The Microcirculation in Severe Heart Failure and Cardiogenic Shock

Cornelis Adrianus den Uil

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The Microcirculation in Severe Heart Failure and Cardiogenic Shock

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Promotor:	Prof.dr. M.L. Simoons
Overige leden:	Prof.dr. J. Bakker
	Dr. A.H.M.M. Balk
	Prof.dr. D.J.G.M. Duncker
Copromotoren:	Dr. W.K. Lagrand
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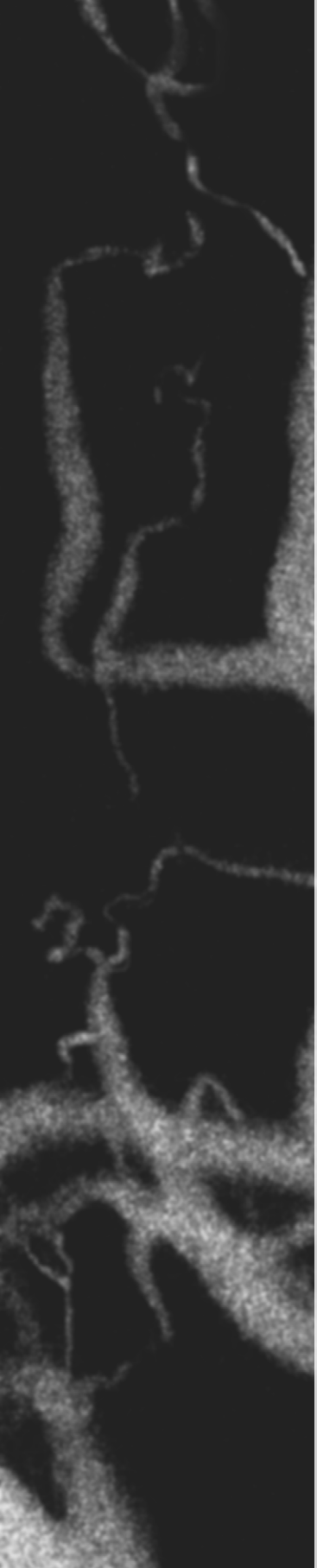
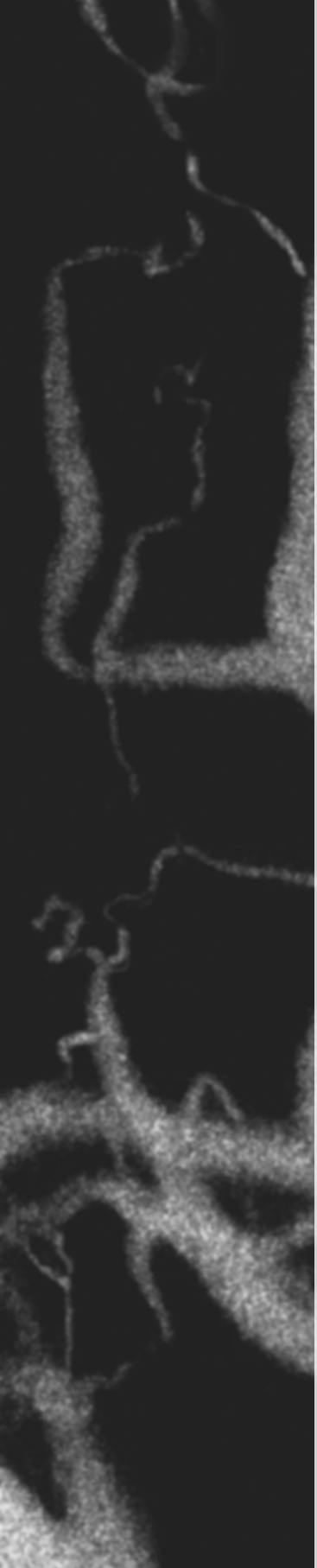


Part A

Introduction



Chapter 1

Aim of the thesis

Microcirculation is the part of the circulation where nutrients, water, gases (such as oxygen), hormones, and waste products are exchanged between the blood and cells.(1) The microcirculation consists of a network of blood vessels less than 100 μm in diameter (arterioles, capillaries and venules, respectively). An adequate blood flow within these microvessels is a prerequisite for normal organ perfusion. The microcirculation also functions as a volume reservoir for blood, so that the microcirculation plays an important role in regulating preload and thus cardiac output.(2) Another major function of the microcirculation is to regulate vascular resistance to maintain adequate mean arterial pressure. Regulation of vascular resistance to preserve arterial pressure (by constriction of the resistance vessels) and allowing each tissue to receive sufficient blood flow to sustain metabolism may be in conflict. Often the temporary compromise is to preserve the mean arterial pressure by increasing arterial resistance at the expense of reduced blood flow to most organs; ultimately, however, the tissue exchange function must be restored.

In patients with circulatory failure, including cardiogenic shock, blood flow is diverted from less important tissues (skin, subcutaneous, muscle, gastrointestinal tract) to vital organs (heart, brain, kidneys). Multiple organ failure is common in these patients, often despite correction of heart rate, mean arterial pressure and cardiac output. It has been reported that redistribution of blood flow away from the splanchnic area may result in translocation of microorganisms from the gut into the blood and that may be one of the factors contributing to the development of multiple organ failure.(3, 4) Microcirculatory blood flow alterations may play an important role in this process. Hypoperfusion of microcirculation may be an etiologic factor in the pathogenesis of multiple organ failure and may contribute to mortality in a considerable proportion of patients with circulatory shock.(5, 6)

In patients admitted to an intensive care unit, assessment of sublingual microcirculation is the easiest way to study the microcirculation. However, it was largely unknown whether microcirculatory changes in the sublingual area are representative of hypoperfusion elsewhere, most importantly in the splanchnic region. Several arguments suggest that this is indeed the case. First, the tongue shares a common embryogenic origin with the gut.(7) Second, indirect evidence comes from studies of sublingual tonometry which demonstrated a good correlation between PCO_2 measurements obtained in the sublingual region and in the stomach. (8, 9) Finally, De Backer et al. demonstrated in a small study that the proportion of perfused sublingual capillaries correlated with survival.(6)

The aim of this thesis was to investigate whether sublingual microcirculation, measured with Sidestream Dark Field imaging and regarded as a surrogate marker for splanchnic perfusion, is a determinant of organ failure and outcome in patients with cardiogenic shock. We hypothesized that impaired sublingual perfusion correlated to organ failure and short-term mortality and that this parameter could be improved using pharmacological (i.e., vasodilators

or inotropic agents) or mechanical therapy (i.e., intra-aortic balloon pump counterpulsation or more sophisticated devices that produce flow on their own). The results from these pioneer studies are described in this thesis.

Part A presents two review articles, which comprehensively highlight the importance of the microcirculation in critical diseases. In **Part B**, we present the results of circulatory support by intra-aortic balloon pump counterpulsation and percutaneous left ventricular assist devices on short- and long-term prognosis of patients with acute cardiac diseases. In **Part C**, we describe the microcirculation in pathological conditions, during cardiopulmonary bypass and in cardiogenic shock, and we propose to focus on tissue perfusion in the management of cardiogenic shock. **Part D** reports a series of observational studies, which present the effects of pharmacologic and mechanical interventions on sublingual microcirculation. In **Part E**, we summarize the main findings and reflect on these from a broader perspective and we tentatively give directions for future research.

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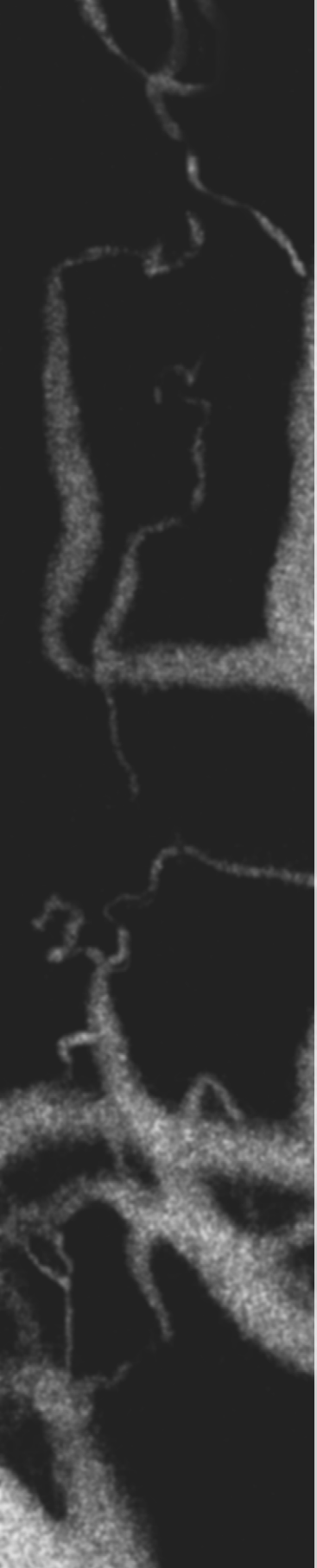


Chapter 2

The microcirculation in health and critical disease

Corstiaan A. den Uil, Eva Klijn, Wim K. Lagrand, J. Jasper Brugts, Can Ince, Peter E. Spronk, Maarten L. Simoons

Progress in Cardiovascular Diseases 2008; 51(2):161-70

ABSTRACT

The microcirculation is a complex system, which regulates the balance between oxygen demand and supply of parenchymal cells. In addition, the peripheral microcirculation has an important role in regulating the hemodynamics of the human body, because it warrants arterial blood pressure as well as venous return to the heart. Novel techniques have made it possible that the microcirculation can be observed directly at the bedside in patients. Currently, research using these new techniques is focusing at the central role of the microcirculation in critical diseases. Experimental studies have demonstrated differences in microvascular alterations between models of septic and hypovolemic shock. In human studies, the microcirculation has most extensively been investigated in septic syndromes and has revealed highly heterogeneous alterations with clear evidence of arteriolar-venular shunting. Until now, the microcirculation in acute heart failure syndromes such as cardiogenic shock has scarcely been investigated. This review concerns the physiologic properties of the microcirculation as well as its role in pathophysiologic states such as sepsis, hypovolemic shock, and acute heart failure.

INTRODUCTION

The microcirculation is that part of the circulation where oxygen, nutrients, hormones, and waste products are exchanged between circulating blood and parenchymal cells.(1) The microcirculation consists of a network of blood vessels less than 100 μm in diameter. According to anatomical features and the direction of the blood flow, these microvessels are subdivided into arterioles, capillaries, and venules. Adequate blood flow in capillaries is a prerequisite for normal organ perfusion and function. In critically ill patients, capillary blood flow in tissues may be impaired. In this article, we systematically review morphology and physiologic function of the microcirculation in tissues outside the heart, such as the splanchnic region, skin, muscles and the sublingual area, because these microcirculatory beds have been studied most extensively. We also comprehensively discuss the current literature on the role of the microcirculation in the pathogenesis of critical illnesses.

NORMAL FUNCTION OF THE MICROCIRCULATION

Capillaries consist of a single layer of epithelium and a basement membrane. The main function of capillaries is to allow exchange of molecules between blood and tissues. Capillary blood flow (a product of driving pressure, arteriolar tone, and hemorheology) and capillary patency are the main determinants of capillary perfusion.(2) Blood flow in one single capillary is not a good indicator of oxygen delivery to the tissue under evaluation due to the temporal and spatial heterogeneity of capillary blood flow.(3, 4) Capillary patency is reflected by *functional capillary density* (FCD), defined as the number of functional capillaries in a given area where functional is defined as capillaries filled with flowing red blood cells. Because oxygen has to diffuse from capillaries to tissue cells, every organ has a rich abundance of microvessels.(5) Density and anatomy of this local microvasculature depend on the metabolic requirement of each specific tissue. Although oxygen transport from the blood in the capillaries to the tissue cells is the key function of the microcirculation, the arteriolar and venular parts of the microcirculation have important functions in maintaining adequate tissue perfusion and hemodynamics. Arterioles are tiny branches of arteries that lead to capillaries and form the major resistive component of the microcirculation. The walls of arterioles are surrounded by circular smooth muscle cells, which are under the control of the sympathetic nervous system. Vascular endothelial cells can respond to alterations in local shear stress and give local stimulatory signals to arterioles via cell-to-cell communication.(6, 7) These central and local control mechanisms regulate constriction and dilatation of the arterioles depending on the metabolic requirements of the tissue cells. Under abnormal conditions, such as shock or heart failure, the balance between vascular resistance to preserve arterial pressure (by constriction of the resistance vessels) and peripheral tissue flow may be lost, causing insufficient blood flow to sustain metabolism in specific organs.

For instance, the temporary compromise as a response to a sudden decline in blood pressure (eg, in shock states) is an increase in arterial resistance, which can result in a reduced blood flow to the less vital organs such as the skin and the splanchnic system. The venular part of the microcirculation serves as a large low-pressure reservoir through which blood is returned to the heart. It may contain as much as 75% of total blood volume.(8) Active and passive changes of venous vascular tone alter the quantity of venous blood, which thereby change cardiac preload and cardiac output and guarantee maintenance of the circulating blood pool.(9)

In addition, intravascular content is important for local regulation of microvascular blood flow. There is increasing evidence that red blood cells (RBCs) not only carry oxygen to the tissues, but are also able to locally sense and regulate oxygen delivery in the microcirculation. (10) RBCs, when exposed to hypoxia, can release nitric oxide (NO) and adenosine triphosphate (ATP), which are potent vasodilators, thus improving oxygen delivery.(11-14)

METHODS TO ASSESS MICROVASCULAR BLOOD FLOW

Gastric tonometry has been introduced as a technique to assess splanchnic perfusion.(15) Using a special gastric tonometry catheter, CO_2 tension (pCO_2) can be measured in the stomach, ileum and sigmoid lumen. The pCO_2 values can be used to estimate, for example, the pH of the gastric mucosa (pHi) or can be related to the value of the arterial pCO_2 (by calculating the so-called pCO_2 gap).(16) Despite substantial initial enthusiasm, this technique has never been widely implemented due to technical problems and difficulties in demonstrating the use of gastric tonometry-derived variables as therapeutic guides.(17) Recently, it became also possible to monitor tissue pCO_2 in other sites. Sublingual capnometry is a promising noninvasive example, although the value of this new technique in critically ill patients still has to be determined.

Intravital microscopy (IVM) is considered the gold standard for in vivo investigation of the microcirculation and has been widely used in animal studies to examine the microcirculation in situ. This technique can be used for investigation of thin tissues that allow transillumination, whereas fluorescent dyes have to be used to allow epiillumination of thicker organ surfaces. Unfortunately, the use of dyes in humans is hindered by safety concerns and IVM studies in humans have therefore been limited to observation of nail fold capillaries that can be observed without using dyes.(18) However, one can question the clinical significance of the nail fold microcirculation due to its high sensitivity to external temperature, which hinders reproducibility of measurements. The large size of an IVM microscope is also a reason why this technique is not extensively used in clinical research and practice.

The recently developed laser-Doppler flowmetry is a technique that is based on frequency shifts in laser light by moving erythrocytes. The technique measures red cell flux in small-volume samples (0.5 mm^3) of organ surfaces, thus providing averages of velocities in all microvessels in the tissue volume that is under investigation. However, this feature of laser-Doppler flowmetry

is also an important limitation of the technique because averaged numbers for microvascular blood flow do not provide information about heterogeneity of blood flow, which actually is a major characteristic of the microcirculation. Modifications of this methodology, called laser-Doppler perfusion imaging and laser-speckle imaging, allow construction of real-time 2-dimensional perfusion maps of a larger area. Hence it has become possible to perform successive measurements in exactly the same area of interest. These techniques, however, are still limited by the fact that individual blood vessels cannot be visualized. Moreover, the laser-Doppler-derived signal is expressed in arbitrary units (flux or perfusion units), which implies that results can only be reported in percentage of change rather than in absolute terms.

Near-infrared spectroscopy (NIRS) is a technique that can be used to noninvasively monitor regional and microcirculatory oxygenation at the bedside. In short, this technique uses near-infrared light that can easily penetrate biological tissues. Hemoglobin has a well-defined absorption spectrum that is influenced by O_2-binding. It is the analysis of the attenuation spectra of such pigments (spectroscopy) that is used to monitor tissue oxygenation (StO_2) in vivo. The technique has been validated and has been applied extensively to evaluate cerebral perfusion and to perform peripheral ischemia/reperfusion experiments.(19, 20) NIRS is a promising method to assess tissue perfusion, although the variety of NIRS devices currently commercially available and the different values generated by these devices, hinder comparison of results from different NIRS studies. Careful calibration of each device and standardization of the method are required to completely use the opportunities provided by the NIRS technique.(21)

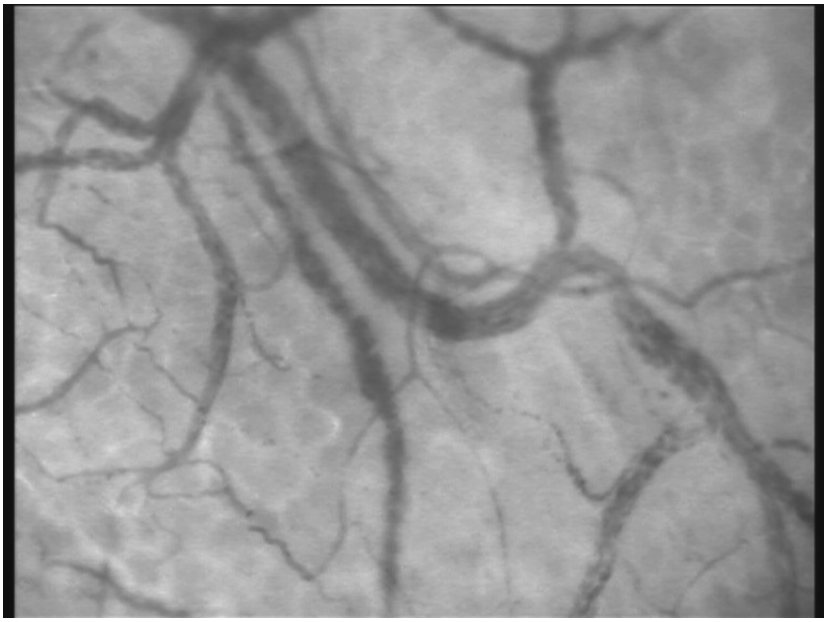
Modern clinically applicable microscopic approaches to investigate the microcirculation are orthogonal polarization spectral imaging (OPS*)* and its successor Sidestream Dark Field (SDF) imaging. Orthogonal polarization spectral imaging as well as SDF imaging are both validated techniques to investigate the microcirculation of tissues covered by a thin epithelial layer (Table 1). Currently, most studies are performed of the well-accessible sublingual microcirculation, and most investigators report the use of OPS imaging to study this particular micro-vascular bed. In OPS imaging, the tissue embedding the microcirculation is illuminated by polarized green light.(22) Back-scattered, depolarized, light is projected onto a charged coupled device video camera after it passes an analyzer, that is, a second polarizer that is orthogonally oriented with respect to the first polarizer. In this way, surface reflections are filtered out and images can be observed of the microcirculation below the surface under investigation. In OPS imaging, the hemoglobin is actually used as contrast agent, so that red blood cells are imaged as dark moving globules against a white/grayish background. The obtained video clips can be analyzed to quantify various parameters such as flow and morphology via precise semiquantitative methods or by using dedicated software packages.(23-26) Recently, SDF imaging was introduced as the successor of OPS imaging. The SDF imaging device consists of a central light guide, surrounded by concentrically placed light emitting diodes that emit stroboscopic green light. The center of the probe is optically isolated from the light emitting diodes so that hindering surface reflections are avoided. This results in similar images compared to OPS-derived

Table 1. Validation studies for OPS and SDF imaging.

Reference	Compared techniques	Subjects	Tissue	Investigated conditions	Analysis method	Conclusions
Harris (76)	IVM vs. OPS imaging	10 hamsters	Dorsal skinfold	Ischemia/ reperfusion	Cap-Image Software	Good agreement for RBC velocity and vessel diameters
Mathura (77)	IVM vs. OPS imaging	10 healthy volunteers	Nailfold	Baseline and after venous occlusion	Cap-Image Software	Good agreement for RBC velocity and capillary diameter. Better capillary contrast with OPS
Langer (78)	IVM vs. OPS imaging	9 rats	Liver	Ischemia/ reperfusion	Cap-Image Software	Good agreement for RBC velocity and vessel diameters
Harris (79)	IVM vs. OPS imaging	9 hamsters	Dorsal skinfold	Standardized hemodilution	Cap-Image Software	Good agreement for vessel diameter and FCD at various levels of hematocrit
Goedhart (27)	OPS vs. SDF imaging	10 healthy volunteers	Nailfold	Baseline, venous and arterial occlusion	Microscan Analysis Software	Good agreement for capillary diameter and RBC velocity
		2 healthy volunteers	Sublingual	-	Image quality analysis	Higher capillary contrast and quality with SDF

video clips (Figure 1), although SDF imaging results in better visualization of capillaries due to complete avoidance of surface reflections and the short, stroboscopic illumination intervals that prevent smearing of flowing RBCs.(27)

Figure 1. Sidestream Dark Field video frame of the sublingual microcirculation. The image represents a tissue area of 0.98 × 0.73 mm.



THE MICROCIRCULATION IN SEPSIS

Sepsis is defined as the clinical syndrome characterized by the presence of both infection and a systemic inflammatory response of the body. The term *severe sepsis* is often used in the literature and refers to sepsis complicated by organ dysfunction. *Septic shock* refers to a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes.(28) Although major progress has been made in the treatment of sepsis, a substantial number of patients will not survive despite early, aggressive correction by volume resuscitation and administration of vaso-active agents and antibiotics.(29-32) Indeed, severe sepsis is the most common cause of death in general (non-cardiac) critical care units.(33) Current guidelines for resuscitation of patients with severe sepsis and septic shock aim at normalizing global hemodynamic and metabolic parameters (ie, central venous pressure, mean arterial pressure, urine output, central venous oxygen saturation and lactate level).(34) Although these parameters are indicative for global tissue perfusion, information about regional perfusion, hypoperfusion and hypoxia in a septic patient is often lacking. Yet, regional hypoxia and associated organ dysfunction is one of the major features of septic shock. This is the reason why microcirculation research has gained so much interest in the last years. One of the key features of the microcirculation in sepsis is a heterogeneous distribution of blood flow. It has been shown that certain vascular beds, or microcirculatory units, become underperfused, whereas others show a normal or even abnormally high blood flow.(24, 35-37) It has been suggested that this phenomenon is explained by autoregulatory dysfunction through heterogeneous expression of inducible nitric oxide synthase, an important system responsible for autoregulatory vasodilation of the microcirculation.(38, 39) Several other phenomena play a role in the pathogenesis of sepsis. Smooth muscle cells that line arterioles and regulate perfusion lose their adrenergic sensitivity and tone in sepsis.(40) Erythrocyte deformability decreases, whereas their ability to aggregate increases.(41, 42) In addition, leukocytes activated by septic inflammation generate reactive oxygen species that may impair glycocalyx function and coagulatory function.(43-45) These defects may further impede microcirculatory perfusion, which can finally result in an oxygen extraction deficit, severe functional shunting, and (multiple) organ failure.(2, 35, 46, 47) Although the microcirculation seems to play an important role in the pathogenesis of severe septic shock, others have argued that mitochondrial dysfunction is the driving mechanism underlying multiorgan dysfunction in sepsis.(48) However, whether mitochondrial failure is indeed a primary cause of oxygen extraction deficit in sepsis is still a source of debate. De Backer et al. used OPS imaging to demonstrate that total vascular density and capillary perfusion are impaired in patients with sepsis, and these micro-vascular alterations have been associated with in-hospital mortality.(24, 31) Subsequent studies showed that micro-vascular alterations could be improved with nitroglycerin(36), dobutamine(49), and red blood cell transfusion.(50, 51) Nevertheless, it remains unknown whether a microcirculation-guided therapy, monitored by OPS or SDF imaging, improves outcome in patients with septic shock.

SEPTIC SHOCK VERSUS HYPOVOLEMIC SHOCK

Kerger et al(52) have demonstrated that functional capillary density can deteriorate in experimental severe hemorrhagic shock with an induced mean arterial pressure (MAP) of 40 mm Hg. These changes were related to mortality. To our knowledge, 3 experimental studies have been performed to investigate whether there is a difference between microcirculatory dysfunction in septic shock relative to mild hypovolemic shock. First, Boczkowski et al(53) used a rat diaphragmatic microcirculation model in which they investigated capillary perfusion using transillumination in experimental sepsis and during controlled hemorrhage. Blood pressure decreased similarly in rats with sepsis vs rats with hemorrhage, but the percentage of nonperfused capillaries was significantly higher in the septic group, whereas it remained at normal values in the group rats with hemorrhage. Second, Nakajima et al.(54) used intravital microscopy to investigate the effects of hemorrhagic shock, normotensive sepsis, and septic shock on the microcirculation of mouse small intestine. Significant decreases in red blood cell velocity were observed in the groups with sepsis and septic shock, whereas it remained preserved in mice with hemorrhage-induced hypotension. Although mean FCD also decreased in mice with hemorrhagic shock, this decrease was much worse in mice with septic shock. Finally, Fang et al.(55) used OPS imaging to estimate buccal micro-vascular blood flow in rats with septic shock vs rats with MAP-matched hemorrhagic shock. These investigators demonstrated that microvascular blood flow was worse in the septic group compared to the MAP-matched hemorrhagic shock group. Additionally, saline infusion resulted in complete restoration of microvascular blood flow in the MAP-matched hemorrhagic shock group whereas saline infusion could not improve microvascular blood flow in the septic shock group. Taken together, these studies have demonstrated that the microcirculation in mild hemorrhagic shock is not affected to such an extent as compared to septic shock. In addition, the results presented by Fang et al.(55) suggested that micro-vascular alterations in hypovolemic shock (conversely to septic shock) at least in part depend on global hemodynamics. These findings have to be confirmed in human studies and it should be realized that administration of allogeneic red blood cell transfusions after hypovolemic shock rather than hypovolemic shock itself may have deleterious effects on the microcirculation in humans.(50, 51)

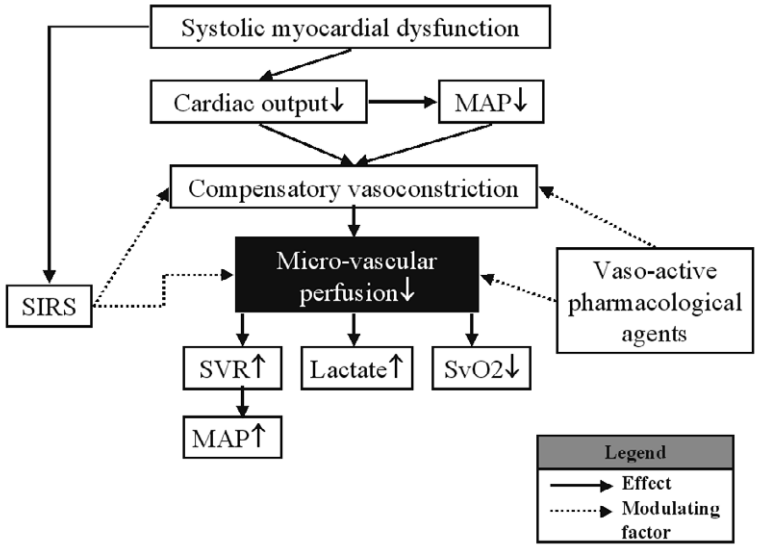
CARDIOGENIC SHOCK

Cardiogenic shock is one of the acute heart failure syndromes and is defined as evidence of tissue hypoperfusion induced by heart failure after correction of preload. Cardiogenic shock is characterized by a reduced arterial blood pressure (systolic <90 mm Hg or a drop of MAP >30 mm Hg) and/or low urine output (<0.5 mL/kg per hour), with a heart rate more than 60 beats per minute.(56) In most cases, cardiogenic shock develops after an acute myocardial

infarction. In patients admitted with acute myocardial infarction, cardiogenic shock is the leading cause of death.(57) Other causes of cardiogenic shock include cardiomyopathy, valvular heart disease, myocarditis, myocardial contusion and previous cardiac surgery. Despite advances in treatment, in-hospital mortality of cardiogenic shock patients remains about 50%.(58) For years, it has been accepted that when cardiac output, and thus systemic blood flow, decreases, compensatory redistribution of blood volume (partly by active venoconstriction) results in a decrease in peripheral vascular capacitance with a compensatory increase in cardiac filling pressures and cardiac output. In this classic paradigm of cardiogenic shock, depression of cardiac output also causes arteriolar vasoconstriction and an elevation of systemic vascular resistance. Studies that investigated the peripheral circulation in patients with chronic, severe heart failure (New York Heart Association class III-IV) and cardiogenic shock have supported this hypothesis.(59-61) However, data on the state of the peripheral microcirculation in acute heart failure is scarce and did not consistently confirm the classic notion of systemic vasoconstriction in all patients with cardiogenic shock. For example, Lim et al.(62) reported that 40% of patients admitted with cardiogenic shock due to myocardial infarction died with a cardiac index more than 2.2 L/min per square meter. In line with these data, post hoc analysis of data from the SHOCK-trial demonstrated that a considerable number of patients, admitted with cardiogenic shock, developed a systemic inflammatory response syndrome (SIRS) during hospital stay. In these patients, systemic vascular resistance (SVR) at shock onset was significantly lower compared to patients who did not develop SIRS, although a wide variation of SVR among patients was observed. A low SVR, suggesting peripheral vasodilation, was a predictor for later development of sepsis.(63) The latter data suggested once again that not all cardiogenic shock patients develop diffuse vasoconstriction as a compensatory response to cardiac pump failure. Figure 2 shows the current theory on the effects of cardiogenic shock on the microcirculation. In fact, inappropriate vasodilation due to SIRS might further impair perfusion at the microvascular level, which might be important in the pathogenesis of multiple organ failure and the persistence of shock.(64) This process may be due to an increased production of nitric oxide by nitric oxide synthase (NOS). Accordingly, strategies were developed to inhibit NOS in patients with cardiogenic shock. Small studies suggested that NOS-inhibition could improve blood pressure.(65-67) The Tilarginine acetate injection in a Randomized International study in Unstable MI Patients with cardiogenic sHock (TRIUMPH)-trial was designed to test whether administration of tilarginine, a NOS-inhibitor, would result in an improved 30-day survival in patients with myocardial infarction complicated by cardiogenic shock. Unfortunately, enrolment of patients was recently terminated at 398 patients because of lack of efficacy. There was no difference in favor of NOS-inhibition in 30-day all-cause mortality between patients who received tilarginine (48% died) relative to placebo (42% died, risk ratio 1.14: 95% confidence interval 0.92-1.41).(68)

This negative study underlines that microcirculatory alterations in cardiogenic shock are still not fully understood. The aforementioned sophisticated 2-dimensional imaging techniques may give better insight in the nature of these alterations. De Backer et al(69) used OPS imaging

Figure 2. The effects of cardiogenic shock on the microcirculation. A decrease in cardiac output, caused by systolic myocardial dysfunction, results in a decrease in mean arterial blood pressure. These phenomena cause compensatory vasoconstriction of the resistance vessels, which decreases microvascular perfusion. The degree of SIRS and the administration of vasoactive pharmacologic agents can both modulate microcirculatory responses and influence perfusion at the microvascular level. In case of severe hypoperfusion of the microcirculation, lactate levels will increase whereas venous oxygen saturation will decrease. Abbreviations: MAP, mean arterial pressure; SIRS, systemic inflammatory response syndrome; SvO_2, venous oxygen saturation; SVR, systemic vascular resistance.



to investigate the sublingual microcirculation in 40 patients with acute heart failure, most of them having cardiogenic shock, who were investigated within 48 hours after the onset of acute heart failure. These investigators reported similar alterations to those observed in sepsis, including a lower proportion of perfused capillaries in patients with heart failure compared to control patients. Moreover, these alterations were related to in-hospital mortality. However, these investigators performed only one measurement per patient, and it remained unclear whether the microcirculation could be improved by pharmacologic therapy and whether such interventions could be beneficial in reducing the high mortality rate in cardiogenic shock patients.

MACROCIRCULATION VERSUS MICROCIRCULATION IN SEPTIC AND CARDIOGENIC SHOCK

An important finding in several studies in SIRS and sepsis was that the alterations in microvascular flow occurred independently of systemic hemodynamic variables.(24, 49, 70) De Backer et al(69) have argued that probably the same principle holds for cardiogenic shock. Conversely, several studies have shown that there is a close correlation between macrocirculation and microcirculation in animals and patients with left ventricular systolic dysfunction. This

was recently confirmed with OPS imaging in pigs subjected to ventricular fibrillation followed by advanced life support.(71, 72) Measured by OPS imaging, Erol-Yilmaz et al(73) recently reported a better sublingual functional capillary density during biventricular pacing relative to either only right ventricular pacing or no pacing. Although cardiac output was not measured in this study, these data suggest a relation between cardiac output and sublingual microcirculatory perfusion. Further well-designed studies in cardiogenic shock patients, preferably using SDF imaging, are needed to completely explain these results. The exact extent of peripheral vasoconstriction may in fact be dependent of the degree of SIRS present in a patient with cardiogenic shock (Figure 2).

FUTURE PERSPECTIVES IN MICROCIRCULATION RESEARCH

There is overwhelming evidence that sepsis is a disease of the microcirculation.(2, 74) However, the exact role in the pathogenesis is still incompletely understood. Ongoing animal studies and 3-dimensional computer models, simulating micro-vascular blood flow and gradients of hypoxia, will improve our understanding of microvascular alterations and will result in new approaches to monitor and treat patients with sepsis.(75) Furthermore, randomized studies are currently underway to test whether microcirculatory flow-guided therapy might be beneficial for patients with severe sepsis and septic shock. The microcirculation does not seem to play a completely independent role in hypovolemic shock, although this has to be confirmed in human studies. Research focusing on the exact role of the microcirculation in cardiogenic shock is still in its premature stages. We have to learn more on nature, severity and duration of peripheral microcirculatory changes in acute heart failure syndromes in order to comprehensively investigate whether these changes can be improved by pharmacologic and mechanical treatment strategies. It is to be hoped that these future studies may in the end result in improved treatment and survival of heart failure patients.

CONCLUSIONS

An adequate function of the peripheral microcirculation in the different organ systems is necessary to maintain adequate tissue perfusion and to preserve normal hemodynamics. Recent technical developments have enabled investigation of the microcirculation at the bedside and confirmed that the microcirculation is impaired in severe sepsis and septic shock. Heterogeneous microvascular alterations in sepsis occur independently of changes in global hemodynamic parameters. Several recent experimental studies have demonstrated that the microcirculation in hypovolemic shock is not affected to such an extent as in septic shock, although it should be realized that allogeneic RBC transfusions following hypovolemic shock

might impair the microcirculation. The role of the peripheral microcirculation in cardiogenic shock is still incompletely understood, although there is growing evidence that systemic inflammation of the body is an important aspect in the pathogenesis. In addition, there is still debate whether microcirculatory alterations in acute heart failure syndromes occur completely independent of changes in the macrocirculation. Novel bedside technology to image the peripheral microcirculation may be helpful to understand the pathogenesis of cardiogenic shock more comprehensively and to learn whether intervention strategies, aimed at improving peripheral microvascular flow, are beneficial for patient outcome.

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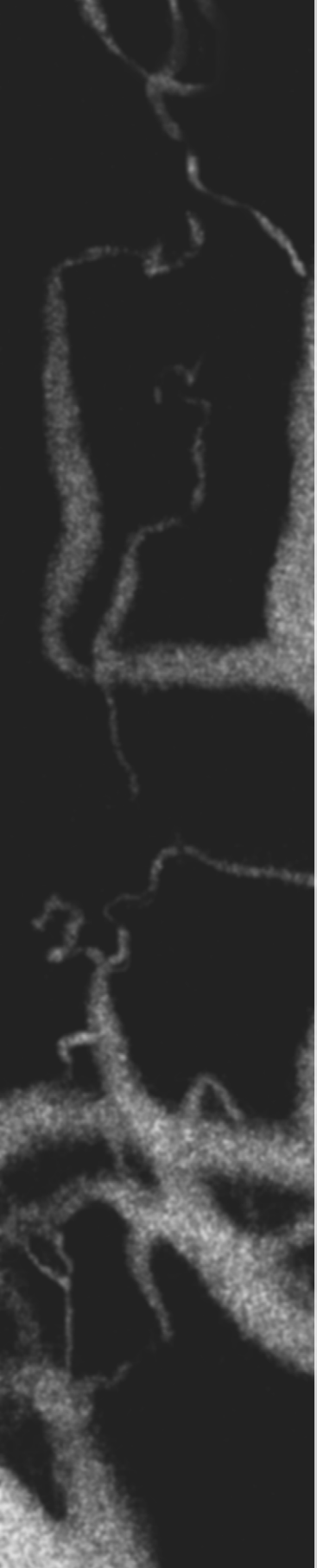

Chapter 3

The heterogeneity of the microcirculation in critical illness

Eva Klijn, Corstiaan A. den Uil, Jan Bakker, Can Ince

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ABSTRACT

Microcirculation, a complex and specialized facet of organ architecture, has characteristics that vary according to the function of the tissue it supplies. Bedside technology that can directly observe microcirculation in patients, such as orthogonal polarization spectral imaging and sidestream dark field imaging, has opened the way to investigating this network and its components, especially in critical illness and surgery. These investigations have underscored the central role of microcirculation in perioperative disease states. They have also highlighted variations in the nature of microcirculation, both among organ systems and within specific organs. Supported by experimental studies, current investigations are better defining the nature of microcirculatory alterations in critical illness and how these alterations respond to therapy. This review focuses on studies conducted to date on the microcirculatory beds of critically ill patients. The functional anatomy of microcirculation networks and the role of these networks in the pathogenesis of critical illness are discussed. The morphology of microvascular beds that have been visualized during surgery and intensive care at the bedside are also described, including those of the brain, sublingual region, skin, intestine, and eyes.

INTRODUCTION

In recent years, interest in the role of microcirculation in critical illness has grown. This seems logical because microcirculation is ultimately responsible for providing oxygen to the tissues. Microcirculation is a complex network, with special morphologic features tailored for the specific function of the tissues it supplies. Recently, new imaging techniques and clinical investigations have identified microcirculation as a pivotal element in the pathogenesis of sepsis.

Although major progress has been made in the treatment of sepsis, morbidity and mortality rates associated with sepsis remain high.(1, 2) Hemodynamic treatment is primarily aimed at correcting global hemodynamic and oxygen-derived variables.(2) Despite aggressive correction of global parameters with volume resuscitation and vasoactive agents, some patients progress into multiorgan failure and die.(3, 4) The ultimate aim of resuscitation is to correct and avoid tissue hypoxia. However, the end points used to evaluate the achievements of resuscitation therapy (eg, lactate levels, venous oxygen saturation, and mean arterial pressure) are not sensitive enough to detect regional hypoxia. This lack of sensitivity is primarily due to the distributive defect associated with septic shock, in which a defect in the distribution of normal cardiac output (or even increased cardiac output) results in regional hypoxia that is not detected by conventional hemodynamic monitoring of systemic circulation. This occult hypoxia highlights the necessity of finding new end points for the treatment of severe sepsis and septic shock.

This review first explores the characteristic features of several microvascular beds that can be visualized at the bedside. Second, the distinctive abnormalities occurring during sepsis are discussed in relation to different types of shock. In addition, we review the response of microcirculation to available therapeutic modalities frequently used to treat septic shock patients. Although many methods exist to study microcirculation, either directly or indirectly, this review mainly focuses on the use of either orthogonal polarization spectral (OPS) imaging or sidestream dark field (SDF) imaging(5, 6) for direct clinical visualization of microcirculation with bedside vital microscopy. Because the heterogeneity of microcirculatory alterations among different organs and within individual organs is a key characteristic of the pathophysiology of hemodynamic dysfunction in sepsis, the preferred technique for identifying these alterations is direct visualization.

THE ANATOMY AND FUNCTION OF DIFFERENT MICROCIRCULATORY BEDS

Microcirculation has evolved from being a hypothesized necessary link between the arteries and veins, in Harvey's theory of circulation, to a possible end point of resuscitation in critical illness. In 1661, Malpighi demonstrated, for the first time in vivo, long, thin-walled tubes, which he termed capillaries. Technical advances made in recent years have made it possible to directly or indirectly study microcirculation in different pathologic states. Most of the information

concerning the functional morphology of microcirculation has been obtained from extensive studies involving experimental animals.

Microvasculature consists of arterioles, capillaries, and postcapillary venules, of which the arterioles are the major determinant of vascular resistance. Blood flow depends on a pressure gradient along the vascular tree, as well on the amount and distribution of resistance across the microvasculature. Circular smooth muscle cells surround the arteriolar walls. By alternately contracting and relaxing, these muscle cells control microvascular flow. In specific microcirculatory beds, such as those of the brain pericytes, surrounding arterioles can also cause constriction and regulate blood flow.(7) This vascular tone controls the diameter of the vessels because, as described by the law of Poiseuille, the resistance to flow is primarily determined by the radius of the vessel. The proximal arteriole determines the total blood flow to the capillaries, whereas the terminal arterioles and precapillary sphincters control the distribution of blood within the capillaries. Capillary walls, which consist of a single layer of endothelium and basement membranes, represent the principal site of oxygen and nutrient exchange between blood and tissue. Changes in systemic blood pressure lead to a corresponding change in microcirculatory flow, which is then compensated for by local readjustments. These changes ensure that the microcirculatory blood flow is adequate to meet the oxygen requirements of the parenchymal cells, a mechanism called autoregulation.

The microvasculature characteristics of each organ system are closely related to the functional role played by the organ as a whole. The number of capillaries per unit mass of organ or tissue (capillary density) may be related to the organ's metabolic requirements (muscles, heart, brain) or to other functional requirements (skin, intestinal mucosa, kidney).(8) Oxygen transport to the tissues occurs via passive diffusion from the capillaries, as was first described by Krogh early in the 20th century. The diffusion of oxygen in this manner is considered to be the main rate-limiting process in oxygen transport to tissue. Besides diffusion from the capillaries, diffusion of oxygen to the parenchymal cells also occurs from the larger vessels, such as the arterioles and venules. Although the microvascular beds of most organs and tissues clearly have both metabolic and functional components, one or the other usually predominates. In this way, the morphology of each microcirculatory bed is designed to fit the function and oxygen requirements of each organ.

Regarding critical illness, skeletal muscle has been the most extensively studied tissue in experimental studies. This is due to its easy accessibility and to the technical limitations of intravital microscopes, the main instruments used in such studies. Interest later shifted to other microvascular beds, such as in the intestine and brain. Upon the introduction of OPS and SDF imaging, microcirculation could be observed in humans, and the location most often studied with these techniques has, to date, been the sublingual microcirculation. This is because this region is easily accessible and its vascularization is close to the brain and heart. The extent to which studies of this region can be extrapolated to other microvascular beds is uncertain. However, sublingual microcirculatory alterations do have clinical significance. The superior

sensitivity of sublingual microcirculation as an indicator of the severity of disease over systemic hemodynamic and oxygen-derived variables (demonstrated in several clinical studies) makes sublingual tissue clinically relevant for detecting microcirculatory alterations.

ORTHOGONAL POLARIZATION SPECTRAL AND SIDESTREAM DARK FIELD IMAGING FOR CLINICAL MONITORING OF MICROCIRCULATION

The intravital microscope has provided much insight into the physiology and pathophysiology of microcirculation in several models of disease. However, the microscope's technical limitations have limited its impact. The main limitation of this technique is the need for transillumination of the microcirculatory bed from below for visualization. Observing the microcirculation of organ surfaces using epi-illumination causes surface reflection of the incident light, resulting in poor visualization of the underlying microcirculatory bed. Therefore, the intravital microscope has been used mainly for the study of organs that permit transillumination, such as the mesenteric, cremaster, and hind limb muscles. Fluorescence microscopy (illumination from above), has facilitated the study of other organs. Not being able to apply these types of techniques to large animal models has limited the clinical relevance in studying the microcirculation. In small animal studies the relation between macro- and microcirculation, an essential link needed to understand the role of the microcirculation in functional hemodynamics, has not been sufficiently elucidated. This limited their translational applicability to clinical scenarios. The technical limitations of transillumination were finally overcome with the introduction of the OPS imaging technique.

OPS imaging illuminates tissues with polarized green light and measures the reflected light from the tissue surface after filtering out the polarized portion of the reflected light.(6) OPS imaging thus makes it possible to visualize microcirculation without transillumination. This modality filters out the surface reflection and permits visualization of subsurface structures. Green light is absorbed by hemoglobin in red blood cells, thereby tracking the movement of red blood cells, which appear in microcirculation as moving dark globules. However, the OPS technique has only limited sensitivity for studying capillary kinetics and morphology in detail. An improved optical modality to address this shortcoming was introduced with SDF imaging (5). Covered by a disposable cap, the SDF probe is placed directly on tissue surfaces. The light from the concentrically positioned light-emitting diodes (530 nm wavelength) penetrates 1 mm into the tissue, thus illuminating the microcirculation and its components. Because hemoglobin absorbs this wavelength, erythrocytes can be clearly observed as flowing cells. Also, because there is no direct optical contact with the sensing central core of the probe, surface reflections do not interfere with image collection. Therefore, remarkably clear images of the microcirculation can be captured. The resulting improved image quality allows for better automatic analysis of the images, and the low energy requirement of SDF imaging further enhances its utility by allowing

battery and portable computer operation. Using these techniques, brain, sublingual, cutaneous, and conjunctival microcirculation have been studied during surgery and intensive care.

CLINICAL EVALUATION OF MICROCIRCULATION DURING SURGERY AND INTENSIVE CARE

Both OPS and SDF imaging can be used to investigate the microcirculation of organ surfaces. OPS imaging has been used to visualize human brain microcirculation during neurosurgery. (6) Given its embryologic association with the gastrointestinal tract and its easy accessibility,

Figure 1. (A) Vascularization of the eye, including microcirculation. (B) SDF image of conjunctival microcirculation.

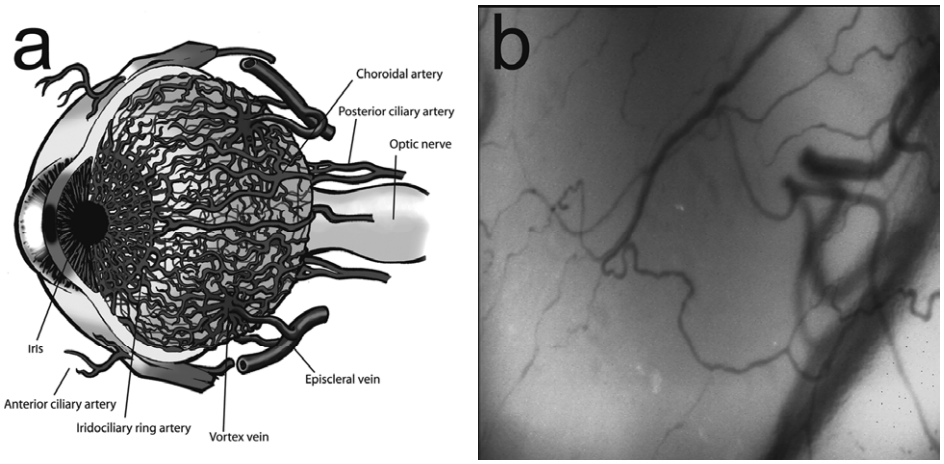
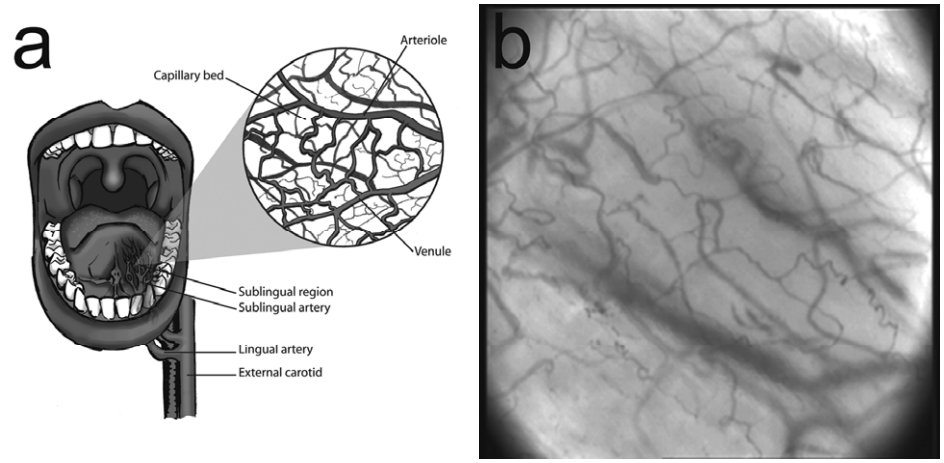


Figure 2. (A) Vascularization of the sublingual area, including microcirculation. (B) OPS image of sublingual microcirculation.



sublingual microcirculation has been extensively studied, especially in intensive care medicine. In addition, these techniques have been applied to the study of microcirculation in the nail fold. (9, 10) From a historic perspective, however, the study of the human brain during surgery represents a new, uncharted area of clinical research.(6) Figures 1-4 illustrate several microcirculatory beds described below, as well as their corresponding microcirculatory images, acquired using OPS or SDF imaging.

Brain microcirculation

The microvascular bed of the cerebral cortex consists of a dense, highly interconnected network that arises from pial arteries. Irregular tortuous capillaries characterize this cerebrocortical

Figure 3. (A) Vascularization of the gut, including microcirculation. (B) OPS image of villus microcirculation.

