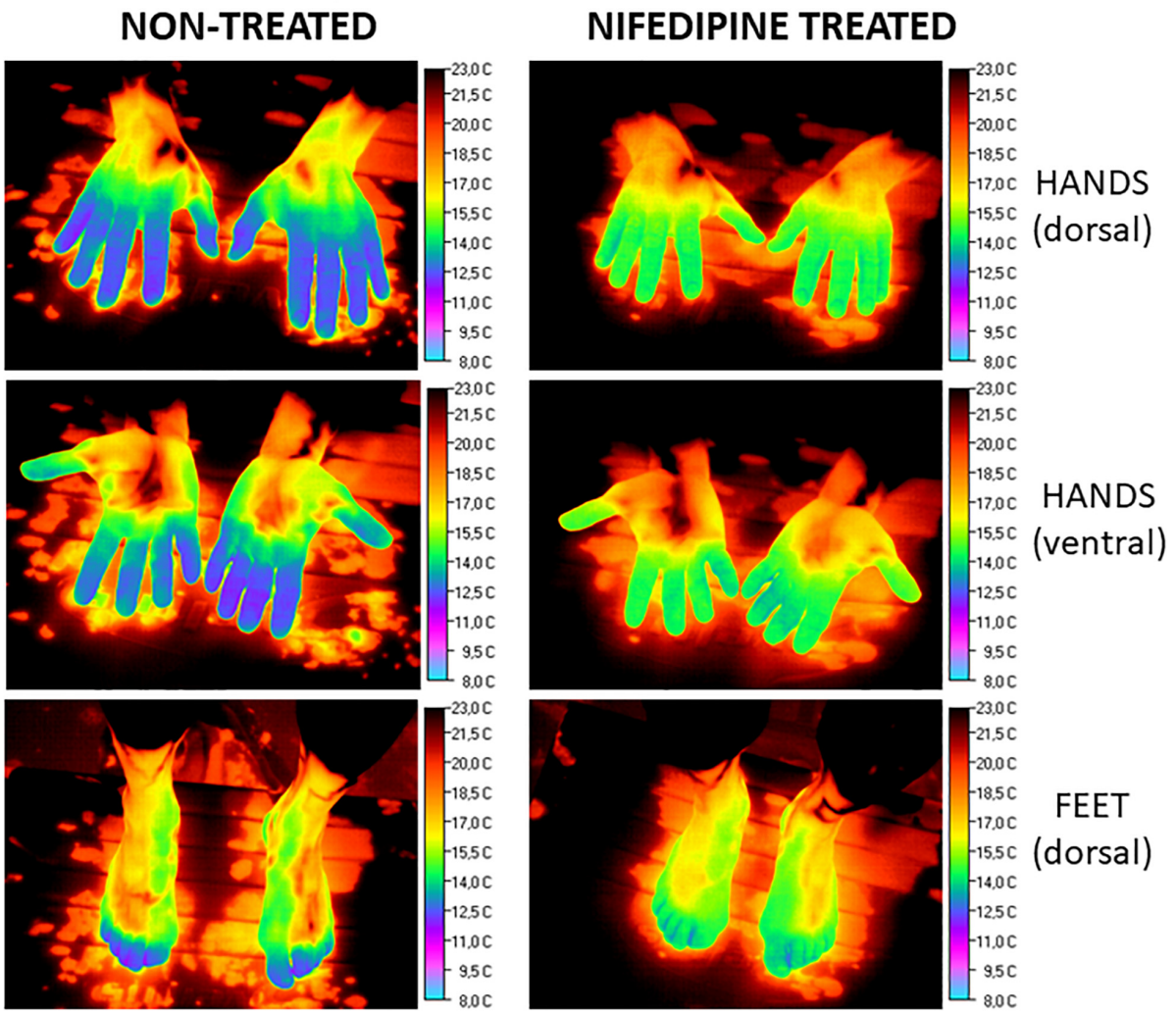

FIGURE 3 | Comparative effect after the third immersion (Subject 3) of nifedipine on the superficial temperature of hands (dorsal and ventral view) and feet. Images obtained without nifedipine treatment are on the **left**. The **right** panel shows the images registered after nifedipine treatment. Temperature scale (°C) is on the **right** of each picture.

after maximal cooling, healthy digits were significantly less cold after application of the treatment; whereas amputated digits lost more temperature when treated with the nifedipine cream (**Tables 2**, **4**).

TABLE 1 | Average temperatures (°C) of healthy or frostbitten fingers and toes under basal and maximal cooling (after third immersion) conditions, without nifedipine treatment.

		Healthy (n = 47)	Frostbitten (n = 43)	p
Fingers	Basal	33.1 ± 1.9	33.2 ± 0.9	NS
	Maximal cooling	13.9 ± 1.2	14.9 ± 0.2	0.04
Toes	Basal	33.1 ± 2.2	34.2 ± 0.5	0.04
	Maximal cooling	12.3 ± 3.8	14.1 ± 0.9	0.04

Regarding toes, significant differences were only reached in healthy digits when the basal measurement was performed, with those toes that did not receive treatment being warmer. Amputated toes, after nifedipine topical cream application, were significantly cooler both in basal measurements and after maximal cooling (**Tables 3**, **4**).

DISCUSSION

Frostbite is a cold-related pathology that involves local cell damage and ischemia, being especially frequent in digits, due to its distal location. We found different thermal responses during fast cooling between hands and feet: hands being warmer, especially the thumb. In toes, the biggest one was the coldest.

TABLE 2 | Effects of the treatment with nifedipine on the temperature (°C) of fingers (average for both hands) considering digit condition.

	Basal			Maximal cooling		
	HD (*n* = 47)	**FNA (*n* = 35)**	**FA (*n* = 8)**	**HD (*n* = 47)**	**FNA (*n* = 35)**	**FA (*n* = 8)**
No Treatment	33.1 ± 1.9	33.6 ± 1.4	33.1 ± 0.9	13.9 ± 1.2	14.9 ± 2.0	14.9 ± 0.4
Nifedipine	27.4 ± 3.5	34.1 ± 0.8	33.1 ± 0.3	14.3 ± 0.7	13.1 ± 0.6	12.8 ± 0.8
p-value	ns	**0.007**	ns	**0.0009**	ns	**0.036**

All measurements are mean ± SD. HD, healthy digits; FNA, frostbitten non-amputated; FA, frostbitten with amputation. Bolded values are statistically significant ($p < 0.05$).

TABLE 3 | Effects of nifedipine treatment on the temperature (°C) of toes (average for both feet) considering digit condition.

	Basal			Maximal cooling		
	HD (*n* = 47)	**FNA (*n* = 35)**	**FA (*n* = 8)**	**HD (*n* = 47)**	**FNA (*n* = 35)**	**FA (*n* = 8)**
No treatment	33.1 ± 2.2	31.1 ± 2.7	34.1 ± 0.5	12.3 ± 1.1	12.6 ± 1.6	14.1 ± 0.8
Nifedipine	21.3 ± 0.4	23.7 ± 4.7	25.7 ± 4.4	13.2 ± 1.3	12.7 ± 0.8	12.3 ± 0.8
p-value	**0.00001**	ns	**0.0009**	ns	ns	**0.008**

All measurements are mean ± SD. HD, healthy digits; FNA, frostbitten non-amputated; FA, frostbitten with amputation. Bolded values are statistically significant ($p < 0.05$).

