PROGRAMA DE DOCTORADO EN BIOMEDICINA

DEPARTAMENTO DE FISIOTERAPIA

FACULTAD DE CIENCIAS DE LA SALUD

UNIVERSIDAD DE GRANADA

ABORDAJE FISIOTERAPÉUTICO DE LAS ALTERACIONES VASCULARES Y SU RELACIÓN CON EL PROCESAMIENTO DEL DOLOR CRÓNICO Y LA FUNCIONALIDAD DEL MIEMBRO SUPERIOR EN PACIENTES CON FENÓMENO DE RAYNAUD

PHYSICAL THERAPY APPROACH TO VASCULAR ALTERATIONS AND THEIR RELATIONSHIP WITH THE PROCESSING OF CHRONIC PAIN AND FUNCTIONALITY OF THE UPPER LIMB IN PATIENTS WITH RAYNAUD'S PHENOMENON

UNIVERSIDAD DE GRANADA

TESIS DOCTORAL INTERNACIONA/INTERNATIONAL PhD THESIS

ROSA MARÍA TAPIA HARO

JUNIO 2019

ABORDAJE FISIOTERAPÉUTICO DE LAS ALTERACIONES VASCULARES Y SU RELACIÓN CON EL PROCESAMIENTO DEL DOLOR CRÓNICO Y LA FUNCIONALIDAD DEL MIEMBRO SUPERIOR EN PACIENTES CON FENÓMENO DE RAYNAUD

Esta tesis doctoral ha sido realizada bajo la dirección de:

Prof. Dra. Dña. María Encarnación Aguilar Ferrándiz

Departamento de Fisioterapia

Facultad de Ciencias de la Salud

UNIVERSIDAD
DE GRANADA

Editor: Universidad de Granada. Tesis Doctorales
Autor: Rosa María Tapia Haro
ISBN: 978-84-1117-167-0
URI: http://hdl.handle.net/10481/71850

A mis padres, mi hermana y mis sobrinos

ÍNDICE/ TABLE OF CONTENTS

RESUMEN

El Fenómeno de Raynaud se describe como un conjunto de síntomas producidos por un trastorno vasoespástico que suele afectar a los pequeños vasos de las zonas distales de las extremidades y que se desencadena en respuesta a diversos estímulos como la exposición al frío o el estrés emocional. Se caracteriza por una disminución aguda, transitoria y reversible del flujo sanguíneo, acompañado de un cambio de coloración de la piel y distintos niveles de dolor e impotencia funcional. Se clasifica en dos formas clásicas, Fenómeno de Raynaud primario y secundario En el Fenómeno de Raynaud, la alteración a nivel vascular debería estar relacionada con los procesos de dolor crónico, así como con menores tasas de funcionalidad. Estos aspectos, aún no se han estudiado en profundidad y no se conoce la relación que puede existir entre los niveles de daño vascular y el grado de dolor, sensibilización central y catastrofismo así como la discapacidad en las personas que padecen Fenómeno de Raynaud. Por otra parte, las terapéuticas propuestas hasta la actualidad para abordar este proceso no han demostrado tener efectos concluyentes. En este sentido, consideramos que un tratamiento mediante iontoforesis podría mejorar la sintomatología y la discapacidad de los miembros superiores en estos pacientes, con mínimos efectos secundarios; sin embargo, no hemos encontrado estudios previos que analicen la eficacia de un tratamiento de este tipo.

Los objetivos principales de esta tesis doctoral fueron: 1) Evaluar la relación entre las alteraciones vasculares y los niveles de dolor, los procesos relacionados con el desarrollo de dolor crónico (Sensibilización Central y Catastrofismo), la funcionalidad de la mano y la discapacidad de los miembros superiores en personas con Fenómeno de Raynaud. 2) Evaluar la efectividad de una intervención de electroterapia mediante iontoforesis con agua corriente, en la severidad de los síntomas vasculares, síntomas y procesos relacionados con el desencadenamiento del dolor y la discapacidad percibida a nivel de los miembros superiores en personas con Fenómeno de Raynaud.

En la presente tesis, se realizaron dos estudios observacionales y un ensayo clínico randomizado, para conseguir los objetivos anteriormente expuestos. Se incluyeron a 37 personas con Fenómeno de Raynaud y 20 controles sanos en los dos primeros estudios y 34 pacientes con Fenómeno de Raynaud en el tercero. En primer lugar, se evaluó la situación vascular analizando el patrón termográfico de las manos, la intensidad del dolor,

los niveles de mecanosensibilidad, los umbrales del dolor eléctrico, la sensibilización central y la catastrofización entre personas con Fenómeno de Raynaud primario, secundario y sujetos sanos. En segundo lugar, valoramos las alteraciones vasculares determinadas mediante la temperatura de las manos, la curva de recuperación de la temperatura, la saturación de oxígeno y el flujo sanguíneo; los rangos de movilidad y fuerza de la mano como indicadores de la funcionalidad de la mano y la discapacidad percibida en la práctica de actividades cotidianas de la vida diaria, trabajo y la práctica de deportes o actividades artísticas en personas con Fenómeno de Raynaud y sujetos sanos. Finalmente, 34 participantes con Fenómeno de Raynaud fueron asignados de forma aleatoria bien a un grupo experimental que completó una intervención mediante electroterapia con iontoforesis (n=17) o a un grupo control (n=17) que mantuvo su tratamiento habitual sin recibir intervención de electroterapia. La intervención se realizó durante 7 semanas, tres veces por semana y con una duración de 20 minutos cada sesión. Las principales herramientas de medida utilizadas fueron la temperatura de las manos, la curva de recuperación de la temperatura, la saturación de oxígenos, el flujo sanguíneo, el nivel de dolor, sensibilización central, catastrofismo y discapacidad percibida en los miembros superiores. Cada una de estas variables fue evaluada en tres momentos temporales, una evaluación basal antes de comenzar la intervención, una evaluación post-tratamiento y una evaluación de seguimiento, realizada a los dos meses de haber finalizado la intervención.

Nuestros resultados sugieren que las personas con Fenómeno de Raynaud tienen una temperatura basal de sus manos menor ($P \leq 0.012$); mayores niveles de dolor ($P \leq 0.001$) y menores umbrales de dolor a la presión ($P \leq 0.05$) que las personas sanas. Las personas con Fenómeno de Raynaud secundario mostraron niveles elevados de sensibilización central en comparación con la forma primaria y las personas sanas ($P=0.001$). La catastrofización fue significativamente más elevada en ambos grupos de sujetos con Fenómeno de Raynaud ($P \leq 0.001$) con respecto a los controles sanos. En cuanto a la discapacidad de la extremidad superior, esta fue significativamente mayor ($P \leq 0.01$) en ambas formas de FR con respecto a los controles y mostraron tener menor flujo sanguíneo en la arteria radial ($P=0.006$). El análisis de regresión multivariante confirmó que la extensión del índice ($\beta=-0.348$, $P=0.010$) y la fuerza de la pinza lateral ($\beta=-0.427$, $P=0.001$) estaban asociadas de forma significativa con la discapacidad que presentaban las

personas con Fenómeno de Raynaud, explicando un 55% de la varianza total. Por último, el tratamiento mediante iontoforesis con agua corriente, demostró producir una mejoría significativa en el número de ataques ($P<0.001$), el dolor ($P=0.002$), el flujo sanguíneo ($P=0.001$), la saturación de oxígeno ($P\leq0.002$), la recuperación de la curva de temperatura ($P\leq0.014$) la sensibilización central ($P<0.003$) y la discapacidad del miembro superior ($P<0.001$) en los pacientes que recibieron esta intervención frente al grupo control.

Las principales conclusiones fueron, en primer lugar, que las personas con Fenómeno de Raynaud tenían menor temperatura en sus manos y un patrón de hipersensibilidad bilateral a la presión, sin embargo, la gravedad de las alteraciones vasculares no parece estar relacionada con la experiencia del dolor central en esta población y la sensibilización central solo parece estar presente en la forma secundaria. Por otro lado, las personas con Fenómeno de Raynaud mostraron niveles de catastrofización más altos que las personas sanas, estos mecanismos adicionales del dolor, pueden contribuir a que el proceso de dolor se mantenga en el tiempo, así como que se produzca una peor evolución y una peor respuesta a los tratamientos en estos pacientes. En segundo lugar, los participantes con Fenómeno de Raynaud mostraron una mayor discapacidad percibida en las manos y extremidades superiores en la práctica de las actividades de la vida diaria, el trabajo y los deportes, especialmente los que presentaban FR secundario; sin embrago esta discapacidad parece estar más relacionada con la pérdida de la amplitud de movimiento a nivel de las articulaciones de la mano y la disminución de la fuerza que con las alteraciones o afectación a nivel vascular. En tercer lugar, el tratamiento mediante iontoforesis con agua corriente parece ser eficaz para mejorar la sintomatología de esta patología en sus dos formas de presentación. Por lo tanto, valorar aspectos como los que hemos presentado en esta tesis relacionados con el dolor, los procesos del dolor crónico, la funcionalidad y la discapacidad deberían tenerse en cuenta para realizar un abordaje integral de estos pacientes. También debería tenerse en cuenta incluir la aplicación de iontoforesis con agua corriente en los protocolos de intervención de las personas con Fenómeno de Raynaud.

ABSTRACT

Raynaud's phenomenon manifests as a set of symptoms produced by a vasospastic disorder usually affecting the small vessels near the surface of the skin in the hands and feet and occurs in response to various stimuli such as exposure to cold or emotional stress. It is characterised by an acute, transient and reversible decrease in blood flow, accompanied by a change in skin colour, different levels of pain and functional impotence. It is classified into two main types, primary and secondary Raynaud's. In Raynaud's phenomenon, the alteration at the vascular level should be related to the processes of chronic pain, as well as with lower rates of functionality. These aspects have not yet been studied in depth and there are little known about the possible relationship between levels of vascular damage and the degree of pain, central sensitization and catastrophizing, as well as disability in people suffering from Raynaud's phenomenon. Furthermore, the effects of treatments proposed to manage this process have so far proved inconclusive. In this sense, we consider that iontophoresis treatment may improve the symptoms and upper limb disability in these patients, with minimal side effects; however, we have found no previous studies analysing the efficacy of this type of treatment.

The main objectives of this thesis were: 1) To evaluate the relationship between vascular abnormalities and levels of pain, the processes related to chronic pain development (Central Sensitization and Catastrophizing), hand functionality and upper limb disability in people with Raynaud's phenomenon. 2) To evaluate the effectiveness of iontophoresis electrotherapy with tap-water on the severity of vascular symptoms, pain-triggering processes and symptoms and perceived upper limb disability in people with Raynaud's phenomenon.

In this thesis, two observational studies and a randomised clinical trial were carried out to achieve the objectives outlined above. The first two studies included 37 people with Raynaud's phenomenon and 20 healthy controls and the third included 34 patients with Raynaud's phenomenon. Firstly, vascular condition were assessed by analysing the thermographic pattern of the hands, pain intensity, level of mechanosensitivity, electrical pain threshold, central sensitization and catastrophizing among people with primary and secondary Raynaud's phenomenon and healthy subjects. Secondly, we assessed the established vascular abnormalities through hand temperature, temperature recovery curve,

oxygen saturation and blood flow; using range of motion and hand strength as indicators of hand functionality and the perceived disability in the carrying out activities of daily living at home, work and practising sports or artistic activities in people with Raynaud's phenomenon and healthy subjects. Lastly, 34 participants with Raynaud's phenomenon were randomly assigned either to an experimental group receiving iontophoresis electrotherapy (n=17) or to a control group (n=17) that continued with its usual treatment without receiving electrotherapy. The procedure was performed for 7 weeks, three times a week and with each session lasting 20 minutes. The main measurement tools used were hand temperature, temperature recovery curve, oxygen saturation, blood flow, pain level, central sensitization, catastrophizing and perceived upper limb disability. Each of these variables were assessed at three different times: a baseline assessment before beginning the intervention, a post-treatment assessment and a follow-up assessment, performed two months after the intervention.

Our results suggest that people with Raynaud's phenomenon have a lower basal hand temperature ($P \leq 0.012$); higher levels of pain ($P \leq 0.001$) and lower pain thresholds on pressure ($P \leq 0.05$) than healthy people. People with secondary Raynaud's phenomenon showed raised levels of central sensitization compared to those with primary Raynaud's and healthy people ($P=0.001$). Catastrophizing was significantly higher in both groups of subjects with Raynaud's phenomenon ($P \leq 0.001$) compared to healthy controls. Disability in the upper extremities was significantly higher ($P \leq 0.01$) in both forms of RP compared to the controls with lower blood flow in the radial artery ($P=0.006$). The multivariate regression analysis confirmed that index finger extension ($\beta=-0.348$, $P=0.010$) and lateral pinch strength ($\beta=-0.427$, $P=0.001$) were significantly associated with the disability presented by people with Raynaud's phenomenon, explaining 55% of the total variance. Ultimately, iontophoresis treatment with tap-water demonstrated a significant improvement in terms of the number of attacks ($P<0.001$), pain ($P=0.002$), blood flow ($P=0.001$), oxygen saturation ($P \leq 0.002$), temperature curve recovery ($P \leq 0.014$), central sensitization ($P<0.003$) and upper limb disability ($P<0.001$) in patients who received this treatment versus the control group.

The main conclusions were, firstly, that people with Raynaud's phenomenon had lower hand temperature and a pattern of bilateral pressure pain hypersensitivity. The

severity of vascular abnormalities does not, however, appear to be related to the experience of central pain in this population and central sensitization only appearing to occur in secondary Raynaud's. Furthermore, people with Raynaud's phenomenon showed higher levels of catastrophizing than healthy people. These additional pain mechanisms may contribute to maintaining the pain process over time, as well as a worse outcome and a worse response to treatments in these patients. Secondly, participants with Raynaud's phenomenon showed greater perceived hand and upper limb disability in carrying out daily activities at home, at work and when practising sports, especially those with secondary RP. This disability, however, appears to be more related to the loss of range of motion in the hand joints and the decrease in strength than with vascular abnormalities or involvement. Thirdly, iontophoresis treatment with tap-water appears to be effective in improving the symptoms of this disease in its two forms of presentation. Therefore, assessing aspects such as those presented in this thesis relating to pain, chronic pain processing, functionality and disability should be considered in order to take a holistic approach to these patients. Consideration should also be given to including iontophoresis with tap-water in the intervention protocols for people with Raynaud's phenomenon.

ABREVIATURAS

ACh	Cloruro de acetilcolina
AAV	Anastomosis arteriovenosas
CIE	Clasificación Internacional de las Enfermedades
EEM	Electroestimulación Medular
ETC	Enfermedad del Tejido Conectivo
EVA	Escala Visual Analógica
FR	Fenómeno de Raynaud
GABA	Ácido G-Aminobutírico
IC	Intervalo de confianza
IR-A	Infrarrojos A
NMDA	N-metil-D-aspartato
OMS	Organización Mundial de la Salud
RM	Rango de movimiento
SEMV	Sociedad Europea de Medicina Vascular
SC	Sensibilización Central
SNC	Sistema Nervioso Central

ABREVIATIONS

ACh	Acetylcholine chloride
AVA	Arteriovenous Anastomoses
CI	Confidence Interval
CNS	Central Nervous System
CS	Central Sensitization
CSI	Central Sensitization Inventory
CST	Cold Stress Test
CTD	Connective tissue diseases
DS	Dominant Side
EAT	European Association of Thermology
ESVM	European Society for Vascular Medicine
GABA	G-Aminobutyric Acid
IASP	International Association for the Study of Pain
ICC	Intraclass Correlation Coefficient
ICD	International Classification of Diseases
IR-A	Infrared A
MD	Mean Difference
NDS	Non- Dominat Side
NMDA	N-methyl-D-aspartate
NSAIDS	Non-steroidal anti-inflammatory drugs

OR	Odd Ratio
PCS	Pain Catastrophizing Scale
PM	Pain Matcher
PPT	Pressure pain threshold
PRP	Primary Raynaud's phenomenon
Quick-DASH	Shortened Disabilities of the Arm, Shoulder and Hand Questionnaire
RCS	Raynaud's Condition Score
ROM	Range of Motion
RP	Raynaud's phenomenon
SCS	Spinal Cord Stimulation
SD	standard deviation
SRP	Secondary Raynaud's phenomenon
VAS	Visual Analog Scale
WHO	World Health Organisation

INTRODUCCIÓN

INTRODUCTION

1. INTRODUCCIÓN

1.1 Fenómeno de Raynaud: Concepto, prevalencia, etiopatogenia, clasificación, clínicas y coste socio-económico.

1.1.1. Concepto

El Fenómeno de Raynaud (FR) es un trastorno vasoespástico transitorio que afecta a las pequeñas arterias, arteriolas y anastomosis arteriovenosas cutáneas. Este vasoespasmo aparece frecuentemente como una reacción exagerada frente a un estímulo térmico (generalmente el frío), frente a cambios de temperatura o alteraciones del estado emocional (ej. estrés). Afecta principalmente a los dedos de las manos y los pies, pero puede presentarse en otras zonas acras del cuerpo como la nariz, las orejas, la lengua o los pezones (García-Carrasco et al., 2008; Ismail et al., 2014b; Stringer & Femia, 2018).

El FR, recibe su nombre del médico francés Maurice Raynaud (1834-1881) (Maverakis et al., 2014), que en 1862 fue el primero en describir en su tesis doctoral *"De l'asphyxie locale et de la gangrène symétrique des extrémités"*(Belch et al., 2017) a un grupo de pacientes que sufrían un fenómeno isquémico caracterizado por ataques transitorios y reversibles de cambios de color, desencadenados por la exposición al frío y/o asociados a diversas condiciones. Raynaud sugirió que el mecanismo subyacente que producía la isquemia era un vasoespasmo a nivel de las arteriolas, secundario a una respuesta exagerada del sistema nervioso periférico, lo que denominó como "asfixia local" (Bakst, Merola, Franks, & Sanchez, 2008; Maverakis et al., 2014).

Desde que fuese descrito por primera vez, no ha existido una nomenclatura estandarizada para referirse a este Fenómeno (Belch et al., 2017). Durante los últimos veinte años, sin embargo, se ha observado una progresión en la literatura a la hora de referirse a este término, restringiendo el uso de "Raynaud" a la descripción clínica inicial de ataques isquémicos inducidos por el frío y manifestados con cambios transitorios y reversibles de la coloración de los dedos. Por lo tanto, "Fenómeno de Raynaud" es el término general para referirse a un vasoespasmo que produce un emblanquecimiento digital (Bakst et al., 2008).

Tras la descripción inicial de Raynaud, el trastorno fue nombrado como enfermedad de Raynaud, durante años, hasta que Hutchison y sus colaboradores en 1901, argumentaron que el término más apropiado para este trastorno era "Fenómeno de Raynaud" subrayando que había múltiples causas, no una sola enfermedad, que podrían causar la isquemia digital y el vasoespamo (Bakst et al., 2008; Porter, Rivers, Anderson, & Baur, 1981).

Posteriormente, Sir Thomas Lewis, en 1929 determinó que el trastorno era causado por un daño a nivel local más que por una alteración del sistema nervioso, pudiendo estar relacionado con otras enfermedades. Así pues, comenzó a describir las características clínicas y fisiológicas que diferenciaban a la forma primaria y secundaria del FR (Bakst et al., 2008).

Los términos de "Enfermedad de Raynaud" y "Síndrome de Raynaud" fueron acuñados y usados durante años para diferenciar los principales subgrupos del Fenómeno de Raynaud. Enfermedad de Raynaud se usaba cunado no existía una causa etiológica primaria conocida y síndrome de Raynaud cuando se manifestaba de forma asociada o subyacente a una enfermedad determinada. Ambas denominaciones tenían inconvenientes. La Enfermedad de Raynaud se usaba como un sinónimo de lo que actualmente se denomina FR primario. En este caso, el uso de la palabra enfermedad, es engañoso y puede llevar a una preocupación a los pacientes y una medicalización innecesaria. Por otro lado, cuando se usa el término síndrome para referirse al Raynaud asociado con otros trastornos, es cierto que es un síndrome, ya que asocia con varios signos y síntomas, sin embargo, estos pueden estar relacionados con muchas etiologías (Belch et al., 2017).

Una guía reciente realizada por la Sociedad Europea de Medicina Vascular, The European Society for Vascular Medicine (ESVM siglas en inglés) (Belch et al., 2017), determina la necesidad de estandarizar y mantener una consistencia en la terminología referente a este tema, ya que resulta fundamental a la hora de realizar estudios epidemiológicos y ensayos terapéuticos. Dichos autores establecen con un Grado IIa - Nivel C, que el término correcto para referirse a este trastorno es "Fenómeno de Raynaud", de forma que deben descartarse los términos «síndrome» y «enfermedad» y usarse «FR

Primario» y «FR Secundario» para referirse a las dos formas clínicas del mismo (Belch et al., 2017).

1.1.2. Prevalencia

Diversos estudios han intentado establecer la prevalencia de este trastorno en diferentes poblaciones. Las estimaciones en la población en general varían y por tanto se desconoce la prevalencia real del Fenómeno de Raynaud (Fraenkel, 2002; Garner, Kumari, Lanyon, Doherty, & Zhang, 2015). La heterogeneidad en las cifras sobre la prevalencia puede reflejar las diferencias en la forma de llevar a cabo los estudios, su diseño, los diferentes criterios utilizados en el reclutamiento, la población estudiada y las encuestas usadas en los mismos (Fraenkel, 2002; Ling & Wigley, 1999).

En líneas generales, los estudios epidemiológicos coinciden en que entre un 3% y un 20% de la población general mundial padece FR (Ling & Wigley, 1999). En cuanto a distribución por género, el FR se manifiesta en mayor proporción en las mujeres, estimándose su prevalencia general entre el 6% y 20% frente a la población masculina cuya cuantificación se sitúa entre el 3% y 12.5% (Bakst et al., 2008). Además, se ha observado una mayor distribución en familiares de individuos afectados, lo que sugiere una susceptibilidad genética o componente hereditario (Wigley & Flavahan, 2016). La prevalencia en la población española se estima bastante inferior al resto de países, variando entre el 2.8 y el 4.7% (Román, Gonzálvez, Fernández, Graña, & Torres, 2001). Estudios realizados en Estados Unidos, lo señalan como uno de los países con mayores tasas de prevalencia, en este caso, la prevalencia del FR en mujeres es de aproximadamente el 9% en el noreste y 4% en el sur, mientras que en hombres afecta al 6% de la población noreste y el 3% de la zona sur. El país estudiado con una menor prevalencia de FR es Japón con una media del 1.6% de la población general, de los cuales el 2.1% son mujeres y el 1.1% hombres (Garner et al., 2015; Stringer & Femia, 2018).

Otros estudios compararon la prevalencia del FR en regiones climáticas diferentes, desde regiones montañosas con climas fríos a zonas costeras cálidas, y concluyeron que esta fue mayor en las zonas de climas más fríos (Bakst et al., 2008) . El efecto del clima sobre la prevalencia de FR persiste incluso en personas con factores de riesgo conocidos.

Por ejemplo, en un estudio realizado en China, encontraron que la prevalencia de FR entre los trabajadores que usan herramientas vibratorias fue del 19% en el norte y del 7% en el sur (Fraenkel, 2002).

Dentro de los factores de riesgo asociados al desarrollo del FR, las diferencias ligadas al género suponen una de las cuestiones más relevantes. Las mujeres son más susceptibles de padecer FR que los hombres en una proporción 7 a 1, debido a factores hormonales, ya que se ha observado una mayor incidencia de ataques vasoespásticos en el periodo preovulatorio. Asimismo, la administración de estrógenos ha demostrado empeorar los síntomas en mujeres con FR secundario (Linnemann & Erbe, 2015). Por otra parte, los cambios hormonales asociados al periodo posterior a la menopausia parecen incidir de forma determinante en la aparición del FR, así el estudio Framingham mostró una incidencia del fenómeno del 8.4% entre las mujeres posmenopáusicas de 52 a 66 años (Fraenkel et al., 1998).

Otro factor determinante a tener en cuenta en la aparición del FR es la edad. El FR se manifiesta de forma más frecuente en el rango de edad que comprende entre los 20 y los 60 años, aunque puede aparecer también en la infancia, adolescencia o en ancianos (Linnemann & Erbe, 2015). El FR primario tiene una edad de inicio más temprana, generalmente aparece entre los 15 y los 30 años y el FR secundario suele aparecer alrededor de la cuarta década de la vida (Wigley & Flavahan, 2016) .

El papel de los factores genéticos en la aparición del FR está aún por determinar. Se ha observado que existe una predisposición poligenética en el 30% de los pacientes y también que hay diferencias de prevalencias entre las etnias (Linnemann & Erbe, 2015). Un estudio observacional realizado en Alemania determinó que había un 3% de antecedentes familiares positivos en pacientes con FR (Heidrich, Helmis, Fahrig, Hövelmann, & Martini, 2008) y un estudio reciente (Munir, Freidin, Brain, & Williams, 2018), ha indicado que el FR está asociado específicamente con la variación en el gen NOS1.

Dentro de los principales factores de riesgo del FR también se incluyen la migraña, el tabaquismo, la enfermedad cardiovascular, la terapia sustitutiva de estrógenos y el uso

de herramientas vibratorias manuales en el trabajo tales como, taladros eléctricos o neumáticos, motosierras, etc (Fraenkel, 2002; Garner et al., 2015). En este sentido, se ha encontrado una fuerte asociación entre migraña y FR primario con una Odd Ratio (OR) de 4.02 y un Intervalo de Confianza (IC) al 95% de 2.62 a 6.17. El tabaquismo también ha mostrado tener una asociación positiva con el FR con una OR de 1.27 y un IC 95% entre 1.06 a 1.53; así como las enfermedades cardiovasculares con una OR de 1.69 y un IC 95% de 1.22 a 2.34 (Garner et al., 2015).

Por último, cabe señalar que parece existir una relación entre el estado civil de la persona y el FR. Estudios realizados en este sentido (Fraenkel et al., 1999; Keil, Maricq, Weinrich, McGregor, & Diat, 1991), coinciden en que los sujetos divorciados, separados o viudos presentan una mayor prevalencia de FR que aquellos que están casados o son solteros. Los autores de estos estudios plantean la hipótesis de que la mayor prevalencia observada en estos sujetos, puede estar relacionada con los componentes emocionales ya que estas personas experimentan mayores niveles estrés asociados a la pérdida del cónyuge.

1.1.3 Etiopatogenia

A pesar de que han pasado más de 100 años desde que Maurice Raynaud describió el FR, todavía no hay un consenso general sobre su fisiopatología exacta (Herrick, 2005; Le & Cho, 2014; Prete, Fatone, Favoino, & Perosa, 2014).

Desde el punto de vista fisiológico, es necesario que haya un equilibrio entre los sistemas vasoconstrictores y vasodilatadores, para que se mantenga un tono vascular adecuado y se produzca una correcta regulación del flujo sanguíneo a nivel periférico. Para ello debe existir una integridad funcional y estructural de los nervios periféricos, de las células de la pared de los pequeños vasos y de la microcirculación celular (Albrecht et al., 2013; Cheung, 2015).

En el FR, el equilibrio entre los factores vasculares, neurógenos y humorales se rompe favoreciendo una vasoconstricción excesiva (Prete et al., 2014). A continuación se detallan los principales hitos fisiopatológicos, según el componente estructural o funcional afectado.

1) **Factores vasculares.** En el FR primario, se produce sobretodo una alteración a nivel endotelial. En este caso el sistema vasoconstrictor, está muy estimulado por una hiperactividad de los sistemas que son potentes vasoespásticos como el alfa-2-adrenérgico, la endotelina-1, la tirosinacinasa, la serotonina y la angiotensina II. Las células endoteliales disfuncionales tienen a su vez una actividad reducida, que afecta a la producción de vasodilatadores como el óxido nítrico y la prostaciclina y además puede incrementarse la actividad trombótica e inflamatoria (Prete et al., 2014; Rychlik-Golema, Mastej, & Adamiec, 2006).

   En el FR secundario, sobre todo a esclerodermia, predomina la alteración vascular sobre disfunción endotelial, en este caso, se producen cambios evidentes en la pared de los vasos sobre todo a nivel de la íntima y también se produce una fibrosis en la capa media y adventicia. Estas lesiones en las paredes vasculares hacen que se altere su función, produciendo la liberación de péptidos vasoactivos, que son secretados por el propio endotelio, lo que a su vez favorece aún más los cambios estructurales en el mismo (Herrick, 2016; Prete et al., 2014; Sunderkötter & Riemekasten, 2006).

2) **Factores neurógenos.** Otra de las causas que pueden originar el FR son las alteraciones a nivel neurógeno. El sistema nervioso autónomo juega un papel fundamental en el control de la temperatura corporal. En este caso, se cree que puede existir una alteración a nivel de los sistemas nerviosos simpático y parasimpático, de las fibras sensitivas aferentes en la zona de la unión neurovascular y de las anastomosis-arteriovenosas (AAV) (Albrecht et al., 2013). Esta alteración podría dar lugar a que se produzca una menor liberación de neuropéptidos vasodilatadores como son el péptido relacionado con el gen de la calcitonina, la sustancia P, la neurocinina A y el neuropétido Y; dando todo ello lugar a una vasoconstricción excesiva.

   Por otro lado, también se ha observado que se produce una mayor respuesta vascular de los recetores alfa-2c-adrenérgicos del músculo liso que incrementan la vasoespasticidad (Flavahan, 2008a; Freedman, Moten, Migály, & Mayes, 1993). Es conocido que el FR se presenta de forma muy localizada, afectando al flujo sanguíneo de áreas de la piel que tienen unas características estructurales y funcionales muy específicas. Estas zonas de la piel, tienen una alta densidad de

AAV, que son unas estructuras que juegan un papel muy importante en el proceso de termorregulación de la temperatura corporal y parecen tener un papel importante en el desarrollo del FR (Walløe, 2016). Revisiones recientes (Cheung, 2015; Walløe, 2016) han concluido que las AAV son conexiones directas entre las pequeñas arteriolas y vénulas, sin segmento capilar, que no pueden transportar sustancias disueltas hacia o desde los tejidos y por lo tanto, su única función es la de transportar calor. Las AAV se encuentran en una proporción muy baja en la mayoría de los órganos y tejidos de nuestro cuerpo, pero son muy numerosas en las mucosas, el lecho ungueal y la piel glabra de las manos (región tenar e hipotenar) y los pies. Para preservar la temperatura corporal normal, en respuesta a la exposición al frío, se produce una vasoconstricción fisiológica periférica de las estructuras termorreguladoras de nuestro cuerpo, como las anastomosis arteriovenosas y las arteriolas precapilares (Flavahan, 2015; Nuzzaci et al., 1988). Cuando aparece un estímulo frío, la pérdida de calor se reduce debido a la dicha vasoconstricción cutánea y la producción de calor basada en la termogénesis (Walløe, 2016). Las AAV, participan de la regulación de la temperatura corporal, manteniendo el organismo cercano a su zona termoneutral, que suele oscilar entre 26-36 grados centígrados en reposo. Actúan como esfínteres y se abren o se cierran produciendo respectivamente una disminución o un aumento del flujo sanguíneo en la zona, derivando la sangre directamente hacia los plexos venosos de las extremidades. Si se produce un descenso de la temperatura, esta información llega hasta centro de control de la temperatura a nivel hipotálamo, que envía ráfagas de impulsos nerviosos simultáneamente a todas las AAV que están muy inervadas por nervios simpáticos (Walløe, 2016; Wigley & Flavahan, 2016). Durante la exposición al frío, las anastomosis-arteriovenosas permanecen predominantemente cerradas, mientras que están completamente abiertas durante la eliminación de calor. En condiciones normales, cuando se produce la vasoconstricción cutánea inducida por el frío o el estrés, hay un aumento de forma refleja de la actividad simpática vasocontrictora lo que puede causar grandes fluctuaciones en el flujo sanguíneo. En personas con FR, la vasoconstricción simpática se amplifica aún más en intensidad y alcance y la exposición al frío puede provocar una vasoconstricción intensa a lo largo de toda la red vascular; incluidas las arterias y arteriolas que proporcionan un soporte nutricional a la piel (Flavahan, 2015).

3) **Factores humorales**. Finalmente, otra de las posibles causas del FR son las alteraciones de los factores humorales. Esto se relaciona sobre todo con el FR secundario, donde se han descrito algunos factores que pueden comprometer el flujo sanguíneo. Algunos de estos factores son un aumento de la actividad plaquetaria, la hipofibrinolisis, la deformidad de los hematíes, la hipeviscosidad, la activación leucocitaria y el estrés oxidativo. Sin embargo, estos factores parecen tener una menor trascendencia en el origen de la patología que los dos anteriores (Herrick, 2005; Prete et al., 2014).

En resumen, parecen existir dos teorías principales para explicar el FR: (1) por un lado se propone que el vasoespasmo característico está causado por la hiperactividad del sistema nervioso simpático, provocada por factores neurológicos centrales y periféricos, como la deficiencia del péptido relacionado con el gen de la calcitonina, la activación de los receptores alfa-2 adrenérgicos, una mayor síntesis de endotelina-1 y un descenso de factores vasodilatoadores como las prostaciclinas y el óxido nítrico (Flavahan, 2015). (2) Otra teoría es que los niveles de actividad simpática en esta población son normales y el FR es una respuesta exagerada de los vasos sanguíneos cutáneos debido a anomalías estructurales en los mismos, secundarios a un aumento de la viscosidad de la sangre, un control disfuncional del tono vascular, lesiones endoteliales, un aumento de la activación de las plaquetas o de la oxidación (Sunderkötter & Riemekasten, 2006).

Las investigaciones más recientes relativas a este tema (Herrick, 2017; Wigley & Flavahan, 2016) están orientadas en la línea de afirmar que estas dos teorías no son excluyentes y que probablemente, la etiología del FR se explique mediante una combinación de ambas, ya que se ha observado que hay factores etiológicos que son específicos, pero también que hay factores que difieren para cada una de las formas del FR (primaria y secundaria). Dichas diferenciaciones han llevado a considerar el FR primario como un trastorno puramente funcional o vasoespástico, mientras que el FR secundario se asocia más con anomalías estructurales de la microcirculación (Block & Sequeira, 2001).

1.1.4 Clasificación

Clásicamente el FR se clasifica en dos formas; FR primario o idiopático y FR secundario.

El FR primario es el más frecuente, representa el 80% de los casos y no está asociado con una enfermedad subyacente (De Angelis, Salaffi, & Grassi, 2008). En general, se considera una condición "benigna" porque el nivel de afectación tiende a ser más leve y generalmente no progresa a una lesión tisular irreversible (Herrick, 2017). El FR primario se caracteriza por tener una edad de inicio más temprana, alrededor de los 20-30 años; los pacientes presentan capilares normales en los pliegues ungueales y autoanticuerpos antinucleares bajos o negativos; los ataques afectan típicamente a todos los dedos en un patrón simétrico y se asocian con niveles más bajos de dolor (Bakst et al., 2008).

La forma secundaria del FR es menos frecuente, representando el 20% del total los casos. El FR secundario está asociado a un proceso patológico conocido o enfermedad subyacente (Linnemann & Erbe, 2015) Las causas principales son las enfermedades autoinmunes, las enfermedades del tejido conectivo (ETC) y las patologías reumáticas. La asociación más frecuente es con la esclerosis sistémica o esclerodermia, de forma que el 90-95% de los pacientes que padecen esta enfermedad presentan FR. Otras patologías relacionadas con el FR secundario son el Lupus (10-40%); Síndrome de Sjögren (30%), dermatomiositis o polimiositis (20%), artritis reumatoide (10%), trastornos neurológicos, exposición a ciertos medicamentos y toxinas, medicamentos vasoconstrictores, trastornos intravasculares asociados con el aumento de la viscosidad de la sangre, neoplasias, tratamientos con medicamentos diversos, uso de instrumentos vibratorios en el trabajo y presencia de lesiones vasculares (Fraenkel, 2002; Hughes & Herrick, 2016). El FR secundario suele tener una peor evolución en el tiempo y puede progresar a un daño tisular irreversible con ulceración digital y gangrena, que puede finalmente requerir realizar una amputación de la estructura dañada (Herrick, 2017). Los pacientes con FR secundario suelen tener una edad de inicio mayor, después de los 40 años; sus capilares en los pliegues ungueales son anormales; presentan niveles de autoanticuerpos antinucleares positivos; los ataques involucran los dedos de forma asimétrica y el dolor que los acompaña es intenso (Block & Sequeira, 2001).

El FR a menudo precede al inicio clínico de muchos de estos trastornos, por lo que las patologías reumatológicas subyacentes deben ser descartadas cuando comiencen los síntomas de FR (Block & Sequeira, 2001). Los pacientes que presentan por primera vez FR entre la tercera y quinta década de su vida están en alto riesgo de desarrollar ETC. Cuando el FR aparece en niños muy pequeños, también debe considerarse una ETC subyacente, sobre todo si aparece muy marcada la primera fase de palidez y los síntomas que la acompañan son severos (Belch et al., 2017). Un estudio restropectivo, ha revelado que en un 37,2% de los casos se produce una transición de FR primario a una ETC y que sólo un 8,1% de los casos desarrolló un FR secundario a otras causas (Pavlov-Dolijanovic et al., 2013).

1.1.5 Manifestaciones clínicas

En cuanto a las manifestaciones clínicas del FR, el síntoma principal es un característico cambio de color de la piel que se desarrolla en tres fases progresivas. En la primera fase aparece una palidez cérea en la piel que se torna blanca, debido al exceso de vasoespasmo/isquemia. Esta fase suele presentarse de forma bien delimitada en los dedos, como si fuese un corte transversal. En la segunda fase, la piel adquiere un color azulado, cianótico causado por la desoxigenación/cianosis. Finalmente, la piel se torna roja, como resultado de la hiperemia reactiva después de la restauración del flujo sanguíneo (Bakst et al., 2008; Linnemann & Erbe, 2015). En la práctica clínica, no siempre aparecen las tres fases de cambio de color de la piel en los pacientes; en la mayoría de las ocasiones alguna de las fases no se produce o es poco aparente (Belch et al., 2017). Se ha descrito que sólo el 9% de los pacientes presentan de forma completa los típicos cambios de color trifásicos (Fraenkel, 2002). Sin embargo, es necesario que se produzca la fase inicial para poder realizar el diagnóstico diferencia (Grossi et al., 2010).

Estos ataques vasoespáticos se manifiestan principalmente en los dedos de las manos y hasta en el 40% de los pacientes también en los dedos de los pies. Otras zonas corporales, como los lóbulos de las orejas, los labios y la nariz, se ven afectados con menor frecuencia (Fraenkel, 2002). La duración media de los ataques es de entre 15-20 minutos, y la gravedad varía de leve a temporalmente incapacitante (Wigley & Flavahan, 2016). La

intensidad y gravedad de los ataques va a depender en gran medida de que haya o no una patología asociada. Normalmente los episodios afectan a uno o varios dedos de una mano y se van extendiendo de forma simétrica a los demás dedos y la otra mano. Generalmente se manifiesta con mayor frecuencia en los dedos anular, índice y medio. La afectación del pulgar es poco frecuente (Belch et al., 2017).

Otros síntomas que clínicamente también acompañan al cambio de color en el FR son un grado variable de dolor, pérdida de funcionalidad, parestesias, sensación de entumecimiento, hormigueo y quemazón. La intensidad con la que se van a manifestar estos síntomas es muy variable y va a depender en gran medida de que se trate de una forma primaria o secundaria de Raynaud (Wigley & Flavahan, 2016) En casos graves de isquemia intensa y prolongada, pueden aparecer úlceras abiertas en los dedos, que pueden evolucionar hacia una infección, necrosis y finalmente a una gangrena de los tejidos (Flavahan, 2008).

1.1.6 Coste Socioeconómico.

Todas las alteraciones que están presentes en el FR y los síntomas relacionados con ellas causan en mayor o menor medida una pérdida de funcionalidad del miembro superior, sufrimiento y reducción de la calidad de vida de las personas que lo padecen (Linnemann & Erbe, 2016). Debido a que el FR es una condición crónica, va generar un coste socio-económico y sanitario importante tanto directo como indirecto, aunque la literatura existente que valora este aspecto aún es escasa (Hughes et al., 2015).

En relación a los gastos que generan las patologías asociadas con dolor crónico, como es el caso del FR, un estudio realizado en Estados Unidos menciona que alrededor de 48 millones de personas padecen un proceso de dolor crónico (Day & Thorn, 2010) lo que se traduce en un coste total anual de 100 billones de dólares derivados de los gastos sanitarios y la pérdida de productividad (Quartana, Campbell, & Edwards, 2009).

En un estudio reciente, Herrick (2017), menciona que tanto en el FR primario como secundario se produce una pérdida significativa de la calidad de vida de las personas que lo padecen, por lo tanto, ambas formas de FR tendrán un coste socio-económico y médico

importante. Sin embargo, se ha constatado que el coste socio-sanitario se incrementa en aquellas ocasiones en las que el FR está asociado con enfermedades sistémicas. En este sentido, Nguyen et al. (2010), realizaron un estudio con pacientes con FR secundario a esclerodermia y determinaron que un 31.8% de estos sujetos recibía una pensión de invalidez total, el 23.9% estaba de baja laboral en ese momento y un 34.5% de estas personas habían tenido que cambiar de trabajo. Por lo tanto, la carga socioeconómica relacionada con el FR y las patologías concomitantes a las que puede estar asociado es importante. Este estudio también se puso de manifiesto que la aparición del FR supuso una disminución de los ingresos de estas personas en un 46.9%, que un 43.3% de los participantes refirió tener menores ocasiones de promocionar en su trabajo y un 10.6% expresó tener mayores sentimientos de discriminación en su entorno laboral debido a su enfermedad. Además también se puso de manifiesto que había una relación directa entre las limitaciones que padecen estos pacientes a nivel funcional y la necesidad de ayuda para realizar las tareas en el hogar, en este caso el 66.1% de los pacientes mencionaron que necesitaban una media de 36 horas por mes de ayuda doméstica remunerada (Nguyen et al., 2010).

Por lo tanto, el FR es una patología crónica, que afecta a un grupo considerable de la población y sus consecuencias generan un elevado impacto a nivel socio-económico y sanitario (Bérezné et al., 2011).

1.2 Dolor crónico, proceso de Sensibilización Central y su relación con las alteraciones vasculares periféricas.

El dolor crónico se define como un dolor que persiste o se repite durante más de 3 meses, de manera que pierde la función fisiológica de advertencia de la nocicepción aguda (Treede et al., 2019). El dolor crónico es una fuente importante de sufrimiento humano y discapacidad, que interfiere con el funcionamiento diario y suele ir acompañado de angustia. Además es una de las causas más frecuentes por la que los pacientes solicitan atención médica, a nivel mundial (Goldberg & McGee, 2011).