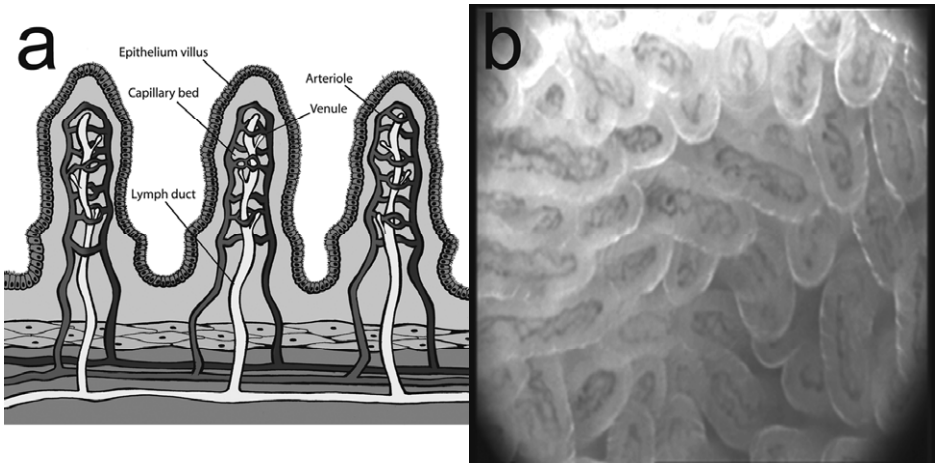
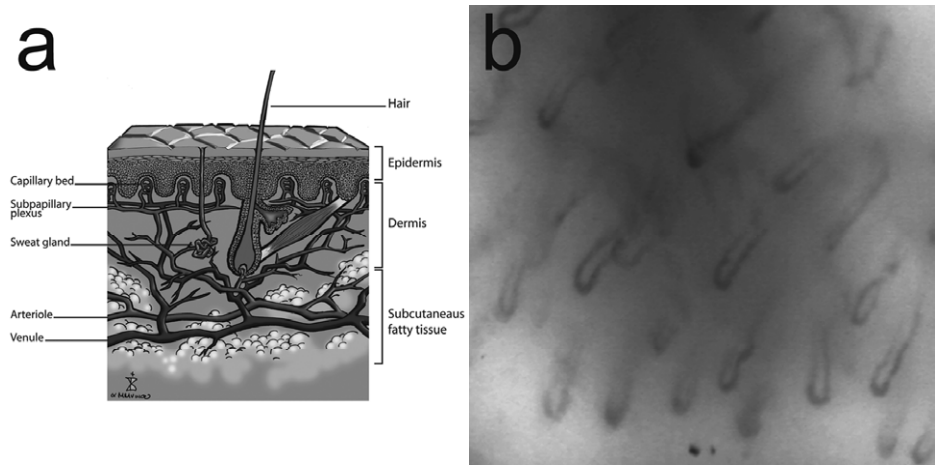


Figure 4. (A) Vascularization of the skin, including microcirculation. (B) SDF image of nail fold microcirculation.



capillary bed, and these capillaries are supplied by branches of cortical penetrating arteries, which cannot be visualized in vivo.(11) The arteriolar system is composed of three main vasculature zones: the pial, cortical, and subcortical vascular networks. When the brain surface is examined with intra-vital microscopy, the capillaries appear to have no preferential orientation or characteristic length, and the capillaries cannot usually be traced back to their pial arteries. On the brain surface, the arterial microanastomoses characterize the pial microarterial network.(12) The capillaries drain into postcapillary venules that give rise to the pial veins. It is still unclear whether arteriovenous anastomoses are present in the cerebral microvasculature. Capillary density in the brain is related to the average metabolic rate at steady state.(13) In addition to the classical factors that control microcirculatory blood flow (myogenic, metabolic, and neurohumoral mechanisms), evidence suggests that pericytes located around the capillaries regulate cerebral blood flow in both normal and pathological states.(7)

The initial observation of normal brain microcirculation using OPS imaging was followed by several other reports on the structure of cerebral cortical microcirculation in different disease states. First, it was shown that, during surgery for subarachnoid hemorrhage, the cortical microvasculature response to hypocapnia was different between patients prone to vasospasm and patients who did not develop vasospasm.(14) In addition, excision of arteriovenous malformations in the brain resulted in increased microcirculatory flow and functional capillary density in the perinidal brain tissue.(15)

Conjunctival microcirculation

Direct access to brain microvasculature is impossible outside the operating room. However, a recent study suggests that the microcirculation of the eye conjunctiva might function as an indicator of the cerebral microcirculation.(16) At the bedside, the most accessible part of the eye for evaluating microcirculation is the bulbar conjunctiva, which offers a complete vascular bed with arterioles, capillaries, and small collecting venules. Earlier studies using intravital microscopy have reported on the behavior of the conjunctival microcirculation in sickle cell patients.(17, 18) The anterior segment of the human eye is supplied by the anterior ciliary arteries, which supply the anterior conjunctival, anterior episcleral, and limbal circulation. The episcleral arterial circle broadly resolves into superficial and deep components.(19) With intravital microscopy or OPS and SDF imaging, collecting venules are visualized as heavy, prominent dark vessels situated parallel to narrower, straighter vessels, which comprise the accompanying terminal arterioles.(20) Capillaries arise at intervals from the end arterioles and form an irregular network of vessels that come together to form the venular system. The arterioles frequently terminate in main arteriovenous channels that communicate directly to the venular tree. This is most notable near the corneo-scleral junction.(21)

The bulbar conjunctiva has been most extensively studied in diabetes and hypertensive patients. In these patient groups, several alterations in microcirculatory morphology and flow

have been demonstrated. Microcirculatory alterations in the conjunctiva, however, have not yet been investigated in sepsis.

Sublingual microcirculation

The sublingual area is one of the most accessible human mucosal surfaces, which is why it has been extensively investigated. Blood is supplied to the sublingual area via the external carotid artery, the lingual artery, and the sublingual artery, subsequently. Only a limited number of sublingual arterioles are present, whereas numerous capillaries (diameter <20 µm) and venules (diameter 20-100 µm) are present in the sublingual area. Because perfusion of the sublingual mucosa is related to blood flow in the external carotid artery, sublingual perfusion may, in part, reflect cerebral blood flow. However, only a few studies have investigated the cerebral and sublingual perfusion simultaneously. Perfusion of the sublingual area could represent blood flow in the splanchnic region for two major reasons. First, this is suspected because the tongue shares a common embryogenic origin with the gut. Second, studies in critically ill patients reported good correlations between sublingual and gastric mucosal carbon dioxide pressures, as measured with sublingual capnometry and gastric tonometry, respectively, further strengthening the hypothesis.(22, 23)

Intestinal microcirculation

Branches from a common submucosal vasculature supply blood to the muscle, submucosal layer, and mucosal layer of the gut. Small arteries that branch extensively in the submucosal layer penetrate the muscularis layer of the intestinal wall. The branches all lead to capillary beds, and though diffusive shunting is thought to occur at the base of the villi, there is no evidence for arteriovenous shunts in the intestinal circulation.(24) Several submucosal arteries that transport blood back to the muscularis layer form a network of arterioles and capillaries around the intestinal smooth muscle cells. Other submucosal arteries supply blood to the mucosa and to each intestinal villus, where dense capillary networks exist. Veins leaving the villi join veins from the mucosal and muscularis layers, and they exit the intestinal wall alongside the mesenteric arteries that supply blood. Because absorption of water and solutes is one of the primary functions of the villi, the capillaries in the mucosal villi are very dense. A critical feature that may facilitate reabsorption of water is that the vessels carrying blood into and out of the villus lie close together, in parallel paths. Because the afferent and efferent blood vessels in the villi are close together, oxygen could diffuse from the arterioles to the venules at the base of the villus.(25) It is probably this organization that makes the tip of the villus the part most vulnerable to shock. The integrity of the intestinal mucosa is important to preventing the translocation of bacteria and toxins into the systemic circulation. Hypoperfusion of the gut mucosa may contribute to mucosal injury.(26, 27) In this context, experimental studies have evaluated the effect of sepsis and also hemorrhagic shock on the intestinal microcirculatory blood flow.(28-30) A recent study by Dubin and colleagues(30) demonstrated that endotoxic

shock in sheep rapidly induced alterations in intestinal and sublingual microcirculation. Fluid resuscitation normalized the systemic and intestinal hemodynamics, while also restoring the microvascular flow at the sublingual and intestinal serosal levels. However, the microvascular flow and percentage of perfused vessels in the intestinal mucosa were not effectively restored after fluid resuscitation. Human data are scarce, and they are limited to the observations in stomas of patients with abdominal sepsis. Boerma and colleagues(31), after comparing the microcirculatory alterations between the sublingual region and stomas in patients admitted with abdominal sepsis, reported no correlation between sublingual and intenstinal microcirculatory alterations on day 1 of sepsis. After 3 days, however, these regional alterations became more systemic and correlations were found between the sublingual and intenstinal microcirculatory alterations The alterations in one microcirculatory bed, therefore, do not necessarily reflect alterations in other microvascular beds. However, although microcirculatory beds may differ substantially in different organs, studies have clearly demonstrated the clinical significance of sublingual microcirculatory alterations in sepsis. These alterations indicate the response to treatment and resuscitation and serve as sensitive and specific indicators of bad outcome.

Dermal microcirculation

The study of the cutaneous microvascularization with IVM, OPS, and SDF has been limited to the nail fold area because of the distinctive construction of the skin, which includes a thick epidermal layer. Other techniques have also been used to study skin microcirculatory blood flow in illness. Using laser Doppler flowmetry, Young and Cameron(32) demonstrated an impaired microcirculatory blood flow response of the forearm after transient ischemia. Using intra-vital microscopy, the blood flow velocity in the capillary bed of the nail fold was found to be decreased in normotensive febrile patients.(33) In investigating cutaneous microcirculation, the question remains: To what extent is microcirculatory flow of the skin important in critical illness? This question arises mainly because of the role thermoregulatory properties play in governing and interfering with the skin microvasculature. Because the major role of cutaneous circulation is thermoregulation, blood flow to the skin typically exceeds metabolic requirements. In the deep dermis, branches from subcutaneous arteries that penetrate the dermis form an arterial plexus.(34) The vessels within this plexus generally run parallel to the surface. Arterioles penetrating from the dermal plexus to the subpapillary region form a subpapillary plexus. Capillaries connect to the subpapillary venous plexus, and single capillary loops ascend to each papilla. The descending portion of the capillary joins the subpapillary venous plexus, which drains into the deeper cutaneous venous plexus. Due to the numerous arteriovenous shunts (only in apical regions) and because many cutaneous veins run close to parallel arteries, the resulting counter-current heat exchange conserves heat. The combination of rich sympathetic innervation of the cutaneous arterioles and a high microvascular blood flow relative to oxygen demand allows a primary control of reflexes.

Other microcirculatory beds

In addition to these areas, other microcirculatory beds have been studied using OPS and SDF imaging. While these applications have been limited to single studies, such studies have demonstrated the applicability of these techniques to other organ surfaces if they can be exposed for investigation. For instance, rectal microcirculation was studied in patients with malaria.(35) During maxillofacial surgery and especially for assessing wound healing, these techniques have also been used to explore additional areas of the oral cavity (36). Finally, during surgery in which several organ surfaces are exposed, investigations have examined microcirculation in the liver, pancreas, and kidney.(37-39)

MICROCIRCULATION IN SEPSIS

Observational studies of sublingual microcirculation in sepsis have contributed to the understanding of the pathophysiology of acute circulatory failure and multiple organ dysfunction. (40) Both clinical and experimental studies have previously indicated that sepsis and septic shock are disorders of microcirculation. In the early phases of sepsis, a persistent deficit in microcirculatory perfusion is associated with poor outcome, as was demonstrated by De Backer and colleagues.(41) These investigators compared the sublingual microcirculation in septic patients versus that of healthy volunteers and detected a significant decrease in the proportion and density of small perfused vessels during sepsis. In addition, the alterations were more severe in nonsurvivors than in survivors. Meanwhile, Sakr and colleagues(3) observed that the recovery of microcirculatory alterations within the first 24 hours indicated good outcome. In this study, the persistent loss of capillary perfusion was one of the most sensitive and specific hemodynamic predictors of survival from septic shock. Trzeciak and colleagues(4) studied the effects of an early goal-directed protocol on indices of microcirculatory perfusion in early sepsis. They demonstrated that, even in the context of early goal-directed therapy, microcirculatory flow was more markedly impaired and more heterogeneous in septic nonsurvivors than in survivors. Interestingly, the investigators found a correlation between microcirculatory and macrocirculatory parameters in early sepsis, but this correlation was weaker in later sepsis. This finding emphasizes the importance of early resuscitation, since time is one of the most important factors affecting therapeutic strategies for improving microcirculation.(42)

Many pathogenic mechanisms contribute to the microcirculatory abnormalities that occur during sepsis. In this context, microcirculation can be regarded as the integrative compartment in which all of these factors come together. Left uncorrected, microcirculatory abnormalilties can lead to multiorgan failure and death. The most challenging septic patients are those who have received treatment but do not improve. Here, the initial hit, in combination with therapy, time, comorbidity, and genetic background, all contribute to the complex pathogenesis of

sepsis that leads to organ failure. Together, these are referred to as the microcirculatory and mitochondrial distress syndrome.(40)

Significant increases in leukocyte rigidity are observed during sepsis. The rigidity subsequently decreases with an improvement in the clinical condition.(43) A significant role has also been attributed to the mechanical behavior of white blood cells in microcirculatory alterations.(44) During sepsis, red blood cells are less likely to become deformed and more likely to aggregate.(45-47) The vasodilatory effects of several mediators released during sepsis, in combination with the excessive amounts of fluids given (which reduce viscosity), result in a low systemic resistance and low arterial pressure. The capillary leakage caused by endothelial injury of the capillaries results in hypovolemia and tissue edema, both of which result in larger diffusion distances between oxygen-carrying red blood cells and parenchymal cells. A possible initial contributing factor to the disruption of the barrier function of the microcirculatory milieu could lie in the disruption of the glycocalyx, which covers the endothelium and forms an important barrier and transduction system.(48) As was previously observed, the glycocalyx can be disrupted during inflammation and cardiovascular disease and this was made visible with OPS or SDF imaging.(49, 50) Recently, in a volunteer study, administration of endotoxin resulted in a shedding of the glycocalyx detected sublingually using OPS imaging. The shedding could be partially prevented by administration of a tumor necrosis factor scavenger.(51) In addition to metabolic, myogenic, and neurohumoral regulatory mechanisms that control microcirculatory blood flow, other regulatory factors can alter vascular tone and affect blood flow. Over the last decade, it has been demonstrated that red blood cells play an important role in the regulation of vascular tone through their ability to sense hypoxia and respond by releasing vasodilatory substances, such as nitric oxide (NO) and ATP.(52) It has been suggested that excessive NO production plays a key role in the pathology of the microcirculatory abnormalities in sepsis. Excessive NO induced by inducible NO synthase (iNOS) has deleterious effects on red blood cell function because it overrides the naturally-occurring regulatory mechanisms of vasodilation and vasoconstriction associated with autoregulation. The iNOS induction caused by cytokine release during bacteremia results in excessive NO formation during inflammation and infection,(53) resulting in the loss of vascular tone and a reduced responsiveness to vasoconstrictors.(54) The inhomogeneous expression of iNOS between different organ compartments could represent the underlying cause of the shunting of the microcirculation in various organ segments.(55) The heterogeneity caused by shunting results in local areas of hypoxia and impairs oxygen extraction. The shunting theory of sepsis could explain why resuscitation strategies based on the correction of upstream hemodynamic variables do not correct the downstream indicators of hypoxia because they are unable to recruit shunted microcirculatory units.(56) The functionally vulnerable microcirculatory units are bypassed, and oxygen is shunted from the arteriole to the venous compartment. As described above, various mechanisms in sepsis could contribute to microcirculatory dysfunction and promote shunting. In sepsis, the perfusion in the capillaries is more severely altered, even while the flow in larger microvessels is preserved

in septic shock patients, which represents direct evidence of shunting pathways in resuscitated sepsis.(57) Direct evidence of functional shunting pathways is derived from microcirculatory pO_2 measurements using palladium porphyrin phosphorescence. During various conditions of shock and resuscitation, microcirculatory pO_2 levels become lower than the pO2 of the venous effluent of an organ, demonstrating the action of functional shunting.(56)

Several experimental studies have been performed to elucidate the differences in microcirculatory response to different types of shock. Particular focus has been placed on differentiating between the effects that distributive (eg, sepsis) and hypovolemic (eg, hemorrhage) types of shock have on microcirculation.(58) Collectively, these studies have shown that the microcirculatory abnormalities in sepsis can occur in the presence of normal (or even supranormal) systemic hemodynamics. In contrast, in hypovolemic shock, the microcirculation and systemic hemodynamics seem to follow each other more closely.

This difference is probably due to the fact that autoregulatory mechanisms still function in hypovolemic shock, whereas these mechanisms are severely impaired in septic shock. In addition, the differing courses of shock could be the result of differing responses from various microvascular beds. At the arteriolar level, the cremaster muscle and diaphragm respond differently from the small intestine.(59-61) In the intestine, arteriolar constriction occurs at all levels of the arteriolar network. In contrast, in the cremaster muscle and diaphragm, larger arterioles constrict and smaller ones dilate. Therefore, there appears to be heterogeneity not only between organs but also within a single organ. Experimental studies have thus demonstrated that an increase in heterogeneity is associated with a decrease in functional capillary density and diminished red blood cell velocity in models of sepsis.(62).

Several studies have reported that global hemodynamics do not necessarily reflect regional blood flow during sepsis and septic shock.(4, 63) Farquhar and colleagues(28), using a subacute model of sepsis, found that capillary density in the distal small bowel mucosa decreases during normotension. Lam and colleagues(62) used a skeletal muscle preparation in the same subacute sepsis model to observe the distributions of perfused capillaries and red blood cell flow. They demonstrated an increase in capillaries with stopped flow and a decrease in the total number of capillaries. In addition, they demonstrated an increase in the spatial heterogeneity of red blood cell-perfused capillaries, similar to what later was demonstrated in clinical sepsis. (4) To underscore the dissociation of the presence of shock and microcirculatory abnormalities in sepsis, Nakajima and colleages(29) compared the effects of hemorrhage and endotoxin shock at the microvascular level in a rat model. They found that, in the intestinal villi, the capillary density, red blood cell velocity, and flux all decreased. Yet, at the same level of hypotension, only moderate changes were detected during hemorrhagic shock. Boczkowski and colleagues(59) showed similar results in the microvascular bed of the diaphragm by comparing an acute model of sepsis with hypotensive hypovolemic controls. Fang and colleagues(64) demonstrated similar findings for buccal microcirculation in a subacute model of septic shock compared with hemorrhagic shock. Additionally, they demonstrated that when both models

where matched according to the cardiac index, the microcirculatory alterations were similarly altered. After resuscitation, the improved global hemodynamics were not effective in improving the buccal capillary blood flow in septic shock, in contrast to hemorrhagic shock, where improved global hemodynamics was found to be bneficial on microcirculation.

Thus, in shock profiles other than distributive shock, microcirculatory alteration seems to be effectively corrected by resuscitating global hemodynamical variables. In septic shock, however, therapeutic modalities aimed at recruiting systemic variables do not always seem to be effective in recruiting microcirculation. Therefore, more specific therapies may be required. (55) All these experimental studies have contributed to the view that sepsis is a disease of microcirculation.

RESUSCITATING THE MICROCIRCULATION

Clinical investigations are currently being conducted to determine whether treatment modalities aimed at recruiting microcirculation provide a beneficial therapeutic target. Several agents and resuscitation strategies have been studied in experimental models and in single center intensive care unit populations. Various animal studies have demonstrated that, under conditions in which autoregulatory mechanisms have not been affected, fluid resuscitation successfully improves the microcirculatory abnormalities and oxygen transport to baseline values. (29, 64) In septic shock, however, fluid resuscitation alone is ineffective in improving microcirculatory function. Even when the systemic variables have been normalized, microcirculatory alterations can persist.(3, 41) Nevertheless, in a fraction of preload-dependent intensive care patients, a fluid loading of 500 mL within a 15 min period was found to significantly improve microcirculatory parameters,(65) although the inclusion criteria were not clear in this study.

In the clinical setting, several therapeutic agents have been demonstrated to effectively improve microcirculatory abnormalities in septic shock patients. One of the important findings from these studies is that the microvasculature, specifically endothelial function, is still responsive in sepsis. This was demonstrated elegantly by De Backer and colleagues,(41) who found that sublingual topical application of acetylcholine was able to recruit microcirculatory units in resuscitated septic patients. The topical sublingual application of acetylcholine reversed the local microcirculation in septic shock patients to normal values. Spronk and colleagues(57) demonstrated that intravenous infusion of an NO donor (nitroglycerin) improved sublingual microcirculation in normovolemic, pressure-resuscitated patients. Whether such therapeutic approaches will improve outcome has yet to be determined. De Backer and colleagues(63) also tested the effect of dobutamine, used at a fixed dosage, on microcirculation of the sublingual region of septic patients. Dobutamine improved sublingual microcirculatory flow, with acetylcholine-induced reserve being preserved. They also found that lactate levels correlated with the degree of microcirculatory improvement, but that microcirculatory alterations did not

correlate to changes in systemic hemodynamic parameters, such as cardiac output and MAP. These studies demonstrate that, in sepsis, microcirculatory alterations can persist, independent of resolving systemic hemodynamic variables, and that these alterations predict poor outcome.

Since the heterogeneous expression of iNOS is one of the factors contributing to the inflammation-induced autoregulatory dysfunction of microcirculatory flow, iNOS inhibition was hypothesized to improve microcirculatory function in sepsis. It has been demonstrated in several animal studies that a combined therapy of fluid and iNOS inhibitors was able to resuscitate weak microcirculatory units.(66) Interestingly, in a clinical study, although MAP improved, mortality in the group treated with non-selective iNOS inhibitors was significantly higher, resulting in early termination of the trial.(67) Clearly, inhibition of the harmful effects of nitric oxide requires a more specific approach.

Although several questions remain concerning the mode of action of activated protein C (APC), there is evidence that it improves the microcirculatory flow indices in experimental models.(68, 69) In humans, improvement in the microcirculatory flow observed with OPS imaging was reported during treatment with activated protein C (APC), which decreased after cessation of the APC treatment.(70) The latter finding may suggest that the timing and length of treatment with APC may be an essential component in its application.

CONCLUSIONS

One of the key features of both experimental and human sepsis is the distributive alteration of microvascular blood flow. These distributive alterations have been demonstrated by a heterogeneous microvascular blood flow between different vascular beds, as has been clearly visualized through the use of imaging techniques as OPS and SDF. Using these techniques, microcirculatory alterations have been demonstrated to be associated with organ dysfunction and impaired outcome in sepsis. In light of the central role of microcirculatory alterations in the pathogenesis of sepsis, it seems logical to hypothesize that restoring microcirculatory function contributes to the treatment of sepsis. However, several questions remain unanswered. First, what is the clinical impact of the sublingual monitoring of microcirculation in terms of response to conventional therapy and clinical benefit? Second, what are the best therapeutic interventions to recruit microcirculation, and how do these differ from conventional therapeutic modalities? Finally, will the outcome of patients with sepsis improve when microcirculation is effectively resuscitated? To answer these questions, more evidence must be gathered. Routine investigation of microcirculation might become a key component in the functional hemodynamic monitoring of critically ill patients.

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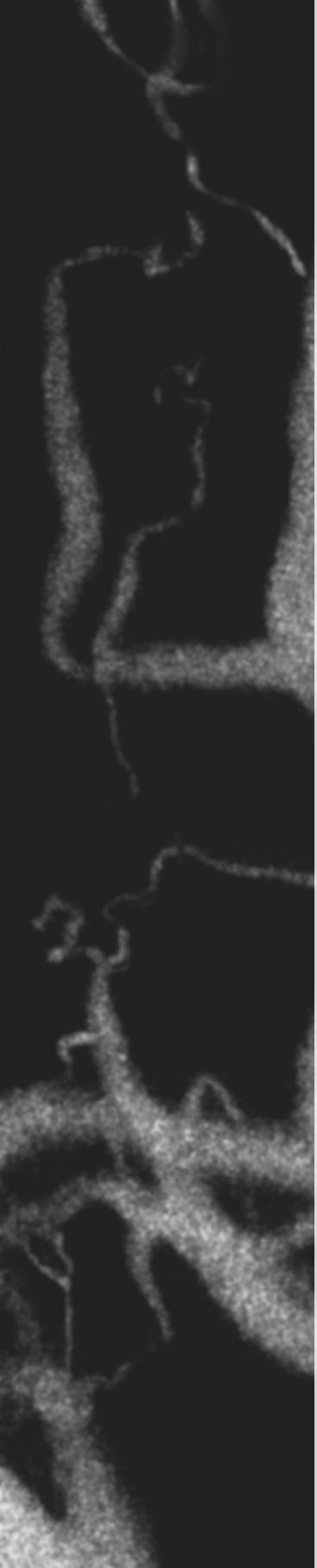
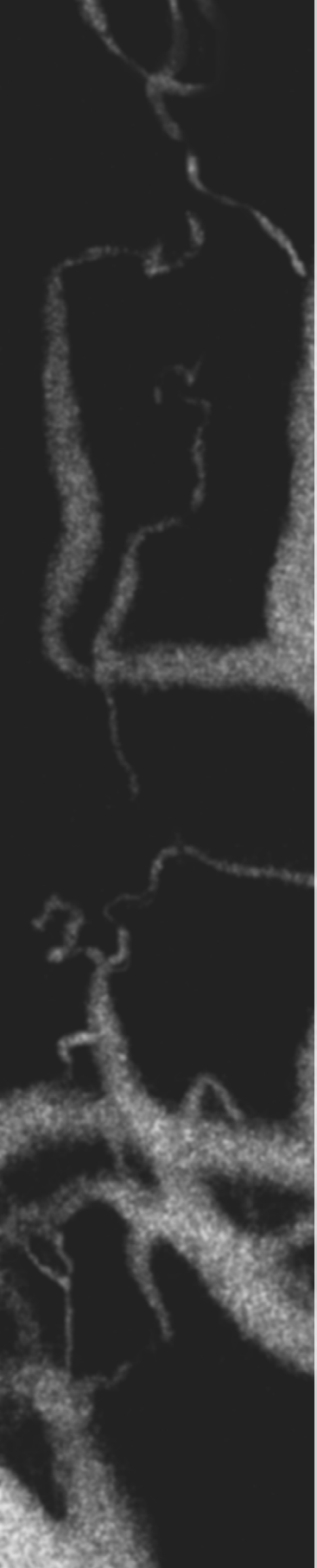


Part B

Outcome of current treatment in acute cardiology



Chapter 4

Prognosis of patients undergoing cardiac surgery and treated with intra-aortic balloon pump counterpulsation prior to surgery: A long-term follow-up study

Corstiaan A. den Uil, Suzanne S.D. Valk, Jin M. Cheng, Arie-Pieter Kappetein, Ad J. Bogers, Ron T. van Domburg, Maarten L. Simoons.

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ABSTRACT

The aim of this study was to evaluate short- and long-term outcome in patients undergoing coronary artery bypass grafting (CABG), who received an intra-aortic balloon pump (IABP) prior to surgery. Between January 1990 and June 2004, all patients (N=154) who received an IABP prior to on-pump CABG in our center were included. Patients received the IABP for vital indications (i.e. either unstable angina refractory to medical therapy or cardiogenic shock; group 1: n=99) or for prophylactic reasons (group 2: n=55). A Cox proportional hazards model was used to identify predictors of long-term all-cause mortality. Compared with the EuroSCORE predictive model, observed 30-day mortality in group 1 (15.2%) was slightly higher than predicted (10.3%). A decrease in 30-day mortality occurred in group 2 (median predicted mortality was 7.2% and observed was 0%). Cumulative 1-, 5-, and 6-year survival was 82.8 ± 3.8%, 70.1 ± 4.9%, and 67.3 ± 5.1% for group 1 versus 98.2 ± 1.8%, 84.0 ± 5.6% and 84.0 ± 5.6% for group 2 (Log-rank: p=0.02). Logistic EuroSCORE (HR 1.03 [1.01-1.05], p=0.007) was an independent predictor of long-term all-cause mortality.

INTRODUCTION

The main effects of intra-aortic balloon pump (IABP) counterpulsation are reduction of ventricular afterload, improvement in coronary perfusion, and enhancement of subendocardial perfusion.(1) Several studies have supported insertion of an IABP prior to high-risk cardiac surgery.(2-4) In addition, preoperative insertion has been associated with lower in-hospital mortality rates compared to intra-operative or postoperative insertion.(5) However, data are lacking on long-term prognosis of patients undergoing high-risk coronary artery bypass grafting (CABG), who were treated with IABP assist preoperatively. We performed a cohort study to address short- and long-term mortality in these patients.

MATERIALS AND METHODS

Patient inclusion and data collection

Between January 1990 and June 2004, all patients (N=154) who received an IABP prior to CABG in our center were included. Data were acquired from patient medical records and from the local hospital database. Retrospectively, the logistic European system for cardiac operative risk evaluation (EuroSCORE) was calculated for each patient.(6) A priori, we made the decision to analyze the data separately dependent on the indication for IABP counterpulsation. Ninety-nine patients (64%) received an IABP for vital indications (cardiogenic shock or unstable angina refractory to pharmacological therapy; group 1). The remaining 55 patients (36%) received the IABP for prophylactic reasons (left ventricular ejection fraction below 40%, redo surgery, or complex coronary artery lesions; group 2).

Intra-aortic balloon pump

All IABPs were inserted at the catheterization laboratory or intensive cardiac care unit. In all patients, the IABP was introduced using the Seldinger technique. Between 1990 and 1995, Datascope (Datascope Corp, Fairfield, NJ, USA) 10.5 and 9.5 French catheters were used. From 1995 through 2000, Arrow (Arrow Corp, Reading, PA, USA) 9 French catheters, and between 2000 and 2004, Arrow (Arrow Corp, Reading, PA, USA) 8 French catheters were used.

Study definitions

Left ventricular function was estimated with echocardiography performed by trained cardiologists. Impaired left ventricular function was defined as an ejection fraction <40% measured by echocardiography. Cardiogenic shock was defined as systolic blood pressure below 90 mmHg with clinical signs of hypoperfusion, i.e. cold extremities, oliguria or altered mental state. Inotropic agents used were catecholamines (dobutamine, dopamine, and/or norepinephrine) and phosphodiesterase inhibitors (enoximone). The following complications

of IABP counterpulsation were registered: leg ischemia requiring IABP removal, IABP-related femoral artery thrombosis, need for vascular surgery, infection, and access site bleeding requiring blood transfusion. Leg ischemia was defined as a novel absence of peripheral pulsations together with a white coloration of the leg.

Management of surgery

In all patients, nonpulsatile cardiopulmonary bypass was established through standard median sternotomy with aortic root and right atrial cannulation. Surgery was performed under mild hypothermia (32 °C).

Follow-up

Follow-up started at the day of surgery (baseline). In 2005, vital status of all patients was acquired from the Registry of Deaths. Median follow-up duration in the database was 5.7 years (range: 0-6 years). Follow-up duration was cut off at 6 years, because, after 6 years, the number of patients at risk decreased significantly and the risk estimates became unstable.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Non-normally distributed variables were presented as median and interquartile range. Discrete variables were noted as numbers and proportions. Differences between groups were tested with one-way analysis of variance (ANOVA), Mann-Whitney, or chi-square test, when appropriate. Cumulative incidence of survival was determined by Kaplan-Meier analysis with survival expressed as calculated probability ± standard error. Kaplan-Meier survival curves were compared by the log-rank test. The Cox proportional hazards model was used to identify predictors of long-term all-cause mortality. Multivariate Cox proportional hazards model analysis was done by entering the clinical characteristics that were significantly different between both groups and that showed the best correlation with long-term mortality in univariate analysis. Hazard ratios (HR) were presented together with their 95% confidence intervals. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

Clinical characteristics of the study population

Between January 1990 and June 2004, 154 consecutive patients were included in this study. Table 1 demonstrates the clinical characteristics of the patients, divided into indication for IABP therapy (group 1: "vital indication"; group 2: "prophylactic" reasons). Mean age of the patients was 64 ± 9 years in group 1 and 66 ± 8 years in group 2. Seventy-six percent of them were male. In 26 cases (17%), CABG was combined with surgery for other sequelae of coronary obstruction.

Table 1. Clinical characteristics of the study population (N=154)

	Group 1 "Vital indication" N=99	Group 2 "Prophylactic" N=55	P-value
Age, yrs (mean ± SD)	64 ± 9	66 ± 8	0.18
Gender, male	75 (76%)	42 (76%)	0.99
Logistic EuroSCORE, % (median and IQR)	10.3 [4.7-18.8]	7.2 [3.8-10.3]	0.002
Preoperative CV risk factors			
Hypertension	37 (37%)	29 (53%)	0.09
Current smoking	36 (36%)	13 (24%)	0.15
Dyslipidemia	42 (42%)	26 (47%)	0.61
Diabetes mellitus	27 (27%)	13 (24%)	0.70
History			
Previous MI	67 (68%)	36 (69%)	0.99
Prior CABG	17 (17%)	8 (15%)	0.82
Impaired LV function (EF<40%)	39 (39%)	16 (29%)	0.22
Clinical parameters			
Body mass index, kg/m^2 (mean ± SD)	26 ± 3	26 ± 3	0.75
Heart rate, bpm (mean ± SD)	84 ± 22	78 ± 15	0.08
Diagnosis			
Acute myocardial infarction	55 (56%)	19 (35%)	0.02
Mechanical complication of AMI	12 (12%)	0 (0%)	0.005
Coronary angiography			
Three-vessel coronary disease or left main stem stenosis >70%	65 (66%)	46 (84%)	0.02
Preoperative treatment			
Inotropic agents for cardiogenic shock	20 (20%)	0 (0%)	<0.001
Type of surgery			
Isolated CABG procedure	76 (77%)	52 (95%)	0.006
CABG plus mitral valve surgery	17 (18%)	2 (4%)	0.01
CABG plus LV reconstruction	2 (2%)	2 (4%)	0.62
CABG plus VSR repair	5 (5%)	0 (0%)	0.16
Anastomoses			
>3 anastomoses	50 (53%)	42 (79%)	0.001
Complications from IABP counterpulsation			
Leg ischemia requiring IABP removal	2 (2%)	3 (6%)	0.35
Arterial thrombosis requiring vascular surgery	1 (1%)	2 (4%)	0.29
Thrombocytopenia	1 (1%)	0 (0%)	0.99

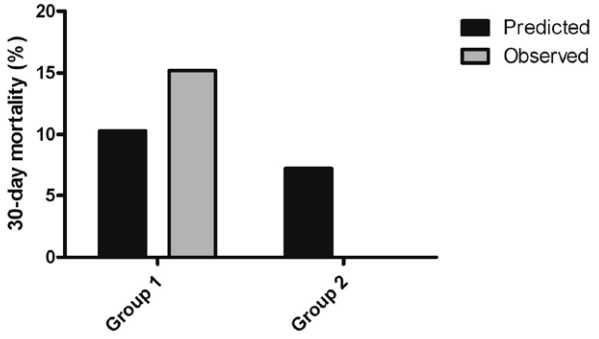
Data represent numbers (%) unless otherwise indicated. Abbreviations: SD, standard deviation; EuroSCORE, European system for cardiac operative risk evaluation; IQR, interquartile range; CV, cardiovascular; (A)MI, (acute) myocardial infarction; CABG, coronary artery bypass grafting; LV, left ventricular; EF, ejection fraction; VSR, ventricular septal rupture.

Logistic EuroSCORE was significantly higher in group 1 relative to group 2 (10.3 [4.7-18.8] % vs. 7.2 [3.8-10.3] % in group 2, p=0.002).

THIRTY-DAY OUTCOME

Fifteen patients (15.2%) in group 1 and no patients (0.0%) in group 2 died in the 30 days following surgery (group 1 vs. group 2: p=0.001). Observed mortality in group 1 was slightly higher

Figure 1. Short-term prognosis. Observed mortality (light gray) compared with mortality predicted by the European System for Cardiac Operative Risk Evaluation (EuroSCORE; black). Group 1: 'vital indication', group 2: 'prophylactic indication' for intra-aortic balloon pump counterpulsation.

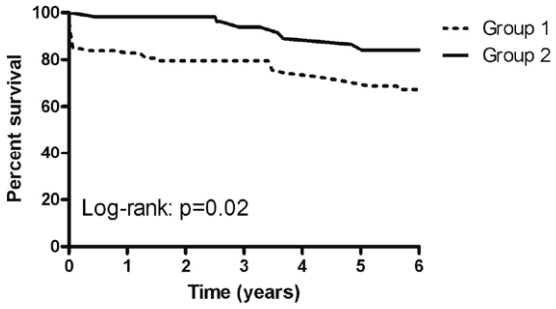


than predicted by EuroSCORE (Figure 1). However, a decrease in mortality occurred in group 2: median predicted mortality was 7.2% and observed was 0% (Figure 1).

LONG-TERM OUTCOME

After six years of follow-up, 3% of the patients were lost. The endpoint (all-cause mortality) occurred in 29 (29%) patients in group 1 and in 7 (13%) patients in group 2. Kaplan-Meier estimated 6-year survival was 67.3 ± 5.1% for group 1 and 84.0 ± 5.6% for group 2, p=0.02 (Figure 2). Logistic EuroSCORE (HR 1.03 [1.01-1.05], p=0.007) was the best independent predictor of long-term all-cause mortality (Table 2).

Figure 2. Kaplan-Meier plot of long-term survival. Long-term survival of the study population stratified to the indication for intra-aortic balloon pump counterpulsation (group 1: 'vital indication', group 2: 'prophylactic indication').



Number at risk	99	80	71	64	56	53	44
Survival (%)	100	83	80	80	74	70	67
Number at risk	55	51	49	43	37	35	29
Survival (%)	100	98	98	94	89	84	84

Table 2. Correlates with long-term mortality found with Cox regression analyses (N=154).

	Univariate		Multivariate	
	HR [95%CI]	P-value	HR [95%CI]	P-value
Age, years	0.99 [0.96-1.03]	0.65	1.00 [0.96-1.04]	0.98
Gender, male	1.47 [0.64-3.36]	0.36	1.51 [0.62-3.66]	0.37
Logistic EuroSCORE, %	1.05 [1.03-1.06]	<0.001	1.03 [1.01-1.05]	0.007
Inotropic agents for cardiogenic shock	3.46 [1.66-7.18]	0.001	1.17 [0.46-2.97]	0.74
CABG plus other type of surgery	3.55 [1.80-7.02]	<0.001	2.30 [0.97-5.49]	0.06
Indication of IABP ("prophylactic" relative to "vital indication")	0.38 [0.17-0.87]	0.02	0.58 [0.24-1.41]	0.23

Abbreviations: HR, hazard ratio; EuroSCORE, European system for cardiac operative risk evaluation; CABG, coronary artery bypass grafting.

COMPLICATIONS OF INTRA-AORTIC BALLOON PUMP COUNTERPULSATION

Overall, six patients (3.9%) developed IABP-related complications. Complications occurred in both groups of patients (Table 1). Five patients (3%) had symptoms of leg ischemia at the side where the IABP was inserted. In two of these cases, IABP removal before initiation of surgery was necessary. The other three patients (2%) developed signs of leg ischemia after postoperative removal of the IABP. This was due to common femoral artery thrombosis, requiring vascular surgery. In two patients, embolectomy was performed and in the third patient a iliaco-femoro-popliteal Goretex bypass was made. These three cases of arterial thrombosis following IABP occurred in the time period 1991-1994. Finally, one patient experienced an episode of thrombocytopenia (lowest thrombocyte count $43*10^9$/L) without signs of hemorrhage. There were no IABP-related access site bleedings requiring red blood cell transfusion. If performed, IABP tip cultures were all negative. All six patients with complications survived the first 30 days following surgery.

DISCUSSION

This is the first study reporting long-term outcome of a unique group of patients who underwent CABG with the use of preoperative IABP, reflecting a 15-year experience in our center. Compared with the EuroSCORE predictive model, we demonstrated that prophylactic intra-aortic balloon pump counterpulsation allowed a reduction in 30-day mortality. In both groups, a considerable number of patients survived until 6 years of follow-up following surgery. Logistic EuroSCORE, used as a continuous variable, was an independent predictor of long-term outcome.

Several studies suggested that preoperative introduction of an intra-aortic balloon pump may have beneficial effects on mortality in specific patient groups undergoing CABG.(4, 7) The low short-term event rate in our subgroup of patients treated prophylactically with IABP, suggests a beneficial effect of counterpulsation as well. Data on long-term survival of patients treated with preoperative IABP is still lacking in the current literature. In our study, consisting of

a considerable number of high-risk patiens, we found that 5-year survival was 70% in unstable patients and 84% in patients treated prophylactically with IABP. Based on large databases of isolated, mainly low risk, CABG patients, recent studies have reported a 5-year probability of survival of about 80-90%(8, 9), which suggests that long-term survival in our study population was relatively favorable. Notably, the difference in long-term survival rates between group 1 and group 2 was determined by the high 30-day mortality rate in group 1, since the Kaplan-Meier curves ran parallel after 30 days of follow-up. Interestingly, Singh et al. reported recently that among survivors of STEMI complicated by cardiogenic shock, annual long-term mortality rates approximate those of STEMI patients without shock.(10) Our findings point out a similar principle in a different cohort of patients.

We used the logistic EuroSCORE, which is known to be more accurate in relatively high risk patients than the simple additive EuroSCORE model.(11) Other investigators have demonstrated the predictive value of the additive EuroSCORE model as well as the logistic EuroSCORE model for long term all-cause mortality.(12, 13) We confirmed the independent association of logistic EuroSCORE and long-term outcome in patients treated with preoperative IABP.

Overall IABP-related complication rate was 3.9%, which is in line with other reports.(4, 14) The complications included arterial thrombosis, occurring in the years that larger catheters were used than nowadays. No IABP-related deaths occurred, indicating a specific area of indication for these devices before moving on to more powerful left ventricular assist devices with a higher complication rate.(15)

Our study has its limitations. First, we investigated a relatively small number of heterogeneous patients. However, we divided our population into two groups of unstable patients, who had a vital indication for IABP therapy and patients who were treated prophylactically. A second limitation is the retrospective nature of our study. However, main data could be retrieved from surgeon's reports and discharge letters in our local computer database. The remaining missing data were all acquired from patient medical records. Third, we compared short-term mortality with logistic EuroSCORE, which may actually overestimate the operative risk.

In conclusion, a considerable number of patients undergoing on-pump cardiac surgery with preoperative IABP, survived at the long-term. Logistic EuroSCORE was an independent predictor of long-term outcome. Further improving outcome in those patients who are hemodynamically compromised prior to surgery remains a challenge for the future.

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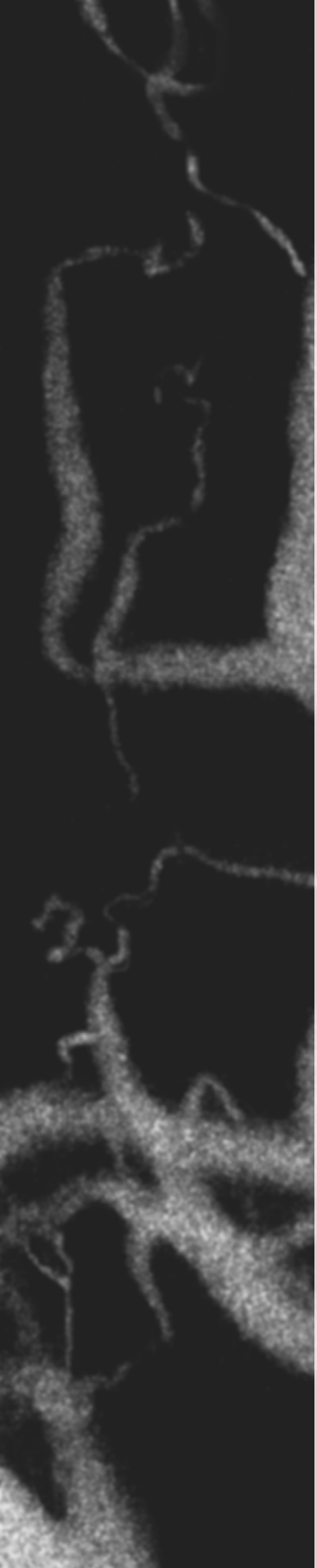

Chapter 5

Usefulness of intra-aortic balloon pump counterpulsation in patients with cardiogenic shock from acute myocardial infarction

Jin M. Cheng, Suzanne D.A. Valk, Corstiaan A. den Uil, Martin van der Ent, Wim K. Lagrand, Meike van de Sande, Ron T. van Domburg, Maarten L. Simoons

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ABSTRACT

Although intra-aortic balloon pump (IABP) counterpulsation is increasingly being used for the treatment of patients with cardiogenic shock from acute myocardial infarction, data on the long-term outcomes are lacking. The aim of the present study was to evaluate the 30-day and long-term mortality, and to identify predictors for 30-day and long-term all-cause mortality of patients with acute myocardial infarction complicated by cardiogenic shock who were treated with IABP. From January 1990 to June 2004, 300 consecutive patients treated with IABP were included. The mean age of the study population was 61±11 years and 79% of the patients were men. The survival rate until IABP removal after successful hemodynamic stabilization was 70% (n=211). The overall cumulative 30-day survival rate was 58%. The 30-day mortality rate decreased over time from 52% in 1990 to 1994 to 36% in 2000 to 2004 (p for trend <0.05). Follow-up ranged from 0 to 15 years. In patients who survived until IABP removal, the cumulative 1-, 5-, and 10-year survival rate was 69%, 58% and 36%, respectively. The adjusted predictors of long-term mortality were arrhythmias during the intensive cardiac care unit stay (hazard ratio [HR] 1.8, 95% confidence interval [CI] 1.2 to 2.9) and renal failure during the intensive cardiac care unit stay (HR 2.5, 95% CI 1.3 to 5.1). After adjustment, treatment with primary percutaneous coronary intervention (HR 0.5, 95% CI 0.3-0.9) and coronary artery bypass grafting (HR 0.4, 95% CI 0.2-0.8) were associated with lower long-term mortality. In conclusion, in patients with AMI complicated by cardiogenic shock treated with IABP, the 30-day survival improved with time and an encouraging number of patients survived in the long term.

INTRODUCTION

Cardiogenic shock is a state of inadequate tissue perfusion due to cardiac dysfunction.(1) The incidence of cardiogenic shock complicating acute myocardial infarction (AMI) ranges from 5% to 10%.(2) Even though the prognosis of patients with cardiogenic shock has improved over time because of aggressive reperfusion strategies, the in-hospital mortality rate from cardiogenic shock remains very high (i.e. 50%).(2, 3) Use of intra-aortic balloon pump (IABP) counterpulsation is associated with improved survival in patients with cardiogenic shock treated with thrombolysis.(4-7) Although IABP use in cardiogenic shock adjunctive to primary percutaneous coronary intervention (PCI) was recently questioned,(8) IABP is the method of first choice for mechanical assistance in patients with cardiogenic shock who do not respond adequately to standard pharmacologic treatment.(9) Also, long-term follow-up data of these patients are lacking. Therefore, the aim of the present study was to evaluate the 30-day and long-term outcomes and to identify predictors of 30-day mortality for patients with cardiogenic shock treated with IABP. In addition, we evaluated the predictors of long-term mortality in patients who survived until IABP removal after successful hemodynamic stabilization.

METHODS

From January 1990 to June 2004, all consecutive patients (n=300) with cardiogenic shock from AMI who were treated with IABP at Erasmus Medical Center in Rotterdam, the Netherlands, were included. Our center is a tertiary referral center for PCI, mechanical treatment of cardiogenic shock and heart transplantation. From 1990 to 2000, about 175 patients with AMI were admitted to our center annually. From 2001 to 2004, the number of admitted AMI patients increased to 350 annually, because primary PCI was implemented as a standard treatment of AMI, and our center was a referral center for primary PCI. The indication for IABP counterpulsation was cardiogenic shock in all cases. IABP insertion was withheld only when it was technically not feasible (e.g. because of severe atherosclerotic peripheral artery disease or aortic disease), or in patients judged to have a definite fatal prognosis because of concomitant disease, which concerned 21 patients during the inclusion period. The data were acquired retrospectively from the patient medical records and hospital database, for which a missing rate of <5% was considered acceptable. We performed a sub-analysis of those patients who survived until IABP removal after successful hemodynamic stabilization.

The IABP was inserted either at the catheterization laboratory or at the intensive cardiac care unit. From 1990 to 1995, Datascope (Datascope, Fairfield, NJ, USA) 9.5F and 10.5F catheters were used. From 1995 through 2000, Arrow (Arrow, Reading, PA, USA) 9F catheters were used, and from 2000 to 2004, Arrow 8F catheters were used.

Recent AMI was defined as AMI at hospital admission. In addition to clinical suspicion of AMI (i.e. typical chest pain and electrocardiographic abnormalities), all patients had a diagnostic

increase in cardiac markers during the hospitalization period. Cardiogenic shock was defined as low systolic blood pressure (<90 mm Hg) owing to cardiac insufficiency, with clinical signs of hypoperfusion (e.g., cold extremities, oliguria, altered mental state) not responsive to fluid resuscitation. Most patients had already received inotropic agents before the collection of baseline data. Blood pressure was measured just before IABP insertion (baseline). Left ventricular function (LVF) was assessed with echocardiography by trained cardiologists and categorized into normal (ejection fraction >40%) or impaired (ejection fraction <40%). The inotropic agents used in our hospital were catecholamines (dobutamine, dopamine, and/or norepinephrine) and phosphodiesterase inhibitors (enoximone). The anti-arrhythmic agents used in our hospital were lidocaine, amiodarone, sotalol and digoxin. The following complications of IABP counterpulsation were registered: limb ischemia requiring IABP removal, bleeding, embolic and thrombotic events, need for vascular surgery, and IABP-related infection. Limb ischemia was defined as diminished or absent peripheral pulsation with a white coloration of the leg at the side of IABP catheter introduction. Major bleeding was defined as a bleeding requiring red blood cell transfusion. Minor bleeding was defined as any access site bleeding not requiring red cell transfusion. Infection was defined as fever, combined with leukocytosis, increased C-reactive protein level (>5 mg/L), and signs of inflammation at the IABP insertion site, with or without positive blood and/or IABP-tip cultures.

Follow-up started at the day of IABP insertion (baseline). In March 2006, vital status of all patients was acquired from municipal civil registries with a response rate of 100%. Ten patients (3%) were lost during follow-up. Median follow-up duration was 6.1 years (range 0 to 15).

All data were analyzed using the Statistical Package for Social Sciences software, version 15.0 (SPSS, Chicago, IL, USA). Continuous variables were compared using Student's *t* test or 1-way analysis of variance and are presented as the mean ± standard deviation. Nonparametric continuous variables were compared using the Mann-Whitney *U* test or Kruskal-Wallis test and are presented as median and range. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate, and are presented in percentages. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Cumulative survival was estimated according to the Kaplan-Meier method. Kaplan-Meier survival curves were compared using the log-rank test. Univariate and multivariate logistic regression analyses were performed to identify predictors of 30-day all-cause mortality. Multivariate Cox proportional hazards regression analyses were performed to identify predictors of long-term all-cause mortality in patients who survived until IABP removal. On multivariate analyses, the variables of age, gender, diabetes mellitus, dyslipidemia, history, LVF, blood pressure, heart rate, IABP running time, ST-elevation myocardial infarction, reperfusion therapy and complications during intensive cardiac care unit stay were entered into the model in a stepwise fashion. The final results are presented as unadjusted and adjusted odds ratios (OR), and as unadjusted and adjusted hazard ratios (HR), both with the associated 95% confidence intervals (CIs). Subanalyses were performed stratified to IABP running time (1, 2 to 5, and ≥6 days). All statistical tests were 2-tailed, and $p < 0.05$ was considered statistically significant.

RESULTS

The baseline characteristics are listed in Table 1. The mean age of the study population was 61±11 years and 79% of the patients were male. Most patients had an ST-segment elevation myocardial infarction (92%). Reperfusion therapy was performed in 80% of the patients; 45%

Table 1. Baseline and procedural characteristics (n=300).

	Total (n=300)
Age (years)	61 ± 11
Gender (male)	79%
Risk factors	
Diabetes Mellitus	20%
Hypertension	35%
Smoking	55%
Dyslipidemia	27%
Peripheral arterial disease	9%
Renal insufficiency	3%
History	
Prior cerebro-vascular accident	6%
Prior myocardial infarction	45%
Prior coronary artery bypass grafting	9%
Prior percutaneous coronary intervention	7%
Systolic blood pressure (mm Hg)*	102±31
Diastolic blood pressure (mm Hg)*	63±19
Heart rate (bpm)	99±26
Impaired left ventricular function	76%
Three vessel / left main stem coronary artery disease	42%
Location of myocardial infarction	
Anterior/septal ST-elevation myocardial infarction	57%
Inferior/posterior ST-elevation myocardial infarction	35%
Non-ST-elevation myocardial infarction	8%
Mechanical complication of myocardial infarction	12%
Reperfusion therapy	
Primary percutaneous coronary intervention	45%
Thrombolysis	27%
Coronary artery bypass grafting	12%
No reperfusion therapy	20%
Complications during stay at intensive cardiac care unit	
Cardiopulmonary resuscitation	33%
Mechanical ventilation	56%
Arrhythmias requiring anti-arrhythmic agents	44%
Renal failure requiring renal replacement therapy	6%
Intra-aortic balloon pump running time	
1 day	31%
2-5 days	49%
≥6 days	20%

Data are presented as mean ± SD or percentages.