TABLE 4 | Effects of nifedipine treatment on the drop in temperature (°C) of fingers and toes from the basal condition (without nifedipine treatment) after the first (1st), second (2nd), and third (3rd) immersions.

			No treatment			Nifedipine		
	Position	**Immersion**	**HD (*n* = 47)**	**FNA (*n* = 35)**	**FA (*n* = 8)**	**HD (*n* = 47)**	**FNA (*n* = 35)**	**FA (*n* = 8)**
Hands	Dorsal	Basal	–	–	–	−7.2 ± 1.7	−1.1 ± 1.7	0.4 ± 0
	Ventral		–	–	–	−6.4 ± 1.0	−0.3 ± 3.2	−0.5 ± 0
Feet	Superior		–	–	–	−11.0 ± 2.6	−7.8 ± 4.5	−10.6 ± 4.1
Hands	Dorsal	1st	−16.3 ± 2.0	−17.5 ± 2.4	−12.8 ± 0	−8.9 ± 0.0	−15.9 ± 2.1	−14.2 ± 0
	Ventral		−15.8 ± 1.5	−15.4 ± 1.9	−15.4 ± 0	−8.9 ± 0.3	−15.7 ± 0.9	−15.6 ± 0
Feet	Superior		−15.9 ± 2.4	−15.4 ± 1.4	−15.4 ± 2.3	−6.1 ± 1.8	−8.4 ± 3.0	−7.0 ± 2.8
Hands	Dorsal	2nd	−18.4 ± 1.6	−19.4 ± 2.0	−16.8 ± 0	−10.4 ± 0.3	−18.0 ± 1.8	−18.8 ± 0.0
	Ventral		−17.3 ± 1.0	−18.5 ± 2.3	−18.6 ± 0	−10.4 ± 0.1	−19.0 ± 2.4	−19.7 ± 0.0
Feet	Superior		−19.0 ± 2.8	−18.9 ± 2.9	−19.2 ± 1.0	−7.8 ± 2.0	−11.2 ± 4.8	−9.3 ± 4.0
Hands	Dorsal	3rd	−11.7 ± 13.0	−14.2 ± 9.4	−17.3 ± 0.0	−11.0 ± 0.5	−19.1 ± 2.4	−19.6 ± 0.0
	Ventral		−10.9 ± 12.7	−13.8 ± 3.9	−19.2 ± 0.0	−11.1 ± 0.1	−18.2 ± 2.6	−21.1 ± 0.0
Feet	Superior		−15.3 ± 10.2	−14.6 ± 11.1	−20.8 ± 1.5	−8.0 ± 1.7	−12.2 ± 6.2	−10.7 ± 5.1

HD, healthy digits; FNA, frostbitten non-amputated; FA, frostbite with amputation; NFD, treated with nifedipine; NOT, no treatment.

Applying a topical preparation of nifedipine leaded to lower digit temperatures in healthy tissues when not exposed to cold, both in hands and toes. Use of topical nifedipine can therefore be considered as unsafe in the absence of cold stress, as it impairs the normal thermoregulatory systems of healthy limbs. This can be extrapolated to amputated toes that conserve the neurovascular system intact. Conversely, regarding the cold response of healthy fingers, we found significantly warmer temperatures when using nifedipine. Regarding toes exposed to the cold, a detrimental effect was found in amputated limbs.

Exposure of a person to cold temperatures implies peripheral vasoconstriction in order to reduce heat loss and maintain core temperature. Vasoconstriction can be as severe as to induce cell death in those distal parts that are non-essential for survival, especially hands and feet, and implies ineffective maintenance of distal local temperature. If central temperature is preserved sufficiently but a part of the body is exposed without protection, frostbite can develop as a local injury not related to systemic defense mechanisms. In both situations, the human capacity to sense the cold and the subsequent ethological active protection responses against it are far more efficient than the physiological capacity of the organism to fight low temperatures by thermogenesis.

Cold sensing is a complex phenomenon involving diverse neural pathways, which vary depending on whether the thermal response is normal or pathological (Yin et al., 2015; Lolignier et al., 2016). In this regard, and considering normal responses to cold, we found differences in the thermal response of hands and

feet after three immersions in cold water (8°C). Fingers showed greater temperatures than toes under all conditions, including basal and immersions. This agrees with previous observations, in which feet were less able to retain heat, mainly because of the greater surface area-to-mass ratio in hands than in feet, and the fact that muscular production of heat in the feet is almost absent (Johnson and Kellogg, 1985; Taylor et al., 2014). We also found a different anatomical pattern of cooling, as the thumbs were significantly more capable of maintaining heat than the other fingers. There was no parallel condition for feet, as the first toe showed lower temperatures than the fifth. This is in agreement with clinical observations of the incidence of frostbite in hands and feet, and may be useful in designing prevention strategies against frostbite regarding clothing and cold protection.

On the other hand, pathological cold pain is considered a neuropathic syndrome and involves cold hyperalgesia, pain response to innocuous temperatures and increased pain sensitivity to cold, which are a nearly universal sequelae after frostbite. In the vast majority of the cases, pathological cold pain implies nerve injury or dysfunction. The vascular system also seems to play an important role in pathological cold sensitivity. Mechanisms underlying vasoconstriction during acute cold exposures involve inhibition of the NO system in the vascular endothelium and increased sympathetic activity in the smooth muscle, with high inter-individual variability. Observations in patients with digit transplantation after trauma show that cold sensitivity is a frequent sequela, implying a persistent vasoconstriction pattern with local temperature changes (Isogai et al., 1995) regardless of the extent of nerve and vascular reconstruction. Presumably this is caused by reduced skin vessel density in the fingertips and abnormalities in vasoactive responses (Klein-Weigel et al., 2007). In the same way, botulinum toxin has been reported to be an effective treatment for frostbite sequelae, as it causes vasodilation, blocking the smooth muscle or sympathetic vasoconstriction, with clinical effects both on pain and hypersensitivity (Norheim et al., 2017).

Putting it all together, it is possible that endothelial damage secondary to frostbite may lead to abnormal vasoconstriction during cold exposure of the digits, and that the local nerve injury caused by deep freezing might play a role in the nearly universal sequelae found in these patients.

The clinical translation of the above mentioned phenomena are neurosensory (pain, cold sensitivity and numbness), vascular (increased peripheral acute vasoreactivity, changes in skin color) and musculoskeletal symptoms (joint pain) with heterogeneous manifestations and role which make it difficult to establish an universal treatment (Blair et al., 1957). In addition, cold injuries do not have to be severe to cause long-term sequelae (Taylor et al., 1989). If these alterations lead to lower digit temperatures, thus increasing the risk of re-freezing in any conditions is still unknown. In previous observations, toe stumps secondary to amputation after frostbite show lower digit temperatures when exposed to cold than healthy toes; but results regarding rewarming times are inconsistent (Morrison et al., 2015; Gorjanc et al., 2018). Conversely, our results show no significant differences between basal and maximal cooling temperatures when comparing healthy and previously frostbitten tissue. It is important to remark that amputated digits lost less temperature in our experiment than those that suffered previous frostbite but are fully conserved. This can be interpreted as a consequence of the neurosensory deficit and vascular damage derived of amputation of the non-viable tissue, which was conserved in patients that do not need surgical treatment. In these latter cases, the endothelial and neural dysfunction would remain, leading to cooler temperatures of the digits and clinical manifestations.

