The use of microcirculatory techniques in the assessment of pathophysiology, diagnosis and management of critical limb ischemia

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Chapter 11

General discussion, clinical implications and suggestions for further research

Improving the diagnosis and management of critical limb ischemia

Microcirculatory techniques

Microcirculatory techniques (capillary microscopy, transcutaneous oxygen pressure [TcpO₂] measurements and laser Doppler) have been available and evaluated in peripheral arterial disease (PAD) for almost 30 years now.¹ These techniques have provided understanding in the pathophysiology of critical limb ischemia (CLI), but have also been studied to investigate their usefulness in the diagnosis and management of CLI. At the time the studies described in this thesis were performed, routine clinical practice was based on the guidelines described in the European Consensus Document, in which an ankle blood pressure <50 mm Hg was the main discerning parameter. However, as shown in the study described in chapter 3 and as implemented in the latest Transatlantic Inter-Society Consensus on the Management of Peripheral Arterial Occlusive Disease (TASC 2000), a definition of CLI based solely on the ankle pressure (AP) is regarded obsolete.² However, the TASC document does not provide other ‘absolute’ guidelines for the diagnosis of CLI. At present, the diagnosis and management of patients suspected of CLI is mainly based on the clinical judgment of a vascular specialist, which tends to be subjective and lacks uniformity. Therefore, new conclusive measurements appear necessary for standardization of clinical practice, as well as careful selection of patients, and a better comparison between different studies.

Recent investigations have shown that the toe pressure (TP) and microcirculatory techniques correlate better with the need for vascular intervention than the conventional macrocirculatory techniques (AP and ankle brachial pressure index [ABPI]).³⁴ In a prospective study in patients with diabetic foot problems, the TcpO₂ showed a good prognostic value as to wound healing and the selection of patients requiring vascular intervention.⁵ The TP and TcpO₂ were found to be simple non-invasive techniques that provide functional information about the endangered most distal macrocirculation (TP) and microcirculation (TcpO₂) in patients suspected of CLI. Therefore, a combination of these techniques might be an objective parameter for the standardization and definition of CLI. However, despite its diagnostic potential, these techniques are rarely used in clinical practice. Hence, the ultimate question regarding the clinical usefulness of these microcirculatory techniques needed to be answered.

Toe blood pressure measurements

At present, the TP is mainly measured by means of photoplethysmography (PPG). However this technique has its shortcomings in the lower pressure ranges, which are most relevant in CLI. At low pressures, the PPG lacks the pulsatile signal necessary to determine resumption of blood during deflation of the cuff surrounding the hallux. To overcome this drawback, we used the laser Doppler (LD) technique instead, which can be done irrespective of the presence of
In Chapter 2 we described the evaluation of the clinical value and reproducibility of laser Doppler vs. conventional PPG in the measurement of TP. Laser Doppler appears to be a reliable alternative for conventional PPG. The results of the measurements of both techniques are comparable and well reproducible (intra-class correlation coefficient [ICC]: 0.86 - 0.92). Moreover, LD seems to be more sensitive in low pressure ranges than PPG. Laser Doppler could measure adequately TP in 19 legs (out of 112 legs) while PPG did not. This is particularly relevant in the assessment of the presence of critical ischemia.

A practical disadvantage of the LD used was that three devices (LD, cuff inflator, and data acquisition system) were necessary. However, this problem has been solved in a new, commercially available, device containing all three elements. The sensitivity of the laser Doppler might be further enhanced by the use of heated probes. Local heat causes hyperemia which increases total skin microcirculatory perfusion without disturbing the measurement. This increased perfusion might pronounce the reappearance of flow during deflation of the cuff. This new application of the laser Doppler and new device are worthwhile to be evaluated.

Measurement variability
One of the reasons that TP and TcpO₂ are not generally used as diagnostic parameters is that these measurements are thought to be unreliable due to the large measurement variability. The ankle/brachial pressure index (ABPI) is known to be a reliable parameter, whereas the reproducibility of TP and TcpO₂ are less thoroughly evaluated in clinical practice. Hence, we performed a study on the intra- and inter-observer reproducibility of TPI, TcpO₂, ankle pressure (AP), brachial pressure (BP) and ABPI. The results of this study are described in chapter 3.