* Blood pressure measured just before insertion of IABP.

were treated with primary PCI, 27% were treated with thrombolysis, and 12% were treated with emergency coronary artery bypass grafting (CABG). Most patients had already received inotropic agents before IABP insertion (82%). Mechanical ventilation and cardiopulmonary

Table 2. Baseline and procedural characteristics of patients who survived until removal of intra-aortic balloon pump (IABP) after successful hemodynamic stabilization

	Total (n=211)	IABP running time 1 day (n=37)	IABP running time 2-5 days (n=123)	IABP running time ≥6 days (n=51)	P-value
Age (years)	60±11	61±12	60±11	59±12	0.7
Gender (male)	81%	84%	81%	80%	0.9
Risk factors					
Diabetes Mellitus	20%	16%	21%	22%	0.8
Hypertension	35%	44%	33%	34%	0.5
Smoking	56%	53%	56%	59%	0.9
Dyslipidemia	28%	35%	25%	31%	0.4
Peripheral arterial disease	8%	9%	8%	7%	0.9
Renal insufficiency	4%	3%	2%	8%	0.1
History					
Prior cerebro-vascular accident	6%	5%	7%	4%	0.8
Prior myocardial infarction	43%	41%	38%	55%	0.1
Prior coronary artery bypass grafting	10%	16%	5%	18%	<0.05
Prior percutaneous coronary intervention	8%	14%	7%	6%	0.4
Systolic blood pressure (mm Hg)*	105±30	114±28	104±32	100±25	0.1
Diastolic blood pressure (mm Hg)*	64±17	69±16	63±18	62±16	0.2
Heart rate (bpm)	96±27	95±28	94±28	101±22	0.3
Impaired left ventricular function	73%	50%	74%	85%	<0.01
Three-vessel / left main stem coronary artery disease	38%	41%	38%	35%	0.9
Location of myocardial infarction					0.2
Anterior/septal STEMI	57%	43%	59%	63%	
Inferior/posterior STEMI	36%	46%	37%	27%	
Non-STEMI	7%	11%	4%	10%	
Mechanical complication of myocardial infarction	11%	11%	13%	8%	0.7
Reperfusion therapy					
Primary percutaneous coronary intervention	47%	63%	49%	31%	<0.05
Thrombolysis	30%	23%	30%	37%	0.4
Coronary artery bypass grafting	15%	11%	14%	20%	0.4
No reperfusion therapy	13%	6%	11%	22%	0.1
Complications during stay at ICCU					
Cardiopulmonary resuscitation	26%	24%	24%	29%	0.8
Mechanical ventilation	51%	38%	51%	59%	0.1
Arrhythmias requiring anti-arrhythmic agents	48%	19%	46%	73%	<0.001
Renal failure requiring renal replacement therapy	6%	0%	6%	12%	0.1

Data are represented as mean ± SD or percentages.

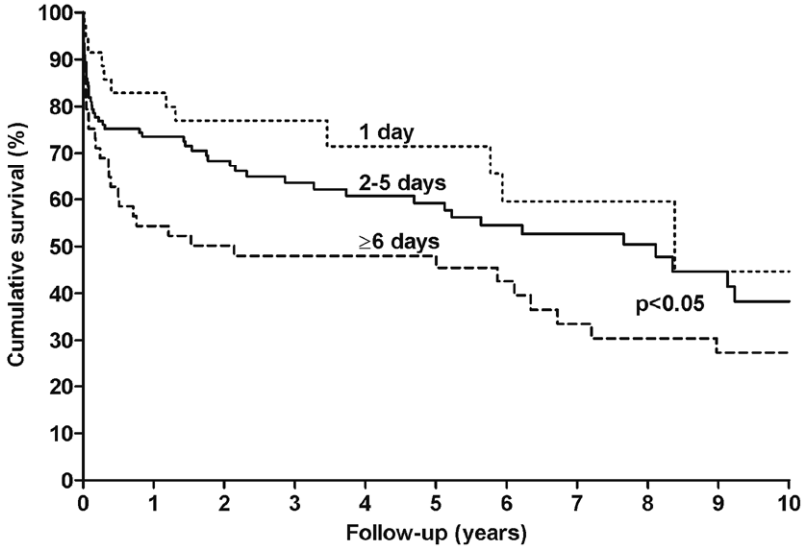
* Blood pressure measured just before insertion of IABP. Abbreviations: STEMI, ST-segment myocardial infarction; ICCU, intensive cardiac care unit.

resuscitation during the intensive cardiac care unit stay were needed in 56% and 33% respectively. Arrhythmias requiring the use of anti-arrhythmic agents and renal failure requiring renal replacement therapy occurred in 44% and 6% of patients, respectively.

The baseline characteristics of the patients who survived until IABP removal after successful hemodynamic stabilization (n=211) are listed in Table 2. The IABP running time in this subgroup was 1 day for 18%, 2 to 5 days for 58%, and ≥6 days in 24% with a median of 3 days (range 1 to 27). A history of CABG ($p<0.05$), impaired LVF ($p<0.01$), and arrhythmias ($p<0.001$) were more frequent in patients with IABP running time ≥6 days than in patients with an IABP running time of 2 to 5 days. Fewer patients with an IABP running time ≥6 days were treated with primary PCI ($p<0.05$).

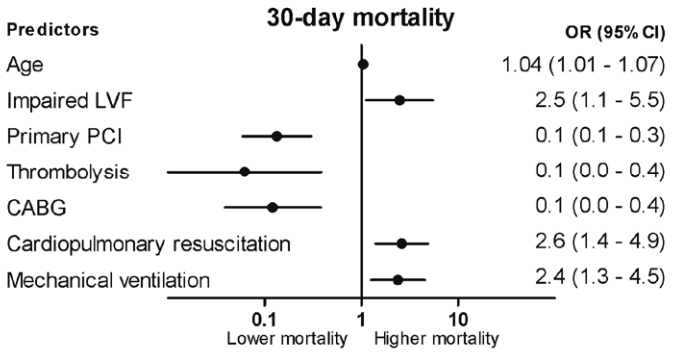
The cumulative survival rate untill IABP removal after successful hemodynamic stabilization was 70% (n=211) and the overall cumulative 30-day survival rate was 58%. Patients who had an IABP for only 1 day had greater 30-day mortality than patients with an IABP running time of >1 day. Mortality was greatest in the first days after IABP insertion. The cumulative long-term survival rate was 48%, 41% and 25% at respectively 1, 5 and 10 years of follow-up. The 10-year estimated cumulative survival in 30-day survivors was 41%. The cumulative long-term

Figure 1. Cumulative long-term survival of patients with cardiogenic shock who survived until removal of IABP after successful hemodynamic stabilization, stratified by IABP running time. P-value was obtained by comparing IABP running time of ≥6 days with IABP running time of 2 to 5 days.



1 day						
Number died	0	0	11	13	13	14
Number at risk	37	24	14	9	7	2
2-5 days						
Number died	0	38	44	48	50	54
Number at risk	123	62	43	32	21	8
≥6 days						
Number died	0	26	27	29	33	34
Number at risk	51	24	22	16	11	9

Figure 2. Adjusted predictors of 30-day mortality in patients with cardiogenic shock treated with IABP, presented as odds ratios with associated 95% confidence intervals. Abbreviations: CABG, coronary artery bypass grafting; LVF, left ventricular function; PCI, percutaneous coronary intervention.



Kaplan-Meier survival estimates of patients who survived until IABP removal after successful hemodynamic stabilization are shown in Figure 1. In these patients, the cumulative long-term survival was 69%, 58% and 36% at 1, 5 and 10 years of follow-up, respectively. Patients with an IABP running time of ≥6 days had significantly greater long-term mortality compared with patients with an IABP running time of 2 to 5 days ($p<0.05$).

The unadjusted predictors of 30-day and long-term mortality are listed in Table 3. The adjusted predictors of 30-day mortality are presented in Figure 2. On multivariate analysis, the adjusted predictors of 30-day mortality were age (OR 1.04, 95% CI 1.01 to 1.07), impaired LVF (OR 2.5, 95% CI 1.1 to 5.5), need for cardiopulmonary resuscitation (OR 2.6, 95% CI 1.4 to 4.9), and need for mechanical ventilation (OR 2.4, 95% CI 1.3 to 4.5). After adjustment, treatment with primary PCI (OR 0.1, 95% CI 0.1 to 0.3), thrombolysis (OR 0.1, 95% CI 0.0 to 0.4), and emergency CABG (OR 0.1, 95% CI 0.0 to 0.4) were associated with improved 30-day survival. The adjusted predictors of long-term mortality in patients who survived until IABP removal after successful

Figure 3. Adjusted predictors of long-term mortality in patients with cardiogenic shock treated with IABP, presented as hazard ratios with associated 95% confidence intervals. Only patients who could be successfully weaned from IABP were included in long-term Cox regression analysis. Variables of age, gender, diabetes mellitus, dyslipidemia, history, LVF, blood pressure, heart rate, IABP running time, period of hospital admission, ST-elevation myocardial infarction, reperfusion therapy, and complications during ICCU stay were entered into the model in a stepwise fashion. Abbreviations: CABG, coronary artery bypass grafting; ICCU, intensive cardiac care unit; PCI, percutaneous coronary intervention.

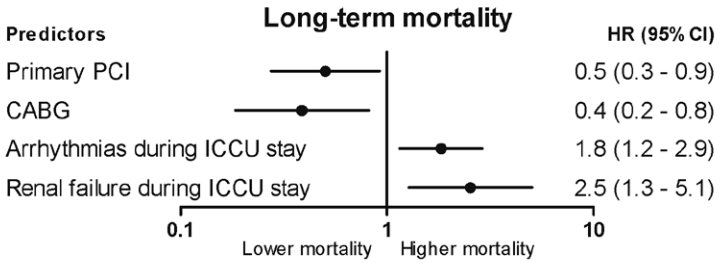


Table 3. Unadjusted predictors of 30-day and long-term mortality.

	30-day mortality (OR [95%CI])	Long-term mortality[a] (HR [95%CI])
Age	1.03 [1.01-1.05]	1.02 [1.00-1.04]
Male	0.7 [0.4-1.2]	1.1 [0.7-1.7]
Risk factors		
Diabetes Mellitus	1.1 [0.6-1.9]	1.2 [0.8-1.9]
Hypertension	1.0 [0.6-1.8]	1.1 [0.7-1.7]
Smoking	0.7 [0.4-1.1]	0.7 [0.5-1.1]
Dyslipidemia	0.7 [0.4-1.2]	0.9 [0.6-1.4]
History		
Prior cerebrovascular accident	1.3 [0.5-3.4]	1.8 [0.9-3.5]
Prior myocardial infarction	1.5 [0.9-2.4	1.5 [1.0-2.2]
Prior coronary artery bypass grafting	0.8 [0.4-1.8]	1.8 [1.0-3.1]
Prior percutaneous coronary intervention	0.5 [0.2-1.4]	1.1 [0.5-2.3]
Impaired left ventricular function	2.8 [1.5-5.2]	1.8 [1.2-2.7]
Systolic blood pressure, units of 10 mm Hg	0.9 [0.8-1.0]	1.0 [1.0-1.1]
Diastolic blood pressure, units of 10 mm Hg	0.9 [0.8-1.0]	1.0 [0.9-1.1]
Heart rate, units of 10 bpm	1.1 [1.0-1.2]	1.0 [1.0-1.1]
Hospital admission in 1995-1999[b]	0.6 [0.3-1.2]	0.7 [0.4-1.1]
Hospital admission in 2000-2004[b]	0.5 [0.3-0.9]	0.7 [0.4-1.1]
IABP running time of 1 day[c]		0.8 [0.5-1.5]
IABP running time of ≥6 days[c]		1.6 [1.0-2.4]
ST-elevated myocardial infarction	2.7 [1.6-2.3]	1.3 [0.6-2.9]
Reperfusion therapy		
Primary percutaneous coronary intervention	0.4 [0.2-0.7]	0.7 [0.4-1.2]
Thrombolysis	0.2 [0.1-1.0]	0.7 [0.3-2.2]
Coronary artery bypass grafting	0.2 [0.1-0.5]	0.5 [0.2-0.9]
Cardiopulmonary resuscitation	2.5 [1.5-4.1]	1.2 [0.8-1.8]
Mechanical ventilation	2.0 [1.3-3.2]	1.4 [0.9-2.0]
Arrhythmias requiring anti-arrhythmic agents	0.9 [0.6-1.4]	1.7 [1.2-2.6]
Renal failure requiring renal replacement therapy	1.3 [0.5-3.4]	2.7 [1.5-5.1]

[a] Only patients who survived until removal of IABP after successful hemodynamic stabilization were included in long-term Cox regression analysis.

[b] Relative to hospital admission in 1990-1994.

[c] Relative to IABP running time of 2-5 days.

hemodynamic stabilization are presented in Figure 3. The adjusted predictors of long-term mortality were arrhythmias requiring the use of anti-arrhythmic agents (HR 1.8, 95% CI 1.2 to 2.9) and renal failure requiring renal replacement therapy during the intensive cardiac care unit stay (HR 2.5, 95% CI 1.3 to 5.1). Treatment with primary PCI (HR 0.5, 95% CI 0.3-0.9) and CABG (HR 0.4, 95% CI 0.2 to 0.8) were associated with improved survival in the long term.

Temporal trends of IABP use from 1990 to 2004 are listed in Table 4. The frequency of IABP insertion increased during the study period from 69 patients with cardiogenic shock in 1990 to 1994 to 132 patients in 2000 to 2004. The frequency of primary PCI increased from 22% in 1990 to 1994 to 65% in 2000 to 2004 ($p<0.001$), and thrombolytic therapy was less frequently administered ($p<0.01$). The thirty-day mortality decreased from 52% in 1990 to 1994 to 36% in 2000 to 2004 (p for trend <0.05).

Table 4. Temporal trends of intra-aortic balloon pump (IABP) use between 1990 to 2004

	1990-1994 (n=69)	1995-1999 (n=99)	2000-2004 (n=132)	P-value
Age (years)	61±10	58±12	63±11	<0.01
Gender (male)	81%	75%	81%	0.8
Reperfusion therapy				
Primary PCI	22%	34%	65%	<0.001
Thrombolysis	31%	37%	18%	<0.01
CABG	19%	13%	7%	<0.05
No reperfusion therapy	34%	23%	11%	<0.001
Median IABP running time (days)	3	3	2	<0.01
Any IABP related complication	32%	26%	10%	<0.001
30-day mortality	52%	41%	36%	<0.05

Data are expressed as mean ± SD, median or percentage. Abbreviations: PCI, primary coronary intervention; CABG, coronary artery bypass grafting.

The overall incidence of IABP-related complications was 20%. Infection (9%), bleeding (6%), and limb ischemia (5%) were the most frequently observed complications. Limb ischemia was mostly transient, with either spontaneous recovery or recovery after IABP removal. However, vascular surgery was needed in 2 patients. Five patients had a major bleeding (at the access site) requiring blood transfusion. Balloon rupture of the IABP occurred in 5 patients. The number of complications decreased from 32% in 1990 to 1994 to 10% in 2000 to 2004 (p<0.001).

DISCUSSION

To our knowledge, this is the first study presenting the long-term follow-up of a large cohort of patients with cardiogenic shock from AMI, all treated with IABP counterpulsation. Despite the high 30-day mortality, a considerable number of patients (36%) survived until 10 years after successful weaning of the IABP.

The 30-day mortality rate in our study (42%) was comparable to those reported from other studies of patients with cardiogenic shock.(2, 4, 10, 11). The Global Utilization of Streptokinase and t-PA [tissue plasminogen activator] for Occluded coronary arteries (GUSTO)-I investigators presented the long-term outcomes of a general group of patients with AMI, of whom some had cardiogenic shock.(12) That study found a 10-year survival rate of 54% in 30-day survivors of cardiogenic shock. In the present study, we found a lower 10-year survival rate (41%) in these patients. However, we have to consider that not all cardiogenic shock patients in the GUSTO-I study were treated with IABP. Therefore, our study population might have been a higher risk population compared with GUSTO-I patients.

The thirty-day mortality was greatest in patients who had an IABP inserted for <1 day. This group mainly consisted of severely compromised patients who could not be stabilized despite hemodynamic support from the IABP and other treatment modalities and who did not survive the first day after IABP insertion. The mortality rate with the IABP in place in this group was

61% on the first day. In contrast, the remaining patients (39%) were in a better hemodynamic condition compared with the patients with an IABP running time >1 day, explaining their better 30-day outcome. Conversely, in patients who survived until IABP removal, those who were treated with an IABP for ≥6 days had greater long-term mortality than patients with an IABP running time of 2 to 5 days. However, the IABP running time was not an independent predictor of long-term mortality.

The adjusted predictors of 30-day mortality were age, impaired LVF, the need for cardiopulmonary resuscitation and the need for mechanical ventilation. Various reperfusion therapies (i.e., PCI, thrombolysis and CABG) were associated with lower 30-day mortality after adjustment. The US National Registry of Myocardial Infarction 2 (NRMI2) investigators reported older age, female gender, diabetes mellitus and a history of congestive heart failure as independent predictors of in-hospital mortality.(11) The predictors of long-term outcomes of patients with cardiogenic shock treated with IABP counterpulsation have not been previously presented. For patients who could be successfully weaned from IABP, we found a strong correlation of arrhythmias and renal failure during the intensive cardiac care unit stay and long-term mortality. In addition, treatment with primary PCI and CABG was beneficial in the long term.

Although the admission period was not an independent predictor of outcome, the 30-day survival rate improved with time. This might have been related to the implementation of early revascularization with primary PCI in the routine treatment of AMI complicated by cardiogenic shock.(13-15) Improving outcomes over time in patients with cardiogenic shock were also found in a recent study.(2)

The incidence of major complications was in line with the incidence reported by the Benchmark registry.(16) In our study, severe bleeding, major limb ischemia, and balloon leak occurred in 2%, 1%, and 2% respectively, compared with 0.8%, 0.9% and 1.0%, respectively, as reported by the Benchmark registry. The number of vascular complications decreased during the study period, probably because of the use of improved IABP-devices (especially, the introduction of smaller size catheters), as well as increased physician's skills and experience, which has also been demonstrated in previous studies.(17-19) We reported an IABP-related incidence of infection of 9%. However, this relatively high rate of infection might have been overestimated because of the robust definition of infection used in our study. However, in most cases, IABP-tip and/or blood cultures to definitely prove IABP-related infections were not available in our study.

Additional limitations of our study included the retrospective nature and that we only included patients who were treated with IABP. Thus, caution is urged in extrapolating these results to patients ineligible for IABP or those in shock but not treated with IABP. The inclusion of a control group with cardiogenic shock without IABP treatment was not possible because IABP counterpulsation has been part of the routine treatment of patients with AMI complicated by shock for years in our center. Hence, benefit of IABP could not be proven by our study. Recently, a randomized controlled trial (clinicaltrials.gov identifier: NCT00491036) has been initiated that will address the potential benefit of IABP in patients with cardiogenic shock.

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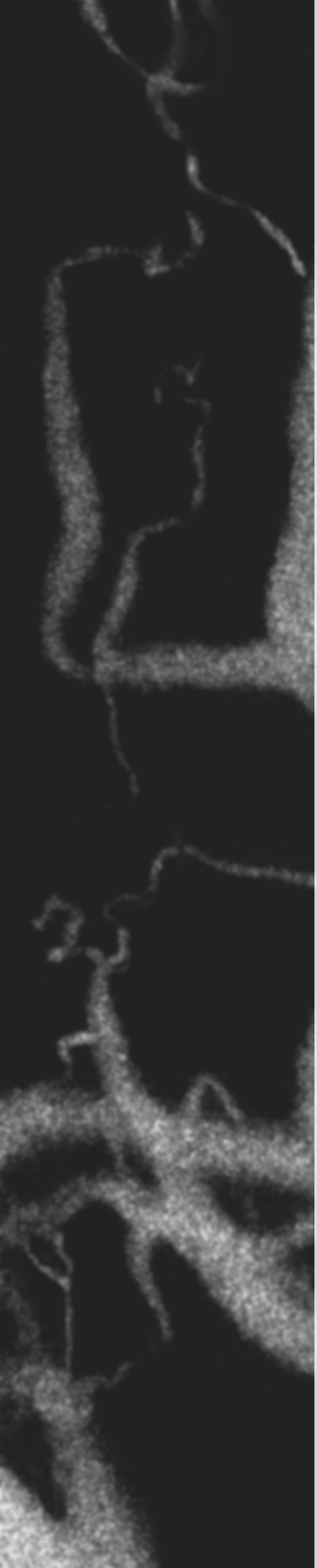

Chapter 6

Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials

Jin M. Cheng, Corstiaan A. den Uil, Sanne E. Hoeks,
Martin van der Ent, Lucia S.D. Jewbali, Ron T. van Domburg, and
Patrick W. Serruys

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ABSTRACT

Aims: Studies have compared safety and efficacy of percutaneous left ventricular assist devices (LVADs) with intra-aortic balloon pump (IABP) counterpulsation in patients with cardiogenic shock. We performed a meta-analysis of controlled trials to evaluate potential benefits of percutaneous LVAD on haemodynamics and 30-day survival.

Methods and results: Two independent investigators searched Medline, Embase and Cochrane Central Register of Controlled Trials for all controlled trials using percutaneous LVAD in patients with cardiogenic shock, where after data was extracted using standardized forms. Weighted mean differences (MD) were calculated for cardiac index (CI), mean arterial pressure (MAP), and pulmonary capillary wedge pressure (PCWP). Relative risks (RRs) were calculated for 30-day mortality, leg ischemia, bleeding and sepsis. In main analysis, trials were combined using inverse-variance random-effects approach. Two trials evaluated the TandemHeart and a recent trial used the Impella device. After device implantation, percutaneous LVAD patients had higher CI (MD 0.35 l/min/m^2, 95% CI 0.09;0.61), higher MAP (MD 12.8 mm Hg, 95% CI 3.6;22.0), and lower PCWP (MD -5.3 mm Hg, 95% CI -9.4;-1.2) compared to IABP patients. Similar 30-day mortality (RR 1.06, 95% CI 0.68;1.66) was observed using percutaneous LVAD compared with IABP. No significant difference was observed in incidence of leg ischemia (RR 2.59, 95% CI 0.75;8.97) in percutaneous LVAD patients compared with IABP patients. Bleeding (RR 2.35, 95% CI 1.40;3.93) was significantly more observed in TandemHeart patients compared with patients treated with IABP**.**

Conclusion: Although percutaneous LVAD provides superior hemodynamic support in patients with cardiogenic shock compared to IABP, the use of these more powerful devices did not improve early survival. These results do not yet support percutaneous LVAD as first-choice approach in the mechanical management of cardiogenic shock.

INTRODUCTION

Cardiogenic shock is a state of inadequate tissue perfusion due to cardiac dysfunction.(1) Despite the fact that prognosis of patients with cardiogenic shock has improved over time due to aggressive reperfusion strategies, in-hospital mortality from cardiogenic shock remains about 50%.(2-8)

Although recent guidelines supported the use of intra-aortic balloon pump (IABP) counterpulsation as method of first choice for mechanical assistance in cardiogenic shock,(1, 9) the efficacy of routine IABP use adjunctive to primary percutaneous coronary intervention in cardiogenic shock was recently questioned.(10, 11) The recent introduction of percutaneous left ventricular assist devices (LVADs) is very promising since these more powerful devices have the potential to reverse cardiogenic shock and to lower the unacceptably high short-term mortality rates.(12, 13) These LVADs might be a better alternative as compared to IABP in the mechanical treatment of cardiogenic shock.(10, 14) The TandemHeart (TandemHeart, Cardiac Assist, Pittsburgh, PA, USA) is a percutaneous left atrial-to-femoral arterial LVAD, driven by a low-speed centrifugal continuous flow pump.(15) The Impella (Impella LP2.5, Abiomed Europe GmbH, Aachen, Germany) LVAD is a catheter-based, impeller-driven, axial flow pump which pumps blood directly from the left ventricle into the ascending aorta.(13)

Several controlled trials have compared safety and efficacy of these percutaneous LVADs with IABP.(16-18) However, the trials were underpowered to adequately evaluate potential benefit on 30-day outcome. We pooled data from these trials and compared (i) differences in hemodynamic parameters following device implantation, (ii) 30-day mortality, and (iii) adverse events in patients receiving percutaneous LVAD vs. those treated with IABP. Aim of the study was to present an overview on the current status of percutaneous assist devices in the management of cardiogenic shock.

METHODS

Trial inclusion

All controlled trials using percutaneous LVAD in patients with cardiogenic shock were included. Follow-up duration had to be at least 30 days. Using Cochrane Central Register of Controlled Trials, Embase and Medline (Pubmed U.S. National Library of Medicine), we performed a literature search from inception to April 2009 using the following MESH terms: "heart-assist device" OR "shock, cardiogenic", as well as using the terms separately as text words.(19) A methodological filter was used to limit the results to clinical trials in humans.(19) No language restrictions were used. Two investigators (J.M.C. and C.A.U.) then independently retrieved potentially eligible reports for evaluation. Both investigators independently examined design, patient population, and interventions in the reports. In case of disagreement, this was resolved in consultation

with a third reviewer (R.T.D.). Trials without control group and trials using surgical LVADs were excluded. In addition, references of included trials were checked, www.clinicaltrials.gov was searched, conference proceedings were checked, and experts were contacted to ensure that no potentially eligible studies were missed. Quality of the reports was assessed in terms of randomization, adequateness of sequence generation, concealment of allocation, blinding, and handling of patient attrition.(20, 21) Data was extracted by two independent investigators (J.M.C. and C.A.U.) using standardized forms.

Study outcomes

Thirty-day all-cause mortality was a priori specified as our primary clinical outcome, as this is the most commonly used clinical endpoint in the literature on cardiogenic shock. Secondary outcomes were the following prespecified haemodynamic parameters: cardiac index (CI), mean arterial pressure (MAP), and pulmonary capillary wedge pressure (PCWP), all measured within 2 h after device implantation. Safety outcomes were chosen a posteriori, and included the following reported device-related adverse events during support: leg ischemia, major bleeding, and fever and/or sepsis. Based on incomplete data reported in the studies, we also evaluated occurrence of thrombocytopenia and haemolysis when reported.

Statistical analysis

All data were analyzed with MIX (MIX 1.7, Kitasato Clinical Research Center, Sagamihara, Kanagawa, Japan)(22) and SPSS (SPSS 15.0, SPSS Inc., Chicago, IL, USA) software. Categorical variables were presented in numbers and in percentages. Continuous variables were presented as mean ± standard deviation. For continuous variables published as median and interquartile range, the mean and standard deviation were estimated. The mean was estimated by the formula $x = (a+2m+b) / 4$ using the values of the median (m), P25 and P75 (a and b, respectively).(23) The estimator $sd = IQR / 1.35$ was used to estimate standard deviation (sd) from the interquartile range (IQR).(21) Weighted mean difference (MD) was used to compare continuous variables and was calculated for the pooled study population. The final results were presented as weighted MD with the associated 95% CI. Relative risk (RR) of unadjusted 30-day mortality and adverse events was calculated for each study and for the pooled study population. The final results were presented as unadjusted RR with the associated 95% CI. Heterogeneity between trials, defined as variation among the results of individual trials beyond that expected from chance, was assessed with Cochran's Q statistic and I^2 statistic. Both inverse variance weighted fixed effect model as well as a random effects model were used for comparison based on MD and RR. Conclusions were drawn based on the random effects models. All statistical tests were analyzed two-tailed and a p-value of <0.05 was considered statistically significant.

RESULTS

Three trials met our inclusion criteria and were included in this study (Figure 1). Study characteristics are presented in Table 1. All three trials randomly assigned patients to treatment with percutaneous LVAD or IABP counterpulsation. Two randomized controlled trials compared the TandemHeart device with IABP,(16, 17) and one randomized controlled trial compared the Impella with IABP counterpulsation.(18) One trial reported adequate sequence generation,(16) while the other two trials omitted description of methods for sequence generation.(17, 18) Methods for allocation concealment were not adequately reported. Complete follow-up was available in all included trials.

Figure 1. Identification of trials. Abbreviation: LVAD, left ventricular assist device.

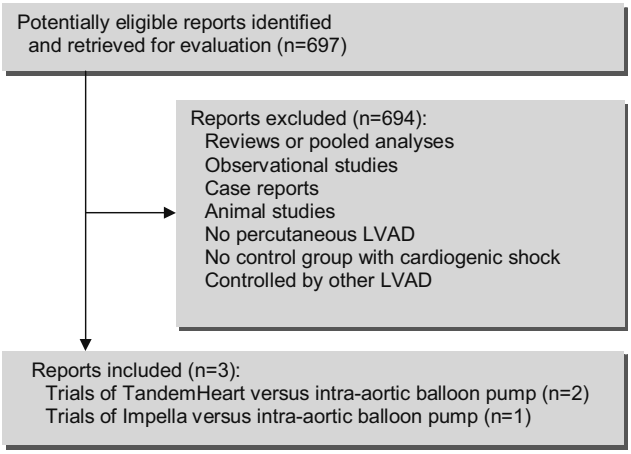


Table 1. Study characteristics of included trials

	Thiele et al.(16)	Burkhoff et al.(17)	Seyfarth et al.(18)
Percutaneous LVAD used	TandemHeart	TandemHeart	Impella LP2.5
Control	IABP	IABP	IABP
Total number of patients	41	33	26
Setting	Single-center	Multi-center	Two-center
Inclusion period	2000-2003	2002-2004	2004-2007
Randomization	Yes	Yes	Yes
Sequence generation	Drawing envelopes	Not reported	Not reported
Concealment of allocation	Sealed envelopes*	Not reported	Not reported
Blinding	Not possible	Not possible	Not possible
Handling of patient attrition	Complete follow-up	Complete follow-up	Complete follow-up

* Not reported whether the envelopes were opaque and sequentially numbered.

Abbreviations: IABP, intra-aortic balloon pump; LVAD, left ventricular assist device.

Baseline characteristics

Baseline characteristics and baseline haemodynamic parameters of patients included in the randomized controlled trials are presented in Table 2. In the study by Thiele et al.(16) 41 patients with revascularized acute myocardial infarction complicated by cardiogenic shock were included for randomization (21 patients assigned to LVAD and 20 patients assigned to IABP). Burkhoff et al.(17) randomized 33 patients with cardiogenic shock caused by acute myocardial infarction or decompensated chronic heart failure (19 patients assigned to LVAD and 14 patients assigned to IABP). Seyfarth at al. (18) randomized 26 patients with acute myocardial infarction complicated by cardiogenic shock (13 patients assigned to LVAD and 13 patients assigned to IABP). In total, 100 patients were included for meta-analysis, of whom 53 patients were treated with LVAD and 47 patients were treated with IABP. Almost all patients were treated with inotropes or vasopressors, mechanical ventilation, and percutaneous coronary intervention.

Table 2. Baseline characteristics

	Thiele et al.(16)		Burkhoff et al.(17)		Seyfarth et al. (18)	
	LVAD (n=21)	IABP (n=20)	LVAD (n=19)	IABP (n=14)	LVAD (n=13)	IABP (n=13)
Age, years ± SD	63 ± 10	66 ± 10	66 ± 14	60 ± 11	65 ± 10	67 ± 19
Male, n (%)	16 (76)	15 (75)	14 (74)	9 (64)	8 (62)	11 (85)
Hypertension, n (%)	19 (90)	15 (75)			7 (54)	9 (69)
Diabetes mellitus, n (%)	11 (52)	11 (55)			5 (39)	3 (23)
Smoking, n (%)	9 (43)	6 (30)			8 (62)	7 (54)
Hypercholesterolemia, n (%)	11 (52)	9 (45)			8 (62)	7 (54)
Multivesseldisease, n (%)	13 (62)	14 (70)			9 (69)	10 (77)
LVEF, % ± SD	26 ± 9	27 ± 7	19 ± 14	22 ± 9	28 ± 14	31 ± 16
AMI, n (%)	21 (100)	20 (100)	11 (58)	10 (71)	13 (100)	13 (100)
Anterior MI, n (%)	18 (86)	13 (65)			7 (54)	8 (62)
Peak creatine kinase, U/L ± SD	5307 ± 4297	4395 ± 3987			4067 ± 6104	4971 ± 5211
Inotropes or vasopressors, n (%)	21 (100)	20 (100)	19 (100)	14 (100)	11 (84)	12 (92)
Mechanical ventilation, n (%)	20 (95)	20 (100)			12 (92)	12 (92)
Primary PCI, n (%)	20 (95)	19 (95)			12 (92)	12 (92)
Hemodynamics						
CI, l/min/m^2 ± SD	1.8 ± 0.4	1.6 ± 0.5	1.8 ± 0.4	1.8 ± 0.6	1.7 ± 0.5	1.7 ± 0.6
MAP, mm Hg ± SD	62 ± 14	65 ± 13	70 ± 16	67 ± 15	78 ± 16	72 ± 17
PCWP, mm Hg ± SD	20 ± 4	26 ± 7	25 ± 8	28 ± 6	22 ± 8	22 ± 7

Abbreviations: AMI, acute myocardial infarction; CI, cardiac index; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; PCI, percutaneous coronary intervention; PCWP, pulmonary capillary wedge pressure.

Haemodynamic parameters following device implantation

Haemodynamic parameters measured after device implantation as well as results obtained from both fixed effect models and random effects models showing the pooled MDs between haemodynamic parameters of LVAD patients compared with IABP patients are presented in Table 3. In the random effects model, patients treated with a percutaneous LVAD had higher CI (MD 0.35 l/min/m^2, 95% CI 0.09-0.61, p<0.01), higher MAP (MD 12.8 mm Hg, 95% CI 3.6-22.0, p<0.01), and lower PCWP (MD -5.3 mm Hg, 95% CI -9.4 to -1.2, p<0.05) compared with patients treated with IABP. (Figure 2)

Table 3. Meta-analysis of outcomes

	Thiele et al.		Burkhoff et al.		Seyfarth et al.		Pooled (fixed effect model)		Pooled (random effects model)	
	LVAD (n=21)	IABP (n=20)	LVAD (n=19)	IABP (n=14)	LVAD (n=13)	IABP (n=13)	Mean difference / Relative Risk	p	Mean difference / Relative Risk	p
Hemodynamics										
CI, l/min/m^2 ± SD	2.3 ± 0.6	1.8 ± 0.4	2.2 ± 0.6	2.1 ± 0.2	2.2 ± 0.6	1.8 ± 0.7	0.35 (0.14 ; 0.55)	<0.001	0.35 (0.09 ; 0.61)	<0.01
MAP, mm Hg ± SD	76 ± 10	70 ± 16	91 ± 16	72 ± 12	87 ± 18	71 ± 22	12.1 (6.3 ; 17.9)	<0.001	12.8 (3.6 ; 22.0)	<0.01
PCWP, mm Hg ± SD	16 ± 5	22 ± 7	16 ± 4	25 ± 3	19 ± 5	20 ± 6	-6.2 (-8.0 ; -4.3)	<0.001	-5.3 (-9.4 ; -1.2)	<0.05
Clinical outcome										
30-day mortality, n (%)	9 (43)	9 (45)	9 (47)	5 (36)	6 (46)	6 (46)	1.06 (0.68 ; 1.66)	0.80	1.06 (0.68 ; 1.66)	0.80
Reported adverse events										
Leg ischemia, n (%)	7 (33)	0 (0)	4 (21)	2 (14)	1 (8)	0 (0)	2.59 (0.75 ; 8.97)	0.13	2.59 (0.75 ; 8.97)	0.13
Bleeding, n (%)	19 (90)	8 (40)	8 (42)	2 (14)			2.35 (1.40 ; 3.93)	<0.01	2.35 (1.40 ; 3.93)	<0.01
Fever of sepsis, n (%)	17 (81)	10 (50)	4 (21)	5 (36)			1.38 (0.88 ; 2.15)	0.16	1.11 (0.43 ; 2.90)	0.83

Abbreviations: CI, cardiac index; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure.

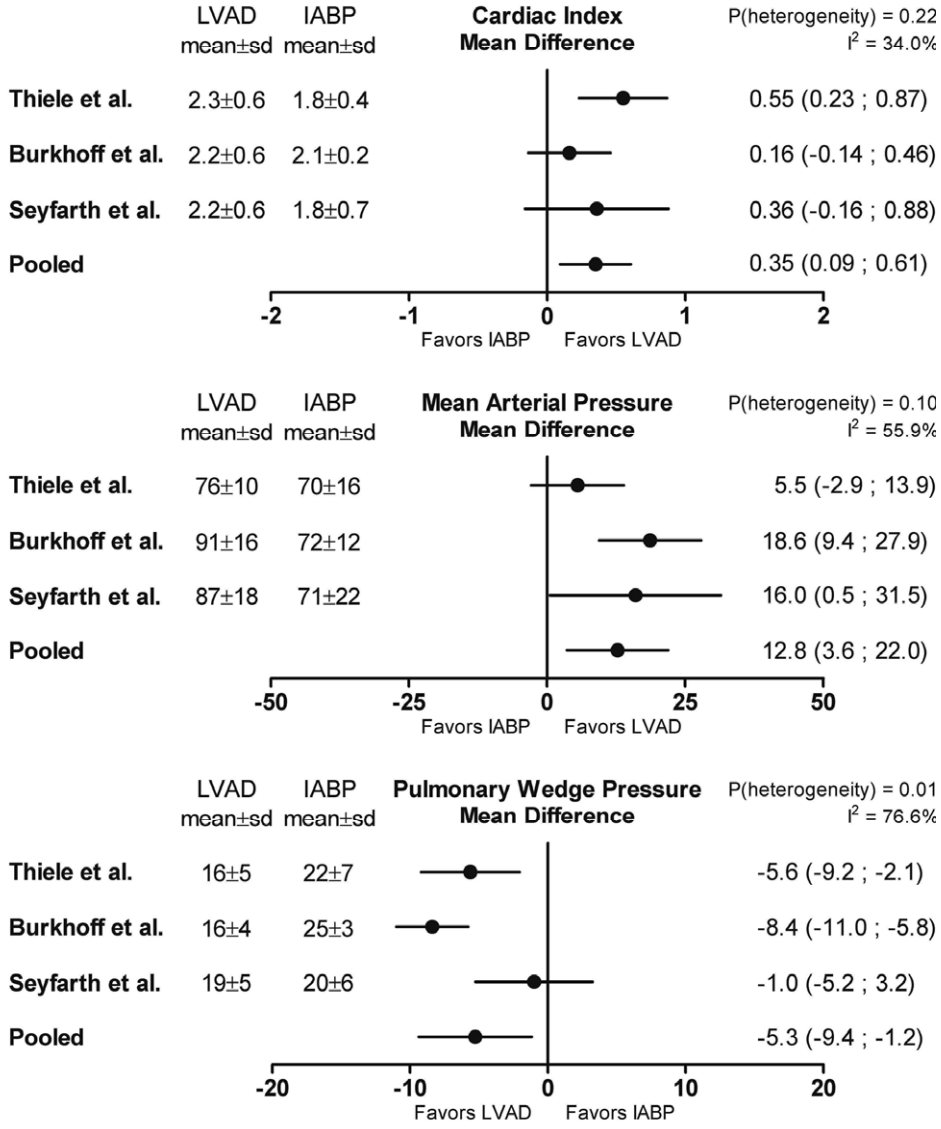
30-day mortality

Reported absolute 30-day all-cause mortality as well as results obtained from both fixed effect model and random effects model showing the relative risk are presented in Table 3. In the pooled study population, 24 patients (45%) treated with LVAD and 20 patients (43%) treated with IABP did not survive 30 days of follow-up (p=0.80). The pooled estimate of the relative risk revealed no significant difference in 30-day mortality using percutaneous LVAD compared with IABP (RR 1.06, 95% CI 0.68-1.66). (Figure 3)

Adverse events

Reported adverse events as well as results obtained from both fixed effect models and random effects models showing the RR are presented in Table 3. Using a random effects model, similar

Figure 2. Meta-analysis showing the mean difference in haemodynamic parameters with use of percutaneous left ventricular assist devices. Random effects models were used for meta-analysis. Weighted mean differences with 95% confidence intervals are presented on the right of the figure. Abbreviations: IABP, intra-aortic balloon pump; LVAD, left ventricular assist device.



incidence rates of leg ischemia were observed using percutaneous LVAD when compared with IABP (RR 2.59, 95% CI 0.75-8.97, p=0.13). (Figure 4) Bleeding (RR 2.35, 95% CI 1.40-3.93, p<0.01) was more frequently reported as a complication related to the TandemHeart. Furthermore, Thiele et al. reported that fresh frozen plasma (p<0.01) and platelets (p<0.05) were more often required in the TandemHeart group. However, Burkhoff et al. found no significant difference in thrombocytopenia, but these investigators did find a trend toward more haemolysis with

Figure 3. Meta-analysis showing the relative risk of crude 30-day mortality with use of percutaneous left ventricular assist devices. Random effects model was used for meta-analysis. Relative risks with 95% confidence intervals are presented on the right of the figure. Abbreviations: IABP, intra-aortic balloon pump; LVAD, left ventricular assist device.

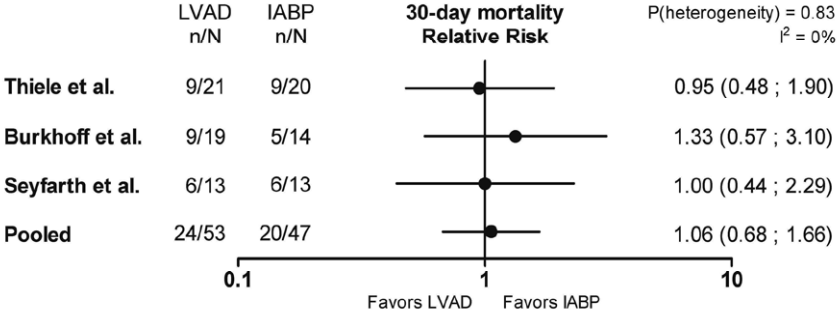
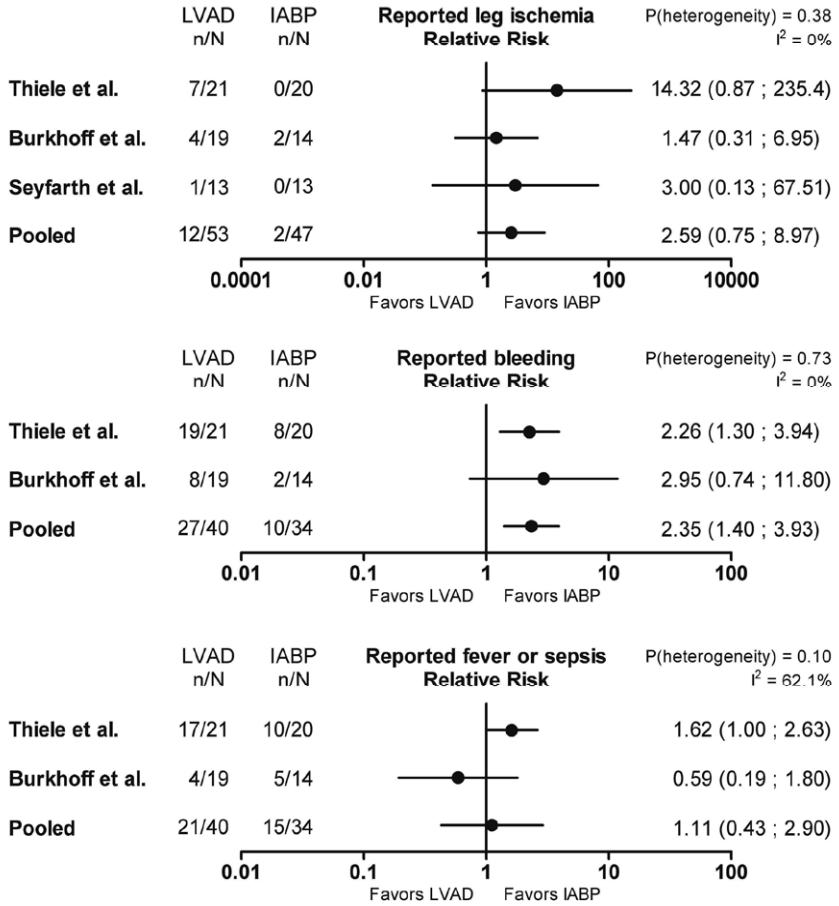


Figure 4. Meta-analysis showing the relative risk of adverse events with use of percutaneous left ventricular assist devices. Random effects models were used for meta-analysis. Relative risks with 95% confidence intervals are presented on the right of the figure. Abbreviations: IABP, intra-aortic balloon pump; LVAD, left ventricular assist device.



higher peak values in plasma-free haemoglobin in patients treated with the Tandemheart (p=0.10).

No reports were found on Impella-related incidence of bleeding and fever and/or sepsis. However, a trend was reported for more packed red blood cells (Impella 2.6 ± 2.7 units versus IABP 1.2 ± 1.9 units, p=0.2) and fresh frozen plasma (Impella 1.8 ± 2.5 units versus IABP 1.0 ± 1.7 units, p= 0.4) administered to Impella patients. Hemolysis was assessed by measurements of free haemoglobin, which was significantly higher in Impella patients ($p<0.05$).

DISCUSSION

This is the first meta-analysis of controlled trials comparing percutaneous LVAD with IABP, presenting a survey of available data. Our main findings were that although use of percutaneous LVAD resulted in a better haemodynamic profile compared with IABP counterpulsation, this did not translate into improved 30-day survival. Moreover, patients treated with a percutaneous LVAD tended to have a higher incidence of leg ischemia and device-related bleeding.

The main limitation of an IABP is the lack of active cardiac support: the IABP requires a certain residual level of left ventricular function. As an alternative, percutaneous LVADs are promising devices since these provide active circulatory support. This meta-analysis indeed confirms that a percutaneous LVAD is a more powerful device than IABP, which is clearly reflected by a better haemodynamic profile after implantation.

Although both types of percutaneous LVADs improved the haemodynamic profile, it is disappointing that both devices did not improve 30-day outcome when compared with current routine treatment including IABP. Besides, it is important to note that both percutaneous LVADs are currently about 10 times as expensive as an IABP catheter.

We reported similar complication rates within both types of percutaneous LVADs. However, it might be possible that the Impella is a safer device than the TandemHeart due to its smaller catheter size, potentially resulting in a lower incidence of leg ischemia or groin bleeding,(24) although this is not clearly demonstrated by this meta-analysis. 17 French cannulas were used in TandemHeart patients and 13 French sheaths were used in Impella patients, whereas most IABPs are currently introduced using 8 French sheaths. Although the way of vascular closure was not consistently reported in the trials, this could also be a factor involved in the development of vascular complications. Whether haemolysis is a clinically significant problem associated with Impella use, has to be investigated further.

Some limitations of our meta-analysis need to be acknowledged. First, we compared different types of percutaneous LVADs (i.e. TandemHeart and Impella) with IABP. However, there was no heterogeneity between TandemHeart and Impella studies in 30-day mortality and in most secondary study outcomes. Because the small number of trials included could possibly lead to a type II error of the heterogeneity test, all conclusions were based on results obtained

from random effects models. Second, the number of patients included in this meta-analysis was small. However, we included all available trials and we did not even observe a trend in a reduced 30-day mortality rate associated with LVAD use. The results from this meta-analysis suggest that potential benefit of percutaneous LVADs on 30-day survival might in fact be very limited. Owing to the small sample size, there is a probability of missing a clinically meaningful benefit if one exists (type II error).(25) However, given a total sample size of 100 patients, an observed p-value (α) of 0.80 and a presumed effect size of at least 10% (event rate of 45% in IABP patients and 40% in percutaneous LVAD patients), *post-hoc* analysis showed that the probability for type II error (β) does not exceed 12%. A third limitation was that we did not have access to individual patient data. It may be very well possible that subgroups of cardiogenic shock patients might benefit from percutaneous LVAD therapy, but we could not perform these analyses, also given the limited number of patients included in the currently available reports. A final limitation was that the included trials were not described in sufficient detail to judge adequateness of randomization, so that we were not able to exclude the potential risk of bias in these trials.

Hopefully, further technical improvements on percutaneous LVAD systems, together with enhanced experience with these devices, will improve prognosis of cardiogenic shock patients in the future. A larger, adequately powered, randomized controlled trial using the Impella device is necessary to provide more definite information about potential benefit on 30-day survival. Some investigators have shown the feasibility of introduction of surgical LVADs in patients with acute myocardial infarction complicated by cardiogenic shock.(26) A major problem of implanting a surgical LVAD includes apical cannulation in infarcted myocardium. The recent development of a micropump, inserted via a mini-thoracotomy and providing substantial left ventricular support, is very promising, but has to be investigated in larger studies and in the setting of cardiogenic shock.(27)

In conclusion, in patients presenting with cardiogenic shock, the use of a percutaneous LVAD provides superior haemodynamic support compared with the use of IABP. However, a better haemodynamic profile associated with percutaneous LVAD use did not result into a reduced 30-day mortality rate. Furthermore, a higher rate of adverse events was encountered by the higher invasive nature of LVAD, especially of the TandemHeart device. Larger randomized controlled trials using the Impella device are needed to better evaluate clinical outcome and adverse events. Until now, we cannot recommend to replace IABP counterpulsation by the more powerful percutaneous LVAD for the treatment of cardiogenic shock patients who do not respond sufficiently to pharmacologic therapy.

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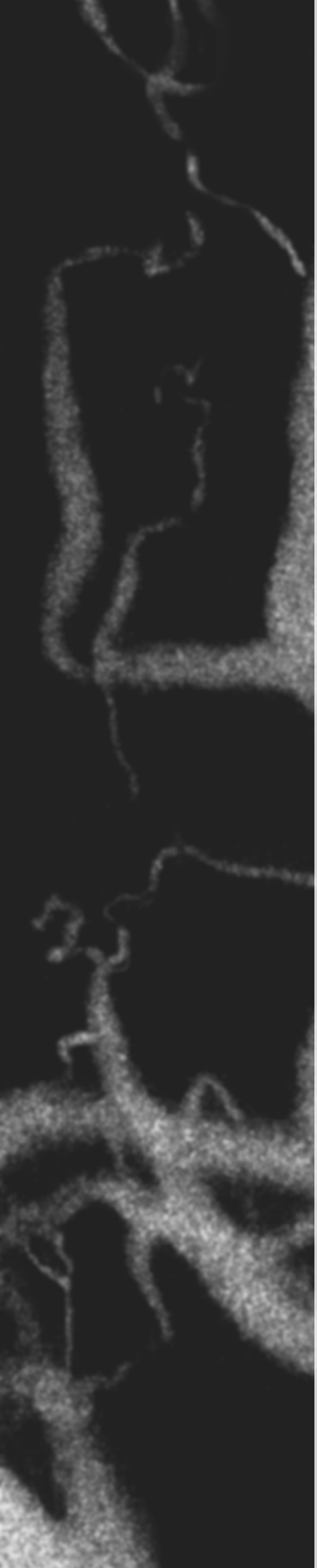
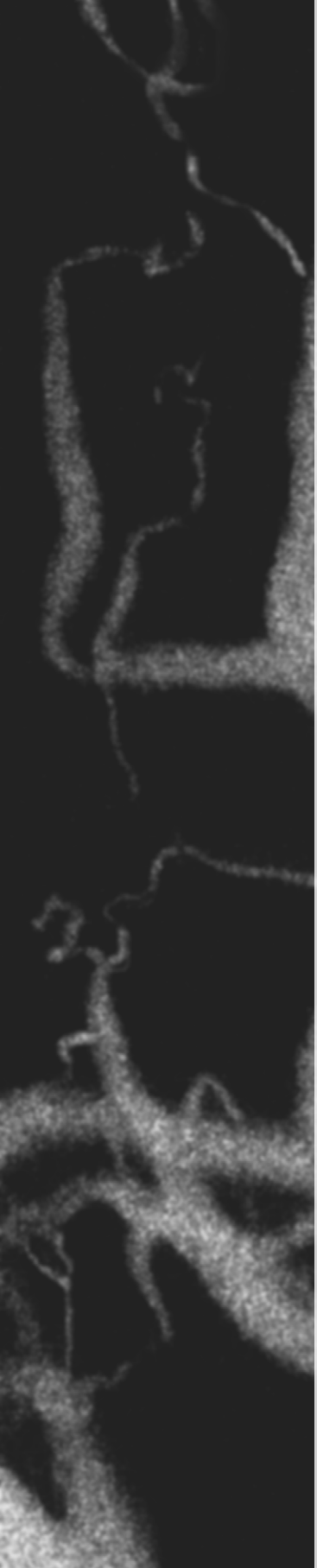


Part C

The microcirculation in pathologic conditions



Chapter 7

Impaired sublingual microvascular perfusion during surgery with cardiopulmonary bypass: A pilot study

Corstiaan A. den Uil, Wim K. Lagrand, Peter E. Spronk, Ron T. van Domburg, Jan Hofland, Christian Lüthen, J. Jasper Brugts, Martin van der Ent, Maarten L. Simoons

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ABSTRACT

Objective: Complications after cardiac surgery may involve multiple organ failure, which carries a high mortality. Development of multiple organ failure may be related to impaired microcirculatory perfusion as a result of systemic inflammation. Microcirculatory blood flow alterations have been associated with impaired outcome. We investigated whether these alterations occurred before, during, and after coronary artery bypass grafting.

Methods: We observed 25 consecutive patients who underwent elective coronary artery bypass grafting with cardiopulmonary bypass. The sublingual microcirculation was investigated using Sidestream Dark Field imaging. Sidestream Dark Field imaging was performed before (baseline), during and after surgery. Microvascular blood flow was analyzed using a semi-quantitative microvascular flow index in small, medium, and large microvessels. Changes in microvascular flow were tested with Wilcoxon signed rank test.

