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Keywords:	Psoriasis < DERMATOLOGY, nailfold capillaroscopy, capillary pattern, capillary morphology

Evaluation of capillary pathologies by nailfold capillaroscopy in patients with psoriasis vulgaris: Study protocol for a prospective, controlled, clinical trial

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ABSTRACT

Introduction

Psoriasis vulgaris was shown to be an independent factor increasing the risk of several comorbidities such as obesity, diabetes and dyslipidemia with an increased risk of stroke and myocardial infarction. We hypothesize that early endothelial dysfunction, which plays a crucial role in the pathogenesis of atherosclerosis, may be detected by digital video nailfold capillaroscopy (DVNC) at the level of the dermal capillary microvasculature as a surrogate parameter. Nailfolds represent the only body site allowing for a non-invasive assessment of the capillary microvasculature at a horizontal plane. DVNC is a well-established diagnostic tool for in-vivo assessment of the peripheral microcirculation by evaluating the morphology of dermal papillary capillaries. To date, reports on morphological changes of the non-lesional nailfold capillaries in patients with psoriasis vulgaris are scarce and the existing data is not conclusive.

Methods and analysis

This is a prospective, single center, non-randomized, controlled pilot study assessing the capillary patterns in 75 subjects affected by psoriasis vulgaris. Non-lesional nailfold capillaries will be imaged by means of DVNC (Optilia Digital Capillaroscopy System, Optilia Instruments AB, Sollentuna, Sweden) in 50 patients affected by psoriasis vulgaris and 25 healthy controls. Assessments will include a qualitative, descriptive analysis of the nailfold capillaries' morphology, as well as a quantitative investigation (frequency, extent) of changes in capillary patterns. Moreover, patients' characteristics associated with the manifestation of nailfold capillaries' pathologies including well-known cardiovascular risk markers will be studied.

Ethics and dissemination

Ethical approval was provided by the ethic committee of the medical faculty of the University of Heidelberg (Ethics approval number S-447/2017). The design and the final results of the study will be published and made available to the public.

Study registration

This study is registered at the German Clinical Trial Register (DRKS): DRKS00012856

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This pilot study addresses important open questions concerning the use of nailfold capillaroscopy as a surrogate parameter for determining the extent of endothelial dysfunction in psoriasis patients.
- After confirmation by an additional larger clinical trial, non-invasive digital nailfold capillaroscopy in psoriasis patients may help to facilitate the identification of patients at increased risk for development of cardiovascular disease.
- Since this is a pilot study, limitations arise from the single-site setting and the small number of subjects in both groups.

INTRODUCTION

Digital video nailfold capillaroscopy (DVNC) is routinely used for in-vivo assessment of the peripheral microcirculation by evaluating the morphology of dermal papillary capillaries [1]. Long before onset of clinical symptoms pathological capillary patterns may be observed in a number of systemic diseases, which are accompanied by vascular damage. Therefore, DVNC might be helpful to define surrogate parameters indicative of initial manifestation of cardiovascular disease [2]. Additionally, capillary abnormalities were shown to potentially reflect the severity and long-term prognosis of underlying diseases. For instance, in systemic sclerosis an association between a decreased capillary density and the development and the severity of pulmonary arterial hypertension was detected [3]. Psoriasis vulgaris is a common chronic skin disease which is accompanied by a number of comorbidities, that are possibly induced by a chronic, low-grade, systemic inflammation leading to vascular insufficiency and finally to clinically relevant atherosclerosis [2,4,5]. Atherosclerosis in psoriasis patients was shown to be caused by a transfer of inflammatory cells and cytokines from the skin to endothelial tissue and internal organs causing systemic inflammation [2,5,6]. Endothelial dysfunction is often used as a surrogate marker for atherosclerosis and several studies have shown impaired endothelial function in patients with moderate to severe psoriasis or psoriatic arthritis [2,6,7]. Besides broad evidence for an increased risk of large vessel atherosclerosis, previous studies also indicated changes of the microvasculature in the papillary dermis of psoriatic plaques and the synovia of psoriatic joints [8,9]. However, until today only little is known about changes in the microcirculation in non-lesional skin of psoriasis patients. The reported data are controversial with regard to pathologies of nailfold capillaries, which most probably reflects the polyetiology and polymorphology of psoriasis. In one of the earliest studies Redisch et al. revealed tortuous capillaries with tight terminal convolutions in lesional and non-lesional skin of psoriasis patients [10]. A decreased capillary density, shorter

capillaries, more nailfold hemorrhages and sluggish blood flow in patients with psoriasis arthritis were observed by Zaric et al. when compared to healthy controls [11]. A pattern with shorter and more tortuous capillaries was significantly correlated with periungual psoriatic plaques, nail pitting, onycholysis, and the extent of the involved body surface in a study by Ohtsuka et al. [12]. A study by Ribeiro et al. showed a lower capillary density, increased avascular areas and an increased number of coiled capillaries in the nailfold of patients with psoriasis [13]. Finally, Bushan et al. reported a significantly decreased capillary loop density and a reduction of arterial and venous capillary limb diameters but found no other of the previously described morphological abnormalities in any of the patients [14].

The aim of our study is to gather further evidence concerning the morphology, frequency and the extent of nailfold capillary changes in patients with psoriasis vulgaris and to identify patient characteristics possibly associated with specific pathological DVNC patterns.

DESIGN/METHODS

Study design and objectives

This is a prospective, single center, non-randomized, controlled pilot study assessing the capillary patterns in 75 individuals by means of DVNC. The primary objective of this study is to investigate the frequency, the extent, and the morphology of changes in capillary patterns in 50 patients that are either affected by psoriasis vulgaris alone (group A) or by psoriasis vulgaris in combination with accompanying psoriasis arthritis (group B) compared to 25 healthy subjects (group C) (Fig. 1). A secondary objective of this study is to identify patient characteristics that are statistically associated with specific DVNC patterns (e.g. psoriasis severity, nail psoriasis, age, gender, duration of the disease, manifest cardiovascular diseases and circulating markers of endothelial damage and inflammation).

Criteria for inclusion/exclusion

Inclusion criteria for group A and B are: patients ≥18 and ≤ 80 years of age with the diagnosis of chronic moderate to severe plaque psoriasis (defined as involved BSA ≥10% and PASI score ≥ 10 and DLQI ≥ 10) with or without psoriatic arthritis for at least 6 months (duration since diagnosis may be reported by the patient). Exclusion criteria for group A and B are: patients under current exposure to any anti-psoriatic or immunosuppressive systemic therapy (discontinuation for at least 4 weeks prior to DVNC is mandatory), patients with any other skin disease or therapy affecting the area of interest for DVNC and subjects with non-plaque forms or drug-induced psoriasis as well as active ongoing inflammatory diseases other than psoriasis that might confound study evaluations. Inclusion criteria for group C (healthy subjects) are: patients ≥18 and ≤ 80 years of age with no skin disease and no inflammatory rheumatic disease. Patients with any skin disease affecting the area of interest for DVNC or any active ongoing inflammatory diseases that might confound study evaluations will be excluded. Patients will be excluded from all three groups if any cosmetic procedure involving the nailfold area was performed over the last 4 weeks since potential micro-traumata may lead to false-positive results in DVNC [15, 16].