The intra- and inter-observer reproducibility at one day and after one week of BP, AP, ABPI and TP is good and comparable (ICC range 0.80-0.99), except for the BP after one week. The TcpO₂ is somewhat less, but still moderate reproducible (ICC range 0.62-0.98). However, the absolute variations of all parameters were found to be larger than assumed thus far (approximately 15%). In contrary to previous reports we not only evaluated the intra-observer measurement variability, but also the biological fluctuation over time and inter-observer variability, which is more like the clinical practice. The finding that the biological variation of the TcpO₂ is greater than the biological variation of the blood pressure parameters, can be explained by the fact that the TcpO₂ is a microcirculatory parameter. The microcirculation is influenced by both central (cardiovascular and pulmonary status) and local factors (local blood flow, skin metabolic activity, and diffusion conditions, such as epidermal thickness and composition). Whereas the other pressure parameters are mainly influenced by central pressure regulating factors.

For clinical practice the reproducibility is expressed as the repeatability coefficient (RC), as it indicates when the difference between two measurements can be interpreted as significant. A significant difference between two measurements, i.e. a difference larger than the RC, indicates that the difference is not caused by the variation of the measurement itself, but by a change in the clinical situation, e.g. when the treatment has been successful or the disease has progressed. In the present study the inter-observer RC of BP was 31 mm Hg, of AP: 44 mm Hg, of ABPI: 27 %, of TP: 41 mm Hg, and of TcpO₂: 30 mm Hg. A RC of 44 mm Hg indicates that two ankle pressure measurements that differ less than
44 mm Hg cannot, with a certainty of more than 95%, be considered to be really different; a difference less than 44 mm Hg could also be a result of measurement variation. In clinical practice, especially when low values (or values around a cut-off value) are measured, the RC should be taken into account. If the measurement result plus or minus its RC includes the cut-off value, repetition of the measurement is advocated. The variation of the measurements has never been expresses in RC thus far, therefore a comparison with literature is not possible.

**Optimum cut-off values**

Thus, knowing the reproducibility, our next goal was to assess the optimal cut-off values of TP and TcpO₂ for CLI in comparison to a reference standard. Although the choice of the reference standard is crucial for the final outcome of the study, a true reference standard for CLI does not exist. Previous studies have used wound healing, success of vascular intervention and need for amputation as a reference standard for CLI. Classification of CLI based on objective parameters is necessary for standardization of clinical practice, a careful selection of patients, and a better comparison between different studies. Therefore, we used the 'clinical indication for vascular intervention' (within six months) as the best 'substitute' reference standard, since this definition is most useful and practical in the daily practice of the medical profession concerned with these patients (chapter 4).

The results of this study show that patients with symptoms of CLI and a high ankle pressure or ABPI may well have leg ischemia requiring treatment (58%), and that the choice for invasive therapy in patients with severe leg ischemia can indeed be facilitated by measuring TP and TcpO₂ using cut-off values of TP below 30 mm Hg and a TcpO₂ below 25 mm Hg. The additional measurement of toe blood pressures and/or TcpO₂ substantially increase the pre-test probability for vascular intervention. Therefore, we concluded that TP and TcpO₂ might improve the management (differentiate between the existence or absence of severe leg ischemia requiring invasive treatment) of patients clinically suspected of CLI.

**Studying the clinical inference; design**

The evaluation of a diagnostic test in relation to a substitute reference standard, as described in chapter 4, is in principle incomplete, because the effect on clinical outcome is not evaluated. The new diagnostic tool has no advantage for clinical practice as long as it does not improve clinical outcome. Therefore we designed a prospective diagnostic randomized clinical trial (D-RCT) to further evaluate the value of TcpO2 and TP in clinical practice. From a methodological point of view a D-RCT is a relatively uncommon model of diagnostic research. In chapter 5 we describe the rational, theoretical considerations, design issues, limitations, and solutions of a RCT, taking the diagnostic and therapeutic issues around critical limb ischemia as an example.