En cooperación con la Organización Mundial de la Salud (OMS), el Grupo de Trabajo de la Asociación Internacional para el Estudio del Dolor cuyas siglas en inglés son

IASP, ha desarrollado un sistema de clasificación con las principales causas de dolor crónico. El dolor crónico tiene asignado un identificador único dentro de la Clasificación Internacional de las Enfermedades (CIE-11) (dolor crónico: http://id.who.int/icd/ entidad / 1581976053), puesto que se ha considerado como una entidad patológica en sí misma. Además hay 7 códigos que conforman los grupos clínicamente más relevantes y comunes de condiciones de dolor crónico (Treede et al., 2019).

En este caso, el dolor que se produce en las personas con FR, tanto primario como secundario, se clasificaría dentro de la forma de dolor visceral secundario crónico. Este se define como un dolor persistente o recurrente que se origina en los órganos internos y suele percibirse en los tejidos somáticos de la pared corporal (piel, tejido subcutáneo y músculo), de las áreas que reciben la misma inervación sensorial del órgano interno en el que se origina el síntoma (dolor visceral referido). Esta categoría se subdivide a su vez, según los principales mecanismos subyacentes, en factores mecánicos (por ejemplo, tracción y obstrucción); inflamación persistente y mecanismos vasculares (isquemia y trombosis). Dentro de estos últimos estarían los mecanismos que originan el dolor en el caso del FR. Además, en el FR Secundario podrían intervenir más causas de dolor crónico dependiendo a su vez de la patología de base que lo origine (Treede et al., 2019).

Tradicionalmente, el dolor en la población con FR, se ha asociado principalmente a la vasoconstricción excesiva y mantenida que se produce debida a la hipereactividad vascular periférica (Devulder et al., 2011). Esta asociación está en línea con la idea de que el dolor persistente es causado por la isquemia mantenida en los tejidos periféricos, lo que origina a su vez una hiperactivación de los nociceptores de los tejidos profundos. Todo ello daría lugar a una sensibilización periférica que podría causar finalmente un proceso de Sensibilización Central (SC) en esta población (Flavahan, 2015; Woolf, 2011).

Es conocido que incluso con el dolor agudo, se producen cambios a nivel del sistema nervioso. Cuando el dolor persiste durante unos días, se produce una adaptación de los nociceptores unimodales que mejora la capacidad de respuesta de las terminaciones nociceptivas polimodales por la liberación de sustancias como la serotonina. A este proceso se le denomina hiperalgesia primaria o periférica por sensibilización de los nociceptores y representa una acción protectora por parte del cuerpo humano para evitar un

mayor uso de las estructuras dañadas y el daño adicional de los tejidos circundantes (Yunus, 2007b, 2007a). En la hiperalgesia secundaria se produce un aumento de la capacidad de respuesta de las neuronas del asta dorsal de la médula espinal. De esta forma, es de considerar que mientras que la sensibilización periférica es un fenómeno local, la sensibilización central es un proceso central que afecta al sistema nervioso de manera global (Nijs, Wilgen, Oosterwijck, Ittersum, & Meeus, 2011).

La SC se define como un fenómeno fisiológico producido por alteraciones del procesamiento a nivel del sistema nervioso central, que causan un funcionamiento neuronal alterado dando lugar a un estado de hiperexcitabilidad (hipersensibilidad) frente a estímulos nocivos y no nocivos (Neblett, Hartzell, Mayer, Cohen, & Gatchel, 2017; Nijs et al., 2011). Clínicamente, se caracteriza por la presencia de alodinia (sensación dolorosa a un estímulo normalmente no doloroso, como el tacto), hiperalgesia (sensibilidad excesiva a un estímulo normalmente doloroso, como la presión), expansión del campo receptivo (dolor que se extiende más allá del área de los nervios periféricos), y dolor inusualmente prolongado después de que se haya eliminado un estímulo doloroso (generalmente palpitante, ardor, hormigueo o entumecimiento) (Nijs & Van Houdenhove, 2009).

La principal teoría que explica el proceso de SC, determina que los impulsos de dolor sostenido van a producir una alteración a nivel de las vías ascendentes y descendentes del sistema nervioso central (Nijs & Van Houdenhove, 2009), por tanto, el dolor persistente puede ocasionar cambios a nivel del sistema nervioso periférico y central (Kindler, Bennett, & Jones, 2011).

El mecanismo exacto de instauración de los procesos de SC aún se desconoce. Se ha descrito que en los estados de dolor crónico, los nociceptores periféricos siguen enviando los impulsos dolorosos que activan las fibras nerviosas tanto A delta y las fibras C, las cuales llevan el impulso nociceptivo a las neuronas del asta dorsal de la médula espinal. La activación persistente de las fibras nociceptivas, estimula la liberación de neurotransmisores (sustancia P, glutamato, péptido relacionado con el gen de la calcitonina y aspartato) que modulan las descargas eléctricas post-sinápticas en la sinapsis neuronales del asta dorsal. Los neurotransmisores incrementados inician las respuestas post-sinápticas y desencadenan una hiperexcitabilidad de los receptores de N-metil-D-aspartato (NMDA)

de las neuronas de segundo orden del asta dorsal. Los receptores NMDA parecen jugar un papel muy importante en este proceso, ya que su activación causa una notable alteración funcional en las neuronas postsinápticas (por ejemplo, aumento de la entrada de calcio, cambios en la membrana y activación de la proteína quinasa). Estos neuroquímicos sensibilizan a las neuronas de amplio rango dinámico (Wide-Dinamic Range), que se hacen hiperexcitables, dando lugar a fenómenos como la alodinia o la hiperalgesia. Algunas de estas neuronas son multimodales y responden a las sensaciones de tacto, presión, temperatura y dolor (Nijs & Van Houdenhove, 2009; Yunus, 2007). Como consecuencia de todo ello, se produce un aumento progresivo de descargas eléctricas en las neuronas de segundo orden de la médula espinal, lo que se traduce en un incremento de la activación de las neuronas de segundo orden que se proyectan al cerebro. Se produce de esta forma una mayor transmisión de las fibras espinales post-sinápticas que ascienden a estructuras supraespinales (tálamo, hipotálamo, corteza cingulada anterior, corteza insular, sistema límbico y finalmente y corteza somatosensorial) a través de las vías ascendentes. Estas áreas están involucradas en el procesamiento de varias dimensiones del dolor como la dimensión sensorial, afectiva y valorativa. Por lo tanto, mediante este mecanismo de la SC, el dolor persistente, produce un estado de hiperexcitabilidad del sistema nervioso central, lo que significa que el cerebro está sensibilizado, y se experimenta como un aumento en la percepción dolor (Nijs & Van Houdenhove, 2009; Yunus, 2007a, 2007b)

Otro mecanismo importante a través del cual la SC modula la hiperalgesia es mediante la expansión de los campos receptivos. En este caso, la excitación mantenida de las neuronas de amplio rango dinámico que incluyen tanto neuronas nociceptivas como no nociceptivas, hace que se activen a su vez las neuronas adyacentes, expandiendo así sus campos receptivos y dando lugar a que se experimente dolor por ejemplo, cuando se estimulan lugares que previamente no producían esa respuesta (Nijs & Van Houdenhove, 2009).

El proceso de sensibilización central, no se limita al asta dorsal, ni a la amplificación del dolor de los impulsos aferentes, sino que además incluye el procesamiento sensorial alterado en el cerebro y un mal funcionamiento de los mecanismos inhibidores descendentes del dolor. En este sentido, el mecanismo fisiológico para la inhibición del dolor desempeñado por las vías descendentes desde el sistema cortico-

reticular, el hipotálamo y el tronco encefálico, se vuelve funcionalmente deficiente. Así pues, se ven alteradas la liberación de neurotransmisores como la serotonina, norepinefrina, encefalinas y ácido g-aminobutírico (GABA), que intervienen activamente en la función inhibitoria (Nijs et al., 2011).

Por lo tanto, las alteraciones a nivel de las vías ascendentes junto con una modulación descendente anormal se pueden combinar para iniciar y mantener la hiperalgesia generalizada y el proceso de SC (Kindler et al., 2011; Yunus, 2007b).

Se han propuesto una serie de Síndromes que cursan con SC, que comprenden un grupo de trastornos médicos como la fibromialgia, el síndrome de fatiga crónica, el síndrome del colón irritable, trastornos de la articulación temporomandibular y migrañas entre otros. Además la SC está frecuentemente presente en varias enfermedades crónicas como la artritis reumatoide, lupus eritematoso sistémico, osteoartritis o fibromialgia entre otras que cursan con FR (Kindler et al., 2011). En este sentido, Yunus (2007a) refiere que un 14% de los pacientes que padecen fibromialgia presentan síntomas similares al FR y que estos síntomas pueden deberse a una mayor percepción sensorial relacionada con la SC, con o sin factores emocionales concomitantes.

Por otra parte, parece que el proceso de SC conlleva mucho más que la hipersensibilidad generalizada al dolor y se caracteriza también por una mayor capacidad de respuesta a una variedad de estímulos, incluyendo la presión mecánica, sustancias químicas, frío, luz, sonido, calor, estímulos eléctricos, estrés y emociones (Nijs et al., 2011; Woolf, 2011). Dicho cuadro clínico sugiere una intolerancia general a todo tipo de estímulos físicos y emocionales en la persona que lo padece (Nijs et al., 2011). Asimismo, también es bien reconocido que los procesos de SC a menudo están muy relacionados con diversos problemas psiquiátricos como la ansiedad, el pánico o la depresión, indicando que existe una importante interacción entre los procesos físicos y psicosociales tal y como nos indica el modelo biopsicosocial del dolor (Nijs & Van Houdenhove, 2009).

La presencia de sensibilización central en los pacientes que padecen dolor crónico implica una mayor complejidad de su cuadro clínico, es decir, un aumento de los síntomas no relacionados y de ahí un proceso de razonamiento clínico más difícil, así como la

disminución de las probabilidades de una recuperación favorable (Nijs, Van Houdenhove, & Oostendorp, 2010).

Como hemos mencionado anteriormente, parece que la hiperreactividad vascular periférica, característica del FR, podría ser la clave para explicar el proceso de SC en estos pacientes. Todo apunta a que este proceso puede ser generado por un trastorno a nivel del sistema vascular encargado de controlar la temperatura corporal, lo que a su vez puede dar lugar a una hipersensibilidad general frente al dolor y a la SC.

En este sentido, un estudio realizado por Albrecht et al. (2013), ha encontrado que existen alteraciones de las respuestas vasculares periféricas en las manos de pacientes con Fibromialgia, similares a las que se producen en el FR. Estos autores destacan que precisamente una alteración a nivel de las AAV, estructuras que juegan un papel fundamental en el proceso de termorregulación corporal y que están especialmente presentes en la piel de las zonas afectadas en el FR, podrían ser la clave para explicar toda esta alteración. En su estudio detectaron que existía un aumento significativo de la inervación simpática y sensorial de las AAV de la piel glabra de la eminencia hipotenar de las manos de las personas con fibromialgia en comparación con sujetos sanos. Esta inervación excesiva consistía en la presencia de una mayor proporción de fibras sensoriales vasodilatadoras en comparación con las fibras simpáticas vasocontrictoras. Además, detectaron que la inervación excesiva de las AAV, daba lugar a una producción anormal de péptidos vasodilatadores relacionados con el dolor. Por tanto, la inervación excesiva de las AAV, parece ser una fuente probable de dolor, hipersensibilidad, fatiga y SC en esta población. Propusieron además que esta alteración neurovascular, no sólo podría explicar los síntomas, sino también la exacerbación de los mismos frente a los cambios de temperatura (Albrecht et al., 2013).

Sin embargo, todo este proceso y la relación de las alteraciones vasculares con la SC, no ha sido aún estudiado de forma específica en el Fenómeno de Raynaud. La bibliografía referente a este aspecto es muy reducida y se limita a estudiar la tasa de permeabilidad de las AAV en las manos de pacientes con FR primario y secundario (Flavahan, 2015). Esto ha servido para corroborar que la respuesta frente al frío en las personas que padecen FR se caracteriza por una vasoconstricción excesiva,

cuantitativamente mayor que la que se produce en las personas sanas, sin embargo, son necesarios estudios que evalúen el rol de la hiperactividad del SNC en la respuesta vascular periférica en esta población.

1.2.1 Enfoque biopsicosocial del dolor crónico, hipervigilancia y catastrofización en el Fenómeno de Raynaud.

El dolor es un mecanismo de defensa y supervivencia del ser humano que actúa como una señal de alarma para proteger nuestro organismo. El concepto de dolor es un constructo amplio y complejo que debe abordarse desde un modelo biopsicosocial ya que no es un fenómeno puramente fisiológico, sino que está influenciado en gran medida por factores psicosociales. Por lo tanto, pueden influir en los procesos de dolor desde la edad, género, genética hasta el estrés, estado emocional, depresión, etc (Gatchel, Peng, Peters, Fuchs, & Turk, 2007).

Para que se produzca una adecuada percepción del dolor, a nivel fisiológico es precisa una participación coordinada del Sistema Nervioso Central (SNC) y periférico. En algunas ocasiones, cuando el dolor persiste y se mantiene durante el tiempo, como ocurre en el FR y muchas de las enfermedades asociadas al mismo, este mecanismo complejo deja de ser funcional. Aparecen entonces problemas derivados de alteraciones en la transmisión o modulación del dolor donde juegan un papel importante aspectos cognitivos y emocionales (Yunus, 2007a, 2007b).

Una de estas alteraciones es la catastrofización del dolor, que se caracteriza por la tendencia a magnificar el valor amenazante de los estímulos del dolor y sentirse impotente en el contexto del dolor, así como la incapacidad de inhibir los pensamientos relacionados con el dolor antes, durante o después de un estímulo doloroso (Edwards, Bingham, Bathon, & Haythornthwaite, 2006). El catastrofismo se entiende como un conjunto de procesos emocionales y cognitivos negativos en el que la rumiación sobre el dolor, los sentimientos de impotencia, magnificación, desamparo y el pesimismo influyen sobre las respuestas relacionados con el dolor (Edwards, Fillingim, Maixner, Sigurdsson, & Haythornthwaite, 2004; M. J. Sullivan, Rodgers, & Kirsch, 2001).

Aunque las investigaciones realizadas en los últimos años destacan que la catastrofización juega un papel fundamental en la experiencia del dolor en patologías como la artritis reumatoide y la fibromialgia, son necesarios más estudios para comprender mejor la naturaleza biopsicosocial del dolor y determinar la influencia del catastrofismo en pacientes que padecen dolor crónico (Edwards et al., 2006).

El catastrofismo está relacionado con mayores niveles de dolor, mayor depresión en los pacientes que lo padecen, mayores niveles de discapacidad y también con mayor atención al dolor (Edwards et al., 2006; Quartana et al., 2009). Asimismo, la evidencia científica pone de manifiesto que existe una relación positiva entre catastrofismo (o impotencia, un componente del catastrofismo) y una mala evolución de las enfermedades. Es decir, cómo las personas se enfrentan al dolor, es un predictor consistente de la situación clínica que van a desarrollar, ya que esto va a influir en la gravedad del dolor, la discapacidad relacionada con el dolor y la adaptación psicológica (Edwards et al., 2004). Un catastrofismo mayor predice una peor evolución de la enfermedad. Esto es debido a que la impotencia se correlaciona con una menor adherencia a los tratamientos médicos y un comportamiento de salud menos positivo, como por ejemplo no realizar ejercicio (Quartana et al., 2009).

Para comprender mejor la relación entre catastrofismo y la percepción del dolor, se ha estudiado en el laboratorio el proceso de catastrofización administrando estímulos nocivos en un entorno controlado (Edwards et al., 2004). Dentro de ellos, varios estudios han utilizado la aplicación de frío como estímulo doloroso y han demostrado que existen relaciones transversales entre las respuestas al estímulo por frío y mayores niveles de catastrofismo, asociándose tiempos de tolerancia más reducidos y puntuaciones de dolor más altas (Geisser, Robinson, & Pickren, 1992; Sullivan, Rodgers, et al., 2001; M Thastum, Zachariae, Schøler, Bjerring, & Herlin, 1997). En esta línea, otros estudios también demostrado que el pensamiento catastrófico, se relaciona con aumentos sostenidos de la contractilidad miocárdica y una elevación de actividad simpática (Edwards et al., 2006; A. Shah et al., 2019). Resultados similares han sido reportados cuando se valoran los umbrales de dolor térmico y la tolerancia (Geisser et al., 2003). En un estudio que valora el dolor eléctrico, se asociaron mayores puntuaciones de catastrofismo con una menor tolerancia y mayores grados de dolor frente a la estimulación eléctrica nociva (France,

France, Absi, Ring, & McIntyre, 2002). En un estudio similar, realizado en personas con artritis crónica juvenil, aquello pacientes con mayores niveles de catastrofismo presentaban menor tolerancia al estímulo por frío y umbrales más bajos de dolor al estímulo eléctrico (Mikael Thastum, Herlin, & Zachariae, 2005). Por lo tanto, se ha observado una asociación positiva entre catastrofismo, mayor sensibilidad al dolor y respuestas hiperalgésicas. Por tanto, la evidencia científica sugiere que el catastrofismo promueve procesos similares a los de la sensibilización central, pudiendo contribuir a sensibilizar el SNC, reportando una relación positiva entre catastrofismo y sensibilización al dolor (Edwards et al., 2006; Quartana et al., 2009).

Uno de los mecanismos hipotéticos por los cuales la catastrofización puede influir en las respuestas al dolor son los efectos directos que tienen de los procesos cognitivos en el procesamiento del dolor por parte del SNC. En este sentido, es sabido que los factores psicosociales se asocian con el desarrollo y mantenimiento del dolor crónico (Linton, 2000), y la presencia de catastrofismo se asocia con una mayor sensibilidad al dolor, por lo tanto, parece justificado que el catastrofismo podría jugar un papel importante en la modulación del dolor similar a la sensibilización (Edwards et al., 2004). Sin embargo, el mecanismo exacto por el cual el catastrofismo puede afectar a los sistemas fisiológicos como el sistema nervioso simpático o el eje hipotalámico hipofisario-suprarrenal aún se desconoce. La catastrofización amplifica el procesamiento del dolor en el SNC. Un mecanismo hipotético por el cual la catastrofización afecta la experiencia del dolor, promueve la sensibilización o interfiere con la inhibición del dolor en el SNC es que se ha observado que la reducción de la catastrofización da como resultado la activación de sistemas opioides endógenos descendentes que inhiben la nocicepción. También en un estudio con resonancia magnética en pacientes con fibromialgia se observó que los pacientes con mayores niveles de catastrofización tenían mayor activación de las regiones corticales involucradas en el procesamiento afectivo del dolor, como la corteza cingulada anterior y la corteza insular (Viane et al., 2003).

En general, la evidencia indica que la catastrofización puede amplificar el procesamiento del dolor y algunos investigadores postulan que las relaciones bidireccionales entre la catastrofización y el procesamiento nociceptivo pueden contribuir a la cronicidad de muchas dolencias (Wideman & Sullivan, 2011).

Otro punto importante a tener en cuenta es que la catastrofización aumenta la atención al dolor (hipervigilancia al dolor). Algunas investigaciones han examinado la hipótesis de que la catastrofización aumenta la experiencia del dolor a través de sus efectos en los procesos de atención (Peters, Vlaeyen, & van Drunen, 2000; Roelofs, Peters, McCracken, & Vlaeyen, 2003). Es decir, los altos niveles de catastrofismo pueden llevar a las personas a atender de manera selectiva e intensa a los estímulos relacionados con el dolor. Las personas con catastrofización experimentan más dificultades para controlar o suprimir los pensamientos relacionados con el dolor, rumian más sobre su dolor y su rendimiento físico y cognitivo se ve más afectado por la anticipación del dolor. En pacientes con fibromialgia, la catastrofización está fuertemente relacionada con una mayor atención al dolor y una mayor vigilancia de las sensaciones corporales (Peters et al., 2000). Tal y como se ha observado en estudios prospectivos, en pacientes con artritis reumatoide y dolor lumbar crónico, unos elevados índices de catastrofismo, se asocian con mayores niveles de hipervigilancia y miedo al movimiento, lo que lleva a estos pacientes a reducir su movilidad lo que se traduce en una pérdida fuerza muscular (Castañeda, Bigatti, & Cronan, 1998; Covic, Adamson, Spencer, & Howe, 2003; Lefebvre & Keefe, n.d.; Picavet, Vlaeyen, & Schouten, 2002).

También se ha podido determinar que la catastrofización tiene un impacto importante en el entorno social. La forma en cómo la comunidad reacciona al catastrofismo indica que las expresiones de catastrofismo generan respuestas de apoyo por los demás y que estás respuestas sociales, a su vez pueden reforzar las manifestaciones de dolor y las expresiones de catastrofismo. Las personas catastrofistas son percibidos por la sociedad como menos capaces de manejar el dolor y buscan un mayor apoyo social (Cano, 2004; Giardino, Jensen, Turner, Ehde, & Cardenas, 2003; Thorn, Keefe, & Anderson, 2004).

En relación el FR, como hemos visto, tanto la sensibilización central como la catastrofización participan en la amplificación de la respuesta al dolor, y pueden contribuir al aumento de las respuestas vasoconstrictoras periféricas frente a una situación estresante o un estímulo doloroso (Nagai, Hoshide, & Kario, 2010; Shah et al., 2019). Investigaciones anteriores han observado que el estrés psicológico y físico puede inducir vasoconstricción arteriolar y reducir el flujo sanguíneo periférico. Aunque los mecanismos concretos de este

proceso aún se desconocen, es probable que la vasoconstricción debida al estrés sea causada en parte, por el aumento de la actividad del sistema nervioso simpático. Estudios previos también han encontrado que la vasoconstricción periférica en respuesta a situaciones de estrés se asoció con una mayor activación en las áreas del cerebro involucradas en la regulación de las emociones como son la corteza prefrontal medial (giro cingulado anterior) la ínsula y la amígdala, que cuentan con vías directas e indirectas que regulan a su vez las respuestas cardiovasculares periféricas al estrés (de Morree, Szabó, Rutten, & Kop, 2013; Kogler et al., 2015; Nagai et al., 2010). En este sentido, la sensibilización central y la catastrofización se han descrito como posibles factores subyacentes que pueden aumentar el estrés percibido y, por lo tanto, pueden influir en la respuesta vascular y la evolución del FR (Devulder et al., 2011; Evers, Kraaimaat, Geenen, Jacobs, & Bijlsma, 2003; A. Shah et al., 2019).

Como hemos podido ver, tanto la catastrofización como la sensibilización están estrechamente relacionadas con el éxito de los tratamientos, la evolución de la enfermedad y el grado de discapacidad. Su abordaje, debería ser un objetivo principal en las intervenciones multidisciplinares para tratar el dolor. Sin embargo, la evidencia científica en este campo aún es escasa, por lo que es necesario seguir realizando investigaciones que nos permitan conocer mejor sus mecanismos de acción y proponer nuevas estrategias de tratamiento para actuar sobre todos estos aspectos determinantes en el procesamiento del dolor.

1.3 Grado de funcionalidad de los miembros superiores y discapacidad percibida en el Fenómeno de Raynaud: descripción y evaluación.

El FR cursa con síntomas físicos debilitantes, que dan lugar a una alteración de la funcionalidad, así como a una insatisfacción con la imagen corporal y una reducción de la calidad de vida en las personas que lo padecen (Herrick, 2017; Hughes & Herrick, 2016).

Debido a los síntomas con los que cursa el FR, la funcionalidad de la mano se ve alterada con frecuencia, lo cual a su vez, va a causar una pérdida de la función general de las extremidades superiores que finalmente se va poner de manifiesto en una dificultad para llevar a cabo las actividades de la vida diaria, actividades laborales o de ocio y tiempo

libre (Uppal, Dhaliwal, & Butler, 2014). La mano es una estructura compleja que juega un papel muy importante para las relaciones entre los seres humanos, está involucrada en prácticamente todas nuestras actividades de la vida diaria, tiene una gran variedad de funciones y necesita una armonía completa entre todas las estructuras para funcionar correctamente (Carvalho R, Mazzer N, & Barbieri C., 2012).

En ambas formas de FR, se produce una pérdida de funcionalidad, que va a variar y depender de múltiples factores, como son la duración, la frecuencia y la gravedad de los ataques, la presencia de úlceras en los dedos, el dolor y las patologías concomitantes relacionadas (Uppal et al., 2014). Los resultados de una encuesta realizada por Huhges et al. (2015), indicaron que el 71% de los pacientes con FR primario y el 87% de los pacientes con FR secundario tenían dificultades en el desempeño de las actividades de la vida diaria y declararon haber tenido que realizar cambios y ajustes en su rutina diaria debido a la discapacidad funcional que les originaba el FR. Estos pacientes presentaron además elevados niveles de ansiedad y una reducción de su calidad de vida. En esta línea, aunque el FR no es una condición potencialmente mortal, se puede observar que tiene un impacto relevante en diferentes aspectos de la vida y las actividades de estos pacientes así como en su estado general de salud, lo que puede afectar a su calidad de vida y a su estado emocional (De Angelis et al., 2008; Giurgea et al., 2015; Herrick, 2017).

Existe una literatura muy limitada basada en la exploración de la discapacidad de las manos y extremidades superiores en pacientes con FR y el papel que esto desempeña en la práctica de sus actividades de la vida diaria, trabajo, deportes o actividades de ocio. Por todo ello, es importante que los profesionales de la salud, como los fisioterapeutas y los terapeutas ocupacionales, dedicados a evaluar y tratar lesiones en las manos, como las que ocurren en el FR, tengan en cuenta y evalúen estos aspectos.

Para realizar una exploración completa de los aspectos musculoesqueléticos que posibilitan la funcionalidad de la mano, se deberían valorar parámetros como los rangos de amplitud articular y la fuerza muscular. Dentro de las medidas que más se utilizan para conocer la funcionalidad de la mano está la medición de los rangos de movimiento (RM) articular activo y pasivo, mediante goniometría. Se utiliza comúnmente en la evaluación y en el seguimiento de los pacientes con discapacidad de la mano debido a múltiples

patologías. Según nuestro conocimiento, no hay estudios previos que incluyan la evaluación de los rangos de movimiento y analicen su relación con la función de la mano en pacientes con FR. Sin embargo, diversos estudios realizados en pacientes con otras patologías reumática determinaron que hay una disminución de los RM de las articulaciones de la mano y que esto está relacionado con mayores niveles de discapacidad del brazo, el hombro y mano (Pérez-Mármol et al., 2017, 2016; Ramos-Casals et al., 2015). Carvalho et al. (2012), enumeraron algunos factores que generalmente pueden influir en los resultados de la medición de los RM en la población general como la presencia de edema o dolor, la edad (las personas más jóvenes tienen RM más altos que las personas de edad avanzada), el sexo (las mujeres tienen una mayor laxitud articular que los hombres) y los RM pasiva o activos (los RM pasivos son mayores que los activos, la medición pasiva hace posible medir el máximo RM de la articulación).

Para desarrollar un diagnóstico óptimo de los pacientes con FR, debe investigarse la afectación articular, especialmente en el FR secundario a esclerodermia, síndrome de Sjögren, lupus sistémico y artritis reumatoide puesto que es conocido que estas patologías causan limitaciones en la movilidad articular, aunque el número de articulaciones involucradas en la artritis varía, las más afectadas son las articulaciones interfalángicas proximales y metacarpofalángicas de las manos en el 35% de los pacientes (Ramos-Casals et al., 2015). Un estudio realizado en pacientes con esclerosis sistémica (Sandqvist, Hesselstrand, & Eberhardt, 2009), determinó que estos pacientes conservaban la movilidad y la capacidad de la mano durante los primeros años de la enfermedad, pero mostraron que los pacientes con FR asociado tuvieron peores resultados de movilidad al inicio y en el seguimiento y que la extensión del dedo era el movimiento más afectado en el 50% de los pacientes.

Por otro lado, para valorar la funcionalidad de la mano, también debería medirse la fuerza muscular. En este sentido, diferentes estudios (Landim et al., 2017; Merkel et al., 2002; Uppal et al., 2014) de la literatura revisada estuvieron de acuerdo en que el FR asociado con esclerodermia tenía un efecto debilitante grave en los pacientes. Generalmente, para obtener una medición objetiva la fuerza muscular, se usa un dinamómetro y se valora la fuerza en movimientos donde se realizan diferentes tipos de

pinzas con los dedos (Dermid, Evenhuis, & Louzon, 2001; Mathiowetz, Weber, Volland, & Kashman, 1984; Pérez-Mármol et al., 2016).

Finalmente, se debería medir la discapacidad que origina el FR en los diferentes ámbitos de la vida cotidiana de estos pacientes. Para ello una de las herramientas que se utilizan de forma más frecuente en la literatura es la versión reducida del cuestionario de discapacidad del brazo, el hombro y la mano o Quick-DASH, Shortened Disabilities of the Arm, Shoulder and Hand Questionnaire (Beaton et al., 2012; Gummesson, Ward, & Atroshi, 2006) Se suele utilizar en pacientes que presentan una o más discapacidades asociadas del brazo, el hombro y la mano y evalúa tanto discapacidad percibida por el paciente para realizar diversas actividades, incluidas las actividades de la vida diaria, como los síntomas asociados de dolor, rigidez o pérdida de fuerza. Es un cuestionario estandarizado y autoadministrado que considera toda la extremidad superior como una sola unidad funcional. Consta de un primer módulo con 11 preguntas, que miden la función física, social y los síntomas en las extremidades superiores en personas con trastornos que afectan la funcionalidad de la extremidad superior. Estas preguntas se puntúan en una escala cuyo rango va de 0 a 5, cada uno de los cinco puntos de la escala está asociado con un adjetivo para referirse al nivel de severidad o función. La suma total ofrece una puntuación de la discapacidad que presenta la persona y puede oscilar entre 0 (sin discapacidad) y 100 (la mayor discapacidad). Las puntuaciones más altas se corresponden con una función más reducida y mayor gravedad de los síntomas. Este cuestionario, tiene además, dos módulos adicionales opcionales, con 4 preguntas cada uno destinadas a medir los síntomas y la función alterada en personas que practican deportes y artes escénicas o realizan un trabajo (Hervás et al., 2006). Para poder calcular la puntuación en todos los módulos no puede haber más de una respuesta sin contestar. Este cuestionario ha demostrado tener una buena fiabilidad, validez y capacidad de respuesta y se puede usar en pacientes con trastornos de las extremidades superiores con un alfa de Cronbach de 0.90 y un coeficiente de correlación de Pearson de 0.70 (Gummesson et al., 2006).

Estudios realizados en diferentes patologías, como la esclerodermia (Sandqvist, Wollmer, Scheja, Wildt, & Hesselstrand, 2018), el síndrome de Sjögren (Ramos-Casals et al., 2015), el síndrome del túnel carpiano (Roh et al., 2017) y el síndrome de vibración mano-brazo (Mason, Poole, & Elms, 2005), donde estaba presente el FR de forma

secundaria, coincidieron en que la presencia del FR afectó a la función de la mano estos pacientes. En este sentido observaron que las tasas de discapacidad fueron significativamente más altas en los pacientes que tenían asociado el FR en comparación con aquellos que no lo tenían. Un estudio en pacientes con esclerosis sistémica (Bérezné et al., 2011) informó que el FR tenía un efecto incapacitante en el desempeño de las actividades de la vida diaria y el trabajo. Estos pacientes presentaban un deterioro de la función de la mano, necesitaban ayuda para realizar las actividades diarias o tenían una pensión por discapacidad.

La forma exacta en la que el FR afecta a la funcionalidad de la mano sigue sin estar clara aún. Debemos tener en cuenta que la función de la mano en estos pacientes puede verse comprometida no solo por las alteraciones vasculares, sino también por el engrosamiento de la piel, el dolor y la inflamación característicos de patologías a las que puede ir asociado. Por tanto, la discapacidad en los pacientes con FR parece depender de múltiples factores. Los últimos estudios realizados al respecto, indican que la discapacidad de la extremidad superior en los pacientes con FR parece estar más relacionada con la frecuencia de los ataques que con la extensión de la afectación en los dedos (Mason et al., 2005; Palmer, Griffin, Syddall, Cooper, & Coggon, 2002). Mason et al. (2005) sugirieron que en pacientes con síndrome de vibración mano-brazo y FR asociado, la discapacidad de la extremidad superior parece estar más relacionada con la alteración de los componentes neurosensoriales que con los síntomas vasculares.

Partiendo de la base de que el FR es una condición clínica compleja, que tiene un impacto relevante en el estado de salud general y la funcionalidad de las personas que lo padecen, consideramos que es necesario explorar en profundidad la relación entre el deterioro vascular y la funcionalidad con la discapacidad en los sujetos con FR primario y secundario. Creemos que son necesarios estudios adicionales, que incluyan medidas que valoren estos aspectos, ya que esto podría ayudar a mejorar el conocimiento sobre el FR, a determinar la carga de la enfermedad (psíquica, socioeconómica) y el impacto del FR en las actividades de la vida diaria y la calidad de vida de las personas que lo padecen.

1.4 Diagnóstico y abordaje terapéutico del Fenómeno de Raynaud.

La Sociedad Europea de Medicina Vascular (SEMV) en su última guía basada en la evidencia de 2017 (Belch et al., 2017), establece recomendaciones básicas para el diagnóstico y el tratamiento del FR en función del grado y de la evidencia que las sustenta. El grado de recomendación se relaciona con la fuerza de la evidencia, no es una medida de la importancia clínica de la recomendación. En dicha guía se establecieron los siguientes criterios que fundamentan los grados y niveles de evidencia: **Grado I**. Evidencia de que un tratamiento o procedimiento es beneficioso y eficaz; **Grado II**. Conflicto de evidencia y/o diferencias en la opinión de expertos en relación con el beneficio/eficacia del tratamiento/procedimiento; **Grado IIa**. El peso de la evidencia u opinión está a favor del beneficio/eficacia; **Grado IIb**. Beneficio/eficacia no están bien establecidos; **Grado III**. Evidencia o acuerdo de que el tratamiento no es beneficioso y no es eficaz, y en algunos casos incluso puede ser nocivo. Niveles de evidencia: **Nivel A**. Datos derivados de muchos ensayos clínicos controlados aleatorizados o de metanálisis; **Nivel B**. Datos derivados de un ensayo clínico controlado aleatorizado o grandes ensayos clínicos no aleatorizados; **Nivel C**. Consenso de expertos o datos de pequeños estudios, registros o estudios retrospectivos.

Las principales recomendaciones consensuadas se desarrollan a continuación (Belch et al., 2017).

1. Se debe realizar una historia completa y un examen de todos los pacientes con FR que acuden a atención primaria para asegurar un diagnóstico correcto de cualquier condición subyacente, ya que el diagnóstico precoz y la detección de la afectación de los órganos mejora una posible ETC. **Grado IIa-Nivel** C.

2. Todos los pacientes que presentan FR deben someterse a pruebas de sangre que incluyan un hemograma completo, con la tasa de sedimentación eritrocítica o proteína C reactiva y los anticuerpos antinucleares, así como una capilaroscopia cuando esté disponible. **Grado IIa-Nivel C**.

3. La capilaroscopia solo debe realizarse con equipos de buena calidad óptica y por una persona experimentada, generalmente en atención secundaria o terciaria. **Grado IIa-Nivel C.**

4. La microscopía capilar es una herramienta de diagnóstico útil para detectar patrones capilares anormales que son fuertes predictores de ETC y debe ser empleada por la atención secundaria. **Grado IIa-Nivel.**

5. Los niños menores de 12 años deben ser remitidos a atención secundaria puesto que el FR Primario es menos común en este grupo de edades. **Grado IIa-Nivel C.**

6. Los pacientes con FR deben ser derivados a atención secundaria cuando haya evidencia de un trastorno asociado o de enfermedad vascular oclusiva, los síntomas sean graves o progresen a pesar de la primera línea de tratamiento de cambios de los estilos de vida y el farmacológico. **Grado IIa-Nivel C.**

7. El cambio de los estilos de vida es un medio eficaz para controlar los ataques en el FR, debe incluir usar una ropa cálida, cesar el tabaquismo, evitar factores desencadenantes como el frío y está indica una evaluación de terapia ocupacional en el caso de necesitar ayudas. **Grado IIa-Nivel C.**

8. Los bloqueadores de los canales de calcio son el tratamiento farmacológico de primera línea recomendado para el FR si la modificación del estilo de vida no ha funcionado. **Grado I-Nivel A**.

9. La nifedipina en su forma de liberación lenta, debe usarse para minimizar los efectos secundarios vasodilatadores debilitantes y la corta duración de la acción. Se debe tener cuidado de aumentar la dosis cuando los síntomas aumenten para evitar efectos secundarios. Si los efectos secundarios no son graves, se debe alentar a los pacientes a que los toleren durante dos o tres semanas, ya que pueden disminuir. **Grado IIa - Nivel C.**

10. No existen pruebas sólidas que respalden el tratamiento quirúrgico del FR, pero este puede estar indicado en ciertas situaciones, por ejemplo, en la ulceración digital relacionada con la esclerosis sistémica. **Grado IIb - Nivel C.** Área donde falta evidencia/área para estudio adicional.

A pesar de las recomendaciones básicas anteriormente mencionadas para la detección del FR, la literatura científica propone muchos métodos de diagnóstico diferentes para definir este fenómeno (Goundry, Bell, Langtree, & Moorthy, 2012; Hughes & Herrick, 2016). En el estudio y diagnóstico del FR se pueden incluir informes autoadministrados, como el diario de puntuación de condición de Raynaud (RCS en inglés); medidas de la duración y frecuencia de los ataques del FR o una evaluación física global y evaluación local de la mano (Hirschl et al., 2006; Hughes & Herrick, 2016). Para evaluar las alteraciones a nivel vascular se pueden utilizar diferentes técnicas no invasivas, como la capilaroscopia ungueal, la termografía y el láser Doppler (Matthieu Roustit, Blaise, Millet, & Cracowski, 2011). Es común que se evalúe la respuesta funcional al frío realizando una prueba de frío local y analizar el perfil bioquímico para completar el diagnóstico (Herrick & Murray, 2018). Los ensayos terapéuticos recientes han propuesto que además, se deben tener en cuenta nuevos métodos para examinar el FR que incluyan medidas de la gravedad y el impacto de los episodios; evaluación del dolor con la Escala analógica visual (EVA) y evaluación de la discapacidad en las actividades diarias, aunque estas medidas de evaluación no se han validado para esta patología. Sin embargo, hasta la fecha, no se ha implementado universalmente ningún método para realizar el diagnóstico del FR (Hirschl et al., 2006; Maverakis et al., 2014).

Desde el punto de vista terapéutico, en la actualidad, existe una amplia variedad de opciones para abordar el tratamiento del FR (García-Carrasco et al., 2008; Herrick, 2017). Hay diferentes modalidades de tratamiento que van desde el uso de medidas conservadoras (educación y cambios en el estilo de vida), hasta los tratamientos farmacológicos, el uso de terapia tópica, cirugía, reparación vascular, uso de toxina botulínica o el uso de medicina complementaria y alternativa; sin embargo, ninguna de estas terapias ha mostrado una eficacia definitiva y muchas de ellas han demostrado tener importantes efectos secundarios (García-Carrasco et al., 2008; Linnemann & Erbe, 2016).

El abordaje terapéutico del FR va a depender de la intensidad y la gravedad de los síntomas que estén presentes, lo que va a venir determinado en gran parte por el tipo de FR que padezca la persona, primario o secundario (Herrick, 2017). En general, el objetivo principal de las terapias usadas en el tratamiento del FR es reducir la gravedad y la frecuencia de las manifestaciones clínicas así como las posibles complicaciones derivadas (Prete et al., 2014). Las diferentes terapéuticas se centran generalmente en favorecer la vasodilatación, inhibir la vasoconstricción, reducir el daño endotelial e inhibir la agregación plaquetaria (Goundry et al., 2012).

La primera línea de tratamiento para ambas formas de FR son las medidas conservadoras que consisten es realizar cambios en el estilo de vida de los pacientes. Dentro de estas medidas conservadoras podemos encontrar por ejemplo mantener una alta temperatura corporal central mediante el uso de ropa y utensilios adecuados (guantes, ropa de abrigo); evitar la exposición al frío; dejar de fumar y evitar consumir café o alcohol (Herrick, 2017; Stringer & Femia, 2018).

El tratamiento de la forma primaria de FR, en un inicio, es generalmente conservador y suele ser suficiente. Si los pacientes no responden adecuadamente a estas medidas, entonces se debe considerar el uso de la terapia farmacológica que consiste fundamentalmente en la administración de medicamentos vasodilatadores (Herrick, 2017). En los pacientes con FR secundario, las medidas conservadoras no son suficientes y por lo general van a requerir un tratamiento con terapia farmacológica (Stringer & Femia, 2018).

A nivel de tratamiento farmacológico, la mayoría de las terapias, siguen siendo insatisfactorias en la actualidad, debido a los efectos adversos que producen y a que presentan una mínima eficacia (García de la Peña Lefebvre et al., 2015). En este sentido, los bloqueadores de los canales de calcio, como la nifedipina, se consideran generalmente la primera opción farmacológica, aunque una revisión sistemática reciente (Rirash et al., 2017) determina que estos medicamentos solo tienen un efecto moderado en la reducción de la frecuencia y la gravedad de los ataques. En los últimos años se está estudiando el uso de nuevos fármacos vasodilatadores (Ennis, Hughes, Anderson, Wilkinson, & Herrick, 2016; Stewart & Morling, 2012), pero aún no hay evidencia suficiente para poder permitir su uso en el FR. Nuevos enfoques farmacológicos para el tratamiento del FR, que están

más avanzados, incluyen a los inhibidores de la fosfodiesterasa-5 como el sildenafil, tadalafil, vardenafil e inhibidores de la fosfodiesterasa-3 tales como como cilostazol (Caglayan, Axmann, Hellmich, Moinzadeh, & Rosenkranz, 2012; Herrick et al., 2011; Shenoy et al., 2010). También se está estudiando el efecto de los suplementos de óxido nítrico (Matthieu Roustit et al., 2013) como los inhibidores de la fosfodiesterasa tipo 5, aunque su eficacia es moderada en la forma secundaria de FR.

Por otro lado, también se están utilizando terapias intravenosas (Ilioprost) y orales con prostaglandinas (Ingegnoli et al., 2019b; Shah et al., 2013), que han demostrado ser potentes vasodilatadores y tener importantes efectos antiagregantes plaquetarios, por lo que son efectivos para reducir la frecuencia y la gravedad de los ataques y las úlceras digitales en pacientes con FR secundario a esclerosis. Sin embargo, el gran inconveniente de estas terapias es que tienen grandes efectos secundarios puesto que producen una vasodilatación sistémica, hipotensión, cefaleas, requieren hospitalización y son caras.

