Focus on flow: Imaging the human microcirculation in perioperative and intensive care medicine
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Citation for published version (APA):
Elbers, P. W. G. (2010). Focus on flow: imaging the human microcirculation in perioperative and intensive care medicine

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Introduction
Setting the Scene

The microcirculation is essential for life. This was probably first recognized by Hippocrates. Around 400 BC, the father of modern medicine observed that “in fevers which do not intermit, if the external parts be cold, and the internal burning hot, and fever prevail, it is a mortal sign”. This is likely a description of a septic individual presenting with severely impaired microvascular flow due to multiple pathophysiological processes, although the concept of the microcirculation as an organ that distributes oxygen and nutrients to tissue was far from developed as it is now. Hippocrates was the first physician to reject superstitions, legends and beliefs which credited supernatural or divine forces with causing illness. Therefore he would have been very pleased that today’s technology has enabled physicians to monitor the human microcirculation at the bedside in real time thus allowing objective assessment of possible disturbances and their causative mechanisms both qualitatively and quantitatively.

Indeed, the publication of this thesis only shortly follows the celebration of the 10th anniversary of Orthogonal Polarization Spectral (OPS) imaging [1]. OPS imaging was a revolution as it brought human microvascular imaging to the bedside. Not much later, Sidestream Dark Field imaging was invented, offering superior imaging while continuing to be small, minimally invasive, safe and relatively inexpensive [2]. Both techniques applied known optical methods to study the microcirculation into hand held microscopes, OPS imaging being based on cross polarization [3] and SDF imaging being based on dark field illumination [4]. Both techniques use green light that is absorbed both by oxygenated and deoxygenated hemoglobin present in the red blood cell flowing in the microcirculation. In this way magnified moving images may be recorded representing an area of approximately 1 mm$^2$ of these flowing red blood cells and thus in the functional microcirculation. These techniques can be applied on exposed organ surfaces, nail fold skin and mucous membranes. At the bedside it has been commonly used for microvascular monitoring at the sublingual site because of its proximity to the brain, its phylogenetic relationship to the gut and ease of access.

Before the introduction of OPS- and SDF imaging, monitoring the human microcirculation was hampered by a lack of suitable techniques because only bulky microscopes were available. At that time, only nail fold video microscopy and laser Doppler techniques were apt for use in humans. However, nail fold video microscopy has limited value as it is extremely sensitive to external temperature and vasoconstrictive agents. Laser Doppler can be used to measure gastric or jejunal mucosal blood flow as well as skin and muscle blood flow, but does not take into account microvascular blood flow heterogeneity. Intravital microscopy used to be the gold standard for imaging the microcirculation in that era. However this technique can only be used in animal models and in a limited number of clinical scenarios as it requires large microscopes, fixed tissue for stability and sometimes the infusion of fluorescent dyes.

As early as the beginning of last century, various pioneers started to use intravital microscopy and found that human ungual blood flow was altered in various conditions including heart failure, hemorrhagic shock and sepsis, as reviewed recently [5]. For septic patients,
this was later confirmed using laser Doppler techniques. These findings were later replicated for various other tissues in many studies using intravital microscopy in animal models of sepsis.

It is interesting that even though microvascular alterations have long been known to exist, clinicians continue to rely on monitoring and optimizing global hemodynamic parameters. This is based on the expectation that optimizing systemic hemodynamic variables will improve oxygen delivery to tissue. Taking sepsis as an example, this idea was strengthened by the so-called goal directive resuscitation strategies that began to emerge during the last decades of last century [6]. This approach has now been embedded in guidelines such as the surviving sepsis campaign that was introduced in 2004 and updated in 2008 [7]. This campaign introduced a treatment bundle based on the concept of early goal directed therapy. Among other interventions, these goals include therapeutic targeting of macrohemodynamic parameters such as arterial and venous blood pressure and central or mixed venous oxygen saturation. Although it is difficult to disentangle the different components of a bundle, its application was repeatedly shown to reduce mortality. This makes quite a strong case for targeting global hemodynamic parameters in sepsis.

However, despite implementation of these goal directed protocols, critically ill septic patients continue to die. In addition, two early trials showed that targeting supra normal values for oxygen delivery did not improve outcome [8, 9]. This may be explained by dissociation between global hemodynamics and microvascular perfusion. Thus, optimizing macrohemodynamic parameters may not necessarily cause all capillaries to be adequately perfused.

This concept made the use of OPS- and SDF imaging highly attractive for characterizing the human microcirculation in sepsis. A landmark study by De Backer et al. included 50 patients with severe sepsis [10]. The density of their microvessels was significantly reduced and these alterations were more severe in nonsurvivors. These findings were later confirmed by Trzeciak et al. [11]. In addition, Sakr et al went on to show that in 49 patients in septic shock persistent lack of small microvessel perfusion was strongly associated with organ failure and death and demonstrated that it was microcirculatory flow which represented the single most specific and sensitive indicator of such outcome [12].