Results: Median microvascular flow index of medium blood vessels decreased after starting cardiopulmonary bypass relative to that after anesthetic induction (2.6, interquartile range 1.6-3.0, vs 3.0, interquartile range 2.8-3.0, p=0.02). There was a trend toward decreased microvascular flow index of small and large vessels relative to baseline (p=0.08 and p=0.05, respectively). Decreases in microvascular flow index occurred irrespective of changes in systemic blood pressure. After each patient's return to the intensive care unit, microvascular flow index increased and normalized in all microvessels.

Conclusions: For the first time, sublingual microvascular blood flow alterations have been observed during cardiopulmonary bypass-assisted coronary artery bypass grafting.

INTRODUCTION

Coronary artery bypass grafting (CABG) is a well-established treatment modality for patients with severe ischemic heart disease. In on-pump CABG surgery, the circulation is preserved with an extracorporeal cardiopulmonary bypass (CPB) device, while the heart is arrested by a cardioplegic solution. These days, excellent results are obtained with both on-pump and off-pump cardiac surgery, with low morbidity and mortality.(1) Nevertheless, cardiac surgery, especially CPB-assisted cardiac surgery, is associated with activation of inflammatory mediators and systemic inflammatory response syndrome. This inflammatory response, together with procedure-related formation of microemboli, may result in capillary dysfunction and postoperative multiple organ dysfunction.(2) Organ dysfunction after cardiac surgery is known to be associated with a prolonged postoperative intensive care unit stay and high 30-day and long-term mortalities.(3) A relationship between microcirculatory dysfunction and the degree of organ failure has previously been suggested in patients with sepsis.(4) In view of the inflammatory response induced by cardiac surgery, we investigated whether microcirculatory blood flow alterations occur during and after CPB-assisted cardiac surgery.

MATERIALS AND METHODS

Study design

We conducted an observational pilot study at our university hospital. Data collection was based on sidestream dark field (SDF) imaging and on routine measurements. The institutional ethical committee approved the protocol and informed consent was obtained from each patient.

Patients

Twenty-five consecutive patients scheduled for elective CABG with CPB were included. Before the operation, in-hospital mortality risk was predicted with the EuroSCORE.(5, 6)

Anesthesia, surgery and CPB management

Anesthesia was intravenously induced with midazolam (0.15-0.25 mg/kg), sufentanyl (1 µg/kg) and pancuronium bromide (0.1 mg/kg), to which an intravenous bolus of enoximone (0.25 mg/kg) was added. Dexamethasone (1 mg/kg) was intravenously administered at the discretion of the attending anesthesiologist. Phenylephrine hydrochloride was given when mean arterial pressure was below 60 mm Hg. A 9.5F five-lumen central venous catheter (Multicath, Vygon, Ecouen, France) was inserted into the right internal jugular vein. A urinary bladder catheter with temperature measurement feature (179360CH14, Willy-Rüsch, Kernen, Germany) was inserted. Bladder temperature was regarded as an estimate of body core temperature. In the operating room, anesthesia was maintained with intravenous midazolam (0.1 mg/kg/hr) and intravenous

sufentanil (0.5-1.0 µg/kg/hr), to which inhalation of sevoflurane (1%-2% by volume) during the pre-bypass period might be added according to the discretion of the attending anesthesiologist. Nonpulsatile CPB (Stockert-Shiley Multiflow Roller Pump, Soma Technology Inc., Cheshire, Conn, USA) was established through a standard median sternotomy with aortic root and right atrial cannulation. Surgery was performed under mild hypothermia (32 ºC). After aortic cross-clamping, antegrade ice-cold St. Thomas' hospital cardioplegia was administered. Anticoagulation was established with intravenous heparin (3-4 mg/kg) given 10 minutes before initiation of CPB. Target activated clotting time was 440 seconds. At the end of CPB, anticoagulation was antagonized with intravenous protamine sulfate (4 mg/kg). Hematocrit was kept above 0.20 L/L. After surgery, patients were rewarmed with warm-air blankets until bladder temperature reached 36.5 ºC.

Macrohemodynamic monitoring

Arterial and central venous pressures were monitored invasively in all cases. Continuous cardiac output measurements were performed in 16 of 25 patients because the PiCCO system was not always available. In these patients, before induction a 4F thermistor-tipped catheter (PV2014L50LGW, Pulsiocath, Pulsion Medical Systems, Munich, Germany) was inserted under local anesthesia into the left radial artery. This catheter was then connected to a monitor (PiCCO Plus, Pulsion Medical Systems). After calibration by transcardiopulmonary thermodilution, cardiac output was continuously measured.

Microcirculatory assessment and analysis

The SDF device (Microscan, Microvision Medical, Amsterdam, the Netherlands) was used to obtain 2-dimensional video images of microcirculatory blood flow.(7) SDF imaging is the successor technology adapted from orthogonal polarization spectral (OPS) imaging, which was validated previously.(8-10) Sublingual SDF imaging and subsequent semiquantitative analysis were performed as reported before.(9) In short, steady video images with duration of ≥20 sec were obtained after gentle removal of saliva by a gauze, avoiding pressure artifacts as much as possible. Pressure artifacts can be noticed by an alteration of flow velocity in the vessels under investigation, depending on application of pressure with the tip of the probe. Video sequences were stored and analyzed blindly and in random order. Each SDF video clip was divided into four equal quadrants. Quantification of flow (0 for no flow, 1 for intermittent flow, 2 for sluggish flow, and 3 for continuous flow) was scored per quadrant in small (diameter 10-25 µm), medium (25-50 µm), and large (50-100 µm) microvessels, as applicable. This score, the microvascular flow index (MFI), was the sum of each quadrant's scores divided by the number of quadrants in which the vessel type was visible.

The first SDF measurements were performed at the day before surgery (T0). Thereafter, sublingual microvascular perfusion was determined in the following measurement periods, successively: after anesthetic induction (T1), on nonpulsatile CPB immediately after complete

administration of cardioplegia (T2), postoperatively, just after admission to the intensive care unit (T3), and when body core temperature had reached 36.5°C (T4).

Statistical analysis

Categorical variables are presented as absolute numbers and percentages. Global hemodynamic data are presented as means ± SD. Variables that were not normally distributed, including MFI, are presented as medians and inter-quartile ranges (IQR, [P25-P75]). Repeated measures analysis of variance (r-ANOVA) and subsequent Bonferroni tests were used to test changes in global hemodynamic variables. Changes in MFI between time points were tested with Wilcoxon signed ranks test. Changes in categorized MFI (preserved vs. impaired) over time were tested with Cochran's Q test. Linear correlations between macro- and microcirculatory parameters were calculated with Spearman's correlation test. Mann-Whitney test was used to assess differences in MFI between subgroups. A two-sided p value of <0.05 was regarded as statistically significant.

RESULTS

Study population

Twenty-five consecutive patients undergoing elective CABG were enrolled in the study. Twenty of them underwent isolated CABG. Table 1 shows the patients' characteristics. Two patients died. An 84-year-old man died in the intensive care unit of failure of the heart and the kidneys 12 days after CABG and mitral valve repair. A 77-year-old man undergoing CABG, aortic valve replacement, and left ventricular reconstruction died in the operating room of progressive cardiac pump failure despite optimal treatment.

Global hemodynamics

After induction of anesthesia mean arterial pressure (MAP) decreased by about 25% (T1 vs. T0; $p<0.001$). Minimal MAP was observed after starting CPB: 63 ± 11 mm Hg versus 75 ± 17 mm Hg after induction ($p<0.05$). MAP recovered after surgery and remained stable during re-warming (Table 2).

The indexed flow delivered by the heart lung machine was 2.5 ± 0.3 mL/min/m^2. This index was similar to the preoperative cardiac index measured by the PiCCO system (2.8 ± 0.6). Postoperatively measured cardiac index values (3.2 ± 0.7 mL/min/m^2) did not differ from preoperative measurements (Table 2).

Central venous pressure after initiation of CPB (7 ± 4 mm Hg) did not change relative to the central venous pressure measured after anesthetic induction (8 ± 4 mmHg). Higher central venous pressure values were observed, however, after return to the intensive care unit relative to the situation during CPB (10 ± 2 vs 7 ± 4 mmHg, $p<0.01$). Large decreases in hemoglobin

Table 1. Characteristics of the study population (n=25).

Variable	Count (%) or median [IQR]
Age (yrs)	65 [61-74]
Gender male	20 (80)
Preoperative cardiovascular risk factors:	
Hypertension	17 (68)
Current smoking	6 (24)
Dyslipidemia	10 (40)
Diabetes mellitus	6 (24)
Logistic EuroSCORE (%)	1.5 [1.2-4.0]
Type of surgery:	
Isolated CABG procedure	20 (80)
CABG + valve surgery	3 (12)
CABG + LV reconstruction procedure	1 (4)
CABG + valve surgery + LV reconstruction procedure	1 (4)
Total anastomoses:	
Left ITA	29*
Right ITA	10
Venous bypass	53
CPB duration (min)	102 [94-140]
Aortic cross-clamping time (min)	65 [56-84]

Continuous variables are presented as medians [IQR]. Categorical variables are presented as numbers and percentages (%). Abbreviations: IQR, interquartile range; EuroSCORE, European system for Cardiac Operative Risk Evaluation; CABG, coronary artery bypass grafting; LV, left ventricular; ITA, internal thoracic artery; CPB, cardiopulmonary bypass. *In some cases, a single internal thoracic artery graft was used to prepare more than one anastomosis.

Table 2. Global and microcirculatory variables - Evolution through time.

	Before surgery (T0)	**After induction (T1)**	**CPB (T2)**	**Arrival ICU (T3)**	**Temp≥36.5°C (T4)**
Temp (°C)	37.0 ± 0.4	36.3 ± 0.5	34.2 ± 1.0	34.9 ± 0.7	36.8 ± 0.6
HR (b/min)	69 ± 16	69 ± 12	-	78 ± 15	84 ± 14
MAP (mmHg)	101 ± 16	75 ± 17	63 ± 11	83 ± 11	80 ± 14
CVP (mm Hg)	-	8 ± 4	7 ± 4	10 ± 2	13 ± 4
CI (mL/min/m^2)*	-	2.8 ± 0.6	2.5 ± 0.3	3.2 ± 0.7	3.1 ± 0.6
Hb (mmol/L)	8.7 ± 0.9	7.0 ± 0.9	4.7 ± 0.4	6.1 ± 0.6	6.2 ± 0.5
Ht (L/L)	0.41 ± 0.0	0.32 ± 0.0	0.22 ± 0.0	0.28 ± 0.0	0.29 ± 0.0
Lactate (mmol/L)	-	1.0 ± 0.3	1.0 ± 0.3	1.2 ± 0.3	1.6 ± 0.7
MFI small	2.8 [2.0-3.0]	3.0 [3.0-3.0]	3.0 [1.3-3.0]	3.0 [3.0-3.0]	3.0 [2.9-3.0]
MFI medium	2.5 [2.0-3.0]	3.0 [2.8-3.0]	2.6 [1.6-3.0]$^{\#}$	3.0 [2.9-3.0]	3.0 [2.6-3.0]
MFI large	2.8 [2.8-3.0]	3.0 [2.8-3.0]	3.0 [1.7-3.0]	3.0 [3.0-3.0]	3.0 [2.9-3.0]

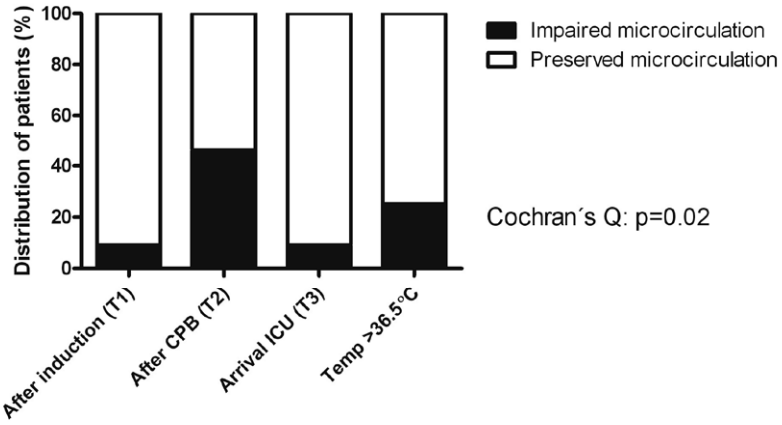
All data, except microvascular flow index, are presented as mean ± SD; microvascular flow index is shown as median with interquartile range. T0, 1day before surgery; T1, after anesthetic induction; T2, after cardioplegia on CPB; T3, arrival to intensive care unit; T4, core body temperature greater than 36.5°C achieved. *Cardiac index values were obtained in 16 of 25 patients. $^{\#}$ $p<0.05$ versus T1.Abbreviations: Temp, body core temperature; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; CI, cardiac index; Hb, hemoglobin; Ht, hematocrit; MFI, microvascular flow index regarding "small", "medium" and "large" micro-vessels.

concentration and hematocrit occurred during surgery, whereas no elevations in serum lactate were observed during CPB (Table 2).

Microcirculatory measurements

In general, sublingual SDF imaging was more difficult to perform 1 day before surgery than under anesthesia, as a result of movement of the tongue in the nonsedated patient. More pressure artifacts were therefore visible at T0. Preoperative MFIs were 2.8 [2.0-3.0], 2.5 [2.0-3.0] and 2.8 [2.8-3.0] for small, medium and large microvessels, respectively (Table 2). In 46% of the investigated patients, MFI less than 2.50 for medium microvessels was observed just after initiation of nonpulsatile CPB (T2; Figure 1). This MFI was lower than the microvascular perfusion after anesthetic induction (T2 vs. T1, $p<0.05$). There was a trend toward a decrease in micro-vascular perfusion at T2 for small ($p=0.08$) and large ($p=0.05$) microvessels as well. Postoperative SDF imaging showed fast microvascular blood flow in all micro-vessels. This resulted in a high MFI in small (3.0 [3.0-3.0]), medium (3.0 [2.9-3.0]) and large (3.0 [3.0-3.0]) microvessels (T3; Table 2). Postoperative MFI had risen to normal values in all microvessels relative to microvascular perfusion assessed during CPB (T3 vs. T2, all $p<0.02$; Table 2). MFI for all sizes of microvessels did not change after central body temperature had reached 36.5°C (T4 vs. T3, all differences not significant; Table 2). Retrospectively, a large decrease in microvascular perfusion during CPB was observed in the patient who finally died of heart and renal failure (patient #1; Figure 2).

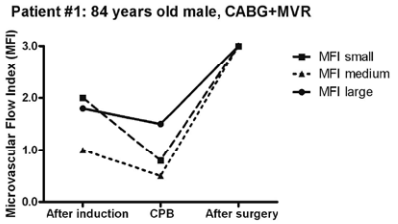
Figure 1. Changes in perfusion of medium sized micro-vessels over time (n=25). Bars indicate distribution of patients who had preserved microcirculation (defined as microvascular flow index ≥2.5, open bars) versus those who had impaired microcirculation (microvascular flow index <2.5, black bars). In 46% of patients, microvascular flow index less than 2.5 was seen after initiation of cardiopulmonary bypass (CPB; T2). T1, After anesthetic induction; T2, cardiopulmonary bypass; T3, arrival at intensive care unit; T4, body temperature greater than 36.5 °C.



Changes in microvascular perfusion in relationship to mean arterial pressure, lactate and preoperative risk factors

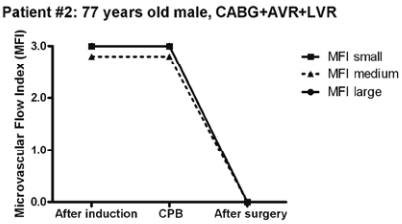
We investigated whether impaired microvascular blood flow during CPB was associated with simultaneous decrease in systemic perfusion pressure (ie, MAP). We plotted the change in MFI (T2-T1) versus change in MAP (T2-T1). No association was visible ($r=0.23$, correlation not significant).

Figure 2. Detailed perioperative macrohemodynamic and microcirculatory parameters through time of 2 patients who died. Both patients had a higher than average mortality risk. Patient #1 died in intensive care unit of multiple organ failure. Retrospectively, hypoperfusion of microcirculation was present after anesthetic induction as well as after initiation of cardiopulmonary bypass. In contrast, sublingual microcirculation was preserved in patient #2, who died in operating room of progressive cardiac failure after cessation of cardiopulmonary bypass.



Central temp (°C)	35.5	33.2	34.6
Heart rate (bpm)	57	-	100
MAP (mm Hg)	75	59	71
Lactate (mmol/L)	1.0	1.0	1.7

Logistic EuroSCORE: 17.5%
CPB duration: 178 min.
Aortic cross-clamping time: 125 min.



Central temp (°C)	36.3	34.1
Heart rate (bpm)	59	-
MAP (mm Hg)	55	51
Lactate (mmol/L)	0.8	0.8

Logistic EuroSCORE: 13.2%
CPB duration: 360 min.
Aortic cross-clamping time: 181 min.

Abbreviations: CABG, coronary artery bypass grafting; MVR, mitral valve repair; AVR, aortic valve replacement; LVR, left ventricular restoration; MFI, microvascular flow index for "small", "medium", and "large" sized micro-vessels; CPB, cardiopulmonary bypass; Temp, body temperature; HR, heart rate; MAP, mean arterial pressure.

Two patients had a slightly elevated serum lactate concentration just after surgery: 1.9 and 2.2 mmol/L, respectively (upper reference limit 1.7 mmol/L in our laboratory). In both patients, intraoperative hypoperfusion of small and medium microvessels occurred. In the first patient, MFIs at T2 was 2.00, 1.25, and 1.50 for small, medium and large sized blood vessels, respectively. In the second patient these values were 1.00, 1.75, and 1.75, respectively.

There were no significant differences in MFI during CPB regarding medium sized blood vessels when patients were stratified according to preoperative risk factors of hypertension (p=0.62), current smoking (p=0.90) and diabetes mellitus (p=0.69). Microvascular blood flow did not differ between patients who underwent isolated CABG and those operated for combined heart disease (p=0.33).

DISCUSSION

For the first time, a 2-dimensional imaging technique, in this case SDF imaging, was used to investigate the human microcirculation during cardiac surgery. We demonstrated the feasibility of using SDF imaging to monitor the microcirculation at the bedside, as well as in the operating room. We found that sublingual microcirculatory flow decreased during CPB. This finding applied significantly to medium blood vessels. MFI recovered in the postoperative state.

Two patients died. In our opinion, the case of patient #1 is more interesting than that of patient #2. We think that the main cause of death in patient #2 was acute heart failure after

cessation of CPB (duration 360 minutes). In contrast, the microcirculation might have played an important role in the bad outcome of patient #1. Impaired microcirculation was also observed in both of the patients who had elevated postoperative lactate levels. Although all these patients represent only case observations, and other factors different from the microcirculation might have played significant roles, these examples indicate that peri-operative optimization of macrohemodynamic parameters (such as blood pressure) is not always sufficient to optimize perfusion at the microvascular level.

Several studies have reported on the use of tonometry to assess microcirculatory function during cardiac surgery. These studies all suggested impaired intestinal perfusion during cardiac surgery, although it is still questionable whether a resuscitation strategy that is based on tonometry measurements is more beneficial than are conventional strategies that are based on classical indexes of perfusion.(11-13). We used a novel imaging modality in our study and the results are consistent with these tonometry reports. We found that the decrease in microvascular perfusion was independent of changes in systemic perfusion pressure, which is in line with previous experimental and clinical data in sepsis.(14-17)

Limitations

Although SDF imaging is an improved technique relative to OPS imaging, it still has its limitations. Pressure artifacts hinder the analysis of the images captured from a nonsedated patient who moves the tongue and the adjacent sublingual area continuously. For the same reason, pressure artifacts thwart comparisons between images captured 1 day before surgery (T0) and images taken after the patient was sedated (T1 and thereafter). This phenomenon raises the question which measurement is the true baseline (T0 or T1). A second limitation of the technique is that it is hardly impossible to record the same selected sublingual area during different measurement periods, resulting in heterogeneous images of the microcirculation. Although quantification partially corrects for this heterogeneity, it makes off-line analysis less easy and emphasizes the importance of blinding the images before final quantification.

Microvascular perfusion did not decrease during CPB in all patients. The period after the start of CPB is an interval in which many factors influence microcirculatory function. Examples of these factors are the switch from pulsatile to nonpulsatile CPB blood flow, the sudden entrance into the circulation of the CPB priming fluid, continuous changes in hematocrit, cardiac manipulations by the surgeon and administration of bolus doses of vasoactive drugs. Interpatient differences in these factors may explain our heterogeneous results.

Clinical perspective and conclusion

The basic task of the cardiovascular system is to provide the metabolic requirements of the tissues. Inadequate perfusion leads to the activation of anaerobic metabolism pathways, oxygen debt and tissue acidosis.(18) Conventional parameters, however, such as cardiac output, blood pressure, heart rate, and diuresis, are limited in predicting the state of the local organ

blood supply.(19) Instruments that monitor perfusion at the microvascular level are therefore valuable.

In conclusion, SDF imaging is a promising technique to visualize microcirculatory alterations at the bedside or even in the operating room. In this pilot study, a decrease in microvascular perfusion, not associated with a decrease in systemic perfusion pressure, was observed after the start of nonpulsatile CPB. Further investigations are necessary to confirm these findings and to discover whether the severity and duration of these changes are associated with patient outcome, as was previously demonstrated for sepsis.(4) A further intriguing question would be whether a resuscitation strategy that is based on, and monitored with, SDF imaging could be beneficial to reduce multiorgan failure after cardiac surgery.

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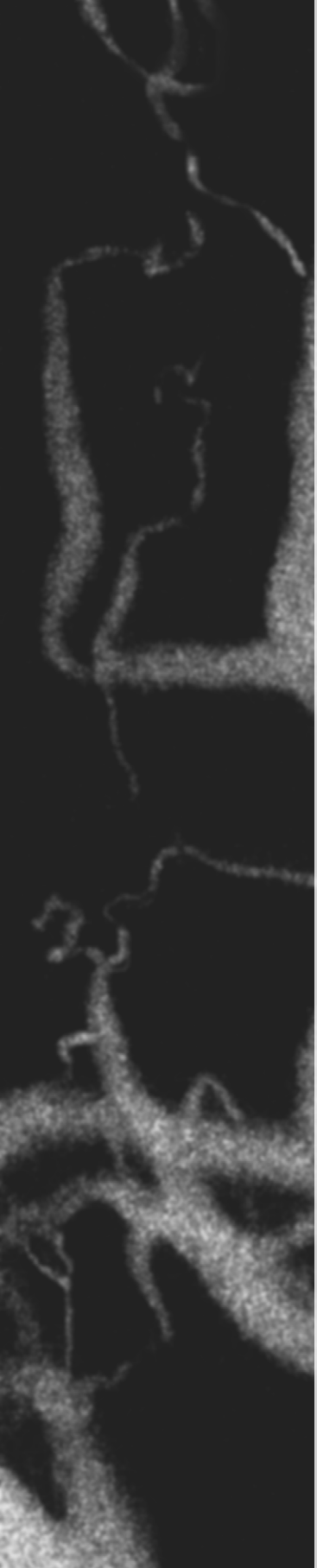

Chapter 8

Intra-operative assessment of human pulmonary alveoli in vivo using Sidestream Dark Field imaging: A feasibility study

Corstiaan A. den Uil, Rick Bezemer, Dinis R. Miranda, Can Ince, Wim K. Lagrand, J. Michael Hartman, Ad J. Bogers, Peter E. Spronk, Maarten L. Simoons

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ABSTRACT

Background: In vivo videomicroscopy has been used for years to visualize subpleural alveoli in animal studies. This has led to a better understanding of alveolar physiology. We tested the hypothesis whether a novel handheld videomicroscope could be used for intraoperative detection of alveoli in surgical patients during mechanical ventilation.

Materials and Methods: Using Sidestream Dark Field imaging, we observed 6 patients (3 adults and 3 children) who underwent elective cardiac surgery. In each patient, the tip of the microscope was placed on the visceral pleural surface of the left upper pulmonary lobe after weaning from cardiopulmonary bypass. The acquired images were converted into a digital signal and captured on a computer.

Results: Although cardiac motion artifacts were present, visceral pleural microvascular blood flow could be observed in adults and infants. Subpleural cavities, i.e. alveoli, were only observed in infants. These alveoli were remarkably similar in dimension and structure as those identified previously as true alveoli in animal studies. Quantification of these alveoli demonstrated that mean alveolar diameter, perimeter and area increased over age among the investigated infants (all parameters $p<0.001$).

Conclusions: High-quality images of visceral pleural microvessels as well as subpleural cavities, reflecting superficial alveoli, could be obtained in infants. These findings create the opportunity to start human intervention studies, which should investigate alveolar dynamics during mechanical ventilation in cardio-thoracic surgery in more detail.

INTRODUCTION

Mechanical ventilation using positive end-expiratory pressure (PEEP) is frequently applied in the treatment of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). It has been shown that application of PEEP can open collapsed alveoli and can maintain their patency.(1, 2) However, it is recognized that providing ventilatory support to ALI and ARDS patients might introduce ventilator-induced lung injury (VILI).(1, 3-6)

Current imaging technology is useful to investigate lung physiology and pathophysiology. Several imaging modalities have received attention in the recent literature: videomicroscopy, magnetic resonance imaging, micro-computed tomography, micro-positron emission tomography, optical imaging, and molecular markers.(7, 8) Videomicroscopy can be used during mechanical ventilation of small animals.(9) Although we gained extensive knowledge and insights on VILI and underlying mechanisms by employing intravital videomicroscopy in animal models, in vivo assessment of alveolar geometry by videomicroscopy could never be done in humans. This was probably due to the relatively thick visceral pleura in humans with respect to animals. As a result of reflection and optical scattering by this membrane, image quality was dramatically reduced which limited the applicability of epi-illumination-based microscopic imaging systems. However, a recently introduced videomicroscopic technique called Sidestream Dark Field (SDF) imaging might overcome this shortcoming of epi-illumination-based systems and provide high quality images of human sub-pleural alveolar structures.(10, 11)

In the present study, we investigated the feasibility of imaging sub-pleural alveoli in patients during cardio-thoracic surgery employing SDF imaging.

MATERIALS AND METHODS

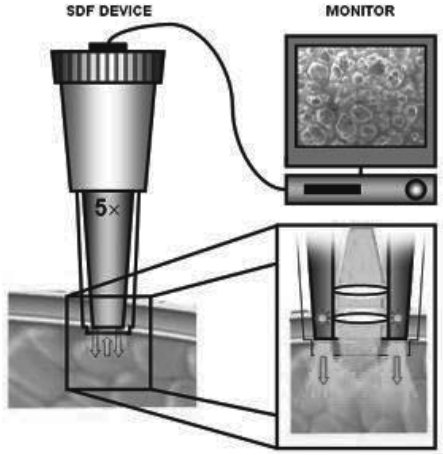
Study design and patient management

We conducted an observational feasibility study in 6 consecutive patients who underwent cardiac surgery (3 infants and 3 adults). This study was performed as a sub-study of the *CARdiac failure and the MicroCIrculation* (CARMICI) study, for which approval was obtained from the institutional ethical committee.(12) All patients underwent median sternotomy and incision of the parietal pleura followed by cardiac surgery with assistance of a non-pulsatile cardiopulmonary bypass device. The lungs were ventilated in a volume-controlled mode. Respiratory frequency was adjusted to maintain $PaCO_2$ between 34 and 49 Torr (4.5 and 6.5 kPa), tidal volume 8-10 ml/kg, I/E ratio 1:2, inspiratory pause 10% and PEEP of 8 cmH_2O. FiO_2 was set at 60%. In infants, PEEP was 5 cmH_2O. During the measurements, an inspiratory hold was performed, resulting in CPAP of 20 cmH_2O.

Microvascular and alveolar imaging

The Microscan (MicroVisionMedical, Amsterdam, the Netherlands) was used as an intravital microscope, employing SDF illumination, to obtain two-dimensional video images (at 25 Hz) of pulmonary structures. Principles of this novel technique have been described previously and are demonstrated in Figure 1.(10) Briefly, the SDF imaging device consists of a central light guide, surrounded by, but isolated from, concentrically placed light emitting diodes that stroboscopically emit green light for illumination, which results in darkly imaged red blood cells due to the optical absorption of (oxy)hemoglobin and lightly imaged alveolar structures due to reflection of the light by alveolar walls. Penetration depth of this light into the tissue is approximately 500 µm. In contrast to epi-illumination microscopy, SDF illumination prevents capturing of reflected and backscattered light by the human pleural membrane (thickness less than 80 µm)(13), which allows imaging of sub-pleural structures. So far, SDF imaging, incorporated in a handheld device, has mainly been applied to investigate the microcirculation in critically ill patients in intensive care units.(14) The tip of the Microscan, in direct contact with the lung surface, was covered with a sterile disposable lens (MicroVisionMedical, Amsterdam, the Netherlands) while the rest of the camera was covered with a sterile camera drape (Drapex Excel, Medical Disposables Manufacturing Ltd., Malta). To improve microvascular and alveolar imaging, the lung surface was cleaned from remaining blood using isotonic saline-drenched gauzes. After the patient was weaned from cardiopulmonary bypass, the attending cardio-thoracic surgeon imaged the pulmonary surface of the left upper pulmonary lobe in three areas. The surgeon served the hand-held camera, which was kept perpendicularly on the lung surface through the sternotomy opening. Acquired images were captured on a computer, allowing offline analysis of alveolar geometry.

Figure 1. Sidestream Dark Field imaging setup.



Images were acquired using a Sidestream Dark Field (SDF) imaging device (left) and displayed on a monitor (upper right). In the SDF device a central light guide is surrounded by, but isolated from concentrically placed light emitting diodes that stroboscopically emit green light for illumination. SDF illumination prevents capturing of reflected and backscattered light by the human pleural membrane (lower right). Modified with permission from (23).

Image analysis

An investigator, not involved in the image acquisition, contoured the individual alveoli manually using a black line (grayscale value of zero) in Photoshop 7.0.1 (Adobe Systems Incorporated, San Jose, CA, USA). Subsequently, alveolar contours were isolated applying a grayscale threshold in NI Vision Assistant (National Instruments Corp., Austin, TX, USA). The contours were filled by the use of a convex hull function, which fills up the space inside a closed polygonal chain (i.e., the contours). Finally, the isolated alveoli were analyzed for major and minor diameters, perimeter, and area. All parameters were obtained in pixel dimensions and were converted to μm and μm^2 via calibration of the imaging setup.

Statistical analysis

Statistical analyses of alveolar diameters, perimeter, and area, were performed with SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov and Shapiro-Wilk tests confirmed the normal distribution of the data sets. All data are presented and reported as mean ± SD. Differences between means were tested with one-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparison test. A p-value <0.05 was considered statistically significant.

RESULTS

All patients (n=6) were non-smokers and had a normal lung function. None of the patients had asthma or chronic obstructive pulmonary disease in the medical history. Characteristics of the patients are shown in Table 1.

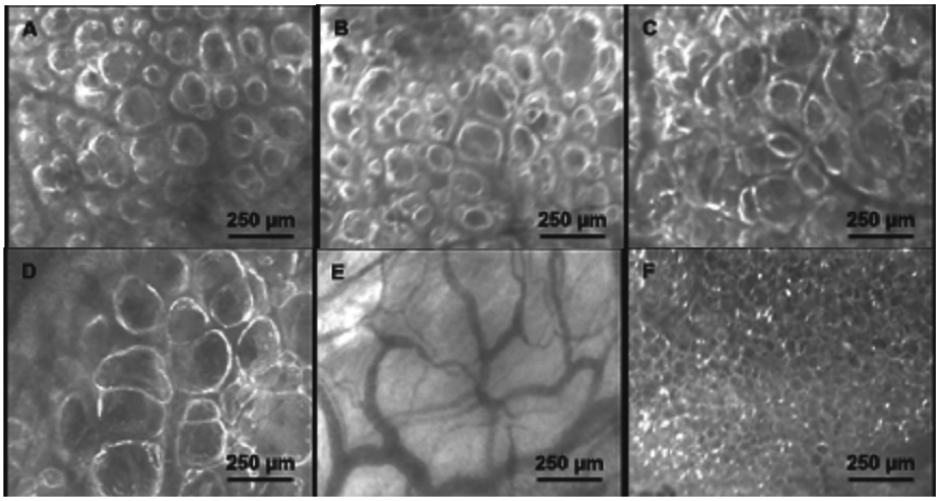
Table 1. Baseline characteristics of the study population.

Patient No.	Age	Gender	Surgery
1	3 months	female	Repair of trunctus arteriosus
2	8 months	female	Closure patent foramen ovale Closure of ventricular septal defect Repair of double-chambered right ventricle
3	3 years	female	Closure of atrial septal defect
4	63 years	male	Coronary artery bypass grafting
5	64 years	male	Coronary artery bypass grafting
6	86 years	female	Coronary artery bypass grafting Aortic valve replacement

Microcirculation

In children (n=3) as well as in adults (n=3), microvasculature in the visceral pleura running on the lung surface could be clearly observed. Panels E and F of Figure 2 show an SDF image of the visceral pleural microvasculature and an SDF image of adipose tissue within the thorax, respectively. Movement artifacts, due to cardiac contractions, hindered analysis of microvascular perfusion. By adjusting the focus of the videomicroscope, sub-pleural alveoli with white

Figure 2. Structures observed with Sidestream Dark Field imaging.



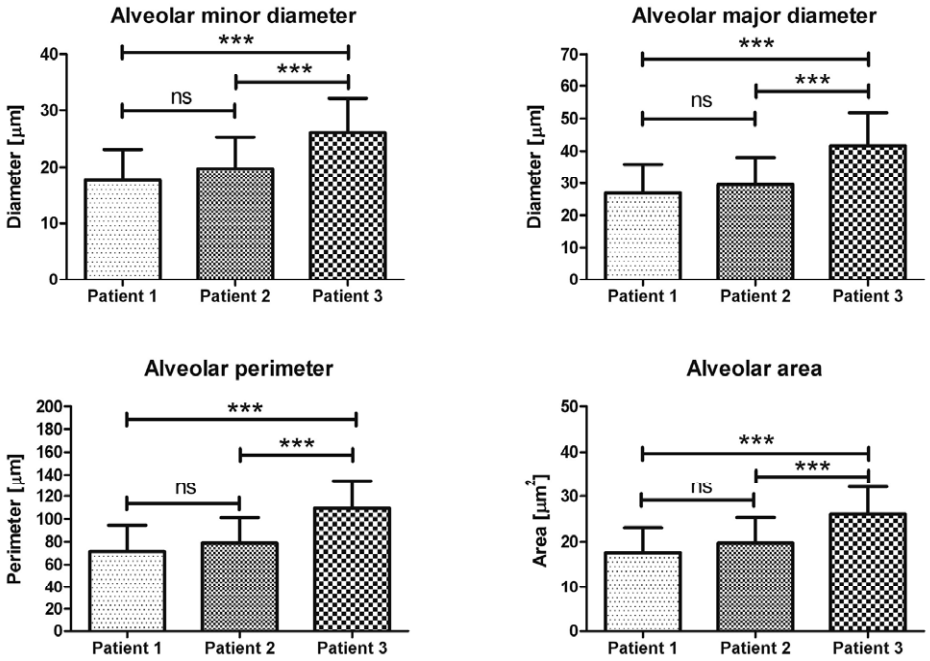
SDF images of alveolar structures in patient 1, 2, and 3 (panels A, B, and C, respectively). Alveolar structures (A, B, and C) and air bubbles (D) are imaged very similarly. However, alveolar structures move as a rigid configuration, whereas air bubbles, in contrast, move and deform independently from each other due to cardiac contractions. Air bubbles were located between the tip of the SDF device and the pleural surface. Additionally, below the air bubbles, moving structures and flowing blood could be observed, which was not the case for the alveoli. Panel E shows an SDF image of the visceral pleural microvasculature. In panel F, an SDF image of adipose tissue within the thorax is shown.

contours and diverse sizes were observed in infants. Microvessels were observed between alveolar walls and in between groups of alveoli, respectively. These observations were much easier in children than in adults, probably because children have a thinner visceral pleura and less anthracosis (i.e., the black spots in figures 4A and 4C).

Alveolar imaging

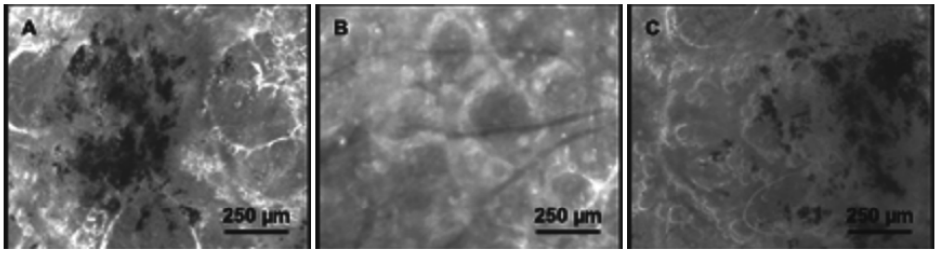
In total, 119 alveoli (Figure 2: panels A, B, and C) could be analyzed in infants (46, 51, and 22 alveoli for patients 1, 2, and 3, respectively). All results with respect to alveolar geometry (i.e., major and minor alveolar diameters, alveolar perimeter, and alveolar area) measured in children are presented in figure 3. All alveolar parameters increased with age ($p<0.001$; Figure 3). Alveolar imaging in adults was much harder than in infants. Besides alveoli also air bubbles were observed between the tip of the SDF device and the pleural surface (Figures 2D and 4). These air bubbles were very similar to alveoli and it was hard to discriminate between the two in still images. However, in video sequences, alveoli moved as rigid structures due to cardiac movement, whereas air bubbles, in contrast, deformed and moved independently from each other. Alveoli, on the contrary, moved due to cardiac contractions, but did not change in size and shape during the inspiratory hold maneuver. Air bubbles were further distinguished from alveoli by the fact that visceral pleural microvessels were seen below transparent air bubbles but these microvessels were in fact observed on top of true alveoli.

Figure 3. Alveolar diameters, perimeter, and alveolar area measured in infants.



Patient numbers correspond to the numbers listed in table 1. Ages of patients were 3 months (patient 1), 8 months (patient 2), and 3 years (patient 3). In total, 119 alveoli could be analyzed (46, 51, and 22 alveoli for patients 1, 2, and 3, respectively). Alveolar size increased with age (all figures: $p<0.001$). Individual comparisons are shown (***: $p<0.0001$, ns: non-significant). Data are presented as mean±SD.

Figure 4. Sidestream Dark Field images of adult lungs.



Still video frames of patient 4 (panel A), patient 5 (panel B), and patient 6 (panel C). The dark spots demonstrate pulmonary anthracosis, whereas the white structures depict air bubbles.

DISCUSSION

To the best of our knowledge, this is the first study demonstrating the feasibility of SDF illumination of the visceral pleura in living humans during cardiac surgery using a novel handheld microscopic technique. Moreover, we were able to observe human alveoli and to quantify alveolar geometry, in terms of diameter, perimeter, and area, in the three investigated infants. Quantitative analysis of alveolar microcirculation, however, failed due to movement artifacts. In

adults, alveoli could hardly be observed due to low image quality. However, the visceral pleural microcirculation could be visualized, although the bronchial circulation might be less interesting from a clinical point of view.

In a previous study using in vivo videomicroscopy, Carney et al. directly observed and quantified alveolar mechanics, defined as the changes in alveolar size throughout a ventilatory cycle during mechanical ventilation in normal and injured lungs.(15) The authors showed that normal alveoli, once recruited, did not change in size during tidal ventilation. In contrast, in lungs after surfactant deactivation, alveolar mechanics showed a pattern of repeated alveolar collapse and expansion (RACE). Several experimental studies have indeed confirmed the importance of RACE, demonstrated by videomicroscopy, as a determinant of VILI and ALI/ARDS in the setting of animal models.(16-20)

Interestingly, the sub-pleural structures observed using SDF imaging are remarkably similar when compared to those observed in the above-mentioned animal studies. A great advantage of our technique is, however, that SDF imaging is incorporated into a clinically applicable handheld device. In addition, we present a method to quantify alveolar size. Standard deviation of alveolar diameter may reflect alveolar instability in future studies. Alveolar instability, reflected by increased alveolar heterogeneity, might be improved by recruitment procedures, which has to be investigated in before-after studies. We believe that our current preliminary study might initiate further research on the development and treatment of lung injury in humans as it can be applied to investigate alveolar mechanics during cardio-thoracic surgery.

However, our study has its limitations. Cardiac movement artifacts hindered focusing and analysis of the acquired images for microvascular blood flow velocities. Carney et al. solved this problem by lifting the animal lung off the heart, thereby eliminating cardiac motion artifacts. (21) Moreover, the presence of anthracosis in adult patients undergoing CABG resulted in worse image quality in comparison with young children. Furthermore, our observations were made at the left upper lobe of the lung, since this part of the lungs was most easily accessible for the current feasibility study. However, the caudal parts of the lung are most prone to atelectasis when the patient is in a supine position(22) and actually it would be more interesting to investigate alveolar mechanics in these basal parts of the lung. However, the caudal pulmonary lobes are not well accessible after median sternotomy. Finally, visualization of alveoli in adult patients was difficult and problems can be expected in those patients in whom the visceral pleural is (subclinically) thickened, e.g. in the presence of empyema. However, although this study describes only the application of a novel method to a small number of patients, it will contribute to the development of clinical studies in this subspecialty.

In conclusion, the handheld SDF imaging device can be used to investigate alveolar mechanics during cardio-thoracic surgery. Further research should address optimization of the SDF imaging technique in this setting, primarily by eliminating cardiac motion artifacts. SDF imaging should be used as a microscopic imaging modality to translate knowledge on VILI and underlying mechanisms, such as RACE, obtained in small and large animal models to clinical practice.

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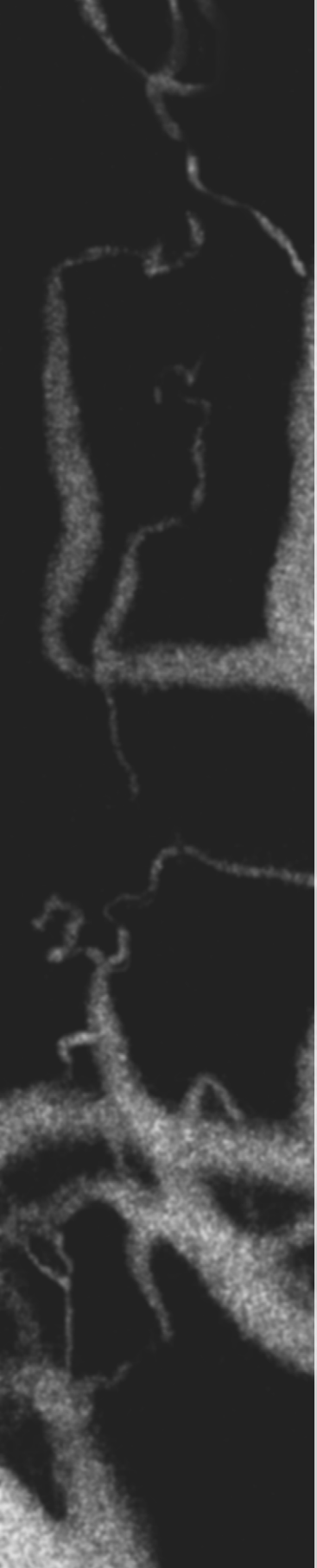

Chapter 9

Impaired microcirculation predicts worse outcome of patients with cardiogenic shock

Corstiaan A. den Uil, Wim K. Lagrand, Martin van der Ent, Lucia S.D. Jewbali, Jin M. Cheng, Peter E. Spronk, Maarten L. Simoons

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ABSTRACT

Aim: To investigate the correlation between sublingual perfused capillary density (PCD) and clinical course (i.e., occurrence of organ failure and mortality) in cardiogenic shock patients.

Methods: We performed a prospective cohort study. Using Sidestream Dark Field imaging, PCD was measured immediately after hospital admission (T0, baseline) and at 24 hours (T1). We compared patients with baseline PCD ≤median ("impaired microcirculation") with patients with baseline PCD >median ("preserved microcirculation"). Sequential Organ Failure Assesment (SOFA) scores were calculated at both time points. Kaplan-Meier cumulative 30-day survival analyses were performed. Univariate and multivariate logistic regression was done to identify predictors of 30-day mortality.

Results: We investigated 104 patients (impaired PCD: n=54; preserved PCD: n=50). Patients with impaired PCD had less improvement in SOFA score relative to patients with preserved PCD (ΔSOFA 0 [-1; 2] vs. –1 [-2; 0], p= 0.03). Organ failure improved more frequently in patients with preserved PCD than in patients with impaired PCD (52% vs. 31%, p=0.04). Thirty-two patients (31%) died: 23 patients (43%) with impaired PCD vs. 9 patients (18%) with preserved PCD (p<0.01). After adjustment, age (OR 1.08, 95%CI [1.03-1.12]), cardiac power index (OR 0.63, 95%CI [0.46-0.86]), and PCD (OR 0.59, 95%CI [0.43-0.80]) remained significant predictors of 30-day outcome. Patients with impaired baseline PCD that improved at T1, had a considerable better prognosis relative to patients who had a persistently impaired PCD.

Conclusion: Diminished sublingual PCD, at baseline or following treatment, is associated with development of organ failure and is a predictor of worse outcome in cardiogenic shock.

INTRODUCTION

Cardiogenic shock is the most important cause of death in patients hospitalized with acute myocardial infarction.(1, 2) Although in-hospital survival of cardiogenic shock is currently improving, 30-day mortality rates remain high.(3, 4)

It has been accepted for years that cardiogenic shock is caused by a decrease of cardiac output. In this classic concept of cardiogenic shock, it is obvious that normalization of hemodynamic parameters is one of the main objectives in the treatment of cardiogenic shock.(5) However, it has been shown that 45% of non-survivors of cardiogenic shock die with a normal cardiac index (i.e. > 2.2 L.min.m^{-2}), indicating that optimization of macrohemodynamic parameters alone may fail to save the patient.(6) In line with these data, post-hoc analysis of data from the SHOCK-trial demonstrated that the classic notion of systemic vasoconstriction did not apply to all patients with cardiogenic shock. This was, furthermore, emphasized by enormous variability in cardiac index and systemic vascular resistance (SVR) among patients during cardiogenic shock, even despite application of vasopressor therapy.(7) These data have changed the concept of cardiogenic shock from being solely a cardiac problem into a disease of derangements in the entire circulatory system.(8) It is currently accepted that cardiogenic shock causes a systemic inflammatory response (SIRS), which is characterized by the release of inflammatory mediators and neurohormones as well as by alterations in tissue microvasculature, which may result in multiple organ failure.(9, 10) Several studies have reported that markers of SIRS are predictive of short-term mortality in cardiogenic shock.(11-15) However, mechanisms involved in the pathogenesis of multiple organ failure in cardiogenic shock patients are largely unknown. It has been postulated that impaired splanchnic perfusion at the micro-vascular level, modulated by the severity of heart failure, the degree of SIRS, and by the administration of vasoactive agents, might play an important role in the pathogenesis of multiple organ failure and the persistence of shock.(16-18)

Sublingual microcirculation is regarded a surrogate marker of splanchnic perfusion and can be measured at the bedside using novel imaging technology.(17, 19, 20) Aim of the current study was to investigate the correlation between sublingual microcirculation and outcome (i.e., (change in) SOFA score, occurrence of multiple organ failure and mortality) in patients with cardiogenic shock.

METHODS

Study design

This prospective study was conducted at the Intensive Cardiac Care Unit of the Thoraxcenter, Erasmus University Medical Center, the Netherlands. We included patients who were admitted with cardiogenic shock from all causes between May 2007 and May 2009. Cardiogenic shock

was defined as a cardiac index <2.2 $L.min^{-1}.m^{-2}$ and clinical signs of hypoperfusion (i.e., cold extremities, oliguria or altered mental state), not responsive to fluid resuscitation. Patients with oral bleeding were excluded from the study. The institutional ethical committee approved the protocol, and written informed consent was obtained from each patient or, in case of patients who were sedated, from a relative authorized to consent on behalf of such a patient.

Hemodynamic monitoring

All patients were monitored with a radial artery catheter (arterial cannula with FloSwitch, Ohmeda, Swindon, UK). Seventy-three (70%) patients were monitored with a pulmonary artery catheter (PAC: Becton Dickinson Criticath SP5107H, Sandy, UT, USA or CCOmbo, Edwards Lifesciences, Saint-Prex, Switzerland). In the remaining patients, central venous pressure was measured via a three-lumen central venous catheter (Multicath; Laboratoires Pharmaceutiques Vygon, Ecouen, France), inserted into the right internal jugular vein. In these patients, cardiac index (CI) was calculated according to the Cuschieri formula, which shows close correlation with the cardiac index measured with a pulmonary artery catheter.(21)

Data collection

Data collection included central body temperature, heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), mean pulmonary artery pressure (MPAP), cardiac index (CI), systemic vascular resistance (SVR), lactate level and central-venous or mixed-venous oxygen saturation (SvO_2). Systemic vascular resistance (SVR) was calculated as (MAP-CVP)*80/cardiac output. Cardiac power index (CPI) was computed as mean arterial pressure*CI/451.(22) Glomerular filtration rate (GFR) was estimated by the Modification of Diet in Renal Disease (MDRD) equation.(23)

Microcirculatory assessment and analysis

The Sidestream Dark Field (SDF) imaging device (MicroScan; Microvision Medical, Amsterdam, The Netherlands) was used to obtain 2-dimensional video images of sublingual microcirculatory blood flow. This technique has been described previously.(24) In short, the camera emits green light that is absorbed by red blood cells within microvessels. In this way, red blood cells are used as the contrast agent to visualize sublingual blood flow in patent microvessels. This is the reason why oral bleeding was an exclusion criterion for the study. Per time point, 3-5 steady video sequences of at least 20 seconds duration were obtained, stored and analyzed in a randomized and blinded fashion. Quantification of the images was done using dedicated software (Automated Vascular Analysis 3.0, MicrovisionMedical, Amsterdam, the Netherlands) by a blinded investigator. Perfused capillary density (PCD) was calculated by measuring total length of perfused capillaries divided by image area. Capillaries were regarded as perfused if they had either of the following flow classifications obtained by visual inspection: sluggish, continuous or hyperdynamic.(25, 26) Since SDF imaging enables visualization of flowing

intravascular erythrocytes rather than microvessel walls, an increase in PCD was regarded as capillary recruitment. This approach has been validated previously.(27, 28) Capillaries were defined as microvessels with a diameter less than 20 μm.

Study protocol

The sublingual microcirculation was investigated immediately after the patient's admission to the hospital and after informed consent had been obtained (T0, baseline). Measurements were repeated 24 hours after the first measurement or earlier, pending the individual clinical course of the patient (i.e., occurrence of death within 24 hours). In addition, at both time points, all components of the Sequential Organ Failure Assesment (SOFA) score were calculated, with the exception of the central nervous system, because the majority of the patients received central nervous system depressant drugs at the time of evaluation.(15, 29) The total SOFA score was calculated by summing the subscores for each of the components (i.e. cardiac, renal, respiratory, coagulation, and liver).(30)

Follow-up

Vital status at 30 days was registered for all patients. In patients who were transported to other hospitals or were discharged during the 30 days following baseline measurements, vital status was acquired from municipal civil registries. Response rate was 100% and no patients were lost during 30 days of follow-up.