A D-RCT is suited when a true reference standard is lacking and two different concepts (functional versus anatomical information) incorporated into a whole management strategy, including the effect on clinical outcome, are to be compared. This is important as the decision for intervention (diagnosis) is not a snapshot, but a continuous interactive process in which the vascular specialist continuously judges the clinical situation, new diagnostic findings, comorbidity, and the risk of complications and failures of invasive therapy. Besides, a D-RCT not only evaluates the effect on diagnosis, but also incorporates the total effect on clinical outcome, side effects of the tests, use of the results by the physician, and side effects of the therapy. On the other hand, the D-RCT has some
disadvantages as to the power and size of the trial, and the influence of treatment on the outcome parameter. Incorporation of treatment in the outcome variables introduces a so-called black box in which many factors (the efficacy and use of the test including subjective judgment of physicians, and effect of therapy) are involved, which could enhance or mitigate the value of the test. Taking these considerations into account, a D-RCT is the best available strategy to evaluate the value of TP and TcpO₂ in clinical practice.

To improve the significance of this study we excluded the so-called clear-cut cases (patients with obviously severe and clearly mild disease) leaving only patients with an uncertain diagnosis, because only in these patients additional diagnostic effort is clinically relevant. Furthermore, inclusion of borderline patients makes it more likely to detect a difference between the randomization groups, since different management strategies are not likely to result in a different clinical outcome in undisputable (clear-cut) cases.

State of the art of microcirculatory techniques in the management of CLI
Many previous reports have suggested the benefit of TP and TcpO₂ in the management of patients suspected of CLI. However, contrary to these previous reports and to our evaluation as described in chapter 4, the D-RCT described in chapter 6 showed that the use of TP and TcpO₂ did not improve clinical outcome. There were no significant differences in pain, wound healing, survival, limb-survival, or quality of life between the two groups of randomization. Furthermore, the number of diagnostic procedures was not reduced by the use of these two objective measurements.

The study failed to show a difference between the two randomization groups because, apparently, the clinical eye of an experienced physician can also sufficiently appreciate the local (micro-) circulation of the endangered tissues of the distal leg, as do the TP and TcpO₂, in order to plan the subsequent management policy. Therefore, we conclude that the routine use of TP and TcpO₂ has no additional clinical value in the management of patients suspected of CLI.

This study might have failed to show a significant difference because the outcome in a D-RCT is influenced by many other factors (black box). Furthermore, we might have increased the number of false positive results (diagnostic duplex or angiography without treatable vascular defect), since we preferred relatively high cut-off values as we did not like to under-treat patients. Additionally, the measurement variation of a single TP and, in particular, TcpO₂ might have introduced a considerable number of false negatives and positives.

The TP (using laser Doppler) and TcpO₂ might still be advocated as an objective instrument in the follow-up in research settings. Therefore, we recommend the use of TcpO₂ only in research settings, and repeated measurements are than advocated. The cut-off values of a TP below 30 mm Hg and a TcpO₂ below 35 mm Hg can be used as objective criteria for CLI in research. Furthermore, the TP is still necessary in the evaluation of patients with diabetes in whom the ankle pressure is not always reliable due to media sclerosis.
Improving our knowledge of the pathophysiology of CLI

The importance of capillary pressure and microcirculation in CLI
Microcirculatory perfusion is essential for the nutrition of the skin, and it is actually the compromised microcirculation that causes the symptoms in patients with CLI. Capillary perfusion and transmural pressure are delicately regulated by microvascular constriction mechanisms, which are activated upon a change in posture, but become deactivated by ischemia and/or metabolic waste products inducing vasodilation. Capillary flow (red blood cell velocity) and total skin perfusion (laser Doppler flux) are known to be disturbed in patients with severe peripheral arterial disease. However, information about the capillary pressures was lacking thus far.