There are also dissimilarities to have in mind when considering the different clinical conditions in response to the topical administration of nifedipine. Nifedipine is a dihydropyridine derivative, which exhibits antagonist effects on calcium channels. Dihydropyridines are widely used as arterial-specific vasodilators of peripheral resistance arteries that block calcium influx into arterial-wall smooth muscle and cause generalized vasodilation (Weiner, 1988; Triggle, 2003; Safak and Simsek, 2006). Oral nifedipine formulations have been investigated as a treatment for diabetic ulcers, peripheral vascular diseases (Rirash et al., 2017), wound healing and hypertrophic scars (Yamamoto et al., 2010; Santis et al., 2013), with moderate evidence of effectiveness. Such oral preparations are associated with secondary systemic effects such as low systemic blood pressure and edema, and have not shown better results than placebos when treating peripheral cold-related injuries such as chilblains (Souwer et al., 2016). Therefore, we decided to use a topical Vaseline®-based preparation of nifedipine at 10% concentration, which we considered a sufficient dosage to induce local vascular action while avoiding clinical systemic symptoms. Digit skin temperature is correlated to skin blood flow (Rubinstein and Sessler, 1990), so measurements of skin temperature after a cold stress test are valid for evaluating the vascular response to cold. We evaluated the local temperature by means of infrared thermography, as it is widely used to assess skin temperature in various conditions and is suggested as a predictive tool to identify peripheral susceptibility to cold, in accordance with digital rewarming times (Brandstrom et al., 2008; Keramidas et al., 2014). This technique is non-invasive and avoids the use of ionizing radiation. The differences found were focused on the clinical translation of the use of nifedipine in means of temperature and vascular response, but the degree of concomitant effect of an eventual neural impairment was not elucidated and can be an interesting starting point for future observations.

Taking in to account the difference in the thermal responses of hands and feet, we analyzed the data on the response to nifedipine treatment also separately. Interestingly, we found lower basal temperatures in both healthy and amputated toes, when treated with nifedipine. Probably, the vasodilator effect of the local treatment in HD leads to skin temperature loss in a thermoneutral environment. Conversely, basal temperatures in FNA were warmer when nifedipine was applied, with significant differences in the hands. This was not reproduced in toes, which otherwise presented significantly lower temperatures in amputated limbs when using nifedipine. It is an interesting hypothesis that this effect implies that, at mild temperatures, nifedipine could be useful for those patients who previously

suffered frostbite without amputation. This question could be addressed and resolved in future clinical research.

Regarding maximal cooling responses, HD were warmer when treated with nifedipine in the hands but not in the toes. FA digits showed significantly lower temperatures when treated with nifedipine. In toes, skin temperature tended toward being lower when applying nifedipine in all conditions, but only in amputated toes did this reach statistical significance.

We found topical nifedipine application can be considered as inadequate at basal temperatures, except in previously frostbitten digits which have not suffered amputation, as normal and conserved thermoregulatory systems of healthy and amputated tissues are impaired by the vasodilation effect. This can be extrapolated to those amputated toes that conserve the neurovascular system intact. At maximal cooling, whereas HD benefit from topical nifedipine, especially in the hands, amputated digits and toes universally failed to respond to the nifedipine application.

LIMITATIONS OF THIS STUDY

We have taken basal temperatures as the control condition for each subject instead of study a second control group of healthy people. Since all recruited subjects keep healthy fingers, in our opinion, the treatment with nifedipine of another group of healthy subjects would not have provided additional information. Another limitation is the small sample size (only five subjects), so further investigations are required to confirm and reinforce our findings. Finally, this study focus on the clinical impact of nifedipine regarding local temperature changes, but we cannot elucidate if the observed differences in thermal behavior are due to neurosensory or vasomotor deficits derived from previous cold damage.

CONCLUSION

Topical nifedipine can be considered as a potentially interesting tool for healthy digits exposed to cold, as it leads to warmer temperatures as long as thermal insulation measures are adequate. Further research is needed to clarify whether, at mild cold temperatures, topical nifedipine application is useful in previously frostbitten tissue with no amputation. However, the potentially harmful effects of this treatment on amputations, both of hands and feet, and on healthy tissues of feet when exposed to cold, should be considered.

The differences observed on individual regional response to cold must be taken in consideration to the design of prevention strategies for subjects habitually exposed to cold environment. Thermography can be a useful, and easy to apply tool, for starting this initiative.

DATA AVAILABILITY STATEMENT

The dataset generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

This study was carried out in accordance with the Spanish regulations and the protocol was approved by the Institutional Ethical Committee from the University of Barcelona (Institutional Review Board number #IRB00003099). All subjects gave written informed consent and all procedures were in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

AC and GV conceived the study and performed the statistical analysis of the data. AC and JG planned and carried out the experiment. JG computed the images and extracted data from the thermography images. AC took the lead in writing the manuscript. All authors contributed to the interpretation of the results, provided critical feedback on drafts, helped to shape the research report, approved the manuscript in its final form prior to submission, and contributed substantially to this report.

ACKNOWLEDGMENTS

We are grateful to the participants in this study for their enthusiasm and commitment. We also want to thank Diego Marro Ramón for preparation of the topical nifedipine treatment. We thank to Dr. Christopher Evans (Servei de Assessorament Lingüístic, Universitat de Barcelona) for his help in editing the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2020.00695/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

5. Informe de los directores de la tesis doctoral sobre el impacto de las publicaciones

Los doctores Casimiro Javierre Garcés y Ginés Viscor Carrasco, como directores de la Tesis Doctoral presentada por Anna Carceller Mallada, hacen constar que la doctoranda ha participado activamente en los artículos que forman esta memoria, tal como queda reflejado en el orden y composición del conjunto de autores en cada uno de ellos. La doctoranda ha jugado un papel fundamental en el diseño experimental y en el tratamiento de los datos en todos los estudios que constituyen el núcleo de su tesis. También ha tenido el protagonismo principal en el proceso de difusión, publicación de los resultados y conclusiones, es decir, en la presentación de avances en diversos congresos y reuniones científicas y en la redacción de los manuscritos y en el proceso de revisión por pares.

Los índices de impacto (IF) de las publicaciones que se han aceptado o se han enviado los artículos que conforman esta tesis son los siguientes:

1. **Título de la publicación:** "Topical nifedipine administration for secondary prevention in frostbitten patients"

Autores (p.o. de firma): Anna Carceller, Juan Pedro González Torcal, Ginés Viscor

Revista: Frontiers in Physiology

Volumen: 11 **Páginas:** e00695 **Año:** 2020 **ISSN:** 1664-042X

Participación del doctorando: Participación en el reclutamiento de los sujetos y en la exploración física y recogida de imágenes termográficas. Realización de los análisis descritos en el manuscrito. Redacción del borrador, participación en la redacción del manuscrito y su aprobación final y en la revisión por pares.