Statistical analysis

Categorical variables are presented as absolute numbers with percentages. Continuous variables are presented as mean ± standard deviation. Non-normally distributed continuous variables are presented as median [interquartile range]. Because this study is the first study that presents PCD measurements in patients with cardiogenic shock, we decided a priori to compare the patients with baseline PCD ≤ median ("impaired microcirculation") with those patients in whom baseline PCD was > median ("preserved microcirculation"). Categorical variables were compared by chi-square test or Fisher's exact test, when appropriate. Differences between groups were tested with Student's T-test or the Mann-Whitney test, when appropriate. Microcirculatory changes between time points were tested with the paired T-test. Correlations between variables were investigated with Pearson or Spearman correlation test, when appropriate. Kaplan-Meier cumulative 30-day survival was calculated and Kaplan-Meier survival curves were compared by the Log-rank test. Univariate and multivariate logistic regression analyses were performed to identify predictors of 30-day all-cause mortality. Final results are presented as unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (95%CI). In multivariate analysis, the following baseline variables were entered into the model: Age, N-terminal pro B-type natriuretic peptide (NT-proBNP), cardiac power index, baseline SOFA score, and sublingual perfused capillary density. Log-transformation of NT-proBNP was

performed to achieve normality. Cardiac power index was categorized into units of 0.10 $W.m^{-2}$. (22) A p-value <0.05 was regarded statistically significant.

RESULTS

We investigated 104 patients with cardiogenic shock. Baseline characteristics of the study population are presented in Table 1. Mean age was 59 ± 14 years and 64% of the patients were male. Cardiogenic shock was most frequently resulting from acute myocardial infarction (65%). Patients with impaired microcirculation (n=54) had higher NT-proBNP levels than patients in whom microcirculation was preserved (n=50: 5924 [2657; 13,945] pg/mL vs. 3462 [1203; 8877] pg/mL, p=0.04, Table 1). Median baseline SOFA score was not significantly different between

Table 1. Baseline characteristics.

	All patients (n=104)	PCD ≤ Median (n=54)	PCD > Median (n=50)	P-value
Age, yrs (mean ± SD)	59 ± 14	58 ± 13	60 ± 15	NS
Gender, male	67 (64%)	36 (67%)	31 (62%)	NS
Etiology				NS
AMI	68 (65%)	36 (67%)	32 (64%)	
Cardiomyopathy	26 (25%)	14 (26%)	12 (24%)	
Valvular heart disease	6 (6%)	1 (2%)	5 (10%)	
Post cardiac surgery	4 (4%)	3 (6%)	1 (2%)	
CV risk factors				
Hypertension	40 (39%)	20 (37%)	20 (40%)	NS
Diabetes mellitus	27 (26%)	16 (30%)	11 (22%)	NS
Current smoking	21 (20%)	12 (22%)	9 (18%)	NS
Dyslipidemia	26 (25%)	15 (28%)	11 (22%)	NS
Mechanical ventilation	68 (65%)	33 (61%)	35 (70%)	NS
IABP	36 (35%)	22 (41%)	14 (28%)	NS
ECMO	5 (5%)	1 (2%)	4 (8%)	NS
NT-proBNP, pg/mL (median, IQR)	4347 [1691; 11,492]	5924 [2657; 13,945]	3462 [1203; 8877]	0.04
Hemoglobin (mmol/L)	6.6 [5.8; 7.6]	6.6 [5.8; 7.6]	6.7 [5.9; 7.7]	NS
WBC count, $*10^9$/L (median, IQR)	11.4 [8.6; 15.4]	11.3 [8.7-15.2]	11.5 [8.6-16.5]	NS
CRP (mg/L) (median, IQR)	47 [13; 131]	55 [21; 133]	38 [9; 129]	NS
GFR (ml/min)	54 [34; 78]	47 [33; 72]	59 [35; 83]	
SOFA score (median, IQR)				
Total	6 [4; 8]	6 [4; 8]	6 [4; 7]	NS
Cardiac	2 [2; 3]	2 [2; 3]	3 [2; 3]	NS
Renal	1 [0; 2]	1 [0; 2]	1 [0; 1]	NS
Respiratory	2 [1; 2]	2 [1; 2]	2 [1; 2]	NS
Coagulation	0 [0; 1]	0 [0; 1]	0 [0; 1]	NS
Liver	0 [0; 1]	0 [0; 0]	0 [0; 1]	NS

Abbreviations: SD, standard deviation; NS, non-significant; AMI, acute myocardial infarction; CV, cardiovascular; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; NT-proBNP, N-terminal proB-type natriuretic peptide; IQR, interquartile range; WBC, white blood cell; CRP, C-reactive protein; GFR, glomerular filtration rate; SOFA, sequential organ failure assessment.

Table 2. Baseline hemodynamic parameters.

	All patients (n=104)	Microcirculation impaired (n=54)	Microcirculation preserved (n=50)	P-value
HR, bpm	90 [71; 104]	92 [73; 106]	89 [71; 100]	NS
MAP, mmHg	69 [61; 82]	66 [59; 81]	73 [65; 83]	NS
CVP, mmHg	15 [12; 18]	16 [12; 19]	14 [12; 17]	NS
PCWP, mmHg*	21 [16; 24]	23 [19; 25]	18 [14; 23]	0.03
MPAP, mmHg*	28 [24; 34]	31 [25; 37]	27 [24; 31]	NS
CI, $L.min^{-1}.m^{-2}$	2.5 [2.0; 3.5]	2.4 [1.9; 3.0]	2.6 [2.0; 3.8]	NS
CPI, $W.m^{-2}$	0.42 [0.31; 0.55]	0.39 [0.28; 0.52]	0.44 [0.34; 0.57]	0.04
SVR, $dynes.sec.cm^{-5}$	1056 [771; 1360]	1071 [735; 1369]	1045 [794; 1369]	NS
SvO_2, %	66 [60; 74]	64 [59; 71]	69 [61; 75]	0.03
Lactate, $mmol.L^{-1}$	1.3 [1.0-2.2]	1.4 [1.0; 2.5]	1.2 [0.9; 2.2]	NS

Abbreviations: HR, heart rate; NS, non-significant; MAP, mean arterial pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; MPAP, mean pulmonary artery pressure; CI, cardiac index; CPI, cardiac power index; SVR, systemic vascular resistance; Sv02, central-venous oxygen saturation.

* Data available in 73 (70%) of the patients.

both groups. Patients with an impaired microcirculation had a higher PCWP (23 [19; 25] mmHg vs. 18 [14; 23] mmHg, p=0.03), a lower CPI (0.39 [0.28; 0.52] $W.m^{-2}$ vs. 0.44 [0.34; 0.57], p=0.04) $W.m^{-2}$ and a lower SvO_2 (64 [59; 71] % vs. 69 [61; 75] %, p=0.03) than patients with a preserved microcirculation (Table 2).

Baseline sublingual perfused capillary density

Median PCD was 10.3 [8.8; 11.9] $mm.mm^{-2}$. PCD correlated to NT-proBNP levels (ρ=-0.20, p=0.04), MAP (ρ=0.27, p=0.005), and PCWP (ρ=-0.26, p=0.03), but not significantly to baseline SOFA score or to the other baseline parameters listed in Table 2. Baseline PCD correlated to the SOFA score at T1 (ρ= -0.23, p=0.02) and to the change in SOFA score between T1 and T0 (ΔSOFA; ρ=-0.27, p=0.006). Patients with an impaired baseline microcirculation had less improvement in SOFA score after 24 hours as compared with patients with preserved PCD (ΔSOFA 0 [-1; 2] vs. –1 [-2; 0], p= 0.03). Patients with preserved PCD improved more frequently in total SOFA score (52% vs. 31%, p=0.04), as well as in cardiac SOFA score (50% vs. 30%, p=0.04) and renal SOFA score (12% vs. 2%, p=0.04), as compared to patients with impaired PCD.

Thirty-two patients (31%) died during 30 days of follow-up. Of the patients who had an impaired microcirculation, twenty-three (43%) died vs. 9 (18%) of the patients with preserved microcirculation (p=0.009, Figure 1). Sublingual PCD had a greater predictive value on 30-day mortality than baseline SOFA score (area under the receiver operator characteristic curve 0.71 vs. 0.61). Age (OR 1.05, 95%CI [1.02-1.09]) was significantly associated with 30-day mortality, whereas CPI (OR 0.67, 95%CI [0.50-0.89]) and PCD (OR 0.68, 95%CI [0.53-0.85]) were significantly associated with improved 30-day survival. After adjustment, age (OR 1.08, 95%CI [1.03-1.12]), CPI (OR 0.63, 95%CI [0.46-0.86]), and PCD (OR 0.59, 95%CI [0.43-0.80]) remained significant predictors of 30-day outcome (Figure 2).

Figure 1. Kaplan-Meier survival curve stratified according to perfused capillary density at baseline.

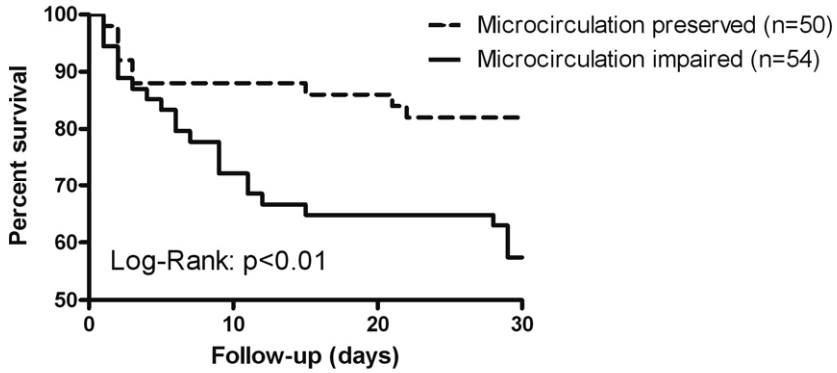


Figure 2. Predictors of 30-day mortality.

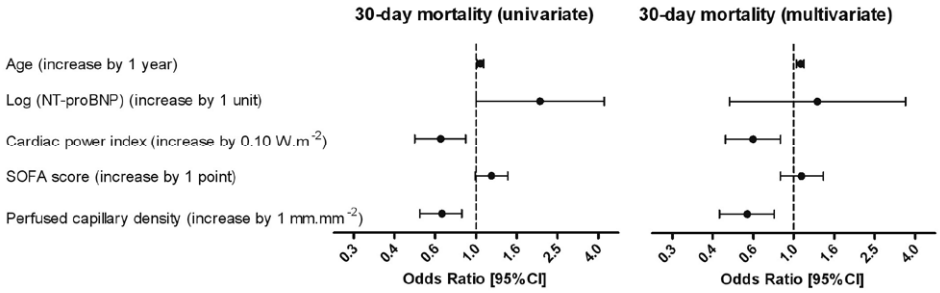
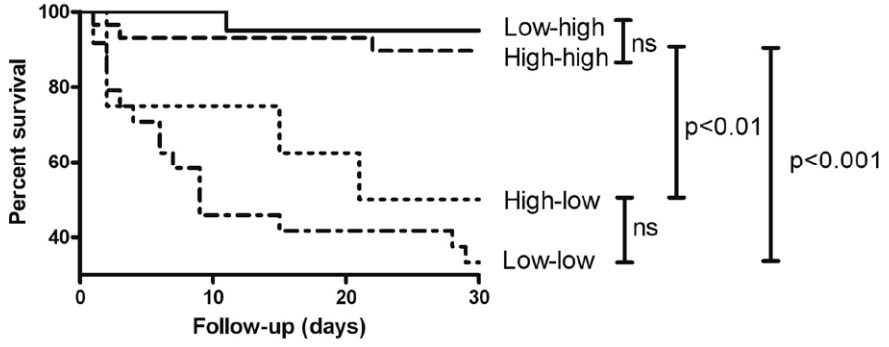


Figure 3. Kaplan-Meier survival curve stratified according to perfused capillary density at baseline and after 24 hours.



Low-high: Impaired microcirculation at T0, preserved microcirculation at T1 (n=20)
High-high: Preserved microcirculation at T0, preserved microcirculation at T1(n=29)
High-low: Preserved microcirculation at T0, impaired microcirculation at T1 (n=8)
Low-low: Impaired microcirculation at T0, impaired microcirculation at T1(n=24)
Abbreviation: ns, non-significant

Impact of changes in PCD on outcome

In 81 patients (78%), PCD measurements were repeated (T1). In the remaining patients, PCD measurements at T1 were not possible because of logistic reasons. Overall, PCD increased at T1

relative to T0 (10.3 ± 2.0 at T0 vs. 10.9 ± 2.1 at T1, p=0.03). In the total study group no significant correlation between changes in PCD and changes in SOFA score was found. However, patients who had an impaired PCD at both T0 and T1 had higher SOFA scores at T1 relative to patients who had a preserved PCD at both T0 and T1 (7 [4; 9] vs. 4 [3; 6], p=0.001). Survival of patients stratified to the level of PCD at both time points is shown in Figure 3. Patients who had an impaired microcirculation at baseline, which improved at T1 ("low-high"), had a considerable better prognosis as compared to patients who had a persistently impaired PCD ("low-low"). An increase in PCD was significantly associated with a better outcome (OR 0.70, 95%CI [0.54-0.92]).

DISCUSSION

In this study, we demonstrated a significant inverse correlation between baseline PCD and SOFA score after 24 hours, as well as an inverse correlation between baseline PCD and change in SOFA score. Patients with an impaired baseline PCD were less likely to improve in total SOFA score, as well as in cardiac and renal SOFA subscores. Moreover, we found that patients with impaired baseline PCD had a higher risk to die and that baseline PCD was strongly and independently associated with 30-day outcome. Finally, in a subgroup of patients in whom measurements were repeated, we demonstrated that patients who had an impaired PCD at both T0 and T1 were at high risk of adverse outcome, as opposed to those patients in whom microcirculation recovered at T1. In the latter patients, survival rates were similar to these of patients with preserved PCD at both T0 and T1.

Using a semi-quantitative analysis technique, De Backer et al. have previously described sublingual microcirculatory alterations in 31 patients with cardiogenic shock.(18) The authors reported a weak correlation of the proportion of perfused capillaries with mean arterial pressure, which is in line with our findings. In this study, we also found that patients with impaired PCD had higher NT-proBNP levels, which has not been reported previously. In general, patients with impaired PCD had more severe heart failure, as demonstrated by higher NT-proBNP levels, higher PCWP, lower CPI and lower SvO_2. Interestingly, PCD did not correlate to cardiac power index. The dissociation between macrocirculation (hemodynamic measurements) and microcirculation (perfusion) has been demonstrated previously and encourages to examine whether monitoring of the microcirculation has an additional prognosticating value in the management of cardiogenic shock patients.(31, 32)

Trzeciak et al. recently demonstrated that increased sublingual microcirculatory flow during resuscitation of septic shock was associated with lower SOFA scores at 24 hours.(33, 34) We did not find a linear correlation between changes in PCD and changes in SOFA score between T0 and T1. Nevertheless, we demonstrated that PCD at baseline was predictive for the occurrence

of (multiple) organ failure. In addition, patients who had an impaired PCD at T0 as well as at T1 had the highest SOFA scores at T1.

Hasdai and colleagues have demonstrated the predictive value of a cold, clammy skin on 30-day mortality in patients with cardiogenic shock complicating acute myocardial infarction.(11) In addition, De Backer et al. demonstrated that the proportion of sublingual perfused capillaries, measured after hospital admission, was higher in patients who survived than in patients who did not survive (64% vs. 43%, $p<0.05$).(18) Using multivariate logistic regression, in our (larger) study, we, furthermore, demonstrated that baseline PCD constitutes an independent predictor of outcome and that baseline PCD is a better predictor of outcome than baseline SOFA score.

These findings arise the question whether PCD can be improved, and, if so, whether such a strategy will be associated with improved outcome. We demonstrated recently that PCD is improved by pharmacologic therapy (nitroglycerin) as well as by mechanical circulatory support devices.(35, 36) The current study demonstrates that patients who had an impaired PCD at both time points were at a high risk of adverse outcome, as opposed to patients in whom microcirculation was initially impaired, but recovered at 24 hours. The latter patients actually had a similar prognosis relative to patients who had a preserved PCD at both time points. These results indeed suggest that therapies directed at improving SDF-imaging-derived sublingual PCD might improve outcome in patients with cardiogenic shock.

Several limitations of our study need to be acknowledged. First, not all patients received a pulmonary artery catheter. It is currently a clinical challenge to convince attending clinicians of the usefulness of this monitoring device, even in research settings.(37) However, the majority of the patients were monitored with a Swan-Ganz catheter. Second, PCD measurements could not be repeated in a minority of patients. Finally, we measured patients only after informed consent had been obtained. This implies that specific patients, e.g. a patient with cardiogenic shock from acute myocardial infarction who died at the catheterization laboratory just after hospital admission, could not be included.

In conclusion, sublingual PCD is associated with the development of (multiple) organ failure. In addition, this parameter is an independent, strong predictor of outcome. Because of the independent and strong association with prognosis in cardiogenic shock, assessment of sublingual PCD using Sidestream Dark Field imaging should be considered as a simple non-invasive approach to assess outcome of patients. Single values obtained after hospital admission, might help in estimating the clinical course of patients with cardiogenic shock. In case of an impaired PCD, much effort should be put to improve not only global hemodynamics, but also microvascular perfusion. Whether such a strategy will improve survival of patients with cardiogenic shock, should preferably be tested in a future, multi-center randomized trial.

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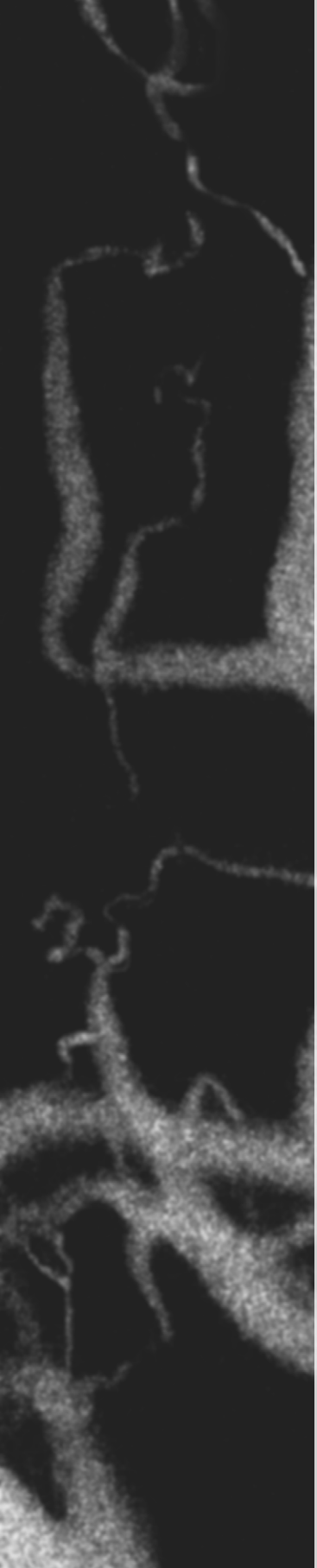

Chapter 10

Management of cardiogenic shock: Focus on tissue perfusion

Corstiaan A. den Uil, Wim K. Lagrand, Suzanne D.A. Valk, Peter E. Spronk, Maarten L. Simoons

Comments made by David R. Holmes, Jr., M.D., F.A.C.C., Professor of Medicine, Mayo Clinic, Rochester, MN, USA

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ABSTRACT

Cardiogenic shock (CS) may result from ischemic heart disease, cardiomyopathy, valvular heart disease, inflammation, myocardial contusion, and cardiac surgery. CS is the leading cause of in-hospital death in patients with acute myocardial infarction. Although early revascularization strategies have resulted in a better prognosis, in-hospital mortality from CS remains exceptionally high. Notably, long-term annual mortality is similar in survivors of CS relative to patients with myocardial infarction without shock. This underlines the importance of aggressive support of the failing heart in the acute phase of CS. Because CS reflects a state of hypoperfusion induced by heart failure, management of CS should aim at improving cardiac function as well as at optimization of tissue perfusion. This review evaluates the current treatment of CS. In addition, novel approaches to monitor and modulate peripheral circulation at the bedside are highlighted. It is expected that these techniques will improve our understanding of the pathogenesis of CS and will offer new opportunities to guide therapy in CS patients to improve prognosis.

INTRODUCTION

CS is the leading cause of death in patients who are admitted to the hospital with acute myocardial infarction.(1) In most cases, CS develops after loss of cardiomyocyte function due to acute myocardial infarction. Other causes of CS include mechanical compliations of acute myocardial infarction, cardiomyopathy, valvular heart disease, myocarditis, myocardial contusion, and following cardiotomy.(2) Among other acute heart failure syndromes, CS is defined as tissue hypoperfusion induced by heart failure after correction of preload.(3) Although CS cannot easily be defined by global hemodynamic parameters, it is usually characterized by reduced mean arterial pressure (MAP, <60 mm Hg) due to heart failure, a low urine output (<0.5 mL/kg/h), and a heart rate exceeding 90 bpm (Table 1). Early mortality rates of patients with CS are very high. However, Global Utilization of Streptokinase and TPA for Occluded coronary arteries (GUSTO)-I investigators recently showed that 30-day survivors of CS had a similar annual long-term mortality rate (2%-4%/yr) relative to patients with ST-segment elevation myocardial infarction who did not have shock.(4) Similarly, at Erasmus University Medical Center, Valk et al. performed a cohort study of patients who received an intra-aortic balloon pump (IABP) for cardiogenic shock between 1990 and 2004.(5) Despite a high mortality at 30 days (32%) in patients who received an IABP for cardiogenic shock, Kaplan-Meier estimated 10-year survival was 41% for 30-day survivors of CS and annual mortality rate beyond the first year was 4.2% (Figure 1). This rate approximates long-term annual mortality after ST-segment elevation myocardial infarction without shock.(4) Moreover, these findings demonstrate that 30-day survivors of cardiogenic shock have a relatively favorable prognosis, which emphasizes the importance of supporting the failing heart intensively in the acute phase of myocardial infarction. In this article, we review the current management of CS due to acute myocardial infarction and focus on tissue microcirculation as a novel target to improve prognosis of CS patients.

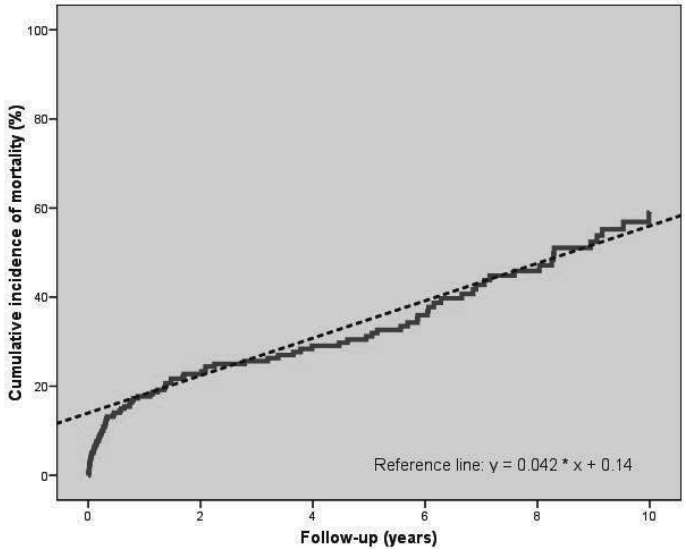
Table 1. Common hemodynamic characteristics in cardiogenic shock

Systolic blood pressure (mmHg)	Low, usually <90
Cardiac index (L/min/m^2)	<2.2
Cardiac power output (W)	Low
Pulmonary capillary wedge pressure (mmHg)	>18
Diuresis	Low
Hypoperfusion of end organs	Yes

Abbreviation: Bpm, beats per minute. Cardiac power output is calculated as mean arterial pressure*cardiac output/451. A cardiac power output ≤0.53 has been demonstrated to be a predictor for in-hospital mortality (c-statistic 0.69).(72)

David R. Holmes Jr: "A crucial aspect in CS is the extraordinarily high early mortality; this is balanced however in those patients who survive the initial hospital stay out to 30 days that the prognosis then becomes similar to that of other patients experiencing acute myocardial infarction who do not have shock. An essential tenet is that we must make urgent efforts to

Figure 1. Kaplan-Meier event curve of cardiogenic shock patients treated with intra-aortic balloon pump counterpulsation – analysis of 30-day survivors. This curve demonstrates long-term estimated all-cause mortality of 30-day survivors of intra-aortic balloon pump counterpulsation (n=222). Despite the known high in-hospital mortality for CS patients treated with IABP counterpulsation, 10-year estimated survival of 30-day survivors was 41%. The slope of the reference line (y=0.042*x+0.14) represents a mean annual mortality rate beyond the first year of 4.2%.

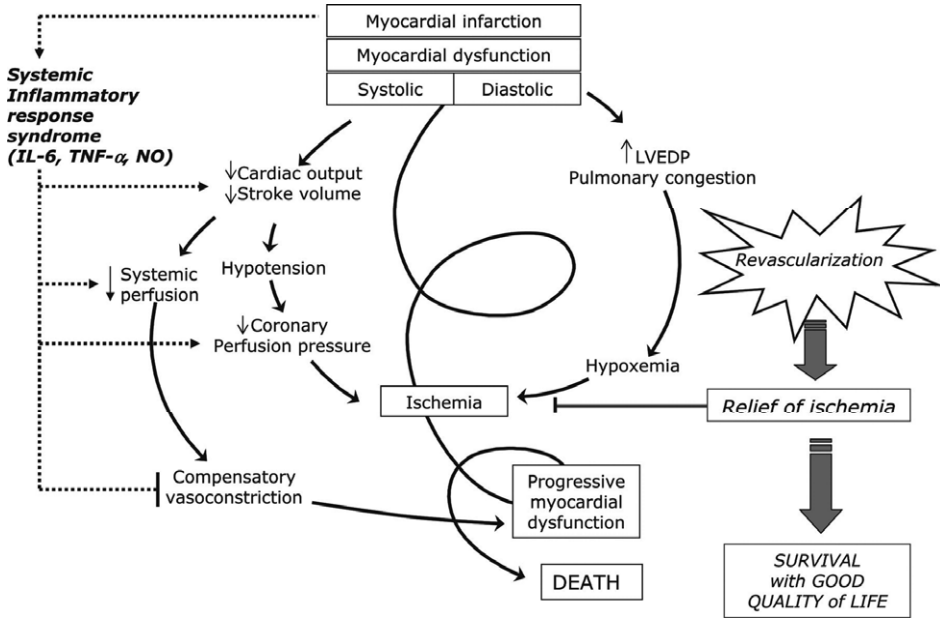


"tide" these shock patients over during the early phase of their illness so that they can have improved longer term outcome."

ANATOMY AND PATHOPHYSIOLOGY

Most patients (about 65%) presenting with acute myocardial infarction complicated by CS have 3-vessel coronary artery disease on coronary angiography.(6, 7) In most cases, the left main coronary artery or the left anterior descending artery is identified as the culprit lesion.(8) It has been accepted for years that CS is caused by a decrease of cardiac output due to cardiomyocyte dysfunction. When cardiac output, and thus systemic blood flow, acutely decreases, compensatory redistribution of blood volume (partly by active venoconstriction) results in a decrease in peripheral vascular capacitance, thereby increasing cardiac filling pressures and cardiac output. In the classic paradigm of CS, outlined above, the depression of cardiac output after acute myocardial infarction also causes intense arteriolar vasoconstriction, in response, resulting in elevation of systemic vascular resistance, thus increasing coronary perfusion pressure.(9) (Figure 2). Normalization of hemodynamic parameters is 1 of the main objectives in the treatment of CS.

Figure 2. Pathophysiology of cardiogenic shock. The classic notion on the pathogenesis of cardiogenic shock is shown in continuous arrows. Myocardial dysfunction causes a decrease in cardiac output and mean arterial pressure. An increase in afterload due to compensatory arteriolar vasoconstriction further contributes to myocardial dysfunction. Systemic inflammation modulates these compensation mechanisms, but may also (further) contribute to impaired tissue microcirculation. Copied from Reynolds and Hochman with permission of the publisher.(54)



PHARMACOLOGIC TREATMENT OF CARDIOGENIC SHOCK

Pharmacologic treatment aims at improving symptoms and at stabilizing the hemodynamic condition to warrant sufficient oxygen delivery at the cellular level. To reach these objectives, normalization of atrial and ventricular filling pressures and optimization of cardiac index are important goals in the treatment of CS. The Forrester classification, based on cardiac index (CI) and pulmonary capillary wedge pressure (PCWP) may still be helpful to guide pharmacologic treatment in CS after mechanical complications have been excluded by echocardiography (Figure 3).(10) In general, several vasoactive pharmacologic agents can be administered after achievement of adequate preload, of which vasodilators (in patients with PCWP >18 mm Hg, CI <2.2 L/min/m^2 and MAP >60 mm Hg) and inotropic agents (PCWP >18 mm Hg, CI <2.2 L/min/m^2 and MAP <60 mm Hg) are discussed below (Table 2).

Vasodilators

Guidelines recommend the use of vasodilators, including nitroglycerin, nitroprusside, or nesiritide, preferably instead of inotropic agents and in addition to diuretics to achieve hemodynamic and symptomatic improvement in patients with elevated filling pressures and a low CI.(3, 11) However, because CS patients have hypotension by definition and because vasodilators may

Figure 3. Forrester classification. Classification of heart failure based on the levels of cardiac index and pulmonary capillary wedge pressure (PCWP). The way of treatment (presented in italic) is still based on this classification. Although vasodilators are the first choice of treatment, a low mean arterial pressure may require administration of inotropic agents or vasopressors.

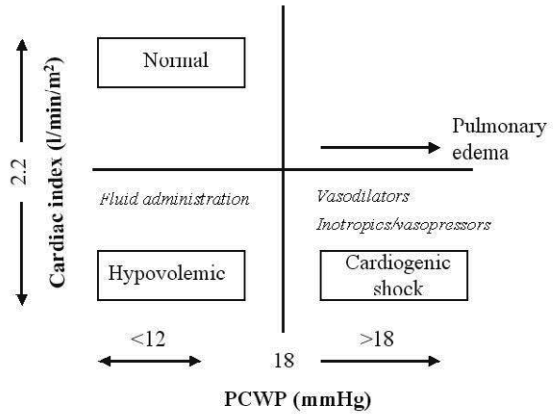


Table 2. Most important classes of intravenously administered pharmacologic agents in cardiogenic shock – Effects on hemodynamic parameters and human study outcomes

	CI	PCWP	MAP	Major trials	Control group	Primary result
Vasodilators						
Nitroglycerin	↑	↓	↓	-	-	-
Nitroprusside	↑	↓	↓↓	Mullens et al. (23)	Conventional therapy	Improvement in hemodynamic measurements ↑ All-cause mortality ↓
Nesiritide	↑	↓	↓	-	-	-
Catecholamines						
Norepinephrine	↑/-/↓*	↑	↑↑	-	-	-
Dopamine	↑	-/↑*	↑	Mueller(73)	-	Cardiac performance ↑ Myocardial oxygen demand ↑
Dobutamine	↑	↓	=	Keung et al.(74) Francis et al.(75)	Dopamine + nitroprusside Dopamine	Hemodynamic benefits = Stroke index and cardiac index increase ↑ PCWP increase ↓
PDE inhibitors						
Enoximone	↑	↓	↓	Caldicott et al.(76)	Dobutamine	Arrhythmias ↓
Milrinone	↑	↓	↓	Seino et al.(77) Loh et al. (78)	Placebo Nitroglycerin	CI ↑, PCWP ↓ Increase in CI ↑ Decrease in PCWP ↓
Ca^{2+}-sensitizers						
Levosimendan	↑	↓	↓	SURVIVE(34) Fuhrmann et al. (35)	Dobutamine Enoximone	180-day mortality = 30-day survival ↑

Abbreviations: CI, cardiac index; PCWP, pulmonary capillary wedge pressure; MAP, mean arterial pressure; PDE, phosphodiesterase.
* Effect depends of dosage. =, equal; ↓, significantly lower or less relative to control; ↑, significantly higher or greater relative to control.

significantly reduce mean arterial pressure, these agents are usually not indicated as monotherapy in the early treatment of CS.

Nitroglycerin is a nitric oxide (NO) donor that is frequently administered intravenously in patients with cardiogenic shock in whom arterial blood pressure has been restored.(12) At low dosages, nitroglycerin primarily dilates venules, resulting in a reduction in cardiac filling pressures, which increases the pressure gradient for myocardial perfusion and decreases myocardial oxygen demand.(13, 14) At higher dosages, nitroglycerin increases cardiac output by reducing left and right ventricular afterload.(15) Recent studies showed that low-dose nitroglycerin, on top of concomitant therapy, improves tissue microcirculation in patients with shock.(16, 17) However, current administration of nitroglycerin is merely based on consensus than on randomized trials incorporating strong endpoints such as mortality.(18) Clinical difficulties include nitrate resistance in heart failure patients as well as nitrate tolerance, which may develop within several hours after initiation of therapy.(19-21)

Sodium nitroprusside is a balanced arterial and venous vasodilator which acts by production of nitrosothiol in the vasculature, which in turn generates cyclic guanosine monophosphate in vascular smooth muscle and evokes relaxation.(22) This agent is currently only recommended in patients with heart failure in whom afterload is severely increased, such as hypertensive heart failure.(3) A recent nonrandomized study reported a beneficial effect of nitroprusside on in-hospital survival in patients with low-output acute heart failure(23). This promising finding should be confirmed in a randomized controlled trial.

Nesiritide is a novel recombinant B-type natriuretic peptide with vasodilatory effects that, in contrast with the United States, is not available for the European market. Several randomized controlled trials have reported a beneficial effect of nesiritide on hemodynamic parameters in patients with acute heart failure, but the agent has not been tested in CS.

Inotropic agents

Inotropic agents are frequently administered as continuous infusion to patients with CS to improve the hemodynamic profile; more specifically to increase cardiac output, to decrease PCWP, and to increase MAP. If possible, these agents may be given in addition to diuretics and vasodilators at optimal dosages.(3) Several classes of inotropic agents exist (ie, catecholamines, phosphodiesterase inhibitors, and Ca^{2+}-sensitizers). Most important agents in those classes are listed in Table 2.

Catecholamines stimulate cardiac beta-receptors, which increases heart rate and cardiac output. Some beta-sympathicomimetics have a high affinity for alfa-receptors and act as vasopressors (ie, dopamine in high doses, norepinephrine, and epinephrine). Catecholamines have been used for years in the treatment of CS. Although catecholamines generally improve the hemodynamic profile and have an important role in the early stabilization of patients with CS, one has to realize that increased contractility induced by inotropic agents has been associated with increased myocardial oxygen demand and cardiac arrhythmias.(24)

Phosphodiesterase inhibitors increase contractility by inhibiting the cAMP-specific phosphodiesterase activity; this indirectly increases cAMP levels which, in turn, increases contractility.(25) Phosphodiesterase inhibitors are inodilators, because they also have a vasodilator action. Potential benefits of phosphodiesterase inhibitors compared to catecholamines may be the minimal chronotropic and arrhythmogenic effects without a substantial increase in myocardial oxygen demand.(26, 27) An important disadvantage of this class is the relatively long half-life, especially in patients with renal dysfunction.

The inodilator levosimendan is a relatively new agent that also has positive lusitropic effects. Levosimendan may be considered in CS patients.(3) Several randomized trials have demonstrated that levosimendan is superior to dobutamine regarding improvement of hemodynamic parameters and renal function in patients with CS.(28-33) Levosimendan was recently compared to dobutamine in patients with acute decompensated heart failure.(34) This trial, called Survival of patients with acute heart failure in need of intravenous inotropic support (SURVIVE), failed to demonstrate a significant difference in all-cause mortality at 180 days between both groups. Because CS patients were not included in the SURVIVE trial, a recent small single-center trial compared levosimendan with enoximone added to current therapy (i.e. revascularization, IABP, and other inotropes) in 32 patients with refractory CS.(35) Survival rate at 30 days was significantly higher in the levosimendan-treated group compared with the enoximone group (69% vs. 37%, p=0.02). In view of the negative results from SURVIVE and bearing in mind that a randomized head-to-head comparison of vasoactive drugs in critically ill patients with small case numbers in both groups remains a great challenge, final conclusions from this study have to be drawn very carefully. The promising findings should be confirmed in a larger, preferably multi-center study.

MECHANICAL SUPPORT OF THE FAILING HEART

IABP counterpulsation has become an important component of the treatment of patients with CS who do not respond adequately to standard treatment.(3) However, the efficacy of IABP counterpulsation in patients with CS has not been evaluated in an adequately powered randomized controlled trial. Evidence for its efficacy was mainly derived from either post-hoc analyses of randomized trials, which investigated revascularization strategies, or from registries. First, post-hoc analysis of the GUSTO-I-database demonstrated that unadjusted 1-year mortality in patients presenting with CS treated with IABP counterpulsation was lower as compared to those who did not receive an IABP (57% vs. 67%, respectively, p=0.04).(36) However, IABP-patients were significantly more treated with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), which hinders interpretation of the results. Second, Sanborn et al. used the data from the Should we emergently revascularize occluded coronaries for cardiogenic shock (SHOCK)-trial registry to investigate whether patients treated with IABP

and thrombolytic therapy had a lower mortality compared to patients who were treated with thrombolytic therapy alone.(37) More than 800 CS patients were evaluated in this study and it was found that those selected for IABP had lower in-hospital mortality than those who did not receive IABP (50% vs. 72%, respectively, p<0.0001). In addition, patients who received IABP and thrombolytic therapy had lower in-hospital mortality (47%) than those receiving IABP alone (52%), only thrombolytic therapy (63%), or neither (77%, p<0.0001). However, once again, revascularization rates were higher in patients treated with IABP, which might have biased the better outcome. Finally, National Registry of Myocardial Infarction **(**NRMI) investigators reported outcomes of 23,180 CS patients.(38) IABP was used in 7,268 (31%) patients. Treatment with IABP was associated with a significant reduction in in-hospital mortality rates in patients who received thrombolytic therapy (67% vs. 49%). After multivariate analysis, IABP use remained significantly associated with in-hospital survival (OR 0.82; 95% CI 0.72-0.93). However, IABP use was not associated with any mortality benefit in patients treated with primary angioplasty. Recent guidelines advised IABP counterpulsation in each patient with cardiogenic shock caused by an acute coronary syndrome (class of recommendation I, level of evidence C).(3)

Besides IABP support, ventricular-assist devices (VADs) can be considered in patients with CS refractory to standard therapy.(3) However, emergency surgical left ventricular-assist device (LVAD) placement in CS patients has been associated with significant morbidity and mortality.(39) Recently, percutaneous ventricular assist devices (PVAD) have become available that can be used as a bridge to surgical LVAD and/or heart transplantation in selected cases. Idelchik et al. treated 18 patients in severe refractory CS with a TandemHeart (CardiacAssist, Inc. Pittsburgh, PA) PVAD.(40) Fourteen of these patients were successfully bridged to LVAD or heart transplantation. Mortality rate was 27% at 30 days and 33% at 6 months. Two randomized studies have compared the TandemHeart with IABP counterpulsation. Burkhoff et al. randomized 42 patients and found no difference in overall 30-day survival and severe adverse events, despite a significant improvement of hemodynamic parameters in the TandemHeart group.(41) Thiele et al. randomized 41 patients with CS to either IABP or TandemHeart support. Although it was observed that cardiac power index (the primary outcome measure) was higher in the VAD group, TandemHeart support was associated with a higher complication rate, whereas 30-day mortality was similar (45% in IABP group and 43% in VAD group).(42) A second promising PVAD is the Impella (Abiomed Europe, Aachen, Germany) device, which efficacy in CS has to be investigated more comprehensively.(43) In summary, results from VAD studies are encouraging, but larger-scale studies are required to assess the effects of improved hemodynamics by VADs on survival.

David R. Holmes Jr: "Given the urgent need to support patients with cardiogenic shock early on, it has been somewhat puzzling that newer devices that provide better hemodynamic support have not impacted on the outcome. As the authors point out, however, the number of patients studied to date has been rather meager. In addition, these devices may have associated unique complications, which could offset a small improvement in mortality."

THE IMPORTANCE OF EARLY REVASCULARIZATION THERAPY IN MYOCARDIAL INFARCTION COMPLICATED BY SHOCK

Because the most important cause of CS is acute myocardial infarction, it has been suggested that early revascularization, using percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery, could improve survival in patients with acute myocardial infarction complicated by cardiogenic shock. This hypothesis was tested in the landmark SHOCK trial that prospectively included 302 patients who developed CS within 36 hours or less after acute myocardial infarction. Patients were randomized to initial medical stabilization versus coronary revascularization with PCI or CABG within 6 hours after randomization. Although early revascularization did not significantly reduce all-cause mortality at 30 days, improved survival was observed after six months as well as during long-term (six years) follow-up.(6, 44) The benefit on survival was also reported for patients with CS who were immediately transferred to hospitals with emergency revascularization capability.(45) In addition to these data, the aforementioned NRMI survey included 25,311 CS patients and demonstrated that primary PCI was associated with decreased odds of death during hospitalization (OR 0.46; 95%CI 0.40-0.53).(46) Accordingly, revascularization by emergency PCI or CABG is advised in the current guidelines for patients with an acute coronary syndrome complicated by cardiogenic shock.(3, 47)

Revascularization in the multicenter SHOCK trial could be percutaneous or surgical, determined by site investigators. One-year survival was similar in PCI-treated patients compared to patients who underwent CABG.(48) However, in clinical practice, more than 60% of patients with an acute coronary syndrome complicated by CS are currently treated with PCI, which is a rapid procedure, whereas CABG is performed in less than 5% of the cases.(49) Patients with mechanical complications of acute myocardial infarction should immediately undergo surgery, but it is currently unclear whether CABG is better than PCI in patients with three-vessel or left main stem coronary artery disease.

David R. Holmes Jr: "The issue of early revascularization therapy is well explored by the authors. It is of interest that the primary endpoint of the SHOCK trial was indeed negative. It was not until later outcomes were tabulated that survival was found to be improved with revascularization. Certainly, revascularization is a mainstay of therapy for these patients."

SHORT-TERM MORTALITY IN CARDIOGENIC SHOCK REMAINS EXCEPTIONALLY HIGH

Although early revascularization has contributed to an improved prognosis of CS patients in the last decade, in-hospital mortality remains over 50% in most studies.(50) NRMI data demonstrated that all-cause in-hospital mortality in CS patients decreased from 60.3% in the year

1995 to 47.9% in the year 2004 (p<0.001).(46) Using the SHOCK trial registry, Fincke et al. found that cardiac power output and cardiac power index were the most important independent hemodynamic correlates of in-hospital mortality.(51)

THE PATHOPHYSIOLOGY OF CARDIOGENIC SHOCK ALSO INVOLVES BLOOD VESSELS

It has been accepted for years that CS is caused by a decrease of cardiac output. In this classic concept of CS, it is obvious that normalization of hemodynamic parameters is one of the main objectives in the treatment of CS. However, it has been shown that 45% of nonsurvivors of CS die with a normal cardiac index (ie, >2.2 L/min/m^2), indicating that optimization of macrohemodynamic parameters alone may fail to save the patient.(52) In line with these data, post-hoc analysis of data from the SHOCK-trial demonstrated that the classic notion of systemic vasoconstriction did not apply to all patients with CS, as demonstrated by a enormous variability in CI and systemic vascular resistance among patients, with median systemic vascular resistance during CS in the normal range, even despite vasopressor therapy.(53) These data have changed the concept of CS from being only a cardiac problem into a disease of derangements in the entire circulatory system.(54) It is currently accepted that myocardial infarction and heart failure can cause the systemic inflammatory response syndrome (SIRS), which is characterized by the release of inflammatory mediators and neurohormones as well as alterations in tissue microvasculature, which may result in multi-organ dysfunction syndrome.(54-58) The level of SIRS may interfere with classically known responses of the body to shock(55) (Figure 2). Several studies have reported that markers of SIRS and impaired tissue perfusion are predictive of short-term mortality in cardiogenic shock. These makers included impaired skin perfusion, elevated lactate concentrations, elevated interleukin-6 plasma concentrations, metabolites in arginine and NO pathways, renal dysfunction, and impaired sublingual microvascular blood flow.(58-63) In addition, it has been postulated that inappropriate vasodilation and thus inadequate perfusion at the micro-vascular level might play an important role in the pathogenesis of multiple organ failure and the persistence of shock.(64, 65) Inappropriate vasodilation may occur during systemic inflammation of the body due to a high production of nitric oxide by nitric oxide synthase (NOS). Accordingly, strategies were developed to inhibit NOS in patients with shock. Small studies indeed demonstrated that NOS inhibition improved blood pressure in patients with cardiogenic shock.(66-68) Next, the TRIUMPH-trial was designed to test whether administration of tilarginine, a nonselective NOS-inhibitor, would improve 30-day survival in patients with myocardial infarction complicated by cardiogenic shock. Enrolment of patients was recently terminated at 398 patients based on a lack of efficacy. There was no difference in 30-day all cause mortality between patients who received tilarginine (48% died) and placebo (42% died, risk ratio 1.14: 95% CI 0.92-1.41).(69)

David R. Holmes Jr: "A fascinating feature that has been increasingly well recognized is that "45% of nonsurivors of CS die with a normal cardiac index (ie, >2.2 L/min/m^2)." There are many things that are unknown about this observation. Perhaps that is why the advanced hemodynamic support devices have so far not been found to be beneficial. As the authors point out, new approaches are needed urgently."

THE ROLE OF TISSUE MICROCIRCULATION IN THE PATHOGENESIS OF CARDIOGENIC SHOCK

The importance of intensive treatment in the acute phase of CS has been outlined above. The negative results of TRIUMPH(69) demonstrated that the pathophysiology of vascular involvement in CS is not completely understood. In fact, microvascular dysfunction in CS may vary over time and among patients. Several investigators have reported direct measurements of tissue microcirculation in CS patients. Using venous air plethysmography, Kirschenbaum and co-workers measured forearm blood flow in patients with CS before and after arterial occlusion. The authors reported an attenuated microcirculatory response during reactive hyperemia, which indicates an impaired capacity for vasodilation.(70) In addition, De Backer et al. measured sublingual microcirculation in patients with cardiogenic shock, using a 2D imaging technique called orthogonal polarization spectral imaging.(58) These investigators reported a decreased proportion of functional capillaries in patients with CS relative to patients with acute heart failure and control patients who were examined before cardiac surgery (49% vs. 63% vs. 92%, respectively, $p<0.001$). These alterations in microcirculatory blood flow correlated to ICU mortality. Time course of microcirculatory alterations during CS was not clear from this study and it is still unclear whether microcirculatory alterations can be improved by vaso-active agents and, if the case, whether this has a favourable effect on survival. Additional research is necessary to understand the nature and mechanisms of impaired tissue perfusion more comprehensively, and how this can be measured and monitored at the bedside. In addition, the effects of vasoactive agents at the microcirculatory level are frequently unpredictable in individual patients. In fact, adequate tissue perfusion (ie, blood flow instead of pressure) should be an ultimate treatment objective in CS.

David R. Holmes Jr: "The role of tissue microcirculation has been accorded increasing importance. The concept of "functional capillaries" needs further study. As the authors point out, it is adequate tissue perfusion rather than maintenance of more normal arterial pressure that is a crucial determinant of outcome."

NOVEL APPROACHES TO IMPROVE TISSUE PERFUSION

Recently, new techniques were introduced to investigate tissue microcirculation at the bedside. These techniques include laser-Doppler flowmetry, near-infrared spectroscopy and Sidestream Dark Field imaging.(55, 71) It is expected that these novel monitoring devices may provide more knowledge on the pathophysiology of cardiogenic shock and its response to pharmacologic treatment.(71) Using orthogonal polarization spectral imaging, Spronk et al. measured a significant improvement in capillary blood flow after intravenous nitroglycerin administration in critically ill patients with severe sepsis.(16) Research on CS related to this topic is still in its premature stages. The novel imaging techniques might be used as future tools to target vasoactive therapy more accurately to patients, thereby making significant savings by more tailored therapy. Such an approach might lower the still dramatic in-hospital mortality rate of patients and aid patients through the critical acute phase of CS.

CONCLUSIONS

CS is a life-threatening state of tissue hypoperfusion, and short-term mortality is still very high despite an increasing number of monitoring tools and treatment modalities. Pharmacologic treatment of patients with CS has not changed substantially in the last decades. Although novel pharmacologic agents were introduced and demonstrated to improve hemodynamic parameters in patients with CS, results from almost all randomized trials incorporating clinical endpoints were either negative or inconclusive. The overwhelming amount of negative studies in the area of critical care is a major problem, which might be due to disease complexity, patient heterogeneity, and lack of statistical power. Early primary revascularization has significantly improved the prognosis of CS patients. The efficacy of intra-aortic balloon pump counterpulsation in cardiogenic shock has not been proven by means of randomized clinical trials, but there is general agreement that this treatment modality is beneficial. Results from VAD studies in selected patients are promising, but we have to wait for further data, taking into account the costs and adverse events of these highly specialized treatment techniques. However, aggressive support of the failing heart in the acute phase of cardiogenic shock is considered of utmost importance, partly because long-term prognosis of patients with cardiogenic shock is not worse compared to the prognosis of patients with myocardial infarction without shock. New approaches like therapy directed by and targeted to microcirculatory imaging parameters may possibly result in a better survival of CS patients. This will be the challenging subject of future studies.

David R. Holmes Jr: "Cardiogenic shock continues to account for the highest mortality in patients with myocardial infarction who survive to hospitalization. Given the morbidity and

mortality associated with shock, there have been intensive efforts to evaluate pathophysiologic mechanisms involved to identify risk stratification algorithms and develop new treatment strategies. The current article reviews these efforts in substantial detail. While there are many take-home messages, several stand out, as follows: (1) cardiogenic shock continues to be a highly lethal event, (2) somewhat surprisingly, a substantial number of nonsurvivors of cardiogenic shock die with a relatively preserved cardiac index, (3) in those patients who survive shock, the long-term outcome is favorable and similar to patients with infarction who do not develop shock, (4) revascularization is an essential component of care, and (5) there is still much that we do not know."

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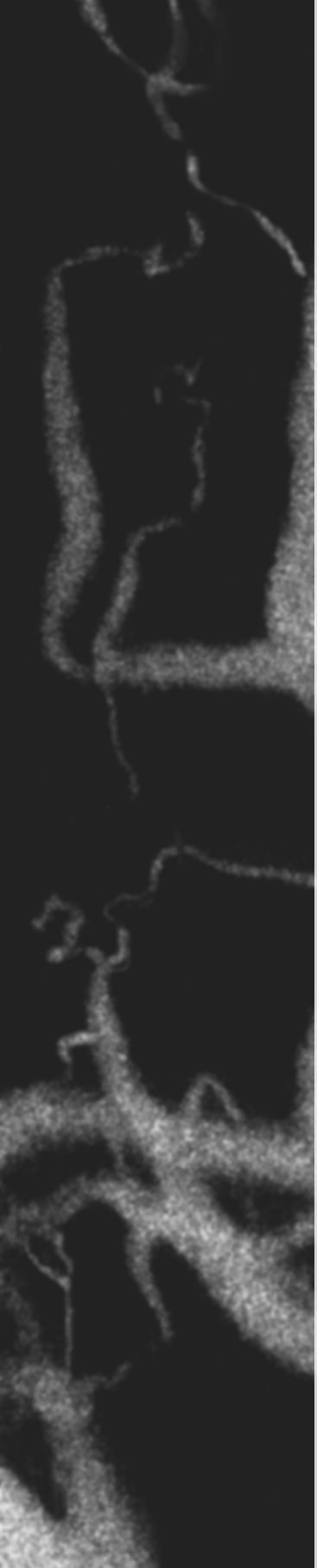
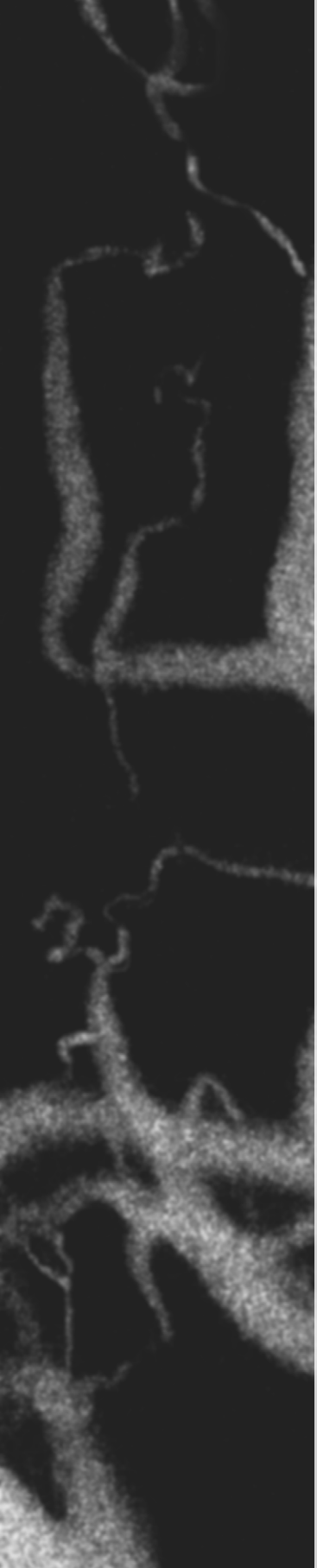


Part D

Approaches to influence the microcirculation



Chapter 11

Low-dose nitroglycerin improves microcirculation in hospitalized patients with acute heart failure

Corstiaan A. den Uil, Wim K. Lagrand, Peter E. Spronk, Martin van der Ent, Lucia S.D. Jewbali, J. Jasper Brugts, Can Ince, Maarten L. Simoons

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ABSTRACT

Aims: Impaired tissue perfusion is often observed in patients with acute heart failure. We tested whether low-dose nitroglycerin (NTG) improves microcirculatory perfusion in patients admitted for acute heart failure.