Indeed, a consistent finding from studies using OPS- and SDF imaging in septic patients was that the human microcirculation showed marked heterogeneity in disease. In addition such microcirculatory alterations were found to occur in otherwise normalized global hemodynamic parameters. This indicates that sepsis is a disease of the microcirculation even during treatment. Direct observations of the septic microcirculation have revealed the coexistence of well perfused and non-perfused capillaries which would lead to a decreased oxygen extraction due to increased diffusion distances [13].

This idea of a dissociation between macro- and microhemodynamics was further exemplified by De Backer et al who showed that the beneficial effects of dobutamine are reflected in the microcirculation in patients with septic shock and that these are independent of its systemic effects [14]. Similarly, Spronk et al. reported on a case series of septic patients
who despite a mean arterial blood pressure of more than 60 mm Hg and central venous pressure greater than 12 mm Hg showed stasis of microcirculatory flow [15]. Infusion of 0.5 mg of nitroglycerin intravenously resulted in a marked increase in microvascular flow. They concluded that instead of focusing on macrohemodynamic parameters, recruitment of the microcirculation could be a new resuscitation endpoint in septic shock. In addition, Boerma et al. used OPS imaging in a patient who was given terlipressin for catecholamine-resistant septic shock. Despite correction of macrohemodynamic parameters, this lead to microvascular shutdown [16]. Finally De Backer et al. showed that administration of activated drotrecogin alpha rapidly improves sepsis-induced microvascular alterations, relatively independent from global hemodynamic parameters, whereas its cessation was associated with a transient deterioration [17].

**Thesis**

The key message from these studies is that in sepsis, and during resuscitation in sepsis, microvascular alterations are heterogeneous and are not necessarily reflected by routinely used measures of global hemodynamic parameters. Hemodynamic management of patients in routine clinical practice in other areas than sepsis also focuses on the stabilization of macrohemodynamic variables. In fact, these parameters including heart rate, arterial and venous blood pressure and sometimes cardiac output and oxygen derived parameters are measured in most patients in perioperative and intensive care medicine. In addition, as reviewed recently, many trials using goal directed therapy aiming at aggressive correction of global hemodynamic showed reduced mortality in high risk surgery [18].

Therefore, again, monitoring and treating global hemodynamics makes sense both from a physiological and evidence based point of view. However, if microvascular heterogeneity and disparity between global hemodynamics and microvascular perfusion observed in sepsis, would also hold for non-septic patients in intensive care and perioperative medicine, today’s clinicians may sometimes be directing their attention and therapies to the wrong parameters. It is well known that many non-septic patients in intensive care medicine and perioperative medicine, especially those being critically ill, having been resuscitated from cardiac arrest or having been subjected to major surgery suffer from a systemic inflammatory response syndrome, not unlike sepsis [19]. This might imply that the same microvascular alterations and possibly the absence of a clear relationship with macrohemodynamic parameters may also exist in other patient groups than in septic patients. In fact, De Backer had already shown that microvascular blood flow alterations are frequently observed in patients with severe heart failure and are more severe in patients who do not survive [20]. It was against this background that the studies in this thesis were conceived.

The hypothesis of this thesis is that discrepancy between macrohemodynamic and microvascular parameters also exists in non-septic patients in perioperative and intensive care medicine. To prove this thesis, a large number of studies were executed, several of which form the core of this publication. A large variety of routine clinical settings were studied, all characterized by the fact that clinical management of patients was routinely guided by
measurement of macrohemodynamic variables. The aim of our studies was to characterize microvascular flow in these perioperative settings using SDF imaging and relating these to routinely measured global hemodynamic parameters in order to unveil the possible disparity between these two physiological compartments.

Outline

The vivid images of moving red blood cells and stagnant flow in various disease states as obtained by OPS- and SDF imaging, have served to remind us that the microcirculation is far more complex than just a collection of connecting pipes. In chapter 1, the concept of viewing the microcirculation as an organ is introduced. Just like other organs, the microcirculation is composed of various cell types such as endothelium, smooth muscle cells, red and white blood cells in complex interaction with each other. Further, also similar to other organs, the microcirculation also consists of a large number of other components including platelets, coagulation factors, and a plethora of cytokines and chemokines. These components display an intricate interplay not unlike an orchestra performing a symphony. In this way the microcirculatory organ is highly regulated to perform its main function mainly of transporting oxygen and nutrients to the tissue cells along with the removal of waste products. This chapter will introduce the reader to the various techniques for monitoring microvascular function including OPS- and SDF imaging. In addition it will summarize what is known on microvascular alterations in the critically ill with a focus on septic patients, and outline potential strategies for resuscitating the microcirculation.