En los últimos años se ha evolucionada hacia un enfoque tópico de la terapia y se está estudiando el uso terapéutico de nitrato tópico (Anderson et al., 2002; Chung et al., 2009), pero actualmente esta terapia aún no tiene licencia para su uso en el tratamiento del FR. En esta línea de tratamiento también se puede incluir la aplicación de toxina botulínica mediante inyecciones en las manos de los pacientes con FR. Una revisión reciente (Zebryk & Puszczewicz, 2016) destaca que la evidencia para evaluar la eficacia de la toxina botulínica en el tratamiento de la FR es aún insuficiente.

Cuando los pacientes no responden al tratamiento farmacológico y presentan síntomas severos como la presencia de úlceras o gangrena se puede realizar un tratamiento quirúrgico (García-Carrasco et al., 2008). Generalmente este consiste en realizar un desbridamiento quirúrgico o una operación bien para retirar una parte de la falange dañada o bien para realizar una amputación completa. Otra intervención quirúrgica que se ha utilizado en el FR es la simpatectomía tanto a nivel de miembros superiores como a nivel digital, pero la bibliografía indica que no existe una buena base de evidencia científica que respalde el uso de esta cirugía en el tratamiento del FR (Belch et al., 2017).

Por otro lado, en los últimos años se siguen estudiando y desarrollado nuevos enfoques de terapéuticos para el FR, como la estimulación de la médula espinal (Wolter & Kieselbach, 2011), la terapia con láser (Al-Awami, Schillinger, Maca, Pollanz, & Minar, 2004), el uso de la acupuntura, terapias alternativas o el uso de complementos alimenticios, pero aún está por determinar el lugar real que estas terapias pueden ocupar en el tratamiento de esta patología debido a la poca evidencia existente (Linnemann & Erbe, 2016).

La gran variedad de tratamientos y los limitados indicios de su efectividad en el FR, ponen de manifiesto la necesidad de seguir investigando nuevas alternativas terapéuticas así como establecer la eficacia de las mismas.

1.4.1 Evidencia científica sobre la utilización de la termoterapia, laserterapia y estimulación eléctrica, para la modulación de la vasodilatación en el Fenómeno de Raynaud.

1.4.1.1 Termoterapia.

Se han utilizado diferentes formas de termoterapia en el tratamiento del FR. Dentro de ellas, un método simple de calentamiento de las manos, que ha sido estudiado es introducir las manos en agua caliente (Goodfield & Rowell, 1988). Según este sistema, los sujetos debían introducir las manos durante 5 minutos en agua caliente cada cuatro horas durante todo el día durante seis semanas alternas. Este sistema demostró reducir el número y la duración de los ataques, así como un aumento del flujo sanguíneo durante las semanas que se aplicaba. Por lo tanto, el simple calentamiento de las manos con agua caliente produce una vasodilatación que parece ser efectiva en el manejo del FR, sin el riesgo de los efectos secundarios de los tratamientos farmacológicos. Posteriormente, se ha descrito que es más práctico que los pacientes se calienten las manos por inmersión en agua tibia entes de salir a la calle, que realizar un calentamiento cada cuatro horas. Los principales inconvenientes de este método son que los efectos no se muestran de forma consistente en todos los pacientes y la duración del efecto nunca es superior a dos horas, aunque el uso combinado de guantes hace que el efecto se prolongue. En otras ocasiones, los pacientes

deciden usar otros dispositivos de calentamiento como botellas de agua caliente o calentadores de mano (Goodfield & Rowell, 1988).

Se ha estudiado también la efectividad de otras formas de termoterapia superficial mediante el uso de guantes de "termoflujo", que son prendas impregnadas de cerámica (95% polipropileno y polietileno; 5% cerámica) que absorben la radiación infrarroja del medioambiente y del cuerpo (0,76 a 4 micrómetros de longitud de onda). Esto se traduce en energía térmica que se refleja en los tejidos subyacentes y produce una elevación de las temperaturas del tejido dérmico y subcutáneo. El uso de estas prendas ha demostrado producir una vasodilatación que mejora la circulación, reduce los niveles de dolor y mejora la destreza de agarre en los pacientes con FR. Sin embargo, los efectos son moderados y puede producirse irritación de la piel (Ko & Berbrayer, 2002).

Otro de los métodos de termoterapia con evidencia contrastada ha sido el tratamiento mediante infrarrojos A (IR-A) en pacientes con FR secundario a esclerodermia. En el FR, la radiación infrarroja, produce una hipertermia leve, que es efectiva para tratar las manifestaciones de la enfermedad ya que reduce su severidad y puede usarse como un tratamiento complementario del tratamiento farmacológico. El efecto a nivel térmico y la reducción del dolor en la EVA tras 5 sesiones se mantiene hasta 6 semanas después de finalizar el tratamiento. Sin embargo esta terapia sólo tuvo un efecto de mejora transitorio sobre el grosor de la piel y el nivel de dolor en las articulaciones por la esclerodermia asociada (Foerster et al., 2005).

1.4.1.2 Laserterapia.

La terapia láser de baja potencia produce una bioestimulación atérmica, usando fuentes de luz (fototerapia), que emiten una energía baja, generalmente dentro del espectro rojo o infrarrojo (Al-Awami et al., 2004). La bibliografía describe que esta terapia se ha utilizado en pacientes con alteraciones vasculares o enfermedades reumáticas y sus efectos son ambiguos (Hirschl, Katzenschlager, Francesconi, & Kundi, 2004).

En el FR, al usar esta terapia, se ha observado que la frecuencia y la intensidad de los ataques, se reducen sustancialmente, pero se observan diferencias de los efectos

terapéuticos en los pacientes que experimentan diferentes intensidades de vasoespasmos y distintas formas de FR (Al-Awami et al., 2004; Hirschl et al., 2004). Los investigadores destacan que esto puede deberse a factores independientes del endotelio que sugieren que hay una heterogeneidad intrínseca entre el FR primario y secundario (Hirschl et al., 2004). Son necesarios más estudios para demostrar la eficacia del tratamiento con terapia láser y poder establecerla como una nueva terapia no farmacológica para el FR.

1.4.1.3 Estimulación eléctrica.

La electroestimulación medular (EEM) es un tratamiento que se puede usar en aquellos casos de FR severo que no responden a los tratamientos convencionales (Report, 2007; Wolter & Kieselbach, 2011). Su uso se basa en la teoría de Melzack y Wall de la doble puerta de control del dolor. Este tratamiento presenta varios inconvenientes, en primer lugar, es invasivo, pues se tiene que realizar una incisión y es necesario el recambio de la batería del dispositivo cada cierto tiempo. Por otro lado nos encontramos con una falta de evidencia científica sobre sus efectos reales. En la actualidad existen pocas publicaciones en relación a este tratamiento y su uso en el FR y la mayoría versan sobre casos aislados o series de casos (Mercader et al., 2003; Münster, Tiebel, Seyer, & Maihöfner, 2012; Report, 2007; Wolter & Kieselbach, 2011).

Otra modalidad de estimulación eléctrica que se ha usado en el tratamiento del FR es la corriente galvánica mediante iontoforesis (Murray, Herrick, Gorodkin, Moore, & King, 2005). En realidad, hasta la fecha, la iontoforesis con fármacos vasodilatadores se ha utilizado más para cuantificar la función endotelial en el FR que como una alternativa terapéutica al tratamiento convencional (Anderson, Moore, Lunt, & Herrick, 2004). Sin embargo, los resultados de estos estudios plantearon la cuestión de si se podría aplicar la iontoforesis terapéuticamente en pacientes con FR. En esta línea Murray et al. (2008), desarrollaron un método para aplicar iontoforesis sobre un solo dedo. El propósito de esta investigación preliminar era probar la hipótesis de que se podían aplicar fármacos vasoactivos, en este caso cloruro de acetilcolina (ACh) en áreas concretas del cuerpo sin que se produjeses efectos sistémicos. Concluyeron que serían necesarios estudios posteriores usando fármacos vasodilatadores para conseguir un efecto más duradero y poder determinar si la iontoforesis es una posible terapia para el FR (Murray et al., 2008).

También se ha usado la iontoforesis en pacientes con FR secundario a esclerodermia y demostró que se produce una mejora clínica de los síntomas, mejoraba la flexibilidad de los tejidos, disminuía la sensibilidad al frío y mejoraba la coloración de la piel (Gollins, Carpenter, Steen, Bulinski, & Mahendran, 2019).

Por otro lado, estudios previos, han aplicado vasodilatadores vasculares periféricos (antagonistas de los canales de calcio), mediante iontoforesis en sujetos adultos sanos solos o en combinación con lidocaína para estudiar sus efectos sobre el umbral del dolor. Cuando los vasodilatadores se aplicaron solos elevaron el umbral del dolor en el mismo grado que la lidocaína: al aplicarse los antagonistas del canal del calcio en combinación con lidocaína, la elevación del umbral del dolor no cambió, pero la duración de la acción analgésica se prolongó durante más tiempo en comparación con la lidocaína sola. Estos resultados sugieren que el canal de calcio juega un papel importante en el mecanismo de control del dolor y plantea la posibilidad de usar de forma clínica la administración mediante iontoforesis de los antagonistas del canal del calcio en el manejo del dolor (Taniguchi, Miyagawa, Mizutani, Honda, & Oyama, 1995).

1.5 Efectos vasculares y analgésicos de la estimulación eléctrica mediante iontoforesis con agua corriente.

Desde el punto de vista terapéutico, podemos utilizar la estimulación eléctrica mediante corriente galvánica debido a los cambios fisiológicos que produce en el organismo. La corriente galvánica es una corriente continua, de baja intensidad (máximo 200 miliamperios) y baja tensión entre 60-80 Voltios (Gollins et al., 2019; Sloan & Soltani, 1986; Zhou et al., 2018). El flujo de la corriente a través de nuestro organismo origina tres efectos principales: efecto electrotermal, efecto electroquímico y efecto electrofísico (Albornoz-Cabello, M., Maya-Martín, J., & Toledo-Marhuenda, 2016).

a. **Efecto electrotermal**. El paso de la corriente por un medio, hace que las partículas del mismo vibren, lo que origina una producción de calor y da lugar a una elevación de la temperatura (Albornoz-Cabello et al., 2016; Watson, 2009)

b. **Efecto electroquímico.** El agua es un buen conductor y por acción de la corriente eléctrica, los iones de la solución migran hacia los electrodos. El cuerpo humano está compuesto en más del 80% por agua y su comportamiento electrolítico al paso de la corriente eléctrica es similar al de una disolución de cloruro sódico. Los líquidos intersticiales y corporales son conductores electrolíticos y al aplicar una corriente se produce en ellos una disociación electrolítica. De esta manera, los cationes se desplazan hacia el cátodo que es el electrodo negativo y los aniones hacia el ánodo positivo, soltando o tomando electrones para transformarse en elementos neutros y poder así reaccionar con el agua. Se produce por tanto una reacción ácida en el electrodo positivo liberándose ácido clorhídrico. En el electrodo negativo se produce liberación de hidróxido sódico. Frente a estas reacciones químicas el organismo responde aumentando el flujo sanguíneo a nivel local para restaurar el pH tisular (Albornoz-Cabello et al., 2016; Rodríguez Martín, 2014).
c. **Efecto electrofísico.** Se produce en aquellas moléculas que tenemos en nuestro organismo que están cargadas eléctricamente como las proteínas y que con el paso de la corriente se mueven hacia alguno de los polos, sin que se produzcan cambios a nivel molecular. Este movimiento iónico produce excitación a nivel de los nervios periféricos, ya que modifica el flujo iónico a través de las membranas celulares, por el paso de sodio y el potasio. Esto puede dar lugar a respuestas vasculares (con un potente estímulo de la circulación de la zona), activación de mecanismos analgésicos endógenos o contracciones de la musculatura (Albornoz-Cabello et al., 2016; Rodríguez-Martín, 2014)

Cuando aplicamos una corriente galvánica sobre una zona corporal, la resistencia de la piel de esa zona va disminuyendo de forma gradual y el paciente puede tolerar cada vez mayores dosis de corriente. El paso de la corriente se percibe inicialmente como una sensación de pinchazos y posteriormente como una sensación agradable de calor. La corriente galvánica va a producir una hiperemia de la piel, sobretodo en el polo negativo. Este enrojecimiento puede durar entre diez minutos y media hora y se debe a la vasodilatación refleja que produce el cambio de pH de la piel, lo que a su vez aumenta el

flujo sanguíneo a la zona. Esto mejora la nutrición tisular y tiene un efecto analgésico y antiinflamatorio. La corriente tiene un efecto estimulante del sistema nervioso bajo el polo negativo bajo y un efecto analgésico bajo el positivo (Watson, 2009).

La forma más frecuente de uso de la corriente galvánica es mediante iontoforesis. La iontoforesis se define como el proceso no invasivo de introducir al interior del organismo iones de sales solubles a través de la piel por medio de un campo eléctrico generado por una corriente continua de baja frecuencia con fines diagnósticos y terapéuticos (Murray et al., 2005; Sloan & Soltani, 1986). Su efecto inmediato es la mejora la absorción de los medicamentos, presentado diversas ventajas frente a otros métodos de administración, ya que se disminuyen los efectos secundarios de los medicamentos a nivel sistémico, la aceptación de los pacientes suele ser buena y se evita el miedo por ejemplo a métodos más invasivos como la inyección (Murray et al., 2005).

La técnica fue descrita por primera vez en 1747 por Veratti y desarrollada posteriormente por Galvani. El uso de la corriente galvánica se hizo muy popular en el siglo XIX y empezó a utilizarse en tratamientos neurológicos, ginecológicos y genitourinarios. Esta técnica perdió temporalmente su popularidad hacia fines del siglo XIX cuando se hicieron nuevos avances en el campo de la electroterapia. A principios del siglo XX Leduc revisó la técnica e introdujo el término de iontoterapia, demostrando que se podían introducir medicamentos en el organismo a través de la piel con el uso de la corriente. Este descubrimiento hizo de nuevo aumentar el foco de atención en esta técnica, lo que condujo al estudio de numerosas aplicaciones posteriores. El interés por el uso de la iontoforesis ha ido variando durante el siglo XX y XXI recibiendo diferentes denominaciones como galvanización o ionización médica (Sloan & Soltani, 1986; Watson, 2009). En la actualidad estamos presenciando una fase más de redescubrimiento ya que esta sencilla técnica tiene aún mucho que ofrecer y quedan por aclarar muchas de sus complejidades (Rodríguez-Martín, 2014).

La iontoforesis ha sido implementada terapéuticamente para una amplia gama de aplicaciones en el campo de la medicina. El más común es el tratamiento de hiperhidrosis (sudoración excesiva) donde se suele utilizar iontoforesis con agua corriente. El

tratamiento ha demostrado tener un éxito considerable, pero se debe aplicar se forma continuada ya que los resultados no son permanentes (Albornoz-Cabello et al., 2016).

Dentro de las aplicaciones de la iontoforesis se incluyen el tratamiento del lupus, cáncer de piel, úlceras en la piel secundaria a diabetes, patología isquémica vascular, esclerodermia, infecciones por hongos, para producir anestesia por otorrinolaringólogos y dentistas, dermatitis, vitíligo, bursitis, neuritis, fibrosis, aplicaciones en oftalmología, iontoforesis antibiótica, entre otras muchas (Murray et al., 2005).

Generalmente se usan dispositivos eléctricos que generan una corriente continua conectada mediante cables a electrodos de carbono introducidos en esponjas mojadas en agua o con el medicamento que se quiera aplicar colocados sobre la zona a tratar. Cuando se utiliza la iontoforesis con agua corriente, se introducen los electrodos dentro de las esponjas en un medio con agua, generalmente pequeños recipientes de plástico. En la actualidad hay disponibles en el mercado una gran variedad de dispositivos de iontoforesis que van desde máquinas conectadas a la red eléctrica hasta pequeños dispositivos portátiles que funcionan con pilas o baterías recargables (Rodríguez-Martín, 2014).

Actualmente, la iontoforesis con agua corriente, es el medio más utilizado en el tratamiento de la hiperhidrosis y ha demostrado ser más eficaz y seguro que el uso de medicamentos anticolinégicos que producen efectos secundarios (Murray et al., 2005). Si bien su eficacia y seguridad está bien documentada, los mecanismos exactos de acción están aún por determinar. Estudios previos demuestran que la aplicación de iontoforesis con agua corriente produce un incremento del flujo sanguíneo en la zona, debido a una inactivación de las glándulas sudoríparas, lo que conlleva a un aumento de la temperatura de la piel y con ello de la vasodilatación. La hipótesis más aceptada es que las glándulas sudoríparas juegan un papel fundamental, aunque no exclusivo, en el proceso de conducir las cargas iónicas a través de la piel. Son necesarios estudios complementarios para investigar el potencial de aplicación de este modo de terapia que puede conducir un uso más eficaz y versátil de este método terapéutico seguro y sencillo (Gollins, Carpenter, Steen, Bulinski, & Mahendran, 2019).

Todo apunta a que el uso de iontoforesis en el tratamiento de FR puede ser una terapia óptima que puede constituir una aplicación innovadora, fácil de realizar, mínimamente invasiva y con efectos secundarios mínimos, por tanto, se requiere seguir realizando investigación adicional de nuevos tratamientos con iontoforesis, para optimizar las opciones terapéuticas existentes de esta patología.

1.6 Justificación de la tesis.

Las personas con FR constituyen una población con riesgo de padecer dolor crónico y pérdida de la funcionalidad, sobre todo aquellos casos que presentan un mayor número factores de riesgo asociados, o los que son secundarios a otras patologías crónicas. Los signos y síntomas característicos del FR y sus dos formas de presentación han sido ampliamente estudiados, sin embargo, hasta donde conocemos, no existe evidencia científica sobre la relación e influencia que pueden tener las alteraciones a nivel vascular que padecen estas personas con los mecanismos de procesamiento del dolor y el grado de funcionalidad de sus miembros superiores.

La evidencia científica también pone de manifiesto que la etiopatogenia del FR está aún por determinar, así como que no existen unos criterios estandarizados de diagnóstico de esta patología. En este sentido, las intervenciones terapéuticas están orientadas sobre todo a la reducción de los ataques vasoespásticos y van a depender de la forma de presentación del FR, bien sea primario o secundario. La terapia de elección junto con el tratamiento conservador suele ser la farmacológica. Sin embargo, a pesar de que se han descrito una gran variedad de terapéuticas, muchas carecen de la evidencia suficiente para su uso y se ha demostrado que la eficacia de la mayoría de los fármacos suele ser moderada y en muchas ocasiones poseen efectos secundarios importantes. En este sentido, en base a la evidencia científica disponible, una nueva opción terapéutica podría emanar del ámbito de la electroterapia, ya que la corriente galvánica aplicada mediante iontoforesis y sus efectos vasodilatadores, termogénicos y analgésicos demostrados, podría redundar en una mejora de la sintomatología y discapacidad a medio-largo plazo de los pacientes con FR. No se han encontrado estudios previos publicados que aborden la valoración de los aspectos relacionados con los procesos de dolor crónico en estos pacientes y su funcionalidad así como la utilización de electroterapia como una alternativa de tratamiento.

La hipótesis de partida para el primer estudio de esta tesis doctoral fue que las personas con FR deberían mostrar un patrón bilateral de hipersensibilidad frente a los estímulos de dolor por presión, como indicadores de sensibilización central en esta población y que este hecho debería estar relacionado con una menor temperatura en sus manos. Es decir, a mayor daño vascular, las personas deberían mostrar menor temperatura en sus manos, relacionado con una mayor vasoconstricción y por tanto, con mayores niveles de dolor y sensibilización central que las personas controles sanas.

La hipótesis de partida para el segundo estudio fue que las personas con FR deberían tener mayores niveles de discapacidad en sus extremidades superiores y por lo tanto, mayores dificultades para realizar las actividades de la vida diaria, practicar deportes y actividades relacionas con las artes o realizar una actividad laboral que las personas sanas. Plantemos la idea de que estos mayores grados de discapacidad deberían estar relacionados con el daño a nivel vascular y con la pérdida de funcionalidad de la mano en los pacientes con FR.

La hipótesis de nuestro tercer estudio fue que la aplicación de un tratamiento de electroterapia mediante una corriente galvánica aplicada en la modalidad de iontoforesis con agua corriente en personas con FR primario y secundario, durante un periodo de siete semanas, mejoraría la sintomatología de estos pacientes, tanto a nivel vascular reduciendo el número de ataques, mejorando la saturación de oxígeno, el flujo sanguíneo, la temperatura basal y la recuperación de la temperatura; como a nivel de dolor, grado de sensibilización central, catastrofismo y discapacidad percibida, en comparación con aquellos pacientes con FR que sólo reciben tratamiento convencional para dicha afección.

1. INTRODUCTION

1.1 Raynaud's phenomenon: Concept, epidemiology, pathogenesis, classification, clinical manifestations and socioeconomic cost.

1.1.1. Concept

Raynaud's phenomenon (RP) is a transient, vasospastic disorder affecting small arteries, arterioles, and arterio-venous anastomoses in the skin. This vasospasm often occurs as an exaggerated reaction to a heat stimulus (usually cold), when there is a change in temperature or emotional state (e.g. stress). It mainly affects the fingers and toes but may occur in other areas of the body such as the nose, ears, tongue or nipples (García-Carrasco et al., 2008; Ismail et al., 2014b; Stringer & Femia, 2018).

RP gets its name from the French doctor, Maurice Raynaud (1834-1881) (Maverakis et al., 2014), who in 1862 was the first to describe in his thesis "De l'asphyxie locale et de la gangrène symétrique des extrémités" (Belch et al., 2017) a group of patients who suffered an ischaemic phenomenon characterised by transient and reversible attacks of colour change, triggered by exposure to cold and/or associated with various conditions. Raynaud suggested that the underlying mechanism that produced the ischaemia was a vasospasm in the arterioles, secondary to an exaggerated peripheral nervous system response, which he called "local asphyxia"(Bakst, Merola, Franks, & Sanchez, 2008; Maverakis et al., 2014).

There has been no standardised nomenclature to refer to this phenomenon since it was first described (Belch et al., 2017). Over the last twenty years, however, there has been a progression in literature when referring to this term, restricting the use of "Raynaud's" to the initial clinical description of ischaemic attacks triggered by the cold and manifested with transient and reversible changes in finger colour. Therefore, "Raynaud's phenomenon" is the general term to refer to a vasospasm that produces a white discolouration of the digits (Bakst et al., 2008).

After Raynaud's initial description, the disorder was known as Raynaud's disease, for years, until Hutchison et al. argued in 1901 that the most appropriate term for this disorder was "Raynaud's phenomenon", highlighting the fact that there were multiple causes, not one single disease, which could cause digital ischaemia and vasospasm (Bakst et al., 2008; Porter, Rivers, Anderson, & Baur, 1981).

Later, in 1929, Sir Thomas Lewis established that the disorder was caused by local damage rather than by a nervous system disorder, which could be related to other diseases. Thus, he began to describe the clinical and physiological characteristics that differentiated the primary and secondary form of RP (Bakst et al., 2008).

The terms "Raynaud's disease" and "Raynaud's syndrome" were coined and used for years to differentiate the main subgroups of Raynaud's phenomenon. Raynaud's disease was used when there was no known primary aetiology and Raynaud's syndrome when it is caused by an associated or underlying disease. Both terms had their disadvantages. Raynaud's disease was used as a synonym for what is now called primary RP. In this case, the use of the word "disease" is misleading and can lead to concern for patients and unnecessary medicalisation. On the other hand, when the term "syndrome" is used to refer to Raynaud's associated with other disorders, it is true that it is a syndrome, as it is associated with several signs and symptoms. These may, however, be related to many different aetiologies (Belch et al., 2017).

A recent guide by the European Society of Vascular Medicine (ESVM)(Belch et al., 2017), establishes the need to standardise and maintain consistency in the terminology used on this issue, as it is critical when it comes to carrying out epidemiological studies and therapeutic trials. With Grade IIa - Level C, these authors establish that the correct term to refer to this disorder is "Raynaud's phenomenon", so the terms "syndrome" and "disease" should be discarded and «Primary RP» and «Secondary RP» should be used to refer to the two clinical types of Raynaud's (Belch et al., 2017).

1.1.2 Epidemiology

Several studies have attempted to establish the prevalence of this disorder in different populations. The estimates in the general population vary and therefore the real

prevalence of Raynaud's phenomenon is unknown (Fraenkel, 2002; Garner, Kumari, Lanyon, Doherty, & Zhang, 2015). The heterogeneity in the prevalence figures may reflect the differences in the way the studies are carried out, their design, the different criteria used in recruitment, the population studied and the surveys used (Fraenkel, 2002; Ling & Wigley, 1999).

In general, epidemiological studies agree that between 3% and 22% of the general world population suffers from RP (Ling & Wigley, 1999). In terms of distribution by gender, RP is more common in women than men, with a general prevalence estimated between 6% and 20% compared to the male population, where it is calculated at between 3% and 12.5%. (Bakst et al., 2008). In addition, a greater distribution has been observed in relatives of affected individuals, suggesting a genetic susceptibility or hereditary component (Wigley & Flavahan, 2016). Prevalence in the Spanish population is considered to be much lower than in other countries, varying between 2.8 and 4.7% (Román, Gonzálvez, Fernández, Graña, & Torres, 2001). Studies conducted in the United States indicate that it is one of the countries with the highest prevalence rates. In this case, RP prevalence in women is approximately 9% in the northeast and 4% in the south, while it affects 6% of men in the northeast and 3% in the south. The country with the lowest RP prevalence rate in the study is Japan with an average of 1.6% of the general population, of which 2.1% are women and 1.1% are men (Garner et al., 2015; Stringer & Femia, 2018).

Other studies compared the prevalence of RP in different climatic regions, from mountainous regions with cold climates to warm coastal areas and concluded that there was a greater prevalence in colder climates (Bakst et al., 2008). Climate still has an impact on RP prevalence even in people with known risk factors. For example, in a study conducted in China, an RP prevalence of 9% in the north and 7% in the south was found among workers using vibration tools (Fraenkel, 2002).

Among the risk factors associated with developing RP, gender differences are one of the most relevant issues. Women are more susceptible to developing RP than men in a 7 to 1 ratio, due to hormonal factors with a higher incidence of vasospastic attacks observed in the pre-ovulation period. Also, oestrogen administration has been shown to aggravate symptoms in women with secondary RP (Linnemann & Erbe, 2015). Furthermore, the

hormonal changes associated with the post-menopausal period seem to have a decisive impact on the appearance of RP, with the Framingham study demonstrating an incidence of 8.4% in postmenopausal women between 52 - 66 years old (Fraenkel et al., 1998).

Age is another determining factor to consider in the onset of RP. RP manifests more frequently in the 20- and 60-year-old age range, although it can also appear in childhood, adolescence or in the elderly (Linnemann & Erbe, 2015). Primary RP has an earlier age of onset, usually appearing between the ages of 15 and 30 and secondary RP usually appears around the fourth decade (Wigley & Flavahan, 2016) .

The role of genetic factors in the appearance of RP is yet to be determined. It has been observed that there is a polygenetic predisposition in 30% of patients and also that there are differences in prevalence between ethnic groups. (Linnemann & Erbe, 2015). An observational study conducted in Germany established that there was a 3% positive family history in patients with RP (Heidrich, Helmis, Fahrig, Hövelmann, & Martini, 2008) and a recent study (Munir, Freidin, Brain, & Williams, 2018), indicated that RP is specifically associated with a variation in the NOS1 gene.

The main risk factors for RP also include migraines, smoking, cardiovascular disease, oestrogen replacement therapy and the use of manual vibrating tools at work such as electric or pneumatic drills, chain saws, etc (Fraenkel, 2002; Garner et al., 2015). In this respect, a strong association between migraine and primary RP has been found with an Odd Ratio (OR) of 4.02 and a Confidence Interval (CI) of 95% from 2.62 to 6.17. Smoking has also shown to be positively associated with RP with an OR of 1.27 and a 95% CI between 1.06 to 1.53; as well as cardiovascular diseases with an OR of 1.69 and a 95% CI of 1.22 to 2.34.(Garner et al., 2015).

Finally, it should be noted that there appears to be a relationship between a person's civil status and RP. Studies conducted on this topic (Fraenkel et al., 1999; Keil, Maricq, Weinrich, McGregor, & Diat, 1991), concur that divorced, separated or widowed subjects have a higher prevalence of RP than those who are married or single. The authors of these studies hypothesise that the higher prevalence observed in these subjects may be related to

emotional factors, as divorced, separated or widowed people experience higher levels of stress associated with the loss of their spouse.

1.1.3 Pathogenesis

Although it has been over 100 years since Maurice Raynaud first described RP, there is still no general consensus about its exact pathophysiology (Herrick, 2005; Le & Cho, 2014; Prete, Fatone, Favoino, & Perosa, 2014).

From the physiological point of view, there must be a balance between vasoconstrictors and vasodilators, to maintain appropriate vascular tone and produce correct regulation of peripheral blood flow. To this end, the peripheral nerves and cells of the small vessels and microcirculation walls must be functionally and structurally robust (Albrecht et al., 2013; Cheung, 2015).

In RP, the balance between vascular, neurogenic and humoral factors breaks down leading to excessive vasoconstriction. (Prete et al., 2014). The main pathophysiological markers are detailed below, according to the affected structural or functional element.

1) **Vascular factors.** In primary RP, there is an endothelial change. Here, the vasoconstriction mechanism is largely stimulated by hyperactivity in powerful vasospasm mechanisms such as alpha-2-adrenergic, endothelin-1, tyrosine kinase, serotonin and angiotensin II. There is also reduced activity in dysfunctional endothelial cells, affecting the production of vasodilators such as nitric oxide and prostacyclin and, in addition, there may be an increase in thrombotic and inflammatory activity (Prete et al., 2014; Rychlik-Golema, Mastej, & Adamiec, 2006).

   In secondary RP, particularly where there is scleroderma, vascular disorders occur before endothelial dysfunction. Here there are clear changes in the vessel wall, especially in the intima, and fibrosis also occurs in the tunica media and tunica adventitia. These lesions in the vascular walls alter their function, stimulating the release of vasoactive peptides, which are secreted by the endothelium itself, causing further structural changes within it (Herrick, 2016; Prete et al., 2014; Sunderkötter & Riemekasten, 2006).

2) **Neurogenic factors.** Neurogenic disorders may also lead to RP. The autonomic nervous system plays a fundamental role in controlling body temperature. Here, it is believed that there may be changes in the sympathetic and parasympathetic nervous systems, the afferent sensory fibres at the neurovascular junction and the arteriovenous anastomoses (AVA) (Albrecht et al., 2013). This change may lead to a decreased release of vasodilator neuropeptides such as calcitonin gene-related peptide, substance P, neurokinin A and neuropeptide Y; all of which leads to excessive vasoconstriction.

   Furthermore, it has been observed that there is a greater vascular response in alpha-2c-adrenergic smooth muscle receptors that increases vasospasmsPor otro lado, también se ha observado que se produce una mayor respuesta vascular de los recetores alfa-2c-adrenérgicos del músculo liso que incrementan la vasoespasticidad (Flavahan, 2008a; Freedman, Moten, Migály, & Mayes, 1993). We know that RP occurs in a very localised way, affecting blood flow to areas of the skin that have very specific structural and functional characteristics. These areas of the skin have a high density of AVA,42,29 structures which play a very important role in the process of body temperature regulation and seem to play an important role in the development of RP (Walløe, 2016). Recent reviews (Cheung, 2015; Walløe, 2016) have concluded that AVA are direct connections between small arterioles and vessels. Since they contain no capillary segment and cannot transport dissolved substances to or from the tissues, their only function is to transport heat. AVA are found in most organs and tissues of our body but in very low numbers. They are numerous, however, in the mucous membranes, nail bed and glabrous skin of the hands (thenar, and hypothenar areas) and feet. To maintain normal body temperature when exposed to cold temperatures, there is a peripheral physiological vasoconstriction in the temperature regulation structures of our body, such as arteriovenous anastomoses and precapillary arterioles (Flavahan, 2015; Nuzzaci et al., 1988). When there is a cold stimulus, heat loss is reduced through this cutaneous vasoconstriction and the production of heat based on thermogenesis (Walløe, 2016). AVA help regulate body temperature, maintaining the organism within its thermoneutral range, which usually varies from 26-36 degrees Celsius at rest. They act as sphincters and open or close respectively producing a decrease or an increase in blood flow to the area, allowing blood to flow straight to the venous

plexuses in the extremities. Where there is a decrease in temperature, this information reaches the temperature control centre in the hypothalamus. This then sends bursts of nerve impulses simultaneously to all AVA which are densely innervated by sympathetic nerves (Walløe, 2016; Wigley & Flavahan, 2016). On exposure to cold, the arteriovenous anastomoses remain predominantly closed, whilst during heat removal they are fully open. Under normal conditions, when cutaneous vasoconstriction induced by cold or stress, there is a reflex increase in vasoconstrictor sympathetic activity which can cause large fluctuations in blood flow. In people with RP, sympathetic vasoconstriction further increases in intensity and range and exposure to cold can cause intense vasoconstriction throughout the entire vascular network, including arteries and arterioles that provide nutritional support to the skin (Flavahan, 2015).

3) **Humoral factors**. Lastly, another of the possible causes of RP is the change in humoral factors. This mainly concerns secondary RP, where some factors that may compromise blood flow have been described. Some of these factors include an increase in platelet activity, hypofibrinolysis, deformity of red blood cells, hyperviscosity, leukocyte activation and oxidative stress. However, these factors seem to be less important at the origin of the pathology than the previous two (Herrick, 2005; Prete et al., 2014).

In summary, there seem to be two main theories to explain RP: (1) on the one hand, it is proposed that the characteristic vasospasm is caused by hyperactivity in the sympathetic nervous system, caused by central and peripheral neurological factors, such as calcitonin gene-related peptide deficiency, alpha-2 adrenergic receptor activation, increased endothelin-1 synthesis and a decrease in vasodilator factors such as prostacyclins and nitric oxide (Flavahan, 2015). (2) Another theory is that the levels of sympathetic activity in this population are normal and RP is an exaggerated response of the cutaneous blood vessels due to structural abnormalities within, secondary to an increase in the blood viscosity, dysfunctional control of vascular tone, endothelial lesions, increased activation of platelets or oxidation (Sunderkötter & Riemekasten, 2006).

The most recent research on this topic aims to establish that these two theories are not exclusive (Herrick, 2017; Wigley & Flavahan, 2016) and they are oriented to theRP aetiology can probably be explained through a combination of both; it has been observed that there are specific aetiological factors, but also that there are differing factors for each type of RP (primary and secondary). These distinctions have led to primary RP being considered as a purely functional or vasospastic disorder, whereas secondary RP is increasingly associated with structural abnormalities in the microcirculation (Block & Sequeira, 2001).

1.1.4 Classification

RP is normally classified in two ways; primary or idiopathic RP and secondary RP.

Primary RP is the most common type, accounting for 80% of cases and is not associated with an underlying disease (De Angelis, Salaffi, & Grassi, 2008). In general, it is considered a "benign" condition because the level of involvement tends to be milder and usually does not progress to irreversible tissue damage (Herrick, 2017). Primary RP is characterised by an earlier age of onset, around the age of 20-30; patients have normal nail fold capillaries and low or negative antinuclear antibodies; attacks typically affect all fingers in a symmetrical pattern and are associated with lower levels of pain (Bakst et al., 2008).

Secondary RP is less common, representing 20% of total cases.10 Secondary RP is associated with a confirmed pathological process or underlying disease (Linnemann & Erbe, 2015) The main causes are autoimmune diseases, connective-tissue diseases (CTD) and rheumatic diseases. It is most frequently associated with systemic sclerosis or scleroderma, with 90-95% of patients with this disease also suffering from RP. Other diseases often linked to secondary RP include lupus (10-40%); Sjögren's syndrome (30%), dermatomyositis or polymyositis (20%), rheumatoid arthritis (10%), neurological disorders, exposure to certain drugs and toxins, vasoconstrictor drugs, intravascular disorders associated with increased blood viscosity, tumours, treatments with various medications, use of vibrating instruments at work and the presence of vascular lesions (Fraenkel, 2002; Hughes & Herrick, 2016). Secondary RP usually has a worse clinical course over time and can progress to irreversible tissue damage with digital ulcers and

gangrene, which may eventually require amputation of the affected structure (Herrick, 2017). Patients with secondary RP usually have a higher age of onset, above age 40; their nail fold capillaries are abnormal; they present with positive antinuclear antibodies; asymmetry in attacks involving the fingers accompanied by intense pain (Block & Sequeira, 2001).

RP often precedes the clinical onset of many of these disorders, so underlying rheumatological conditions should be ruled out when RP symptoms begin. (Block & Sequeira, 2001). Patients who present with RP for the first time between the third and fifth decade of their life are at high risk of developing CTD. When RP appears in very young children, an underlying CTD should also be considered, especially if the initial pallor appears very marked and is accompanied by severe symptoms (Belch et al., 2017). A retrospective study revealed that in 37.2% of the cases there was a transition from primary RP to a CTD and that only 8.1% of the cases developed RP secondary to other causes (Pavlov-Dolijanovic et al., 2013).

1.1.5 Clinical manifestations

In terms of the clinical manifestations of RP, the main symptom is a characteristic change in skin colour that develops in three progressive phases. Initially, the skin has a waxed pallor that turns white, due to excess vasospasm/ischaemia. This phase usually presents clearly in the fingers, as if it were a cross section. In the second phase, the skin takes on a bluish, cyanotic colour caused by deoxygenation/cyanosis. Finally, the skin turns red, due to reactive hyperaemia after blood flow is restored. In clinical practice, the three phases of skin colour change in patients do not always appear; in most cases, some of the phases do not occur or are not apparent (Bakst et al., 2008; Linnemann & Erbe, 2015). In clinical practice, the three phases of skin colour change in patients do not always appear; in most cases, some of the phases do not occur or are not apparent. (Belch et al., 2017). It has been described that only 9% of patients present all of the typical three-phase colour changes (Fraenkel, 2002). However, the initial phase must occur for a differential diagnosis to be made (Grossi et al., 2010).

These vasospastic attacks manifest mainly in the fingers and, in up to 40% of patients, also in the toes (Fraenkel, 2002). Other body areas, such as the earlobes, lips and nose, are less commonly affected. The average duration of an attack is between 15-20 minutes, and the severity varies from mild to temporarily disabling (Wigley & Flavahan, 2016). The intensity and severity of attacks will depend to a large extent on whether or not there is an associated disease. Normally, the episodes affect one or more fingers on one hand and extend symmetrically to the other fingers and the other hand. It usually manifests more frequently in the ring, index and middle fingers. It is rare for it to affect the thumb (Belch et al., 2017).

Other symptoms that also present clinically with the change in colour in RP include varying degrees of pain, loss of functionality, paraesthesia, numbness, tingling and a burning sensation. The intensity with which these symptoms manifest is very variable and depend to a great extent on whether it is primary or secondary Raynaud's (Wigley & Flavahan, 2016). In severe cases of intense and prolonged ischaemia, open ulcers may appear on the fingers, which may lead to infection, necrosis and, eventually, gangrenous tissues. (Flavahan, 2008).

1.1.6 Socioeconomic cost

All the disorders present in RP and the symptoms related to them cause, to a greater or lesser extent, loss of upper limb functionality, suffering and reduced quality of life for sufferers (Linnemann & Erbe, 2016). As RP is a chronic condition, it generates significant direct and indirect socioeconomic and health costs, although there is still limited existing literature assessing this (Hughes et al., 2015).

In relation to the costs generated by diseases associated with chronic pain, as is the case with RP, a study conducted in the United States mentions that around 48 million people suffer from chronic pain (Day & Thorn, 2010), which translates into a total annual cost of 100 trillion dollars in health costs and loss of productivity (Quartana, Campbell, & Edwards, 2009).

In a recent study Herrick (2017), notes that in both primary and secondary RP there is a significant loss of quality of life for these patients, therefore, both forms of RP will have a significant socioeconomic and medical cost. However, it has been found that the public health cost increases where RP is associated with systemic diseases. In this context, Nguyen et al. (2010), conducted a study among patients with RP secondary to scleroderma and established that 31.8% of these subjects received a full invalidity pension, 23.9% were unemployed at that time and 34.5% had to change jobs. Therefore, there is a significant socioeconomic burden linked with RP and the concomitant diseases to which it may be associated. This study also showed that the onset of RP implied a drop in these patients' income of 46.9%, that 43.3% of the participants reported having fewer opportunities for promotion at work and 10.6% expressed having greater feelings of discrimination in their work environment due to their illness. It was also shown that there is a direct relationship between the limitations that these patients experience functionally and the need for help to perform tasks at home, in this case 66.1% of patients mentioned that they needed an average of 36 hours per month of paid domestic help (Nguyen et al., 2010).

RP is, therefore, a chronic disease that affects a considerable part of the population with consequences which have a significant socioeconomic and public health impact (Bérezné et al., 2011).

1.2 Chronic pain, central sensitization and the relationship with peripheral vascular disorders.

Chronic pain is defined as persistent or recurrent pain lasting longer than 3 months, so that it loses the acute warning function of physiological nociception (Treede et al., 2019). Chronic pain is a major source of human suffering and disability, which interferes with daily activities and is often accompanied by distress. Globally, it also accounts for one of the most common reasons for patients to seek medical attention (Goldberg & McGee, 2011).

In cooperation with the World Health Organisation (WHO), the International Association for the Study of Pain (IASP) working group, has developed a system to classify the main causes of chronic pain. Chronic pain is assigned a unique identifier

within the International Classification of Diseases (ICD-11) (chronic pain: http://id.who.int/icd/entity/1581976053), given that it has been considered as a pathological entity in itself. In addition, there are 7 codes that make up the most clinically relevant and common groups of chronic pain conditions (Treede et al., 2019).

Here, the pain that occurs in people with both primary and secondary RP, would be classified as chronic secondary visceral pain. This is defined as a persistent or recurrent pain originating in the internal organs and is usually perceived in the somatic body wall tissues (skin, subcutaneous tissue and muscle) of the areas that receive the same sensory innervation from the internal organ in which the symptom originates (visceral referred pain). This category is subdivided in turn, according to the main underlying mechanisms, into mechanical factors (for example, traction and obstruction); persistent inflammation and vascular mechanisms (ischaemia and thrombosis). The latter would include the pain-causing mechanisms in RP. In addition, there may be more causes of chronic pain in secondary RP depending in turn on the underlying pathology (Treede et al., 2019).

