General Discussion
OUTLINE

This chapter summarises the main findings of the thesis, puts these findings in perspective, and gives pointers to future studies.

WHAT ARE THE MAIN FINDINGS OF THIS THESIS?

The reliable assessment of nailfold abnormalities and the answer which parameters could be used in capillaroscopic studies was one of the first issues we addressed. The international study we undertook with the groups in Manchester (UK) and Lund (Sweden) on the reliability of nailfold capillaroscopic assessment (chapter 3) showed that with the use of digitised mosaic nailfold images, reliable assessment can be made in terms of inter- and intra-observer agreement. All quantitative parameters, such as capillary density and capillary loop dimensions, showed high reliability. The same, although to a lesser extent, was true for quantitative parameters such as architecture, avascularity, haemorrhage, crossed, ramified, and bushy capillaries. Scoring of tortuous and bizarre capillaries showed poor reliability and could be omitted.

Having a reliable tool in terms of inter-and intra-observer variability to investigate nailfold capillary abnormalities, we focused on the association between systemic microvascular abnormalities and pulmonary arterial hypertension (PAH), mainly in systemic sclerosis (SSc), which is the prototype of a connective tissue disease (CTD) associated with PAH. Using only quantitative assessments, it was shown that differences were present between SSc patients with and without PAH (chapter 4). Capillary density was significant lower in SSc patients complicated by PAH compared to SSc patients without PAH. In addition, capillary density
negatively correlated with the severity of PAH in patients with SSc PAH, as well as in patients with idiopathic PAH.

Capillaroscopy can visualise structural nailfold abnormalities, but cannot assess functional integrity of the microcirculation. After having observed structural nailfold abnormalities SSc-PAH patients, we asked ourselves if microvascular ability to dilate in response to vasodilator drugs could also be impaired. Iontophoresis combined with laser Doppler ultrasound revealed a significant reduction in endothelium-dependent vasodilation in SSc PAH, but not in SSc patients without PAH (chapter 5). In contrast, endothelium-independent vasodilation was unaffected.

SSc is the prototype of CTD characterised by microvascular abnormalities and associations between organ complications such as digital ulcers and PAH have been most extensively studied in the context of this disease. However, PAH can occasionally complicate other CTD’s. In contrast with SSc, not all patients with other CTD than SSc have nailfold abnormalities. However, studies on other CTD patients were scarce, and only CTD patients without PAH were included. We showed that the majority of patients with CTD other than SSc and without PAH indeed did not show significant nailfold abnormalities. However, if such non-SSc CTD patients had PAH, nailfold capillary abnormalities were severe and indistinguishable from those seen in SSc patients with PAH (chapter 6).

Patients with chronic graft-versus-host-disease (cGVHD) following allogenic bone marrow transplantation may develop skin abnormalities resembling those seen in SSc. Given the presumed involvement of the immune system in the pathogenesis of both diseases, interest
has raised in the potential involvement of microvascular abnormalities in cGVHD. Recent studies suggested that indeed microvascular abnormalities were highly prevalent in sclerodermatous cGVHD. If this were true, nailfold capillaroscopy could be used as a predictor of sclerodermatous cGVHD. However, contrary to patients with SSc, we found that patients with cGVHD showed no capillaroscopic abnormalities (chaper 7).

**HOW CAN THESE FINDINGS BE PLACED IN PERSPECTIVE?**

In recent years, nailfold capillaroscopy has gained much popularity in the analysis of patients with Raynaud’s phenomenon and, more recently, in the early diagnosis of SSc. Indeed, the technique is easy to use and non-invasive. However, to be a reliable diagnostic and research tool, an easy way of assessing nailfold abnormalities is a prerequisite for use in daily practice and in research. The international study we undertook showed that some of the parameters were highly reliable, especially the ones that could be quantified. However, only quantitative parameters are not enough to describe the complex pattern that can sometimes be observed. With the results of our study we show which parameters can be used to describe nailfold abnormalities in a reliable way.

The pathophysiology of CTD and its complications is poorly understood. Some, but fortunately not all CTD patients develop PAH. In both SSc and other CTD patients with PAH, it was clearly shown that the systemic microcirculation is severely affected, irrespective of disease duration. This implies that the subdivision of scleroderma patterns seen with nailfold capillaroscopy in an ‘early’, ‘active’, and ‘late’ may be a marker of disease severity in terms of organ complications. One could also postulate that several different CTD’s may have more
in common than previously thought, and that shared pathophysiologic pathways are involved in CTD complications like PAH. It is evident that the microcirculation is involved in these pathways, either as a cause or as a consequence. It is remarkable in this respect that structural microvascular abnormalities could be observed in almost all SSc patients, but microvascular function was reasonably well preserved in SSc patients without PAH. Could it be that the development of PAH in CTD follows a route of deterioration of systemic endothelial structure and function, also in the lung? And could it be that preserved endothelial function in CTD protects patients with CTD from developing organ complications? A better understanding of the mechanisms influencing this process could eventually lead to targets for pharmacologic interventions. This field is already in progress. Conceivably, measurement of endothelial function and early intervention as soon as endothelial function declines, before complaints develop, could protect patients from complications like PAH.

The similarities between SSc and cGVHD, where immunologic and skin abnormalities can be observed, led to the hypothesis that microcirculatory abnormalities are involved in both diseases. As far as structural abnormalities concerned, no abnormalities could be detected in cGVHD patients. This does not exclude the possibility that the microcirculation is involved in cGVHD, since only microvascular structure, not function, was addressed in these patients. However, the lack of (structural) microvascular abnormalities could explain why PAH without lung parenchyma involvement (as can be seen in SSc) is not observed in cGVHD. On the other hand, the hindsight of nailfold abnormalities precludes nailfold capillaroscopy as a suitable tool to predict sclerotic skin disease, or to monitor response to therapy in cGVHD.
WHAT CAN BE DONE NEXT?

Nailfold capillaroscopy has to be further refined. There is need for a clear, easy to use, reliable, and validated scoring system. This will further stimulate research aimed at identification of the proper role of nailfold capillaroscopy in the diagnosis of CTD, CTD-related complications, and assessment of response to therapy. Although this thesis sheds some light on the complex pathophysiology of microvascular abnormalities in CTD and associated complications like PAH, the study design only allows for generating hypotheses. Future studies are needed to prospectively evaluate the predictive value of nailfold abnormalities for future organ complications like PAH. If capillaroscopy can predict such complications, further studies are needed to show if early treatment will change the prognosis of high-risk CTD patients. Capillaroscopy holds promise as an outcome measure of CTD-related microvascular disease, including studies of treatment response.