Technological aspects of capillary pressure measurements
At present, capillary pressure measurements in humans are performed using a servonulling micropressure system containing an oil-water interface. Such a system has some drawbacks, e.g. the system needs to be absolutely free of air and the measurements are performed through a layer of water, which reduces the visualization of the capillaries with time. In an attempt to overcome these drawbacks, we assessed the feasibility and reproducibility of capillary pressure measurements in the fingers using an alternative micropressure system using an air-water interface.

In chapter 7 we describe the results of this study which showed that capillary pressure can be measured well with the alternative set-up. The pressures obtained are in agreement with the results reported by other investigators using a micropressure system containing an oil-water interface. The reproducibility of the present system was found to be acceptable and comparable with the conventional method. Irrespective of the system, dynamic capillary pressure measurements might have two other drawbacks which influence reliability. First, insertion of the relatively large pipette tip (Ø approx. 4 µm) in the tiny capillary (Ø approx. 8 µm) can disturb the flow and, consequently, the pressure. Second, the puncture of capillaries by the fragile pipettes require preparation of the skin by paring away the cuticle and upper layer of the stratum corneum, which might induce a local inflammatory response with disturbance of flow and pressure. Although the effects of both interventions on capillary pressure have not been evaluated directly, the results of this study show that capillary pressure can be measured without hampering capillary flow. This indicates that direct capillary pressure measurements can be performed reliably with this technique.

Influence of leg dependency on skin microcirculation in healthy volunteers
According to the literature, capillary pressure in the foot has only been investigated in two healthy subjects by static pressure measurements, as is described in the classical work of Levick and Michel: "The effects of position and skin temperature on the capillary pressures in the fingers and toes." They showed that capillary pressure increases upon leg dependency, and that capillary pressure is related to venous pressure. In chapter 8 we described and evaluated a setup that provides simultaneous information of local flow (capillary density, capillary diameter, capillary blood cell velocity and laser Doppler) and dynamic capillary pressure in both sitting and supine positions in the toes of healthy volunteers.
The results show that capillary pressure in the hallux increases significantly upon dependency, albeit not as much as the toe blood pressure does. Local flow did not change significantly upon postural changes. These observations show that activation of the peripheral vasoconstriction mechanisms appears to reduce the transmission of the orthostatic rise in arteriolar pressure upon dependency to the capillaries. This would be in agreement with our hypothesis that arteriolar vasoconstriction mechanisms prevent transmission of the increase in arterial pressure to the capillaries as an oedema preventing factor. However, the constant microcirculatory flow indicates that flow regulation outweighs pressure regulation in the microcirculation of the foot skin. Arteriolar vasoconstriction seems to adapt to venous pressure (probably by the venoarteriolar reflex) to guarantee a constant flow through the microcirculation. However this theory is not confirmed by previous observations showing that microcirculatory perfusion in the foot changes upon a change in posture, as was shown by a reduced red blood cell velocity and a decreased laser Doppler flux (LDF), probably caused by arteriolar vasoconstriction. This difference could be caused by the difference in measurement technique and location. Our observations might have clinical implications for the evaluation of vascular interventions. Since capillary pressure can be regulated by vasoconstriction mechanisms, capillary flow (and possibly macrocirculatory flow) might give more important information about the function and effectiveness of vascular interventions than peripheral blood pressure measurements.

Influence of leg dependency on skin microcirculation in patients with PAD
The same appeared to be true in situations with a critically reduced peripheral arterial blood pressure as in patients with PAD. The results presented in chapter 9 show that capillary pressure in patients with PAD is not significantly different from capillary pressure in healthy volunteers. In contrast with pressure, microcirculatory flow (assessed by laser Doppler fluxmetry) and red blood cell velocity, is significantly reduced in patients with severe PAD (Fontaine stages III and IV) as compared to healthy volunteers and patients with intermittent claudication. This implies that the local, pre-capillary resistance appears to be an essential factor in the regulation of capillary perfusion pressure keeping capillary transmural pressure differences within limits to maintain physiological transcapillary transport. These observations suggest a narrow balance between transcapillary transport, capillary pressure and capillary flow. Generally, capillary (transmural) pressure is maintained at a minimum closing pressure (about 20 mm Hg) at the expense of flow. Above this minimum level, e.g. in the sitting position, capillary pressure in the foot increases upon a rise in venous pressure, maintaining capillary flow. These early observations support the idea that conservative therapeutic options that increase flow by reducing the venous pressure (like venous compression therapy) can be effective. However, further research in the microcirculatory regulation mechanisms in ischemic tissue including peripheral vascular disease is necessary to unravel the regulation mechanisms and therapeutic prospects.
Future perspectives of capillary pressure measurements