I.F. (2019): 3.367 **5 years I.F.** (2019): 3.697

Rank (2019): 20/81 (Q1 - Physiology)

Times cited: No aplicable

2. **Título de la publicación**: "Amputation risk factors in severely frostbitten patients"

Autores (p.o. de firma): Anna Carceller, Casimiro Javierre, Martín Ríos, Ginés Viscor

Revista: International Journal of Environmental Research and Public Health

Volumen: 16 **Número:** 8 **Páginas:** e1351 **Año:** 2019 **ISSN:** 1660-4601

Participación del doctorando: Participación en el diseño de la encuesta, reclutamiento de los sujetos y en la recogida de datos. Realización de los análisis descritos en el manuscrito. Redacción del borrador, participación en la redacción del manuscrito y su aprobación final y en la revisión por pares.

I.F. (2019): 2.849 **5 years I.F.** (2019): 3.127

Rank (2019): 32/170 (Q1 – Public, Environmental and Occupational Health)

Times cited: 0

3. **Título de la publicación**: "Differences in Cardiorespiratory Responses in Winter Mountaineering According to the Pathway Snow Conditions"

Autores (p.o. de firma): Anna Carceller, Casimiro Javierre, Jordi Corominas, Ginés Viscor.

Revista: High Altitude Medicine and Biology

Volumen: 20 **Número:** 1 **Páginas:** 89-93 **Año:** 2019 **ISSN:** 1557-8682

Participación del doctorando: Participación en el reclutamiento de los sujetos y en la exploración física, pruebas de esfuerzo en el laboratorio y dirección logistica y recogida de muestras en el terreno. Realización de los análisis descritos en el manuscrito. Redacción del borrador, participación en la redacción del manuscrito y su aprobación final y en la revisión por pares.

I.F. (2019): 1.430 **5 years I.F.** (2019): 1.751

Rank (2019): 144/19370 (Q3) Public, Environmental and Occupational Health; 1533/2176 (Q3) Clinical Medicine

Times cited: 0

4. **Título de la publicación**: "Frostbite: management update"

Autores (p.o. de firma): Anna Carceller, Manuel Avellanas, Javier Botella, Casimiro Javierre, Ginés Viscor.

Revista: Archivos de Medicina del Deporte

Volumen: 34 **Número:** 6 **Páginas:** 345-352 **Año:** 2017 **ISSN:** 1660-4601

Año: 2017 **ISSN:** 0212-8799

Participación del doctorando: Participación en el análisis y discusión de la temática abordada en el manuscrito. Colaboración en la redacción del manuscrito y su aprobación final y en la revisión por pares.

I.F. (2017): No consta **5 years I.F.** (2016): No consta

Scimago SJR (2017): 0.117

Scimago **Rank** (2017): (Q4) Sport Sciences

Times cited: N/A

5. **Título de la publicación**: "Drug Use and Misuse in the Mountains: A UIAA MedCom Consensus Guide for Medical Professionals"

Autores (p.o. de firma): Enrico Donegani,, Peter Paal, Thomas Kupper, Urs Hefti, Buddha Basnyat, Anna Carceller, Pierre Bouzat, Rianne van der Spek, David Hillebrandt.

Revista: High Altitude Medicine and Biology

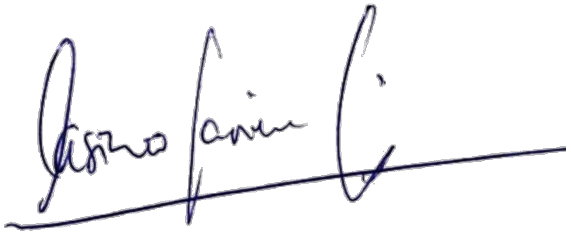
Volumen: 17 **Número:** 3 **Páginas:** 157–184 **Año:** 2016 **ISSN:** 1557-8682

Participación del doctorando: Participación en el análisis y discusión de la temática abordada en el manuscrito. Colaboración en la redacción del manuscrito y su aprobación final y en la revisión por pares.

I.F. (2016): 1.705 **5 years I.F.** (2016): 1.857

Rank (2019): 40/81 (Q2) Sport Sciences; 98/176 (Q3) Public, Environmental and Occupational Health; 1301/2029 (Q3) Clinical Medicine

Times cited: 9



Dr Ginés Viscor Carrasco

Dr. Casimiro Javierre Garcés

Directores de la tesis doctoral

6. Resumen global de resultados

Actualmente, se calcula que alrededor de 100 millones de personas al año se desplazan a terrenos montañosos por ocio. Aunque la actividad física está relacionada con muchos beneficios para la salud, los deportes de montaña se asocian a cierto riesgo de lesión, accidente o muerte. Al tratarse de un deporte exigente que se lleva a cabo sobre un terreno complejo, asociado a riesgos objetivos y subjetivos, existe cierta preocupación para estratificar el riesgo y establecer estrategias de seguridad, en especial en lo que se refiere a la exposición al frío y a la altitud.

Considerando el tiempo de exposición, uno de los objetivos de esta tesis es dilucidar la diferencia entre un ascenso por nieve virgen o por una ruta previamente pisada (ver publicación 4). Este hecho tiene implicaciones directas en una buena estrategia en la escalada, en cuanto a que los miembros de una misma cordada pueden realizar rotaciones durante el ascenso o repartirse diferente el peso en sus mochilas en función de si lideran el grupo (abren traza) o no. Por otro lado, en el momento de la preparación de una ruta o en la planificación de un rescate, resulta muy interesante conocer los tiempos estimados de progresión, como una de las herramientas básicas de seguridad.

En este mismo estudio, observamos que el progresar sobre nieve virgen resulta un 12% más costoso energéticamente a intensidades máximas y un 11% a intensidades submáximas que el hacerlo sobre nieve con una traza establecida. Considerando que de forma prácticamente universal los alpinistas se encuentran en un balance energético negativo durante la mayor parte de las expediciones, resulta importante considerar que si la ruta de ascenso es de exploración, por una vía poco concurrida o sobre la que ha nevado recientemente, los requerimientos energéticos del deportista que lidere el grupo serán mayores a los del resto, asumiendo que el resto de variables que condicionan su balance energético fueran iguales entre los diferentes individuos. Así, cabría esperar un mayor grado de fatiga y de necesidades hídricas y energéticas en el sujeto que se encuentre abriendo la traza, siendo la rotación entre los diferentes miembros de la expedición o la gestión de las cargas en las mochilas elementos a tener en cuenta para equilibrar la fatiga. De forma paralela, observamos que los tiempos de progresión aumentan en nieve virgen, prácticamente en 430 metros/hora en ejercicio máximo y de 500 metros/hora en ejercicio submáximo, por lo que los tiempos de ascenso estimados en nieve virgen deben preverse más largos que en nieve compacta, en concreto, y considerando las características de la pendiente donde realizamos el estudio, un 13% a esfuerzos máximos y un 16% en submáximos.

Así, la potencia que el alpinista puede desarrollar andando por nieve pisada es considerablemente mayor que por nieve virgen.

Los consumos máximos de oxígeno fueron mayores durante el ascenso por dentro de la traza a intensidad máxima, lo que sugiere que no se consigue desarrollar la potencia aeróbica máxima por una limitación periférica.

Las explicaciones más plausibles a este hecho pueden ser 1) el aumento de los requerimientos biomecánicos del ascenso por nieve virgen, que requiere una mayor flexión de rodilla y de cadera al tener que vencer el espesor de nieve durante la locomoción, 2) la pérdida del componente elástico de rebote por el hecho de que el pie se hunde en la nieve durante el apoyo y 3) la adopción de posturas ineficientes biomecánicamente con objeto de mantener el equilibrio.