Methods and results: In 20 acute heart failure patients, NTG was given as intravenous infusion at a fixed dose of 33 µg/min. Using Sidestream Dark Field (SDF) imaging, sublingual microvascular perfusion was evaluated before (T0, average of two baseline measurements) and 15 minutes after initiation of NTG (T1). In a subgroup of 7 patients, SDF measurements were repeated after NTG had been stopped for 20 min. Capillaries were defined as microvessels with a diameter of <20 µm. Perfused capillary density (PCD) was determined as the parameter of tissue perfusion. Values are expressed as median and inter-quartile range [P25; P75]. The median age of the subjects was 60 [52; 73] years and 65% were male. Patients were stable before starting NTG. Nitroglycerin decreased central venous pressure (17 [13;19] mmHg at T0 vs. 16 [13;17] mmHg at T1, p=0.03) and pulmonary capillary wedge pressure (23 [18;31] mmHg at T0 vs. 19 [16;25] mmHg at T1, p=0.03). It increased PCD (10.7 [9.9;12.5] $mm.mm^{-2}$ at T0 vs. 12.4 [11.4;13.6] $mm.mm^{-2}$ at T1, p=0.01). After cessation of NTG, PCD returned to baseline values (p=0.04).

Conclusion: Low-dose NTG significantly reduces cardiac filling pressures and improves microvascular perfusion in patients admitted for acute heart failure.

INTRODUCTION

Patients with acute heart failure are haemodynamically compromised, and are at risk for impaired perfusion of organs and tissues. Cardiac filling pressures as well as lactate levels are often elevated whereas mixed venous oxygen saturation is low. Various drugs, including nitroglycerin (NTG), may be given to stabilize patients clinically, to normalize filling pressures, and to optimize perfusion to vital organs.(1) However, global haemodynamic and laboratory measurements may severely underestimate local tissue hypoperfusion, i.e. the imbalance between tissue oxygen delivery and oxygen consumption.(2) Novel two-dimensional imaging techniques provide direct visualization of capillaries in tissues covered by a thin epithelial layer at the bedside. Using these techniques, changes in microvascular blood flow can be analysed in patients with a variety of disease states, including acute heart failure. Impaired microvascular perfusion, as assessed by these methods, has been shown to be associated with worse intensive care unit survival.(2)

Cardiac and vascular nitric oxide (NO) bioavailability is reduced in heart failure, contributing to contractile dysfunction, ventricular hypertrophy, and remodelling, as well as endothelial dysfunction.(3, 4) Nitrates are powerful NO donors, that are frequently administered to patients with acute heart failure.(5) Low-dose NTG administration primarily results in venodilation, thus lowering cardiac filling pressures, increasing the pressure gradient for myocardial perfusion and decreasing myocardial oxygen demand.(1, 6, 7) Recent guidelines recommended the use of vasodilators, including nitroglycerin (NTG), in order to achieve haemodynamic and symptomatic improvement.(8) However, the effect of nitroglycerin on tissue perfusion has not been studied in patients with acute heart failure. In this study, we tested the hypothesis that enhancement of NO bioavailability by intravenous administration of NTG at a fixed, low dose improves microvascular tissue perfusion in patients with acute heart failure.

METHODS

Study design

This pre-post intervention study was conducted at the Intensive Cardiac Care Unit of the Thoraxcenter, Erasmus Medical Center, the Netherlands. Twenty patients admitted with acute heart failure were included. Exclusion criteria were: (i) oral bleeding, (ii) mean arterial pressure (MAP) below 65 mmHg, and (iii) acute right ventricular myocardial infarction.

In addition, 20 age-matched patients without heart failure, who were evaluated 1 day before undergoing coronary artery bypass grafting,(9) served as controls for the baseline measurements only. Nitroglycerin was given to the patients for study purposes. The institutional Ethics Committee approved the protocol, and written informed consent was obtained from each patient or, in case of patients who were sedated, from a relative authorized to consent on behalf of such a patient.

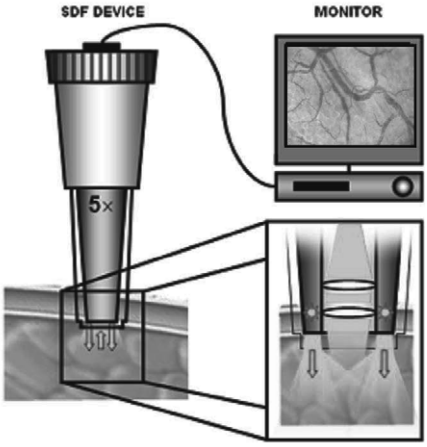
Haemodynamic monitoring

Patients were monitored with a radial artery catheter (arterial cannula with FloSwitch, Ohmeda, Swindon, UK). Ten patients were monitored with a pulmonary artery catheter (PAC: Becton Dickinson Criticath SP5107H, Sandy, UT, USA). In the other 10 patients, central venous pressure (CVP) was measured via a three-lumen central venous catheter (Multicath; Laboratoires Pharmaceutiques Vygon, Ecouen, France), inserted into the right internal jugular vein. In these patients, cardiac index (CI) was calculated according to the Cuschieri formula, which shows close correlation with the cardiac index measured with a PAC.(10) Data collection included central body temperature, heart rate (HR), MAP, CVP, pulmonary capillary wedge pressure (PCWP), mean pulmonary artery pressure (PAP), CI, systemic vascular resistance (SVR), lactate level and mixed-venous oxygen saturation (SvO_2).

Microcirculatory assessment and analysis

The Sidestream Dark Field (SDF) imaging device (MicroScan; Microvision Medical, Amsterdam, The Netherlands) was used to obtain two-dimensional video images of sublingual microcirculatory blood flow (Figure 1). This technique has been described and validated previously.(11, 12) In short, the camera emits green light that is absorbed by red blood cells within microvessels. In this way, red blood cells are used as the contrast agent to visualize sublingual blood flow in patent microvessels. This is the reason why oral bleeding was an exclusion criterion for the study. Three to five steady video sequences of at least 20 seconds duration, were obtained, stored and analyzed by an investigator blinded to the patient's diagnosis and therapy. Quantification

Figure 1. Sidestream Dark Field imaging setup. Video frames of the sublingual microcirculation were acquired using a Sidestream Dark Field (SDF) imaging device (left) and captured on a computer (upper right). In the SDF device a central light guide is surrounded by, but isolated from concentrically placed light emitting diodes that stroboscopically emit green light for illumination. This green light is absorbed by erythrocytes flowing through the tissue under investigation. The haemoglobin is actually used as the contrast agent, so that red blood cells are imaged as dark moving globules against a white/grayish background. This implies that intravascular erythrocytes rather than microvessel walls are visualized.



of the images was performed using software (AVA 3.0, MicrovisionMedical, Amsterdam, the Netherlands). Perfused capillary density (PCD) was calculated by measuring the total length of perfused capillaries divided by the image area. As SDF imaging enables visualization of flowing intravascular erythrocytes rather than microvessel walls, an increase in PCD was regarded as capillary recruitment. Capillaries were defined as microvessels with a diameter <20 µm.

Study protocol

To minimize the effect of regression to the mean due to spontaneous variation in microcirculatory perfusion, two baseline measurements were performed with a time interval of 15 min. Perfused capillary densities from both baseline measurements were averaged to produce one baseline value (T0). After the second baseline measurement, NTG was given as a bolus equal to the volume of the particular intravenous line (i.e. a volume of <2 mL). Immediately thereafter, a continuous intravenous infusion of NTG at a fixed dose of 33 µg/min was started. After 15 min, the microcirculation was assessed again (T1). In the second part of the study, we also investigated whether the observed changes in microcirculatory flow were reversed by discontinuation of the NTG infusion. Hence, in 7 patients, the measurements were repeated after the NTG infusion had been stopped for 20 min (T2). Patients did not receive NTG between hospital admission and baseline measurements. During execution of the study, ventilator settings and dosages of other intravenous medications were stable.

Statistical analysis

Categorical variables are presented as absolute number with percentage. All continuous variables are presented as median with interquartile range (IQR, [25th; 75th percentiles]). Changes over time were tested with the Wilcoxon signed ranks test. The Mann–Whitney test was used to assess differences between groups. Pearson's chi-square test was used to test the association between categorical variables.

RESULTS

Study population

Twenty patients admitted for acute heart failure were included in this study: 14 patients had new onset acute heart failure after acute myocardial infarction, and 6 patients had acute worsening of pre-existing chronic heart failure (Table 1). Median age was 60 [52;73] years, 65% were male and the median NT-proBNP level was 264 [83;641] pmol/L (reference values 0-17 pmol/L). Median central body temperature was 36.7 [34.1-37.9] °C. Twelve patients (60%) required mechanical ventilation and 9 patients (45%) were treated with at least one inotropic agent during execution of the study protocol. The median time period between hospital admission and the start of the measurements was 22 [11-29] h.

Table 1. Clinical characteristics of the study population (n=20).

Characteristic	
Age, years (median [IQR])	60 [52; 73]
Male	13 (65%)
CV risk factors:	
Hypertension	9 (45%)
Current smoking	4 (20%)
Dyslipidaemia	6 (30%)
Diabetes mellitus	5 (25%)
Diagnosis at admission:	
New onset AHF due to AMI	14 (70%)
Acute decompensation of CHF	6 (30%)
Classification of heart failure based on SBP at presentation[21]:	
Hypotensive (SBP <120 mmHg)	9 (45%)
Normotensive (SBP 120-139 mmHg)	9 (45%)
Hypertensive (SBP >140 mmHg)	2 (10%)
Left ventricular function:	
Reduced (ejection fraction <40%)	17 (85%)
Preserved (diastolic dysfunction)	3 (15%)
NT-proBNP level, pmol/L (median [IQR])	264 [83; 641]
Mechanical ventilation	12 (60%)
Intravascular cooling after OHCA	5 (25%)
IABP counterpulsation	6 (30%)
Pulmonary artery catheterization	10 (50%)
Cumulative fluid balance, mL (median [IQR])	307 [-551; 1663]
Pharmacologic therapy	
Any inotropic agent	9 (45%)
Dobutamine	6 (30%)
Dopamine	1 (5%)
Norepinephrine	2 (10%)
Enoximone	3 (15%)
ICU stay, days (median [IQR])	6 [3; 11]
Death during ICU stay	3 (15%)

Values are expressed as n (%) unless otherwise noted. Abbreviations: IQR, interquartile range; AHF, acute heart failure; AMI, acute myocardial infarction; CHF, chronic heart failure; SBP, systolic blood pressure; NT-pro-BNP, N-terminal brain natriuretic propeptide; OHCA, out-of-hospital cardiac arrest; IABP, intra-aortic balloon pump; ICU, intensive care unit.

Global haemodynamic parameters and sublingual perfused capillary density

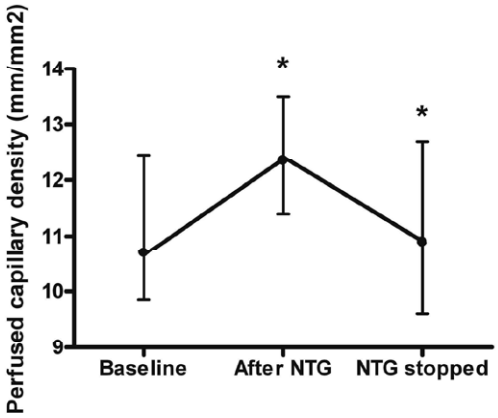
There were no significant differences in global haemodynamic or microcirculation parameters between the two baseline measurements, indicating that patients were in a stable condition before NTG was started. Averaged baseline PCD in the acute heart failure group was significantly lower compared with baseline values in control patients (10.7 [9.9-12.5] mm.mm^{-2} vs. 12.4 [12.0-13.1] mm.mm^{-2}, p=0.003). NTG infusion decreased CVP (17 [13;19] mmHg at T0 vs. 16 [13;17] mmHg at T1, p=0.03) as well as PCWP (23 [18; 31] mmHg at T0' vs. 19 [16; 25] mmHg at T1, p=0.03). Median PCD increased significantly after NTG infusion (10.7 [9.9;12.5] mm.mm^{-2} at T0 vs. 12.4 [11.4;13.6] mm.mm^{-2} at T1, p=0.01), and this effect was reversed in seven patients in whom NTG was stopped for 20 minutes (12.4 [11.4;13.6] mm^{-1} at T1 vs. 10.9 [9.6;12.7 mm^{-1}) at T2, p=0.04, Table 2 and Figure 2).

Table 2. Parameters of macro- and microcirculation at baseline and changes induced by low-dose nitroglycerin.

	T0 Averaged baseline measurements (n=20)	ΔT1-T0 After NTG (n=20)	P-value (T1 vs. T0)	ΔT2-T1 NTG stopped (n=7)	P-value (T2 vs. T1)
HR (bpm)	102 [68; 108]	+0 [-1; 3]	0.82	+0 [-3; 3]	0.75
MAP (mmHg)	81 [77; 90]	-5 [-10; 2]	0.02	+7 [-3; 12]	0.12
CVP (mmHg)	17 [13; 19]	-1 [-2; 0]	0.03	+1 [-4; 2]	0.89
PCWP (mmHg)*	23 [18; 31]	-2 [-4; -1]	0.03	+0 [-7; 4]	0.68
Mean PAP (mmHg)*	35 [29; 41]	-3 [-3; -2]	0.07	+1 [-5; 12]	0.53
CI ($L.min^{-1}.m^{-2}$)	2.2 [1.9; 3.0]	+0.1 [-0.2; 0.3]	0.70	-0.1 [-1.3; 0.0]	0.17
SVR ($dynes.sec.cm^{-5}$)	1137 [822; 1489]	-35 [-326; 83]	0.31	+8 [-60; 113]	0.48
Lactate ($mmol.L^{-1}$)	1.5 [1.0; 2.3]	+0.0 [-0.6; 0.3]	0.83	-0.3 [-1.3; 0.1]	0.20
SvO_2 (%)*	68 [56; 78]	-1[-3; +1]	0.28	+0 [0; 0]	0.29
PCD ($mm.mm^{-2}$)	10.7 [9.9; 12.5]	+1.1 [-0.3; 2.5]	0.01	-1.6 [-2.7; 0.0]	0.04

T0: averaged baseline measurements; T1: 15 minutes after initiation of nitroglycerin; T2: 20 minutes after cessation of the nitroglycerin infusion. Changes in variables between time points are depicted as delta(T..-$T_{previous\ measurement}$). All values are shown in medians [25th;75th percentiles]. Abbreviations: CI, cardiac index; CVP, central venous pressure; HR, heart rate; MAP, mean arterial pressure; PAP, pulmonary artery pressure; PCD, perfused capillary density; PCWP, pulmonary capillary wedge pressure; SvO_2, mixed-venous oxygen saturation; SVR, systemic vascular resistance. *Pulmonary artery catheterization was performed in 10 of 20 patients.

Figure 2. Change in sublingual perfused capillary density over time. Values are expressed as median and interquartile range. *P<0.05 relative to previous measurement. NTG was stopped in 7 of 20 patients.



Changes after nitroglycerin administration for responders vs. non-responders

Perfused capillary density improved in 14 patients ("responders", 70%, $\Delta PCD_{T1-T0} > 0$), whereas PCD did not improve in 6 patients ("non-responders", 30%, $\Delta PCD_{T1-T0} \leq 0$: figure 3). There were no differences in the clinical characteristics listed in Table 1 between these subgroups. Changes in global haemodynamic and microcirculatory parameters at T1 versus T0 were calculated ($\Delta\ldots_{T1-T0}$) for both responders and non-responders (Table 3). Responders had a greater decrease in central venous pressure (ΔCVP_{T1-T0}) compared to non-responders (–2 [-3;-1] mmHg vs. 0 [-1;2] mmHg, respectively, p=0.02, Table 3).

Figure 3. Change in perfused capillary density (ΔPCD) after nitroglycerin administration compared with two consecutive baseline measurements at the individual patient level. Lines represent medians. Dots depict the change in perfused capillary density (ΔPCD) between both baseline measurements and after nitroglycerin administration (i.e. T1 minus averaged baseline measurements).

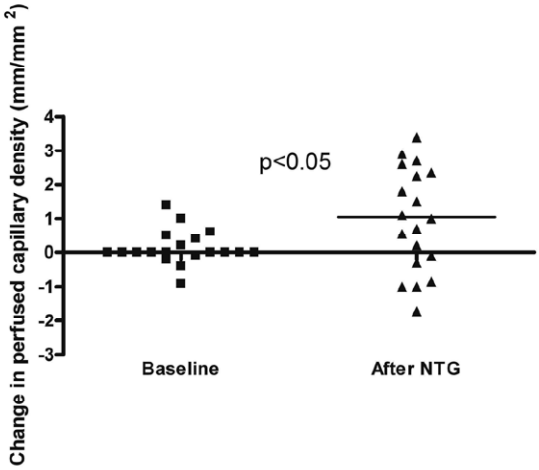


Table 3. Change in global haemodynamic and microcirculatory parameters between T1 (after nitroglycerin) and averaged baseline measurements for all subjects and both subgroups.

	All subjects (n=20)	Responders (n=14)	Non-responders (n=6)	P-value*
Δ HR (bpm)	0 [-1; 3]	0 [-1; 2]	0 [-13; 3]	0.62
Δ MAP (mmHg)	-5 [-10; 2]	-3 [-14; 2]	-5 [-9; -1]	0.97
Δ CVP (mmHg)	-1 [-2; 0]	-2 [-3; -1]	0 [-1; 2]	0.02
Δ CI (L.min^{-1}.m^{-2})	0.1 [-0.2; 0.3]	-0.1 [-0.7; 0.3]	0.2 [-0.2; 0.4]	0.31
Δ SVR (dynes.sec.cm^{-5})	-35 [-326; 83]	9 [-522; 117]	-145 [-310; 17]	0.43
Δ PCD (mm.mm^{-2})	1.1 [-0.3; 2.5]	2.0 [0.9; 2.8]	-0.9 [-1.2; -0.3]	

All values are shown in median [25th;75th percentiles]. Abbreviations: HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; CI, cardiac index; SVR, systemic vascular resistance; PCD, perfused capillary density. *Comparing improvers in perfused capillary density (responders) versus PCD non-improvers (non-responders).

DISCUSSION

This is the first study demonstrating that the NO donor nitroglycerin can increase the number of patent capillaries in patients admitted for acute heart failure. A significant increase in PCD was found after administration of low-dose, intravenous nitroglycerin at a fixed dose of 33 µg/min. In addition, we documented the venodilator effect of low-dose NTG on the pulmonary and systemic circulation. The observed improvement in microcirculation was reversed after discontinuation of NTG in the 7 patients in whom these measurements were available.

De Backer et al.(2) have shown that severe micro-vascular alterations are present in patients with acute heart failure. These alterations did not correlate to CI and probably demonstrated locally impaired tissue perfusion. The severity of these alterations was found to be associated with ICU mortality. However, the pathophysiology of an altered microcirculation in the setting

of acute heart failure is complex and not completely understood.(13) There is a critical balance between vasoconstrictor and vasodilator stimuli in patients with acute heart failure. Both compensatory vasoconstriction as a response to low cardiac output and impaired production of NO may impair tissue perfusion.(13-15) In addition, patients with acute heart failure may present with distinct clinical conditions (e.g. hypertensive heart failure or cardiogenic shock) (16, 17) and whether the severity of microcirculatory alterations and the response to therapy differs among these clinical conditions needs to be investigated.

Our data demonstrate that low-dose intravenous nitroglycerin is safe and beneficial for the microcirculation in a specific tissue away from the heart, i.e. the sublingual area. This beneficial effect was observed on top of routine therapy in a stabilized, heterogeneous population of patients admitted for acute heart failure. However, 30% of the investigated patients did not respond. To find an explanation for the lack of response in these subjects, we performed a subgroup analysis of responders versus non-responders. We found that responders had a greater decrease in CVP after NTG. The clinical response to NTG is known to be highly variable between patients; this may be explained by vascular resistance to NTG in patients with heart failure.(6, 18). Katz et al. reported a two-fold increase in femoral artery blood velocity after intra-arterial infusion of NTG in normal subjects.(19) However, this response was markedly attenuated in patients with heart failure and could be overcome only by increasing the dose, suggesting vascular resistance to NTG in patients with heart failure. This resistance to NTG has been explained by impaired enzymatic bioconversion of nitroglycerin to NO.(20) Since we gave low-dose nitroglycerin, non-responders might simply have less venodilation than responders due to an insufficient dose of NTG in those patients. Future studies might examine the response to higher doses of nitroglycerin, to nitroprusside (which releases nitric oxide by non-enzymatic means) and to hydralazine (a non-NO donor vasodilator) in order to better understand the non-responders.

Several limitations of our study should be acknowledged. The small and heterogeneous sample size limits drawing strong conclusions. Whether the beneficial effects of nitroglycerin also apply to other microvascular beds, and whether recruitment of microcirculation will reduce cellular dysfunction, organ failure and mortality in patients with acute heart failure, needs to be investigated further.

In conclusion, this is the first study demonstrating that an impaired microcirculation can be improved by a simple strategy, i.e. starting a low-dose intravenous NTG infusion. Whether dosing of vasodilator agents can be optimized by monitoring tissue microcirculation has to be investigated in future studies.

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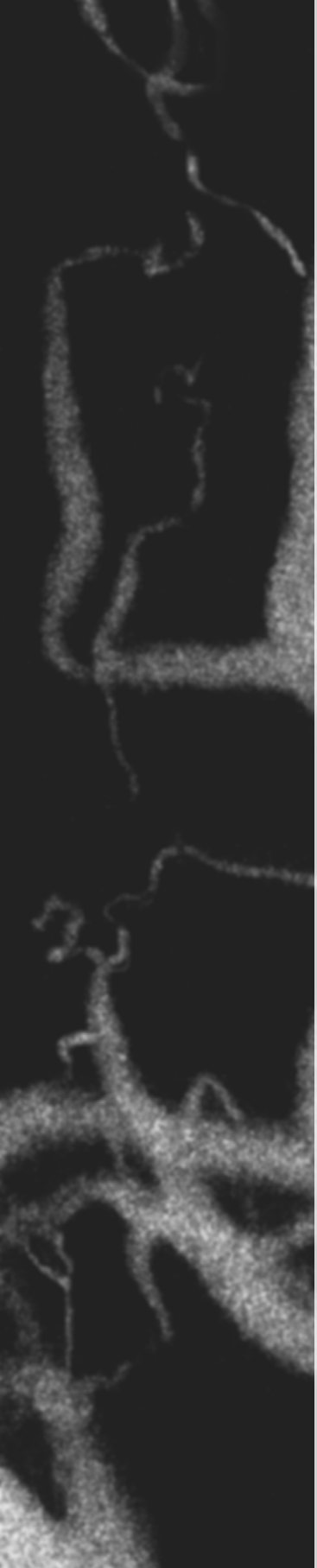

Chapter 12

Dose-dependent benefit of nitroglycerin on microcirculation of patients with severe heart failure

Corstiaan A. den Uil, Kadir Caliskan, Wim K. Lagrand, Martin van der Ent, Lucia S.D. Jewbali, Jan P. van Kuijk, Peter E. Spronk, and Maarten L. Simoons

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ABSTRACT

Introduction: Microcirculatory abnormalities are frequently observed in patients with severe heart failure and correlate to worse outcome. We tested the hypothesis that nitroglycerin dose-dependently improves perfusion in severe heart failure and that this could be monitored by measuring central-peripheral temperature gradient and with Sidestream Dark Field imaging of the sublingual mucosa.

Methods: A dose-response study was performed in 17 patients with cardiogenic shock (n=9) or end-stage chronic heart failure (n=8) admitted to Erasmus University Medical Center. We did hemodynamic measurements at baseline and during increasing infusion rates of nitroglycerin (up to a maximum dose of 133 $\mu g.min^{-1}$). As parameters of tissue perfusion, we measured central-peripheral temperature gradient (delta-T) and sublingual perfused capillary density (PCD).

Results: Nitroglycerin dose-dependently decreased mean arterial pressure ($p<0.001$) and cardiac filling pressures (both central venous pressure (CVP) and pulmonary capillary wedge pressure: $p<0.001$). It increased cardiac index ($p=0.01$). Nitroglycerin decreased delta-T ($p<0.001$) and increased sublingual PCD ($p<0.001$). Significant changes in delta-T and PCD occurred earlier, i.e. at a lower dose of NTG, than changes in global hemodynamics. Macrohemodynamic and microcirculatory responses to nitroglycerin infusion were consistent in patients with either cardiogenic shock or end-stage chronic heart failure. Changes in microcirculatory parameters occurred independently of changes in cardiac index.

Conclusions: Nitroglycerin dose-dependently increases tissue perfusion in patients with severe heart failure, as observed by a decrease in central-peripheral temperature gradient and an increase in sublingual perfused capillary density.

INTRODUCTION

In recent years, investigators have increasingly acknowledged severe heart failure and cardiogenic shock not only as a cardiac problem but also as a disease of derangements in the entire circulatory system (1, 2). Moreover, it has been found that global hemodynamic parameters do not reflect differential patterns of regional organ blood flow or compromised tissue perfusion of the splanchnic bed associated with shock states (3-10). Therefore, optimization of tissue microcirculation should be an objective of the treatment of critically ill patients (11). However, it is still largely unknown whether pharmacologic interventions do improve tissue capillary perfusion. Goal-directed manipulation of hemodynamics is the key to understanding the interventions required to reduce the morbidity and mortality associated with multi-organ and hepatorenal failure in patients with end-stage heart disease or cardiogenic shock.

Nitric oxide (NO) bioavailability is reduced in patients with heart failure, contributing to contractile dysfunction, ventricular hypertrophy and remodelling, as well as microvascular endothelial dysfunction (12-14). In addition, hypervolemia, as reflected by an elevated central venous pressure, may cause organ dysfunction (15). To overcome this clinical problem, nitrates, which are powerful NO donors and venodilators, are often given to patients with heart failure (16, 17). We recently demonstrated that, in patients with decompensated heart failure, nitroglycerin (NTG), administered at a fixed low dose, lowered cardiac filling pressures and increased sublingual perfused capillary density (PCD) (18), which is an important measure for tissue perfusion (19). However, in 30% of the patients measured in this study, the microcirculation did not respond. To investigate whether significant changes in PCD occur at the same dose as global hemodynamic changes, and to investigate the maximum response of the microcirculation to NTG, we performed the current dose-response study. We tested the hypothesis that NTG, presumably by enhancement of NO bioavailability and venodilation, dose-dependently improves tissue perfusion, as assessed by measurements of central-peripheral temperature gradient (delta-T) and sublingual PCD in patients with cardiogenic shock or end-stage chronic heart failure.

MATERIALS AND METHODS

Study design

This dose-response study was conducted at the Intensive Cardiac Care Unit and at the Heart Failure/Heart Transplant ward of the Thoraxcenter, Erasmus University Medical Center, the Netherlands. We included patients who were admitted with cardiogenic shock or end-stage chronic heart failure. Cardiogenic shock was defined as a cardiac index <2.2 $L.min^{-1}.m^{-2}$ and clinical signs of hypoperfusion (cold extremities, oliguria or altered mental state), not responsive to fluid resuscitation. The patients with end-stage heart failure were included after they

underwent right heart catheterization for screening for cardiac transplantation. Exclusion criteria were: (i) oral bleeding, (ii) mean arterial pressure below 55 mmHg, (iii) acute right ventricular myocardial infarction and (iv) severe aortic valve stenosis. In cardiogenic shock patients, nitroglycerin was given for study purposes. In chronic heart failure patients, nitroglycerin was routinely given to assess reversibility of pulmonary hypertension (i.e. mean pulmonary artery pressure >25 mmHg). The institutional ethical committee approved the protocol, and written informed consent was obtained from each patient or, in case of patients who were sedated, from a relative authorized to consent on behalf of such a patient.

Haemodynamic monitoring

Cardiogenic shock patients were monitored with a radial artery catheter (arterial cannula with FloSwitch, Ohmeda, Swindon, UK). In the other patients, arterial blood pressure was measured non-invasively. All patients were monitored with a pulmonary artery catheter (Criticath SP5107H, Becton Dickinson, Sandy, UT, USA or CCOmbo, Edwards Lifesciences, Saint-Prex, Switzerland). Macro-hemodynamic data collection included central body temperature (measured at the tip of the pulmonary artery catheter), heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), mean pulmonary artery pressure (PAP), cardiac index (CI), systemic vascular resistance (SVR), and mixed-venous oxygen saturation (SvO_2). SVR was calculated as (MAP-CVP)*80/Cardiac output.

Microcirculatory assessment and analysis

Central-peripheral temperature gradient (delta-T) was defined and calculated as the difference between central blood and skin temperature. Skin temperature was measured with a probe affixed to the dorsum of the foot under constant room temperature (temperature probe 170075; Ellab Inc., Centennial, CO, USA).

The Sidestream Dark Field (SDF) imaging device (MicroScan; Microvision Medical, Amsterdam, the Netherlands) was used to obtain 2-dimensional video images of sublingual microcirculatory blood flow. This technique has been described and validated previously (20). In short, the camera emits green light that is absorbed by red blood cells within microvessels. In this way, red blood cells are used as the contrast agent to visualize sublingual blood flow in patent microvessels. This is the reason why oral bleeding was an exclusion criterion for the study. Per time point, three steady video sequences of at least 20 s duration were obtained, stored and analyzed. Quantification of the images was performed using software (Automated Vascular Analysis 3.0, MicrovisionMedical, Amsterdam, the Netherlands) by an investigator blinded to the timing of the images. Perfused capillary density (PCD) was calculated by measuring total length of perfused capillaries divided by image area. Capillaries were regarded as perfused if they had either of the following flow classifications obtained by visual inspection: sluggish, continuous or hyperdynamic (21). Since SDF imaging enables visualization of flowing intravascular erythrocytes rather than microvessel walls, an increase in PCD was regarded as capillary

recruitment. This approach has been validated previously (22, 23). Capillaries were defined as microvessels with a diameter less than 20 µm.

Study protocol

To minimize the effect of regression to the mean due to spontaneous variation in microcirculatory perfusion, two series of baseline measurements were performed with a time interval of 15 min. PCD values from both baseline measurements were averaged to obtain one baseline value (T0). After the second baseline measurement, NTG was given as a bolus equal to the volume of the used intravenous line. Immediately thereafter, a continuous intravenous infusion of NTG was started at a dose of 8 $\mu g.min^{-1}$ for 15 min. Then, all measurements were repeated (T1). Eight micrograms per minute (i.e., 0.5 mg/h) is the lowest nitroglycerin infusion rate given in our hospital. Subsequently, the nitroglycerin infusion rate was doubled stepwise (i.e. 17 $\mu g.min^{-1}$ (T2); 33 $\mu g.min^{-1}$ (T3); 67 $\mu g.min^{-1}$ (T4); 133 $\mu g.min^{-1}$ (T5)). Each infusion rate was maintained for 30 min, which was the time period necessary to reach the intended effect (15 min) plus the time period necessary to collect all data (15 min). The nitroglycerin infusion was stopped when patients developed significant hypotension (i.e. MAP <50 mmHg). In each patient, all measurements were repeated when NTG had been stopped for 20 min (T6). During execution of the study, dosages of other intravenous medications were stable.

Statistical analysis

Categorical variables are presented as absolute numbers with percentages. Continuous variables are presented as mean ± standard deviation (SD) or as median and interquartile range (IQR), when appropriate. The one-sample Kolmogorov-Smirnov goodness of fit test was used to test normal distribution of the data. Reproducibility of the PCD measurements was defined as the standard deviation of the differences between both baseline measurements. Changes over time were tested with one-way repeated measures analysis of variance (ANOVA), followed by Bonferroni's multiple comparison tests. Comparisons between repeated measurements within subgroups were tested with two-way repeated measures ANOVA. We defined improvement of cardiac index as an increase ≥ two times the standard deviation of the differences between both baseline measurements, relative to T0. A p-value <0.05 was regarded statistically significant.

RESULTS

Study population and execution of the protocol

Seventeen patients were included in this study. Nine patients (53%) had cardiogenic shock and 8 patients (47%) had end-stage chronic heart failure and were screened for heart transplantation (Table 1). Mean age was 55 ± 12 years, 65% were male and median NT-proBNP level was 418 [204-733] $pmol.L^{-1}$ (reference values 0-17 $pmol.L^{-1}$). Mean central body temperature was

Table 1. Baseline characteristics of the study population (n=17).

Characteristic	
Age, years (mean ± SD)	55 ± 12
Gender, male	11 (65%)
Cardiovascular risk factors	
Hypertension	5 (29%)
Current smoking	3 (18%)
Dyslipidaemia	2 (12%)
Diabetes mellitus	3 (18%)
Diagnosis at admission	
Cardiogenic shock	9 (53%)
End-stage chronic heart failure	8 (47%)
Underlying disease	
Acute myocardial infarction (complicated by shock)	8 (47%)
Mitral valve disease (complicated by shock)	1 (6%)
Dilated cardiomyopathy	7 (41%)
Ischemic cardiomyopathy	1 (6%)
NT-proBNP level, $pmol.L^{-1}$ (median [IQR])	418 [204-733]
Mechanical ventilation	7 (41%)
IABP counterpulsation	4 (24%)
Pharmacologic therapy	
Any inotropic agent	9 (53%)
Dobutamine	5 (29%)
Norepinephrine	3 (18%)
Enoximone	1 (6%)

Values are expressed as n (%) unless otherwise noted.

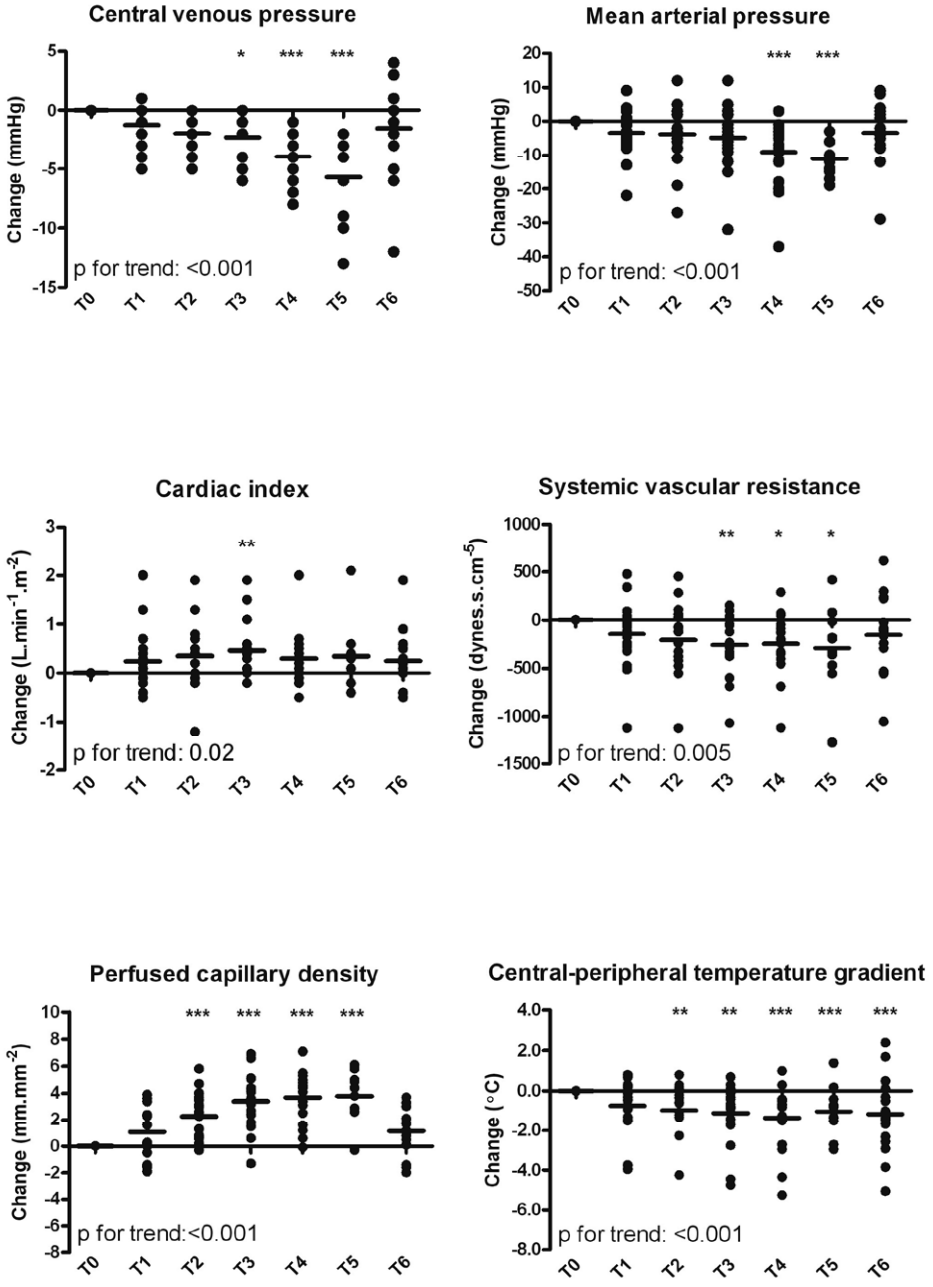
Abbreviations: SD, standard deviation; IQR, interquartile range; NT-pro-BNP, N-terminal brain natriuretic propeptide; IABP, intra-aortic balloon pump.

36.0 ± 1.7°C. All patients received NTG up to 67 $\mu g.min^{-1}$ (T4). In seven patients, the highest dose of nitroglycerin (i.e. T5) could not be given because of arterial hypotension (MAP below 50 mmHg; n=6) or pulmonary shunting and hypoxia (PaO_2 60 torr; n=1). Accordingly, the dose of 133 $\mu g.min^{-1}$ was given to ten patients.

Effects of nitroglycerin on parameters of global hemodynamics

There were no significant differences in global hemodynamic parameters between the two baseline measurements, indicating that patients were in a stable condition before NTG was started. NTG infusion decreased MAP ($p<0.001$) and cardiac filling pressures (CVP: $p<0.001$; PCWP: $p<0.001$; Table 2 and Figure 1). It increased cardiac index ($p=0.01$). Between time points T4 and T5, there were no further changes in macrocirculatory parameters. Systemic parameters returned to baseline values after cessation of NTG infusion. Haemodynamic responses to nitroglycerin infusion were consistent in patients with either cardiogenic shock or end-stage chronic heart failure.

Figure 1. Aligned dot plots demonstrating the effects of nitroglycerin at individual patient level. Each time point, changes relative to the averaged baseline measurements are shown.



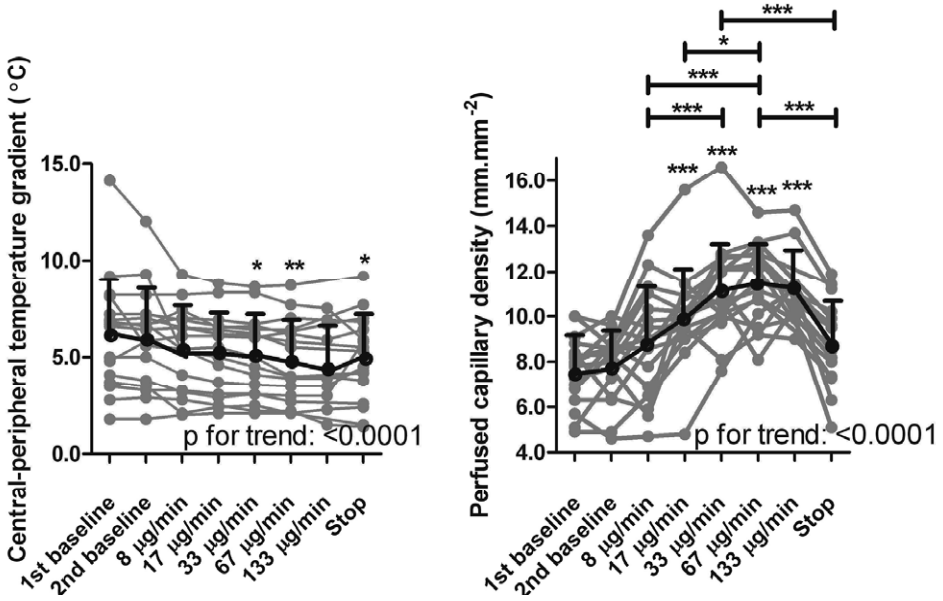
T0, averaged baseline; T1, NTG 8 µg/min; T2: NTG 17 µg/min; T3: NTG 33 µg/min; T4: NTG 67 µg/min; T5: NTG 133 µg/min; T6: NTG stopped. Lines represent means. P-values were obtained with repeated measures ANOVA, followed by Bonferroni's multiple comparison test of the specific time point compared to baseline (*, $p<0.05$; **, $p<0.01$; ***, $p<0.001$).

Table 2. Parameters of macro- and microcirculation during execution of the study protocol (n=17).

	T0 (Averaged baseline)	T1 (8 μg.min^{-1})	T2 (17 μg.min^{-1})	T3 (33 μg.min^{-1})	T4 (67 μg.min^{-1})	T5* (133 μg.min^{-1})	T6 (NTG stop)	P-value for trend
HR (bpm)	73 ± 16	72 ± 15	72 ± 15	71 ± 15	72 ± 16	74 ± 16	70 ± 13	0.08
MAP (mmHg)	78 ± 14	75 ± 14	75 ± 14	74 ± 13	70 ± 13	67 ± 15	75 ± 12	<0.001
CVP (mmHg)	11 ± 6	10 ± 6	9 ± 6	9 ± 6	6 ± 5	4 ± 3	10 ± 7	<0.001
PCWP (mmHg)	21 ± 8	18 ± 8	18 ± 8	16 ± 7	14 ± 7	13 ± 6	17 ± 7	<0.001
Mean PAP (mmHg)	31 ± 7	28 ± 6	29 ± 6	28 ± 6	24 ± 5	23 ± 5	28 ± 6	<0.001
CI (L.min^{-1}.m^{-2})	2.2 ± 0.5	2.5 ± 0.5	2.6 ± 0.6	2.7 ± 0.6	2.5 ± 0.4	2.4 ± 0.5	2.5 ± 0.5	0.01
SVR (dyne.sec. cm^{-5})	1327 ± 348	1182 ± 440	1120 ± 356	1069 ± 355	1081 ± 334	1175 ± 376	1173 ± 394	0.005
SvO_2 (%)	68 ± 9	68 ± 8	67 ± 8	67 ± 7	66 ± 7	64 ± 7	66 ± 8	0.07
Lactate (mmol.L^{-1})	1.3 ± 0.8	1.3 ± 0.8	1.3 ± 0.8	1.3 ± 0.8	1.2 ± 0.7	0.9 ± 0.4	1.3 ± 0.8	0.99
Delta-T (°C)	6.1 ± 2.7	5.4 ± 2.2	5.2 ± 2.1	5.0 ± 2.1	4.8 ± 2.1	4.5 ± 2.1	5.0 ± 2.2	<0.001
PCD (mm. mm^{-2})	7.8 ± 1.4	8.8 ± 2.5	10.0 ± 2.1	11.1 ± 2.1	11.4 ± 1.8	11.2 ± 1.7	8.9 ± 1.8	<0.001

Values represent median [interquartile range]. * Measurements were performed in 10 patients. T0, averaged baseline values; T1, NTG 8 μg.min^{-1}; T2: NTG 17 μg.min^{-1}; T3: NTG 33 μg.min^{-1}; T4: NTG 67 μg.min^{-1}; T5: NTG 133 μg.min^{-1}; T6: NTG stop. Abbreviations: HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; PAP, pulmonary artery pressure; CI, cardiac index; SVR, systemic vascular resistance; SvO_2, mixed-venous oxygen saturation; Delta-T, central-peripheral temperature gradient; PCD, perfused capillary density.

Figure 2. Individual values of microcirculatory parameters at each dose of nitroglycerin.

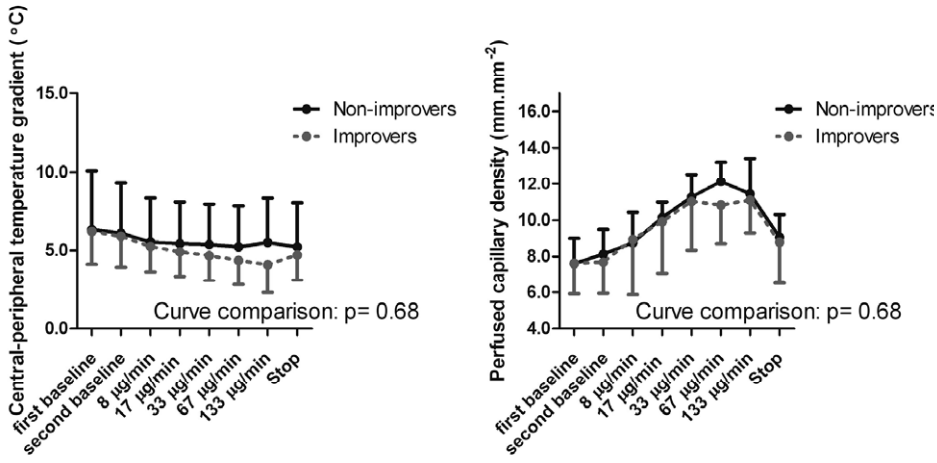


P-values were obtained with one-way repeated measures ANOVA, followed by Bonferroni's multiple comparison tests comparing all pairs of time points. Asterisks just above the upper individual line represent statistical significance vs. second baseline measurement, whereas the other asterisks represent significance between time points (*, p<0.05; **, p<0.01; ***, p<0.001). Black lines represent mean + SD.

Effects of nitroglycerin on parameters of microcirculation

There were no statistically significant differences in microcirculatory parameters between the two baseline measurements. Mean difference ± standard deviation (reproducibility) in PCD between both baseline measurements was 0.3 ± 1.1 mm.mm^{-2}. Nitroglycerin decreased delta-T ($p<0.001$) and improved sublingual PCD ($p<0.001$, Table 2 and Figure 2). Significant changes in delta-T and PCD occurred earlier, i.e. at a lower dose of NTG (T2), than changes in global hemodynamics. Between time points T4 and T5, there were no further changes in microcirculatory parameters. Mean PCD values returned to baseline after the NTG infusion had been stopped for 20 minutes, but mean delta-T values did not. Microcirculatory responses to nitroglycerin infusion were consistent in patients with either cardiogenic shock or end-stage chronic heart failure. Finally, temporal behaviour of microcirculatory parameters was not different between patients who improved in cardiac index vs those who did not improve (Figure 3).

Figure 3. Temporal behaviour of microcirculatory parameters in patients with and without improvement in cardiac index. Lines represent mean ± SD for improvers and non-improvers in cardiac index. Improvement of cardiac index was defined as an increase ≥ two times the standard deviation of the differences between both baseline measurements (i.e., 0.6 L.min-1.min-2), relative to T0. Curve comparison was performed using two-way repeated measures ANOVA.



DISCUSSION AND CONCLUSIONS

Using conventional and novel microcirculation assessment technologies, this is the first study demonstrating that the nitric oxide (NO) donor and venodilator nitroglycerin dose-dependently improves tissue perfusion, as demonstrated by a gradual decrease in temperature gradient and a progressive increase in perfused capillary density in patients with severe heart failure.

Global hemodynamics

Elkayam et al. have demonstrated the hemodynamic effects of nitroglycerin given to eight patients hospitalized for acute decompensated heart failure. These investigators up-titrated NTG to achieve a 30% or greater reduction in pulmonary capillary wedge pressure or until a maximum dose of 560 $\mu g.min^{-1}$ (24, 25). They reported a substantial reduction in right and left ventricular filling pressures, systemic vascular resistance, and systemic blood pressure, as well as an increase in cardiac index. Our study confirms those findings.

Microcirculation

We observed a significant improvement in tissue perfusion, measured by two independent parameters, i.e. delta-T and sublingual PCD. Measuring peripheral temperature is a conventional approach to assess peripheral perfusion (26), that can be used to monitor changes in tissue perfusion as also demonstrated by our study. However, the accuracy of this technique depends highly on the stability of ambient temperature (27). The novel, validated, bed-side Sidestream Dark Field imaging technique allows clinicians to directly observe blood flow in capillaries covered by a thin epithelial layer, as is the case in the sublingual area (20). De Backer et al. (6) were the first to describe sublingual microvascular alterations in patients with severe heart failure, and they found that these alterations correlated with in-hospital mortality. Our study is the first to demonstrate a progressive improvement of microcirculatory parameters following increasing rates of nitroglycerin. Due to the microcirculation's autoregulatory nature, changes in the microcirculation may occur independently from changes in macrocirculation (28-30). Interestingly, as clearly demonstrated by our study, changes in microcirculation (i.e., both delta-T and PCD) occurred earlier, at a lower dose of NTG, than did changes in global hemodynamics. In addition, these changes occurred independently of changes in cardiac index. These findings underline the great value of monitoring microcirculation in critically ill patients.

Methodological considerations

Microcirculation experts recently published an important concensus statement.(21) Core of this statement was that measurement of flow alone, such as microvascular flow index (MFI), is regarded as insufficient reporting. However, as opposed to several previous studies which presented only MFI (10, 31-33), we used a software-derived parameter in which flow and density are combined, i.e. perfused capillary density. This parameter has recently been demonstrated to be accurate and precise (22, 23). The relatively low standard deviation (1.1 $mm.mm^{-2}$) of the differences between both baseline measurements confirms the precision of PCD measurements.

Limitations

Several limitations of our study should be acknowledged. The small and heterogeneous sample size limits drawing strong conclusions. Nevertheless, the consistent and reproducible

microvascular response to NTG in almost all patients strengthens our findings. Moreover, whether the beneficial effects of nitroglycerin also apply to other microvascular beds, and whether recruitment of the microcirculation will reduce cellular dysfunction, organ failure and mortality in patients with severe heart failure, needs to be investigated.

Clinical perspective

Measuring tissue perfusion with SDF imaging might be a novel tool to tailor inotropic and vasodilator therapy to patients with severe heart failure. Our study is a preliminary confirmation of this concept, demonstrating the feasibility of serial monitoring of the microcirculation, while a gradual and consistent improvement of tissue perfusion was observed by titration of an intravenous vasodilator.

In conclusion, this study provides evidence for a dose-dependent improvement of microvascular perfusion by administration of nitroglycerin. Whether monitoring of tissue microcirculation optimizes current treatment strategies in patients with severe heart failure, and whether such a strategy will favorably affect outcome, warrants further investigation.