I feel that capillary pressure measurements (in hands and feet) can offer new insights in the pathophysiology of various diseases. The present study is the first exploration of toe capillary pressure in patients with PAD, and has only been performed in 7 patients with CLI and 8 patients with intermittent claudication. The presence and formation of oedema before and after a revascularization procedure has not been evaluated yet. Further investigation in patients with and without oedema formation before and after vascular intervention should reveal the role of capillary pressure in the formation of oedema, which is also known as an important compounding factor in other diseases. In addition, the relation to vascular interventions or non-invasive therapeutic options in PAD and to the presence of diabetes and diabetic neuropathy appear worthwhile to be investigated. Beside PAD, this method might also add to our insight in the pathophysiology of various other vascular diseases, like chronic venous insufficiency and microcirculatory disorders such as primary and secondary Raynaud’s disease (vasospastic disorders). Also, the influence of various cardiovascular drugs on capillary pressure is still unknown. Last but not least, the role of capillary pressure in the formation of oedema and treatment of sepsis (‘vasodilation’ or ‘vasoconstriction’) remains unresolved thus far.

Improving our knowledge of the impact of CLI on quality of life

Finally, health related quality of life (HRQOL), was studied. The results of the study presented in chapter 10 show that patients with PAD have a seriously reduced HRQOL on all domains of the SF-36. Patients with PAD score exceptionally low on domains related to their complaints, such as physical functioning and role limitations by physical functioning, but also on other domains not directly related to their complaints, like role limitations by emotional problems and social functioning. Remarkably, these aspects only slightly improve in time despite intensive treatment, as can be derived from the graphs presented in chapter 6. The present vascular surgical policy seems to reduce pain and the number of wounds, but only slightly improves physical and mental health. This observation is also confirmed in a recent publication by Hernandez-Osma and Cairois who concluded that changes in dimensions of QOL obtained by limb revascularization do not differ from those of other therapeutic approaches like conservative treatment and primary amputation.

At present, the treatment of CLI mainly focuses on the improvement of leg survival, whereas other aspects of the patient’s well being (physical functioning and emotional support) are underexposed. Hence, more research on and attention to the status and treatment of HRQOL of patients with CLI seems necessary for optimal treatment. However, the SF-36 has its limitations, and may not detect small changes in patients with PAD because it focuses on general health, has large variability and is rather subjective. Therefore, new specific questionnaires for PAD should be developed, evaluated and used to generate knowledge about the patients sufferings and needs.
Conclusion

Microcirculatory techniques can provide important (additional) information about the severity and pathophysiology of patients with CLI, but have no additional value in the routine clinical diagnostic and therapeutic work up. Apparently, a clear judgment on the basis of skilled physical examination does not need additional microcirculatory techniques.

However, the microcirculatory techniques are still useful in research. The combination of TP and TcpO$_2$ can be used as objective criteria for CLI in the standardization of research (new guidelines). Furthermore, the TP can be measured with a laser Doppler.

With the development of capillary pressure measurements in the foot, further examination of the pathophysiology of CLI and other (vascular) diseases by microcirculatory flow and pressure parameters is now possible. New pathophysiological insights may offer new perspectives in conservative (non-invasive) treatment of CLI.

PAD has a large impact on the quality of life. Much more attention should be paid to improve HRQOL in patients with CLI. Further disease-specific research in this field is mandatory.

Reference List
