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General Introduction

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RAYNAUD’S PHENOMENON

Raynaud’s phenomenon (RP) is named after Maurice Raynaud, who first described a clinical condition characterised by episodic events of color changes of the digits in response to cold or emotion in 1862.\(^1\) Classically, the digits turn white (ischaemia), then blue (deoxygenation), then red (reperfusion, reactive hyperaemia)(see figure 1). In the vast majority of patients, RP is simply an exaggeration of the physiologic response to cold temperatures\(^2\), called primary (idiopathic) Raynaud’s phenomenon (PRP). The estimated prevalence of RP in the general population is 3-5%, with a higher prevalence in colder zones.\(^2,3\)

![Figure 1](image)

**Figure 1.** Sharp demarcation and blue and white discoloration of the left ring finger and right little finger during an attack of Raynaud’s phenomenon in a woman

RAYNAUD’S PHENOMENON AND CONNECTIVE TISSUE DISEASE

In about 13% of patients, RP can be secondary to serious underlying disease, particularly a connective tissue disease (CTD) such as systemic sclerosis (SSc), mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE) or undifferentiated connective tissue
disease (UCTD). Other secondary causes include extrinsic or intrinsic vascular obstruction as in thoracic outlet syndrome and atherosclerosis, paraproteinemias, and certain drugs/chemicals (for example β blockers). Although a secondary cause may be obvious in most cases of RP, diagnosing a (developing) CTD may be difficult. Recognition of underlying CTD in patients with RP is important as it is associated with complications such as digital ulcers, renal disease, and pulmonary arterial hypertension (PAH).

PULMONARY ARTERIAL HYPERTENSION

PAH is described as a group of disorders characterised by a progressive increase of pulmonary vascular resistance (PVR), causing elevated pulmonary artery pressure (PAP) and right ventricular dysfunction, and carries a poor prognosis in terms of survival. PAH includes idiopathic PAH (iPAH), a familial form (fPAH), and secondary PAH in the setting of CTD, especially SSc. PAH secondary to CTD is more treatment resistant and has a worse prognosis than iPAH.

INVolVEMENT OF THE Microcirculation in Raynaud’S Phenomenon, CONNECTIVE Tissue Disease, AND PULMONARY Arterial HYPERTENSION

The smallest components of the blood vessels - the arterioles, capillaries and venules- are collectively named microcirculation. Each component has a characteristic structure and function. The microcirculation controls tissue perfusion, blood-tissue exchange and tissue blood volume. The endothelium is the monolayer of cells that lines the inner surface of all blood vessels and plays an important function in vascular physiology and pathophysiology.
Although the exact pathophysiology of RP has not been elucidated, there is an imbalance between vasoconstriction and vasodilation in favor of vasoconstriction in RP (see figure 2).

Several possible contributors are noteworthy. Firstly, functional abnormalities in the microcirculation may lead to increased vasospasm and reduced vasodilation. Secondly, structural abnormalities of large and small vessels may play a role. Finally, coagulopathy has been suggested to contribute to RP in at least some cases.8

**Figure 2.** Schematic representation of the pathophysiologic factors contributing to RP. RP is the resultant of an imbalance between vasoconstriction and vasodilation in favor of vasoconstriction. (adapted from previous publications8,9) CGRP = calcitonin gene-related peptide; VIP = vasoactive intestinal peptide

**MICOVASCULAR ABNORMALITIES ARE A HALLMARK OF CTD ASSOCIATED RAYNAUD’S PHENOMENON**

A convenient site to study microvascular abnormalities are the nailfolds where capillary loops run parallel with the skin surface and capillary loops are best visualised. Both invasive
and non-invasive techniques can be used to study microvascular abnormalities. Examples of non-invasive techniques are nailfold capillaroscopy and iontophoresis of the skin (see Methods & Techniques section). Several studies have shown that RP secondary to CTD (especially the scleroderma spectrum disorders) is characterised by strucural nailfold capillary abnormalities and identification of these abnormalities can be of aid in establishing a CTD diagnosis.^{10-13} Recent studies have shown that structural nailfold capillary abnormalities in patients with RP, but without other signs of CTD, predict a future CTD, independently of autonuclear antibodies (ANA).^{4,14}

**MICROVASCULAR ABNORMALITIES AND CTD ASSOCIATED COMPLICATIONS**

There has been considerable interest in the hypothesis that microcirculatory abnormalities not only predict CTD associated RP, but also predict CTD-associated complications such as digital ulcers and pulmonary arterial hypertension (PAH).

**UNANSWERED QUESTIONS**

Although nailfold capillaroscopy (together with the detection of autoantibodies in the blood) plays an important diagnostic role in the evaluation of patients with RP, unanswered questions remain. Firstly, data on capillary nailfold assessment and parameters used to describe abnormalities, are scarce. Establishing the reliability of these assessment methods and parameters are of paramount importance not only to use nailfold capillaroscopy in daily practice, but also as a research tool to evaluate prognosis and response to therapy. Secondly, in order to prospectively study the association between nailfold abnormalities and organ complications such as PAH, cross-sectional studies using sound methods have to show
whether there is any association between systemic nailfold abnormalities and pulmonary vascular abnormalities as in PAH. Thirdly, although SSc is the prototype of a disorder characterised by microvascular abnormalities and organ complications like PAH, little information is available on other CTD associated with PAH. Fourthly, an association between structural abnormalities and organ complications is suspected, but whether microvascular function is also compromised, is unknown. Finally, patients undergoing allogenic bone marrow transplantation for hematologic malignancies, may develop chronic graft-versus-host disease. The skin manifestations of these GVHD patients may be indistinguishable from the sclerotic skin changes seen in SSc patients. The question is whether GVHD patients show the same microvascular abnormalities as in SSc patients.

**OUTLINE OF THE THESIS**

The aim of the thesis is presented in the figure below, representing the presumed association of microvascular involvement with RP, (suspected) CTD, and CTD associated complications like PAH.
To study these associations, the following chapters were included:

- **Chapter 2** describes the materials & methods used to study the microvasculature
- **Chapter 3** shows the results of an international multicenter study on the reliability of nailfold capillary assessment
- **Chapter 4** answers the question if PAH in SSc is associated with systemic and structural microvascular involvement
- **Chapter 5** relates to chapter 4, and shows the results of functional microvascular abnormalities in SSc associated PAH
- **Chapter 6** describes the microvascular involvement in CTD associated PAH other than SSc
- **Chapter 7** shows the results of microvascular abnormalities in patients with sclerodermatous skin changes (resembling the skin changes in SSc) as a manifestation of chronic graft-versus-host disease following allogenic bone marrow transplantation
- **Chapter 8** gives a general discussion of the results found in this thesis and gives pointers to further research
- **Chapter 9** contains a layman’s summary of the thesis, acknowledgements, and Curriculum Vitae in Dutch, and a list of publications
REFERENCE LIST