Traditionally, pain in the RP population has been associated mainly with excessive and maintained vasoconstriction that occurs due to peripheral vascular hyperreactivity (Devulder et al., 2011). This association is in line with the idea that persistent pain is caused by prolonged ischaemia in the peripheral tissues, which in turn causes hyperactivation of the deep tissue nociceptors. This would result in peripheral sensitization that could ultimately lead to central sensitization (CS) in this population (Flavahan, 2015; Woolf, 2011).

We know that even with acute pain, changes occur in the nervous system. When the pain persists for a few days, there is a change in the unimodal nociceptors that improves polymodal nociceptor ending responsiveness by releasing substances such as serotonin. This process is called primary or peripheral hyperalgesia as it sensitises the nociceptors and has a protective effect on the human body to avoid further use of the damaged structures and additional damage to the surrounding tissues (Yunus, 2007b, 2007a). In secondary hyperalgesia, there is an increase in the responsiveness of the spinal cord dorsal horn neurons. So, it is important to consider that while peripheral sensitization is a local

phenomenon, central sensitization is a central process that affects the nervous system in a holistic way (Nijs, Wilgen, Oosterwijck, Ittersum, & Meeus, 2011).

CS is defined as a physiological phenomenon produced by changes in central nervous system processing, which causes a change in the functional state of neurons leading to high reactivity (hypersensitivity) to harmful and non-harmful stimuli (Neblett, Hartzell, Mayer, Cohen, & Gatchel, 2017; Nijs et al., 2011). Clinically, it is characterised by the presence of allodynia (experiencing pain with stimuli that are not normally painful, such as touch), hyperalgesia (excessive sensitivity to a normally painful stimulus, such as pressure), expansion of the receptive field (pain that extends beyond the area of the peripheral nerves), and unusually prolonged pain after a painful stimulus (usually throbbing, burning, tingling or numbness) has been removed (Nijs & Van Houdenhove, 2009).

The main theory that explains CS states that persistent pain impulses will produce a change in the ascending and descending central nervous system pathways (Nijs & Van Houdenhove, 2009), therefore, persistent pain may cause changes in the peripheral and central nervous system (Kindler, Bennett, & Jones, 2011).

The exact CS onset mechanism is still unknown. It has been described that in states of chronic pain, peripheral nociceptors continue to send the pain impulses that activate both A-delta and C nerve fibres, which carry the nociceptive impulse to the spinal cord dorsal horn neurons. The persistent activation of the nociceptive fibres stimulates the release of neurotransmitters (substance P, glutamate, calcitonin gene-related peptide and aspartate) that modulate post-synaptic electrical discharges in the dorsal horn neuronal synapses. Increased neurotransmitters initiate postsynaptic responses and trigger hyperexcitability of the N-methyl-D-aspartate (NMDA) receptors of the second-order neurons in the dorsal horn. NMDA receptors appear to play a very important role in this process, since their activation causes a remarkable functional change in postsynaptic neurons (for example, increased calcium influx, changes in the membrane and protein kinase activation). These neurochemicals sensitise the wide dynamic range neurons, which become hyperexcitable, leading to phenomena such as allodynia or hyperalgesia. Some of these neurons are multimodal and respond to sensations of touch, pressure, temperature

and pain. (Nijs & Van Houdenhove, 2009; Yunus, 2007). As a result, there is a progressive increase in electrical discharges in the second-order neurons of the spinal cord, which results in an increase in the activation of second-order neurons that are projected to the brain. This produces a higher degree of postsynaptic spinal fibre transmission ascending to supraspinal structures (thalamus, hypothalamus, anterior cingulate cortex, insular cortex, limbic system and finally the somatosensory cortex) through the ascending pathways. These areas are involved in processing various dimensions of pain such as the sensory, affective and evaluative dimensions. Therefore, through this mechanism of CS, persistent pain produces a state of hyperexcitability in the central nervous system, meaning that the brain is sensitised and experiences an increase in pain perception (Nijs & Van Houdenhove, 2009; Yunus, 2007a, 2007b)

Another important mechanism through which CS modulates hyperalgesia is through the expansion of receptive fields. Here, the sustained stimulation of the wide dynamic range neurons, including both nociceptive and non-nociceptive neurons, causes the adjacent neurons to switch on, thus expanding their receptive fields and causing pain to be experienced, for example when areas that previously did not produce that response are stimulated (Nijs & Van Houdenhove, 2009).

Central sensitization is not limited to the dorsal horn, nor to the amplification of pain in the afferent impulses, but also includes changes in sensory processing in the brain and a descending inhibitory pain mechanism dysfunction. In this context, the physiological mechanism for pain inhibition performed by the descending pathways from the cortico-reticular system, the hypothalamus and the brain stem, becomes functionally deficient. Thus, there is a change in the release of neurotransmitters such as serotonin, norepinephrine, enkephalins and g-aminobutyric acid (GABA), which are active in inhibitory brain function (Nijs et al., 2011).

Therefore, changes in the ascending pathways, together with abnormal descending modulation, can combine to initiate and maintain generalised hyperalgesia and CS (Kindler et al., 2011; Yunus, 2007b).

A series of syndromes that present along with CS have been proposed, which include a group of medical disorders such as fibromyalgia, chronic fatigue syndrome, irritable colon syndrome, temporomandibular joint disorders and migraines, among others. In addition, CS frequently presents in several chronic diseases such as rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis, or fibromyalgia, among others that present with RP (Kindler et al., 2011). In this sense, Yunus (2007a) report that 14% of patients with fibromyalgia have symptoms similar to RP and that these symptoms may be due to a greater sensory perception related to CS, with or without concomitant emotional fact.

On the other hand, it seems that CS involves much more than generalised hypersensitivity to pain and is also characterised by a greater capacity to respond to a variety of stimuli, including mechanical pressure, chemicals, cold, light, sound, heat, electrical stimuli, stress and emotions (Nijs et al., 2011; Woolf, 2011). This clinical picture suggests a general intolerance of all types of physical and emotional stimuli in the sufferer (Nijs et al., 2011). It is also well known that CS is often closely related to various mental illnesses such as anxiety and panic disorders or depression, indicating that there is an important interaction between physical and psychosocial processes as indicated by the biopsychosocial model of pain (Nijs & Van Houdenhove, 2009).

The presence of central sensitization in patients suffering from chronic pain suggests a more complex clinical picture, that is, an increase in unrelated symptoms and hence a more difficult clinical reasoning process, as well as a decreased likelihood of favourable recovery (Nijs, Van Houdenhove, & Oostendorp, 2010).

As mentioned previously, it appears that peripheral vascular hyperresponsiveness, which is characteristic of RP, could be the key to explaining CS in these patients. There is every indication that this process may be generated by a disorder in the vascular system responsible for controlling body temperature, which in turn can lead to a general hypersensitivity to pain and CS.

Accordingly, in their study Albrecht et al. (2013), found that there are changes in peripheral vascular responses in the hands of patients with fibromyalgia, similar to those that occur in RP. These authors especially highlight that a change in AVA, structures that

play a fundamental role in the body's thermoregulation process and which are especially present in the skin of the affected areas in RP, could be the key to explain these changes. In their study, it was found that there was a significant increase in the sympathetic and sensory innervation of AVA in the glabrous skin of the hypothenar eminence in the hands of people with fibromyalgia in comparison with healthy subjects. This excessive innervation was characterised by the presence of a greater proportion of vasodilatory sensory fibres compared with vasoconstrictor sympathetic fibres. It was also found that excessive AVA innervation led to an abnormal production of vasodilator peptides related to pain. Therefore, excessive AVA innervation would appear to be a probable source of pain, hypersensitivity, fatigue and CS in this population. They also suggested that this neurovascular change could not only explain the symptoms, but also the exacerbation of symptoms with regard to temperature changes (Albrecht et al., 2013).

This whole process and the relationship between vascular changes with CS, however, has not yet been studied specifically in the context of Raynaud's phenomenon. The literature on this aspect is limited and mainly studies the AVA permeability rate in the hands of patients with primary and secondary RP (Flavahan, 2015). This has allowed us to confirm that the response to cold in people suffering from RP is characterised by excessive vasoconstriction, which is quantitatively greater than in healthy people. We need studies, however, which evaluate the role of CNS hyperactivity in peripheral vascular response in this population.

1.2.1 Biopsychosocial approach to chronic pain, hypervigilance and catastrophizing in Raynaud's phenomenon.

Pain is a human defence and survival mechanism that acts as a warning sign to protect our body. The concept of pain is a broad and complex construct that must be approached using a biopsychosocial model since it is not a purely physiological phenomenon, but is influenced to a large extent by psychosocial factors. Therefore, factors ranging from age, gender and genetics to stress, emotional state and depression, may all influence pain processes (Gatchel, Peng, Peters, Fuchs, & Turk, 2007).

To properly perceive pain, physiologically coordinated involvement of the Central Nervous System (CNS) and peripheral system is required. Sometimes, when pain persists and recurs over time, as it happens in RP and many of its associated diseases, this complex mechanism stops being functional. Problems arise from changes in the transmission or modulation of pain, where cognitive and emotional aspects play an important roles (Yunus, 2007a, 2007b).

One of these changes is catastrophizing pain, which is characterised by the tendency to magnify the threatening value of painful stimuli and feel helpless in the context of pain, as well as the inability to inhibit thoughts related to pain before, during or after a painful stimulus (Edwards, Bingham, Bathon, & Haythornthwaite, 2006). Catastrophizing is understood as a set of negative emotional and cognitive processes in which thinking about pain, feelings of impotence, magnification, helplessness and pessimism influence the responses related to pain (Edwards, Fillingim, Maixner, Sigurdsson, & Haythornthwaite, 2004; M. J. Sullivan, Rodgers, & Kirsch, 2001).

Although research carried out in recent years highlights that catastrophizing plays a fundamental role in the experience of pain in diseases such as rheumatoid arthritis and fibromyalgia, further studies are needed to better understand the biopsychosocial nature of pain and determine the influence of catastrophizing on patients suffering from chronic pain (Edwards et al., 2006).

Catastrophizing is related to higher levels of pain, increased depression in sufferers, increased disability and also a greater focus on pain (Edwards et al., 2006; Quartana et al., 2009). Likewise, scientific evidence shows that there is a positive relationship between catastrophizing (or impotence, a component of catastrophizing) and an unfavourable course of illness. In other words, how people deal with pain is a consistent predictor of the clinical situation that they will develop, as this will influence the severity of pain, disability related to pain and psychological adjustment (Edwards et al., 2004). A higher degree of catastrophizing predicts a worse course of illness. This is because impotence correlates with lower adherence to medical treatments and less positive health behaviour, such as not exercising (Quartana et al., 2009).

In order to better understand the relationship between catastrophizing and the perception of pain, the process of catastrophizing by administering harmful stimuli in a controlled environment was studied in the laboratory (Edwards et al., 2004). Among these, several studies have used the application of cold as a painful stimulus and have shown that there are cross-sectional relationships between responses to the cold stimulus and higher levels of catastrophizing, along with shorter tolerance times and higher pain scores (Geisser, Robinson, & Pickren, 1992; Sullivan, Rodgers, et al., 2001; M Thastum, Zachariae, Schøler, Bjerring, & Herlin, 1997). In this regard, other studies have also shown that there is a link between catastrophic thinking and sustained increases in myocardial contractility and an increase in sympathetic activity (Edwards et al., 2006; A. Shah et al., 2019). Similar results have been reported when assessing thermal pain thresholds and tolerance (Geisser et al., 2003). In a study assessing electrical pain, higher catastrophic scores were associated with lower tolerance and higher degrees of pain compared to harmful electrical stimulation (France, France, Absi, Ring, & McIntyre, 2002). In a similar study, carried out in people with juvenile chronic arthritis, patients with higher levels of catastrophizing had lower tolerance to cold stimulation and lower pain thresholds to electrical stimulation (Mikael Thastum, Herlin, & Zachariae, 2005). Therefore, there is a positive association between catastrophizing, increased sensitivity to pain and hyperalgesic responses. Therefore, scientific evidence suggests that catastrophizing causes processes similar to those in central sensitization, and may contribute to CNS sensitization, demonstrating a positive relationship between catastrophizing and sensitivity to pain (Edwards et al., 2006; Quartana et al., 2009).

One of the hypothetical mechanisms through which catastrophizing may influence response to pain is their direct effect on cognitive processes in CNS pain processing. In this context, we know that psychosocial factors are associated with the development and maintenance of chronic pain (Linton, 2000), and that catastrophizing is associated with increased sensitivity to pain. It seems reasonable, therefore, that catastrophizing may play an important role in the modulation of pain similar to sensitization (Edwards et al., 2004). However, the exact mechanism by which catastrophizing can affect physiological systems such as the sympathetic nervous system or the hypothalamic pituitary-adrenal axis, is still unknown. Catastrophizing amplifies pain processing in the CNS. A hypothetical mechanism by which catastrophizing affects the experience of pain, promotes sensitization,

or interferes with pain inhibition in the CNS, as it has been observed that the reduction of catastrophizing results in the activation of descending endogenous opioid systems that inhibit nociception. Moreover, in an study in patients with fibromyalgia, it was observed that patients with higher levels of catastrophizing also had greater activation of the cortical regions involved in the effective processing of pain, such as the anterior cingulate cortex and the insular cortex (Viane et al., 2003).

In general, the evidence indicates that catastrophizing can amplify pain processing and some researchers postulate that bidirectional relationships between catastrophizing and nociceptive processing can contribute to the chronicity of many conditions (Wideman & Sullivan, 2011).

Another important point to keep in mind is that catastrophizing increases sensitivity to pain (hypervigilance to pain). Some research has examined the hypothesis that catastrophizing increases the experience of pain through its effects on sensitivity processes (Peters, Vlaeyen, & van Drunen, 2000; Roelofs, Peters, McCracken, & Vlaeyen, 2003). That is, high levels of catastrophizing can lead people to selectively and intensely focus on the stimuli related to pain. Patients who experience catastrophizing encounter more difficulties in controlling or suppressing thoughts related to pain, they tend to dwell more on their pain and their physical and cognitive performance is highly affected by the anticipation of pain. In patients with fibromyalgia, catastrophizing is strongly related to a heightened awareness of pain, as well as bodily sensations (Peters et al., 2000). As observed in prospective studies, high rates of catastrophizing are associated with increased levels of hypervigilance and a fear of movement in patients with rheumatoid arthritis and chronic lower back pain, which leads these patients to reduce their mobility, thus resulting in a loss of muscle strength (Castañeda, Bigatti, & Cronan, 1998; Covic, Adamson, Spencer, & Howe, 2003; Lefebvre & Keefe, n.d.; Picavet, Vlaeyen, & Schouten, 2002).

It has also been determined that catastrophizing has a significant impact on the social environment. The way in which the community reacts to catastrophizing, indicates that presentations of catastrophizing generate responses of support from others and that these social responses, in turn, can reinforce the manifestations of pain and feelings of catastrophizing. Catastrophizing patients are perceived by society as having a low pain

threshold and seeking greater social support (Cano, 2004; Giardino, Jensen, Turner, Ehde, & Cardenas, 2003; Thorn, Keefe, & Anderson, 2004).

In relation to RP, as we have seen, both central sensitization and catastrophizing are involved in the amplification of the pain response, and can contribute to the increase of peripheral vasoconstrictive responses when the patient is presented with a stressful situation or painful stimulus (Nagai, Hoshide, & Kario, 2010; Shah et al., 2019). Investigaciones anteriores han observado que el estrés psicológico y físico puede inducir vasoconstricción arteriolar y reducir el flujo sanguíneo periférico. Aunque los mecanismos concretos de este proceso aún se desconocen, es probable que la vasoconstricción debida al estrés sea causada en parte, por el aumento de la actividad del sistema nervioso simpático. Previous research has observed that psychological and physical stress can induce arteriolar vasoconstriction and reduce peripheral blood flow. Although the specific mechanisms of this process are still unknown, it is likely that the vasoconstriction due to stress is partially caused by the increased activity of the sympathetic nervous system. Previous studies have also found that peripheral vasoconstriction in response to stressful situations was associated with greater activation in areas of the brain involved in the regulation of emotions. For example, the medial prefrontal cortex (anterior cingulate gyrus), the insula and the amygdala, which all have direct and indirect pathways that in turn regulate peripheral cardiovascular responses to stress (de Morree, Szabó, Rutten, & Kop, 2013; Kogler et al., 2015; Nagai et al., 2010). In this sense, central sensitization and catastrophizing have been described as possible underlying factors that can increase the perceived stress[13] and, therefore, can influence the vascular response and evolution of RP (Devulder et al., 2011; Evers, Kraaimaat, Geenen, Jacobs, & Bijlsma, 2003; A. Shah et al., 2019).

As we have seen, both catastrophizing and awareness are closely related to the success of treatments, the evolution of the disease, and the degree of disability. Its approach should be one of the main objectives in multidisciplinary pain treatment interventions. However, scientific evidence in this field is still lacking, so it is necessary to continue with research that allows us to gain insight into its mechanisms of action and propose new treatment strategies that act on all these determining aspects of pain processing.

1.3 Degree of upper-limb functionality and perceived disability in Raynaud's phenomenon: description and evaluation.

RP presents with debilitating physical symptoms, which give rise to an alteration in functionality, issues with body image, and a reduction in the quality of life for RP sufferers (Herrick, 2017; Hughes & Herrick, 2016).

Due to the symptoms of RP, the functionality of the hand is frequently impaired, which in turn will cause a loss of the general function of the upper limbs which will eventually lead to difficulties in carrying out activities of daily living , work or leisure activities (Uppal, Dhaliwal, & Butler, 2014). The hand is a complex structure that plays a very important role in human interactions, is involved in practically all our day-to-day activities, has a great variety of functions and needs a complete harmony between all structures to function correctly (Carvalho R, Mazzer N, & Barbieri C., 2012).

In both forms of RP, there is a loss of functionality, which will vary and is dependent on multiple factors, such as the duration, frequency and severity of attacks, the presence of ulcers on the fingers, pain and related concomitant conditions (Uppal et al., 2014). The results of a survey conducted by Huhges et al. (2015), indicated that 71% of patients with primary RP and 87% of patients with secondary RP experienced difficulties when carrying out activities of daily living and stated that they were forced to make changes and adjustments to their daily routine due to the functional disability caused by RP. These patients also presented with high levels of anxiety and a reduction in their quality of life. In addition, although RP is not a life-threatening condition, it can be observed that it has a relevant impact on different aspects of daily life and the activities of these patients, as well as on their general health status, which can affect their overall quality of life and emotional state (De Angelis et al., 2008; Giurgea et al., 2015; Herrick, 2017).

To perform a complete exploration of the musculoskeletal factors that facilitate the functionality of the hand, parameters such as range of joint movements and muscle strength should be evaluated. Among the measures that commonly used to assess the

functionality of the hand, is the measurement of active and passive joint movement (RM) ranges, using goniometry. It is commonly practised in the evaluation and monitoring of patients with hand disabilities due to multiple conditions. According to current knowledge, there are no previous studies that include the evaluation of the movement ranges and analyse their relationship with hand function in patients with RP. However, several studies conducted in patients with other rheumatic diseases determined that there is a decrease in MR of the hand joints and that this is related to higher levels of disability of the arms, shoulders and hands (Pérez-Mármol et al., 2017, 2016; Ramos-Casals et al., 2015). Carvalho et al. (2012), listed a number of factors that can generally influence the results of MR measurement in the general population such as the presence of oedema or pain, age (younger people have a higher MR than elderly people), sex (women have greater joint laxity than men) and passive or active MRs (passive MRs are greater than active ones, passive measurement makes it possible to measure the maximum MR of the joint).

To develop an optimal diagnosis of patients with RP, joint involvement should be investigated, especially in RP secondary to scleroderma, Sjögren's syndrome, systemic lupus and rheumatoid arthritis since it is known that these conditions cause limitations in joint mobility, although the number of joints involved in arthritis varies, the joints most commonly affected are the proximal interphalangeal and metacarpophalangeal joints of the hands in 35% of patients (Ramos-Casals et al., 2015). One study conducted with patients suffering from systemic sclerosis (Sandqvist, Hesselstrand, & Eberhardt, 2009), determined that these patients maintained mobility and hand use during the first years of the disease, but showed that patients with RP associated with worse initial mobility results at the beginning and during follow-up. In 50% of patients, the extension of the finger was the most affected movement.

Alternatively, muscle strength should also be measured in order to assess the functionality of the hand. In this sense, different studies (Landim et al., 2017; Merkel et al., 2002; Uppal et al., 2014) in the literature reviewed agreed that RP associated with scleroderma had a serious debilitating effect in patients. Generally, to obtain an objective measurement of muscle strength, a dynamometer is used and the force of movement is assessed, whereby fingers must grip in different ways (Dermid, Evenhuis, & Louzon, 2001; Mathiowetz, Weber, Volland, & Kashman, 1984; Pérez-Mármol et al., 2016).

Finally, the disability that causes RP should be measured in the different areas of these patients' daily lives. For this, one of the most frequently used tools in the literature is the reduced version of the arm, shoulder and hand disability questionnaire or Quick-DASH, Shortened Disabilities of the Arm, Shoulder and Hand Questionnaire in patients who have one or more associated disabilities of the arm, shoulder and hand (Beaton et al., 2012; Gummesson, Ward, & Atroshi, 2006). This assesses both perceived disability by the patient to perform various activities, including activities of daily living, as well as the associated symptoms of pain, stiffness or loss of strength. It is a standardised and self-administered questionnaire that considers the entire upper extremity as a single functional unit. It consists of just the first section with 11 questions, which measure the physical and social functions, as well as symptoms in the upper extremities in people with disorders affecting the functionality of the upper limb. These questions are scored on a scale ranging from 0 to 5, each of the five points of the scale is associated with an adjective to refer to the level of severity or function. The total sum offers a disability score of the person and can range from 0 (without disability) to 100 (the greatest disability). Higher scores correspond to a reduced function and greater severity of symptoms. This questionnaire also has two additional optional sections, with 4 questions each, which are designed to measure symptoms and altered functions in people who practise sports and performing arts, or have a job. (Hervás et al., 2006). To effectively calculate the score across all sections, there cannot be more than one answer for each question. This questionnaire has been shown to have good reliability, validity and responsiveness. It can be used in patients with upper limb disorders with a Cronbach's alpha of 0.90 and a Pearson correlation coefficient of 0.70 (Gummesson et al., 2006).

Studies performed in the context of different conditions such as scleroderma (Sandqvist, Wollmer, Scheja, Wildt, & Hesselstrand, 2018), Sjögren's syndrome (Ramos-Casals et al., 2015), carpal tunnel syndrome[16] (Roh et al., 2017) and hand-arm vibration syndrome (Mason, Poole, & Elms, 2005), where RP was present secondarily, it was found that RP affected the hand function of these patients. In this sense, they observed that disability rates were significantly higher in patients who had associated RP, than those who did not. A study in patients with systemic sclerosis (Bérezné et al., 2011) reported that RP had a disabling effect on the performance of activities of daily living of and work. These

patients presented with deterioration in the hand functions, and required assistance when performing activities of daily living, or received the disability pension.

The exact way in which the RP affects the functionality of the hand is still unclear. We must bear in mind that hand functions in these patients can be compromised not only by vascular alterations, but also by the thickening of the skin, pain and inflammation, characteristic of conditions with which they may be associated. Thus, disability in RP patients seems to depend on multiple factors. The latest studies in this field indicate that disability of the upper extremity in RP patients seems to be more related to the frequency of attacks than to the length of each attack in the fingers (Mason et al., 2005; Palmer, Griffin, Syddall, Cooper, & Coggon, 2002). Mason et al. (2005) suggested that in patients with hand-arm vibration syndrome and associated RP, the disability of the upper limb appears more related to the alteration of sensorineural components than to the vascular symptoms.

On the basis that RP is a complex clinical condition, which has a relevant impact on the general health status and functionality of its sufferers, we consider it necessary to fully explore the relationship between vascular deterioration and impaired functionality in subjects with primary and secondary RP. We believe that additional studies, including measures that quantify these factors, are necessary, since this could help to improve understanding of RP, to determine the overall burden of the disease (psychic, socioeconomic), to assess the impact of RP on activities of daily living and to evaluate the quality of life of RP sufferers.

1.4 Diagnosis and treatment of Raynaud's phenomenon.

In its latest guide based on evidence from 2017, the ESVM (Belch et al., 2017), establishes basic recommendations for the diagnosis and treatment of RP, according to the grade and supporting evidence. The grade of recommendation is related to the strength of the evidence; it is not a reflection of the recommendation's clinical importance. In this guide, the following criteria were established, which support the levels and grading of evidence: **Grade I**. Evidence that a treatment or procedure is beneficial and effective; **Grade II.** Conflict of evidence and/or differences in the opinion of experts in relation to

the benefit/efficacy of the treatment/procedure; **Grade IIa**. The weight of the evidence or opinion is in favour of benefit/efficacy; **Grade IIb**. Benefit/efficacy are not well established; **Grade III**. Evidence or agreement that the treatment is not beneficial or effective, and in some cases may even be harmful. Levels of evidence: **Level A**. Data derived from many randomised controlled trials or meta-analyses; **Level B**. Data derived from a randomised controlled clinical trial or large non-randomised clinical trials; **Level C**. Expert opinion or data from small studies, registers or retrospective studies.

The main consensus recommendations are outlined below (Belch et al., 2017).

1. A complete history and examination of all patients with RP who receive primary care should be performed, to ensure a correct diagnosis of any underlying condition, as early diagnosis and detection of organ involvement improves possible CTE. **Grade IIa-Level C**.

2. All patients with RP should undergo blood tests that include a complete blood count, with erythrocyte sedimentation rate or C-reactive protein and antinuclear antibody tests, as well as capillaroscopy when available. **Grade IIa-Level C**.

3. Capillaroscopy should only be performed with equipment of good optical quality and by a trained professional, usually in secondary or tertiary care. **Grade IIa-Level C.**

4. Capillary microscopy is a useful diagnostic tool used to detect abnormal capillary patterns, which are strong predictors of CTD and should be employed by secondary care. **Grade IIa-Level.**

5. Children under the age of 12 should be referred for secondary treatment, as primary RP is less common in this age group. **Grade IIa-Level C.**

6. Patients with RP should be referred for secondary treatment when there is evidence of an associated or occlusive vascular disease disorder, if the symptoms are severe, or if symptoms progress despite the first line of treatment including lifestyle and medication changes. **Grade IIa-Level C.**

7. Lifestyle changes are an effective way of controlling RP attacks. These should include wearing warm clothes, quitting smoking, avoiding triggers such as cold temperatures and assessing the need for occupational therapy should the patient require help. **Grade IIa-Level C.**

8. Calcium channel blockers are the recommended first-line pharmacological treatment for RP if lifestyle changes have not improved the condition. **Grade I-Level A.**

9. Slow release nifedipine should be used to minimise debilitating vasodilatory side effects and shorten the duration of episodes. Care must be taken to only increase the dosage if symptoms deteriorate, to avoid unnecessary side effects. If the side effects are not serious, patients should be encouraged to tolerate them for two or three weeks, as they may subside. **Grade IIa-Level C.**

10. There is no solid evidence to support the surgical treatment of RP, but this may be indicated in certain situations, for example, in cases of digital ulceration related to systemic sclerosis. **Grade IIb - Level C.** Areas where evidence is lacking/areas for further study.

Despite the aforementioned basic recommendations for RP detection, scientific literature proposes many different diagnostic methods to define this phenomenon (Goundry, Bell, Langtree, & Moorthy, 2012; Hughes & Herrick, 2016). Self-administered reports, such as the Raynaud's Condition Score (RCS) diary, may be included in the study and diagnosis of RP as well as measures of the duration and frequency of RP attacks, or an overall physical assessment and local evaluation of the hand (Hirschl et al., 2006; Hughes & Herrick, 2016). Various non-invasive techniques can be used to evaluate abnormalities at the vascular level, such as nail capillaroscopy, thermography and Doppler lasers (Matthieu Roustit, Blaise, Millet, & Cracowski, 2011). The functional response to cold temperatures is often evaluated by performing a localised cold test, as well as analysis of the biochemical profile, in order to complete the diagnosis (Herrick & Murray, 2018). Recent clinical trials have proposed that, in addition, new methods should be considered to

examine RP, which include measures of the severity and impact of episodes; pain assessment using the Visual Analog Scale (VAS) and assessment of disability in activities of daily living, although these evaluation measures have not been validated for this condition. However, to date, no method has been universally implemented in the diagnosis of RP (Hirschl et al., 2006; Maverakis et al., 2014).

From a therapeutic point of view, at present, there are a wide variety of options to address the treatment of RP (García-Carrasco et al., 2008; Herrick, 2017). There are different treatment methods that range from the use of conservative measures (education and lifestyle changes), to pharmacological treatments including the use of topical therapy, surgery, vascular repair, use of the botulinum toxin or use of complementary and alternative medicines. However, none of these therapies has shown definitive efficacy and many of them have significant side effects (García-Carrasco et al., 2008; Linnemann & Erbe, 2016).

The therapeutic approach to RP will depend on the intensity and severity of the symptoms that are present, which will be determined largely by the type of RP of the sufferer, whether it is primary or secondary In general, the main objective of the treatments used in the treatment of RP is to reduce the severity and frequency of clinical manifestations as well as possible complications (Prete et al., 2014). The different treatments generally focus on encouraging vasodilation, inhibiting vasoconstriction, reducing endothelial damage and inhibiting platelet aggregation (Goundry et al., 2012).

The first line of treatment for both forms of RP is the patient implementation of conservative measures such as lifestyle changes. These conservative measures include maintaining a high core body temperature by wearing suitable clothing and materials (gloves, warm clothes); avoiding exposure to cold temperatures; quitting smoking and avoiding the consumption of coffee and alcohol (Herrick, 2017; Stringer & Femia, 2018).

The initial treatment of the primary form of RP, is usually conservative and is usually sufficient. If patients do not respond adequately to these measures, the use of pharmacological therapy, consisting mainly of vasodilation medications, should be considered (Herrick, 2017). In patients with secondary RP, conservative measures are not

sufficient and these patients will usually require treatment with pharmacological therapy (Stringer & Femia, 2018).

In terms of pharmacological treatment, the majority of therapies remain unsatisfactory at present, due to the adverse effects that they produce, compared to their minimal efficacy (García de la Peña Lefebvre et al., 2015). In this regard, calcium channel blockers, such as nifedipine, are generally considered the first pharmacological option, although a recent systematic review (Rirash et al., 2017) determines that these medications only have a moderate effect in reducing the frequency and severity of attacks. In recent years, the use of new vasodilator medications has been studied (Ennis, Hughes, Anderson, Wilkinson, & Herrick, 2016; Stewart & Morling, 2012), but there is still not enough evidence to allow its use in the treatment of RP. New, more advanced, pharmacological approaches in RP treatment include phosphodiesterase-5 inhibitors such as sildenafil, tadalafil, vardenafil, phosphodiesterase-3 inhibitors such as cilostazol (Caglayan, Axmann, Hellmich, Moinzadeh, & Rosenkranz, 2012; Herrick et al., 2011; Shenoy et al., 2010). The effect of nitric oxide supplements as inhibitors of type 5 phosphodiesterase is also being studied, although its efficacy is moderate in secondary RP (Matthieu Roustit et al., 2013). On the other hand, intravenous (Iloprost) and oral therapies with prostaglandins are also being used (Ingegnoli et al., 2019b; Shah et al., 2013), which have been shown to be potent vasodilators and have important platelet antiaggregation effects, thus making them effective in reducing the frequency and severity of attacks, as well as digital ulcers, in patients with RP secondary to sclerosis. However, the main disadvantage of these therapies is that they present notable side effects as they result in systemic vasodilation, hypotension, headaches and hospital visits, not to mention being expensive.

In recent years, a topical approach to therapy has evolved and the therapeutic use of topical nitrate is being studied (Anderson et al., 2002; Chung et al., 2009), but for now, this therapy is not yet licensed for use in the treatment of RP. The application of botulinum toxin can also be included in this line of treatment, in the form of injections into the hands of RP patients. A recent review (Zebryk & Puszczewicz, 2016) highlights that the evidence evaluating the efficacy of botulinum toxin in the treatment of RP is still insufficient.

When patients do not respond to pharmacological treatment and present with severe symptoms such as ulcers or gangrene, surgical treatment can be performed (García-Carrasco et al., 2008). Generally, this consists of performing a surgical debridement or an operation to either remove part of the damaged phalanx or to perform a complete amputation. Another surgical intervention that has been used in RP treatment is sympathectomy, both in the upper limbs and in the fingers, but the literature indicates that there is not a sufficient scientific evidence base to support the use of this surgery in the treatment of RP (Belch et al., 2017).

On the other hand, new therapeutic approaches have been studied and developed for RP in recent years, such as spinal cord stimulation (Wolter & Kieselbach, 2011), laser therapy (Al-Awami, Schillinger, Maca, Pollanz, & Minar, 2004), acupuncture, alternative therapies or the use of food supplements. However, the real value of these therapies in the treatment of RP is yet to be determined due to the lack of current evidence(Linnemann & Erbe, 2016).

The wide variety of treatments, and the limited indications of their efficacy regarding RP, highlights the need to continue investigating new therapeutic alternatives, as well as to establish their efficacy.

1.4.1 Scientific evidence on the use of thermotherapy, laser therapy and electrical stimulation for the modulation of vasodilation in Raynaud's phenomenon.

1.4.1.1 Thermotherapy.

Different forms of thermotherapy have been used to treat RP. Among those studied, is the simple method of warming the hands, by immersing them in hot water (Goodfield & Rowell, 1988). According to this method, subjects were required to place their hands in hot water for 5 minutes every 4 hours throughout the day, for 6 alternate weeks. This system demonstrated a reduction in the number and duration of attacks, as well as an increase in blood flow during the weeks of application. Thus, the simple heating of the hands with hot water results in vasodilation that seems to be effective in the management of RP, without

the risk of side effects that come with pharmacological treatments. Subsequently, it has been described that it is more practical for patients to warm their hands by immersing them in warm water before going outside, than to warm them up every 4 hours. The main drawbacks of this method are that effects are not consistently shown in all patients and the duration of the effect is never more than 2 hours, although the combined use of gloves causes the effect to be extended. In other instances, patients decided to use other heating devices such as hot water bottles or hand warmers (Goodfield & Rowell, 1988).

The efficacy of other forms of surface thermotherapy has also been studied through the use of "thermoflow" gloves, which are garments interwoven with ceramic powder (95% polypropylene and polyethylene, 5% ceramic powder) that absorbs infrared radiation from the environment and the body (0.76 to 4 micrometres wavelength). This is converted into thermal energy that is reflected in the underlying tissues and triggers a rise in temperature of the subcutaneous and dermal tissues. The use of these garments has been shown to produce vasodilation that improves circulation, reduces pain levels and improves grip ability in patients with RP. However, the effects are moderate and skin irritation may occur (Ko & Berbrayer, 2002).

Another thermotherapy method with proven evidence has been infrared A (IR-A) treatments in patients with RP that is secondary to scleroderma. In RP patients, infrared radiation produces mild hyperthermia, which is effective in treating manifestations of the disease as it reduces severity and can be used as a complementary treatment alongside pharmacological treatment. The effect on a thermal level and the reduction of pain on the VAS after 5 sessions last for up to 6 weeks after finishing the treatment. However, this therapy only had a temporary improvement on the skin thickness and the level of pain in the joints due to the associated scleroderma (Foerster et al., 2005).

1.4.1.2 Laser therapy.

Low-power laser therapy promotes athermic biostimulation, using light sources (phototherapy), which emit a low energy, generally within the red or infrared spectrum (Al-Awami et al., 2004). The literature describes how this therapy has been used in

patients with vascular disorders or rheumatic diseases and its effects are ambiguous (Hirschl, Katzenschlager, Francesconi, & Kundi, 2004).

When using this therapy in RP patients, it has been observed that the frequency and intensity of the attacks are substantially reduced, but different therapeutic effects are observed in patients who experience different intensities of vasospasms and different forms of RP (Al-Awami et al., 2004; Hirschl et al., 2004). Researchers emphasise that this may be due to factors independent of the endothelium, thereby suggesting that there is an intrinsic heterogeneity between primary and secondary RP (Hirschl et al., 2004). Further studies are needed to demonstrate the efficacy of laser therapy treatment and to establish it as a new non-pharmacological therapy for RP

1.4.1.3 Electrical stimulation.

Spinal cord stimulation (SCS) is a treatment that can be used in cases of severe RP that do not respond to conventional treatments (Report, 2007; Wolter & Kieselbach, 2011). Its use is based on the work of Melzack and Wall, on the gate control theory of pain management. This treatment has several drawbacks. To start, it is invasive, as an incision must be made and it is necessary to replace the battery of the device every so often. On the other hand, we find a lack of scientific evidence on its real effects. At present, there are a few publications related to this treatment and its use in RP patients. Most of them refer to isolated cases or a series of cases (Mercader et al., 2003; Münster, Tiebel, Seyer, & Maihöfner, 2012; Report, 2007; Wolter & Kieselbach, 2011).

Another method of electrical stimulation used in the treatment of RP is the galvanic current by iontophoresis (Murray, Herrick, Gorodkin, Moore, & King, 2005).

In fact, to date, iontophoresis with vasodilation drugs has been used more to quantify endothelial function in RP than as a therapeutic alternative to conventional treatment.(Anderson, Moore, Lunt, & Herrick, 2004). However, the results of these studies raised the question of whether iontophoresis could be applied therapeutically in patients with RP. In this line Murray et al. (2008), developed a method to perform iontophoresis on a single finger. The purpose of this preliminary investigation was to test the hypothesis that vasoactive drugs, in this case acetylcholine chloride (ACh), could be applied to specific

areas of the body without producing systemic effects. They concluded that further studies using vasodilation drugs would be necessary to achieve a more lasting effect and to determine whether iontophoresis is a possible therapy for RP (Murray et al., 2008). [2008] Iontophoresis has also been used in patients with RP secondary to scleroderma and resulted in the clinical improvement of symptoms, improved tissue flexibility, decreased sensitivity to cold and improved skin colour (Gollins, Carpenter, Steen, Bulinski, & Mahendran, 2019).

On the other hand, previous studies have applied peripheral vascular vasodilators (calcium channel antagonists) by iontophoresis in healthy adult subjects, either alone or in combination with lidocaine, in order to study their effects on pain thresholds. When the vasodilators were applied alone, they raised the pain threshold to the same extent as lidocaine. When the calcium channel antagonists were administered in combination with lidocaine, the pain threshold elevation did not change, but the duration of the analgesic action was extended when compared to lidocaine alone. These results suggest that the calcium channel plays an important role in the mechanism of pain control and raises the possibility of using clinical iontophoresis administration of calcium channel antagonists in pain management (Taniguchi, Miyagawa, Mizutani, Honda, & Oyama, 1995).

1.5 Vascular and analgesic effects of electrical stimulation by iontophoresis with tap-water.

From the therapeutic point of view, we can use electrical stimulation by means of galvanic current on account of the physiological changes it produces in the body. The galvanic current is a direct current, low intensity (maximum 200 milliamps) and low voltage between 60-80 Volts (Gollins et al., 2019; Sloan & Soltani, 1986; Zhou et al., 2018). The flow of current through the body causes three main effects: electrothermal, electrochemical and electrophysical effects (Albornoz-Cabello, M., Maya-Martín, J., & Toledo-Marhuenda, 2016).

a. **Electrothermal effect**. When the current passes through a medium, it causes the particles of the medium to vibrate, which causes a heating effect

and leads to a rise in temperature (Albornoz-Cabello et al., 2016; Watson, 2009)

b. **Electrochemical effect.** Water is a good conductor and the action of the electric current causes the ions in the solution migrate towards the electrodes. The human body is composed of more than 80% water and its electrolytic behaviour in relation to the passage of electric current is similar to that of a sodium chloride solution. Interstitial and bodily fluids are electrolytic conductors and when a current is applied, an electrolytic dissociation is produced in them. In this way, the cations move towards the cathode which is the negative electrode and the anions towards the positive anode, releasing or gaining electrons to transform into neutral elements, thus reacting with the water. An acid reaction is thereby produced at the positive electrode, releasing hydrochloric acid. Sodium hydroxide is released at the negative electrode. Faced with these chemical reactions, the body responds by increasing blood flow locally to restore tissue pH (Albornoz-Cabello et al., 2016; Rodríguez Martín, 2014).

c. **Electrophysical effect.** This manifests in the body's molecules that are electrically charged, such as proteins, and arises with the passage of current towards one of the poles. However, no changes occur at a molecular level. This ionic movement triggers excitation of the peripheral nerves, as it modifies the ionic flow through the cell membranes, via the passage of sodium and potassium. This can lead to vascular responses (with a powerful stimulation of circulation in the area), activation of endogenous analgesic mechanisms or muscle contractions (Albornoz-Cabello et al., 2016; Rodríguez-Martín, 2014)

When we apply a galvanic current to an area of the body, the resistance of the skin in that area gradually decreases and the patient can tolerate increasing doses of current. The current is initially perceived as a pinching sensation and later as a pleasant sensation of warmth. The galvanic current will result in hyperaemia of the skin, especially at the negative pole. This redness can last between ten minutes and half an hour, and is a result of reflex vasodilation that produces pH changes in the skin, which in turn increases the blood flow to the area. This improves tissue nutrition and has both an analgesic and anti-

inflammatory effect. The current has a stimulating effect on the nervous system at the negative low pole and an analgesic effect at the positive one (Watson, 2009).

The most frequent use of galvanic current is through iontophoresis. Iontophoresis is defined as the non-invasive process of introducing soluble salt ions into the body through the skin using an electric field generated by a low frequency continuous current for diagnostic and therapeutic purposes (Murray et al., 2005; Sloan & Soltani, 1986). Its immediate effect is the improved absorption of medications, presenting several advantages over other methods of administration, as the medication side effects are reduced at the systemic level. Patient acceptance is usually good and the unease associated with more invasive methods such as injection, is avoided (Murray et al., 2005).

The technique was first described in 1747 by Veratti and later developed by Galvani. The use of galvanic current became very popular in the nineteenth century and was first used in neurological, gynaecological and genitourinary treatments. This technique temporarily lost its popularity towards the end of the 19th century when new advancements were made in the field of electrotherapy. At the beginning of the 20th century, Leduc reviewed the technique and introduced the term ionotherapy, demonstrating that drugs could be introduced into the body via the skin with the use of current. This discovery once again increased the focus on this technique, which led to the study of many subsequent applications. Interest in the use of iontophoresis has varied during the 20th and 21st century, receiving different names such as galvanisation or medical ionisation (Sloan & Soltani, 1986; Watson, 2009). We are currently witnessing another phase of rediscovery, as this simple technique still has much to offer and many of its complexities remain to be clarified (Rodríguez-Martín, 2014).