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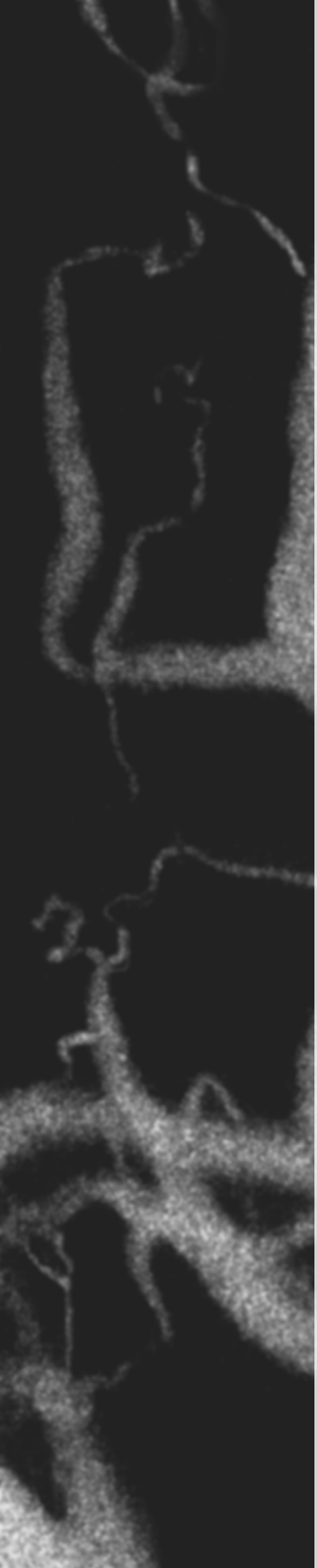


Chapter 13

The response of the microcirculation to inotropic agents in patients with cardiogenic shock

Corstiaan A. den Uil, Wim K. Lagrand, Martin van der Ent, Koen Nieman, Lucia S.D. Jewbali, Peter E. Spronk, Maarten L. Simoons

Submitted for publication

ABSTRACT

Aim: To investigate the effects of inotropic agents on parameters of tissue perfusion in patients with cardiogenic shock.

Methods and Results: Thirty-two patients with cardiogenic shock were included. Patients received dobutamine (n=10), enoximone (n=13), or norepinephrine (n=9). We performed hemodynamic measurements at baseline and after titration of the inotropic agent until cardiac index (CI) ≥2.5 $L.min^{-1}.m^{-2}$ or mixed-venous oxygen saturation (SvO_2) ≥70% (dobutamine or enoximone), and mean arterial pressure (MAP) ≥70 mmHg (norepinephrine). As parameters of tissue perfusion, we measured central-peripheral temperature gradient (delta-T) and sublingual perfused capillary density (PCD).

Both dobutamine and enoximone decreased pulmonary capillary wedge pressure (PCWP) (p=0.02 and p=0.01), increased CI (p=0.02 and p=0.003), decreased systemic vascular resistance (SVR; p=0.02 and p=0.005), decreased delta-T (p=0.02 and p=0.008), and increased PCD (p=0.04 and p=0.001). Norepinephrine increased MAP (p=0.008), central-venous pressure (p=0.007), PCWP (p=0.008), mean pulmonary artery pressure (p=0.01), SVR (p=0.008) and SvO_2 (p=0.02), whereas it decreased PCD (p=0.02).

Conclusion: This study demonstrates a beneficial effect of dobutamine and enoximone on parameters of tissue perfusion in patients with cardiogenic shock. Conversely, norepinephrine decreased PCD. Interventions directed at improving microcirculation may eventually help bridge the gap between improved hemodynamics and the dismal patient outcome in cardiogenic shock.

INTRODUCTION

Patients with cardiogenic shock are at risk for impaired perfusion of organs and tissues.(1) Low peripheral skin temperature as well as impaired sublingual tissue perfusion have been associated with multiple organ failure and adverse outcome in hemodynamically compromised patients.(2-5) Inotropic agents have the potential to maintain or restore adequate end-organ perfusion and function, but their use in heart failure has been associated with increased myocardial oxygen demand and cardiac arrhythmias.(6) Nevertheless, inotropic therapy is often considered necessary in patients with cardiogenic shock to improve the hemodynamic status; more specifically to increase cardiac output, to decrease pulmonary capillary wedge pressure, and to increase mean arterial pressure.(7) Pharmacologic treatment of patients with cardiogenic shock has several clinical challenges. First, the utility of inotropic therapy in restoring end-organ perfusion in patients with cardiogenic shock is based primarily on clinical experience rather than clinical trial data.(6) However, clinical examination may be inaccurate in identifying patients with low output states and impaired organ perfusion.(8) Second, global hemodynamic parameters do not reflect differential patterns of regional organ blood flow or compromised tissue perfusion of the splanchnic bed associated with shock states. For example, mean arterial blood pressure is often clinically used as a surrogate marker for tissue perfusion. However, not all patients with low output states present with hypotension and not all patients with hypotension have impaired organ perfusion.(8, 9) This is further demonstrated by the results of the ESCAPE trial which did not support the routine use of pulmonary artery catheter guided therapy in acute heart failure.(10) Therefore, there is a great need for techniques that directly assess tissue perfusion in patients at the bedside.(11) These novel techniques should provide guidance for the evaluation of existing and future vasoactive therapies for acute heart failure syndromes and may be the key to understand the interventions required to reduce the morbidity and mortality associated with multiple organ failure in patients with cardiogenic shock. Aim of this pilot study was therefore to investigate the effects of inotropic therapy on parameters of tissue perfusion, including sublingual microcirculation as a surrogate for splanchnic perfusion.

METHODS

Study design

This observational study was conducted at the Intensive Cardiac Care Unit of the Thoraxcenter, Erasmus University Medical Center, the Netherlands. We included patients who were admitted with cardiogenic shock. Cardiogenic shock was defined as a cardiac index <2.2 $L.min^{-1}.m^{-2}$ and clinical signs of hypoperfusion (cold extremities, oliguria or altered mental state), not responsive to fluid resuscitation. Patients with oral bleeding were excluded from the study. The decision to start inotropic agents was made by the attending physician. Dobutamine or enoximone,

depending on the preference of the attending physician, were given when cardiac index was <2.2 $L.min^{-1}.m^{-2}$ or when mixed-venous oxygen saturation was <65%. Both inotropic agents were up titrated until cardiac index was ≥2.5 $L.min^{-1}.m^{-2}$ or SvO_2 was ≥70%. Norepinephrine was given to patients when mean arterial pressure (MAP) was <60 mmHg. Norepinephrine was up titrated until MAP ≥70 mmHg. The institutional ethical committee approved the protocol, and written informed consent was obtained from each patient or, in case of patients who were sedated, from a relative authorized to consent on behalf of such a patient.

Hemodynamic monitoring

All patients were monitored with a radial artery catheter (arterial cannula with FloSwitch, Ohmeda, Swindon, UK) and a pulmonary artery catheter (Criticath SP5107H, Becton Dickinson, Sandy, UT, USA or CCOmbo, Edwards Lifesciences, Saint-Prex, Switzerland). Data collection included central body temperature, heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), mean pulmonary artery pressure (PAP), cardiac index (CI), systemic vascular resistance (SVR), and mixed-venous oxygen saturation (SvO_2). SVR was calculated as (MAP-CVP)*80/cardiac output.

Microcirculatory assessment and analysis

Central-peripheral temperature gradient (delta-T) was defined and calculated as the difference between central blood and skin temperature. Skin temperature was measured with a probe sticked on the dorsum of the foot under constant room temperature (temperature probe 170075; Ellab Inc., Centennial, CO, USA).

The Sidestream Dark Field (SDF) imaging device (MicroScan; Microvision Medical, Amsterdam, The Netherlands) was used to obtain 2-dimensional video images of sublingual microcirculatory blood flow. This technique has been described previously.(12) In short, the camera emits green light that is absorbed by red blood cells within microvessels. In this way, red blood cells are used as the contrast agent to visualize sublingual blood flow in patent microvessels. This is the reason why oral bleeding was an exclusion criterion for the study. Per time point, three steady video sequences of at least 20 seconds duration were obtained, stored and analyzed. Quantification of the images was done using dedicated software (Automated Vascular Analysis 3.0, MicrovisionMedical, Amsterdam, the Netherlands). An investigator who was blinded for the patient's therapy performed quantification. Perfused capillary density (PCD) was calculated by automated measuring the total length of perfused capillaries divided by image area. Since SDF imaging enables visualization of flowing intravascular erythrocytes rather than microvessel walls, an increase in PCD was regarded as capillary recruitment. This approach has been validated previously.(13, 14) Capillaries were defined as microvessels with a diameter less than 20 μm.

Study protocol

To minimize the effect of regression to the mean due to spontaneous variation in microcirculatory perfusion, two series of baseline measurements were performed with a time interval of 15 minutes. Values from both baseline measurements were averaged to obtain single baseline values. After the second baseline measurement, the inotropic agent was given as a bolus equal to the volume of the used intravenous line. Immediately thereafter, a continuous intravenous infusion was started and titrated. All measurements were repeated 10 minutes (dobutamine or norepinephrine) or 30 minutes (enoximone) after the maximum infusion rate had been started.

Statistical analysis

Categorical variables are presented as absolute numbers with percentages. All continuous variables are presented as median and interquartile range (IQR). Differences between groups were tested with the chi-square test, the Mann-Whitney test or the Kruskal-Wallis test, when appropriate. Changes between time points were tested with the Wilcoxon signed ranks test. Correlations between variables were investigated with Spearman's correlation test. A p-value <0.05 was regarded statistically significant.

RESULTS

Study population

Thirty-two patients with cardiogenic shock were included in this study. Ten patients received dobutamine (dobu), 13 patients received enoximone (enox), and 9 patients received norepinephrine (nor). There were no major differences in baseline characteristics between the groups (Table 1). The following maximum dosages of intropic agents were administered: 5 [5-5] $\mu g.kg^{-1}.min^{-1}$ (dobutamine), 2.0 [1.5-2.0] $\mu g.kg^{-1}.min^{-1}$ (enoximone), and 0.10 [0.05-0.25] $\mu g.kg^{-1}.min^{-1}$ (norepinephrine). No inotrope-induced arrhythmias occurred during execution of the study.

Effects on systemic and pulmonary circulation

There were no significant differences in global hemodynamic or microcirculatory parameters between the two baseline measurements in the three groups, indicating that patients were in a stable condition before the inotropic agent was started. Baseline hemodynamic parameters were not significantly different between patients receiving dobutamine or enoximone. However, patients treated with norepinephrine had a lower baseline MAP (dobu vs. nor: $p=0.001$; enox vs. nor: $p<0.001$), and a lower baseline SVR (dobu vs. nor: $p=0.01$; enox vs. nor: $p<0.001$) (Table 2).

Absolute changes in parameters are shown in Table 3. Figure 1 shows the changes in CVP and CI at individual patient level. Both dobutamine and enoximone decreased PCWP ($p=0.02$ and $p=0.01$, respectively), increased CI ($p=0.02$ and $p=0.003$, respectively), and decreased SVR

Table 1. Baseline characteristics of the study population.

Characteristic	Dobutamine (n=10)	Enoximone (n=13)	Norepinephrine (n=9)	P-value
Age, years (median [IQR])	61 [49-77]	57 [49-72]	63 [56-80]	NS
Male	5 (50%)	9 (69%)	5 (56%)	NS
CV risk factors				
Hypertension	5 (50%)	6 (46%)	3 (33%)	NS
Current smoking	2 (20%)	2 (15%)	1 (11%)	NS
Dyslipidaemia	4 (40%)	5 (39%)	5 (56%)	NS
Diabetes mellitus	2 (20%)	6 (46%)	2 (22%)	NS
Main cause of cardiogenic shock				
AMI				NS
Cardiomyopathy	9 (90%)	7 (54%)	4 (44%)	
Post CP resusctitation	1 (10%)	4 (31%)	2 (22%)	
Post cardiac surgery	0 (0%)	0 (0%)	1 (11%)	
	0 (0%)	2 (15%)	2 (22%)	
NT-proBNP level, pmol.L^{-1} (median [IQR])	844 [189-1386]	708 [435-1966]	1176 [393-1819]	NS
Mechanical ventilation	8 (80%)	4 (31%)	7 (78%)	0.02
IABP counterpulsation	4 (40%)	8 (62%)	1 (11%)	NS

Abbreviations: IQR, interquartile range; CV, cardiovascular; AMI, acute myocardial infarction; CP, cardiopulmonary; NT-proBNP, N-terminal-pro B-type natriuretic peptide; IABP, intra-aortic balloon pump. P-values >0.05 (NS, non-significant) are not shown.

Table 2. Parameters at baseline.

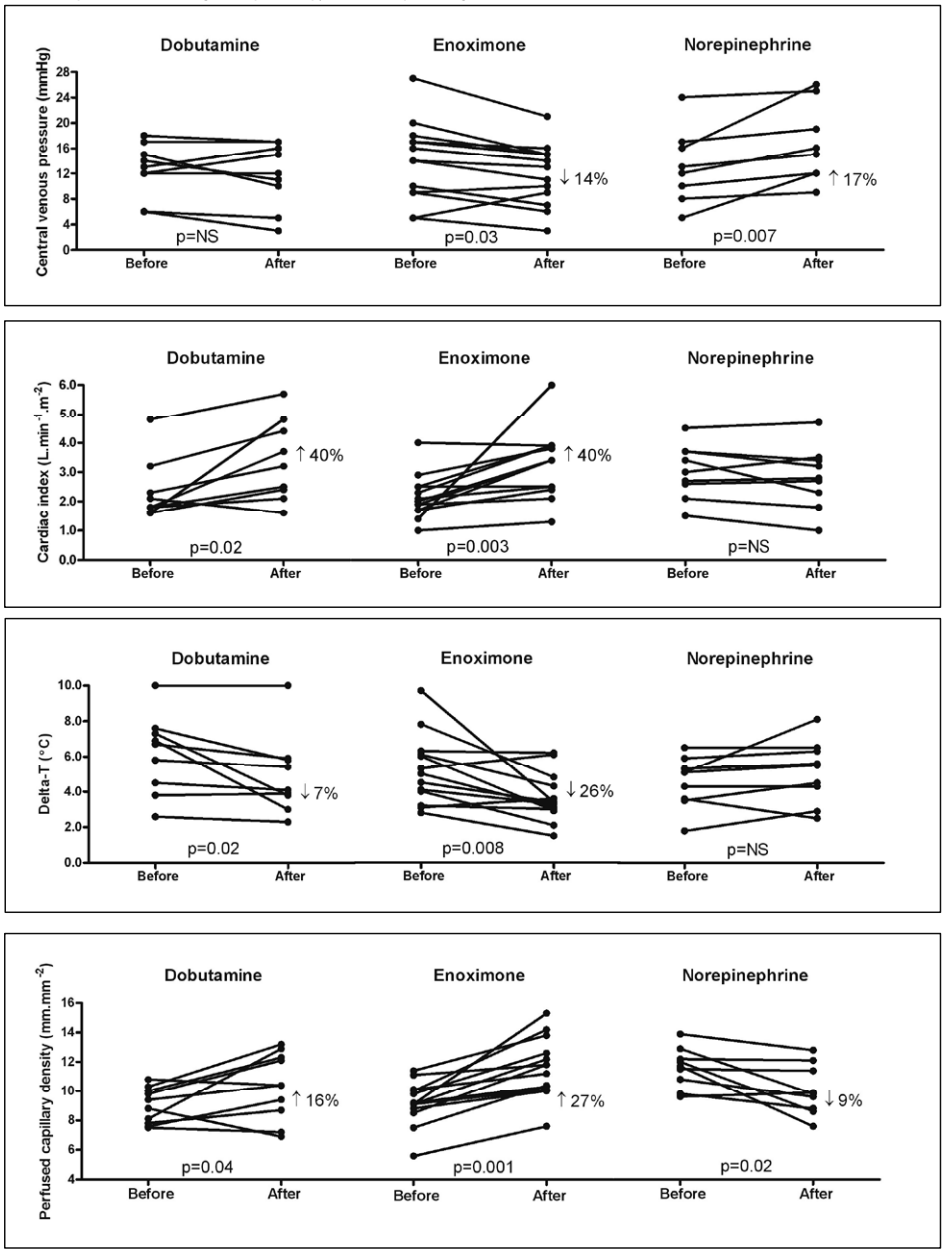
	Dobutamine (n=10)	Enoximone (n=13)	Norepinephrine (n=9)	P-value
HR, bpm	84 [57-96]	89 [78-109]	96 [86-116]	NS
MAP, mmHg	70 [61-84]	66 [62-82]	53 [51-57]	<0.001
CVP, mmHg	13 [9-16]	14 [9-18]	12 [8-17]	NS
PCWP, mmHg	21 [16-23]	23 [17-28]	20 [14-23]	NS
MPAP, mmHg	30 [22-34]	31 [25-34]	27 [24-31]	NS
CI, L.min^{-1}.m^{-2}	2.0 [1.7-3.4]	2.0 [1.7-2.5]	3.0 [2.4-3.7]	NS
SVR, dynes.sec.cm^{-5}	1268 [927-1636]	1023 [829-1677]	589 [497-612]	0.003
SvO2, %	67 [59-69]	61 [56-64]	69 [63-74]	NS
Lactate, mmol.L^{-1}	1.1 [1.0-1.3]	1.2 [1.0-2.1]	1.1 [0.9-2.1]	NS
Delta-T, °C	6.8 [4.3-8.2]	5.0 [3.6-6.2]	5.1 [3.6-5.6]	NS
PCD, mm.mm^{-2}	9.1 [7.7-10.1]	9.4 [8.7-10.6]	11.7 [10.3-12.6]	0.002

Abbreviations: HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; MPAP, mean pulmonary artery pressure; CI, cardiac index; SVR, systemic vascular resistance; SvO_2, mixed-venous oxygen saturation; delta-T, central-peripheral temperature gradient; PCD, perfused capillary density. Values represent median [interquartile range]. P-values >0.05 (NS, non-significant) are not shown.

(p=0.02 and p=0.005, respectively). Norepinephrine increased MAP (p=0.008), CVP (p=0.007), PCWP (p=0.008), MPAP (p=0.01), SVR (p=0.008), and SvO_2 (p=0.02).

Dobutamine increased heart rate significantly more than the other inotropes (dobu vs. enox: p=0.003; dobu vs. nor: p=0.02; Table 3). Changes in other macrohemodynamic parameters were not significantly different between patients receiving dobutamine or enoximone. ΔMAP was higher in patients receiving norepinephrine (dobu vs. nor: p<0.001; enox vs. nor: p<0.001),

Figure 1. Changes in central venous pressure, cardiac index, delta-T, and perfused capillary density at individual patient level. ↓↑, decrease or increase of parameter following inotropic therapy in terms of percentage relative to baseline.



as well as ΔCVP (dobu vs. nor: p=0.01; enox vs. nor: p<0.001), ΔPCWP (dobu vs. nor: p<0.001; enox vs. nor: p<0.001), ΔMPAP (dobu vs. nor: p=0.01; enox vs. nor: p=0.02), ΔSVR (dobu vs. nor: p<0.001; enox vs. nor: p<0.001), and Δlactate (dobu vs. nor: p=0.04; enox vs. nor: p=NS). ΔCI was lower in patients receiving norepinephrine (dobu vs. nor: p=0.004; enox vs nor: p=0.001).

Table 3. Changes in macro- and microcirculation after administration of inotropic agents.

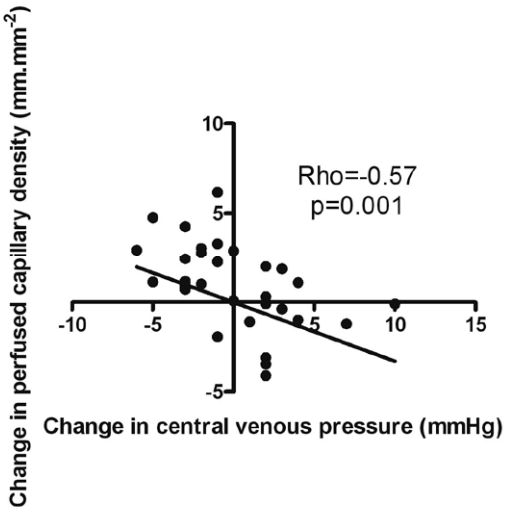
	Dobutamine (n=10)	Enoximone (n=13)	Norepinephrine (n=9)	P-value
ΔHR, bpm	+11 [+8; +16]**	-2 [-7; +5]	+1 [-7; +7]	0.01
ΔMAP, mmHg	-1 [-10; +14]	0 [-5; +8]	+25 [+17; +36]**	<0.001
ΔCVP, mmHg	-1 [-3; +2]	-2 [-3; -1]*	+2 [+2; +6]**	0.002
ΔPCWP, mmHg	-1 [-2; 0]*	-2 [-7; -1]*	+5 [+3; +9]**	<0.001
ΔMPAP, mmHg	0 [-3; +2]	-3 [-1; +1]	+4 [+2; +9]*	0.02
ΔCI, $L.min^{-1}.m^{-2}$	+0.8 [+0.5; +1.6]*	+0.8 [+0.3; +1.6]**	-0.3 [-0.5; +0.2]	0.003
ΔSVR, $dynes.sec.cm^{-5}$	-364 [-715; -54]*	-379 [-738; -122]**	+467 [+138; +504]**	<0.001
ΔSvO2, %	+4 [+2; +10]*	+2 [-1; +8]	+3 [+1; +7]*	NS
ΔLactate, $mmol.L^{-1}$	-0.3 [-0.5; -0.1]*	+0.1 [-0.1; +0.3]	0.0 [-0.2; +0.2]	0.02
ΔDelta-T, °C	-0.5 [-2.4; -0.3]*	-1.3 [-2.5; -0.2]**	+0.4 [+0.0; +1.1]	0.004
ΔPCD, $mm.mm^{-2}$	+1.5 [-0.3; +2.5]*	+2.5 [+1.1; +3.2]**	-1.1 [-3.3; -0.1]*	<0.001

Values represent median [interquartile range]. Asterisks indicate statistical significance versus baseline: *, p<0.05; **,p<0.01; ***, p<0.001. P-values >0.05 (NS, non-significant) are not shown. Abbreviations: HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; MPAP, mean pulmonary artery pressure; CI, cardiac index; SVR, systemic vascular resistance; SvO_2, mixed-venous oxygen saturation; delta-T, central-peripheral temperature gradient; PCD, perfused capillary density.

Effects on microcirculation

Baseline delta-T and PCD were not significantly different between patients receiving dobutamine or enoximone. Patients who received norepinephrine had a higher baseline sublingual perfused capillary density (nor vs. dobu: p=0.001; nor vs. enox: p=0.001, Table 2). Figure 1 shows the changes in delta-T and PCD at individual patient level. Both dobutamine and enoximone decreased delta-T (p=0.02 and p=0.008, respectively), and increased PCD (p=0.04 and p=0.001, respectively, Table 3). Norepinephrine decreased PCD (p=0.02). Changes in delta-T and PCD were not significantly different between patients receiving dobutamine or enoximone.

Figure 2. Inverse correlation between (pooled) changes in central venous pressure and changes in sublingual perfused capillary density.



However, norepinephrine had a different effect on delta-T (dobu vs. nor: p=0.003; enox vs. nor: p=0.003) and PCD (dobu vs. nor: p=0.003; enox vs. nor: p<0.001; Table 3).

Correlations

In this (small) study, we found no significant correlations between changes in CI or SVR and changes in either delta-T or PCD. However, there was an inverse correlation between (pooled) changes in CVP and changes in PCD (Rho=-0.57, p=0.001, Figure 2). There was no correlation between changes in CVP and changes in delta-T.

DISCUSSION

This is the first study demonstrating the direct effects of various inotropes on the microcirculation measured at the bedside in patients with cardiogenic shock. Dobutamine and enoximone decreased central-to-peripheral temperature gradient and increased the number of sublingual patent capillaries, whereas norepinephrine decreased perfused capillary density.

Effects on systemic and pulmonary circulation

Dobutamine and enoximone are the most commonly used intravenous inotropes for the management of cardiogenic shock in our center. Both agents are given to increase cardiac contractility by increasing intracellular levels of cyclic adenylate monophosphate (cAMP), although they affect cAMP by different mechanisms. Caldicott et al. compared the effects of enoximone with dobutamine in patients with severe heart failure following myocardial infarction.(15) These authors reported that both agents similarly increased cardiac output. Dobutamine, opposite to enoximone, also significantly increased heart rate and produced significantly more runs of supraventricular and ventricular tachycardia. Our findings agree with this report. Although enoximone is a potent vasodilator, we found no consistent change in mean arterial pressure following enoximone infusion. This limited risk of (further) reducing mean arterial pressure has been reported previously by Vincent et al.(16, 17) and suggests that, whenever possible, enoximone should be preferred over dobutamine in the setting of cardiogenic shock. Norepinephrine is an inotropic agent with high affinity for alfa-adrenergic receptors and acts therefore mainly as vasopressor.

Norepinephrine increases mean arterial pressure(18), and is therefore frequently used in the acute phase of cardiogenic shock to restore mean arterial pressure. In addition, norepinephrine may increase coronary blood flow in cardiogenic shock.(19)

Effects on microcirculation

The beneficial effect of dobutamine on parameters of microcirculatory perfusion, i.e. delta-T and PCD, was significant in our study, albeit not consistent in all patients. Similarly, De Backer

et al. reported a modest improvement of sublingual capillary perfusion in patients with septic shock receiving dobutamine, but with large individual variation.(20)

Enoximone improved capillary skin blood flow, measured by a laser Doppler technique, in a study in patients undergoing cardiopulmonary bypass surgery.(21) In addition, Kern et al. demonstrated a beneficial effect of enoximone on hepatosplanchnic oxygen consumption and on liver function in fluid-optimized septic shock patients.(22) Our study demonstrates a consistent increase in PCD and decrease of delta-T in a different patient population, i.e. cardiogenic shock.

The effects of norepinephrine on tissue perfusion are largely unknown. Most studies performed in patients with septic shock demonstrated no effect of norepinephrine on splanchnic perfusion.(23, 24) We are not aware of any reports on the effects of norepinephrine on the microcirculation in cardiogenic shock. Maier et al. recently investigated the response of the sublingual microcirculation to the pure alfa-adrenergic agonist phenylephrine during cardiopulmonary bypass surgery. Increasing perfusion pressure from (mean) 47 to (mean) 68 mmHg using phenylephrine significantly decreased sublingual capillary microvascular flow index, whereas global tissue blood flow, measured with a laser Doppler flowmeter, increased.(25) These findings were explained as significant microcirculatory shunting induced by phenylephrine. Indeed, using microspheres, Saxena and Verdouw demonstrated in the year 1985 the presence of arteriovenous anastomoses in the tongue.(26) In our study, norepinephrine modestly but significantly decreased sublingual PCD, whereas cardiac index remained constant and SvO_2 increased. These findings also suggest development of microcirculatory shunting induced by norepinephrine in patients with cardiogenic shock.

Correlations between macrocirculation and microcirculation

The apparent lack of correlation between cardiac index and microcirculatory parameters has been shown previously.(20, 27) This finding emphasizes that global hemodynamic parameters do not predict microcirculatory perfusion and it underlines the importance of monitoring macro- as well as microcirculation in patients with cardiogenic shock.(28) Nevertheless, in our study we found a modest, but significant correlation between changes in central venous pressure and changes in PCD, which confirms the concept that a strategy of reducing CVP may favourably affect organ perfusion.(29, 30) There is indeed growing evidence that hypervolemia in patients with heart failure is an independent predictor for disease progression and death from pump failure.(31) In addition, Mullens et al recently demonstrated that the development of renal failure was significantly associated with an elevated central venous pressures and that central venous pressure on hospital admission, rather than impaired cardiac output, was a predictor for worsening renal function during hospital admission for heart failure.(32)

Limitations

Several limitations of our study should be acknowledged. The small and heterogeneous sample size limits drawing strong conclusions. Next, the fact that our study was nonrandomized might

have introduced bias. Finally, whether the beneficial effects of nitroglycerin also apply to other microvascular beds, whether the observed changes in microcirculatory perfusion are clinically significant, and whether recruitment of the microcirculation will reduce cellular dysfunction, organ failure and mortality in patients with cardiogenic shock, needs to be investigated.

CONCLUSION

This study demonstrates the beneficial effects of both dobutamine and enoximone on parameters of tissue perfusion. Conversely, norepinephrine decreased perfused capillary density. These findings add to the concept that administration of vaso-active agents may potentially be guided by monitoring microcirculation in the setting of acute cardiac care. Interventions directed at improving macro- as well as microvascular perfusion may eventually help bridge the gap between improved hemodynamics and the dismal patient outcome in cardiogenic shock. Whether monitoring of tissue microcirculation optimizes current treatment strategies in patients with severe heart failure and whether such a strategy will favourably affect outcome, warrants further investigation.

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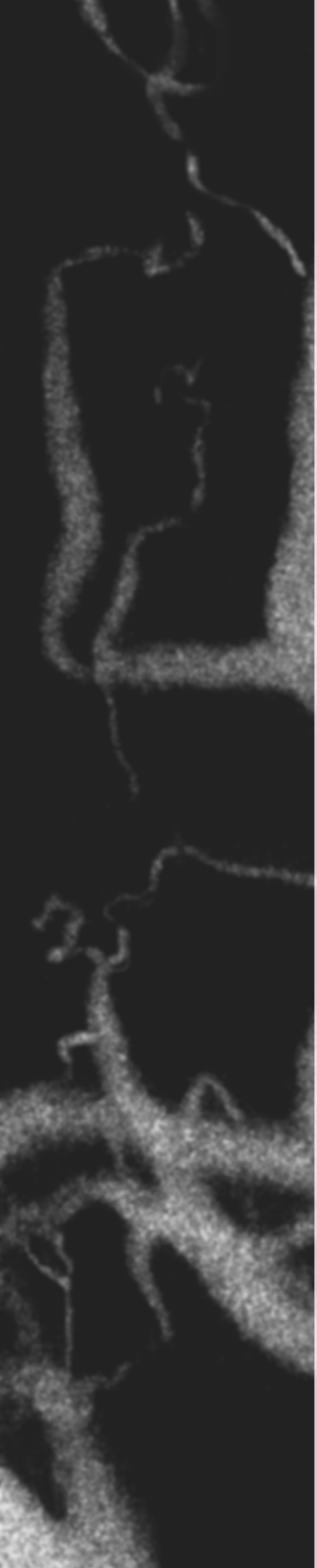

Chapter 14

The effects of intra-aortic balloon pump counterpulsation on macrocirculation and tissue microcirculation in patients with cardiogenic shock

Corstiaan A. den Uil, Wim K. Lagrand, Martin van der Ent, Lucia S.D. Jewbali, J. Jasper Brugts, Peter E. Spronk, Maarten L. Simoons

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ABSTRACT

Objectives: It was the aim of this study to evaluate the effects of intra-aortic balloon pump (IABP) counterpulsation on sublingual microcirculation as a model for splanchnic perfusion.

Methods: In 13 patients with cardiogenic shock treated with IABP, the IABP assist ratio was reduced from 1:1 to 1:8 for 15 min. Using sidestream dark field imaging, 117 movie files of the sublingual microcirculation were obtained and quantified at different IABP assist ratios at 3 time points: 1:1 (T0), 1:8 (T1), and 1:1 (T2). Data are presented as the median and interquartile range.

Results: The median age of the patients was 59 [56-73] years and 62% were males. Discontinuation of IABP decreased the mean arterial pressure (75 [71-84] mmHg at T0 vs. 69 [64-79] mmHg at T1, $p<0.001$), cardiac index (2.9 [1.6-3.3] L/min/m^2 at T0 vs. 2.4 [1.5-2.8] L/min/m^2 at T1, $p=0.005$), and cardiac power index (0.46 [0.29-0.59] W/m^2 at T0 vs. 0.36 [0.24-0.50] W/m^2 at T1, $p=0.006$). However, these modest changes in macrohemodynamics did not significantly influence sublingual perfused capillary density and capillary red blood cell velocity ($p=0.28$ and 0.73, respectively).

Conclusion: A temporary, modest decrease in microcirculatory driving force, induced by lowering the IABP assist ratio, does not impair sublingual microcirculatory perfusion as measured by a novel 2-dimensional imaging technique.

INTRODUCTION

Tissue hypoperfusion is considered an important factor in the pathophysiology of critical diseases and has been associated with in-hospital mortality.(1-3) Optimization of tissue microcirculation is one of the objectives of modern treatment of critically ill patients.(4, 5) Microcirculatory impairment is thought to play a crucial role in the phenomenon of established or improved macrocirculatory hemodynamics, but still poor prognosis in critically ill patients. However, the influence of macrocirculatory therapeutic maneuvers on tissue microcirculation is largely unknown.

Intra-aortic balloon pump (IABP) counterpulsation has been increasingly used over time to improve mean arterial blood pressure, increase diastolic coronary perfusion pressure, reduce afterload, and decrease myocardial demand by reducing cardiac work. However, the effects of IABP counterpulsation on tissue perfusion have not been investigated extensively. Intra-aortic balloon pump counterpulsation increases mean arterial pressure (MAP), which is a prerequisite for peripheral blood flow.(6, 7) In addition, Fries and coworkers have reported a close correlation between peripheral capillary blood flow and coronary perfusion pressure in pigs subjected to cardiac arrest and resuscitation.(8) We hypothesized that perfusion in a microvascular bed away from the heart might be impaired by an interruption in intra-aortic counterpulsation. Using a novel handheld videomicroscope applying sidestream dark field imaging (SDF), we investigated whether alterations in macrocirculation, induced by a decrease in IABP assist ratio, impaired sublingual microcirculation.

MATERIALS AND METHODS

Study design

This real-time pre-/postintervention study was conducted at the Thoraxcenter of Erasmus University Medical Center. Data collection was based on SDF imaging and on routine measurements. The institutional ethics committee on human research approved the protocol, and written informed consent was obtained from each patient or, in case of patients who were sedated, from a relative authorized to consent on behalf of such a patient.

Patients

Thirteen consecutive patients who received an IABP for cardiogenic shock were included in this study. All IABPs (AutoCAT2 WAVE; FiberOptix, Arrow International Inc., Reading, PA, USA) were inserted at the catheterization laboratory.

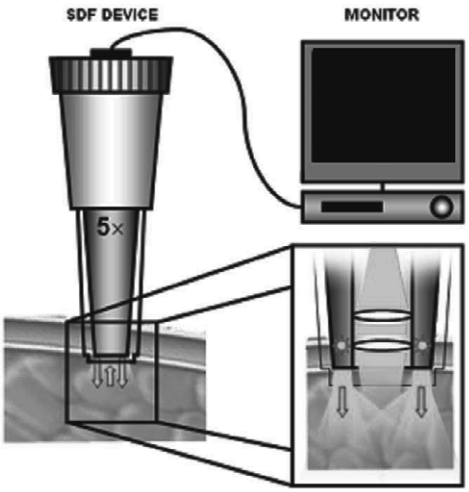
Macrohemodynamic monitoring

Patients were monitored with a radial artery catheter (arterial cannula with FloSwitch, Ohmeda, Swindon, UK) and a pulmonary artery catheter (Becton Dickinson Criticath SP5107H, Sandy, UT, USA). The following parameters of systemic and pulmonary circulation were collected: central body temperature, heart rate, MAP, central venous pressure, pulmonary capillary wedge pressure, mean pulmonary artery pressure, cardiac index (CI), systemic vascular resistance, lactate level, and mixed venous oxygen saturation. The cardiac power index was calculated as MAP*CI/451.(9)

Microcirculatory assessment and analysis

The SDF device (MicroScan; Microvision Medical, Amsterdam, The Netherlands) was used to obtain 2-dimensional video images of sublingual microcirculatory blood flow. This technique has been described and validated previously(2, 10, 11) and is demonstrated in Figure 1. Each time point, 3 steady video sequences with a duration of at least 20 s were obtained, stored and subsequently analyzed blindly. In total, 117 video sequences were obtained. Quantification of the images was performed using software (AVA 3.0, MicrovisionMedical). Perfused capillary density (PCD) was calculated by measuring the total length of perfused capillaries divided by image area. Capillaries were defined as the microvessels with a diameter <20 μm. Using space-time diagrams, erythrocyte velocity was measured in 5 representative capillaries per video sequence. Velocities were calculated by determination of the slope of moving centerline intensity of a microvessel, expressed as vertical lines for 10 consecutive frames.

Figure 1. SDF imaging setup. Video frames of the sublingual microcirculation were acquired using an SDF imaging device (left) and captured on a computer (upper right). The SDF device applies a central light guide that is surrounded by but isolated from concentrically placed light emitting diodes that stroboscopically emit green light for illumination. This green light is absorbed by erythrocytes flowing through the tissue under investigation. The hemoglobin is actually used as contrast agent, so that red blood cells are imaged as dark moving globules against a white/grayish background. Modified from (15).



Study protocol

Microcirculation and global hemodynamic parameters were measured at 3 subsequent time points. First, all measurements were performed at an IABP assist ratio of 1:1 (T0). Then, the IABP assist ratio was set at 1:8 and all measurements were repeated after a time period of 15 minutes at an IABP assist ratio of 1:8 (T1). After these measurements, the IABP console was reprogrammed at 1:1 and all measurements were performed again after an interval of 15 min (T2). During execution of the study, dosages of intravenous medications were stable.

Statistical analysis

Categoric variables are presented as absolute number, with percentage. All measurements are presented as the median with interquartile range (IQR, [25th–75th percentiles]). Changes over time were tested with the Friedman test. Linear correlations between macrocirculatory and microcirculatory parameters were calculated with the Spearman correlation test.

RESULTS

Baseline characteristics of the study population are shown in Table 1. Median age was 59 [56-73] years and 62% were males. Most patients had cardiogenic shock due to acute myocardial infarction (69%). All patients tolerated the study protocol without adverse events. Global

Table 1. Clinical characteristics of the study population (n=13).

Characteristic		
Age, years (median and IQR)		59 [56-73]
Male		8 (62%)
CV risk factors:	Hypertension	8 (62%)
	Current smoking	3 (23%)
	Dyslipidemia	3 (23%)
	Diabetes mellitus	3 (23%)
Main cause of cardiogenic shock:	Acute MI	8 (62%)
	Post resuscitation	1 (8%)
	Dilated cardiomyopathy	2 (15%)
	Mechanical complication of acute MI	1 (8%)
	Post cardiotomy	1 (8%)
Cooling after out-of-hospital CA		3 (23%)
Mechanical ventilation		11 (85%)
NT-pro-BNP level, pmol/L (median and IQR)		673 [265-1674]
CRP level, mg/L (median and IQR)		20 [13-92]
Pharmacologic therapy	Any inotropic agent*	11 (85%)
	Vasopressors†	4 (31%)
	Vasodilators‡	7 (54%)

Values are number of patients, with percentages in parentheses, unless otherwise noted. Abbreviations: IQR, interquartile range; CV, cardiovascular; MI, myocardial infarction; CA, cardiac arrest; NT-pro-BNP, N-terminal portion of pro-B-type natriuretic peptide; CRP, C-reactive protein; ASA, acetyl salicylic acid. * Dobutamine, dopamine, norepinephrine, enoximone or Levosimendan. † Norepinephrine or dopamine at a dose >5 $\mu g.kg^{-1}.min^{-1}$. ‡ Nitroglycerin, enoximone or levosimendan.

Table 2. The effects of lowering the IABP assist ratio on global hemodynamic parameters and sublingual microcirculation.

	IABP1:1 (T0)	IABP 1:8 (T1)	IABP 1:1 (T2)	P-value
Central body temperature (°C)	36.6 [33.1-37.4]	36.5 [33.1-37.4]	36.6 [33.1-37.5]	0.22
HR (bpm)	99 [77-112]	99 [78-112]	99 [78-112]	0.27
MAP (mmHg)	75 [71-84]	69 [64-79]	72 [70-82]	<0.001
CVP (mmHg)	14 [13-15]	14 [13-16]	13 [12-15]	0.14
Wedge pressure (mmHg)	20 [15-22]	20 [17-23]	18 [14-21]	0.08
Mean PAP (mmHg)	27 [21-34]	28 [25-34]	26 [21-34]	0.50
CI ($L.min^{-1}.m^{-2}$)	2.9 [1.6-3.3]	2.4 [1.5-2.8]	2.6 [1.8-3.0]	0.005
SVR ($dynes.sec.cm^{-5}$)	1107 [635-1714]	1063 [821-1845]	1118 [752-1502]	0.58
CPI (W/m^2)	0.46 [0.29-0.59]	0.36 [0.24-0.50]	0.41 [0.29-0.52]	0.006
Lactate ($mmol.L^{-1}$)	1.8 [1.1-4.8]	2.7 [1.0-4.1]	1.9 [1.0-4.2]	0.35
SvO_2 (%)	78 [73-82]	70 [69-73]	76 [73-80]	0.18
PCD (mm^{-1})	10.4 [8.1-11.6]	9.6 [7.8-11.5]	10.0 [7.5-12.0]	0.28
Capillary RBC velocity ($\mu m.s^{-1}$)	340 [236-428]	281 [202-417]	301 [237-377]	0.73

T0: situation at baseline; T1: 15 minutes after switching the IABP ratio to 1:8; T2: 15 minutes after switching the IABP ratio back to 1:1. All values are shown in median [25th-75th percentiles]. Abbreviations: IABP, intra-aortic balloon pump; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; PAP, pulmonary artery pressure; CI, cardiac index; SVR, systemic vascular resistance; CPI, cardiac power index; SvO2, mixed-venous oxygen saturation; PCD, perfused capillary density; RBC, red blood cell.

hemodynamic and microcirculatory parameters over time are shown in Table 2. Lowering the IABP assist ratio decreased the MAP (75 [71-84] mmHg at T0 vs. 69 [64-79] mmHg at T1, p<0.001), CI (2.9 [1.6-3.3] L/min/m^2 at T0 vs. 2.4 [1.5-2.8] L/min/m^2 at T1, p=0.005), and cardiac power index (0.46 [0.29-0.59] W/m^2 at T0 vs. 0.36 [0.24-0.50] W/m^2 at T1, p=0.006). However, sublingual PCD (10.4 [8.1-11.6] mm^{-1}, 9.6 [7.8-11.5] mm^{-1} and 10.0 [7.5-12.0] mm^{-1} at T0, T1 and T2, respectively, p=0,28) and red blood cell (RBC) velocity in capillaries (340 [236-428] $\mu m.s^{-1}$, 281 [202-417] $\mu m.s^{-1}$ and 301 [237-377] $\mu m.s^{-1}$ at T0, T1, and T2, respectively, p=0.73) did not change significantly.

In this (small) study, the baseline MAP, CI, and cardiac power index did not correlate with baseline PCD or capillary RBC velocity. In addition, changes in mean arterial pressure (ΔMAP), cardiac index (ΔCI) or cardiac power index (ΔCPI) did not significantly correlate to changes in either PCD (ΔPCD) or capillary RBC velocity (Δ capillary RBC velocity) between T1 and T0.

DISCUSSION AND CONCLUSIONS

The most important finding of this study was that, despite statistically significant changes in macrohemodynamics, there were no direct, major changes in sublingual microvascular perfusion during lowering of the IABP assist ratio from 1:1 to 1:8.

Future monitoring of critically ill patients admitted to the intensive cardiac care unit might increasingly include parameters of tissue perfusion. To our knowledge, this is the first study reporting the direct effects of intra-aortic counterpulsation on microcirculation measured at the bedside. Although we expected a decrease in microvascular perfusion after reducing the

IABP assist ratio, there was no change in either PCD or capillary RBC velocity. Several explanations can be offered for our findings. First, lowering IABP assist ratio decreased MAP with median 6 mm Hg, whereas the CI decreased with median 0.5 L/min/m^2 and cardiac power index decreased with median 0.10 W/m^2. With such modest changes in microcirculatory driving forces, the precapillary sphincter (arterioles) will adapt in radius and thereby hold flow within a constant value by the well-know physiological concept termed autoregulation.(12) Second, central venous pressure, which in fact reflects microcirculatory afterload, did not change in the study. Microcirculatory afterload might be an even more important determinant of tissue perfusion(13), which was also demonstrated by recent studies investigating the effects of vasodilators in critically ill patients.(14, 15) Third, 54% of the patients were treated with vasodilators, which might have influenced the results.

During IABP support, MAP is a complex number. While the overall MAP may increase, the diastolic augmentation combined with systolic unloading and a decreased absolute diastolic pressure may have a neutral effect on tissue perfusion. Indeed, most studies demonstrated little effect of IABP counterpulsation on mean coronary, carotid or cerebral blood flow.(16-19) Our findings are consistent with these data. In addition, microcirculatory autoregulation may explain why the changes in MAP could not be correlated with alterations in microcirculatory parameters, which is conform to a previous study in patients during surgery with cardiopulmonary bypass.(20)

Several limitations of our study should be acknowledged. First, we measured mean red blood cell (RBC) velocities for 10 averaged video frames without information on the period of the cardiac cycle at that specific time moment. In pulsatile conditions, erythrocyte velocity in the microcirculation is variable and coincides with the cardiac cycle.(21) It is very well possible that fluctuation in RBC velocities increases during intra-aortic counterpulsation. Unfortunately, due to current technical limitations, we did not analyze RBC velocity synchronized to the cardiac cycle. Second, due to the limited frame rate of the SDF video camera (25 images/sec), very high velocities in microvessels (>1000 μm/s) could not reliably be measured. However, velocities in our study were far below this limit. Finally, a time period of 15 minutes between measurements might be too short to induce changes in microvascular perfusion. This point is underlined by a previous study that demonstrated that several macrohemodynamic parameters increased significantly only 3 hours after IABP insertion.(22)

In conclusion, we demonstrated the feasibility of combined monitoring of macrocirculation and tissue microcirculation in patients with cardiogenic shock treated with IABP counterpulsation. This study demonstrated that a decrease in the IABP assist ratio lasting 15 min does not change sublingual microcirculation, providing a novel argument that modest changes in macrocirculatory parameters do not necessarily imply alteration of microcirculatory blood flow. Further studies should include baseline measurements prior to IABP insertion in order to elucidate the full effects of IABP counterpulsation on tissue perfusion.

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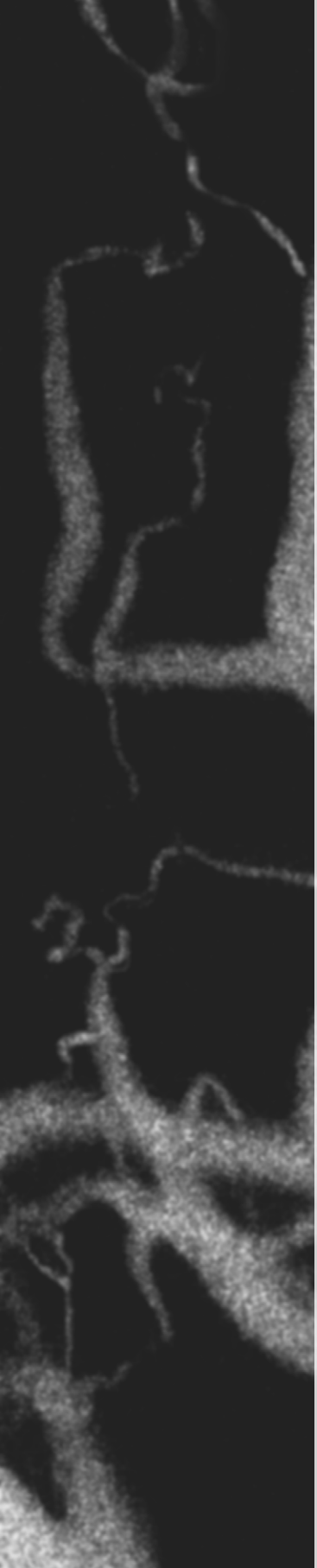

Chapter 15

Mechanical circulatory support devices improve tissue perfusion in patients with end-stage heart failure or cardiogenic shock

Corstiaan A. den Uil, Alexander P. Maat, Wim K. Lagrand, Martin van der Ent, Lucia S.D. Jewbali, Robert J. van Thiel, Peter E. Spronk, Maarten L. Simoons

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ABSTRACT

Objectives: This study evaluated the effects of mechanical circulatory support (MCS) on sublingual microcirculation as a surrogate for splanchnic microvascular perfusion.

Methods: Between May 2008 and April 2009, 10 consecutive patients received an MCS device or extracorporeal membrane oxygenation for end-stage chronic heart failure (n=6) or cardiogenic shock (n=4). Microcirculation was investigated using a hand-held Sidestream Dark Field imaging device. Perfused capillary density (PCD) and capillary red blood cell velocity (cRBCv) were assessed before device implantation (T0), immediately after implantation (T1), and 1 day post implantation (T2). Data are presented as median [interquartile range].

Results: Median patient age was 45 [38-52] years and 70% were men. MCS significantly decreased pulmonary capillary wedge pressure (p=0.04). Cardiac power index increased (0.29 [0.21-0.34] $W.m^{-2}$ at T0 vs. 0.48 [0.39-0.54] $W.m^{-2}$ at T1, p=0.005) as well as central venous oxygen saturation (54 [46-61] % at T0 vs. 78 [67-85] % at T1, p=0.007). There was a 3-fold increase in tissue perfusion index (sublingual PCD * cRBCv) during mechanical circulatory support (573 [407-693] at T0 vs. 1909 [1771-2835] at T1, p=0.005). Microcirculatory parameters remained improved at T2.

Conclusion: Mechanical circulatory support for severe heart failure is associated with a consistent, significant and sustained improvement in tissue perfusion, as measured at the bedside by a 2-dimensional microcirculation imaging technique.

INTRODUCTION

Mechanical circulatory support (MCS) devices, including ventricular assist devices (VADs), are used to provide effective hemodynamic support as a bridge to myocardial recovery or in patients awaiting heart transplantation.(1-4) Patients who are eligible to receive a MCS device are at high risk that multiple organ failure will develop.(5) MCS devices have the potential to reverse the syndrome of severe heart failure, and to improve functional status, quality of life, and outcome in patients with severe cardiac dysfunction.(1, 6)

Tissue hypoperfusion is an important factor in the pathophysiology of multiple organ failure and has been associated with in-hospital death.(7, 8) Global hemodynamic parameters do not reflect differential patterns of regional organ blood flow or compromised tissue perfusion of the splanchnic bed associated with shock states. Therefore, optimization of tissue microcirculation should be an objective of the treatment of critically ill patients.(9) However, it is largely unknown whether interventions that significantly increase cardiac output, including implantation of a MCS device, do improve tissue capillary perfusion. Goal-directed manipulation of hemodynamics is the key to understanding the interventions required to reduce the morbidity and mortality associated with multiorgan and hepatorenal failure in patients with end-stage heart disease.

We hypothesized that MCS devices do have beneficial effects on perfusion in a microvascular bed away from the heart. Using a novel handheld videomicroscope applying Sidestream Dark Field (SDF) imaging, we investigated perfusion of the sublingual mucosa, as a prognosticating surrogate for splanchnic microperfusion, before and after implantation of a MCS device.

METHODS

Study design

This observational study was conducted at the Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands. The Institutional Ethical Committee on Human Research approved the protocol. Written informed consent was obtained from each patient or, in case of patients who were sedated, from a relative authorized to consent on behalf of the patient.

Patients and devices

We included 10 consecutive patients with end-stage heart failure or cardiogenic shock, who received a MCS device between May 2008 and April 2009 in our center. Cardiogenic shock was defined as a cardiac index (CI) <2.2 $L.min^{-1}.m^{-2}$ and clinical signs of hypoperfusion (cold extremities, oliguria or altered mental state), not responsive to fluid resuscitation. The cardiac assist devices used were HeartMate II (Thoratec Corp, Pleasanton, CA, USA) in 7 patients, Centrimag (Levitronix, LLC, Walthan, MA, USA) in 2 patients, and TandemHeart (CardiacAssist

Inc, Pittsburgh, PA, USA) in 1 patient. Extracorporeal membrane oxygenation (ECMO/ECLS, Maquet Inc, Bridgewater, NJ, USA) was used in 2 patients.