La forma física para solventar las altas demandas energéticas del alpinismo se considera uno de los pilares básicos en cuanto a la seguridad en montaña. A pesar de que la forma más práctica y precisa de estimar la potencia aeróbica es la calorimetría indirecta en una prueba de esfuerzo con análisis de gases, cuando cruzamos los datos de campo con los resultados de las ergometrías en el laboratorio vimos que existe una correlación franca entre los tiempos en recorrer el trazado pisado al 100% de la intensidad máxima con el consumo máximo de oxígeno medido en la ergometría. Esto nos permite tener un test de campo para la valoración de la potencia aeróbica máxima en los alpinistas.

$$VO2max = 110.9 - 11.73 * t$$

Siendo t el tiempo que tarda en completar el ascenso por dentro de la traza a intensidad máxima.

Por otra parte, los factores que impliquen el pasar más tiempo expuestos a las bajas temperaturas favorecerán la aparición de patologías derivadas del frío. Como se ha comentado con anterioridad, el retraso en alcanzar la cumbre es uno de los principales factores de riesgo para sufrir una eventualidad en montaña. Se ha comprobado que el tiempo de exposición al frío es un factor más agravante que la temperatura absoluta alcanzada en el caso de las congelaciones (ver publicación 1). Así, y en base a nuestras observaciones, un ascenso por nieve no pisada aumentará el tiempo de exposición al frío y, con ello, el riesgo de sufrir patología derivada. En otro estudio (ver publicación 5), y siguiendo esta línea, realizamos un análisis mediante termografía infrarroja sobre la respuesta en diferentes tejidos (sanos, congelados no amputados y congelados amputados) de una crema tópica con un 10% de nifedipino. Observamos una respuesta térmica distinta según las diferentes zonas en manos y pies, siendo las manos más calientes, y en especial el primer dedo. En el caso de los pies, y acorde también a las observaciones clínicas, el primer dedo fue el más frío en todas las condiciones.

Estas observaciones ponen de manifiesto la distribución regional de la respuesta al frío y pueden ser germen de medidas preventivas específicas para aquellas zonas más susceptibles, disminuyendo así el riesgo de lesión. El porqué de esta distribución anatómica no está claro todavía: puede deberse al índice superficie/volumen del primer dedo, o bien a que es el que más pérdida de calor sufre por conducción y microtraumatismos en un ascenso de puntas.

En base a las propiedades vasodilatadoras del nifedipino, diseñamos una crema con base de vaselina para aplicar en las zonas más susceptibles de sufrir congelaciones, como son las manos y los pies, con objeto de valorar la respuesta térmica regional. La vasodilatación provocada por la aplicación de la crema originó una disminución de la temperatura en los tejidos sanos y en los amputados cuando estaban expuestos a temperatura neutra. Esto puede justificarse en base a que el nifedipino impide la respuesta fisiológica de protección frente al frío de los tejidos sanos, asumiendo que en los muñones la afectación microvascular no existe ya que el tejido afecto se

retira de forma quirúrgica. En el caso de los dedos de las manos, el nifedipino ayudó a prevenir el estrés térmico en el caso de las zonas sanas y aquellas que previamente se habían congelado pero que no precisaron de amputación, así que podría ser un buen punto de partida para posteriores investigaciones sobre el uso de este preparado de forma tópica y su perfil de seguridad sobre el terreno. Contrariamente a estas observaciones, la aplicación del nifedipino en los pies, en cualquiera de las situaciones (tejido sano, congelado no amputado y amputado) supuso una disminución de la temperatura, por lo que probablemente tenga efectos perjudiciales en los miembros inferiores.

Otro factor a tener en cuenta en las actividades en montaña es el retraso en la atención médica. Esto se pone de manifiesto en varios aspectos relacionados con el riesgo: por una parte, según un estudio descriptivo que llevamos a cabo con 92 pacientes afectos de congelaciones, uno de los factores más favorables a la necesidad de amputación fue el retraso en recibir la primera atención a la lesión (ver publicación 2) añadido a que, de forma paralela, la probabilidad de tener una congelación grave con posterior necesidad de cirugía aumentaba de forma franca con la altitud.

Ahora bien, el aumento del riesgo de amputación con la altitud no es meramente debido a la hipoxia hipobárica sino que es multifactorial, añadiendo probablemente a la respuesta vasoconstrictora frente al frío y a la altitud, el deterioro del organismo y el retraso en realizar el primer recalentamiento rápido (según nuestras observaciones, de 23,6 horas en aquellos alpinistas que posteriormente no precisaron amputación y de 48 horas en los que la gravedad de la lesión lo requirió). La relación fue tan fuerte, que pudimos desarrollar una fórmula matemática de predicción de amputación basado sólo en el factor altura:

$$(AI) = -4.04446 + 0.000535925 * altitud\ (expresada\ en\ metros)$$

El desarrollo de este tipo de modelos es de utilidad para estratificar el riesgo y diseñar las estrategias de seguridad en una expedición; según los datos de los que disponemos hasta ahora, un sujeto que sufre una congelación a 7547 metros de altitud tiene las mismas probabilidades de ser amputado que de no serlo. Si la congelación ocurre por encima de los 8573 metros, la probabilidad es del 100%. Así, la prevención farmacológica y logística puede ajustarse al mejor conocimiento de la exposición al riesgo.

Por último, desde la Unión Internacional de Asociaciones de Alpinismo se redactó un documento de consenso acerca del uso (y mal uso) de fármacos en montaña (ver publicación 3), cuyo objetivo fue mejorar el conocimiento de los alpinistas y los prescriptores al respecto de los fármacos (profilácticos o terapéuticos) en base a la información científica disponible en el momento: perfiles de seguridad, efectos secundarios, indicaciones, contraindicaciones, riesgos e interacciones.

7. Discusión

La popularidad de los deportes de montaña conlleva un incremento del número de sujetos expuestos a condiciones ambientales adversas, como son el frío y la altitud. Actualmente, se calcula que alrededor de 100 millones de personas al año se desplazan a terrenos montañosos por ocio (88). Aunque la actividad física está relacionada con muchos beneficios para la salud, los deportes de montaña se asocian a cierto riesgo de lesión, accidente o muerte. El uso de sistemas de rescate helitransportados ha aumentado en la mayoría de cordilleras del mundo (89), siendo el principal motivo de rescate las caídas. Al tratarse de un deporte exigente que se lleva a cabo sobre un terreno complejo, asociado a riesgos objetivos y subjetivos, existe cierta preocupación para estratificar el riesgo y establecer estrategias de seguridad, en especial en lo que se refiere a la exposición al frío y a la altitud (90,91).

Los principales factores de riesgo asociados con la morbimortalidad, en especial en altitud, son la fatiga y el retraso en llegar a la cumbre (77). Otro aspecto a tener en cuenta es el de la exposición al medio: en la cascada de hielo del Khumbu, en la ruta sur al Everest, la mayor parte de las muertes son de trabajadores Sherpas, que al equipar las rutas se exponen durante más tiempo a los peligros objetivos de la montaña (92); en varias publicaciones, se describe un aumento del riesgo de accidente asociado a la mayor experiencia en montaña (94,95), incluido el riesgo de sufrir congelaciones severas que requieren amputación (ver publicación 2) probablemente debido a que los alpinistas con más experiencia asumen proyectos con mayores riesgos objetivos, acumulan más horas expuestos y quizá se muevan a más altitud.