Iontophoresis has been therapeutically implemented in a wide range of applications within the medical field. The most common is in the treatment of hyperhidrosis (excessive sweating) where iontophoresis is usually used with a tap-water. The treatment has shown considerable success, but must be routinely applied because the results are not permanent (Albornoz-Cabello et al., 2016).

Applications of iontophoresis include the treatment of lupus, skin cancer, skin ulcers secondary to diabetes, vascular ischaemic disease, scleroderma, fungal infections, dermatitis, vitiligo, bursitis, neuritis, fibrosis, the production of otolaryngology and dental anaesthesia, applications in ophthalmology, and antibiotic iontophoresis, among many others (Murray et al., 2005).

Generally, electrical devices are used to generate a direct current and are connected by cables to carbon electrodes placed in sponges soaked in either water or the medicine that is to be applied, and these are subsequently placed on the area to be treated. When iontophoresis is used with tap-water, the electrodes are inserted into the sponges in a medium with water, usually small plastic containers. Today, a wide variety of iontophoresis devices are available on the market, ranging from machines connected to the power supply to small portable devices that work with rechargeable batteries or standard batteries (Rodríguez-Martín, 2014).

Currently, iontophoresis with tap-water is commonly used in the treatment of hyperhidrosis and has proven to be more effective and safer than the use of anticholinergic drugs that produce side effects (Murray et al., 2005). While their efficacy and safety is well documented, the exact mechanisms of action are yet to be determined. Previous studies show that the application of iontophoresis with tap-water produces an increase in blood flow to the area, due to an inactivation of the sweat glands, which leads to an increase in the temperature of the skin and thus, vasodilation. The hypothesis that the sweat glands play a fundamental role, though not exclusively, in the process of driving the ionic charges through the skin, is widely accepted. Further studies are necessary to investigate the application potential of this mode of therapy, that may lead to a more effective and versatile use of this safe and simple therapeutic method (Gollins, Carpenter, Steen, Bulinski, & Mahendran, 2019).

Everything points to the fact that iontophoresis can be an optimal therapy in the treatment of RP as it is an innovative application which is easy to perform, minimally invasive and yields minimal side effects. Therefore, it is necessary to continue conducting additional research into new treatments with iontophoresis, to optimise the existing therapeutic options of this condition.

1.6 Justification of the thesis.

RP sufferers constitute a population at risk of suffering chronic pain and loss of functionality, especially those cases with a greater number of associated risk factors, or those that are secondary to other chronic conditions. The characteristic signs and symptoms of RP and its two forms of presentation have been widely studied. However, as far as we know, there is no scientific evidence on the relationship and influence of the vascular abnormalities suffered by these patients or the mechanisms of pain processing and degree of functionality of the upper limbs.

The scientific evidence also shows that the aetiopathogenesis of RP is yet to be determined, plus there are no standardised diagnostic criteria for this condition. In this sense, therapeutic interventions are primarily aimed at the reduction of vasospasm attacks and will depend on the form of RP presentation, whether it is primary or secondary. The therapy of choice, along with conservative treatment, is usually pharmacological. However, despite the fact that a great variety of therapies have been described, many lack sufficient evidence for their use and it has been shown that the efficacy of most medications is usually moderate and, in many cases, they have significant side effects. In this sense, based on the available scientific evidence, a new therapeutic option could stem from the field of electrotherapy, as galvanic current applied by iontophoresis and its demonstrated vasodilatory, thermogenic and analgesic effects, could lead to an improvement of the symptomatology and medium-long-term disability of patients with RP. No previously published studies have been found that address the assessment of the factors related to chronic pain processes in these patients and their functionality, nor the use of electrotherapy as an alternative treatment.

The initial hypothesis for the first study of this thesis was that RP sufferers would show a bilateral pattern of hypersensitivity to pressure pain stimuli, indicating central sensitization in this population, and that this would be related to lower temperatures in their hands. That is, sufferers with greater vascular damage would present with lower temperatures in their hands, due to greater vasoconstriction, thus having higher levels of pain and central sensitization than the healthy control patients.

The initial hypothesis for the second study was that RP sufferers would have higher levels of disability in their upper extremities and therefore, greater difficulties in carrying out activities of daily living , practising sports, carrying out activities related to the arts, or performing a work activity compared to healthy people. Let us also raise the idea that these higher degrees of disability could be related to damage at the vascular level and to the loss of functionality of the hand in RP sufferers.

The hypothesis of our third study was that the application of electrotherapy treatment by means of a galvanic current applied in the iontophoresis modality with tap-water, in people with primary and secondary RP, would improve the symptomatology of these patients over a period of seven weeks. Improvements would be made at the vascular level in reducing the number of attacks, improvement of oxygen saturation, blood flow, basal temperature and recovery of temperature, pain levels, degree of central sensitization, catastrophizing and perceived disability, compared to RP patients who only receive conventional treatment for this condition.

.

OBJETIVOS

OBJECTIVES

2. OBJETIVOS

2.1 Generales.

- Evaluar la relación entre las alteraciones vasculares y los niveles de dolor, los procesos relacionados con el desarrollo del dolor crónico (Catastrofismo y Sensibilización Central), la funcionalidad de la mano y la discapacidad de los miembros superiores en personas con Fenómeno de Raynaud.

- Evaluar la efectividad de una intervención de electroterapia mediante iontoforesis con agua corriente, en la severidad de los síntomas vasculares, síntomas y procesos relacionados con dolor crónico y la discapacidad percibida a nivel de los miembros superiores en personas con Fenómeno de Raynaud.

2.2 Específicos.

- Comparar el grado de severidad vascular, la intensidad del dolor, los niveles de mecanosensibilidad, los umbrales del dolor eléctrico, la sensibilización central y la catastrofización entre personas con Fenómeno de Raynaud primario, secundario y sujetos sanos.

- Evaluar la relación entre el patrón termográfico de las manos, como un indicador del deterioro vascular, con la intensidad del dolor, la mecanosensibilidad, la sensibilización central y el catastrofismo en personas con Fenómeno de Raynaud.

- Evaluar el grado de afectación vascular, la funcionalidad de la mano y la discapacidad de miembros superiores en personas con Fenómeno de Raynaud primario, secundario y sujetos sanos.

- Analizar la relación entre las alteraciones vasculares determinadas mediante la temperatura de las manos, la curva de recuperación de la temperatura, la saturación de oxígeno y el flujo sanguíneo; con los rangos de movilidad y fuerza de la mano como indicadores de la funcionalidad de la mano y la discapacidad percibida en la

práctica de actividades cotidianas de la vida diaria, trabajo y la práctica de deportes o actividades artísticas en personas con FR primario y secundario.

- Analizar la eficacia de la aplicación de una corriente galvánica mediante iontoforesis con agua corriente, sobre el número de ataques, la recuperación de la temperatura, la saturación de oxígeno y el flujo sanguíneo en personas con Fenómeno de Raynaud.

- Objetivar la eficacia de la aplicación de un tratamiento con electroterapia en la intensidad del dolor, la funcionalidad de la extremidad superior, el proceso de sensibilización central y el catastrofismo asociado al dolor en personas con Fenómeno de Raynaud.

2. OBJECTIVES

2.1 General

- To evaluate the relationship between vascular abnormalities and pain levels, the processes related to the development of chronic pain (Catastrophizing and Central Sensitivity), the functionality of the hand and the disability of the upper limbs in Raynaud's phenomenon sufferers.

- To evaluate the efficacy of iontophoresis electrotherapy with tap-water, on the severity of vascular symptoms, pain-triggering processes and symptoms, and perceived upper limb disability in Raynaud's phenomenon sufferers.

2.2 Specific

- To compare the degree of vascular severity, pain intensity and mechanosensitivity levels, as well as electrical pain thresholds, central sensitization and catastrophizing between people with primary and secondary Raynaud's phenomenon, and healthy subjects.

- To evaluate the relationship between the thermographic pattern of the hands, as an indicator of vascular deterioration, and pain intensity, mechanosensitivity, central sensitization and catastrophizing in Raynaud's phenomenon sufferers.

- To assess the degree of vascular involvement, hand functionality and disability of the upper limbs in people with primary or secondary Raynaud's phenomenon, and healthy subjects.

- To assess the established vascular abnormalities through hand temperature, temperature recovery curve, oxygen saturation and blood flow. We used the range of mobility and hand strength as indicators of hand functionality and the perceived disability of RP sufferers and healthy subjects, in carrying out activities of daily living at home, work and practising sports or artistic activities.

- To analyse the efficacy of galvanic current application by iontophoresis with tap-water on the number of attacks, the recovery of temperature, oxygen saturation and blood flow in Raynaud's phenomenon sufferers.

- To objectify the efficacy of electrotherapy treatment application on the intensity of pain, the functionality of the upper extremity, the central sensitization process and the catastrophizing associated with pain in Raynaud's phenomenon sufferers.

METODOLOGÍA

METHODS

3. METODOLOGÍA/METHODS

Tables 1, 2 and 3 show a summary of the methodology used in the studies included in the PhD thesis.

3.1 Study I: "Pain intensity, pressure pain hypersensitivity, central sensitization and pain catastrophizing related to vascular alterations in Raynaud's phenomenon: a preliminary case-control study".

The methods section of the Study I, included in the PhD thesis, has been summarized below. This study has been published in the journal *Pain Medicine.* (Appendix 1). Table 1 show a summary of the methodology used in this observational study.

Table 1. Summary of Material and Methods in Study I.

PAPER	STUDY DESING	PARTICIPANTS	PROCEDURES	MAIN VARIABLES	METHODS
Pain intensity, pressure pain hypersensitivity, central sensitization and pain catastrophizing related to vascular alterations in Raynaud's phenomenon: a preliminary case-control study.	Controlled cross-sectional study.	• Participants with Primary RP (n=18). • Participants with Secondary RP (n=19). • Healthy controls (n=20).	• Screening to identification selection criteria. • Sociodemographic and clinical information were registered: - Sex. - Age. - Time since onset. - Number of attacks per day. - Smoking history. - Color pattern.	• Peripheral vascular response. • Pain intensity. • Pressure pain sensitivity. • Pain magnitude. • Pain threshold. • Central sensitization. • Pain catastrophizing.	• Digital thermal camera (FLIR B335, Flir Systems AB, Täby, Sweden). • 10 cm Visual analogue scale • Digital algometer FDIXTM (Wagner Instruments, Greenwich, CT, USA). • Pain Matcher® device (Cefar-Compex Scandinavia Inc, Medical AB, Lund, Sweden). • Central Sensitization Inventory (CSI). • Pain Catastrophizing Scale (PCS).

RP, Raynaud´s phenomenon.

3.1.1 Study Design and Participants

A sample of 60 persons was approached to participate in this preliminary case-control study. After applying the selection criteria, 18 persons with PRP and 19 with SPR were consecutively recruited from the Rheumatology Service of the Virgen de las Nieves Hospital in Granada (Spain). Twenty healthy control participants were recruited from among volunteers who responded to a university-wide call. The participation rate was 92.5% (a final sample of 37 participants with RP among the 40 participants initially recruited)..

Inclusion criteria for RP participants were: 1) Age greater than 18 years. 2) Diagnosis of PRP or SRP according to the criteria of LeRoy and Medsger [14]. 3) A history of at least one year of regular attacks of RP. 4) Having signed the informed consent document. Exclusion criteria were: 1) Presence of skin alterations such as stings, scars, ulcers or gangrene in the examined area. 2) Upper limb entrapment syndrome, central nervous system polyneuropathy, renal failure, cerebral or cardiac ischemic disease. 3) History of drug or alcohol abuse. 4) Pregnant or breastfeeding women. 5) Use of vibratory tools. 6) Any tumoral process. 7) Chronic pain or trauma in the upper limb or hand due to other conditions. The exclusion criteria in the healthy control group were the same as in the RP group plus the following: 1) Cardiovascular or neurovascular disease. 2) Any dermatological or overt immunological disease. 3) Hypertension.

3.1.2 Procedures

All participants were informed about the study characteristics, objectives and procedures. Sociodemographic and clinical variables were recorded and comprised: sex, age, time since onset, number of attacks per day, color pattern, smoking history, hand dominance and temperature assessment. Each participant was evaluated on the same day, over a total time of 90 minutes, in the following order: Firstly, participants completed the questionnaires about pain intensity, CS and catastrophizing. Subsequently, thermography was performed since the vascular response may be altered by pain evaluation. Thirdly, we evaluated pain with the Pain Matcher device and algometry, with a rest time of 30 minutes between tests.

Written informed consent was obtained from all participants. The study was approved by the Ethics Research Committee of Granada province-CEI (Andalusian Health Service, Granada, Spain) (Appendix 2) and was conducted in accordance with the amended version of the Declaration of Helsinki, 2013. Both groups of participants were assessed using the same procedures.

3.1.3 Measures

3.1.3.1 Vascular Assessment

Peripheral vascular response was evaluated in thermography images obtained with a digital thermal camera (FLIR B335, Flir Systems AB, Täby, Sweden). Thermography provides indirect information about blood flow, circulation, skin thermal properties and thermoregulatory functionality of the cutaneous tissue, since cutaneous temperature depends on e local blood perfusion and thermal tissue properties (Grossi et al., 2010). All thermograms were obtained under the same stable conditions, in compliance with the recommendations of the European Association of Thermology (EAT) (Chlebicka, Matusiak, Maj, Baran, & Szepietowskiki, 2013) and a previously reported protocol (Lim et al., 2014). The mean of all temperature values from each point in each participant was calculated and used in the analyses. All participants were asked to avoid physical activities or consume vasoactive substances in the 2 hours before testing. This method has demonstrated good reproducibility (Schlager et al., 2010). Thermography has a sensitivity of 90% (73-97%) and a specificity of 86% (68-94%). Values are given as percentages with 95% confidence intervals (CI) (Mirbod & Sugiura, 2017).

3.1.3.2 Pain Assessment

3.1.3.2.1 Pain Intensity

To assess the intensity of pain we used a visual analog scale (VAS) consisting of a 10-cm line from 0 (no pain) to 10 (the worst pain imaginable). This instrument has demonstrated good reliability and internal consistency, with Cronbach's alpha coefficients ranging from 0.71 to 0.97, and an intraclass correlation coefficient (ICC) of 0.97 (95% CI=0.96–0.98) (Bijur, Silver, & Gallagher, 2001; Gallagher, Liebman, & Bijur, 2001).

3.1.3.2.2 Pressure Pain Sensitivity

Pressure pain threshold (PPT) is defined as the minimum amount of pressure at which a person perceives that the sensation of pressure first changes to pain (Cantarero-Villanueva et al., 2012). To measure PPT we used a FDIXTM digital algometer (Wagner Instruments, Greenwich, CT, USA).

The algometer pressure gauge was calibrated in kg/cm^2, and we applied pressure at a rate of 1 kg/sec. We instructed participants to tell the examiner when the sensation of pressure changed to pain. All PPTs were bilaterally assessed at the following points according to published protocols used in previous studies: over the C5-C6 zygapophyseal joints, the second metacarpals, the deltoid muscles, and the tibialis anterior muscles (Cantarero-Villanueva et al., 2012; Fernández-Lao et al., 2011). We performed three measurements and calculated the mean. High scores were obtained for the reliability of this method, with intra-rater reliabilities (Cronbach's alpha) of (0.94–0.98) and an ICC of 0.91, (95% CI=0.82–0.97) (Chesterton, Sim, Wright, & Foster, 2007).

3.1.3.2.3 Pain Matcher

We measured pain magnitude and pain threshold with the electrical stimulation device Pain Matcher® (Cefar-Compex Scandinavia Inc, Medical AB, Lund, Sweden). The Pain Matcher (PM) is an instrument for comparing pain intensity that allows users to match perceived pain in a certain region of the body with the pain generated by an electrical stimulus between the right thumb and index finger (Käll, Kowalski, & Stener-Victorin, 2008). The instrument is controlled by a microprocessor that provides constant electrical current at an amplitude of 15 mA, in monophasic rectangular pulses at random velocity, at a frequency of 10 Hz. To create an electrically closed circuit, the instrument was held by participants by gripping it firmly between their thumb and index finger of the right hand, and carbon rubber electrodes with a contact area of 6 cm^2 were placed. The cathode (negatively charged electrode) was placed under the index finger (Aguilar-Ferrándiz et al., 2015). Pulse width was increased successively from 0 to a possible maximum of 450 -μsec in increments of 4 μsec for a total of up to 60 steps. The PM score is from 0 to 60. The participants were instructed to hold the PM with a firm grip. The device causes an increasing current that eventually becomes painful. In order to obtain the pain magnitude, participants were instructed to release their grip from the PM when the physical sensation of pain in their fingers matched the intensity of their RP pain. To establish the pain

threshold, they were instructed to release their grip from the device as soon as they experienced the first sensation of pain. Each outcome was recorded three times and the mean of the three values was calculated. The PM devices has demonstrated good test–retest reliability, (95% CI=0.39– 0.14) (Lund et al., 2005).

3.1.3.2.4 Central Sensitization Inventory

The Central Sensitization Inventory (CSI) (Neblett et al., 2013) is a self-assessment inventory that contains 25 statements with current health symptoms related to Central Sensitization Syndrome. Responses regarding the frequency of each symptom are recorded using a 5-point Likert scale. The score ranges from 0 to 100 and the cutoff score is 40 (Mayer et al., 2012) Higher scores indicate increased frequency and severity of symptoms (Neblett et al., 2017) This inventory has been shown to have high reliability and validity (test–retest reliability = 0.82; Cronbach's alpha = 0.88) (Neblett et al., 2013).

3.1.3.2.5 Pain Catastrophizing Scale

We used the Pain Catastrophizing Scale (PCS) (Sullivan, Bishop, & Pivik, 1995) to assess cognitive and affective aspects of pain catastrophizing. This self-report questionnaire consists of 13 items related to three sub-dimensions of catastrophizing: magnification, helplessness and rumination. It uses a 5-point Likert scale ranging from 0 (not at all) to 4 (all the time) (Sullivan et al., 1995). The range of possible scores is from 0 to 52; higher scores indicate a greater frequency of catastrophic thoughts (García-Campayo et al., 2008). Previous research showed that the PCS has good internal reliability (Cronbach's alpha = 0.87) and high internal consistency (Cronbach's alpha = 0.93) (D'Eon, Harris, & Ellis, 2004).

3.1.4 Statistical Analysis

The sample size needed in order to compare the pressure pain threshold at the tibialis anterior point between case and control participants was calculated with the G-Power 3.1.2 program for an α error of 5% and a power of 80% to detect a minimal clinical difference of 20% [24]. A sample of 16 participants per group was needed; however the sample size was increased to a total of 60 in order to allow for a 20% rate of loss during the study.

The data were analyzed with SPSS© version 20.0 (IBM Corporation, Armonk, NY, USA). The Kolmogorov–Smirnov test was used to verify normality of the distribution of the variables (P >0.05). Baseline demographic and clinical variables were examined in all three groups by using ANOVA for continuous data and $\chi 2$ for categorical data. A three-way analysis of covariance (ANCOVA) was used to assess the main objective of the study: groups (patient and control) were evaluated, in which the key variables were the between-subject factor as dependent outcomes, and age and gender were covariates. Because ANOVA did not show differences in the thermography results between the dominant and non-dominant hand in any of the three groups, we pooled these values. We added the temperatures in both hands (dominant and non-dominant) and calculated the mean temperature value in the 3rd finger at the dorsal and palmar sites, and the mean value of temperature in the center of the hand at the dorsal and palmar sites, to render the variables for vascular alterations. Finally, to evaluate the relationship between pain and vascular-thermographic findings, Pearson correlations were also calculated performed. The statistical analysis was performed at a 95% confidence level, and P<0.05 was considered to be statistically significant.

3.2 Study II: "Disability in Raynaud's phenomenon seems to be more related with hand´s mobility and strength than severity of vascular alterations".

The methods section of the Study II, included in the PhD thesis, has been summarized and described below. Table 2 shows a summary of the methodology used in this observational study.

Table 2. Summary of Material and Methods in Study II.

PAPER	STUDY DESING	PARTICIPANTS	PROCEDURES	MAIN VARIABLES	METHODS
Disability in Raynaud's phenomenon seems to be more related with hand´s mobility and strength than severity of vascular alterations	Controlled cross-sectional study.	• Participants with Primary RP (n=18). • Participants with Secondary RP (n=19). • Healthy controls (n=20).	• Screening to identification selection criteria. • Sociodemographic and clinical information were registered: - Sex. - Age. - Hand dominance. - Number of attacks per week. • Associated Pathologies: - Arterial Hypertension - Hypercholeste-rolemia - Diabetes	• Temperature. • Vascular response. • Oxygen saturation. • Arterial blood flow: - Radial. - Ulnar. • Upper limb disability. • Total range of motion in right and left: - Index finger. - Thumb. • Pinch strength: - Tip. - Lateral.	• Infrared thermographic scanner (Derma Temp®, Model: 104920 – DT-1001-LT [USA]). • Cold stress test. • Pulse oximeter, MEGOS Oxi- Pulse®, SONMEDICA S.A, (Barcelona, Spain). • Hadeco Bi-Directional Vascular Doppler®, BIDOP ES-100 VII (Japan). • Shortened Disabilities of the Arm, Shoulder and Hand Questionnaire (Q-DASH). • Finger goniometer (SAHEAN®). • Mechanical Pinch Gauge (Baseline®)

RP, Raynaud´s phenomenon.

3.2.1 Study design and participants

This was a pilot case-control study. A total of 60 subjects were considered for the study. After application of the selection criteria, 57 subjects were included: 18 with Primary Raynaud's phenomenon, 19 with Secondary Raynaud to Scleroderma and 20 healthy controls. The participation rate was 95 %. The Raynaud participants were recruited from the Rheumatology Service of the Virgen de las Nieves Hospital in Granada (Spain) and the controls from among volunteers who responded to a local advertisement by the Physiotherapy Department of the University of Granada.

Inclusion criteria were: a) age over 18 years; b) previous diagnosis of Raynaud (primary or secondary), according to the criteria established by LeRoy and Medsger (LeRoy & Medsger, 1992); c) a history of at least one year of regular attacks of Raynaud; d) a signed informed consent form.

Exclusion criteria were: a) the presence of skin alterations (scars, ulcers, gangrene or bites in the area to be examined); b) the presence of upper limb entrapment syndrome, polyneuropathy or renal failure; c) pregnant or lactating women; d) the use of vibratory tools; e) a history of drug or alcohol abuse; f) the presence of a tumoral process.

3.2.2 Procedures

Informed consent forms were signed by all the participants in the study, which was approved by the Bioethics Committee of the University of Granada (Spain) and conducted in accordance with the amended version of the Declaration of Helsinki, 2013. All the participants were informed about the study characteristics, objectives and procedures.

3.2.3 Measures

Each participant was evaluated over a total time of 90 minutes on the same day. The procedure was structured as follows: first, participants were asked for their sociodemographic and clinical data, such as age, sex, hand dominance, number of

Raynaud's phenomenon attacks per week, presence of comorbidities and disability by using the Shortened Disabilities of the Arm, Shoulder and Hand Questionnaire (Q-DASH). Measurements were then obtained of the blood flow, oxygen saturation, pinch strength and range of motion. Temperature and cold test assessments were carried out at the end since cold provocation can alter the rest of the evaluation parameters. All evaluations were obtained under the same stable conditions: participants were acclimatized for 20 minutes in a climate-controlled room without direct ventilation at 24ºC with humidity of 50-60%, seated in a comfortable position with both hands placed on a table and forearms uncovered. They had previously been informed that they should avoid physical activities and refrain from consuming any vasoactive substance (alcohol, caffeine, nicotine) in the two hours prior to the evaluation.

3.2.3.1 Vascular assessment

3.2.3.1.1 Temperature assessment and Cold Stress Test

A hand-held infrared thermographic scanner (Derma Temp®, Model: 104920 – DT-1001-LT [USA]) was used to measure the temperature in the fingertip of the third finger on both hands of the participants. Three parameters were obtained: pre- Cold Stress Test, post- Cold Stress Test and recovery temperature. The pre- Cold Stress Test temperature was obtained after acclimatization (Grossi et al., 2010; Ismail et al., 2014). The Cold Stress Test was then used to evaluate vascular response to changes in temperature following the protocol described in previous studies, where both hands were immersed for 2 min in cool water at 10ºC (Grossi et al., 2010; Ismail et al., 2014). After the Cold Stress Test, the temperature was taken to obtain the post- Cold Stress Test. Finally, the recovery temperature was obtained by subtracting the basal temperature minus the final temperature after 45 minutes of the Cold Stress Test.

3.2.3.1.2 Oxygen saturation

A finger pulse oximeter (MEGOS Oxi- Pulse®, SONMEDICA S.A, [Barcelona, Spain]) was used to determine the oxygen saturation, the percentage of haemoglobin that had bound oxygen in the patients´ blood (Plana et al., 2015). The oximeter was placed on the middle finger and the percentage of oxygen saturation values on both hands was used for statistical analysis. Pulse oximetry is a quick and well-established test used to quantify

oxygen saturation. The devices available today for measuring oxygen saturation are very reliable (Akdogan et al., 2015; Plana et al., 2015).

3.2.3.1.3 Arterial blood flow

Blood flow in the radial and ulnar artery was evaluated with a Hadeco Bi-Directional Vascular Doppler® (Japan). Measurements were taken following the protocol described in previous studies (Toprak et al., 2009). The radial and ulnar arteries were evaluated in the same way on the volar surface of the wrists of both hands. The result was expressed in cm/s^{-2} and the mean of the three measurements was calculated.

3.2.3.2 Functionality Assessment

3.2.3.2.1 Shortened Disabilities of the Arm, Shoulder and Hand Questionnaire (Q-DASH).

Upper limb disability was measured with the Spanish version of the Q-DASH (Hervás et al., 2006). This is a standardized self-administered questionnaire used by patients presenting with one or more disabilities of the arm, shoulder, and hand that assesses the patient's perceived disability to perform various activities. This questionnaire has demonstrated good reliability, validity and responsiveness, with a Cronbach alpha of 0.90 and a test-retest Pearson correlation coefficient of 0.70 (Gummesson et al., 2006).

3.2.3.2.2 Range of motion in index finger and thumb

Range of motion was assessed with a stainless-steel finger goniometer (SAHEAN®) with two branches and two opposite scales of 180º graded in intervals of 5º. A protocol based on scientific evidence was used (Bain, Polites, Higgs, Heptinstall, & McGrath, 2015; Carey, Laird, Murray, & Stevenson, 2010). The range of motion of active and passive flexion and extension of the metacarpophalangeal joint, flexion of the proximal interphalangeal joint, and flexion of the distal interphalangeal joint in the index (second) finger was evaluated in both hands of all the patients. Active and passive flexion was evaluated in the thumb at the interphalangeal joint, and flexion and extension at the metacarpophalangeal joint (Engstrand, Krevers, & Kvist, 2012). Each outcome was recorded three times following the same sequence of angles, and the mean of the three values was used in the analysis; goniometer measurements have a high inter-rater reliability and are considered a valid tool (Carvalho, Mazzer, & Barbieri, 2012).

3.2.3.2.3 Pinch strength

A mechanical Pinch Gauge (Baseline®) was used to assess pinch strength. This is a finger dynamometer calibrated in kg (Pérez-Mármol et al., 2016). Two types of pinch strength between thumb and index fingers were measured for both hands: the tip and lateral pinch strength. Participants were instructed to compress the dynamometer as hard as possible with the fingers. The final score for each pinch was defined by calculating the mean of the three values measured (Mathiowetz et al., 1984). The Pinch Gauge has demonstrated high inter-rater and test-retest reliability, with an intraclass correlation coefficient higher than 0.90 (Mathiowetz et al., 1984; Pérez-Mármol et al., 2017).

3.2.4 Statistical analysis

The Ene 3.0 software (Autonomous University of Barcelona, Spain) was used to calculate the sample size, using the data from our pilot study phase of this project, which included a total of 18 participants. For Q-DASH, the power analysis revealed that 14 patients were necessary in each group to obtain a desired power (β) of 90% with a significance level $\alpha = 0.05$ and to allow 50% of losses. The SPSS© version 20.0 (IBM Corporation, Armonk, NY, USA) was used for data analysis. Firstly, normality of the variables ($P > 0.05$) was evaluated by the Kolmogorov-Smirnov test. Descriptive statistic were calculated for demographic, vascular and functionality. Between groups were compared using ANOVA for continuous data and χ^2 for categorical data. Data were expressed as the mean and standard deviation (SD) for quantitative variables or frequency and % for qualitative outcomes. In order to assess the main objective of the study, between-groups differences were evaluated through an ANCOVA analysis in which the key variables (vascular and functional outcomes) were the between-subjects factor, and the covariates were age and gender. Post-hoc analyses were carried out using Bonferroni correction for multiple comparisons. Since there were no differences between dominant and non-dominant sides, the unified average value of both hands was calculated for key variables: temperature pre cold test, temperature post cold test, recovery temperature, blood flow of radial and ulnar arteries, range of motion for index and thumb fingers and tip and lateral pinch strength. A Pearson bivariate correlation analysis was subsequently performed to evaluate the relationship between vascular, functional variables and Q-DASH in Raynaud groups. Finally, a multivariate regression analysis was carried out. After the collinearity analysis, index extension, thumb flexion, oxygen saturation and lateral pinch

strength were included as independent variables, and Q-DASH (and its subscales) as the dependent variable. Flexion of index and flexion of thumb were excluded. The statistical analysis was performed at 95% confidence level. All analyses were two-tailed and a p-value less than 0.05 were considered to be statistically significant.

3.3 Study III: "Effectiveness of a vasodilatory intervention through tap-water iontophoresis in patients with Raynaud's phenomenon: A Randomized Clinical Trial.".

The methods section of the Study III, included in the PhD thesis, has been summarized and described below. Table 3 shows a summary of the methodology used in this randomized clinical trial study.

Table 3. Summary of Material and Methods in Study III.

PAPER	STUDY DESING	PARTICIPANTS	INTERVENTION	MAIN VARIABLES	METHODS
Effectiveness of a vasodilatory intervention through tap-water iontophoresis in patients with Raynaud's phenomenon: a Randomized Clinical Trial.	Double-blinded randomized clinical trial.	✓ Participants with RP (n=34). • Tap-water iontophoresis group (n=17). • Conservative treatment control Group (n=17).	✓ Tap- water iontophoresis invervention: • Continuous polarized galvanic current. • The intensity was increased until the maximum tolerated by the patients (considering a maximum of 30 mA). • Application: 20 minutes, polarity was changed after 10 minutes, 3 times/week for a total of 20 sessions.	• Weekly averages number of attacks. • Blood flow. - Radial - Ulnar. • Oxygen saturation. • Skin temperature: - Baseline. - After cold stress test. - Recovery temperature: ▪ At 5, 10, 15, 20, 25, 30, 35 minutes • Pain intensity • Central sensitization • Catastrophizing • Upper limb disability	• Daily record of the number of RP attacks. • Hadeco Bi-Directional Vascular Doppler®, BIDOP ES-100 VII (Japan). • Pulse oximeter, MEGOS Oxi- Pulse®, SONMEDICA S.A, (Barcelona, Spain). • Infrared thermographic scanner (Derma Temp®, Model: 104920 – DT-1001-LT [USA]). • Cold stress test. • 10 cm Visual analogue Scale • Central Sensitization Inventory (CSI). • Pain Catastrophizing Scale (PCS). • Shortened Disabilities of the Arm, Shoulder and Hand Questionnaire (Q-DASH).

RP, Raynaud´s phenomenon.

3.3.1 Study design and participants

A double-blinded randomized control trial with a parallel design (allocation ratio 1:1) was performed to test the main objective of the study. A total of 48 subjects were recruited from the Rheumatology Service of the Virgen de las Nieves Hospital in Granada (Spain). After the selection criteria were applied, 34 subjects were included. Participants were randomly assigned to a control group (n=17) to receive conservative treatment, or to an experimental group (n=17) for the application of tap water iontophoresis.

Inclusion criteria were: 1) age over 18; 2) diagnosis of RP; 3) at least one year of regular RP attacks; and 4) signed informed consent form. Exclusion criteria were: 1) the presence of skin alterations (scars, gangrene or ulcers in the area to be treated); 2) the presence of upper limb entrapment syndrome; 3) pregnant or lactating women; and 4) the presence of a tumoral process.

3.3.2 Procedures

The study received approval from the Bioethics Committee of the University of Granada (Spain) on May 12, 2015, and was conducted in accordance with the amended version of the Declaration of Helsinki, 2013. This study was conducted between October 2018 and February 2019 to perform trials in the coldest months of autumn and winter in the Northern Hemisphere to minimize seasonal variability. The study was registered on ClinicalTrials.gov (NCT03699436).

3.3.3 Interventions

Both groups (experimental and controls) received a conservative approach and pharmacological treatment mainly based on anti-inflammatory, vasodilatory and analgesic drugs. It was maintained consistently throughout the study, and patients were encouraged not to change the dosages that the rheumatologist had established until the end of the experimental phase.

The experimental group also received tap water iotophoresis applications. An Enraf Nonius-Mod Myomed 932 galvanic generator was used with an input current of 220-240 V and 50/60 + 10% Hz. The output current was a continuous polarized galvanic current with a maximum amplitude of 30 milliamps. For the treatment application, two electrodes of flexible rubber 12 x 8 cm in size were used. First, water was deposited into two trays of polyvinyl that whose surfaces were 315 cm^2 and whose volumes were 1.260 cm^3. After the

electrodes were applied with their corresponding pads (13.5 x 0.5 cm) at the bottom of the tray, the patient's hands were immersed.

Prior to the treatment, a skin protectant was applied (petroleum jelly over possible erosions or wounds). The patient was seated with his or her hands inside of the two containers filled with water up to the limit of the nails, with the patient not touching them. A galvanic current was administrated for 20 minutes (the polarity was changed after 10 minutes). The intensity of the current was increased to the maximum amount that a patient could tolerate (considering a maximum of 30 milliamps).This protocol was administered three times per week for a total of 20 sessions.

3.3.4 Outcomes Measures

Sociodemographic data and clinical characteristics were registered for each participant at the beginning of the study. Data were gathered on the number of attacks as the primary outcome. The participants registered the number of attacks per day, and then, the weekly averages were calculated. Blood flow, oxygen saturation, skin temperature at baseline, recovery temperature after cold stress test, pain intensity, central sensitization, pain catastrophizing and upper limb disability were the secondary outcomes. This information was collected and registered at three time points: baseline, post-treatment (24 hours after the last session of treatment) and after two months' follow-up. All evaluations were obtained under the same stable conditions (Chlebicka et al., 2013). Participants were previously informed that they should refrain from consuming any vasoactive substances (nicotine, alcohol, caffeine) and avoid physical activities in the two hours prior to the evaluation.

A visual analog scale was used to evaluate the intensity of pain. It consists of a10 cm line from 0 (no pain) to 10 (the worst pain imaginable) (Bijur et al., 2001). For the purpose of determining the oxygen saturation, a finger pulse oximeter (MEGOS Oxi-Pulse®, SONMEDICA S.A,) was used. The oximeter was placed on the middle finger to obtain values for both hands (Plana et al., 2015).

We evaluated the blood flow in the radial and ulnar artery in both hands with a Hadeco Bi-Directional Vascular Doppler®. Measurements were taken following the protocol described in a previous study (Toprak et al., 2009). To obtain the temperature, we used a hand-held infrared thermographic scanner (Derma Temp® – DT-1001) on the fingertip of the third finger of both hands of the participants. Three parameters were

obtained: pre–cold stimulation test (pre-CST), post–cold stimulation test (post-CST) and recovery temperature. The CST was performed by immersing both hands in cool water for two minutes at 10ºC (Grossi et al., 2010). Finally, the recovery temperature was obtained for 35 minutes, with temperatures acquired every five minutes (Ismail et al., 2014).

For our disability assessment, we used the Spanish version of the Shortened Disabilities of the Arm, Shoulder and Hand Questionnaire (Q-DASH) (Hervás et al., 2006), where higher scores indicate a greater level of disability (Gummesson et al., 2006).

To obtain information about central sensitization and pain catastrophizing, we used the Central Sensitization Inventory (CSI) (Neblett et al., 2013), in which higher scores indicate increased frequency and severity of symptoms,24 and the Pain Catastrophizing Scale (PCS) (M. J. L. Sullivan et al., 1995), where higher scores indicate a greater frequency of catastrophic thoughts.

3.3.5 Statistical analysis

The sample size was calculated using Ene 3.0 software (Autonomous University of Barcelona, Spain). The calculations were based on detecting a post-treatment difference of 3.4 in the primary outcome measures and weekly attack numbers, following a previous study (Denton et al., 2017). Assuming a standard deviation (SD) of 1.30 points, a two-tailed test, an alpha level (α) of 0.05 and a desired power (β) of 95%, we made the estimated desired sample size 12 subjects per group. The sample size was increased to a total of 48 to allow for a loss to follow-up of up to 50%.

We used SPSS© version 20.0 for Windows for data analyses. The normality of the variables was tested by using the Kolmogorov-Smirnov test. Demographic variables between groups were compared by using Student's t-test for continuous data, and chi-squared tests for categorical data. We performed a separate 2×3 repeated-measures analysis of variance (ANOVA) to evaluate the effect of the intervention on the number of attacks per week as the primary outcome and pain intensity, oxygen saturation, blood flow, recovery temperature, upper limb disability, pain catastrophizing and central sensitization as secondary outcomes. Time (baseline, after treatment and two months of follow-up) was the within-subject variable, and group (experimental or control) was the between-subjects variable. All analyses followed the intention-to-treat principle, and groups were analysed as randomized. We measured the changes in variable scores within and between groups by

means (95% confidential interval) of t-tests for paired or independent samples as appropriate. We calculated the effect size according to Cohen´s d statistic. An effect size of <0.2 indicates a negligible difference, between ≥0.2 and <0.5 indicates a small difference, between ≥0.5 and< 0.8 indicates a moderate difference, and ≥0.8 indicates a large difference. P <0 .05 was considered to be significant in all tests.

RESULTADOS

RESULTS

4. RESULTADOS/ RESULTS

4.1 Study I: "Pain intensity, pressure pain hypersensitivity, central sensitization and pain catastrophizing related to vascular alterations in Raynaud's phenomenon: a preliminary case-control study".

The results section of the Study I is showed below.

4.1.1 Sociodemographic and Clinical Characteristics

A total of 18 participants with Primary RP (PRP), 19 with Secondary RP (SRP) to Scleroderma and 20 healthy controls were included.

ANOVA analysis showed significant differences between groups for age, which was significantly lower in PRP group than in the control group (P=0.004) and group SRP (P<0.001). Regarding thermography findings, ANOVA demonstrated significant differences between groups in the fingers and hands on both sides. Post-hoc analysis showed that the temperature at the 3rd finger and hand was significantly lower in groups PRP ($P\leq0.007$) and SRP ($P\leq0.046$) in comparison to controls; there were no differences between groups PRP and SRP**.**

The sociodemographic and clinical characteristics of participants in each sample are shown in **Table 1**.

4.1.2 Pain Intensity

ANOVA showed significant differences between groups for pain intensity. A post-hoc analysis showed that pain intensity was significantly higher in SRP group (P=0.001) in comparison to healthy controls; there were no differences between the control and PRP group (P=0.391) **(Table 2).** Pearson correlation analysis showed no relationship between temperature in the 3rd finger or hand and pain intensity in any of the three groups **(Tables 3, 4, 5).**

Table 1. Characteristics of participants at baseline and thermograph-vascular assessment.

Outcomes	PRP	SRP	Controls	*P*-value
Sex (females, %)	13/72.2%	15/78.9%	16/80%	0.829
Age (yrs)	28.4(10.4)	55.8 (6.2)	47.3 (14.3)	0.001*
Time since onset (yrs)	11.4 (5.8)	17.3 (12.6)	-	0.139
Crisis (nº/day)	3.3 (1.03)	4 (3)	-	1.000
Smoking History (%)				
Active smoker	1(5.6)	1(5.3)	2(10)	0.391
Non-smoker	15 (83.3)	13(68.4)	17(85)	
Ex-smoker	2 (11.1)	5(26.3)	1(5)	
Color Pattern				0.008
Pallor	1/5.6%	-	-	
Cyanosis	1/5.6%	-	-	
Rubor	-	6/31.6%	-	
Normal	16/88.9%	13/68.4%	20/100%	
Thermography Temperature				
Dorsal 3rd finger tip				
Dominant Side	26.05 (4,45)	28.80 (4.89)	30.72 (4.13)	0.009*
Non Dominant Side	26.35 (4,49)	28.88 (4.46)	30.73 (4.12)	0.012*
Palm 3rd Finger				
Dominant Side	25.19 (4.0)	27.95 (4.65)	29.61 (4.19)	0.009*
Non Dominant Side	25.36 (4.11)	28.05 (4.37)	29.55 (4.17)	0.010*
Dorsal Center of the Hand				
Dominant Side	28.93 (2.44)	29.94 (2.57)	31.67 (2.08)	0.003*
Non Dominant Side	29.06 (2,36)	30.01 (2.63)	31.72 (2.02)	0.003*
Palm Center of the Hand				
Dominant	29.87 (2.51)	30.93 (2.46)	32.62 (1.68)	0.002*
Non Dominant	29.73 (2.43)	31.01 (2.48)	32.42 (1.60)	0.002*

*$P < 0.05$ significant differences between groups.

Data are expressed as the mean and ± standard deviation

PRP: Primary Raynaud's phenomenon . SRP: Secondary Raynaud's phenomenon.

Table 2. Characteristics of participants at perceived pain intensity, central sensitization, catastrophizing, pressure pain thresholds, electrical pain threshold and magnitude.