Methods

In this study the nailfold capillaries of 75 individuals will be evaluated by DVNC (Optilia Digital Capillaroscopy System, Optilia OP-120 021, Optilia Instruments AB, Sweden) (Fig. 1). DVNC will be performed with low magnification (x20; for global evaluation of the entire nailfold area) and high magnification (x200; for more detailed observations of separate capillaries). Nailfolds of the 2nd to the 5th finger of both hands will be examined. For the high magnification setting a total of 32 pictures (4 consecutive images per nailfold, each covering 1 mm) will be taken [15, 16]. For standardization and quality assurance the DVNC is performed after 15–20 min of acclimatization at room temperature in a sitting position. Smoking and caffeinated beverages should be avoided at least four hours before DVNC to

avoid capillary constriction. In our study a semiquantitative image analysis based on the microangiopathy evolution score presented by Cutolo et al. will be applied [15]. The intra- and inter-rater reliability of this semiquantitative scoring-algorithm has been demonstrated [17]. Several capillaroscopic parameters will be evaluated and scored, e.g. presence of enlarged (>20 µm loop diameter) and giant capillaries (loop diameter > 50 µm), hemorrhages and/or hemosiderin deposits, capillary loss (< 9-10 capillaries per linear mm counted at the distal row of the nailfold), disorganization of the vascular array (distribution and orientation) and ramified capillaries/neoangiogenesis (tortuous, branching, bushy, coiled) (Table 1). Optionally, further morphological characteristics may be described. To evaluate patient characteristics possibly associated with specific DVNC patterns, the following parameters will prospectively be assessed: the psoriasis area and severity index score (PASI), presence of nail psoriasis such as pitting, onycholysis, hyperkeratosis, discoloration, disfiguring, or hemorrhages, presence of psoriasis arthritis, demographic and clinical data (e.g. age, gender, duration of the disease, drug intake, circulating markers of endothelial damage and inflammation, accompanying medical conditions (incl. history of cardiovascular disease).

Parameter	Definition	Physiological image
Capillary morphology	Vascular structure	U-shaped, parallel to nail surface
Capillary density	Number of capillaries per linear mm	>9 -10/ linear mm
Capillary loop diameter	Distance between afferent and efferent loop	<20 µm
Capillary enlargement	> 20 µm loop diameter	Usually absent
Megacapillaries	Homogeneously enlarged loops with a diameter > 50 µm	Absent
Capillary blood flow	Blood circulation in the capillary	Dynamic, no stasis/thrombosis
Tortuosity	Afferent and efferent portion cross at least two times	Usually absent
Haemorrhages	Extravasal detection of erythrocytes or their degradation products (Type A: point-like microbleeding, Type B: larger confluent bleeding)	Usually absent
Elongation	Increased length of the capillaries by 50 % or 350 µm	Usually absent
Ramification	Abnormal connections between afferent and efferent portion or e.g. tortuous, branching, bushy or coiled	Absent
Capillary loss	Multifocal (avascular areas) or diffuse loss of capillaries	Absent
Pericapillary oedema	Pericapillary increase in interstitial fluid	Absent

Table 1 Parameters and morphologic findings in capillaroscopy [18,15,19,20]

Statistical considerations

As this is a first pilot study investigating capillary pathologies by DVNC in patients with psoriasis vulgaris, a formal sample size calculation is neither applicable nor feasible. A sample size of 75 complete and evaluable datasets is sufficient to assess the potential impact of psoriasis on capillary pathologies by descriptive statistics. It is planned to investigate 50 patients with psoriasis vulgaris alone or psoriasis vulgaris accompanied by psoriasis arthritis and to compare the results to 25 healthy subjects. Taking into account a dropout rate of 20%, at least 96 patients shall be recruited. All endpoints will be analyzed descriptively by tabulation of the measures of the empirical distributions. Depending on the scale level of the variables, means, standard deviations, medians, and first and third quartiles, as well as either minimum and maximum or absolute and relative frequency, will be reported. Descriptive P-values of the corresponding statistical tests comparing results of patients to healthy subjects will be given, together with the associated 95% confidence intervals. When appropriate, graphical methods will be used to visualize the findings.

Ethical considerations and regulatory obligations

The study is conducted in accordance with the Declaration of Helsinki principles (2013), applicable local government regulations, and independent Ethics Committee policies and procedures. Before initiation of the study, the protocol was presented and approved by the independent ethics committee of the medical faculty of the University of Heidelberg (Ethics approval number S-447/2017). There are no personal benefits and no additional risks for study participants.

Recruitment and status of the study

Ethical approval was granted in September 2017. Planned date of first enrollment is January 2018. The estimated time required for recruitment of 96 patients is 12 months. The total duration of the study is expected to be 24 months, including statistical analysis.

FOOTNOTES

Funding statement

This work was supported by a grant from Novartis Pharma GmbH, Nürnberg, Germany.

Study registration

This study was registered at the German Clinical Trial Register (DRKS): DRKS00012856 (https://www.germanctr.de/).

Conflicts of interest

The authors declared that they have no competing interests.

Authors' contribution

C. Fink, I. Bertlich, E. Hoxha, A. Enk and H.A. Haenssle participated in the development and the implementation of the study (writing of the protocol, submission to ethics committee, data management). C. Fink, I. Bertlich, E. Hoxha, A. Enk and H.A. Haenssle helped to draft and to review the paper. All authors read and approved the final manuscript.

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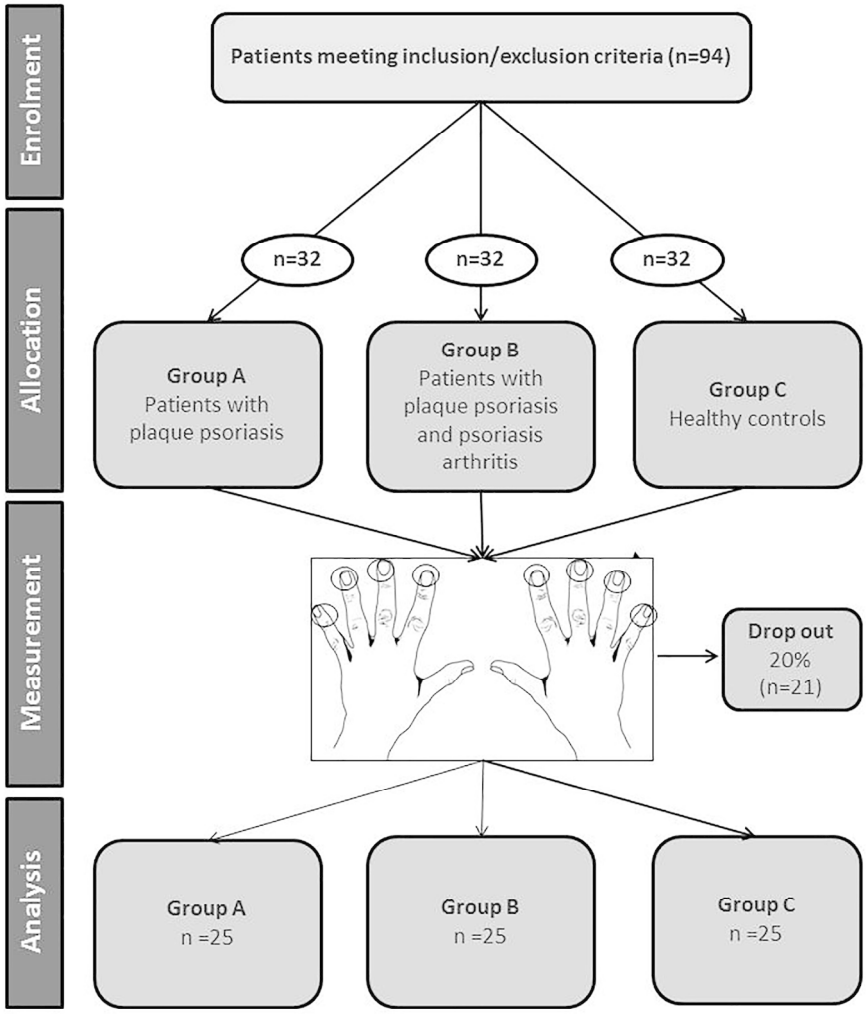
FIGURE Legend