Considerando el tiempo de exposición, uno de los objetivos de esta tesis es dilucidar la diferencia entre un ascenso por nieve virgen o por una ruta previamente pisada. Este hecho tiene implicaciones directas en una buena estrategia de ascenso, en cuanto a que los miembros de una misma cordada pueden realizar rotaciones durante el ascenso o repartirse diferente el peso en sus mochilas en función de si lideran el grupo (abren traza) o no. Por otro lado, en el momento de la preparación de una ruta o en la planificación de un rescate, resulta muy interesante conocer los tiempos estimados de progresión, como una de las herramientas básicas de seguridad. Así, durante la locomoción en ascenso, la frecuencia de pisada aumenta de forma proporcional a la pendiente, incrementando el trabajo mecánico de las extremidades inferiores y con una fase aérea mucho menor que cuando la progresión se realiza en terreno llano (96,97).

Los apoyos se vuelven más anteriores en el pie (98), hasta alcanzar la progresión de puntas cuando la pendiente deja de poder superarse en bipedestación y debe ser escalada.

Jordi Tosas progresa de puntas en una arista en los Alpes

El estrés articular es mayor durante el ascenso, especialmente en la cadera, lo que provoca un aumento del coste energético en la progresión (99). De esta forma, el ascenso implica un mayor consumo de oxígeno, gasto metabólico y actividad muscular que la locomoción en llano, y su correcto manejo biomecánico radica en el desarrollo de una correcta activación muscular específica para esta tarea (100). Por ello, los alpinistas deben adaptar su estrategia neuromuscular para disminuir el gasto metabólico que supone progresar en ascenso, máxime si este se realiza con carga en la espalda.

Añadido a lo previo, se estima que un mismo ejercicio físico realizado en terreno nevado aumenta en un 20% su coste energético (101) y que la altitud tiene un efecto perjudicial sobre la función muscular (102).

En este estudio (ver publicación 4), observamos que el progresar sobre nieve virgen resulta un 12% más costoso energéticamente a intensidades máximas y un 11% a intensidades submáximas que el hacerlo sobre nieve con una traza establecida. Considerando que de forma prácticamente universal los alpinistas se encuentran en un balance energético negativo durante la mayor parte de las expediciones, resulta importante considerar que si la ruta de ascenso es de exploración, por una vía poco concurrida o sobre la que ha nevado recientemente, los requerimientos energéticos del deportista que lidere el grupo serán mayores a los del resto, asumiendo que el resto de variables que condicionan su balance energético fueran iguales entre los diferentes

individuos. Así, cabría esperar un mayor grado de fatiga y de necesidades hídricas y energéticas en el sujeto que se encuentre abriendo la traza, siendo la rotación entre los diferentes miembros de la expedición o la gestión de las cargas en las mochilas elementos a tener en cuenta para equilibrar la fatiga. De forma paralela, observamos que los tiempos de progresión aumentan en nieve virgen, prácticamente en 430 metros/hora en ejercicio máximo y de 500 metros/hora en ejercicio submáximo, por lo que los tiempos de ascenso estimados en nieve virgen deben preverse más largos que en nieve compacta, en concreto, y considerando las características de la pendiente donde realizamos el estudio, un 13% a esfuerzos máximos y un 16% en submáximos (ver perfil).

Perfil altitudinal del experimento (adaptado de Carceller A, Javierre C, Corominas J, Viscor G *Differences in Cardiorespiratory Responses in Winter Mountaineering According to the Pathway Snow Conditions*. High Alt Med Biol. 2019)

Jordi Corominas abre traza a unos 7000m en la “Magic Line” al K2.

Así, la potencia que el alpinista puede desarrollar andando por nieve pisada es considerablemente mayor que por nieve virgen. Es interesante tener en cuenta que el test de campo se realizó sin mochila a la espalda, por lo que los valores de potencia probablemente variarían en caso de calcularse con peso añadido en ambas situaciones.

Los consumos máximos de oxígeno fueron mayores durante el ascenso por dentro de la traza a intensidad máxima, lo que sugiere que no se consigue desarrollar la potencia aeróbica máxima por una limitación periférica.

Edurne Toro en el test de campo progresando fuera de la traza

Las explicaciones más plausibles a este hecho pueden ser 1) el aumento de los requerimientos biomecánicos del ascenso por nieve virgen, que requiere una mayor flexión de rodilla y de cadera al tener que vencer el espesor de nieve durante la locomoción (103,104), 2) la pérdida del componente elástico de rebote por el hecho de que el pie se hunde en la nieve durante el apoyo (105) y 3) la adopción de posturas biomecanicamente ineficientes con objeto de mantener el equilibrio (106).

La ruta al Montblanc, como a otras montañas concurridas, está trazada habitualmente

Este hecho podría compensarse con la adquisición de habilidades con la experiencia y con el trabajo específico de tren inferior y musculatura del "core", que permitieran un mejor control sobre la zancada y el equilibrio en estas condiciones.