Outcomes		PRP Group	SRP Group	Control Group
Visual Analog Scale[*] (0-10)[a]		0.82 (1.54)	4.59 (2.44)	0.35 (0.74)
Central Sensitization Inventory[*]		31.05 (14.17)	66.84 (12.31)	23.55 (8.84)
Pain Catastrophizing Scale[*]		12.56 (13.11)	25.74 (9.99)	0.95 (3.05)
C5-C6 Zygapophyseal Joint	Dominant[*]	3.16 (0.94)	2.95 (1.08)	4.65 (1.33)
	Non dominant[*]	3.40 (1.55)	3.12 (0.97)	4.61 (1.30)
Deltoid Muscle	Dominant[*]	4.51 (1.78)	3.97 (1.37)	5.55 (1.25)
	Non dominant[*]	3.87 (1.73)	3.43 (1.07)	5.41 (1.40)
Second Metacarpal	Dominant[*]	3.77 (1.57)	3.52 (1.36)	5.78 (1.38)
	Non dominant[*]	3.75 (1.47)	3.15 (1.39)	5.54 (1.40)
Tibialis Anterior Muscle	Dominant [*]	8.18 (2.41)	6.21 (1.93)	9.02 (1.96)
	Non dominant	12.08 (19.06)	6.30 (1.75)	8.62 (1.97)
Pain Matcher Threshold	Dominant[*]	2.84 (0.70)	4.58 (0.89)	3.74 (1.49)
	Non dominant[*]	2.54 (0.47)	3.69 (0.81)	3.23 (1.04)
Pain Matcher Magnitude	Dominant[*]	7.00 (2.05)	13.64 (15.28)	1.40 (0.50)
	Non dominant[*]	6.44 (2.13)	10.88 (6.99)	1.62 (0.67)

[*] $P < 0.05$ significant differences between groups ANOVA analysis

Data are expressed as mean and standard deviation (SD)

[a](x-x) Range of normal scores for the variable.

PRP: Primary Raynaud's phenomenon; SRP: Secondary Raynaud's phenomenon.

4.1.3 Pressure Pain Thresholds

ANCOVA showed statistically significant differences between the groups in PPT at C5-C6 [dominant side (DS): F=12.82, *P*<0.001; non-dominant side (NDS) F=7.35, *P*=0.001; the deltoid (DS: F=5.77, *P*=0.005; NDS: F=10.55, *P*<0.001; the second metacarpal (DS: F=14.43, *P*<0,001; NDS: F=14.89, *P*<0.001); and the tibialis anterior (DS: F=9.05, *P*=0.001)] **(Table 2)**. Post-hoc analysis revealed that PPT was significantly lower in participants with RP than healthy controls at C5-C6 (DS, PRP: *P*=0.001; SRP: *P*<0.001; NDS, PRP: *P*=0.017; SRP: *P*=0.002), the deltoid (DS, PRP: *P*=0.05; SRP: *P*=0.005; NDS, PRP: *P*=0.05; SRP: *P*=0.001), the second metacarpal (DS, PRP: *P*=0.001; SRP: *P*=0.001; NDS, PRP: *P*=0.001; SRP: *P*<0.001) and the tibialis anterior (DS, PRP: *P*=0.05/SRP: *P*=0.001). At the tibialis anterior site, PPT on the non-dominant side was significantly lower in group SRP than group PRP (*P*=0.019). ANCOVA also revealed a significant effect of the covariate age on PPT at the C5-C6 zygapophyseal joint (both sides: F≤8.43, *P*≤0.005), the deltoid (both sides: F≤7.63, *P*≤0.024) and the second metacarpal (both sides: F≤15.58, *P*≤0.001).

Pearson correlation analysis also showed no relationship between temperature in the 3rd finger or hand and PPT in group PRP **(Table 3)** or group SRP **(Table 4).**

However, a significant positive relationship was observed in the control group between temperature in the fingers or hands and C5-C6 (fingers: *r*≤ 0.499, *P*≤0.037; hands: *r*≤0.460, *P*≤0.042), the deltoid (fingers: *r*≤0.598, *P*≤0.036; hands: *r*≤−0.641, *P*≤0.042), second metacarpal (fingers: *r*≤0.783, *P*≤0.006; hands: *r*≤0.747, *P*≤0.06) and dominant tibialis anterior (hands: *r*≤0.493, *P*≤0.039). **(Table 5).**

Table 3. Bivariate correlations between temperature (vascular alterations) and perceived pain intensity, central sensitization, catastrophizing, pressure pain thresholds, electrical pain threshold and pain magnitude in the Primary Raynaud's phenomenon group (n=18)

Outcomes measures		Temperature Dorsal 3rd finger		Temperature Palm 3rd finger		Temperature Dorsal Center of the Hand		Temperature Palmar Center of the Hand	
		Pearson (r)	*P*-value	Pearson (r)	*P*-value	Pearson (r)	*P*-value	Pearson (r)	*P*-value
Visual Analog Scale		-0.206	0.413	-0.203	0.419	-0.100	0.693	-0.093	0.714
Central Sensitization Inventory		-0.134	0.595	-0.149	0.556	0.080	0.752	0.037	0.883
Pain Catastrophizing Scale		-0.136	0.590	-0.084	0.741	0.095	0.707	0.096	0.704
C5-C6 Zygapophyseal Joint									
	D	-0.019	0.939	0.037	0.883	-0.072	0.775	-0.124	0.625
	ND	-0.141	0.577	-0.144	0.569	-0.322	0.193	-0.358	0.145
Deltoid Muscle									
	D	0.245	0.328	0.331	0.180	0.167	0.508	0.159	0.529
	ND	0.360	0.142	0.430	0.075	0.330	0.182	0.330	0.181
Second Metacarpal									
	D	0.005	0.984	0.025	0.923	-0.166	0.510	-0.112	0.658
	ND	0.199	0.429	0.203	0.420	-0.010	0.969	0.030	0.904
Tibialis Anterior Muscle									
	D	0.133	0.600	0.184	0.465	0.027	0.915	0.078	0.760
	ND	0.354	0.149	0.313	0.205	0.098	0.699	0.185	0.462
Pain Matcher Threshold									
	D	-0.063	0.803	-0.040	0.875	-0.242	0.333	-0.229	0.361
	ND	-0.229	0.360	-0.169	0.502	-0.370	0.130	-0.378	0.122
Pain Matcher Magnitude									
	D	0.132	0.603	0.197	0.434	0.262	0.294	0.230	0.359
	ND	0.116	0.646	0.177	0.482	0.307	0.216	0.288	0.246

*$P<0.05$

D: Dominant side; ND: Non dominant side

Table 4. Bivariate correlations between temperature (vascular alterations) and perceived pain intensity, central sensitization, catastrophizing, pressure pain thresholds, electrical pain threshold and pain magnitude in the Secondary Raynaud's phenomenon group (n=19).

Outcomes measures		Temperature Dorsal 3rd finger		Temperature Palm 3rd finger		Temperature Dorsal Center of the Hand		Temperature Palmar Center of the Hand	
		Pearson (r)	*P*-value	Pearson (r)	*P*-value	Pearson (r)	*P*-value	Pearson (r)	*P*-value
Visual Analog Scale		0.080	0.745	0.005	0.983	0.118	0.630	0.050	0.840
Central Sensitization Inventory		-0.560	0.013*	-0.578	0.010*	-0.520	0.023*	-0.637	0.003*
Pain Catastrophizing Scale		0.034	0.891	0.166	0.497	-0.062	0.801	-0.014	0.954
C5-C6 Zygapophyseal Joint									
	D	0.018	0.941	0.105	0.669	0.136	0.579	0.216	0.376
	ND	0.001	0.997	0.105	0.669	0.105	0.668	0.190	0.437
Deltoid Muscle									
	D	0.056	0.820	0.166	0.496	0.140	0.567	0.148	0.545
	ND	0.141	0.565	0.225	0.355	0.169	0.490	0.235	0.334
Second Metacarpal									
	D	0.043	0.862	0.121	0.623	0.059	0.811	0.145	0.555
	ND	0.041	0.869	0.130	0.595	0.057	0.815	0.189	0.439
Tibialis Anterior Muscle									
	D	-0.081	0.741	-0.008	0.975	0.057	0.818	0.069	0.779
	ND	-0.039	0.873	0.035	0.887	0.054	0.827	0.114	0.642
Pain Matcher Threshold									
	D	-0.387	0.102	-0.441	0.059	-0.353	0.138	-0.319	0.184
	ND	0.169	0.488	-0.067	0.784	0.284	0.239	0.238	0.325
Pain Matcher Magnitude									
	D	-0.512	0.055	-0.592	0.058	-0.326	0.174	-0.407	0.083
	ND	-0.436	0.062	-0.511	0.065	-0.162	0.279	-0.332	0.164

*$P<0.05$

D: Dominant side; ND: Non dominant side

Table 5. Bivariate correlations between temperature (vascular alterations) and perceived pain intensity, central sensitization, catastrophizing, pressure pain thresholds, electrical pain threshold and pain magnitude in the healthy control group (n=20).

Outcomes measures		Temperature Dorsal 3rd finger		Temperature Palmar 3rd finger		Temperature Dorsal Center of the Hand		Temperature Palmar Center of the Hand	
		Pearson (r)	*P*-value	Pearson (r)	*P*-value	Pearson (r)	*P*-value	Pearson (r)	*P*-value
Visual Analog Scale		-0.334	0.150	-0.340	0.143	-0.329	0.157	-0.361	0.118
Central Sensitization Inventory		-0.290	0.214	-0.304	0.192	-0.261	0.266	-0.268	0.252
Pain Catastrophizing Scale		0.048	0.842	0.108	0.650	0.127	0.594	0.133	0.577
C5-C6 Zygapophyseal Joint									
	D	0.404	0.077	0.433	0.056	0.390	0.089	0.368	0.111
	ND	0.470	0.037*	0.499	0.025*	0.458	0.042*	0.460	0.041*
Deltoid Muscle									
	D	0.414	0.069	0.471	0.036*	0.459	0.042*	0.512	0.021*
	ND	0.598	0.005*	0.625	0.003*	0.591	0.006*	0.641	0.002*
Second Metacarpal									
	D	0.591	0.006*	0.609	0.004*	0.605	0.005*	0.590	0.006*
	ND	0.741	0.000*	0.783	0.000*	0.699	0.001*	0.747	0.001*
Tibialis Anterior Muscle									
	D	0.422	0.064	0.462	0.040*	0.493	0.027*	0.464	0.039*
	ND	0.351	0.129	0.350	0.131	0.309	0.185	0.341	0.141
Pain Matcher Threshold									
	D	0.350	0.130	0.330	0.155	0.275	0.241	0.241	0.306
	ND	0.380	0.098	0.354	0.126	0.288	0.218	0.299	0.201
Pain Matcher Magnitude									
	D	-0.013	0.956	-0.047	0.845	-0.063	0.792	-0.112	0.637
	ND	0.298	0.202	0.293	0.210	0.302	0.196	0.265	0.259

*P<0.05

D: Dominant side; ND: Non dominant side

4.1.4 Electrical Pain Magnitude and Electrical Pain Threshold

ANCOVA analysis showed statistically significant differences between groups in electrical pain threshold (DS: F=11.62, $P<0.001$; NDS: F=9.25, $P<0.001$) and electrical pain magnitude (DS: F=9.22, $P<0.001$; NDS: F=23.39, $P<0.001$) on both sides **(Table 2)**. Post-hoc analysis revealed that participants with PRP had significantly lower electrical pain thresholds than controls (DS, $P=0.43$; NDS, $P=0.036$) and group SRP (DS, $P=0.001$; NDS, $P=0.001$); there were no differences between participants with SRP and controls. Electrical pain intensity was significantly higher in group SRP (DS, $P=0.001$; NDS, $P=0.003$) and group PRP (DS, $P=0.05$; NDS, $P=0.003$) in comparison to controls. In addition, electrical pain intensity was significantly higher in group SRP than group PRP (DS, $P=0.042$; NDS, $P=0.007$). ANCOVA also revealed a significant effect of the covariate age on electrical pain thresholds (both sides: $F\leq14.49$, $P<0.001$).

Pearson correlation analysis showed no relationship between temperature in the 3rd finger or hand and electrical assessment in any of the three groups (**Tables 3 to 5).**

4.1.5 Central Sensitization and Catastrophizing

ANCOVA showed statistically significant differences between group PRP (31.05±14.17), group SRP (66.84±12.31) and the control group (23.55±8.84) for CS (F=72.68, $P<0.001$). Post-hoc analysis revealed that SRP participants had a significantly higher level of CS compared to healthy controls ($P=0.001$) and participants with PRP ($P=0.001$).
Similar results were found for catastrophizing: ANCOVA demonstrated significant differences (F=33.00, $P<0.001$) between group PRP (12.55±13.11), group SRP (25.73±9.99) and the control group (0.95±3.05). Post-hoc analysis showed that the level of catastrophizing was higher in group PRP ($P=0.001$) and group SRP ($P<0.001$) in comparison to controls. Participants with SRP had higher scores than those with PRP ($P<0.001$). **(Table 2)**.

No correlations between temperature in the 3rd finger or hand and CS or catastrophizing were observed in group PRP **(Table 3)** or the control group **(Table 5)**; the only significant association was found between temperature and central sensitization in group SRP ($r\leq-0.637$ $P\leq0.023$). **(Table 4)**.

4.2 Study II: "Disability in Raynaud's phenomenon seems to be more related with hand´s mobility and strength than severity of vascular alterations".

The results section of the Study II is showed below.

4.2.1 Sociodemographic and clinical characteristics.

A total sample of 57 subjects were recruited for this study: eighteen patients with Primary Raynaud (72.2% females), nineteen with Secondary Raynaud (78.9% females) and twenty healthy controls (80% females). The mean (standard deviation) age was 41.7 (15.5) years. The sociodemographic and clinical characteristics of the sample are shown in **Table 6**.

Table 6. Sociodemographic, vascular and functionality characteristics of participants

Outcomes	Primary RP n=(18)	Secondary RP n=(19)	Controls n=(20)
Age in years, mean (standard deviation)	28.4 (10.4)	55.8 (6.2)	47.3 (14.3)
Sex, n (%)			
Male	5/27.8	4/21.1	4/20
Female	13/72.2	15/78.9	16/80
Hand dominance, n (%)			
Right	18/100	19/100	18/90
Left	-	-	2/10
RP attacks (nº/week), n (%)	23.3 (7.2)	28.0 (21.0)	-
Associated Pathologies, n (%)			
Arterial Hypertension	-	6/31.6	2/10
Hypercholesterolemia	-	2/10.5	1/5
Diabetes	-	2/10.5	-
Vascular Items, mean (standard deviation)			
Temperature pre-CST (ºC)			
Dominant	26.3 (3.8)	29.0 (4.3)	29.8 (3.9)
Non Dominant	26.6 (4.0)	29.4 (4.0)	30.1 (3.8)
Both hands	26.5 (3.9)	29.2 (4.1)	30.0 (3.9)
Temperature post-CST (^{0}C)			
Dominant	24.4 (4.4)	27.7 (5.2)	30.3 (3.7)
Non Dominant	24.1 (4.7)	27.8 (4.9)	29.9 (4.0)
Both hands	24.2 (4.6)	27.8 (5.0)	30.1 (3.8)
Recovery Temperature (^{0}C)			
Dominant	1.8 (3.2)	1.3 (3.5)	-0.4 (2.9)
Non Dominant	2.6 (3.3)	1.6 (3.1)	0.2 (2.4)
Both hands	2.2 (3.2)	1.5 (3.2)	-0.1 (2.6)
Blood flow radial artery (cm/s^{-2})			
Dominant	8.5 (2.7)	8.6 (4.8)	12.4 (5.0)
Non Dominant	8.5 (2.2)	8.8 (3.6)	12.5 (3.9)

Data are expressed as the mean and standard deviation (SD) for quantitative variables or frequency and % for qualitative outcomes.

RP: Raynaud's phenomenon; CST: Cold Stress Test; Quick-DASH: Shortened Disability of the Arm, Shoulder and Hand Questionnaire; ROM: Range of motion

Table 6. Sociodemographic, vascular and functionality characteristics of participants. (Continuation)

Blood flow ulnar artery (cm/s^{-2})			
Dominant	10.0 (3.6)	10.9 (6.8)	11.8 (3.4)
Non Dominant	8.3 (2.3)	15.0 (24.0)	12.4 (4.2)
Oxygen Saturation (%)			
Dominant	97.5 (0.9)	96.6 (1.1)	97.1 (1.2)
Non Dominant	97.6 (0.8)	96.9 (0.9)	97.0 (1.3)
Functionality Items, mean (standard deviation)			
Quick-DASH (%)			
Upper limb disability	15.9 (11.4)	57.3 (13.9)	2.5 (7.6)
Work Module	21.9 (19.1)	72.7 (24.6)	1.9 (8.4)
Sports/Performing Arts Module	22.9 (25.5)	69.7 (19.8)	0 (0.0)
ROM Active index finger flexion			
Dominant	93.2 (6.2)	81.5 (9.9)	84.8 (8.9)
Non Dominant	93.2 (6.8)	81.8 (9.4)	85.7 (9.1)
ROM Passive index finger flexion			
Dominant	103.2 (5.3)	93.3 (8.9)	95.7 (8.0)
Non Dominant	104.2 (5.5)	93.9 (7.6)	96.0 (7.7)
ROM Active index finger extension			
Dominant	32.5 (6.0)	30.5 (6.6)	30.6 (6.1)
Non Dominant	31.8 (5.6)	30.8 (7.5)	32.0 (5.6)
ROM Passive index finger extension			
Dominant	60.8 (9.7)	49.7 (12.8)	49.5 (14.4)
Non Dominant	61.9 (9.1)	49.0 (12.5)	52.1 (12.3)

Data are expressed as the mean and standard deviation (SD) for quantitative variables or frequency and % for qualitative outcomes.

RP: Raynaud's phenomenon; CST: Cold Stress Test; Quick-DASH: Shortened Disability of the Arm, Shoulder and Hand Questionnaire; ROM: Range of motion

Table 6. Sociodemographic, vascular and functionality characteristics of participants. (Continuation).

ROM Passive thumb flexion			
Dominant	87 (5)	72.1 (18.8)	82.3 (8.9)
Non Dominant	87.9 (6.2)	79.2 (9.9)	84.4 (7.8)
ROM Passive thumb extension			
Dominant	51.9 (8.9)	43.9 (9.5)	46.6 (11.3)
Non Dominant	51.9 (8.6)	44.2 (8.7)	46.5 (12.9)
Tip pinch strength			
Dominant	4.8 (1.6)	4.7 (2.4)	5.1 (1.5)
Non Dominant	4.5 (1.8)	4.5 (2.4)	4.9 (1.4)
Lateral pinch strength			
Dominant	7.5 (1.6)	6.4 (2.0)	7.4 (2.5)
Non Dominant	7.6 (1.7)	6.1 (2.0)	7.1 (2.6)

Data are expressed as the mean and standard deviation (SD) for quantitative variables or frequency and % for qualitative outcomes.

RP: Raynaud's phenomenon; CST: Cold Stress Test; Quick-DASH: Shortened Disability of the Arm, Shoulder and Hand Questionnaire; ROM: Range of motion

4.2.2 Vascular assessment

ANCOVA analysis showed significant differences between groups in finger temperature for both hands at pre-Cold Stress Test ($F=4.04$, $p=0.023$) and post-Cold Stress Test ($F= 8.22$, $p=0.001$). Significant differences between groups were only achieved at recovery temperature for the non-dominant side: $F=3.28$, $p=0.045$.

There were not differences for the rest of variables ($F\geq 2.30$, $p\geq 0.054$). Mean and standard deviation are shown in Table 6.

Post-hoc analysis showed that the pre-Cold Stress Test temperature was significantly lower in the Primary Raynaud in comparison to the controls. Similarity, post- Cold Stress Test temperature was significantly lower in the Primary Raynaud group in comparison to Secondary Raynaud and controls group. The recovery temperature was significantly higher in Primary Raynaud in comparison to controls.

On the other hand, ANCOVA analysis showed statistically significant differences between groups for blood flow in the radial artery (dominant side: F=5.24, p=0.008; non-dominant side: F=8.29, p=0.001). There were not differences for the rest of variables (F≥ 0.76, p≥0.360).

Post-hoc analysis showed that patients with Primary and Secondary Raynaud had significantly lower blood flow in the radial artery than the healthy controls.
However, there were no differences between primary and secondary Raynaud and controls in ulnar artery blood flow and oxygen saturation **(Table 7).**

4.2.3 Functionality assessment

ANCOVA analysis showed statistically significant differences between groups in the Q-DASH (Total: F=81.56, p<0.001; Work: F=56.46, p<0.001; Sports/Arts: F=54.16, p<0.001)**.** Post-hoc analysis revealed that patients with Primary and Secondary Raynaud showed significantly higher upper limb disability than healthy controls; higher disability for Work and on the Sports/Arts subscales. Furthermore, significant differences were found between Primary and Secondary Raynaud groups in upper limb disability, Work and Sports/Arts modules. Secondary Raynaud showed significantly higher disability for the three Q-DASH subscales.

ANCOVA analysis showed statistically significant differences between groups in range of motion for passive index finger extension (dominant side: F=3.593, p=0.034; non-dominant side: F= 3.233, p=0.047); active thumb flexion (dominant side: F=3.540, p=0.036; non-dominant side: F= 3.449, p=0.039) and active thumb extension (non-dominant side: F=6.87, p=0.002). There were not differences for the rest of functionality variables (F≥0.07, p≥0.063).

Post-hoc analysis revealed that patients with Primary Raynaud had significantly higher range of motion than healthy controls for passive flexion and passive extension of the index finger, and Secondary Raynaud participants for active flexion and active extension of the thumb **(Table 7).**

Table 7. Mean Difference (MD), 95% Confidence Interval (CI) and between groups level of significance for vascular and functionality assessments.

Outcomes	Controls vs Primary RP MD (95% CI)	*P-value*	Controls vs Secondary RP MD (95% CI)	*P-value*	Primary vs Secondary RP MD (95% CI)	*P-value*
Vascular Items						
Temperature pre-CST (ºC)						
Dominant	3.540 (0.307;6.772)	0.027*	0.818 (-2.368;4.006)	1.000	-2.721 (-5.994;0.551)	0.134
Non Dominant	3.440 (0.288;6.591)	0.028*	0.626 (-2.481;3.734)	1.000	-2.813 (-6.004;0.377)	0.101
Both hands	3.490 (-0.317;6.662)	0.026*	0.722 (-2.405;3.851)	1.000	-2.767 (-5.978;0.444)	0.114
Temperature post-CST (^{0}C)						
Dominant	5.918 (2.320;9.517)	0.000*	2.569 (-0.979;6.118)	0.238	-3.349 (-6.992;0.293)	0.081
Non Dominant	5.848 (2.193;9.503)	0.001*	2.104 (-1.499;5.708)	0.465	-3.743 (-7.444;-0.043)	0.046*
Both hands	5.883 (2.285;9.482)	0.001*	2,336 (-1.211;5.885)	0.328	-3.546 (-7.189;0.096)	0.059
Recovery Temperature (^{0}C)						
Dominant	-2.267 (-4.844;0.308)	0.102	-1.750 (-4.291;0.790)	0.283	0.517 (-2.091;3.125)	1.000
Non Dominant	-2.408 (-4.756;-0.060)	0.043*	-1.451 (-3.766;0.863)	0.382	0.957 (-1.419;3.334)	0.973
Both hands	-2.338 (-4.741;0.065)	0.059	-1.600 (-3.971;0.769)	0.303	0.737 (-1.690;3.170)	1.000
Blood flow radial artery (cm;s^{-2})						
Dominant	4.522 (0.707;8.338)	0.015*	2.954 (-1.050;6.957)	0.221	-1.569 (-6.644;3.507)	1.000
Non Dominant	3.973 (0.975;6.970)	0.006*	3.694 (0.549;6.840)	0.016*	-0.279 (-4.266;3.709)	1.000

*P< 0.05 for Bonferroni pairwise comparison between groups.

RP: Raynaud's phenomenon; CST: Cold Stress Test; Quick-DASH: Shortened Disability of the Arm, Shoulder and Hand Questionnaire; ROM: Range of motion

Table 7. Mean Difference (MD), 95% Confidence Interval (CI) and between groups level of significance for vascular and functionality assessments. (Continuation).

Blood flow ulnar artery (cm;s^{-2})						
Dominant	2.155 (-2.180;6.490)	0.674	0.423 (-4.126;4.972)	1.000	-1.732 (-7.499;4.035)	1.000
Non Dominant	5.408 (-7.147;17.963)	0.875	-4.222 (-17.396;8.952)	1.000	-9.630 (-26.331;7.071)	0.480
Oxygen Saturation (%)						
Dominant	-0.129 (-1.064;0.807)	1.000	0.281 (-0.700;1.262)	1.000	0.410 (-0.834;1.654)	1.000
Non Dominant	-0.262 (1.141;0.617)	1.000	-0.353 (-1.275;0.570)	1.000	-0.091 (-1.261;1.078)	1.000
Functionality Items						
Quick-DASH (%)						
Upper limb disability	-14.330 (-24.294;-4.367)	0.002*	-53.596 (-64.051;-43.141)	0.000*	-39.266 (-52.520;-26.012)	0.000*
Work Module	-17.982 (-34.354;-1.610)	0.027*	-73.468 (-56.289;-90.647)	0.000*	-55.486 (-33.707;-77.265)	0.000*
Sports;Performing Arts Module	-21.885 (-38.203;-5.568)	0.005*	-71.089 (-88.211;-53.976)	0.000*	-49.203 (-70.910;27.497)	0.000*
ROM Active index finger flexion						
Dominant	-6.612 (-14.110;0.887)	0.101	-0.989 (-6.880;8.856)	1.000	7.600 (-2.375;17.575)	0.195
Non Dominant	-5.106 (-12.455;2.244)	0.275	0.728 (-6.983;8.440)	1.000	5.834 (-3.942;15.610)	0.438

*P< 0.05 for Bonferroni pairwise comparison between groups.

RP: Raynaud's phenomenon; CST: Cold Stress Test; Quick-DASH: Shortened Disability of the Arm, Shoulder and Hand Questionnaire; ROM: Range of motion

Table 7. Mean Difference (MD), 95% Confidence Interval (CI) and between groups level of significance for vascular and functionality assessments. (Continuation).

ROM Pasive index finger flexion						
Dominant	-6.095 (-12.780;0.591)	0.085	0.506 (-6.509;7.521)	1.000	6.600 (-2.293;15.493)	0.216
Non Dominant	-6.099 (-12.160;-0.038)	0.048*	-0.619 (-6.979;5.740)	1.000	5.480 (-2.583;13.542)	0.296
ROM Active index finger extension						
Dominant	-2.080 (-7.655;3.495)	1.000	0.310 (-5.540;6.160)	1.000	2.390 (-5.026;9.806)	1.000
Non Dominant	0.571 (-5.310;6.173)	1.000	0.753 (-5.125;6.631)	1.000	0.182 (-7.269;7.634)	1.000
ROM Passive index finger extension						
Dominant	-11.871 (-23.052;-0.689)	0.034*	0.583 (-11.150;12.316)	1.000	12.453 (-2.420;27.327)	0.130
Non Dominant	-9.583 (-19.819;0.652)	0.074	2.926 (-7.814;13.666)	1.000	12.510 (-1.106;26.125)	0.082
ROM Active thumb flexion						
Dominant	-3.614 (-9.430;2.201)	0.391	4.696 (-1.406;10.798)	0.188	8.310 (0.574;16.046)	0.031*
Non Dominant	-5.451 (-12.33;1.436)	0.167	4.152 (-3.074;11.378)	0.484	9.603 (0.442;18.764)	0.037*
ROM Passive thumb flexion						
Dominant	-3.351 (-14.364;7.662)	1.000	8.510 (-3.046;20.066)	0.223	11.861 (-2.789;26.511)	0.151
Non Dominant	-2.236 (-9.403;4.932)	1.000	3.626 (-3.895;11.147)	0.716	5.862 (-3.673;15.397)	0.430

*P< 0.05 for Bonferroni pairwise comparison between groups.

RP: Raynaud's phenomenon; CST: Cold Stress Test; Quick-DASH: Shortened Disability of the Arm, Shoulder and Hand Questionnaire; ROM: Range of motion

Table 7. Mean Difference (MD), 95% Confidence Interval (CI) and between groups level of significance for vascular and functionality assessments. (Continuation).

ROM Active thumb extension						
Dominant	-4.475 (-9.713;0.762)	0.118	1.828 (-3.668;7.324)	1.000	6.0303 (-0.664;13.271)	0.089
Non Dominant	-4.538 (-9.286;0.210)	0.065	4.930 (-0.051;9.912)	0.053	9.468 (3.153;15.784)	0.002*
ROM Passive thumb extension						
Dominant	-4.790 (-13.719;4.139)	0.571	2.041 (-7.328;11.411)	1.000	6.832 (-5.046;18.709)	0.483
Non Dominant	-5.524 (-14.742;3.693)	0.433	2.394 (-7.278;12.066)	1.000	7.919 (-4.343;20.180)	0.349
Tip pinch strength						
Dominant	0.546 (-1.519;1.882)	1.000	0.546 (-1.238;2.331)	1.000	0.365 (-1.897;2.627)	1.000
Non Dominant	0.462 (-1.258;2.182)	1.000	0.359 (-1.446;2.164)	0.730	-0.103 (-2.392;2.185)	1.000
Lateral pinch strength						
Dominant	-0.011 (-1.884;1.861)	1.000	0.805 (-1.160;2.770)	0.947	0.817 (-1.674;3.307)	0.817
Non Dominant	-0.160 (-2.057;1.736)	1.000	0.651 (-1.339;2.641)	1.000	0.811(-1.711;3.334)	1.000

*P< 0.05 for Bonferroni pairwise comparison between groups.

RP: Raynaud's phenomenon; CST: Cold Stress Test; Quick-DASH: Shortened Disability of the Arm, Shoulder and Hand Questionnaire; ROM: Range of motion

4.2.4 Vascular and functional factors associated with disability in Raynaud's phenomenon participants.

Bivariate correlation analysis showed that flexion and extension of the index finger, flexion and extension of the thumb, and lateral pinch strength were statistically indirectly associated with general upper limb disability and disability related to work/sports/arts activities in Raynaud's phenomenon subjects ($0.348 \leq r \geq 0.613$, $0.000 \leq p \geq 0.035$).In addition, lower levels of oxygen saturation and temperature post-Cold Stress Test were also significant and were associated with higher scores in work disability **(Table 8).**

Table 8. Bivariate correlations between Quick-DASH/ vascular outcomes, range of motion and strength in RP participants (n=37)

Outcomes measures	Quick-DASH Upper limb disability		Quick-DASH Work module		Quick-DASH Sports/performing arts module	
	Pearson (r)	*P*-value	Pearson (r)	*P*-value	Pearson (r)	*P*-value
RP attacks (nº/week)	0.141	0.406	0.648	0.078	0.412	0.139
Temperature pre-CST	0.219	0.193	0.254	0.129	-0.089	0.602
Temperature post-CST	0.293	0.079	-0.348	0.035*	0.027	0.876
Recovery Temperature	-0.166	0.326	-0.213	0.205	-0.151	0.374
Blood flow radial artery	0.169	0.318	0.161	0.341	0.723	-0.060
Blood flow ulnar artery	0.284	0.089	0.239	0.153	0.111	0.512
Oxygen Saturation	-0.394	0.016*	-0.535	0.001**	-0.183	0.278
ROM index finger flexion	-0.613	0.000***	-0.517	0.001**	-0.522	0.001**
ROM index finger extension	-0.525	0.001**	-0.459	0.004**	-0.401	0.014*
ROM thumb flexion	-0.394	0.016*	-0.408	0.012*	-0.204	0.226
ROM thumb extension	-0.442	0.006**	-0.473	0.003**	-0.354	0.032*
Tip pinch strength	-0.046	0.789	0.107	0.530	-0.079	0.642
Lateral pinch Strength	-0.459	0.004**	-0.230	0.171	-0.389	0.017*

*$P<0.05$; **$P<0.01$; ***$P<0.001$

Quick-DASH: Shortened Disability of the Arm, Shoulder and Hand Questionnaire; CST: Cold Stress Test; ROM: Range of motion

4.2.5 Final multiple regression model of predictive factors associated with disability in Raynaud's phenomenon participants.

Firstly, multivariate regression analysis showed that extension of the index finger and lateral pinch strength were significantly associated with the dependent variable Q-DASH, predicting almost 55% of the total variance on upper limb disability in Raynaud's phenomenon patients **(Table 9).** Similar results were achieved when Sports/Arts disability was used as the dependent variable, with both independent variables explaining almost 27% of the total variance **(Table 10).** Finally, when disability in the work subscale was taken into account as a dependent variable, the multivariate model showed that oxygen saturation and extension of the index finger were significantly associated with the dependent variable, predicting almost 42% of the total variance **(Table 11)**

Table 9. Final multiple regression model of predictive associated factors to upper limb disability in RP participants (n=37).

Quick-DASH: Upper limb disability (r^2=0.551)							
Independent variables	Raw B	95% CI		Standardized β	SE	t	*P*-value
		Upper limit	Lower limit				
Oxygen Saturation	-7.400	-0.016	-14.785	-0.273	3.625	-2,041	0.050
ROM index finger extension	-1.122	-0.291	-1.954	-0.348	0.408	-2,749	0.010*
ROM thumb flexion	-0.474	0.298	-1.246	-0.164	0.379	-1,252	0.220
Lateral pinch strength	-5.706	-2.400	-9.012	-0.427	1.623	-3,516	0.001*

*P <0.05

Quick-DASH: Shortened Disability of the Arm, Shoulder and Hand questionnaire; r^2: regression coefficient of determination; B: regression coefficient; CI: confidence interval; β: adjusted coefficient from multiple linear regression analysis; SE: coefficient standard error; ROM: Range of motion.

Table 10. Final multiple regression model of predictive associated factors to sports/performing arts disability in RP participants.

Quick-DASH: Sports/performing arts disability (r^2=0.275)							
Independent variables	Raw B	95% CI		Standardized β	SE	t	*P*-value
		Upper limit	Lower limit				
ROM index finger extension	-1.530	-0.242	-2.817	-0.356	0.634	-2,414	0.021*
Lateral pinch strength	-6.095	-0.755	-11.43	-0.342	2.627	-2,320	0.026*

*P <0.05

Quick- DASH: Shortened Disability of the Arm, Shoulder and Hand questionnaire;r^2: Regression coefficient of determination; B: regression coefficient; CI: Confidence interval; β: Adjusted coefficient from multiple linear regression analysis; SE: Coefficient standard error; ROM: Range of motion

Table 11. Final multiple regression model of predictive associated factors to work disability in RP participants.

Quick-DASH: Work disability (r^2=0.418)							
Independent variables	Raw B	95% CI		Standardized β	SE	t	*P*-value
		Upper limit	Lower limit				
Temperature post-CST	-0.419	2.239	-3.078	-0.063	1.305	-0,321	0.750
Oxygen Saturation	-15.532	-0.696	-30.368	-0.416	7.283	-2,133	0.041*
ROM index finger extension	-1.319	-0.011	-2.627	0.642	-0.297	-2,054	0.048*
ROM thumb flexion	-0.791	0.466	-2.048	0.617	-0.199	-2,054	0.209

*P <0.05

Quick-DASH: Shortened Disability of the Arm, Shoulder and Hand questionnaire; r^2: regression coefficient of determination; B: regression coefficient; CI: confidence interval; β: adjusted coefficient from multiple linear regression analysis; SE: coefficient standard error; CST: Cold Stress Test; ROM: Range of motion

4.3 Study III: "Effectiveness of a vasodilatory intervention through tap-water iontophoresis in patients with Raynaud's phenomenon: a Randomized Clinical Trial.".

4.3.1 Sociodemographic and clinical characteristics

The results section of the Study III is showed below.

Of the 48 patients recruited for the study, 34 patients with a mean age of 43.41±17.62 years met the inclusion criteria. A flow diagram of the participants throughout the study is depicted in Figure 1. No significant differences in the sociodemographic, co-morbidities and pharmacologic treatment characteristics of participants were found across groups, ($P \geq 0.48$) (Table 12).

Table 12. Sociodemographic, co-morbidities and pharmacologic treatment characteristics of participants.

Outcomes	Treatment Group	Control Group	*P*-value
Age (years)	43.29±18.10	43.53±17.68	0.97
Sex			0.71
Male	5 (29.4)	6 (35.3)	
Female	12 (70.6)	11 (64.7)	
Hand dominance			0.83
Right	14 (82.4)	15 (88.2)	
Left	2 (11.8)	1 (5.9)	
Ambidextros	1 (5.9)	1 (5.9)	
Time since onset (years)	12.76±10.47	12.82±9.76	0.98
Type of RP			0.72
PRP	6 (35.3)	7 (41.2)	
SRP	11 (64.7)	10 (58.8)	
Smoking History (%)			0.72
Active smoker	1 (5.9)	2 (11.8)	
Non-smoker	13 (76.5)	11 (64.7)	
Ex-smoker	3 (17.6)	4 (23.5)	
Co-morbidity (%)			
Hypertension	8 (47.1)	6 (35.3)	0.48
Hypercholesterolemia	6 (35.3)	7 (41.2)	0.72
Diabetes Mellitus	1 (5.9)	2 (11.8)	0.54
Fibromyalgia	6 (35.3)	5 (29.4)	0.48
Rheumatoid arthritis	5 (29.4)	4 (23.5)	0.69
Scleroderma	3 (17.6)	4 (23.5)	0.67
Depression	6 (35.3)	7 (41.2)	0.72
Hyperhidrosis	3 (17.6)	2 (11.8)	0.62
Pharmacologic treatment			
Antihypertensive	7 (41.2)	7 (41.2)	1.00
Statins	6 (35.3)	5 (29.4)	0.71
NSAIDs	8 (47.1)	8 (47.1)	1.00
Analgesics	10 (58.8)	11 (64.7)	1.00
Vasodilators	3 (17.6)	5 (29.4)	0.41
Antidepressants	5 (29.4)	7 (41.2)	0.47
Insulin	1 (5.9)	2 (11.8)	0.54

* $P < 0.05$. Data are expressed as the mean ± standard deviation (SD) for quantitative variables or frequency and (%) for qualitative outcomes. RP: Raynaud's phenomenon; PRP: Primary Raynaud's phenomenon; SRP: Secondary Raynaud's phenomenon; NSAIDs: Nonsteroidal anti-inflammatory drugs

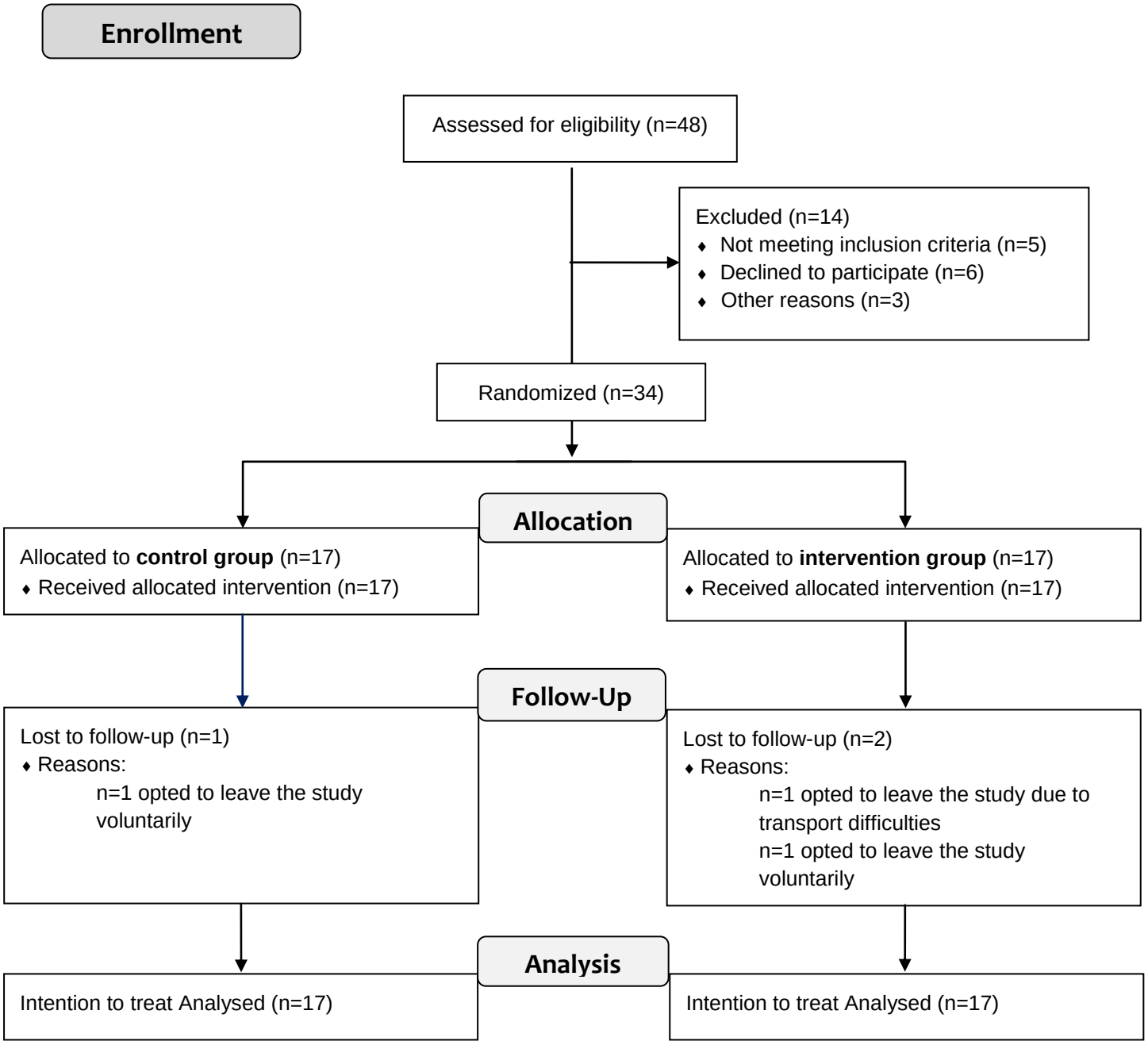

Figure 1. Flow diagram of the recruitment and follow-up of patients in the study following Consort guidelines.

4.3.2 Weekly average number of RP attacks, pain intensity, blood flow and oxygen saturation

The group × time interaction for the 2 ×3 repeated-measures ANOVA showed significant differences in the experimental versus control group on the weekly average number of RP attacks, ($F=17.99$, $P<0.001$), EVA pre-CST ($F=7.43$, $P=0.005$), blood flow of the radial artery [dominant side (DS): $F=3.96$, $P=0.035$; non-dominant side (NDS) $F=14.56$, $P=0.001$], blood flow of the ulnar artery (DS: $F=5.47$, $P=0.026$) and oxygen saturation (DS: $F=7.91$, $P=0.002$; NDS: $F=10.05$, $P=0.003$) (Table 12).