Figure 1 Flowchart of the study



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ABSTRACT

Introduction

Psoriasis vulgaris was shown to be an independent factor increasing the risk of several comorbidities such as obesity, diabetes and dyslipidemia with an increased risk of stroke and myocardial infarction. We hypothesize that early endothelial dysfunction, which plays a crucial role in the pathogenesis of atherosclerosis, may be detected by digital video nailfold capillaroscopy (DVNC) at the level of the dermal capillary microvasculature as a surrogate parameter. Nailfolds represent the only body site allowing for a non-invasive assessment of the capillary microvasculature at a horizontal plane. DVNC is a well-established diagnostic tool for in-vivo assessment of the peripheral microcirculation by evaluating the morphology of dermal papillary capillaries. To date, reports on morphological changes of the non-lesional nailfold capillaries in patients with psoriasis vulgaris are scarce and the existing data is not conclusive.

Methods and analysis

This is a prospective, single center, non-randomized, controlled pilot study assessing the capillary patterns in 75 subjects affected by psoriasis vulgaris. Non-lesional nailfold capillaries will be imaged by means of DVNC (Optilia Digital Capillaroscopy System, Optilia Instruments AB, Sollentuna, Sweden) in 50 patients affected by psoriasis vulgaris and 25 healthy controls. Assessments will include a qualitative, descriptive analysis of the nailfold capillaries' morphology, as well as a quantitative investigation (frequency, extent) of changes in capillary patterns. Moreover, patients' characteristics associated with the manifestation of nailfold capillaries' pathologies including well-known cardiovascular risk markers will be studied.

Ethics and dissemination

Ethical approval was provided by the ethic committee of the medical faculty of the University of Heidelberg (Ethics approval number S-447/2017). The design and the final results of the study will be published and made available to the public.

Study registration

This study is registered at the German Clinical Trial Register (DRKS): DRKS00012856

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a pilot case-control study designed to investigate the frequency and extent of morphological changes of nailfold capillaries in patients with psoriasis vulgaris in comparison to healthy controls.
- Pathological changes in nailfold capillaries of psoriasis patients and healthy controls will be statistically correlated with collected biomarkers and clinical findings indicative of cardiovascular disease.
- Statistical analyses of associations between pathological patterns of nailfold capillaries and cardiovascular disease will be performed to assess the usefulness of capillaroscopy as a surrogate parameter for determining the extent of endothelial dysfunction in psoriasis patients.
- Since this is a pilot study, limitations arise from the single-site setting and the small number of subjects in both groups.

INTRODUCTION

Digital video nailfold capillaroscopy (DVNC) is routinely used for in-vivo assessment of the peripheral microcirculation by evaluating the morphology of dermal papillary capillaries [1]. Long before onset of clinical symptoms pathological capillary patterns may be observed in a number of systemic diseases, which are accompanied by vascular damage. Therefore, DVNC might be helpful to define surrogate parameters indicative of initial manifestation of cardiovascular disease [2]. Additionally, capillary abnormalities were shown to potentially reflect the severity and long-term prognosis of underlying diseases. For instance, in systemic sclerosis an association between a decreased capillary density and the development and the severity of pulmonary arterial hypertension was detected [3]. Psoriasis vulgaris is a common chronic skin disease which is accompanied by a number of comorbidities, that are possibly induced by a chronic, low-grade, systemic inflammation leading to vascular insufficiency and finally to clinically relevant atherosclerosis [2,4,5]. Atherosclerosis in psoriasis patients was shown to be caused by a transfer of inflammatory cells and cytokines from the skin to endothelial tissue and internal organs causing systemic inflammation [2,5,6]. Endothelial dysfunction is often used as a surrogate marker for atherosclerosis and several studies have shown impaired endothelial function in patients with moderate to severe psoriasis or psoriatic arthritis [2,6,7]. Besides broad evidence for an increased risk of large vessel atherosclerosis, previous studies also indicated changes of the microvasculature in the papillary dermis of psoriatic plaques and the synovia of psoriatic joints [8,9]. However, until today only little is known about changes in the microcirculation in non-lesional skin of psoriasis patients. The reported data are controversial with regard to pathologies of nailfold capillaries, which most probably reflects the polyetiology and polymorphology of psoriasis. In one of the earliest studies Redisch et al. revealed tortuous capillaries with tight terminal convolutions in lesional and non-lesional skin of psoriasis patients [10]. A decreased capillary density, shorter

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The aim of our study is to gather further evidence concerning the morphology, frequency and the extent of nailfold capillary changes in patients with psoriasis vulgaris and to identify patient characteristics possibly associated with specific pathological DVNC patterns. We hypothesize that early endothelial dysfunction as caused by the systemic inflammatory immune response in psoriasis patients may be detected by DVNC at the level of the dermal capillary microvasculature.

DESIGN/METHODS

Study design and objectives

This is a prospective, single center, non-randomized, controlled pilot study assessing the capillary patterns in 75 individuals by means of DVNC. The primary objective of this study is to investigate the frequency, the extent, and the morphology of changes in capillary patterns in 50 patients that are either affected by psoriasis vulgaris alone (group A) or by psoriasis vulgaris in combination with accompanying psoriasis arthritis (group B) compared to 25 healthy subjects (group C) (Fig. 1). A secondary objective of this study is to identify patient characteristics that are statistically associated with specific DVNC patterns (e.g. psoriasis

severity, nail psoriasis, age, gender, duration of the disease, manifest cardiovascular diseases and circulating markers of endothelial damage and inflammation).

Criteria for inclusion/exclusion

Inclusion criteria for group A and B are: patients ≥18 and ≤ 80 years of age with the diagnosis of chronic moderate to severe plaque psoriasis (defined as involved BSA ≥10% and PASI score ≥ 10 and DLQI ≥ 10) with or without psoriatic arthritis for at least 6 months (duration since diagnosis may be reported by the patient). Exclusion criteria for group A and B are: patients under current exposure to any anti-psoriatic or immunosuppressive systemic therapy (discontinuation for at least 4 weeks prior to DVNC is mandatory), patients with any other skin disease or therapy affecting the area of interest for DVNC and subjects with non-plaque forms or drug-induced psoriasis as well as active ongoing inflammatory diseases other than psoriasis that might confound study evaluations. Inclusion criteria for group C (healthy subjects) are: patients ≥18 and ≤ 80 years of age with no skin disease and no inflammatory rheumatic disease. Patients with any skin disease affecting the area of interest for DVNC or any active ongoing inflammatory diseases that might confound study evaluations will be excluded. Patients will be excluded from all three groups if any cosmetic procedure involving the nailfold area was performed over the last 4 weeks since potential micro-traumata may lead to false-positive results in DVNC [15, 16].