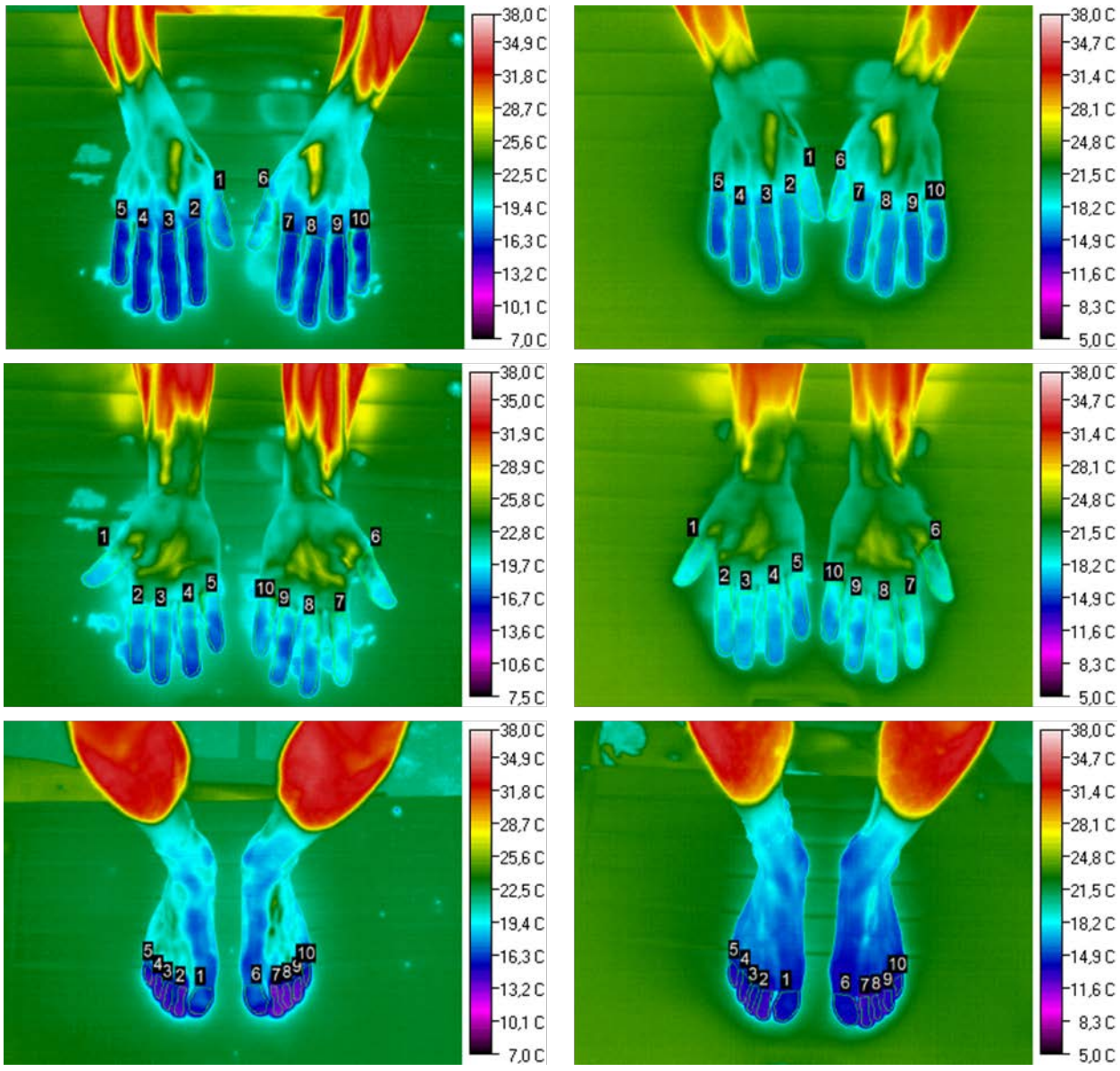
La forma física para solventar las altas demandas energéticas del alpinismo se considera uno de los pilares básicos en cuanto a la seguridad en montaña (39). A pesar de que la forma más práctica y precisa de estimar la potencia aeróbica es la calorimetría indirecta en una prueba de esfuerzo con análisis de gases, cuando cruzamos los datos de campo con los resultados de las ergometrías en el laboratorio vimos que existe una correlación franca entre los tiempos en recorrer el trazado pisado al 100% de la intensidad máxima con el consumo máximo de oxígeno medido en la ergometría. Esto nos permite tener un test de campo para la valoración de la potencia aeróbica máxima en los alpinistas.

$$VO2max = 110.9 - 11.73 * t$$

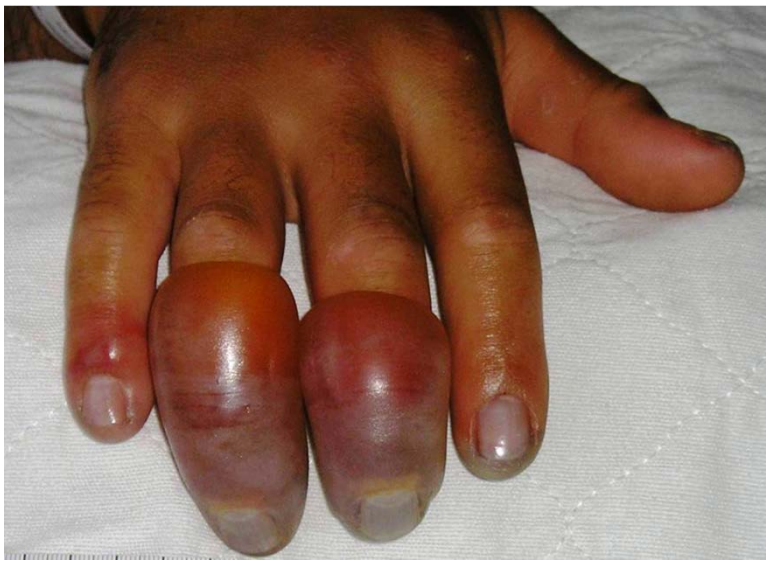
Siendo t el tiempo que tarda en completar el ascenso por dentro de la traza a intensidad máxima.

Por otra parte, los factores que impliquen el pasar más tiempo expuestos a las bajas temperaturas favorecerán la aparición de patologías derivadas del frío. Como se ha comentado con anterioridad, el retraso en alcanzar la cumbre es uno de los principales factores de riesgo para sufrir una eventualidad en montaña. Se ha comprobado que el tiempo de exposición al frío es un factor más agravante que la temperatura absoluta alcanzada en el caso de las congelaciones (107, 108) (ver publicación 1 y publicación 2). Así, y en base a nuestras observaciones, un ascenso por nieve no pisada aumentará el tiempo de exposición al frío y, con ello, el riesgo de sufrir patología derivada. En otro estudio (ver publicación 5), y siguiendo esta línea, realizamos un análisis mediante termografía infrarroja sobre la respuesta en diferentes tejidos (sanos, congelados no amputados y congelados amputados) de una crema tópica con un 10% de nifedipino. Observamos una respuesta térmica distinta según las diferentes zonas en manos y pies, siendo las manos más calientes, y en especial el primer dedo. En el caso de los pies, y acorde también a las observaciones clínicas, el primer dedo fue el más frío en todas las condiciones.

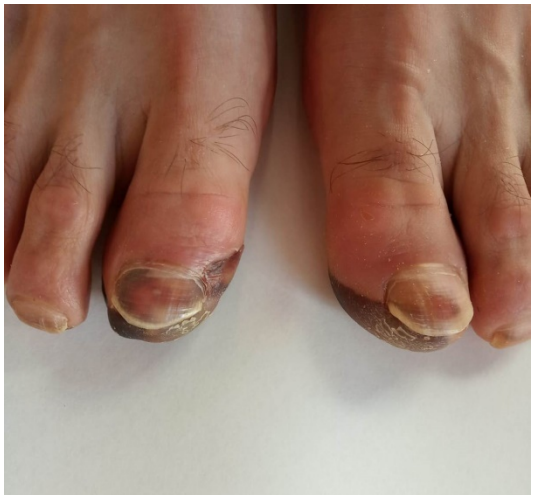
SIN NIFEDIPINO	CON NIFEDIPINO

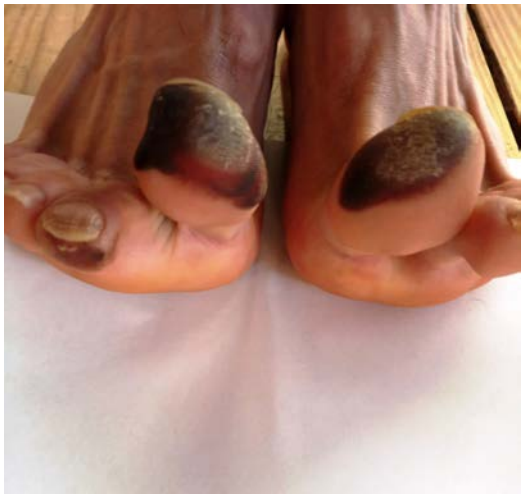


Termografía que muestra el partrón de respuesta térmica en manos y pies tras la primera inmersión, con o sin nifedipino.