Within-group comparisons demonstrated a significant time effect in the iontophoresis group on the number of attacks ($F=16.80$, $P<0.001$), EVA pre-CST ($F=8.06$, $P=0.002$), blood flow of the radial artery (NDS: $F=4.37$, $P=0.027$) and oxygen saturation (DS: $F=4.14$, $P=0.025$). In the control group, a within-group comparison showed a significant decrease in the blood flow of the radial artery (DS: $F=9.19$, $P=0.001$) and ulnar artery (DS: $F=14.33$, $P=0.001$; NDS: $F=12.53$, $P<0.001$), as well as oxygen saturation (DS: $F=4.69$, $P=0.023$; NDS: $F=7.59$, $P=0.002$) **(Table 13).**

Table 13. Baseline, post-treatment, follow-up differences, and change scores in each group (95% confidence interval) for weekly average number of RP attacks, pain intensity, blood flow and oxygen saturation

Outcomes	Baseline	Post-Treatment	2 Months Follow-up	Cohen's *d* Within groups (Baseline/Follow-up)	Within groups Score change	Between groups Score change	Cohen's *d* Between groups (Follow-up)
Average number of RP attacks							
Experimental	31.29±21.02	11.53±8.55	8.23±9.97	1.40	23.06 (11.21, 34.91)	26.35 (14.37, 38.33)*	2.20
Control	25.11±9.91	27.17±8.16	28.00±7.83	0.32	-2.88 (-7.30, 1.54)		
Pain intensity pre-CST							
Experimental	2.64±2.22	1.66±1.92	2.59±2.64	0.02	0.05 (-0.97, 1.07)	1.22 (0.57, 2.39)*	0.88
Control	3.60±2.58	4.4±2.66	4.79±2.33	0.48	-1.17 (-1.83, -0.51)		
Pain intensity post-CST							
Experimental	7.34±2.65	8.41±0.97	8.25±1.16	0.44	-0.91 (-2.89, 0.14)	-1.01 (-2.44, 0.42)	0.26
Control	8.72±1.38	8.46 ±1.56	8.62±1.56	0.06	0.11 (-0.62, 0.84)		
Blood flow radial artery							
Experimental							
D	9.12±5.11	9.82±2.69	9.30±2.90	0.04	-0.17 (-2.63, 2.30)	-3,32 (-6.24, 0.39)*	1.18
ND	8.73±3.72	11.40±3.04	10.13±3.25	0.39	-1.40 (-3.51, 0,73)	-5.10 (1.34, -7.82)*	1.27
Control							
D	9.29±2.80	7.26±1.59	6.14±2.40	1.20	3.15 (1.36, 4.94)		
ND	10.11±3.22	7.76±1.53	6.40±2.56	1.27	3.71 (1.84, 5,59)		
Blood flow ulnar artery							
Experimental							
D	10.39±6.32	10.08±3.97	10.70±4.06	0.04	-0.31 (-3.75, 3.27)	-4.62 (-8.63, -0.60)*	1.37
ND	9.53±3.24	9.21±3.13	8.79±2.07	0.27	0.74 (-0.89, 2.37)	-1.57 (-3.50, 0.35)	1.16
Control							
D	10.63±4.02	8.60±2.98	6.25±2.10	1.36	4.38 (2.10, 6.66)		
ND	8.79±2.08	7.93±1.73	6.40±2.03	1.16	2.39 (1.15, 3,47)		
Oxygen saturation							
Experimental							
D	97.00±1.27	97.82±0.73	97.41±0.79	0.38	-0.41 (-1.12, 0.29)	-0.94 (-1.76, -0.12)*	0.61
ND	97.29±0.85	97.65±0.93	98.47±0.80	0.22	-1.18 (-0.59, 1.24)	-0.82 (-1.35, -0.29)*	1.96
Control							
D	97.51±0.80	96.88±0.78	96.88±0.93	0.72	0.63 (0.04, 1.01)		
ND	97.47±0.72	97.06±0.83	96.82±0.88	0.80	0.65 (0.29, 1.01		

*Significant group × time interaction (analysis of variance, $P < 0.05$).

CST: Cold Stress Test; D: Dominant side; ND: Non dominant side. Values are expressed as means ± standard deviation (SD) for baseline, post-treatment and 2 months follow-up and as mean (95% confidence interval) for within-group (baseline to follow-up) and between-group change scores (at follow-up).

4.3.3 Temperature pre-CST, temperature post-CST and recovery curve temperature.

The group × time interaction for the 2×3 ANOVA showed differences between groups for the recovery curve in the temperature at 25 minutes (DS: F=4.53, P=0.014), temperature at 30 minutes (DS: F=4,70, P=0.016; NDS: F= 4.84; P=0.014) and temperature at 35 minutes (DS: F=3.74, P=0.030; NDS: F=3.89, P=0.029). A within-group comparison showed an improvement in the iontophoresis group for the recovery curve in the temperature post-CST (DS: 3.78, P=0.040), temperature at five minutes (DS: F=4.28, P=0.023), temperature at 25 minutes (DS: F=7.40, P=0.004), temperature at 30 minutes (DS: F=7.58, P=0.004; NDS: F= 4.67, P= 0.023) and temperature at 35 minutes (DS: F= 4.81, P=0.020; NDS: F= 4.94, P=0.019). In the control group, the temperature was increased only in the variables post-CST (DS: 4.54, P=0.019) and the temperature at five minutes (DS: F=7.11, P=0.003; NDS: F= 6.67, P=0.009) **(Table 14).**

Table 14. Baseline, post-treatment, follow-up differences, and change scores in each group (95% confidence interval) for temperature pre-CST, temperature post-CST and recovery curve temperature.

Outcomes	Baseline	Post-Treatment	2 Months Follow-up	Cohen's *d* Within groups (Baseline/Follow-up)	Within groups Score change	Between groups Score change	Cohen's *d* Between Groups (Follow-up)
Temperature pre-CST							
Experimental							
D	26.77±4.35	28.39±4.69	29.61±3.38	0.72	-2.84 (-5.24, -0-46)	-2.60 (-5.88, 0.68)	0.04
ND	27.04±4.34	28.36±4.81	30.39±3.26	0.87	-3.34 (-5.75, -0.93)	-0.58 (-4.23, 3.06)	0.00
Control							
D	29.51±3.68	28.80±4.10	29.75±3.40	0.06	-0.24 (-2.68, 2.19)		
ND	28.39±4.69	29.28±3.71	30.37±3.35	0.48	-1.98 (-4.80, 0.83)		
Temperature post-CST							
Experimental							
D	16.63±3.08	15.58±2.45	18.44±3.52	0.54	-1.80 (-3.99, 0.38)	0.43 (-2.28, 3.15)	0.00
ND	16.54±3.32	15.35±2.88	16.31±2.76	0.07	0.22 (-1.75, 2.21)	1.98 (1.11, -0.28)	0.36
Control							
D	16.17±2.44	16.51±3.03	18.41±3.55	0.73	-2.24 (-4.02, -0.45)		
ND	15.94±2.28	16.34±2.45	17.38±3.02	0.53	-1.44 (-2.71, -0.17)		
Temperature at 5 minutes							
Experimental							
D	19.41± 4.21	19.91±5.41	22.04±5.49	0.53	-2.62 (-4.50, -0.75)	-0.52 (-2.75, 1.73)	0.21
ND	19.44±3.60	19.97±5.45	18.85±3.18	0.17	0.59 (-0.66, 1.85)	2.27 (0.85, 3.68)	0.31
Control							
D	18.87±3.06	18.88±4.35	20.98±4.18	0.57	-2.11 (-3.50, -0.72)		
ND	18.33±3.33	18.72±3.99	20.01±4.17	0.44	-1.67 (-2.44, -0.91)		
Temperature at 10 minutes							
Experimental							
D	22.35±5.55	22.12 ±5.79	22.18±4.10	0.03	0.16 (-2.72, 3.05)	2.34 (-0.87, 5.56)	0.14
ND	21.67±5.21	23.07±5.71	22.52±5.54	0.15	-0.84 (-3.54, 1.85)	0.05 (-2.86, 2.97)	0.11
Control							
D	20.69±4.03	21.44±5.59	22.87±5.47	0.45	-2.17 (-3.87, -0.47)		
ND	22.20±4.77	21.55±5.46	23.11±5.00	0.18	-0.90 (-2.30, 0.49)		

*Significant group × time interaction (analysis of variance, $P < 0.05$).

CST: Cold Stress Test; D: Dominant side; ND: Non dominant side. Values are expressed as means ± standard deviation (SD) for baseline, post-treatment and 2 months follow-up and as mean (95% confidence interval) for within-group (baseline to follow-up) and between-group change scores (at follow-up).

Table 14. Baseline, post-treatment, follow-up differences, and change scores in each group (95% confidence interval) for temperature pre-CST, temperature post-CST and recovery curve temperature. (Continuation)

Temperature at 15 minutes							
Experimental							
D	22.83±5.62	24.84±5.79	25.90±4.83	0.58	-3.06 (-5.79, -0.33)	-2.36 (1.60, 5.62)	0.34
ND	23.51±5.25	24.44±5.29	25.39±5.30	0.35	-1.87 (-4.65, 0.89)	-1.22 -4.42, 1.96)	0.09
Control							
D	23.63±4.53	24.03±6.11	24.33±4.24	0.15	-0.70 (-2.71, 1.31)		
ND	24.30±3.85	23.88±5.51	24.95±3.72	0.17	-0.64 (-2.48, 1.19)		
Temperature at 20 minutes							
Experimental							
D	23.61±5.52	25.72±5.69	25.90±4.83	0.44	-2.28 (-5.04, 0.46)	-1.95 (-5.08, 1.18)	0.27
ND	24.52±5.34	26.12±5.30	26.68±5.35	0.40	-2.15 (-4.99, 0.68)	-1.08 (-4.36, 2.19)	0.04
Control							
D	24.37±4.76	24.74±6.21	24.70±3.89	0.07	-0.33 (-2.09, 1.41)		
ND	25.38±4.62	25.81±6.05	26.45±4.06	0.24	-1.07 (-2.96, 0.82)		
Temperature at 25 minutes							
Experimental							
D	24.24±5.46	26.41±5.62	27.65±4.81	0.66	-3.44 (-5.38, -1.43)	-2.35 (-5.02. 0.32)*	0.39
ND	25.00±5.15	27.00±5.28	27.14±4.96	0.42	-2.14 (-4.57, 0.27)	-3.17 (-5.55, -0.79)	0.15
Control							
D	26.87±4.69	25.87±5.71	26.01±3.35	0.21	0.85 (-1.32, 3.04)		
ND	26.69±3.74	25.89±5.33	26.48±3.75	0.05	0,20 (-1.16, 0.319)		
Temperature at 30 minutes							
Experimental							
D	24.28±5.25	27.00±5.79	27.65±4.81	0.67	-3.37 (-5.46, -1.27)	-3.17 (-5.59, -0.79)*	0.14
ND	24.91±4.78	27.21±5.05	27.51±4.67	0.55	-2.59 (-4.65, -0.53)	-3.04 (-5.42, -0,65)*	0.16
Control							
D	26.86±3.76	26.32±5.11	27.05± 3.13	0.05	-0.19 (-1.51, 1.13)		
ND	27.31±3.74	26.49±4.97	26.86±3.53	0.12	0.44 (-0,94, 1.83)		
Temperature at 35 minutes							
Experimental							
D	24.92±5.16	27.05±5.17	27.61±4.28	0.57	-2.68 (-4.93, -0.42)	-2.80 (-5.70, 0.10)*	0.01
ND	24.85±4.89	27.44±4.79	27.45±4.34	0.56	-2.60 (-4.69, -0.50)	-2.75 (-5.73, 0.21)*	0.03
Control							
D	27.78±4.37	26.54±4.98	27.66±3.09	0.03	0.11 (-1.9, 2.13)		
ND	27.50±4.40	26.57±4.68	27.29±3.66	0.05	0.21 (-2.12, 2.44)		

*Significant group × time interaction (analysis of variance, $P < 0.05$).

CST: Cold Stress Test; D: Dominant side; ND: Non dominant side. Values are expressed as means ± standard deviation (SD) for baseline, post-treatment and 2 months follow-up and as mean (95% confidence interval) for within-group (baseline to follow-up) and between-group change scores (at follow-up).

4.3.4 Upper limb disability, central sensitization and pain catastrophizing.

At the end of the two months of the follow-up period, the group × time interaction for the 2×3 ANOVA showed that the iontophoresis group presented significantly lower values for the total score of Quick-DASH (F=3.37, P=0.046), sports/ performing arts module score (F=3.19, P=0.048) and CSI (F= 9.72, P <0.001) in comparison with the control group.
A within-group comparison showed an improvement in the iontophoresis group for the total score of Quick-DASH (F=3.69, P=0.038) and sports/ performing arts module score (F=3.42, P=0.048). Also, a significant time effect was observed in the control group for the total score of CSI (F= 8.27, P <0.003) **(Table 15).**

Table 15. Baseline, post-treatment, follow-up differences, and change scores in each group (95% confidence interval) for upper limb disability, central sensitization and catastrophizing.

Outcomes	Baseline	Post-Treatment	2 Months Follow-up	Cohen's *d* Whiting Groups (Baseline/Follow-up)	Within groups Score change	Score change Between groups	Cohen's d Between Groups (Follow-up)
Quick-DASH (%)							
Upper limb disability							
Experimental	45.20±22.25	37.75±18.70	37.03±23.50	0.36	8.17 (1.17, 15.16)	11.69 (1.10, 22.29)*	0.19
Control	38.10±24.10	39.13±21.07	41.64±23.59	0.15	-3.54 (-12.06,4.99)		
Work Module							
Experimental	57.35±31.96	45.96±35.28	46.53±32.59	0.33	10.82 (-2.88, 23.64)	17.82 (1.75, 33.89)	0.23
Control	56.97±34.50	49.26±32.69	54.41±35.34	0.07	2.56 (-17.63, 2.74)		
Sports/Performing Arts							
Experimental	61.39±30.32	47.06±33.59	48.16±36.23	0.39	13.23 (-1.04, 27.51)	20.95 (4.56, 37.34)*	0.22
Control	48.15±35.21	44.85±26.90	55.83±31.36	0.23	-7.68 (-17.06, 1.62)		
Central Sensitization Inventory							
Experimental	53.94±21.41	50.59±20.84	50.90±20.90	0.14	3.04 (0.79, 7.44)	12.47 (6.68, 18.25)*	0.34
Control	49.82±20.35	51.88±21.90	58.18±21.56	0.39	-8.36 (-13.37, -3.34)		
Pain Catastrophizing Scale							
Experimental	21.23±12.41	18.94±10.94	18.40±14.90	0.20	2.83 (0.19, 8,86)	6.94 (-0.72, 14.60)	0.04
Control	16.70±13.81	21.23±12.36	19.11±13.79	0.17	-2.41 (-9.10, 4.28)		

*Significant group × time interaction (analysis of variance, $P < 0.05$).

Quick-DASH: Shortened Disability of the Arm, Shoulder and Hand Questionnaire.Values are expressed as means ± standard deviation (SD) for baseline, post-treatment and 2 months follow-up and as mean (95% confidence interval) for within-group (baseline to follow-up) and between-group change scores (at follow-up).

DISCUSIÓN

DISCUSSION

5. DISCUSIÓN/ DISCUSSION

5.1 Differences in hands temperature, blood flow, oxygen saturation and recovery curve of temperature between subjects with Raynaud and healthy controls.

The results of both observational studies highlight that subjects with Raynaud's phenomenon had lower hand temperature in their hands at baseline than the healthy controls. They also showed lower temperature in their hands after the Cold Stress Test, therefore worse recovery of the temperature and less blood flow on the radial artery than control. With respect to temperature, the current results were consistent with previous studies (Brown, Middaugh, Haythornthwaite, & Bielory, 2001; Reilly, Taylor, El-Hadidy, & Jayson, 1992; Matthieu Roustit et al., 2011) that showed similar findings for temperature record before and after Cold Stress Test and recovery patterns in Primary and Secondary Raynaud's phenomenon participants and healthy controls. The blood flow measurements were also consistent with previous studies (Gaillard-Bigot et al., 2014; Maga et al., 2016; Mirbod & Sugiura, 2017; Stoyneva, 2004) that reported lower baseline blood flow in Raynaud patients than in the controls. Furthermore, some authors found no significant difference in the basal blood flow between the Primary and Secondary Raynaud's phenomenon groups (Mirbod & Sugiura, 2017; Stoyneva, 2004).

As regards oxygen saturation, our results coincide with those of a recent study (Bello et al., 2017) on Secondary Raynaud patients, which determined that there was no statistically significant difference between the groups at baseline.

5.2 Relationship between vascular impairment, pain levels and central sensitization in Raynaud's phenomenon.

Our first study shows that patients with primary and secondary RP had lower PPTs and exhibited bilateral hypersensitivity in comparison to healthy controls. However, only participants with SRP showed altered pain intensity and signs of CS. Therefore, widespread

PPTs found in the PRP group may not be sufficient to conclusively confirm the presence of CS in the primary form of the illness. In addition, our hypothesis that pain is related to lower temperature in the hands is not supported by our results.

Although the PPTs and Pain Matcher thresholds in both RP groups were lower than in the control group, this hypersensivity was indicative of CS only in the SRP group. Research in different populations has reported pain, decreased pressure or electrical pain thresholds, for example, in patients with whiplash pain disorders (Käll et al., 2008), acute oral pain (Alstergren & Forstrom, 2003) or chronic pain (Lund et al., 2005) (Lund et al., 2005) in comparison to healthy controls. Earlier work proposed that bilateral hypersensitivity is a consequence of a continuum of peripheral nociceptive stimulation, which may induce signs of central sensitization at in the medium or long term (Aguilar-Ferrándiz et al., 2015). Therefore, peripheral vascular impairment could act as a peripheral source of nociception, thus contributing to central pain mechanisms. In contrast, no differences were observed in pain intensity between participants with PRP and controls in the present study, indicating that the level of pain was insufficient to activate CS processes. Only participants with SRP reported significantly higher levels of pain intensity, probably due to the greater alterations related to their underlying rheumatic pathology.

According to theories that attribute pain in RP to peripheral vasoconstriction in the hands as a source of peripheral nociceptive stimulation, the peripheral vascular disorder may also contribute to central sensitization through general thermoregulation (Albrecht et al., 2013). This thermoregulation is produced in specific skin areas through the structural and functional features of the vascular system, such as AVA (Walløe, 2016). A study (Flavahan, 2015) of designed to determine the patency rate of AVA in the hands of patients with PRP and SRP and healthy volunteers found that the response to cold in patients with RP was quantitatively greater than in controls and was characterized by excessive vasoconstriction. This peripheral hyperreactivity may be considered a disorder of the vascular thermoregulatory control system, and may contribute to general pain hypersensivity and CS.

Finally, higher pain levels were not related to the lower temperature or greater arterial vasoconstriction in the hands of persons with RP. In fact, signs of CS were observed only in the SRP group, which also had a higher basal temperature than the PRP group. This finding is further evidence that the pathophysiology of RP is complex and probably related to interactions between vascular, intravascular, genetic and hormonal factors, neural control mechanisms, risk factors such as smoking and alcohol consumption, and psychological aspects such as catastrophizing and/or stress and depression, which can also influence central sensitization and therefore pain experiences (Herrick, 2017; Prete et al., 2014).

5.3 Influence of catastrophization in the pain processing in Raynaud's phenomenon.

Our results show that patients with PRP and SRP had higher levels of catastrophizing in comparison to controls, with higher scores the SRP group. Perrot and colleagues (Perrot, Dieudé, Pérocheau, & Allanore, 2013) highlighted that catastrophizing plays an important role in pain experiences associated with systemic sclerosis and rheumatoid arthritis, with higher levels of pain in rheumatic processes. This role may explain our finding of higher levels of catastrophizing in patients with SRP than PRP or controls, in association with these rheumatic diseases. Evidence has shown that catastrophizing is a key risk factor and is associated with a poor prognosis for pain in patients with musculoskeletal conditions (Edwards et al., 2011). According to a previous study in patients with arthritis, FM and other rheumatic diseases, catastrophizing and depression are negative factors related to physical disability, and associated with limitations and deterioration in physical performance, disease progression and poor response to drug treatments (Edwards et al., 2006). Moreover, catastrophic thinking has been related to maladaptive beliefs about pain and more central sensitization. To our knowledge, no previous studies have analyzed psychological variables such as catastrophizing, which may contribute to pain in RP. Therefore, clinically, the treatment of patients with RP should focus not only on the vascular response but should also contemplate new approaches

involving “desensitizing” mechanisms such as pain education, cognitive behavioral therapy and exercise therapy (Nijs, Malfliet, Ickmans, Baert, & Meeus, 2014).

5.4 Vascular and functional factors associated with disability in Raynaud's phenomenon.

In our second study, both groups of Raynaud´s showed loss of hand function. Disability rates measured by the Q-DASH were significantly higher among Secondary Raynaud patients than in Primary form patients. Along these lines, previous studies (De Angelis et al., 2008) reported that functionality was influenced by age and comorbidities; an older age may be associated with more comorbidities, which may be related to worse Q-DASH scores. A study on patients with Systemic Sclerosis (Bérezné et al., 2011) reported that the disease had a disabling effect on activities of daily living and work. They also showed more disability scores in all subscales of the Q-DASH. Another study (Roh et al., 2017) also mentioned that daily activities are less affected in Primary Raynaud patients than in those with the secondary form of Raynaud's phenomenon.

The multivariate regression analysis confirmed that index finger extension, lateral pinch strength and oxygen saturation were significantly associated with disability in Raynaud's phenomenon participants. These results are in line with the hypothesis of our study, which was that patients suffering from Raynaud's phenomenon should have greater disability when compared with healthy controls. However, disability in Raynaud participants seems to be more related to range of motion impairment and hand strength than the severity of vascular alterations.

It can be interpreted from our findings that disability in Raynaud's phenomenon patients depends on multiple factors and that the relationship between vascular impairment and activity limitations is not evident. Disability of the upper limbs, work and sport/arts in Raynaud´s patients is more related to loss of hand mobility and pinch strength grip. Previous studies along these lines mentioned (Mason et al., 2005; Palmer et al., 2002) that

upper limb disability in Raynaud's phenomenon patients is related to the frequency of blanching attacks, but this is not reflected in our results. Mason et al. (2005) suggested that in patients with Secondary Raynaud and hand–arm vibration syndrome, upper limb disability is related more to sensorineural components than to vascular symptoms. A recent study (Sandqvist et al., 2018) in patients with Secondary Raynaud and early systemic sclerosis concluded that the number of Raynaud attacks and the difficulties associated with them were linked to limitations in all activities of daily living domains.

According to our knowledge, there are no previous studies that include the range of motion assessment and the relationship between range of motion and disability in Raynaud's phenomenon patients. Some studies in rheumatoid patients show that a decreased range of motion in the joints is related to disabilities of the arm, shoulder and hand (Pérez-Mármol et al., 2017; Ramos-Casals et al., 2015). A previous study (Carvalho et al., 2012) listed some of the factors that can influence the results of range of motion, like the presence of edema or pain, age, sex and passive range of motion. This list supports our results. Participants with Secondary Raynaud presented lower range of motion than those with Primary. They usually had an underlying disease, such as systemic sclerosis or arthritis which caused pain and edema. The Primary Raynaud group had the higher range of motion, which coincided with them being the younger group, and passive ranges of motion were higher in all the measurements of the three groups. Bain et al.(2015) mentioned in their study that patients with loss of finger joint extension have difficulties forming a grip (Bain et al., 2015). This relates to our results, where index extension is a predictive factor associated with disability in the three Q-DASH subscales in Raynaud's phenomenon participants in the final multiple regression analysis.

With respect to pinch strength, different studies (Landim et al., 2017; Merkel et al., 2002; Uppal et al., 2014) of the reviewed literature agree that Raynaud associated with scleroderma has a severe debilitating effect on patients. This supports our results, in which tip and lateral pinch strength measurements were lower in the Secondary Raynaud group.

Our data support the concept that Raynaud's phenomenon is a complex clinical condition that has a significant impact on the general health status of people who suffer it. To the best of our knowledge, our second study represents the first attempt to explore the relationship between vascular and functional impairment and disability in different activity domains (activities of daily living, work, sports and arts) in subjects with primary and secondary Raynaud. The present findings should provide valuable information for future studies to improve the diagnosis and treatment of this pathology.

5.5 The use of iontophoresis in the treatment of vascular pathologies.

The use of iontophoresis in the treatment of pathologies with a microvascular dysfunction, such as hyperhidrosis (Gollins et al., 2019; Wechter, Feldman, & Taylor, 2019) or nail psoriasis (Saki, Hosseinpoor, Heiran, Mohammadi, & Zeraatpishe, 2018), is widely reported; however studies about its effectiveness in RP are still scarce. A previous research study (Roustit et al., 2014) that used iontophoresis in patients with secondary RP to systemic sclerosis showed that the digital skin perfusion was increased after a single session. Murray et al (Murray et al., 2005) in their pilot study designed a special device to iontophorese chemicals locally (over the index finger) and demonstrated that vasoactive drugs could be administered without systemic side effects in healthy controls. In a later study (Murray et al., 2008) performed in patients with Systemic sclerosis demonstrated that iontophoresis application is effective in increasing blood flow and digital ischaemia.

The exact mechanism of action of iontophoresis is still unclear. Some authors have proposed, that benefits obtained from the electrical current are based on the vasodilator effect produced in the hands, whose skin presents a higher density of vessels and arteriovenous anastomoses(M. Roustit et al., 2014). Other authors described that tap- water iontophoresis decreases the activity of the sweat glands, acting on the process of thermogenesis. Diminishing the transpiration of the hands produces an increase in blood flow and temperature in the digital skin (Kolkhorst, DiPasquale, & Buono, 2002).

5.6 Effectiveness of an electrotherapy intervention in the vascular symptoms, upper limb disability, central sensitization and catastrophizing in Raynaud's phenomenon.

After 2 months of a electrotherapy treatment with galvanic current trough iontophoresis; patients with RP improved their weekly average number of RP attacks, pain intensity pre-CST, blood flow, oxygen saturation, the recovery curve of the temperature, upper limb disability and central sensitization in comparison with the control group. Our treatment had no effect on pain catastrophizing. Therefore, our hypothesis that the protocol treatment proposed improve the main symptoms of RP is supported by our results.

Our results showed a reduction of 23.06 points in the number of weekly attacks. A recent systematic review (Rirash et al., 2017) on the use of calcium channel blockers in RP determined that this therapy reduced the average number of attacks per week by six points. Denton et al (Denton et al., 2017) in their study with an analogy oral prostacyclin reported that it does not reduce the number of RP attacks in patients with secondary RP to systemic sclerosis compared with a placebo group. In a recent review Ingegnoli et al., (2019) highlighted that intravenous therapies with prostanoids also reduced the frequency and severity of RP attacks and digital ulcers in patients with severe secondary RP; however, the therapy showed important disadvantages such as systemic vasodilator side effects (Ingegnoli et al., 2019).

The application of tap-water inotophoresis in our study produced an increase in the peripheral temperature and a significant improvement in the arterial blood flow. Recent studies (Anderson et al., 2002; Chung et al., 2009) showed that applying topical nitrate therapy to the fingers causes vasodilation, increases the blood flow locally and improves the number of attacks and the time recovery after a cold challenge, but no licence for the use of this therapy in RP patients is currently available. In contrast, studies with botulinum toxin injections in patients with severe RP (Bello et al., 2017; Uppal et al., 2014) determined that no improvement was made in the blood flow to the hands of these patients.

Discrepancies may be related to the lack of a vasodilatory local effect because the botulinum toxin only blocks the sweat glands of the hands, modifying thermogenesis.

Regarding upper limb disability, our results showed a reduction of eight points in the DASH questionnaire. A study that applied a treatment based on the administration of phosphodiesterase type 5inhibitors also reported an improvement of 2.85 points in the scleroderma specific Health Assessment Questionnaire in comparison with a placebo (Shenoy et al., 2010). No more previous evidence exits regarding functionality and disability after the treatment of RP.

Our results showed that patients with RP presented significantly lower levels of central sensitization after the intervention; nevertheless no changes were achieved for pain catastrophizing. The improvements may be partially related to the reduction of symptoms; however, a study on patients with chronic pain highlighted that it is important to introduce new approaches, such as pain education or cognitive behavioural therapy, to improve the cognitive and affective aspects of pain, such as catastrophizing or central sensitization (Nijs et al., 2014).

Thus, the use of this topical therapy, with tap- water iontophoresis is a safe, easy, cheap an effective modality of treatment to improve the symptoms of both RP forms, with minimal side effects. Nevertheless, there is no previous scientific evidence evaluating the effectiveness of galvanic current in RP attacks and symptom. The present findings can support further investigation of novel treatments with iontophoresis like introducing drug with the current or develop devices for treatment at home, to optimize existing therapeutic options of this pathology.

5.7 Limitations of this PhD thesis

The results of these studies should be considered in light of some limitations:

Firstly, despite the fact that sample size calculations indicate that the study is powered enough, a larger sample size would be needed in future studies to extrapolate the data and to corroborate our conclusions. Secondly, two heterogeneous age groups of Raynaud participants were studied, however, so as not to alter the results obtained, age was included as a covariate in the ANCOVA analysis and added to the regression model as a continuous variable. Hence, the results should be interpreted with caution. Thirdly two of the studies were cross-sectional studies; we therefore refrain from offering speculation regarding causation, we cannot be certain that the differences observed were not due to differences between groups related to diverse factors, such as medical comorbidities. Fourthly, in the case of the Q-DASH, we chosed an instrument that was validated for hand and upper extremity conditions, but was not specifically for Raynaud's phenomenon**.** Finally, the short period of an electrotherapy application makes it necessary to evaluate the effects of multiple applications over a longer period.

CONCLUSIONES

CONCLUSIONS

6. CONCLUSIONES

6.1 Generales

- En general, nuestros resultados muestran que las personas con fenómeno de Raynaud presentan menor temperatura en sus manos (más vasoconstricción) mayores niveles de dolor y catastrofización, menor movilidad funcional de las manos y mayor discapacidad percibida en los miembros superiores que los sujetos sanos sin patología.

- La iontoforesis con agua corriente, parece ser una modalidad terapéutica eficaz para el control sintomático y funcional de los pacientes con FR.

6.2 Específicas.

- Las personas con fenómeno de Raynaud presentan menor temperatura en sus manos, mayores niveles de dolor, mayor hipersensibilidad al dolor por presión y mayores niveles de catastrofización que los sujetos controles sanos.

- La gravedad de las alteraciones vasculares no parece estar relacionada con la experiencia del dolor y los síntomas en los sujetos con FR. La sensibilización central solo parece estar presente en el FR secundario, es decir, cuando está asociado a otra patología. Además, ambos grupos de FR mostraron niveles de catastrofización más altos que las personas sanas. Estos mecanismos adicionales del dolor, pueden contribuir a que el proceso de dolor se mantenga en el tiempo, así como a una peor evolución y una peor respuesta a los tratamientos.

- Los participantes con Fenómeno de Raynaud mostraron menores rangos de movimiento en las articulaciones de las manos y una mayor discapacidad percibida de las extremidades superiores en la práctica de las actividades de la vida diaria, el trabajo y los deportes, especialmente los que presentaban FR secundario.

- La discapacidad en el Fenómeno de Raynaud parece estar más relacionada con la pérdida de la amplitud de movimiento a nivel de las articulaciones de la mano y la disminución de la fuerza que con las alteraciones o afectación a nivel vascular.

- Por lo tanto, los profesionales que intervienen en esta patología deberían desfocalizar la atención tradicionalmente centrada en la severidad vascular e incorporar los aspectos relacionados con el procesamiento central del dolor, la funcionalidad y la discapacidad de los miembros superiores de los pacientes con FR, a la hora de planificar y ejecutar las intervenciones terapéuticas.

- El tratamiento mediante iontoforesis con agua corriente, por un parte redujo el número de ataques, la intensidad del dolor, la discapacidad de la extremidad superior y la sensibilización central y por otro mejoró el flujo sanguíneo, la saturación de oxígeno y la recuperación en la curva de temperatura de los pacientes con Fenómeno de Raynaud.

- Esta tesis doctoral ofrece un abordaje completo e integral del FR que puede ayudar a diseñar y mejorar estrategias de diagnóstico y tratamiento para estos pacientes. Tanto los clínicos como los investigadores podrían considerar la actividad utilizada en este trabajo para optimizar el abordaje de esta patología desde un punto de vista más global.

6. CONCLUSIONS

6.1 General

- Our results show in general, that Raynaud's phenomenon sufferers have lower temperatures in their hands (more vasoconstriction), higher levels of pain, greater hypersensitivity to pressure pain, higher levels of catastrophizing, a lower range of movement in their hand joints and a greater perceived disability of the upper limbs than healthy controls.

- Tap-water iontophoresis seems to be an effective therapeutic modality for the symptomatic and functional control of patients with RP.

6.2 Specific

- People with Raynaud's phenomenon have lower temperature in their hands, higher levels of pain, greater hypersensitivity to pain due to pressure and higher levels of catastrophizing than healthy control subjects.

- The severity of the vascular abnormalities does not seem to be related to the experience of centralised pain in the subjects with RP, the central sensitization only seems to be present in secondary RP, that is, when it is associated with another condition. In addition, both RP groups showed higher levels of catastrophizing than healthy people. These additional pain mechanisms can contribute to the pain process being maintained over time, as well as to a worse evolution and response to treatment in these patients.

- Participants with Raynaud's phenomenon showed greater perceived disability in the hands and upper extremities when carrying out activities of daily living, practising sports or carrying out work tasks, especially those with secondary RP.

- The disability associated with Raynaud's phenomenon seems to be more related to the loss of the range of motion in the hand joints and the loss of strength, rather than abnormalities or involvement at the vascular level.

- Therefore, professionals involved with this condition, should defocus the traditionally focused attention on vascular severity and incorporate aspects related to central processing of pain, functionality and disability of the upper limbs of patients with RP, to planning and executing therapeutic interventions.

- The treatment with tap-water iontophoresis, on the one hand, reduced the number of attacks, pain intensity, disability of the upper extremity and central sensitization and on the other, improved blood flow, oxygen saturation and the recovery temperature curve of Raynaud's phenomenon sufferers.

- This thesis offers a complete and comprehensive approach to RP that can help facilitate the design and improvement of diagnostics and treatment strategies for these patients. Both clinicians and researchers can consider the activities used in this work to optimise their approach to this condition, from a more global point of view.

MENSAJES CLÍNICOS

CLINICAL MESSAGES

7. MENSAJES CLÍNICOS YPERSPECTIVAS FUTURAS

- El proceso de catastrofización parece estar relacionado con los mayores niveles de dolor y la hipersensibilidad en personas con Fenómeno de Raynaud, por tanto, la valoración puramente clínica del FR, que se ha venido realizando de manera tradicional debería de evolucionar hacia un enfoque biopsicosocial, donde el catastrofismo se incluyera tanto de forma diagnostica como terapéutica. Estos hallazgos también resaltan la importancia de introducir nuevos enfoques como la educación sobre el dolor o la terapia cognitiva conductual para mejorar los aspectos cognitivos y afectivos relacionados con el dolor, como el catastrofismo o la sensibilización central.

- Los resultados del presente estudio aportan una nueva perspectiva sobre la relación existente entre las alteraciones vasculares, los procesos de dolor y la discapacidad de los miembros superiores en el Fenómeno de Raynaud. Las medidas descritas y utilizadas para valorar estos aspectos se deberían incorporar la evaluación de esta patología para conseguir un diagnóstico más eficaz. Por lo tanto, estos hallazgos pueden estimular futuros proyectos de investigación para obtener información de valor que puede ayudar mejorar el diagnóstico y tratamiento de este trastorno.

- La presente tesis doctoral señala la necesidad de considerar el uso de la corriente eléctrica mediante iontoforesis con agua corriente como una forma complementaria de tratamiento del Fenómeno de Raynaud.

- El protocolo de intervención de este estudio puede ser utilizado por fisioterapeutas para llevar a cabo el tratamiento del Fenómeno de Raynaud, ofreciendo una forma económica, práctica, sencilla de aplicar, mínimamente invasiva y con mínimos efectos secundarios. Además, se necesitan más estudios para investigar nuevos tratamientos de rehabilitación que se centren en mejorar la discapacidad de las extremidades superiores.

7. CLINICAL MESSAGES AND FUTURE PERSPECTIVES

- The process of catastrophizing seems to be related to the higher levels of pain and hypersensitivity in Raynaud's phenomenon sufferers. Therefore, the purely clinical assessment of RP, which has been carried out in a traditional manner, should evolve towards a biopsychosocial approach, where catastrophism is included both in a diagnostic and therapeutic way. These findings also highlight the importance to introduce new approaches as pain education or cognitive behavioural therapy to improve cognitive and affective aspects related of pain, such us catastrophizing or central sensitization.

- The results of this study provide a new perspective on the relationship between vascular abnormalities, pain processes and disability of the upper limbs in the context of Raynaud's phenomenon. The measures described and used to assess these factors should incorporate the evaluation of this condition to achieve a more effective diagnosis. Therefore, these findings may stimulate future research projects to obtain valuable information that can help improve the diagnosis and treatment of this disorder.

- The present thesis highlights the need to consider the use of electric current by means of iontophoresis with tap-water, as a parallel form of treatment for Raynaud's phenomenon.

- The intervention protocol of this study can be used by physiotherapists to treat Raynaud's phenomenon, offering a method that is economical, practical, simple to apply, minimally invasive and yields minimal side effects. In addition, more researches are need for investigating new rehabilitation treatments focusing on improving upper limb disability.

BIBLIOGRAFÍA

REFERENCES

8. BIBLIOGRAFÍA/ REFERENCES

Aguilar-Ferrándiz, M. E., Castro-Sánchez, A. M., Matarán-Peñarrocha, G. A., De Dios Luna, J., Moreno-Lorenzo, C., & Del Pozo, E. (2015). Evaluation of pain associated with chronic venous insufficiency in Spanish postmenopausal women. *Menopause*, *22*(1), 88–95.

Akdogan, A., Kilic, L., Dogan, I., Karadag, O., Bilgen, S. A., Kiraz, S., & Ertenli, I. (2015). Effect of capillaroscopic patterns on the pulse oximetry measurements in systemic sclerosis patients. *Microvascular Research*, *98*, 183–186.

Al-Awami, M., Schillinger, M., Maca, T., Pollanz, S., & Minar, E. (2004). Low level laser therapy for treatment of primary and secondary Raynaud's phenomenon. *Vasa - Journal of Vascular Diseases*, *33*(1), 25–29.

Albornoz Cabello, M., Maya Martín, J., & Toledo Marhuenda, J. (2016). *Electroterapia práctica : avances en investigación clínica*. (Elsevier, Ed.) (6ª). Barcelona.

Albrecht, P. J., Hou, Q., Argoff, C. E., Storey, J. R., Wymer, J. P., & Rice, F. L. (2013). Excessive peptidergic sensory innervation of cutaneous arteriole-venule shunts (AVS) in the palmar glabrous skin of fibromyalgia patients: implications for widespread deep tissue pain and fatigue. *Pain Medicine (Malden, Mass.)*, *14*(6), 895–915.

Alstergren, P., & Forstrom, J. (2003). Acute oral pain intensity and pain threshold assessed by intensity matching to pain induced by electrical stimuli. *Journal of Orofacial Pain*, *17*(2), 151–159.

Anderson, M. E., Moore, T. L., Hollis, S., Jayson, M. I. V, King, T. A., & Herrick, A. L. (2002). Digital vascular response to topical glyceryl trinitrate, as measured by laser Doppler imaging, in primary Raynaud's phenomenon and systemic sclerosis. *Rheumatology (Oxford, England)*, *41*(3), 324–328.

Anderson, M. E., Moore, T. L., Lunt, M., & Herrick, A. L. (2004). Digital iontophoresis of vasoactive subtances as measured by laser Doppler imaging - A non-invasive technique by which to measure microvascular dysfunction in Raynaud's phenomenon. *Rheumatology*, *43*(8), 986–991.

Bain, G. I., Polites, N., Higgs, B. G., Heptinstall, R. J., & McGrath, A. M. (2015). The functional range of motion of the finger joints. *Journal of Hand Surgery: European Volume*, *40*(4), 406–411.

Bakst, R., Merola, J. F., Franks, A. G., & Sanchez, M. (2008, October). Raynaud's phenomenon: Pathogenesis and management. *Journal of the American Academy of Dermatology*.

Beaton, D. E., Katz, J. N., Fossel, A. H., Wright, J. G., Tarasuk, V., & Bombardier, C. (2012). Measuring the whole or the parts? *Journal of Hand Therapy*, *14*(2), 128–142.

Belch, J., Carlizza, A., Carpentier, P. H., Constans, J., Khan, F., Wautrecht, J.-C., … Zeman, Z. (2017). ESVM guidelines – the diagnosis and management of Raynaud's phenomenon. *Vasa*, *46*(6), 413–423.

Bello, R. J., Cooney, C. M., Melamed, E., Follmar, K., Yenokyan, G., Leatherman, G., … Lifchez, S. D. (2017). The Therapeutic Efficacy of Botulinum Toxin in Treating Scleroderma-Associated Raynaud's Phenomenon: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Arthritis and Rheumatology*, *69*(8), 1661–1669.

Bérezné, A., Seror, R., Morell-Dubois, S., De Menthon, M., Fois, E., Dzeing-Ella, A., … Mouthon, L. (2011). Impact of systemic sclerosis on occupational and professional activity with attention to patients with digital ulcers. *Arthritis Care and Research*,

Bijur, P. E., Silver, W., & Gallagher, E. J. (2001). Reliability of the visual analog scale for measurement of acute pain. *Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine*, *8*(12), 1153–1157.

Block, J. A., & Sequeira, W. (2001). Raynaud's phenomenon. *The Lancet*, *357*(9273), 2042–2048.

Brown, K. M., Middaugh, S. J., Haythornthwaite, J. A., & Bielory, L. (2001). The Effects of Stress, Anxiety, and Outdoor Temperature on the Frequency and Severity of Raynaud's Attacks: The Raynaud's Treatment Study. *Journal of Behavioral Medicine*, *24*(2), 137–153.

Caglayan, E., Axmann, S., Hellmich, M., Moinzadeh, P., & Rosenkranz, S. (2012). Vardenafil for the treatment of raynaud phenomenon: a randomized, double-blind, placebo-controlled crossover study. *Archives of Internal Medicine*, *172*(15), 1182–1184.

Cano, A. (2004). Pain catastrophizing and social support in married individuals with chronic pain: the moderating role of pain duration. *Pain*, *110*(3), 656–664.

Cantarero-Villanueva, I., Fernández-Lao, C., Fernández-de-las-Peñas, C., López-Barajas, I. B., Del-Moral-Ávila, R., de la-Llave-Rincón, A. I., & Arroyo-Morales, M. (2012). Effectiveness of Water Physical Therapy on Pain, Pressure Pain Sensitivity, and Myofascial Trigger Points in Breast Cancer Survivors: A Randomized, Controlled Clinical Trial. *Pain Medicine (United States)*, *13*(11), 1509–1519.