Almost 40 years ago, Weil and Shubin proposed their now famous classification of shock states [21]. Based on their understanding they distinguished four types of shock, which they identified as obstructive, hypovolemic, cardiogenic and distributive shock. They recognized the relevance of the microcirculation in distributive shock in which malfunction in the distribution of a normal or even of an elevated cardiac output may hamper microvascular perfusion. Therefore, in chapter 2, it is hypothesized that in addition to classifying shock states based on global hemodynamics, it may be necessary to also classify them according to microvascular hemodynamic patterns as observed by bedside microvascular imaging. Such classification may be helpful to discriminate patterns of microvascular dysfunction and may offer guidance when selecting strategies to improve microvascular flow.

In 2006, an international round table conference was held in Amsterdam, the Netherlands [22]. Here, international experts including delegates from our group, reached consensus on how to best evaluate the microcirculation using OPS- and SDF imaging. Among other recommendations, it was proposed that comprehensive description of the functional state of the microcirculation must include Perfused Vessel Density, Percentage of Perfused Vessels and Microvascular Flow Index as well as an index of flow heterogeneity. This effort should be applauded, as uniform and thorough analysis assures quality and enables direct comparison between studies. However, the proposed approach may be time consuming as despite advances in computer analysis, current practice is still predominantly manual. Therefore, chapter 3 proposes a standard operating procedure for microvascular analysis.
that simplifies and speeds up this often daunting task without any compromise to the proposed recommendations. Although many groups now adhere to the proposed guidelines, some continue to either use their own scoring systems or only partly implement the recommendations. This is addressed in chapter 4, in which the case for uniform microvascular analysis is further reinforced.

The core of this thesis is formed by six studies. Four of these are original papers while two are case reports. All of these use SDF imaging in a large variety of clinical settings in perioperative and intensive care medicine. Their common aim was to relate findings from microvascular imaging to the macrohemodynamic parameters that are routinely used for monitoring and targeting interventions in these settings.

In leukemic patients, the abundance of white blood cells may sometimes cause a syndrome known as leukostasis. It was hypothesized that microvascular flow impairment due to white blood cell clumping may be the root of the problem. Therefore, SDF imaging was used to characterize microvascular flow in a patient with extreme leukocytosis. The results may be found in chapter 5.

Following cardiac surgery, it is important to treat hypertension to avoid suture line rupture [23]. In the Netherlands, ketanserin is sometimes used to achieve this goal. It reliably decreases blood pressure within minutes. However, it is unknown whether this decrease in blood pressure is accompanied by changes in microvascular perfusion. Therefore SDF imaging was used to study patients before and after ketanserin administration for hypertension after cardiac surgery. The results are given in chapter 6.

During cardiopulmonary resuscitation, clinicians traditionally focus on global hemodynamics. While this is obviously very important, only animal data is available on microvascular flow during cardiopulmonary resuscitation [24]. Human data is lacking and hence the behavior of microvascular flow in this setting is unknown, especially in comparison to that in a resuscitated patient in whom spontaneous circulation has returned. SDF imaging was used to record microvascular images in a victim of submersion trauma both during mechanical cardiopulmonary resuscitation and after return of spontaneous circulation. Chapter 7 contains the results.

Elaborating on the many unknowns in microvascular perfusion in the setting of cardiac arrest, a controlled study was performed to explore the behavior of the microcirculation in the setting of aortic surgery. The response of the microcirculation to intentional deep hypothermic cardiac arrest was assessed by SDF imaging as a model for spontaneous cardiac arrest. Previously it was unknown when microvascular flow would cease after the heart stops, with estimates ranging from 50 seconds up to 5 minutes [25]. In addition, there was no previous information on microvascular kinetics in the different types of microvessels, e.g. capillaries or venules, in this setting. Our results are reported in chapter 8.

During cardiopulmonary bypass for cardiac surgery the heart-lung machine is responsible for maintaining circulation. This can be done in continuous and pulsatile modes. The benefits of pulsatile perfusion are subject of great debate [26]. Advocates claim that pulsatile
perfusion may improve organ function and even survival, however the evidence is conflicting. The possible protective effects of pulsatile perfusion are usually thought to occur because of an improvement in microvascular perfusion. However, there is no evidence for this in humans. Thus a crossover study was designed in which patients were subjected to pulsatile followed by non-pulsatile perfusion during cardiopulmonary bypass or vice versa. SDF imaging was used during both types of perfusion to record microvascular images, the results of which may be found in chapter 9.

In the ICU, intra aortic balloon pump counter pulsation is frequently used to mechanically support the failing heart. There have been conflicting reports on microvascular changes during IABP support [27]. In addition, the best time to cease IABP support in recovered patients is currently unknown. Chapter 10 reports on the effects on microvascular flow when IABP support is terminated in patients deemed ready for its discontinuation.

This thesis concludes with a discussion on how these studies have contributed to a deeper understanding of the behavior of the microcirculation in perioperative and intensive care medicine especially in relation to commonly measured global hemodynamic parameters. In addition the clinical implications and direction of future research will be examined.

References