Patrón anatómico de unas congelaciones en la mano, a la vuelta del Denali (Alaska)





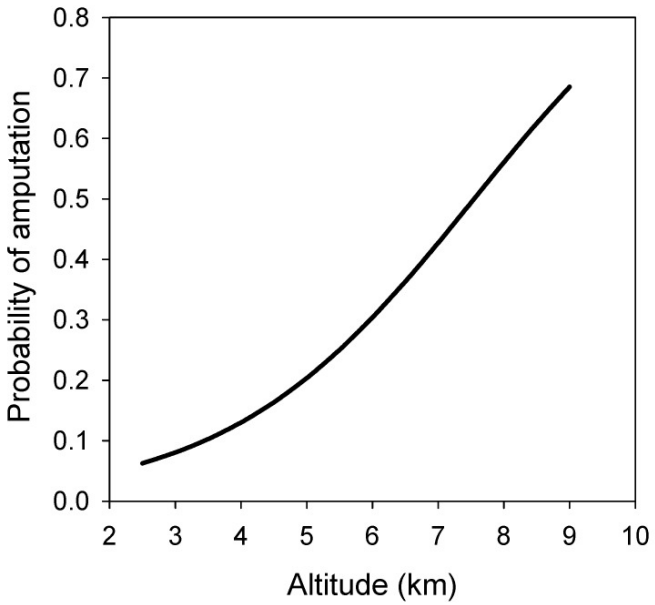
Jonatan García, en su intento a la primera invernal al Everest, sufrió congelaciones en los pies con el patrón anatómico descrito.

Estas observaciones ponen de manifiesto la distribución regional de la respuesta al frío y pueden ser germen de medidas preventivas específicas para aquellas zonas más susceptibles, disminuyendo así el riesgo de lesión. El porqué de esta distribución anatómica de las lesiones no está claro todavía: puede deberse al índice superficie/volumen del primer dedo, o bien a que es el que más pérdida de calor sufre por conducción y microtraumatismos en un ascenso de puntas.

En base a las propiedades vasodilatadoras del nifedipino, diseñamos una crema con base de vaselina para aplicar en las zonas más susceptibles de sufrir congelaciones, como son las manos y los pies, con objeto de valorar la respuesta térmica regional. La vasodilatación provocada por la aplicación de la crema originó una disminución de la temperatura en los tejidos sanos y en los

amputados cuando estaban expuestos a temperatura neutra. Esto puede justificarse en base a que el nifedipino impide la respuesta fisiológica de protección frente al frío de los tejidos sanos, asumiendo que en los muñones la afectación microvascular no existe ya que el tejido afecto se retira de forma quirúrgica. En el caso de los dedos de las manos, el nifedipino ayudó a prevenir el estrés térmico en el caso de las zonas sanas y aquellas que previamente se habían congelado pero que no precisaron de amputación, así que podría ser un buen punto de partida para posteriores investigaciones sobre el uso de este preparado de forma tópica y su perfil de seguridad sobre el terreno. Contrariamente a estas observaciones, la aplicación del nifedipino en los pies, en cualquiera de las situaciones (tejido sano, congelado no amputado y amputado) supuso una disminución de la temperatura, por lo que probablemente tenga efectos perjudiciales en los miembros inferiores.

Otro factor a tener en cuenta en las actividades en montaña es el retraso en la atención médica. Esto se pone de manifiesto en varios aspectos relacionados con el riesgo: por una parte, según un estudio descriptivo que llevamos a cabo con 92 pacientes afectos de congelaciones, uno de los factores más favorables a la necesidad de amputación fue el retraso en recibir la primera atención a la lesión (ver publicación 2) añadido eso a que, de forma paralela, la probabilidad de tener una congelación grave con posterior necesidad de cirugía aumentaba de forma franca con la altitud.



Probabilidad de amputación en función de la altitud. Adaptado de: Carceller, A, Javierre C, Ríos M, Viscor G Amputation Risk Factors in Severely Frostbitten Patients . Int J Environ Res Public Health (2019).

Ahora bien, el aumento del riesgo de amputación con la altitud no es meramente debido a la hipoxia hipobárica sino que es multifactorial, añadiendo probablemente a la respuesta vasoconstrictora frente al frío y a la altitud (109,110) el deterioro del organismo (111) y el retraso en realizar el primer recalentamiento rápido (según nuestras observaciones, de 23,6 horas en aquellos alpinistas que posteriormente no precisaron amputación y de 48 horas en los que la gravedad de la lesión lo requirió). La relación fue tan fuerte, que pudimos desarrollar una fórmula matemática de predicción de amputación basado sólo en el factor altura:

$$(\boldsymbol{AI}) = \boldsymbol{-4.04446 + 0.000535925 * altitud\ (expresada\ en\ metros)}$$

El desarrollo de este tipo de modelos es de utilidad para estratificar el riesgo y diseñar las estrategias de seguridad en una expedición; según los datos de los que disponemos hasta ahora, un sujeto que sufre una congelación a 7547 metros de altitud tiene las mismas probabilidades de ser amputado que de no serlo. Si la congelación ocurre por encima de los 8573 metros, la probabilidad es del 100%. Así, la prevención farmacológica y logística puede ajustarse al mejor conocimiento de la exposición al riesgo.

La evacuación de un alpinista herido es lenta y difícil (Dhaulagiri, ruta normal, 1991)

En definitiva, la práctica del alpinismo está sujeta a riesgos cuya prevención debe basarse en su identificación y conocimiento para poder actuar en consecuencia dentro de las posibilidades logísticas de una expedición. Los principales riesgos no traumáticos están asociados a la patología ambiental, que se muestra más agresiva de forma proporcional a la altitud y a la lejanía del socorro. La exposición al medio es, entonces, uno de los factores clave en la práctica de esta disciplina deportiva.

8. Conclusiones

General:

Es posible establecer medidas de prevención concretas para la práctica del alpinismo basadas en las observaciones de esta tesis, como el diseño de la estrategia en función de las condiciones de la nieve, la protección específica de ciertas zonas en manos y pies, la logística de socorro necesaria para un ascenso a altitud en lo que concierne a la patología por frío y la adecuación de la ingesta de medicación preventiva.

Específicas

1) La altitud, probablemente influenciada por otros factores como la lejanía y el frío, es el principal factor de riesgo para desarrollar una congelación severa que requiera amputación quirúrgica posteriormente.
2) El retraso en la primera atención a un paciente congelado más allá de las primeras 24 horas, empeora su pronóstico de forma clara.
3) El patrón térmico de manos y pies es diferente con el enfriamiento progresivo, observándose variaciones en la respuesta entre los diferentes dedos.
4) En consecuencia, los dedos de las extremidades, incluso las inferiores, tienen diferentes probabilidades de congelación.
5) Una preparación de nifedipino tópico tiene la capacidad de generar respuestas objetivables en la temperatura de los dedos, pudiendo ser útil su aplicación en dedos sanos de las manos y dedos previamente congelados sin amputación con la protección adecuada.
6) Avanzar por nieve virgen a pie supone un gasto energético mayor (1.2 ± 2.3 mL·kg·min^{-1}) a intensidades submáximas y requiere de más tiempo (12% a intensidades máximas y 11% a intensidades submáximas) que hacerlo sobre nieve pisada.
7) A intensidades máximas, progresar en nieve trazada implica poder desarrollar mayor potencia aeróbica máxima (2,6%) que sobre nieve virgen.

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