Carey, M. A., Laird, D. E., Murray, K. A., & Stevenson, J. R. (2010). Reliability, validity, and clinical usability of a digital goniometer. *Work (Reading, Mass.)*, *36*(1), 55–66.

Carvalho R, Mazzer N, & Barbieri C. (2012). Analysis of the reliability and reproducibility goniometry photogrammetry regarding the hand. *Acta Ortopédica Brasileira*, *3*, 139–149. Retrieved from http://www.scielo.br/aob.

Castañeda, D. M., Bigatti, S., & Cronan, T. A. (1998). Gender and Exercise Behavior Among Women and Men with Osteoarthritis. *Women & Health*, *27*(4), 33–53.

Chesterton, L. S., Sim, J., Wright, C. C., & Foster, N. E. (2007). *Interrater Reliability of Algometry in Measuring Pressure Pain Thresholds in Healthy Humans, Using Multiple Raters*.

Cheung, S. S. (2015). Responses of the hands and feet to cold exposure. *Temperature*, *2*(1), 105–120

Chlebicka, I., Matusiak, Ł., Maj, J., Baran, E., & Szepietowskiki, J. C. (2013). Freezing fingers syndrome, primary and secondary raynaud's phenomenon: Characteristic features with hand thermography. *Acta Dermato-Venereologica*, *93*(4), 428–432.

Chung, L., Shapiro, L., Fiorentino, D., Baron, M., Shanahan, J., Sule, S., … Wigley, F. M. (2009). MQX-503, a novel formulation of nitroglycerin, improves the severity of Raynaud's phenomenon: a randomized, controlled trial. *Arthritis and Rheumatism*, *60*(3), 870–877

Covic, T., Adamson, B., Spencer, D., & Howe, G. (2003). A biopsychosocial model of pain and depression in rheumatoid arthritis: a 12-month longitudinal study. *Rheumatology (Oxford, England)*, *42*(11), 1287–1294.

D'Eon, J. L., Harris, C. A., & Ellis, J. A. (2004). Testing factorial validity and gender invariance of the pain catastrophizing scale. *Journal of Behavioral Medicine*, *27*(4), 361–372.

Day, M. A., & Thorn, B. E. (2010). The relationship of demographic and psychosocial variables to pain-related outcomes in a rural chronic pain population. *Pain*, *151*(2), 467–474.

De Angelis, R., Salaffi, F., & Grassi, W. (2008). Health-related quality of life in primary raynaud phenomenon. *Journal of Clinical Rheumatology*, *14*(4), 206–210.

de Morree, H. M., Szabó, B. M., Rutten, G.-J., & Kop, W. J. (2013). Central nervous system involvement in the autonomic responses to psychological distress. *Netherlands Heart Journal : Monthly Journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation*, *21*(2), 64–69.

Denton, C. P., Hachulla, É., Riemekasten, G., Schwarting, A., Frenoux, J. M., Frey, A., … Herrick, A. L. (2017). Efficacy and Safety of Selexipag in Adults With Raynaud's Phenomenon Secondary to Systemic Sclerosis: A Randomized, Placebo-Controlled, Phase II Study. *Arthritis and Rheumatology*, *69*(12), 2370–2379.

Devulder, J., van Suijlekom, H., Van Dongen, R., Diwan, S., Mekhail, N., van Kleef, M., & Huygen, F. J. P. M. (2011). Ischemic Pain in the Extremities and Raynaud's Phenomenon. In *Evidence-Based Interventional Pain Medicine: According to Clinical Diagnoses* (pp. 196–201). Wiley-Blackwell.

Edwards, R. R., Bingham, C. O., Bathon, J., & Haythornthwaite, J. A. (2006, April 15). Catastrophizing and pain in arthritis, fibromyalgia, and other rheumatic diseases. *Arthritis Care and Research*.

Edwards, R. R., Cahalan, C., Mensing, G., Smith, M., Haythornthwaite, J. A., & Haythornthwaite, J. A. (2011). Pain, catastrophizing, and depression in the rheumatic diseases. *Nature Reviews Rheumatology*, *7*(4), 216–224.

Edwards, R. R., Fillingim, R. B., Maixner, W., Sigurdsson, A., & Haythornthwaite, J. (2004). Catastrophizing predicts changes in thermal pain responses after resolution of acute dental pain. *Journal of Pain*, *5*(3), 164–170.

Engstrand, C., Krevers, B., & Kvist, J. (2012). Interrater reliability in finger joint goniometer measurement in Dupuytren's disease. *American Journal of Occupational Therapy*, *66*(1), 98–103.

Ennis, H., Hughes, M., Anderson, M. E., Wilkinson, J., & Herrick, A. L. (2016). Calcium channel blockers for primary Raynaud's phenomenon. *Cochrane Database of Systematic Reviews*, *2*, CD002069. https://doi.org/10.1002/14651858.CD002069.pub5

Evers, A. W. M., Kraaimaat, F. W., Geenen, R., Jacobs, J. W. G., & Bijlsma, J. W. J. (2003). Stress-vulnerability factors as long-term predictors of disease activity in early rheumatoid arthritis. *Journal of Psychosomatic Research*, *55*(4), 293–302.

Fernández-Lao, C., Cantarero-Villanueva, I., Fernández-De-Las-Peñas, C., Del-Moral-Ávila, R., Menjón-Beltrán, S., & Arroyo-Morales, M. (2011). Widespread Mechanical Pain Hypersensitivity as a Sign of Central Sensitization after Breast Cancer Surgery: Comparison between Mastectomy and Lumpectomy. *Pain Medicine*, *12*(1), 72–78.

Flavahan, N. A. (2008). Regulation of Vascular Reactivity in Scleroderma: New Insights into Raynaud's Phenomenon. *Rheumatic Disease Clinics of North America*, *34*(1), 81–87.

Flavahan, N. A. (2015). A vascular mechanistic approach to understanding Raynaud phenomenon. *Nature Reviews. Rheumatology*, *11*(3), 146–158.

Foerster, J., Fleischanderl, S., Wittstock, S., Storch, A., Meffert, H., Riemekasten, G., & Worm, M. (2005, December). Infrared-mediated hyperthermia is effective in the treatment of scleroderma-associated Raynaud's phenomenon. *Journal of Investigative Dermatology*. https://doi.org/10.1111/j.0022-202X.2005.23938.x

Fraenkel, L. (2002). Raynaud's Phenomenon: Epidemiology and Risk Factors. *Current Rheumatology Reports*, *4*, 123–128.

Fraenkel, L., Zhang, Y., Chaisson, C. E., Evans, S. R., Wilson, P. W. F., & Felson, D. T. (1998). The association of estrogen replacement therapy and the Raynaud phenomenon in postmenopausal women. *Annals of Internal Medicine*, *129*(3), 208–211.

Fraenkel, L., Zhang, Y., Chaisson, C. E., Maricq, H. R., Evans, S. R., Brand, F., … Felson, D. T. (1999). Different factors influencing the expression of raynaud's phenomenon in men and women. *Arthritis and Rheumatism*, *42*(2), 306–310.

France, C. R., France, J. L., al'Absi, M., Ring, C., & McIntyre, D. (2002). Catastrophizing is related to pain ratings, but not nociceptive flexion reflex threshold. *Pain*, *99*(3), 459–463.

Freedman, R. R., Moten, M., Migály, P., & Mayes, M. (1993). Cold-induced potentiation of alpha 2-adrenergic vasoconstriction in primary Raynaud's disease. *Arthritis and Rheumatism*, *36*(5), 685–690.

Gaillard-Bigot, F., Roustit, M., Blaise, S., Gabin, M., Cracowski, C., Seinturier, C., … Cracowski, J. L. (2014). Abnormal amplitude and kinetics of digital postocclusive reactive hyperemia in systemic sclerosis. *Microvascular Research*, *94*, 90–95.

Gallagher, E. J., Liebman, M., & Bijur, P. E. (2001). Prospective validation of clinically important changes in pain severity measured on a visual analog scale. *Annals of Emergency Medicine*, *38*(6), 633–638.

García-Carrasco, M., Jiménez-Hernández, M., Escárcega, R. O., Mendoza-Pinto, C., Pardo-Santos, R., Levy, R., … Cervera, R. (2008). Treatment of Raynaud's phenomenon. *Autoimmunity Reviews*, *8*(1), 62–68.

García Campayo, J., Rodero, B., Alda, M., Sobradiel, N., Montero, J., & Moreno, S. (2008). Validación de la versión española de la escala de la catastrofización ante el dolor (Pain Catastrophizing Scale) en la fibromialgia. *Medicina Clinica*, *131*(13), 487–492.

García de la Peña Lefebvre, P., Nishishinya, M. B., Pereda, C. A., Loza, E., Sifuentes Giraldo, W. A., Román Ivorra, J. A., … Muñoz-Fernández, S. (2015). Efficacy of Raynaud's phenomenon and digital ulcer pharmacological treatment in systemic sclerosis patients: a systematic literature review. *Rheumatology International*, *35*(9), 1447–1459.

Garner, R., Kumari, R., Lanyon, P., Doherty, M., & Zhang, W. (2015). Prevalence, risk factors and associations of primary Raynaud's phenomenon: Systematic review and meta-analysis of observational studies. *BMJ Open*, *5*(3), e006389. https://doi.org/10.1136/bmjopen-2014-006389

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: Scientific advances and future directions. *Psychological Bulletin*, *133*(4), 581–624.

Geisser, M. E., Casey, K. L., Brucksch, C. B., Ribbens, C. M., Appleton, B. B., & Crofford, L. J. (2003). Perception of noxious and innocuous heat stimulation among healthy women and women with fibromyalgia: association with mood, somatic focus, and catastrophizing. *Pain*, *102*(3), 243–250.

Geisser, M. E., Robinson, M. E., & Pickren, W. E. (1992). Differences in cognitive coping strategies among pain-sensitive and pain-tolerant individuals on the cold-pressor test. *Behavior Therapy*, *23*(1), 31–41.

Giardino, N. D., Jensen, M. P., Turner, J. A., Ehde, D. M., & Cardenas, D. D. (2003). Social environment moderates the association between catastrophizing and pain among persons with a spinal cord injury. *Pain*, *106*(1–2), 19–25.

Giurgea, G. A., Mlekusch, W., Charwat-Resl, S., Mueller, M., Hammer, A., Gschwandtner, M. E., … Schlager, O. (2015). Brief report: Relationship of age and body mass index to skin temperature and skin perfusion in primary Raynaud's phenomenon. *Arthritis and Rheumatology*, *67*(1), 238–242.

Goldberg, D. S., & McGee, S. J. (2011). Pain as a global public health priority. *BMC Public Health*, *11*(1), 770. https://doi.org/10.1186/1471-2458-11-770

Gollins, C., Carpenter, A., Steen, C., Bulinski, H., & Mahendran, R. (2019). A Retrospective Analysis of the use of Tap Water Iontophoresis for Focal Hyperhidrosis at a District General Hospital: The Patients' Perspective. *Journal of Dermatological Treatment*, 1–9.

Goodfield, M. J. D., & Rowell, N. R. (1988). Hand warming as a treatment for Raynaud's phenomenon in systemic sclerosis. *British Journal of Dermatology*, *119*(5), 643–646.

Goundry, B., Bell, L., Langtree, M., & Moorthy, A. (2012, February 11). Diagnosis and management of Raynaud's phenomenon. *BMJ (Online)*. https://doi.org/10.1136/bmj.e289

Grossi, G., Mariotti, A., Di Donato, L., Amerio, P., Tulli, A., Romani, G. L., & Merla, A. (2010). Functional infrared imaging of paroxysmal ischemic events in patients with Raynaud's phenomenon. *International Journal of Immunopathology and Pharmacology*, *23*(2), 627–632.

Gummesson, C., Ward, M. M., & Atroshi, I. (2006). The shortened disabilities of the arm, shoulder and hand questionnaire (QuickDASH): Validity and reliability based on responses within the full-length DASH. *BMC Musculoskeletal Disorders*, *7*. https://doi.org/10.1186/1471-2474-7-44

Heidrich, Helmis, Fahrig, Hövelmann, & Martini. (2008). Clinical characteristics of primary, secondary and suspected secondary Raynaud's syndrome and diagnostic transition in the long-term follow-up. A retrospective study in 900 patients. *Vasa*, *37*(Supplement 73), 3–25.

Herrick, A. L. (2005). Pathogenesis of Raynaud's phenomenon. *Rheumatology*, *44*(5), 587–596.

Herrick, Ariane L. (2016). Recent advances in the pathogenesis and management of Raynaud's phenomenon and digital ulcers. *Current Opinion in Rheumatology*.

Lippincott Williams and Wilkins. https://doi.org/10.1097/BOR.0000000000000332

Herrick, Ariane L. (2017). Therapeutic implications from the pathogenesis of Raynaud's phenomenon. *Expert Review of Clinical Immunology*. Taylor and Francis Ltd. https://doi.org/10.1080/1744666X.2017.1279052

Herrick, Ariane L., & Murray, A. (2018). The role of capillaroscopy and thermography in the assessment and management of Raynaud's phenomenon. *Autoimmunity Reviews*. Elsevier B.V. https://doi.org/10.1016/j.autrev.2017.11.036

Herrick, Ariane L, van den Hoogen, F., Gabrielli, A., Tamimi, N., Reid, C., O'Connell, D., … Denton, C. P. (2011). Modified-release sildenafil reduces Raynaud's phenomenon attack frequency in limited cutaneous systemic sclerosis. *Arthritis and Rheumatism*, *63*(3), 775–782.

Hervás, M. T., José, M., Collado, N., Peiró, S., Luis, J., Pérez, R., … Tello, I. M. (2006). *Versión española del cuestionario DASH. Adaptación transcultural, fiabilidad, validez y sensibilidad a los cambios*. *Med Clin (Barc)* (Vol. 127).

Hirschl, M., Hirschl, K., Lenz, M., Katzenschlager, R., Hutter, H. P., & Kundi, M. (2006). Transition from primary Raynaud's phenomenon to secondary Raynaud's phenomenon identified by diagnosis of an associated disease: Results of ten years of prospective surveillance. *Arthritis and Rheumatism*, *54*(6), 1974–1981.

Hirschl, M., Katzenschlager, R., Francesconi, C., & Kundi, M. (2004). Low level laser therapy in primary Raynaud's phenomenon - Results of a placebo controlled, double blind intervention study. *Journal of Rheumatology*, *31*(12), 2408–2412.

Hughes, M., & Herrick, A. L. (2016). Raynaud's phenomenon. *Best Practice & Research Clinical Rheumatology*, *30*(1), 112–132.

Hughes, M., Snapir, A., Wilkinson, J., Snapir, D., Wigley, F. M., & Herrick, A. L. (2015). Prediction and impact of attacks of Raynaud'S phenomenon, as judged by patient perception. *Rheumatology (United Kingdom)*, *54*(8), 1443–1447.

Ingegnoli, F., Schioppo, T., Allanore, Y., Caporali, R., Colaci, M., Distler, O., … Matucci-Cerinic, M. (2019b). Practical suggestions on intravenous iloprost in Raynaud's phenomenon and digital ulcer secondary to systemic sclerosis: Systematic literature review and expert consensus. *Seminars in Arthritis and Rheumatism*, *48*(4), 686–693.

Ismail, E., Orlando, G., Corradini, M. L., Amerio, P., Romani, G. L., & Merla, A. (2014a). Differential diagnosis of Raynaud's phenomenon based on modeling of finger thermoregulation. *Physiological Measurement*, *35*(4), 703–716.

Käll, L. B., Kowalski, J., & Stener-Victorin, E. (2008). Assessing pain perception using the Painmatcher® in patients with whiplash-associated disorders. *Journal of Rehabilitation Medicine*, *40*(3), 171–177.

Keil, J. E., Maricq, H. R., Weinrich, M. C., McGregor, A. R., & Diat, F. (1991). Demographic, social and clinical correlates of Raynaud phenomenon. *International Journal of Epidemiology*, *20*(1), 221–224.

Kindler, L. L., Bennett, R. M., & Jones, K. D. (2011, March). Central Sensitivity Syndromes: Mounting Pathophysiologic Evidence to Link Fibromyalgia with Other Common Chronic Pain Disorders. *Pain Management Nursing*.

Ko, G., & Berbrayer, D. (2002). Raynaud ' s Syndrome Effect of Ceramic-Impregnated " Thermoflow " Gloves on Patients with Raynaud ' s Syndrome : *Alternative Medicine Review*, *7*(4), 328–335.

Kogler, L., Müller, V. I., Chang, A., Eickhoff, S. B., Fox, P. T., Gur, R. C., & Derntl, B. (2015). Psychosocial versus physiological stress — Meta-analyses on deactivations and activations of the neural correlates of stress reactions. *NeuroImage*, *119*, 235–251.

Kolkhorst, F. W., DiPasquale, D. M., & Buono, M. J. (2002). Effect of tap-water iontophoresis on sweat gland recruitment, skin temperature and skin blood flow. *Journal of Dermatological Science*, *28*(2), 97–101.

Landim, S. F., Bertolo, M. B., Marcatto de Abreu, M. F., Del Rio, A. P., Mazon, C. C., Marques-Neto, J. F., … de Paiva Magalhães, E. (2017). The evaluation of a home-based program for hands in patients with systemic sclerosis. *Journal of Hand Therapy*. https://doi.org/10.1016/j.jht.2017.10.013

Le, J. H., & Cho, K. I. (2014). Association between endothelial function and microvascular changes in patients with secondary Raynaud's phenomenon. *Clinical Rheumatology*, *33*(11), 1627–1633.

Lefebvre, J. C., & Keefe, F. J. (n.d.). Memory for pain: the relationship of pain catastrophizing to the recall of daily rheumatoid arthritis pain. *The Clinical Journal of Pain*, *18*(1), 56–63.

LeRoy, E C; Medsger, T. A. (1992). Raynaud's phenomenon: a proposal for classification. *Clinical and Experimental Rheumatology*, *10*(5), 485–488.

Lim, M. J., Kwon, S. R., Jung, K. H., Joo, K., Park, S. G., & Park, W. (2014). Digital thermography of the fingers and toes in Raynaud's phenomenon. *Journal of Korean Medical Science*, *29*(4), 502–506.

Ling, S. M., & Wigley, F. M. (1999). Raynaud's phenomenon in older adults. Diagnostic considerations and management. *Drugs and Aging*. Springer Nature. https://doi.org/10.2165/00002512-199915030-00002

Linnemann, B., & Erbe, M. (2015). Raynaud's phenomenon - assessment and differential diagnoses. *Vasa*, *44*(3), 0166–0177.

Linnemann, B., & Erbe, M. (2016). Raynaud's phenomenon and digital ischaemia - pharmacologic approach and alternative treatment options. *Vasa*, *45*(3), 201–212.

Linton, S. J. (2000). A review of psychological risk factors in back and neck pain. *Spine*, *25*(9), 1148–1156.

Lund, I., Lundeberg, T., Kowalski, J., Sandberg, L., Budh, C. N., & Svensson, E. (2005). Evaluation of variations in sensory and pain threshold assessments by electrocutaneous stimulation. *Physiotherapy Theory and Practice*, *21*(2), 81–92.

MacDermid, J. C., Evenhuis, W., & Louzon, M. (2001). Inter-instrument reliability of pinch strength scores. *Journal of Hand Therapy*, *14*(1), 36–42.

Maga, P., Henry, B. M., Kmiotek, E. K., Gregorczyk-Maga, I., Kaczmarczyk, P., Tomaszewski, K. A., & Niżankowski, R. (2016). Postocclusive Hyperemia Measured with Laser Doppler Flowmetry and Transcutaneous Oxygen Tension in the Diagnosis of Primary Raynaud's Phenomenon: A Prospective, Controlled Study. *BioMed Research International*, *2016*, 1–9.

Mason, H. J., Poole, K., & Elms, J. (2005). Upper limb disability in HAVS cases - How does it relate to the neurosensory or vascular elements of HAVS? *Occupational Medicine*, *55*(5), 389–392.

Mathiowetz, V., Weber, K., Volland, G., & Kashman, N. (1984). Reliability and validity of grip and pinch strength evaluations. *Journal of Hand Surgery*, *9*(2), 222–226.

Maverakis, E., Patel, F., Kronenberg, D. G., Chung, L., Fiorentino, D., Allanore, Y., … Gershwin, M. E. (2014). International consensus criteria for the diagnosis of Raynaud's phenomenon. *Journal of Autoimmunity*, *48–49*, 60–65.

Mayer, T. G., Neblett, R., Cohen, H., Howard, K. J., Choi, Y. H., Williams, M. J., … Gatchel, R. J. (2012). The Development and Psychometric Validation of the Central Sensitization Inventory. *Pain Practice*, *12*(4), 276–285.

Mercader, P., Rodríguez-Serna, M., De Andrés, J., García-Covisa, N., Valia, J. C., & Fortea, J. M. (2003). Tratamiento del fenómeno de Raynaud mediante electroestimulación medular. *Actas Dermo-Sifiliograficas*, *94*(7), 450–453.

Merkel, P. A., Herlyn, K., Martin, R. W., Anderson, J. J., Mayes, M. D., Bell, P., … Wigley, F. M. (2002). Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. *Arthritis and Rheumatism*, *46*(9), 2410–2420.

Mirbod, S. M., & Sugiura, H. (2017). A non-invasive technique for the evaluation of peripheral circulatory functions in female subjects with Raynaud's phenomenon. *Industrial Health*, *55*(3), 275–284.

Munir, S., Freidin, M. B., Brain, S., & Williams, F. M. K. (2018). Association of raynaud's phenomenon with a polymorphism in the NOS1 gene. *PLoS ONE*, *13*(4). https://doi.org/10.1371/journal.pone.0196279

Münster, T., Tiebel, N., Seyer, H., & Maihöfner, C. (2012). Modulation of Somatosensory Profiles by Spinal Cord Stimulation in Primary Raynaud's Syndrome. *Pain Practice*, *12*(6), 469–475.

Murray, A K, Moore, T. L., King, T. A., & Herrick, A. L. (2008). Vasodilator iontophoresis a possible new therapy for digital ischaemia in systemic sclerosis? *Rheumatology (Oxford, England)*, *47*(1), 76–79.

Murray, Andrea K., Herrick, A. L., Gorodkin, R. E., Moore, T. L., & King, T. A. (2005). Possible therapeutic use of vasodilator iontophoresis. *Microvascular Research*, *69*(1–2), 89–94.

Nagai, M., Hoshide, S., & Kario, K. (2010). The insular cortex and cardiovascular system: a new insight into the brain-heart axis. *Journal of the American Society of Hypertension*, *4*(4), 174–182.

Neblett, R., Cohen, H., Choi, Y., Hartzell, M. M., Williams, M., Mayer, T. G., & Gatchel, R. J. (2013). The central sensitization inventory (CSI): Establishing clinically significant values for identifying central sensitivity syndromes in an outpatient chronic pain sample. *Journal of Pain*, *14*(5), 438–445. 2

Neblett, R., Hartzell, M. M., Mayer, T. G., Cohen, H., & Gatchel, R. J. (2017). Establishing Clinically Relevant Severity Levels for the Central Sensitization Inventory. *Pain Practice*, *17*(2), 166–175.

Nguyen, C., Poiraudeau, S., Mestre-Stanislas, C., Rannou, F., Bérezné, A., Papelard, A., … Mouthon, L. (2010). Employment status and socio-economic burden in systemic sclerosis: a cross-sectional survey. *Rheumatology (Oxford, England)*, *49*(5), 982–989.

Nijs, J., Malfliet, A., Ickmans, K., Baert, I., & Meeus, M. (2014). Treatment of central sensitization in patients with "unexplained" chronic pain: an update. *Expert Opinion on Pharmacotherapy*, *15*(12), 1671–1683.

Nijs, J., Paul van Wilgen, C., Van Oosterwijck, J., van Ittersum, M., & Meeus, M. (2011). How to explain central sensitization to patients with "unexplained" chronic musculoskeletal pain: Practice guidelines. *Manual Therapy*, *16*(5), 413–418.

Nijs, J., & Van Houdenhove, B. (2009). From acute musculoskeletal pain to chronic widespread pain and fibromyalgia: Application of pain neurophysiology in manual therapy practice. *Manual Therapy*, *14*(1), 3–12.

Nijs, J., Van Houdenhove, B., & Oostendorp, R. A. B. (2010). Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice. *Manual Therapy*, *15*(2), 135–141.

Nuzzaci, G., Pesciullesi, E., Lucarelli, F., Lucente, E., Ferri, P., Tonarelli, A. P., … Mangoni, N. (1988). Arteriovenous anastomoses' function and Raynaud's phenomenon. *Angiology*, *39*(9), 812–818.

Palmer, K. T., Griffin, M. J., Syddall, H., Cooper, C., & Coggon, D. (2002). The clinical grading of Raynaud's phenomenon and vibration-induced white finger: relationship between finger blanching and difficulties in using the upper limb. *Int Arch Occup Environ Health*, *75*(1–2), 29–36.

Pavlov-Dolijanovic, S., Damjanov, N. S., Vujasinovic Stupar, N. Z., Radunovic, G. L., Stojanovic, R. M., & Babic, D. (2013). Late appearance and exacerbation of primary Raynaud's phenomenon attacks can predict future development of connective tissue disease: a retrospective chart review of 3,035 patients. *Rheumatology International*, *33*(4), 921–926.

Pérez-Mármol, J. M., García-Ríos, M. C., Ortega-Valdivieso, M. A., Cano-Deltell, E. E., Peralta-Ramírez, M. I., Ickmans, K., & Aguilar-Ferrándiz, M. E. (2017). Effectiveness of a fine motor skills rehabilitation program on upper limb disability, manual dexterity, pinch strength, range of fingers motion, performance in activities of daily living, functional independency, and general self-efficacy in hand osteoarthritis: A randomized clinical trial. *Journal of Hand Therapy*, *30*(3), 262–273.

Pérez-Mármol, J. M., Ortega-Valdivieso, M. A., Cano-Deltell, E. E., Peralta-Ramírez, M. I., García-Ríos, M. C., & Aguilar-Ferrándiz, M. E. (2016). Influence of upper limb disability, manual dexterity and fine motor skill on general self-efficacy in institutionalized elderly with osteoarthritis. *Journal of Hand Therapy*, *29*(1), 58–65.

Perrot, S., Dieudé, P., Pérocheau, D., & Allanore, Y. (2013). Comparison of pain, pain burden, coping strategies, and attitudes between patients with systemic sclerosis and patients with rheumatoid arthritis: a cross-sectional study. *Pain Medicine (Malden, Mass.)*, *14*(11), 1776–1785.

Peters, M. L., Vlaeyen, J. W., & van Drunen, C. (2000). Do fibromyalgia patients display hypervigilance for innocuous somatosensory stimuli? Application of a body scanning reaction time paradigm. *Pain*, *86*(3), 283–292.

Picavet, H. S. J., Vlaeyen, J. W. S., & Schouten, J. S. A. G. (2002). Pain catastrophizing and kinesiophobia: predictors of chronic low back pain. *American Journal of Epidemiology*, *156*(11), 1028–1034.

Plana, M. N., Zamora, J., Suresh, G., Fernandez-Pineda, L., Thangaratinam, S., & Ewer, A. K. (2015). Diagnostic accuracy of pulse oximetry screening for critical congenital heart defects. *Cochrane Database of Systematic Reviews*, *2015*(10). https://doi.org/10.1002/14651858.CD011912

Porter, J. M., Rivers, S. P., Anderson, C. J., & Baur, G. M. (1981). Evaluation and management of patients with Raynaud's syndrome. *The American Journal of Surgery*, *142*(2), 183–189.

Prete, M., Fatone, M. C., Favoino, E., & Perosa, F. (2014). Raynaud's phenomenon: From molecular pathogenesis to therapy. *Autoimmunity Reviews*. Elsevier.

Quartana, P. J., Campbell, C. M., & Edwards, R. R. (2009). Pain catastrophizing: a critical review. *Expert Review of Neurotherapeutics*, *9*(5), 745–758.

Ramos-Casals, M., Brito-Zerón, P., Seror, R., Bootsma, H., Bowman, S. J., Dörner, T., … Vitali, C. (2015). Characterization of systemic disease in primary Sjögren's syndrome: EULAR-SS Task Force recommendations for articular, cutaneous, pulmonary and renal involvements. *Rheumatology (United Kingdom)*, *54*(12), 2230–2238.

Reilly, D. O., Taylor, L., El-Hadidy, K., & Jayson, M. I. V. (1992). Measurement of cold challenge responses in primary Raynaud's phenomenon and Raynaud's phenomenon associated with systemic sclerosis. *Annals of the Rheumatic Diseases*, *51*(11), 1193–1196.

Report, A. C. (2007). A Case of Spinal Cord Stimulation in Raynaud's Phenomenon: Can Subthreshold Sensory Stimulation Have an Effect?, (3), 473–478.

Rirash, F., Tingey, P. C., Harding, S. E., Maxwell, L. J., Tanjong Ghogomu, E., Wells, G. A., … Pope, J. (2017, December 13). Calcium channel blockers for primary and secondary Raynaud's phenomenon. *Cochrane Database of Systematic Reviews*. John Wiley and Sons Ltd. https://doi.org/10.1002/14651858.CD000467.pub2

Rodríguez Martín, J. M. (2014). *Electroterapia en fisioterapia*. Editorial Médica Panamericana.

Roelofs, J., Peters, M. L., McCracken, L., & Vlaeyen, J. W. S. (2003). The pain vigilance and awareness questionnaire (PVAQ): further psychometric evaluation in fibromyalgia and other chronic pain syndromes. *Pain*, *101*(3), 299–306.

Roh, Y. H., Noh, J. H., Gong, H. S., Baek, G. H., Roh, Y H, Noh, J H, … Joint, B. (2017). Comparative study on the effectiveness of a corticosteroid injection for carpal tunnel syndrome in patients with and without Raynaud's phenomenon, *99*(12).

Román Ivorra, J. A., Gonzálvez Perales, J. L., Fernández Carballido, C., Graña, J., & Torres, M. J. (2001). Prevalence of Raynaud's phenomenon in general practice in the East of Spain. *Clinical Rheumatology*, *20*(2), 88–90.

Roustit, M., Gaillard-Bigot, F., Blaise, S., Stanke-Labesque, F., Cracowski, C., Seinturier, C., … Cracowski, J. L. (2014). Cutaneous iontophoresis of treprostinil in systemic sclerosis: A proof-of-concept study. *Clinical Pharmacology and Therapeutics*, *95*(4), 439–445.

Roustit, Matthieu, Blaise, S., Allanore, Y., Carpentier, P. H., Caglayan, E., & Cracowski, J.-L. (2013). Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomised trials. *Annals of the Rheumatic Diseases*, *72*(10), 1696–1699.

Roustit, Matthieu, Blaise, S., Millet, C., & Cracowski, J.-L. (2011). Impaired transient vasodilation and increased vasoconstriction to digital local cooling in primary Raynaud's phenomenon. *American Journal of Physiology-Heart and Circulatory Physiology*, *301*(2), H324–H330.

Rychlik-Golema, W., Mastej, K., & Adamiec, R. (2006). The role of endothelin-1 and selected cytokines in the pathogenesis of Raynaud's phenomenon associated with systemic connective tissue diseases. *International Angiology : A Journal of the International Union of Angiology*, *25*(2), 221–227.

Saki, N., Hosseinpoor, S., Heiran, A., Mohammadi, A., & Zeraatpishe, M. (2018). Comparing the Efficacy of Triamcinolone Acetonide Iontophoresis versus Topical Calcipotriol/Betamethasone Dipropionate in Treating Nail Psoriasis: A Bilateral Controlled Clinical Trial. *Dermatology Research and Practice*, *2018*, 1–7.

Sandqvist, G., Hesselstrand, R., & Eberhardt, K. (2009). A longitudinal follow-up of hand involvement and activities of daily living in early systemic sclerosis. *Scandinavian Journal of Rheumatology*, *38*(4), 304–310.

Sandqvist, G., Wollmer, P., Scheja, A., Wildt, M., & Hesselstrand, R. (2018). Raynaud's phenomenon and its impact on activities in daily life during one year of follow-up in early systemic sclerosis. *Scandinavian Journal of Rheumatology*, *47*(3), 206–209.

Schlager, O., Gschwandtner, M. E., Herberg, K., Frohner, T., Schillinger, M., Koppensteiner, R., & Mlekusch, W. (2010). Correlation of infrared thermography and skin perfusion in Raynaud patients and in healthy controls. *Microvascular Research*, *80*(1), 54–57.

Shah, A. A., Schiopu, E., Hummers, L. K., Wade, M., Phillips, K., Anderson, C., … Rollins, K. D. (2013). Open label study of escalating doses of oral treprostinil diethanolamine in patients with systemic sclerosis and digital ischemia: pharmacokinetics and correlation with digital perfusion. *Arthritis Research & Therapy*, *15*(2), 40-54.

Shah, A., Chen, C., Campanella, C., Kasher, N., Evans, S., Reiff, C., … Bremner, J. D. (2019). Brain correlates of stress-induced peripheral vasoconstriction in patients with cardiovascular disease. *Psychophysiology*, *56*(2). https://doi.org/10.1111/psyp.13291

Shenoy, P. D., Kumar, S., Jha, L. K., Choudhary, S. K., Singh, U., Misra, R., & Agarwal, V. (2010). Efficacy of tadalafil in secondary Raynaud's phenomenon resistant to vasodilator therapy: A double-blind randomized cross-over trial. *Rheumatology*, *49*(12), 2420–2428.

Sloan, J. B., & Soltani, K. (1986). Iontophoresis in dermatology: A review. *Journal of the American Academy of Dermatology*, *15*(4), 671–684.

Stewart, M., & Morling, J. R. (2012). Oral vasodilators for primary Raynaud's phenomenon. *Cochrane Database of Systematic Reviews*, (7), CD006687. https://doi.org/10.1002/14651858.CD006687.pub3

Stoyneva, Z. (2004). Laser Doppler-recorded venoarteriolar reflex in Raynaud's phenomenon. *Autonomic Neuroscience : Basic & Clinical*, *116*(1–2), 62–68.

Stringer, T., & Femia, A. N. (2018). Raynaud's phenomenon: Current concepts. *Clinics in Dermatology*, *36*(4), 498–507.

Sullivan, M. J. L., Bishop, S. R., & Pivik, J. (1995). *The Pain Catastrophizing Scale: Development and Validation*. *Psychological Assessment* (Vol. 7).

Sullivan, M. J., Rodgers, W. M., & Kirsch, I. (2001). Catastrophizing, depression and expectancies for pain and emotional distress. *Pain*, *91*(1–2), 147–154.

Sunderkötter, C, & Riemekasten, G. (2006). Pathophysiology and clinical consequences of Raynaud's phenomenon related to systemic sclerosis. *Rheumatology (Oxford, England)*, *45(3)*33-35.

Taniguchi, K., Miyagawa, A., Mizutani, A., Honda, N., & Oyama, T. (1995). The effect of calcium channel antagonist administered by iontophoresis on the pain threshold. *Acta Anaesthesiologica Belgica*, *46*(2), 69–73.

Thastum, M, Zachariae, R., Schøler, M., Bjerring, P., & Herlin, T. (1997). Cold pressor pain: comparing responses of juvenile arthritis patients and their parents. *Scandinavian Journal of Rheumatology*, *26*(4), 272–279.

Thastum, Mikael, Herlin, T., & Zachariae, R. (2005). Relationship of pain-coping strategies and pain-specific beliefs to pain experience in children with juvenile idiopathic arthritis. *Arthritis & Rheumatism*, *53*(2), 178–184.

Thorn, B. E., Keefe, F. J., & Anderson, T. (2004). The communal coping model and interpersonal context: problems or process? *Pain*, *110*(3), 505–507.

Toprak, U., Selvi, N. A., Ateş, A., Erhuner, Z., Bostanoğlu, S., Karademir, M. A., & Karaaslan, Y. (2009). Dynamic Doppler evaluation of the hand arteries of the patients with Raynaud's disease. *Clinical Rheumatology*, *28*(6), 679–683.

Treede, R. D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., … Wang, S. J. (2019, January 1). Chronic pain as a symptom or a disease: The IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain*. Lippincott Williams and Wilkins. https://doi.org/10.1097/j.pain.0000000000001384

Uppal, L., Dhaliwal, K., & Butler, P. E. (2014). A prospective study of the use of botulinum toxin injections in the treatment of Raynaud's syndrome associated with scleroderma. *Journal of Hand Surgery: European Volume*, *39*(8), 876–880.

Viane, I., Crombez, G., Eccleston, C., Poppe, C., Devulder, J., Van Houdenhove, B., & De Corte, W. (2003). Acceptance of pain is an independent predictor of mental well-being in patients with chronic pain: empirical evidence and reappraisal. *Pain*, *106*(1–2), 65–72.

Walløe, L. (2016). Arterio-venous anastomoses in the human skin and their role in temperature control. *Temperature*, *3*(1), 92–103.

Watson, T. (2009). *Electroterapia : práctica basada en la evidencia*. Elsevier.

Wechter, T., Feldman, S. R., & Taylor, S. L. (2019). The Treatment of Primary Focal Hyperhidrosis. *Skin Therapy Letter*, *24*(1), 1–7.

Wideman, T. H., & Sullivan, M. J. L. (2011). Differential predictors of the long-term levels of pain intensity, work disability, healthcare use, and medication use in a sample of workers' compensation claimants. *Pain*, *152*(2), 376–383.

Wigley, F. M., & Flavahan, N. A. (2016). Raynaud's Phenomenon. *New England Journal of Medicine*, *375*(6), 556–565.

Wolter, T., & Kieselbach, K. (2011). Spinal cord stimulation for Raynaud's syndrome: Long-term alleviation of bilateral pain with a single cervical lead. *Neuromodulation*, *14*(3), 229–232.

Woolf, C. J. (2011, March). Central sensitization: Implications for the diagnosis and treatment of pain. *Pain*. https://doi.org/10.1016/j.pain.2010.09.030

Yunus, M. B. (2007a). Fibromyalgia and Overlapping Disorders: The Unifying Concept of Central Sensitivity Syndromes. *Seminars in Arthritis and Rheumatism*, *36*(6), 339–356.

Yunus, M. B. (2007b). Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with widespread pain. *Best Practice and Research: Clinical Rheumatology*, *21*(3), 481–497.

Zebryk, P., & Puszczewicz, M. J. (2016, August 1). Botulinum toxin A in the treatment of Raynaud's phenomenon: A systematic review. *Archives of Medical Science*. Termedia Publishing House Ltd. https://doi.org/10.5114/aoms.2015.48152

Zhou, Y., Liu, Y., Hao, Y., Feng, Y., Pan, L., Liu, W., … Nie, Z. (2018). The mechanism of botulinum A on Raynaud syndrome. *Drug Design, Development and Therapy*, *12*, 1905–1915.

APPENDIX 1

Pain Intensity, Pressure Pain Hypersensitivity, Central Sensitization, and Pain Catastrophizing Related to Vascular Alterations in Raynaud's Phenomenon: A Preliminary Case-Control Study.

Pain Medicine, 00(), 2019, 1–11
doi:10.1093/pm/pnz089
Original Research Article

Pain Intensity, Pressure Pain Hypersensitivity, Central Sensitization, and Pain Catastrophizing Related to Vascular Alterations in Raynaud's Phenomenon: A Preliminary Case–Control Study

Rosa María Tapia-Haro, OT, PT,* Rafael Guisado-Barrilao, MD, PhD,† María del Carmen García-Ríos, PT, PhD,‡ Enrique Raya-Álvarez, PhD,*,§ José Manuel Pérez-Mármol, OT, PhD,¶ and María Encarnación Aguilar-Ferrándiz, PT, PhD¶

*Department of Physical Therapy, Faculty of Health Science; †Department of Nursing; ‡Department of Physical Therapy, University of Granada, Granada, Spain; §Rheumatology Division, University Hospital "San Cecilio," Granada, Spain; ¶Instituto de Investigación Biosanitaria Granada, Department of Physical Therapy, Faculty of Health Science, University of Granada, Granada, Spain

Correspondence to: María Encarnación Aguilar-Ferrándiz, PT, PhD, Physical Therapy, University of Granada, Spain. Tel: 0034-953989166; Fax: 0034-950214384; E-mail: encaguilar@hotmail.com.

Funding sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest: The authors have declared no conflicts of interest.

Abstract

Objective. To evaluate pain intensity, widespread pressure pain, central sensitization (CS), and catastrophizing between subjects with primary and secondary Raynaud's phenomenon (RP) and healthy controls and to compare the relationships between vascular impairment and pain perception. **Methods.** A preliminary case–control study was performed with a total sample of 57 participants (37 with RP). Sociodemographic data, clinical/vascular data, and pain variables (pain intensity, pressure pain sensitivity, pain magnitude and threshold, CS, and catastrophizing) were registered. Results were analyzed by analysis of covariance and Pearson correlation. **Results.** Participants with RP had a lower basal temperature (more vasoconstriction) in their hands ($P \leq 0.012$), higher pain intensity ($P \leq 0.001$), higher electrical pain magnitude ($P < 0.001$), and lower pressure pain ($P \leq 0.05$) and electrical pain ($P < 0.001$) thresholds in comparison with healthy controls. Secondary RP participants showed a significantly higher level of CS compared with controls and primary RP participants ($P = 0.001$). Catastrophizing was higher in the primary and secondary RP ($P \leq 0.001$) groups than in controls. No correlations were observed between severity of vasoconstriction and pain variables. **Conclusions.** RP participants showed bilateral hypersensitivity to pressure pain. However, the severity of vascular alterations seems not to be related to central pain experiences. Additional mechanisms such as catastrophizing may influence pain in RP; nevertheless, central sensitization only appears to be involved in the secondary form of RP.

Key Words: Peripheral Vascular Diseases; Raynaud Disease; Pain; Central Nervous System Sensitization; Catastrophization

Introduction

Raynaud's phenomenon (RP) is a vascular disorder characterized by sudden, transient, and recurrent episodes of decreased blood flow due to an increased vasospasmic response of the arteries when exposed to a cold environment or stressful situation [1,2]. It typically involves the fingers and toes but can also affect other areas such as the ears or nose [1]. This disease affects 3–5% of the world population, with a higher prevalence in women living in areas with cold climates [3]. The prevalence in the Spanish population ranges between 2.8% and 4.7% [4]. Episodes of changes in skin color develop in three phases: pallor (white), cyanosis (blue), and hyperemia (red). The ischemic process can cause distal pain, burning, numbness and paresthesia, depending on the intensity of the vasospasmic episode [5]. Attacks can last from minutes to hours [6].