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high magnification setting a total of 32 pictures (4 consecutive images per nailfold, each covering 1 mm) will be taken [15, 16]. For standardization and quality assurance the DVNC is performed after 15–20 min of acclimatization at room temperature in a sitting position. Smoking and caffeinated beverages should be avoided at least four hours before DVNC to avoid capillary constriction. In our study a semiquantitative image analysis based on the microangiopathy evolution score presented by Cutolo et al. will be applied [15]. The intra- and inter-rater reliability of this semiquantitative scoring-algorithm has been demonstrated [17]. Interpretation of findings will be based on criteria established by the EULAR study group [18]. Several capillaroscopic parameters will be evaluated and scored, e.g. presence of enlarged (>20 µm loop diameter) and giant capillaries (loop diameter > 50 µm), hemorrhages and/or hemosiderin deposits, capillary loss (< 9-10 capillaries per linear mm counted at the distal row of the nailfold), disorganization of the vascular array (distribution and orientation) and ramified capillaries/neoangiogenesis (tortuous, branching, bushy, coiled) (Table 1). Optionally, further morphological characteristics may be described. To evaluate patient characteristics possibly associated with specific DVNC patterns, the following parameters will prospectively be assessed: the psoriasis area and severity index score (PASI), presence of nail psoriasis such as pitting, onycholysis, hyperkeratosis, discoloration, disfiguring, or hemorrhages, presence of psoriasis arthritis, demographic and clinical data (e.g. age, gender, duration of the disease, drug intake, circulating markers of endothelial damage and inflammation, accompanying medical conditions (incl. history of cardiovascular disease).

Parameter	Definition	Physiological image
Capillary morphology	Vascular structure	U-shaped, parallel to nail surface
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Capillary enlargement	> 20 µm loop diameter	Usually absent
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Pericapillary oedema	Pericapillary increase in interstitial fluid	Absent

Table 1 Parameters and morphologic findings in capillaroscopy [15,19, 20,21]

Statistical considerations

As this is a first pilot study investigating capillary pathologies by DVNC in patients with psoriasis vulgaris, a formal sample size calculation is neither applicable nor feasible. A sample size of 75 complete and evaluable datasets is sufficient to assess the potential impact of psoriasis on capillary pathologies by descriptive statistics. It is planned to investigate 50 patients with psoriasis vulgaris alone or psoriasis vulgaris accompanied by psoriasis arthritis and to compare the results to 25 healthy subjects. Taking into account a dropout rate of 20%, at least 96 patients shall be recruited. All endpoints will be analyzed descriptively by tabulation of the measures of the empirical distributions. Depending on the scale level of the variables, means, standard deviations, medians, and first and third quartiles, as well as either minimum and maximum or absolute and relative frequency, will be reported. Descriptive P-values of the corresponding statistical tests comparing results of patients to healthy subjects will be given, together with the associated 95% confidence intervals. When appropriate, graphical methods will be used to visualize the findings.

Ethical considerations, dissemination plan and regulatory obligations

The study is conducted in accordance with the Declaration of Helsinki principles (2013), applicable local government regulations, and independent Ethics Committee policies and procedures. Before initiation of the study, the protocol was presented and approved by the independent ethics committee of the medical faculty of the University of Heidelberg (Ethics approval number S-447/2017). The design and the final results of the study will be presented

at meetings and congresses, will be published in written form in international scientific journals.

Recruitment and status of the study

Ethical approval was granted in September 2017. Planned date of first enrollment is January 2018. The estimated time required for recruitment of 96 patients is 12 months. The total duration of the study is expected to be 24 months, including statistical analysis.

Patient and public involvement

Within this study 75 participants will be recruited which have no personal benefits and no additional risks. However, specific pathological changes in non-invasive nailfold capillaries might be identified and future patients might benefit from this study. Study results will be made available to the public via press releases as launched by the media departments of the authors' institutions.

FOOTNOTES

Funding statement

This work was supported by a grant from Novartis Pharma GmbH, Nürnberg, Germany.

Study registration

This study was registered at the German Clinical Trial Register (DRKS): DRKS00012856 (https://www.germanctr.de/).

Conflicts of interest

The authors declared that they have no competing interests.

Authors' contribution

C. Fink, I. Bertlich, E. Hoxha, A. Enk and H.A. Haenssle participated in the development and the implementation of the study (writing of the protocol, submission to ethics committee, data management). C. Fink, I. Bertlich, E. Hoxha, A. Enk and H.A. Haenssle helped to draft and to review the paper. All authors read and approved the final manuscript.

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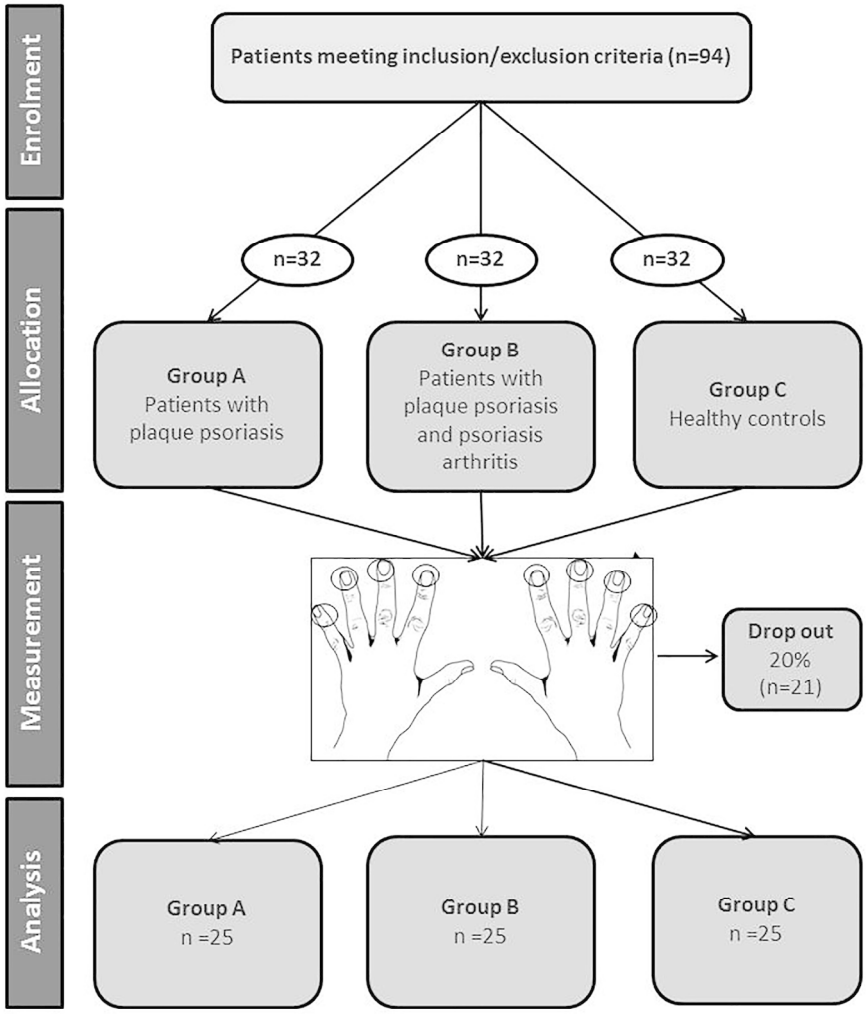
FIGURE Legend

Figure 1 Flowchart of the study



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Evaluation of capillary pathologies by nailfold capillaroscopy in patients with psoriasis vulgaris: Study protocol for a prospective, controlled exploratory study

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Evaluation of capillary pathologies by nailfold capillaroscopy in patients with psoriasis vulgaris: Study protocol for a prospective, controlled exploratory study

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ABSTRACT

Introduction

Psoriasis vulgaris was shown to be an independent factor increasing the risk of several comorbidities such as obesity, diabetes and dyslipidemia with an increased risk of stroke and myocardial infarction. We hypothesize that early endothelial dysfunction, which plays a crucial role in the pathogenesis of atherosclerosis, may be detected by digital video nailfold capillaroscopy (DVNC) at the level of the dermal capillary microvasculature as a surrogate parameter. Nailfolds represent the only body site allowing for a non-invasive assessment of the capillary microvasculature at a horizontal plane. DVNC is a well-established diagnostic tool for in-vivo assessment of the peripheral microcirculation by evaluating the morphology of dermal papillary capillaries. To date, reports on morphological changes of the non-lesional nailfold capillaries in patients with psoriasis vulgaris are scarce and the existing data is not conclusive.

Methods and analysis

This is a prospective, single center, non-randomized, controlled, exploratory study assessing the capillary patterns in 100 subjects affected by psoriasis vulgaris. Non-lesional nailfold capillaries will be imaged by means of DVNC (Optilia Digital Capillaroscopy System, Optilia Instruments AB, Sollentuna, Sweden) in 50 patients affected by psoriasis vulgaris and 50 healthy controls. Assessments will include a qualitative, descriptive analysis of the nailfold capillaries' morphology, as well as a quantitative investigation (frequency, extent) of changes in capillary patterns. Moreover, patients' characteristics associated with the manifestation of nailfold capillaries' pathologies including well-known cardiovascular risk markers will be studied.

Ethics and dissemination

Ethical approval was provided by the ethic committee of the medical faculty of the University of Heidelberg (Ethics approval number S-447/2017). The design and the final results of the study will be published and made available to the public.

Study registration

This study is registered at the German Clinical Trial Register (DRKS): DRKS00012856

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Until today, there are only very few prospective, controlled studies investigating the frequency and extent of morphological changes of nailfold capillaries in patients with psoriasis vulgaris.
- Within this study, several patient characteristics that are associated with specific capillaroscopy patterns will be investigated in a prospective controlled setting in an unprecedented scale.
- Since this is an exploratory study, limitations arise from the small number of subjects in both groups and the non-feasibility of a formal sample size calculation due to the absence of a-priori knowledge.

INTRODUCTION

Digital video nailfold capillaroscopy (DVNC) is routinely used for in-vivo assessment of the peripheral microcirculation by evaluating the morphology of dermal papillary capillaries [1]. Long before onset of clinical symptoms pathological capillary patterns may be observed in a number of systemic diseases, which are accompanied by vascular damage. Therefore, DVNC might be helpful to define surrogate parameters indicative of initial manifestation of cardiovascular disease [2]. Additionally, capillary abnormalities were shown to potentially

reflect the severity and long-term prognosis of underlying diseases. For instance, in systemic sclerosis an association between a decreased capillary density and the development and the severity of pulmonary arterial hypertension was detected [3]. Psoriasis vulgaris is a common chronic skin disease which is accompanied by a number of comorbidities, that are possibly induced by a chronic, low-grade, systemic inflammation leading to vascular insufficiency and finally to clinically relevant atherosclerosis [2,4,5]. Atherosclerosis in psoriasis patients was shown to be caused by a transfer of inflammatory cells and cytokines from the skin to endothelial tissue and internal organs causing systemic inflammation [2,5,6]. Endothelial dysfunction is often used as a surrogate marker for atherosclerosis and several studies have shown impaired endothelial function in patients with moderate to severe psoriasis or psoriatic arthritis [2,6,7]. Besides broad evidence for an increased risk of large vessel atherosclerosis, previous studies also indicated changes of the microvasculature in the papillary dermis of psoriatic plaques and the synovia of psoriatic joints [8,9]. However, until today only little is known about changes in the microcirculation in non-lesional skin of psoriasis patients. The reported data are controversial with regard to pathologies of nailfold capillaries, which most probably reflects the polyetiology and polymorphology of psoriasis. In one of the earliest studies Redisch et al. revealed tortuous capillaries with tight terminal convolutions in lesional and non-lesional skin of psoriasis patients [10]. A decreased capillary density, shorter capillaries, more nailfold hemorrhages and sluggish blood flow in patients with psoriasis arthritis were observed by Zaric et al. when compared to healthy controls [11]. A pattern with shorter and more tortuous capillaries was significantly correlated with periungual psoriatic plaques, nail pitting, onycholysis, and the extent of the involved body surface in a study by Ohtsuka et al. [12]. A study by Ribeiro et al. showed a lower capillary density, increased avascular areas and an increased number of coiled capillaries in the nailfold of patients with psoriasis [13]. Finally, Bushan et al. reported a significantly decreased capillary loop density

and a reduction of arterial and venous capillary limb diameters but found no other of the previously described morphological abnormalities in any of the patients [14].

The aim of our exploratory study is to generate hypotheses concerning the morphology, frequency and the extent of nailfold capillary changes in patients with psoriasis vulgaris and to identify patient characteristics possibly associated with specific pathological DVNC patterns. We hypothesize that early endothelial dysfunction as caused by the systemic inflammatory immune response in psoriasis patients may be detected by DVNC at the level of the dermal capillary microvasculature. In addition, this exploratory study will provide the necessary prerequisites for a full-scale study with a formal sample size calculation since there is only little a-priori knowledge.

DESIGN/METHODS

Study design and objectives

This is a prospective, single center, non-randomized, controlled exploratory study assessing the capillary patterns in 100 individuals by means of DVNC. The primary objective of this study is to generate hypotheses regarding the frequency, the extent, and the morphology of changes in capillary patterns in 50 patients that are either affected by psoriasis vulgaris alone (group A) or by psoriasis vulgaris in combination with accompanying psoriasis arthritis (group B) compared to 50 healthy subjects (group C) (Fig. 1). A secondary objective of this study is to identify patient characteristics that are statistically associated with specific DVNC patterns (e.g. psoriasis severity, nail psoriasis, age, gender, duration of the disease, manifest cardiovascular diseases and circulating markers of endothelial damage and inflammation).

Criteria for inclusion/exclusion

Inclusion criteria for group A and B are: patients ≥18 and ≤ 80 years of age with the diagnosis of chronic moderate to severe plaque psoriasis (defined as involved BSA ≥10% and PASI score ≥ 10 and DLQI ≥ 10) with or without psoriatic arthritis for at least 6 months (duration since diagnosis may be reported by the patient). Exclusion criteria for group A and B are: patients under current exposure to any anti-psoriatic or immunosuppressive systemic therapy (discontinuation for at least 4 weeks prior to DVNC is mandatory), patients with any other skin disease or therapy affecting the area of interest for DVNC and subjects with non-plaque forms or drug-induced psoriasis as well as active ongoing inflammatory diseases other than psoriasis that might confound study evaluations. Inclusion criteria for group C (healthy subjects) are: patients ≥18 and ≤ 80 years of age with no skin disease and no inflammatory rheumatic disease. Patients with any skin disease affecting the area of interest for DVNC or any active ongoing inflammatory diseases that might confound study evaluations will be excluded. Patients will be excluded from all three groups if any cosmetic procedure involving the nailfold area was performed over the last 4 weeks since potential micro-traumata may lead to false-positive results in DVNC [15, 16].

Methods

In this study the nailfold capillaries of 100 individuals will be evaluated by DVNC (Optilia Digital Capillaroscopy System, Optilia OP-120 021, Optilia Instruments AB, Sweden) (Fig. 1). DVNC will be performed with low magnification (x20; for global evaluation of the entire nailfold area) and high magnification (x200; for more detailed observations of separate capillaries). Nailfolds of the 2nd to the 5th finger of both hands will be examined. For the high magnification setting a total of 32 pictures (4 consecutive images per nailfold, each covering 1 mm) will be taken [15, 16]. For standardization and quality assurance the DVNC is performed after 15–20 min of acclimatization at room temperature in a sitting position. Smoking and caffeinated beverages should be avoided at least four hours before DVNC to

avoid capillary constriction. In our study a semiquantitative image analysis based on the microangiopathy evolution score presented by Cutolo et al. will be applied [15]. The intra- and inter-rater reliability of this semiquantitative scoring-algorithm has been demonstrated [17]. Interpretation of findings will be based on criteria established by the EULAR study group [18]. Several capillaroscopic parameters will be evaluated and scored, e.g. presence of enlarged (>20 µm loop diameter) and giant capillaries (loop diameter > 50 µm), hemorrhages and/or hemosiderin deposits, capillary loss (< 9-10 capillaries per linear mm counted at the distal row of the nailfold), disorganization of the vascular array (distribution and orientation) and ramified capillaries/neoangiogenesis (tortuous, branching, bushy, coiled) (Table 1). Optionally, further morphological characteristics may be described. To evaluate patient characteristics possibly associated with specific DVNC patterns, the following parameters will prospectively be assessed: the psoriasis area and severity index score (PASI), presence of nail psoriasis such as pitting, onycholysis, hyperkeratosis, discoloration, disfiguring, or hemorrhages, presence of psoriasis arthritis, demographic and clinical data (e.g. age, gender, duration of the disease, drug intake, circulating markers of endothelial damage and inflammation, accompanying medical conditions (incl. history of cardiovascular disease).

Parameter	Definition	Physiological image
Capillary morphology	Vascular structure	U-shaped, parallel to nail surface
Capillary density	Number of capillaries per linear mm	>9 -10/ linear mm
Capillary loop diameter	Distance between afferent and efferent loop	<20 µm
Capillary enlargement	> 20 µm loop diameter	Usually absent
Megacapillaries	Homogeneously enlarged loops with a diameter > 50 µm	Absent
Capillary blood flow	Blood circulation in the capillary	Dynamic, no stasis/thrombosis
Tortuosity	Afferent and efferent portion cross at least two times	Usually absent
Haemorrhages	Extravasal detection of erythrocytes or their degradation products (Type A: point-like microbleeding, Type B: larger confluent bleeding)	Usually absent
Elongation	Increased length of the capillaries by 50 % or 350 µm	Usually absent
Ramification	Abnormal connections between afferent and efferent portion or e.g. tortuous, branching, bushy or coiled	Absent
Capillary loss	Multifocal (avascular areas) or diffuse loss of capillaries	Absent
Pericapillary oedema	Pericapillary increase in interstitial fluid	Absent

Table 1 Parameters and morphologic findings in capillaroscopy [15,19, 20,21]

Statistical considerations

This is a first exploratory study investigating capillary pathologies by DVNC in patients with psoriasis vulgaris since there is only little a-priori knowledge about the frequency and extent of morphological changes of nailfold capillaries in patients with psoriasis vulgaris. Thus, a formal sample size calculation is not possible. This exploratory study will provide the necessary prerequisites for a formal sample size calculation for a full-scale study.

A total of 100 complete and evaluable datasets will allow obtaining a first impression of the potential impact of psoriasis on capillary pathologies by descriptive statistics. It is planned to investigate 50 patients with psoriasis vulgaris alone or psoriasis vulgaris accompanied by psoriasis arthritis and to compare the results to 50 healthy subjects. The resulting group allocation is sufficient to determine an effect size of 0.7 (Cohen's d) with a t test at 5% significance level and 80% power. Taking into account a dropout rate of 20%, at least 125 patients shall be recruited. All endpoints will be analyzed descriptively by tabulation of the measures of the empirical distributions. Depending on the scale level of the variables, means, standard deviations, medians, and first and third quartiles, as well as either minimum and maximum or absolute and relative frequency, will be reported. Descriptive P-values of the corresponding statistical tests comparing results of patients to healthy subjects will be given, together with the associated 95% confidence intervals. When appropriate, graphical methods will be used to visualize the findings.

Ethical considerations, dissemination plan and regulatory obligations

The study is conducted in accordance with the Declaration of Helsinki principles (2013), applicable local government regulations, and independent Ethics Committee policies and procedures. Before initiation of the study, the protocol was presented and approved by the independent ethics committee of the medical faculty of the University of Heidelberg (Ethics approval number S-447/2017). The design and the final results of the study will be presented

at meetings and congresses, will be published in written form in international scientific journals.

Recruitment and status of the study

Ethical approval was granted in September 2017. Planned date of first enrollment is January 2018. The estimated time required for recruitment of 96 patients is 12 months. The total duration of the study is expected to be 24 months, including statistical analysis.

Patient and public involvement

Within this study 100 participants will be recruited which have no personal benefits and no additional risks. However, specific pathological changes in non-invasive nailfold capillaries might be identified and future patients might benefit from this study. Study results will be made available to the public via press releases as launched by the media departments of the authors' institutions.

FOOTNOTES

Funding statement

This work was supported by a grant from Novartis Pharma GmbH, Nürnberg, Germany.

Study registration

This study was registered at the German Clinical Trial Register (DRKS): DRKS00012856 (https://www.germanctr.de/).

Conflicts of interest

The authors declared that they have no competing interests.

Authors' contribution

C. Fink, S. Kilian, I. Bertlich, E. Hoxha, A. Enk and H.A. Haenssle participated in the development and the implementation of the study (writing of the protocol, submission to ethics committee, data management). C. Fink, S. Kilian, I. Bertlich, E. Hoxha, A. Enk and H.A. Haenssle helped to draft and to review the paper. All authors read and approved the final manuscript.

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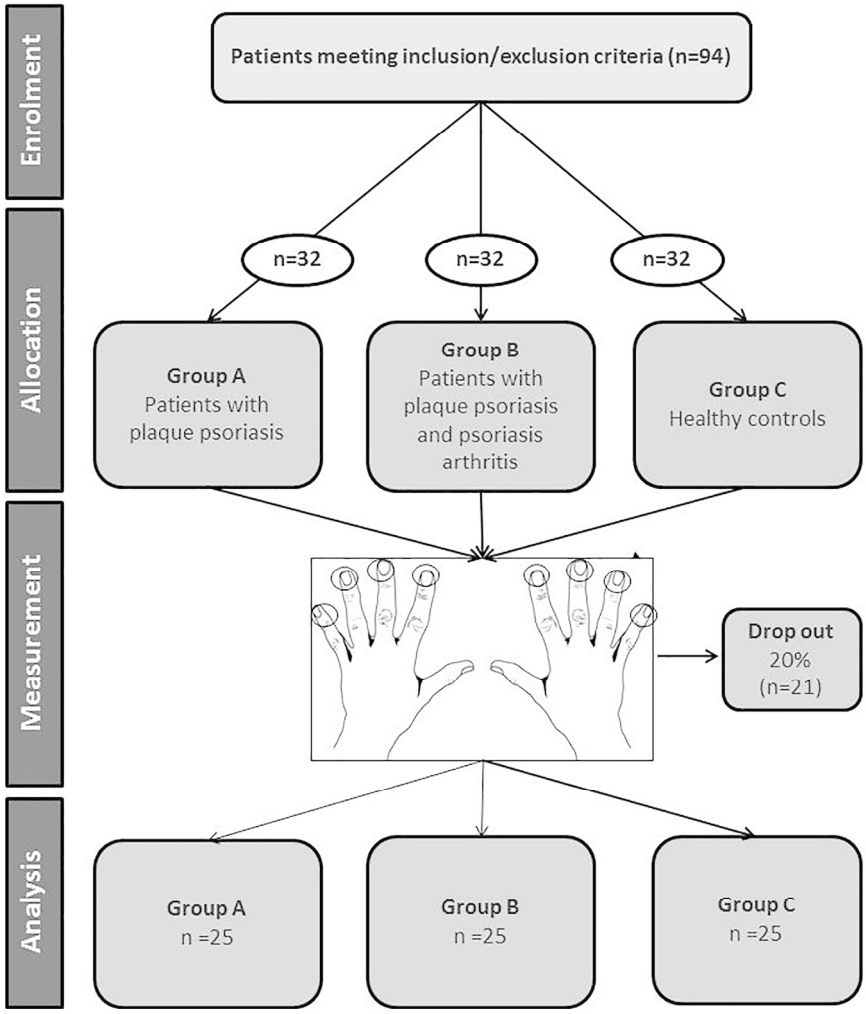
FIGURE Legend

Figure 1 Flowchart of the study



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ABSTRACT

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- Within this study, several patient characteristics and their associated specific capillaroscopy patterns will be investigated in a prospective controlled setting on an unprecedented scale.
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DESIGN/METHODS

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This is a prospective, single center, non-randomized, controlled exploratory study assessing the capillary patterns in 100 individuals by means of DVNC. The primary objective of this study is to generate hypotheses regarding the frequency, the extent, and the morphology of capillary patterns in non-lesional skin of 50 patients that are either affected by psoriasis vulgaris alone (group A) or by psoriasis vulgaris in combination with accompanying psoriasis arthritis (group B) compared to 50 healthy subjects (group C) (Fig. 1). A secondary objective of this study is to identify patient characteristics that are statistically associated with specific DVNC patterns (e.g. psoriasis severity, nail psoriasis, age, gender, duration of the disease, manifest cardiovascular diseases and circulating markers of endothelial damage and inflammation).

Criteria for inclusion/exclusion

Inclusion criteria for group A and B are: patients ≥18 and ≤ 80 years of age with the diagnosis of chronic moderate to severe plaque psoriasis (defined as involved BSA ≥10% and/or PASI score ≥ 10 and DLQI ≥ 10) with or without psoriatic arthritis for at least 6 months (duration since diagnosis may be reported by the patient). Exclusion criteria for group A and B are: patients under current exposure to any anti-psoriatic or immunosuppressive systemic therapy (discontinuation for at least 4 weeks prior to DVNC is mandatory), patients with any other skin disease or therapy affecting the area of interest for DVNC and subjects with non-plaque forms or drug-induced psoriasis as well as active ongoing inflammatory diseases other than psoriasis that might confound study evaluations. Inclusion criteria for group C (healthy subjects) are: patients ≥18 and ≤ 80 years of age with no skin disease and no inflammatory rheumatic or cardiovascular disease. Patients with any skin disease affecting the area of interest for DVNC or any active ongoing inflammatory disease that might confound study evaluations will be excluded. Patients will be excluded from all three groups if any cosmetic procedure involving the nailfold area was performed over the last 4 weeks since potential micro-traumata may lead to false-positive results in DVNC [15, 16].

Methods

In this study the nailfold capillaries of 100 individuals will be evaluated by DVNC (Optilia Digital Capillaroscopy System, Optilia OP-120 021, Optilia Instruments AB, Sweden) (Fig. 1). DVNC will be performed with low magnification (x20; for global evaluation of the entire nailfold area) and high magnification (x200; for more detailed observation of separate capillaries). Nailfolds of the 2nd to the 5th finger of both hands will be examined. For the high magnification setting a total of 32 pictures (4 consecutive images per nailfold, each covering 1 mm) will be taken [15, 16]. For standardization and quality assurance the DVNC is performed after 15–20 min of acclimatization at room temperature in a sitting position. Smoking and caffeinated beverages should be avoided at least four hours before DVNC to

avoid capillary constriction. In our study a semiquantitative image analysis based on the microangiopathy evolution score presented by Cutolo et al. will be applied [15]. The intra- and inter-rater reliability of this semiquantitative scoring-algorithm has been demonstrated [17]. Interpretation of findings will be based on criteria established by the EULAR study group [18]. Several capillaroscopic parameters will be evaluated and scored, e.g. presence of enlarged (>20 µm loop diameter) and giant capillaries (loop diameter > 50 µm), hemorrhages and/or hemosiderin deposits, capillary loss (< 9-10 capillaries per linear mm counted at the distal row of the nailfold), disorganization of the vascular array (distribution and orientation) and ramified capillaries/neoangiogenesis (tortuous, branching, bushy, coiled) (Table 1). Optionally, further morphological characteristics may be described. To evaluate patient characteristics possibly associated with specific DVNC patterns, the following parameters will prospectively be assessed: the psoriasis area and severity index score (PASI), presence of nail psoriasis such as pitting, onycholysis, hyperkeratosis, discoloration, disfiguring, or hemorrhages, presence of psoriasis arthritis, demographic and clinical data (e.g. age, gender, duration of the disease, drug intake, circulating markers of endothelial damage and inflammation (Table 2), accompanying medical conditions (incl. history of cardiovascular disease).

Parameter	Definition	Physiological image
Capillary morphology	Vascular structure	U-shaped, parallel to nail surface
Capillary density	Number of capillaries per linear mm	>9 -10/ linear mm
Capillary loop diameter	Distance between afferent and efferent loop	<20 µm
Capillary enlargement	> 20 µm loop diameter	Usually absent
Megacapillaries	Homogeneously enlarged loops with a diameter > 50 µm	Absent
Capillary blood flow	Blood circulation in the capillary	Dynamic, no stasis/thrombosis
Tortuosity	Afferent and efferent portion cross at least two times	Usually absent
Haemorrhages	Extravasal detection of erythrocytes or their degradation products (Type A: point-like microbleeding, Type B: larger confluent bleeding)	Usually absent
Elongation	Increased length of the capillaries by 50 % or 350 µm	Usually absent
Ramification	Abnormal connections between afferent and efferent portion or e.g. tortuous, branching, bushy or coiled	Absent
Capillary loss	Multifocal (avascular areas) or diffuse loss of capillaries	Absent
Pericapillary oedema	Pericapillary increase in interstitial fluid	Absent

Table 1 Parameters and morphologic findings in capillaroscopy [15,19, 20,21]

Parameter	Standard values (SI units)
C-Reactive Protein (CRP)	< 0,005 g/l
Von Willebrand factor	50-160%
Fibrinogen	150-350 mg/dl
Leukocytes	4 - 10 x 10^9/l
Blood sedimentation	0–20 mm/h
D-Dimer	≤ 300 µg/l
Total Cholesterol (TC)	3,88–5,15 mmol/l
Triglycerides	< 2,82 mmol/l
High-Density-Lipoprotein cholesterol (HDL-C)	≥ 1,04 mmol/l
Low-Density-Lipoprotein cholesterol (LDL-C)	≤ 3,36 mmol/l

Table 2 Circulating markers of endothelial damage and inflammation

Statistical considerations

This is a first exploratory study investigating capillary pathologies by DVNC in patients with psoriasis vulgaris since there is only little a-priori knowledge about the frequency and extent of morphological changes of nailfold capillaries in patients with psoriasis vulgaris. Thus, a formal sample size calculation is not possible. This exploratory study will provide the necessary prerequisites for a formal sample size calculation for a full-scale study.

A total of 100 complete and evaluable datasets will allow obtaining a first impression of the potential impact of psoriasis on capillary pathologies by descriptive statistics. It is planned to investigate 50 patients with psoriasis vulgaris alone or psoriasis vulgaris accompanied by psoriasis arthritis and to compare the results to 50 healthy subjects. The resulting group allocation is sufficient to determine an effect size of 0.7 (Cohen's d) with a t test at 5% significance level and 80% power. Taking into account a dropout rate of 20%, at least 127 patients shall be recruited. All endpoints will be analyzed descriptively by tabulation of the measures of the empirical distributions. Depending on the scale level of the variables, means, standard deviations, medians, and first and third quartiles, as well as either minimum and maximum or absolute and relative frequency, will be reported. Descriptive p-values of the corresponding statistical tests comparing results of patients to healthy subjects will be given, together with the associated 95% confidence intervals. When appropriate, graphical methods will be used to visualize the findings.

Ethical considerations, dissemination plan and regulatory obligations

The study is conducted in accordance with the Declaration of Helsinki principles (2013), applicable local government regulations, and independent Ethics Committee policies and procedures. Before initiation of the study, the protocol was presented and approved by the independent ethics committee of the medical faculty of the University of Heidelberg (Ethics approval number S-447/2017). The design and the final results of the study will be presented at meetings and congresses, will be published in written form in international scientific journals.

Recruitment and status of the study

Ethical approval was granted in September 2017. Planned date of first enrollment is July 2018. The estimated time required for recruitment of 96 patients is 12 months. The total duration of the study is expected to be 24 months, including statistical analysis.

Patient and public involvement

Patients or public were not involved in the design or conduct of the study. . Study results will be made available to the public via press releases as launched by the media departments of the authors' institutions.

FOOTNOTES

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Study registration

This study was registered at the German Clinical Trial Register (DRKS): DRKS00012856 (https://www.germanctr.de/).

Conflicts of interest

The authors declared that they have no competing interests.

Authors' contribution

C. Fink, S. Kilian, I. Bertlich, E. Hoxha, A. Enk and H.A. Haenssle participated in the development and the implementation of the study (writing of the protocol, submission to ethics committee, data management). C. Fink, S. Kilian, I. Bertlich, E. Hoxha, F. Bardehle, A. Enk and H.A. Haenssle helped to draft and to review the paper. All authors read and approved the final manuscript.

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FIGURE Legend

Figure 1 Flowchart of the study

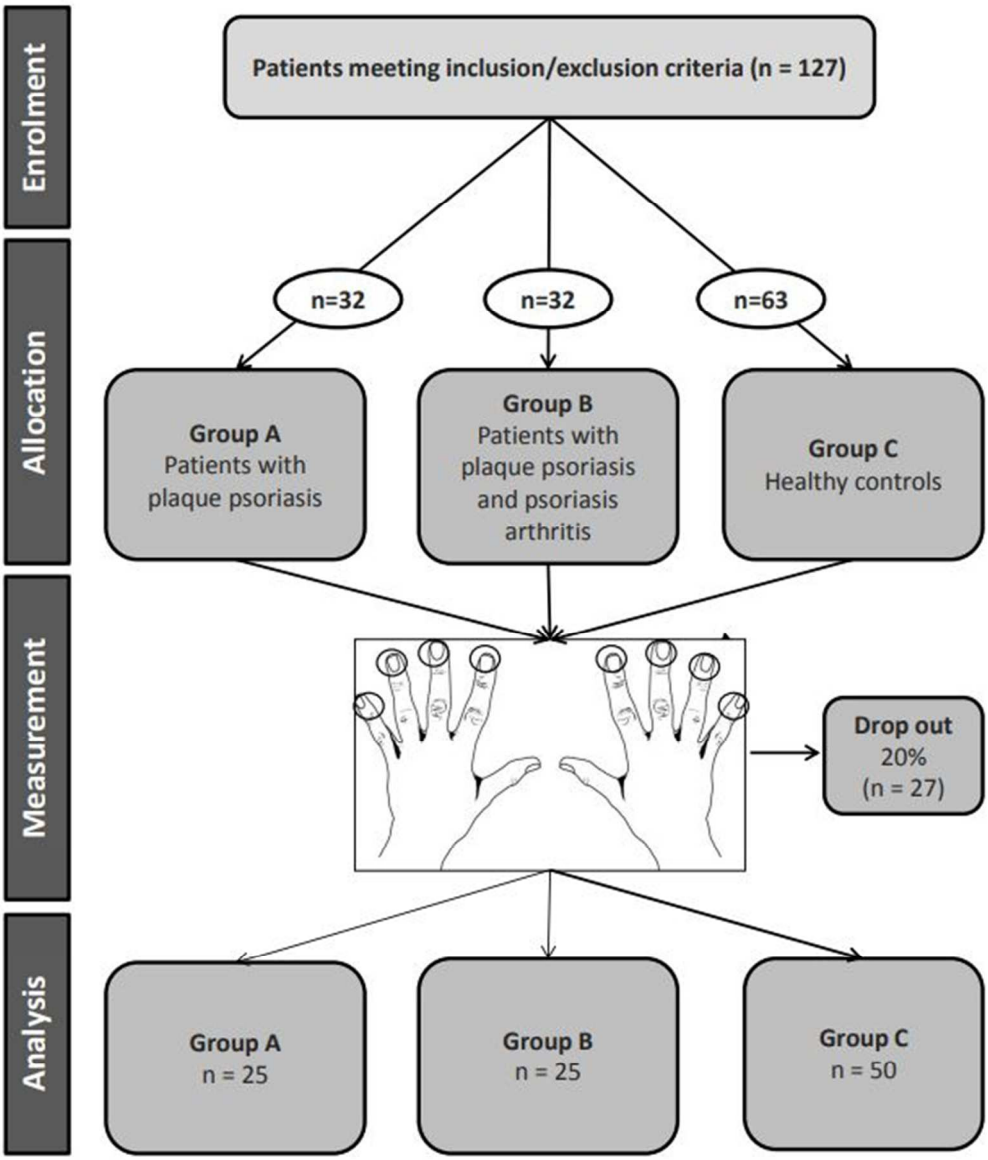

Figure 1 Flowchart of the study

52x61mm (300 x 300 DPI)