Hemodynamic monitoring

Patients were monitored with a pulmonary artery catheter (Becton Dickinson Criticath SP5107H, Sandy, UT, USA). The following parameters of systemic and pulmonary circulation were collected: central body temperature, heart rate, mean arterial pressure (MAP), central venous pressure, pulmonary capillary wedge pressure (PCWP), mean pulmonary artery pressure (PAP), CI, systemic vascular resistance, lactate level, and mixed-venous oxygen saturation (SvO_2). Cardiac power index (CPI) was calculated as MAP*CI/451.(10)

Microcirculatory assessment and analysis

The Microscan (MicroVision Medical, Amsterdam, The Netherlands) was used to obtain 2-dimensional video images of sublingual microcirculatory blood flow. This technique has been described and validated previously.(7, 11-13) During each measurement, at least 3 video sequences with duration of 20 seconds were obtained and analyzed. Quantification of these video files was performed using dedicated software (Automated Vascular Analysis 3.0, MicroVisionMedical).(11) After automated image stabilization and frame averaging, perfused capillary density (PCD) was calculated by measuring total length of perfused capillaries divided by image area. Capillaries were defined as the microvessels with a diameter less than 20 µm. Space-time diagrams were used to measure capillary red blood cell velocity (cRBCv) in 5 representative capillaries per video sequence. The velocities measured in 5 capillaries were averaged. PCD and cRBCv values obtained from the 3 video sequences were averaged to produce single mean values for each measurement. Tissue perfusion index was calculated as PCD * cRBCv.(14)

Study protocol

Microcirculation and global hemodynamic parameters were measured at three subsequent time points. First, baseline measurements were performed at the intensive cardiac care unit or at the heart transplant ward before device implantation. Baseline measurements were performed twice within 15 minutes and the results for each variable were averaged to produce single baseline values (T0). The HeartMate II and ECMO devices were implanted at the operating room. The TandemHeart device was introduced in the catheterization laboratory. Measurements were repeated immediately after device implantation when the patient was admitted to the intensive care unit (T1) and 1 day after device implantation (T2). Cardiogenic shock patients were also investigated after weaning of the MCS device or at hospital discharge (T3). Postoperatively, all HeartMate II patients received temporary mechanical ventilation with inhaled nitric oxide to decrease right ventricular afterload. During the measurements, dosages of vasoactive agents were stable.

Statistical analyses

Categoric variables are presented as the number with percentage. All measurements are presented as median with interquartile range (IQR, [25th–75th percentiles]). The Wilcoxon signed ranks test was used to establish differences in global hemodynamic and microcirculatory parameters between 2 subsequent time points. A value of $p<0.05$ was regarded as statistically significant.

RESULTS

Baseline characteristics

Baseline and clinical characteristics of the study population are presented in Table 1. Median age was 45 [38-52] years and 70% were male. Six patients had end-stage chronic heart failure and were on the waiting list for heart transplantation. These patients received a Heartmate II LVAD for progressive heart failure and as a bridge to cardiac transplantation. Four patients received a MCS device for cardiogenic shock: 3 had an acute myocardial infarction complicated by shock (1 received a TandemHeart, 1 received a HeartMate II, and 1 received ECMO). One patient had acute graft failure and cardiogenic shock after cardiac transplantation and received ECMO. Hemodynamic and microcirculatory responses to the different devices were similar.

Table 1. Baseline and clinical characteristics of the study population (N=10).

Characteristic		No. (%) or median [IQR]
Age, years (median and IQR)		45 [38-52]
Gender, male		7 (70%)
CV risk factors:	Hypertension	1 (10%)
	Dyslipidemia	4 (40%)
	Diabetes mellitus	0 (0%)
	Current smoking	1 (10%)
Etiology of heart failure:	Ischemic cardiomyopathy	5 (50%)
	Non-ischemic cardiomyopathy	4 (40%)
	Acute graft failure post-HTx	1 (10%)
Baseline pharmacologic therapy:	Any inotropic agent*	7 (70%)
	Vasopressors†	2 (20%)
	Vasodilators‡	5 (50%)
Mechanical ventilation		3 (30%)
NT-pro-BNP level, pmol/L (median and IQR)		814 [529-1474]
Type of device:	Heartmate II LVAD	5 (50%)
	Heartmate II LVAD + Levitronics RVAD	2 (20%)
	TandemHeart	1 (10%)
	ECMO	2 (20%)

Abbreviations: IQR, interquartile range; CV, cardiovascular; HTx, heart transplantation; NT-pro-BNP, N-terminal portion of pro-B-type natriuretic peptide; LVAD, left ventricular assist device; RVAD, right ventricular assist device; ECMO, extracorporeal membrane oxygenation. * Dobutamine, dopamine, norepinephrine or enoximone. † Norepinephrine or dopamine at a dose >5 $\mu g.kg^{-1}.min^{-1}$. ‡ Nitroglycerin or enoximone.

Macrohemodynamic parameters

Device implantation lowered PCWP (20 [17-23] mm Hg at T0 vs. 17 [16-19] mm Hg at T1, p=0.04, Table 2), and increased CI (1.8 [1.2-2.2] $L.min^{-1}.m^{-2}$ at T0 vs. 2.4 [2.0-3.1] $L.min^{-1}.m^{-2}$ at T1, p=0.007) as well as SvO_2 (54 [46-61] % at T0 vs. 78 [67-85] % at T1, p=0.007). CPI significantly increased after MCS implantation (0.29 [0.21-0.34] at T0 vs. 0.48 [0.39-0.54] at T1, p=0.005). There was a significant decrease in central venous pressure at T2 relative to T1 (15 [13-18] mmHg at T1 vs. 14 [12-15] mmHg at T2, p=0.04) and in lactate concentration (2.1 [1.4-5.1] $mmol.L^{-1}$ at T1 vs. 1.5 [0.9-2.1] $mmol.L^{-1}$, p=0.009). The other parameters remained constant between T1 and T2.

Table 2. The effects of active mechanical circulatory support on global hemodynamics and sublingual microcirculation (N=10).

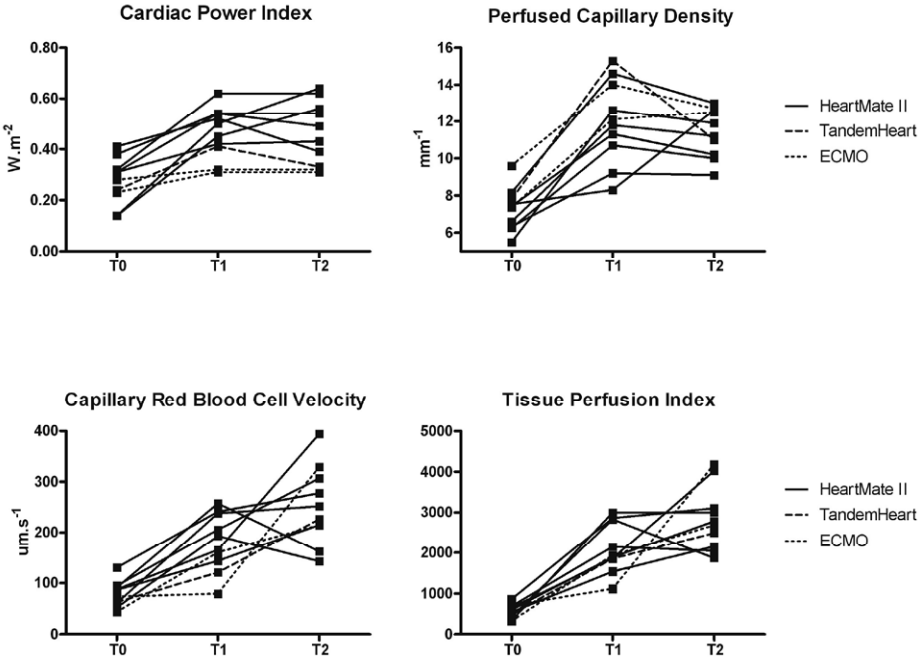
	Baseline (T0)	Immediately after device implantation (T1)	P-value (T0 vs. T1)	One day after device implantation (T2)	P-value (T2 vs. T1)
Core temperature (°C)	37.3 [36.8-37.7]	36.7 [36.1-37.1]	0.02	37.1 [36.4-37.3]	NS
HR (bpm)	97 [78-107]	97 [69-114]	NS	95 [74-107]	NS
MAP (mmHg)	77[71-82]	82 [71-94]	NS	82 [71-90]	NS
CVP (mmHg)	20 [14-23]	15 [13-18]	NS	14 [12-15]	0.04
PCWP (mmHg)	20 [17-23]	17 [16-19]	0.04	17 [13-17]	NS
MPAP (mmHg)	29 [23-30]	27 [25-33]	NS	25 [20-29]	NS
CI ($L.min^{-1}.m^{-2}$)	1.8 [1.2-2.2]	2.4 [2.0-3.1]	0.007	2.4 [2.1-3.1]	NS
SVR (dynes.sec. cm^{-5})	1425 [1193-2306]	1077 [901-1347]	NS	1185 [982-1273]	NS
CPI ($W.m^{-2}$)	0.29 [0.21-0.34]	0.48 [0.39-0.54]	0.005	0.46 [0.33-0.58]	NS
Lactate ($mmol.L^{-1}$)	1.7 [1.2-4.1]	2.1 [1.4-5.1]	NS	1.5 [0.9-2.1]	0.009
SvO_2 (%)	54 [46-61]	78 [67-85]	0.007	76 [74-83]	NS
PCD (mm^{-1})	7.4 [6.3-7.9]	12.0 [10.3-14.2]	0.005	11.5 [10.2-12.6]	NS
cRBCv ($\mu m.s^{-1}$)	80 [59-92]	179 [138-239]	0.005	239 [201-312]	NS
TPI	573 [407-693]	1909 [1771-2835]	0.005	2731 [2125-3333]	NS

All values are shown in median [25th-75th percentiles]. T0, before device implantation (averaged baseline values); T1, immediately after device implantation; T2, one day after device implantation. Abbreviations: HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; MPAP, mean pulmonary artery pressure; CI, cardiac index; SVR, systemic vascular resistance; CPI, cardiac power index; SvO2, mixed-venous oxygen saturation; PCD, perfused capillary density; cRBCv, capillary red blood cell velocity; TPI, tissue perfusion index; NS, non-significant. Formulas: Cardiac power index = cardiac index * mean arterial pressure / 451; Tissue perfusion index = perfused capillary density * capillary red blood cell velocity.

Microcirculation

In general, MCS device implantation resulted in a non-pulsatile blood flow in sublingual microvessels. All devices consistently increased both sublingual perfused capillary density and cRBCv, which resulted in a better tissue perfusion index in all patients (573 [407-693] at T0 vs. 1909 [1771-2835] at T1, p=0.005). No significant change in PCD or cRBCv was documented between T1 and T2. Individual patient data for the cardiac power index and microcirculatory

Figure 1. Evolution of macrocirculation and microcirculation before device implantation (T0), immediately after device implantation (T1), and 1 day after device implantation (T2) at the individual patient level for cardiac power index, (cardiac index * mean arterial pressure / 451), perfused capillary density, capillary red blood cell velocity, and tissue perfusion index (perfused capillary density * capillary red blood cell velocity). Abbreviation: ECMO, extracorporeal membrane oxygenation.

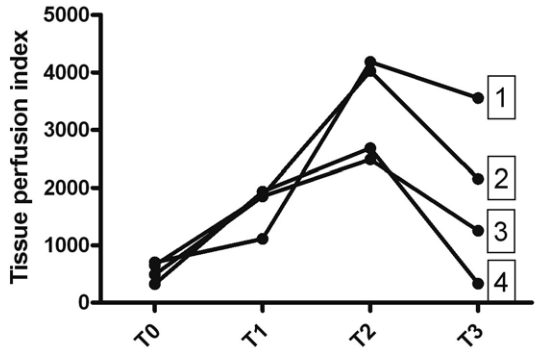


parameters are shown in Figure 1. This small study found no significant correlation between change in CI and change in tissue perfusion index.

Clinical outcome

Through April 2009, the 6 patients with end-stage heart failure who received a HeartMate II device were alive. Two of these patients underwent successful heart transplantation. Only 2 patients admitted with cardiogenic shock survived: 1 was bridged with ECMO to urgent heart transplantion, and the other received a HeartMate II device and is still on the waiting list for heart transplantation. The patient with the TandemHeart device underwent percutaneous aortic valve replacement for concomitant severe aortic valve stenosis 4 days after hospital admission. Unfortunately, irreversible multiple organ failure developed in this patient and in the patient receiving ECMO for primary cardiac graft failure after weaning and removal of the devices. This occurred despite initial recovery of macrocirculatory parameters. Microvascular perfusion in these patients returned to baseline (shock) values after weaning and removal of the devices (Figure 2). Further treatment was stopped after multiple organ failure developed, and both patients died, at 15 days and 9 days after hospital admission. Retrospectively, the

Figure 2. Correlation between microcirculation and clinical outcome in patients with cardiogenic shock. Patient 1: Cardiogenic shock (T0); stabilized with extracorporeal membrane oxygenation (T1-T2); patient survived after cardiac transplantation (T3). Patient 2: Cardiogenic shock (T0); stabilized with HeartMate II (T1-T3); patient discharged alive, HeartMate II is still in situ and the patient is still on the waiting list for cardiac transplantation (T3). Patient 3: Cardiogenic shock (T0); stabilized with TandemHeart (T1-T2); multiple organ failure developed after weaning of mechanical circulatory support (T3), and the patient died. Patient 4: Cardiogenic shock (T0); stabilized with ECMO (T1-T2); multiple organ failure developed after weaning of mechanical circulatory support (T3), and the patient died. T0, before device implantation; T1, immediately after device implantation; T2, 1 day after device implantation; T3, follow-up.



patient with graft failure had an obstructed inferior caval vein anastomosis that might have contributed to the adverse outcome.

In the 7 HeartMate II patients, major adverse events included bleeding requiring re-exploration in 2 patients. Right ventricular (RV) failure in 2 patients required initiation of right ventricular support (Levitronix Centrimag). The RVAD was successfully weaned and removed in both patients, at 6 and 7 days after surgery. Device-related infection developed in 3 patients, and all were successfully treated with antibiotics. No patients experienced device-related neurologic or thromboembolic events.

DISCUSSION

This study demonstrates that mechanical circulatory support improves microvascular tissue perfusion in a heterogeneous series of patients with severe heart failure or cardiogenic shock. Sublingual perfused capillary density and capillary red blood cell velocity increased in all patients, which resulted in a 3-fold increase in the tissue perfusion index immediately after cardiac assist device implantation (p=0.005).

Several recent case reports have described a relatively preserved microvascular blood flow in single patients with cardiogenic shock being treated with an Impella device (Abiomed, Danvers, MA, USA)(15), or ECMO.(16) We analyzed the microcirculation before and after MCS implantation, thus providing direct evidence for a beneficial effect of cardiac assist devices on tissue microcirculation. Although no apparent correlation existed between improvement in CI and the tissue perfusion index, we believe that a better hemodynamic profile due to MCS is the

main cause for improved perfusion of organs and tissues. Dissociation between changes in systemic circulation and microcirculation is a well-known phenomenon that might be explained by local autoregulatory mechanisms. Nevertheless, improved organ perfusion may result in a lower incidence of multiple organ failure and improved functional status and short-term survival.(1,9,17,18) In an earlier study, we demonstrated no major effect of changing intra-aortic balloon pump (IABP) assist ratio on sublingual microcirculation. In that study, however, we did not perform microcirculation measurements before the IABP was introduced.(19) Nevertheless, it is interesting to observe the pronounced benefit on sublingual microcirculation induced by the more powerful MCS devices investigated in the current study.

In the patients with cardiogenic shock who did not survive, microvascular perfusion only temporarily improved but returned to baseline values after weaning and removal of the MCS devices. A recent microcirculation landmark study by De Backer et al(8) also demonstrated a correlation between impaired microcirculation and in-hospital death. These preliminary case observations should be confirmed and investigated more comprehensively in larger studies.

Limitations

Several limitations of this study should be acknowledged. First, we investigated a small, heterogeneous group of patients receiving different types of MCS devices. However, the effect of MCS on tissue perfusion was consistent. Second, factors other than MCS support, especially inhaled nitric oxide ventilation and administration of sedative and vasoactive pharmacologic agents, might have been confounders for improved microcirculatory perfusion after MCS implantation. However, effects were present in patients treated with or without inhaled nitric oxide. In addition, one would not expect that inhaled nitric oxide affects sublingual microvascular perfusion because nitric oxide-hemoglobin is immediately broken down in the circulation.

Clinical perspective and conclusions

In conclusion, MCS devices improve the hemodynamic profile and microvascular perfusion. We propose that future larger studies on outcomes of patients receiving MCS devices should also report the effects of MCS devices on tissue perfusion. Frequent real-time monitoring of microcirculation, followed by prompt interventions in case of tissue hypoperfusion, might prevent multiple organ failure before as well as during institution of MCS. Our findings suggest that improvement of tissue perfusion by MCS devices is a key factor responsible for improvement of functional status, quality of life, and outcome in patients with severe cardiac dysfunction.

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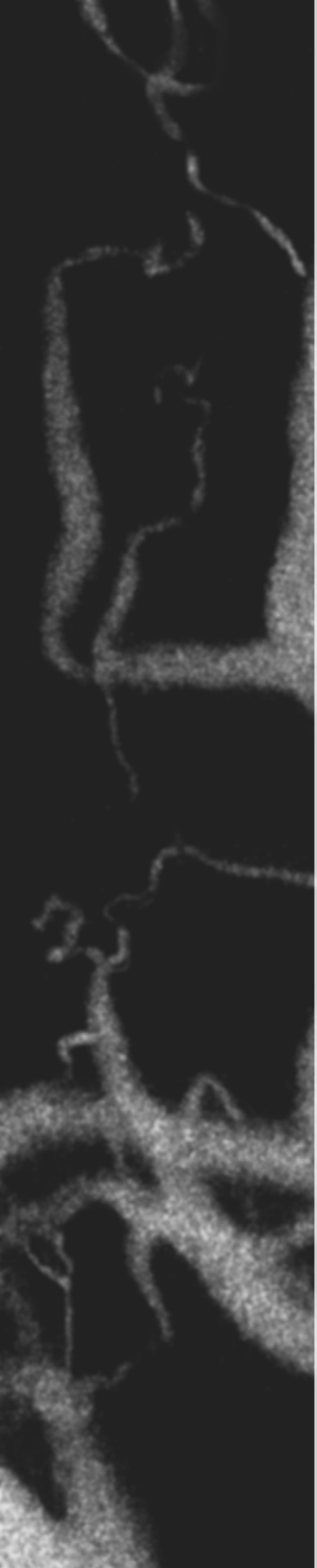
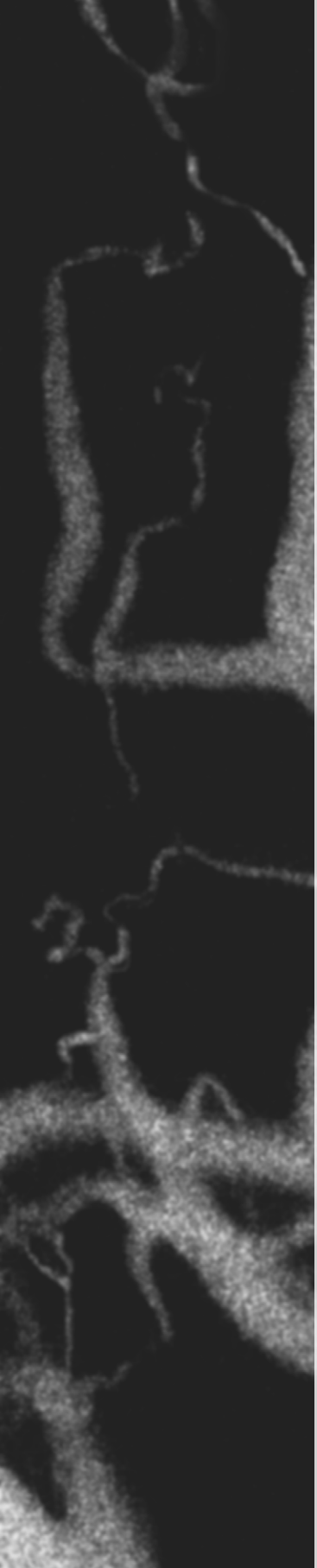


Part E

General discussion and summary of the thesis



Chapter 16

General discussion

Corstiaan A. den Uil

INTRODUCTION

In this thesis, we investigated the feasibility and relevance of monitoring of the microcirculation in patients with severe heart failure and cardiogenic shock. In this section, I will discuss our main findings, and consider implications of the findings with respect to clinical practice and future research.

MAIN FINDINGS

Thirty-day mortality rates among patients with cardiogenic shock remain very high, about 50%.(1) However, in-hospital survivors of cardiogenic shock have a favorable prognosis. Singh et al. reported similar long-term annual survival rates for patients with ST-segment elevation myocardial infarction (STEMI) complicated by shock relative to STEMI patients without shock.(2) Using the Rotterdam Intra-Aortic Balloon Pump (IABP) database, we found comparable results for patients treated in the Thoraxcenter (Chapter 4 and Chapter 5). In addition, we found a decrease in 30-day mortality of cardiogenic shock over time (52% within the time period 1990-1994 vs. 36% within 2000-2004, $p<0.05$, Chapter 5). This improvement in short-term prognosis is probably due to the concomitant implementation of immediate reperfusion therapy, mainly primary percutaneous coronary intervention, in cardiogenic shock from acute myocardial infarction (AMI, Chapter 5). However, although revascularization in cardiogenic shock from AMI is a mainstay of therapy, cardiogenic shock patients are still at high risk of dying. Therefore, it has been investigated whether active temporary support of the circulation in patients with failing hearts would be beneficial. Chapter 6 reviews the results of the three available efficacy studies that compared IABP counterpulsation with the more powerful percutaneous left ventricular assist devices (LVADs) in the mechanical treatment of cardiogenic shock. We demonstrated that, although percutaneous LVADs are superior to IABPs with respect to improvement in hemodynamics, this does not translate into a better prognosis. Pooling the results from the available studies, there was no survival benefit of the use of LVADs.

A fascinating feature that has been increasingly well recognized is that almost half of the nonsurvivors of cardiogenic shock die with a normal cardiac index but with multi-organ failure.(3) Many things are unknown about this observation and new approaches are needed urgently to better understand the pathogenesis of cardiogenic shock to come to better treatment.

Part C contains explorative studies in patients without cardiogenic shock, but at risk of developing multi-organ failure following on-pump cardiac surgery (Chapter 7 and 8). Measurements were performed of sublingual as well as pleural microcirculation. In patients admitted to an intensive care unit, assessment of sublingual microcirculation is the easiest way to study the microcirculation. However, it is largely unknown whether microcirculatory changes in the sublingual area are representative of hypoperfusion elsewhere, most importantly in the splanchnic

region. Several arguments suggest that this is indeed the case. First, the tongue shares a common embryogenic origin with the gut.(4) Second, indirect evidence comes from studies of sublingual tonometry which demonstrated a good correlation between PCO_2 measurements obtained in the sublingual region and in the stomach.(5, 6) Finally, De Backer et al. demonstrated in a small study that the proportion of perfused sublingual capillaries correlated with survival.(7) We found that patients with an impaired microcirculation, defined as a sublingual perfused capillary density (PCD) ≤ median, had more severe heart failure, as demonstrated by higher levels of N-terminal proB-type natriuretic peptide, as well as higher pulmonary capillary wedge pressure, lower cardiac power index and lower SvO_2.

In addition, impaired sublingual perfused capillary density (PCD) was related to the development of organ failure and was an independent predictor for 30-day mortality in a large cohort of patients with cardiogenic shock (Chapter 9). This chapter provides evidence that the microcirculation, measured sublingually and regarded as a surrogate of splanchnic perfusion, is an important factor contributing to the development of organ failure and adverse outcome. These findings raise the question whether an impaired PCD can be improved, and, if so, whether such a strategy will be associated with improved outcome. Chapter 9 demonstrates that patients who had an impaired PCD at baseline as well as after 24 hours were at a high risk to die, as opposed to patients in whom microcirculation was initially impaired, but recovered at 24 hours. The latter patients actually had a similar prognosis relative to patients who had a preserved PCD at both time points. These results indeed suggest that therapies directed at improving microcirculation as assessed by SDF-imaging-derived sublingual PCD might improve outcome in patients with cardiogenic shock.

Having studied descriptives of patients with cardiogenic shock and impaired microcirculation, and the correlation with clinical outcome, we focused on intervention studies in order to investigate whether sublingual PCD could be changed by pharmacologic or mechanical treatment. We investigated the effect of the vasodilator and nitric oxide donor nitroglycerin (NTG) at a low dose of 33 μg/min in patients with acute heart failure (Chapter 11) and found a median increase in sublingual PCD of 10%, although 30% of the patients did not respond. Interestingly, responders had a greater decrease in central venous pressure after NTG. In fact, non-responders might simply have received an insufficient dose of NTG. To better understand the response of the microcirculation in patients with heart failure, we performed an NTG dose-response study (Chapter 12), which provided direct evidence for improvement of tissue perfusion induced by NTG, which could be monitored with Sidestream Dark Field imaging. In addition, we investigated the effects of the inotropic agents dobutamine, enoximone, and norepinephrine on sublingual microcirculation (Chapter 13). Dobutamine and enoximone improved sublingual PCD, whereas norepinephrine diminished sublingual perfusion. Finally, we studied the effects of mechanical support of the failing heart in cardiogenic shock patients. Since no before-after study could be performed in patients receiving IABP counterpulsation, we switched the IABP assist ratio, in patients already treated with IABP, from 1:1 to 1:8 for a time period of 15

minutes (Chapter 14). We found only moderate effects on systemic and pulmonary circulation and no effect on microcirculation, which could be explained by autoregulatory mechanisms, which prevent decreases of microcirculatory blood flow in case of modest changes in global hemodynamics. In Chapter 15, we presented the results of the effects of mechanical circulatory support devices, including HeartMate II devices, on sublingual microcirculation in patients with end-stage chronic heart failure or cardiogenic shock. The effects were beneficial and consistent in all patients, but this study also demonstrated that in patients who died, improvement of microcirculation was only temporary, which underlines the importance of frequent monitoring of not only macro- but also microcirculation.(8)

CLINICAL IMPLICATIONS

The studies described in this thesis potentially have direct implications for current clinical practice.

First of all, clinicians should be aware of the favorable long-term prognosis of in-hospital survivors of cardiogenic shock.(2) This means that great efforts must be made to stabilize patients with cardiogenic shock as much as possible, if necessary with mechanical support devices, to aid them through the acute, critical phase.

Second, most clinicians would still classify cardiogenic shock as an almost entirely macrocirculatory disorder due to pump failure. The studies described in this thesis add significantly to the paucity of evidence on the clinical significance of microcirculatory impairment in this disease.

Third, the introduction of Sidestream Dark Field imaging has allowed to directly observing microcirculatory alterations of the sublingual tissue in patients with cardiogenic shock at the bedside. A problem is still that the video sequences, obtained with SDF imaging, have to be quantified off-line for research purposes. However, in clinical practice, it might be very well possible that a first impression of the quality of microvascular perfusion, comparable to echocardiography, might be sufficient to tailor vaso-active therapy. In addition, a transition from semi-quantitative analysis of video frames towards a software-based analysis reduces analysis time substantially and might readably become available at the bedside in the future.(9-13)

Fourth, in order to reduce multi-organ failure in patients with cardiogenic shock, it is important to understand its etiology. This thesis demonstrates the predictive value of impaired functional capillary density on organ failure and worse outcome in patients with cardiogenic shock.

Fifth, we demonstrated the feasibility of serial monitoring of the microcirculation, which opens the door to a microcirculation-guided, individualized therapy to patients with cardiogenic shock.

DIRECTIONS FOR FUTURE RESEARCH

Although this thesis demonstrated the predictive value of impaired microcirculation on organ failure and patient outcome, it is difficult to prove causal relationships in observational studies. The pathogenesis of impaired microcirculation might involve multiple factors, including diminished cardiac output and systemic inflammation. However, as also demonstrated by the studies presented in this thesis, a correlation between diminished cardiac output and impaired microcirculation, if present, is far from straightforward. Several studies recently demonstrated the correlation between elevated markers of systemic inflammation, especially interleukin-6, on outcome in cardiogenic shock.(14-16) It would be interesting to investigate the correlation between these parameters of inflammation and impaired microcirculation. Finally, a logical next step in microcirculation research would be to perform a multi-center trial to test whether a therapy, guided by monitoring of microcirculation and directed at improving microcirculation, added to current management, would improve outcome (i.e., measures of organ failure, length-of-stay in the hospital, and 30-day survival) in patients with cardiogenic shock.

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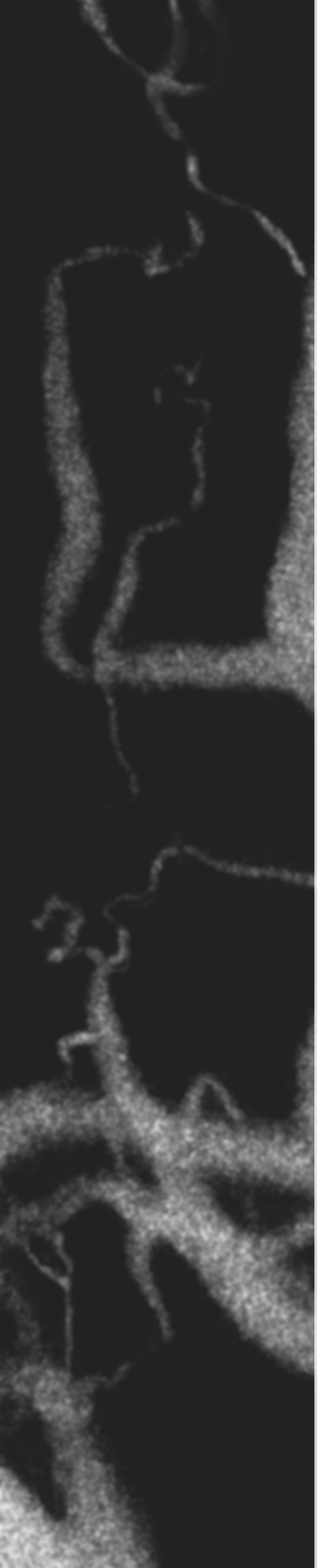


Chapter 17

Summary

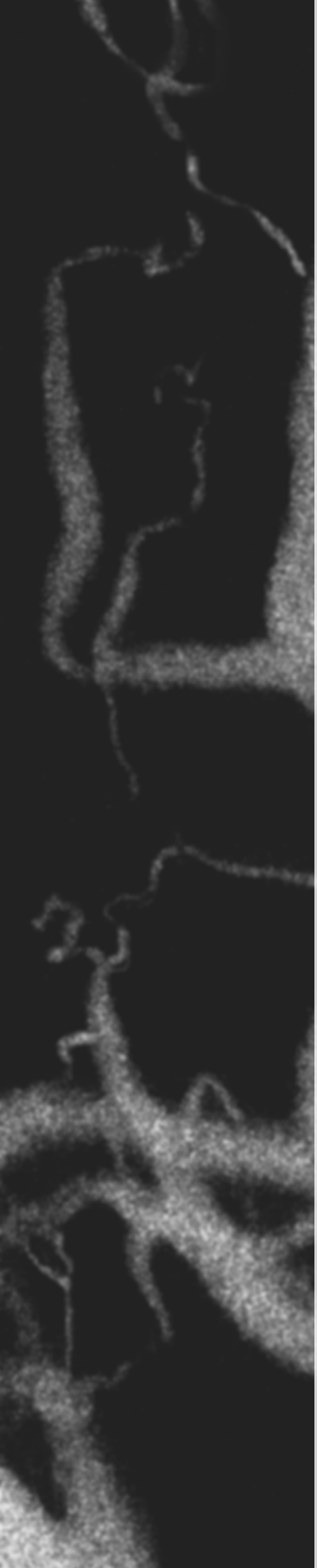
An adequate function of the microcirculation is absolutely essential in providing oxygen to all tissues and organs of the human body, especially in severe heart failure and cardiogenic shock. Untill recently, the microcirculation could not be directly measured at the bedside in patients. The aim of this thesis was to investigate whether sublingual microcirculation, regarded as a surrogate marker for splanchnic perfusion and measured with the novel Sidestream Dark Field (SDF) imaging technique, was a determinant of organ failure and outcome in patients with cardiogenic shock. We hypothesized that impaired sublingual perfusion correlated to organ failure and short-term mortality and that this parameter could be improved using pharmacologic or mechanical therapy.

Part A of this thesis reviews the available literature on the microcirculation in critical diseases. In **Part B**, we presented the short- as well as long-term outcomes of patients with cardiogenic shock. These chapters have several important messages. First of all, 30-day prognosis of patients with cardiogenic shock from acute myocardial infarction improved last years, due to early revascularization strategies. Nevertheless, short-term mortality rates remain very high, which underlines the malignancy of the disease. Interestingly, long-term prognosis of in-hospital survivors is rather favourable and similar to the long-term prognosis of patients admitted to the hospital with acute myocardial infarction without shock. Finally, sophisticated percutaneous left ventricular assist devices have better effects on hemodynamic parameters than conventional intra-aortic balloon pumping, but fail to increase short-term survival (Chapter 6). New approaches are therefore needed urgently.

In **Part C**, we have investigated the feasibility of applying SDF imaging in patients undergoing coronary artery bypass grafting and in patients with cardiogenic shock. In Chapter 7, we describe a modest impairment of sublingual microcirculation in patients undergoing coronary artery bypass grafting. Whether these microcirculatory changes contribute to and predict postoperative multiple organ failure should be investigated in a larger study. In Chapter 8, we describe the results of our efforts to visualize pulmonary alveoli and alveolar microvessels in patients undergoing cardiac surgery. The results obtained in infants were succesfull, however, in adults it was very hard to obtain high-quality images, presumably due to the thicker visceral pleura, as compared to children. In Chapter 9, we found that impaired sublingual microcirculation was associated with organ failure, and was an independent predictor of 30-day mortality. Accordingly, we explained the tentative importance of monitoring of the microcirculation in cardiogenic shock (Chapter 10).

In **Part D,** we investigated whether several routinely applied pharmacological and mechanical treatment options influence sublingual microcirculation and whether it was feasible to monitor these changes using Sidestream Dark Field imaging of the sublingual microcirculation. We found that nitroglycerin, administered at a low dose, improved microcirculation in most patients admitted to the Intensive Cardiac Care Unit with decompensated heart failure (Chapter 11). However, a subgroup of patients did not respond to nitroglycerin. To further investigate the response of the microcirculation to nitroglycerin and to investigate the maximal reponse

of the microcirculation investigated with SDF imaging and quantified with dedicated software, we performed a nitroglycerin dose-response study in patients with severe heart failure or cardiogenic shock (Chapter 12). We found that nitroglycerin progressively improved sublingual perfused capillary density as well as central-peripheral temperature gradient in these patients. It was also possible to visalize the effects of several inotropic agents on the microcirculation in patients with cardiogenic shock (Chapter 13). Finally, we found that a temporary break in intra-aortic balloon pumping did not impair sublingual microcirculation (Chapter 14), but that institution of an active circulatory support device substantially improved microcirculation in patients with severe heart failure or cardiogenic shock (Chapter 15). In our opinion, **Part D** demonstrates the feasibility and value of the SDF measurements in patients with severe heart failure. Whether a microcirculation-based therapy will have a beneficial outcome on patients with severe heart failure and cardiogenic shock should be investigated in a future randomized controlled trial.



Chapter 18

Samenvatting

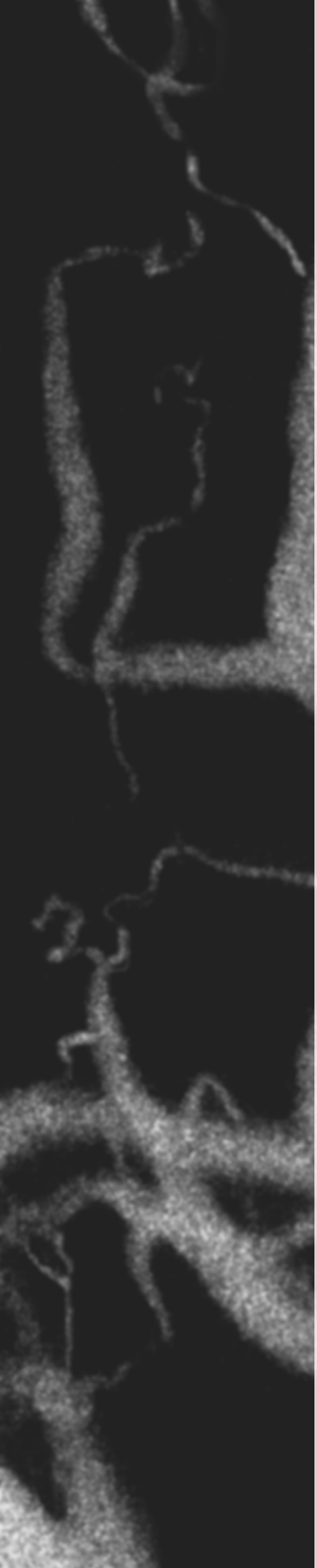
Een goede functie van de microcirculatie is onontbeerlijk om alle organen en weeefsels van het menselijk lichaam van bloed en zuurstof te voorzien. Bij patiënten met ernstig hartfalen of cardiogene shock (d.w.z.: verstoorde weefseldoorbloeding als gevolg van een falende hartfunctie) schiet de microcirculatie vaak tekort. Tot op heden kon de microcirculatie niet direct worden onderzocht. De introductie van de "Sidestream Dark Field (SDF) imaging" techniek heeft het mogelijk gemaakt om de allerkleinste bloedvaatjes (capillairen) onder de tong zichtbaar te maken. Het doel van dit proefschrift was om te onderzoeken of we door middel van microcirculatiemetingen, gemeten met SDF imaging onder de tong, kunnen bepalen of de doorbloeding in de kleine bloedvaten in het lichaam adequaat is. We onderzochten onder andere of een verstoorde microcirculatie samenhangt met het ontwikkelen van orgaanfalen en ziekenhuissterfte bij patiënten met cardiogene shock. Verder hadden we de hypothese dat medicatie die actief op het hart en de bloedvaten werkt ("vaso-actieve medicatie") alsmede mechanische ondersteuning van de hartspier met behulp van een pomp, de microcirculatie kunnnen beïnvloeden en dat we deze veranderingen zichtbaar kunnen maken met SDF imaging.

Deel A van dit proefschrift vatten de beschikbare literatuur over de microcirculatie bij ernstig zieke patiënten samen. In **Deel B** presenteren we de korte en lange termijn resultaten van op dit moment beschikbare behandelingen bij patiënten met cardiogene shock. Deze hoofdstukken bevatten enkele belangrijke boodschappen. Ten eerste, hoewel de korte termijn prognose van patiënten met een hartinfarct gecompliceerd door cardiogene shock slecht is, is deze de laatste jaren verbeterd, waarschijnlijk met name door implementatie van het routinematig toepassen van een spoed-dotterbehandeling. Desalniettemin is de kans om binnen 30 dagen na ziekenhuisopname te overlijden nog steeds 35-50%. Een interessante observatie is dat de lange termijn prognose van een patiënt die cardiogene shock heeft overleefd en levend het ziekenhuis verlaat, gunstig is. Dit gegeven suggereert dat er alles aan gedaan moet worden om de patiënt door de kritieke eerste 30 dagen heen te loodsen. Ten slotte worden in Hoofdstuk 6 twee methoden van mechanische ondersteuning van het falende hart met elkaar vergeleken: de intra-aortale ballonpomp versus nieuwere, geavanceerde pompen die zelf flow genereren. We vonden dat ondersteuning van het hart middels de geavanceerde pompen leidt tot een grotere verbetering van hemodynamische parameters, maar niet tot een betere 30-daagse overleving van cardiogene shock patiënten. Nieuwe benaderingen in de behandeling van cardiogene shock patiënten zijn daarom dringend noodzakelijk.

In **Deel C** van het proefschrift worden de resultaten gepresenteerd van de studies die we hebben gedaan om meer inzicht te verkrijgen in de microcirculatie van patiënten die een kans hebben op het ontwikkelen van orgaanfalen, zoals patiënten die openhartoperaties ondergaan en patiënten met cardiogene shock. In Hoofdstuk 7 beschrijven we dat er sprake is van een voorbijgaande, milde verslechtering in microcirculatie bij een deel van de patiënten die gecirculeerd worden door de hartlongmachine. Of deze verslechtering in microcirculatie klinisch belangrijk is, en bijdraagt aan het postoperatief optreden van multipel orgaanfalen,

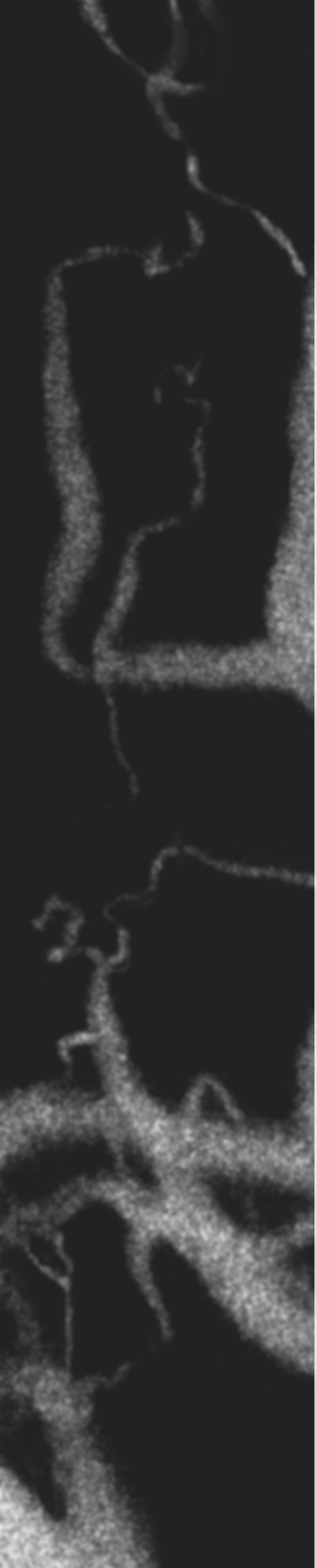
dient te worden onderzocht in een grotere studie. Verder is bij deze patiënten ook gekeken of we de microcirculatie van de longen alsmede longblaasjes zichtbaar konden maken met SDF imaging (Hoofdstuk 8). Dit lukte goed bij kinderen, omdat het longvlies (waaronder de longblaasjes zich bevinden) bij kinderen nog dun is. Deze bevindingen banen de weg voor nieuwe studies, waarin bijvoorbeeld de reactie van de longen op mechanische ventilatie direct bij mensen zou kunnen worden bestudeerd. Tot op heden waren deze studies slechts mogelijk bij proefdieren. In Hoofdstuk 9 beschrijven we een groep van 104 patiënten met cardiogene shock bij wie de microcirculatie is gemeten. We vonden dat een verstoorde microcirculatie geassocieerd was met het optreden van orgaanfalen, en dat deze verstoringen in microcirculatie 30-daagse mortaliteit konden voorspellen. Vervolgens legden we uit waarom monitoring van de microcirculatie dus belangrijk is bij de patiënt met cardiogene shock (Hoofdstuk 10).

Vervolgens is onderzocht wat de effecten zijn van farmacologische behandeling en van mechanische ondersteuning van cardiogene shock op de microcirculatie (**Deel D**). Van belang was met name of we deze veranderingen konden monitoren met behulp van SDF imaging. We vonden dat de microcirculatie verbeterde wanneer we patiënten met gedecompenseerd hartfalen een lage dosering, intraveneus toegediend, nitroglycerine gaven (Hoofdstuk 11). Bij een subgroep van deze patiënten vonden we echter geen effect. Om dit fenomeen beter te onderzoeken en om te bestuderen wat de maximale repons was van de microcirculatie op nitroglycerine, besloten we om een dose-response studie uit te voeren bij patiënten met ernstig hartfalen (Hoofdstuk 12). We vonden dat nitroglycerine geleidelijk microcirculatie verbeterde, wat bleek uit een toename van geperfundeerde capillaire dichtheid en een afname van de gradiënt tussen centrale en perifere lichaamstemperatuur. Het was ook mogelijk om de effecten van verschillende inotropica op de microcirculatie te bestuderen (Hoofdstuk 13). Tenslotte bestudeerden we de effecten van mechanische ondersteuning van de hartspier door middel van verschillende typen steunharten (Hoofdstuk 14 en 15). Naar onze mening demonstreert Deel D van het proefschrift de werkzaamheid van de techniek en de waarde van microcirculatiemetingen bij patiënten met ernstig hartfalen. Of de microcirculatie een nieuwe parameter is die een rol zou moeten spelen binnen de therapeutische benadering van de patiënt met ernstig hartfalen, zou in de nabije toekomst bij voorkeur getest moeten worden met behulp van een klinische, gerandomiseerde en gecontroleerde trial.



Part F

Epilogue



Chapter 19

Dankwoord

Vier jaar geleden startte ik mijn oudste co-assistentschap op de afdeling Cardiologie in het Thoraxcentrum van het Erasmus MC. Onder de inspirerende begeleiding van **Remon Baak** en **Chris van der Lee** raakte ik snel enthousiast voor dit bijzondere vakgebied. In de afgelopen jaren is er veel gebeurd. Ik wil een poging wagen om alle mensen te bedanken die het werken en promoveren mede hebben mogelijk gemaakt. Er bestaat een kans dat ik iemand ten onrechte niet noem, maar in dat geval is mijn dank voor de samenwerking niet minder.

Mijn co-promotor, **Wim Lagrand**, dank ik voor zijn initiatief om dit promotieonderzoek te starten. Je bent een goede clinicus en daarnaast ben je zeer geïnteresseerd in wetenschappelijk onderzoek binnen de acute Cardiologie. Ik heb het altijd jammer gevonden dat je Rotterdam verliet. Maar ook na je vertrek was je betrokken, je was aanwezig bij de vergaderingen op de 5e verdieping, en we hebben veelvuldig gebruik gemaakt van Skype (+headset!). Laten we dat blijven doen.

Peter Spronk, ik ben blij dat je mijn tweede co-promotor bent. Het is fantastisch dat we tijdens onze eerste vergadering in oktober 2006 het raamwerk voor dit boekje hebben gevormd. Maar weinig mensen weten hoe belangrijk je bent geweest om "de vaart erin te houden" en te "focussen". Je inzicht in de literatuur heeft me vaak verrast en was erg leerzaam. Ik ben je erg dankbaar en zou het prachtig vinden om onze samenwerking te continueren.

Verder gaat mijn dank uit naar mijn promotor, **Prof.Dr. Maarten Simoons**. Prof. Simoons, dit boekje is een bewijs van uw gelijk dat er maar weinig ideeën zijn die echt onuitvoerbaar zijn. U leerde me schrijven en presenteren. Verder hebben uw aanmoedigingen om me niet te veel te laten afleiden mij zeer geholpen.

De overige leden van de kleine promotiecommissie, **Prof.Dr. Jan Bakker, Dr. Aggie Balk, en Prof.Dr. Dirk Jan Duncker** dank ik voor hun commentaar op de manuscripten en voor hun bereidheid om het proefschrift te beoordelen.

Ik dank **Prof.Dr. D. Tibboel** voor zijn aanwezigheid bij de verdediging. Dat geldt ook voor **Prof.Dr. Can Ince**, die ik tevens dank voor zijn inspirerende ideeën en voor de dag Amsterdam/Leeuwarden, nu 5 maanden geleden. Uw netwerk binnen de wereld van de microcirculatie is enorm en daar heb ik bewondering voor. I would like to thank **Prof.Dr. Daniel de Backer**, who is the associate editor of "Intensive Care Medicine" and should be regarded as an established investigator of the microcirculation, for his interest in the present thesis and his enthusiasm to take part in the jury.

Mijn paranimfen **Jasper Brugts** en **Annemieke den Uil** wil ik bedanken voor hun steun. Jasper, je bent belangrijk geweest. Ik heb veel geleerd van jouw onderzoekservaring, je kennis van statistiek, en van je ambitieuze houding. Onder het genot van een Swirl hebben we keer op keer toekomstplannen besproken en nieuwe strategieën verzonnen. Je bent er mede voor verantwoordelijk dat ik enthousiast ben geworden voor research. Ik wens je veel succes met het afronden van je eigen promotie.

Martin van der Ent bedank ik voor zijn belangrijk aandeel in de inclusie van patiënten. Jij hebt het praktische gedeelte van mijn onderzoek voor een groot gedeelte gefaciliteerd en

gaf me de vrijheid om volledig mijn gang te gaan met vasoactieve medicatie. Ik bewonder je daadkracht in de kliniek. **Lucia Jewbali** en **Koen Nieman** dank ik voor hun enthousiasme voor het microcirculatie onderzoek en voor alle hulp bij het includeren van patiënten. Lucia, ook bedankt voor de vele gesprekken die we hebben gehad en die me hielpen om door te gaan. Ik heb altijd erg gewaardeerd dat je die tijd voor me nam. **Kadir Caliskan** bedank ik voor zijn ideeën en zijn enthousiaste houding. Hartfalen is een interessant onderwerp, waarover in de toekomst nog wel meer te schrijven is! **Joke en Nathalie**, ook hartelijk bedankt voor de gezellige gesprekken tussen het werk door.

Ik bedank **verpleegkundigen en overig personeel** van de afdelingen OK, ICCU, IC-thorax, 1200 en 800 voor de gezelligheid en hulp bij de vele (Swan-Ganz!) metingen.

Ron van Domburg en **Suzanne Valk** dank ik voor hun toestemming en medewerking om te schrijven op de IABP-database, waaruit verschillende hoofdstukken in dit boek zijn voortgekomen.

Veel dank ben ik verschuldigd aan de **patiënten** die ik heb onderzocht en tevens aan **familie** van patiënten, die niet in staat waren tot het geven van toestemming. Onder moeilijke omstandigheden kregen ze mij aan het bed met de vraag of ik onder de tong mocht kijken.

Ik ben trots op **Jin Ming Cheng**. Jin, ik heb je, naast Ron, begeleid bij het schrijven van enkele artikelen. Ik vind het erg leuk dat je ons idee voor het schrijven van de meta-analyse zo enthousiast hebt uitgewerkt. Je hebt je enorm ingezet en dat is beloond geworden met artikelen in mooie tijdschriften. Veel succes met je co-schappen. Daarna zien we je hopelijk terug.

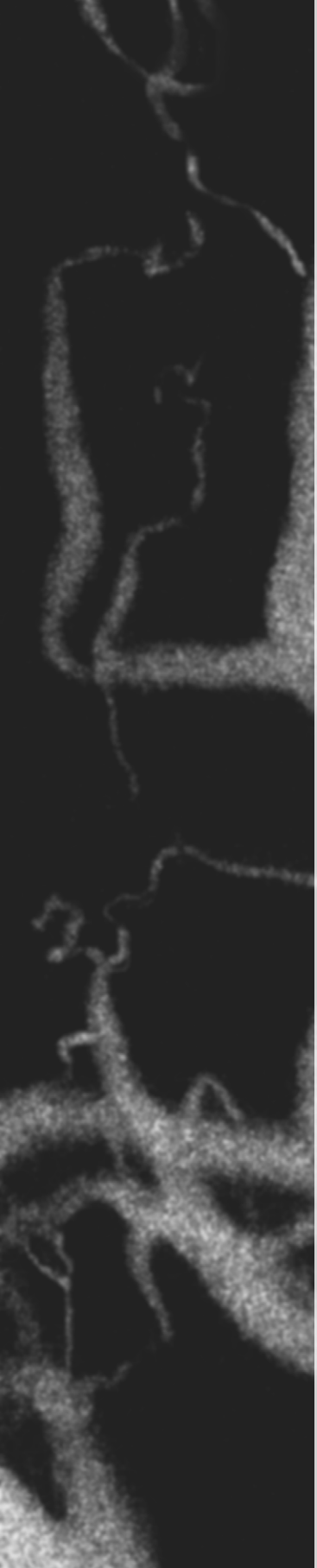
I would like to thank my roommates **Harm Feringa, Radosav Vidakovic, Jasper Brugts, Wael Galal, Jan-Peter van Kuijk, Willem-Jan Flu, Amber Otten, Tuncay Yetgin,** and **Olivier Witteveen.** Dear friends, we had a great time together. What a gigantic amounts of coffee were required to produce the scientific output we had! I really enjoyed the nice moments with all of you and I wish you all the best. **Eva Klijn**, bedankt voor de microcirculatie discussies en de samenwerking bij de reviews. Ik wens je veel succes met je eigen promotie.

Medewerkers van **MIT-groep, afdeling ICT en thoraxlaboratorium** dank ik voor hun snelle en adequate steun tijdens de studies. Ik dank **Maud van Nierop** en **Willeke van der Bent** voor jullie hulp bij de praktische afronding van het proefschrift.

Ik dank mijn **familie en vrienden** voor alle gezellige en goede momenten. Ik bedank mijn ouders voor wat ze mij hebben meegegeven. Ik ben bevoorrecht. Ik dank jullie ook voor het aanhoren van de "promotieverhalen".

Lieve **Therése**, dankjewel voor wie je voor me bent. Je klaagde nooit als ik je weer eens moest bellen met "het wordt wat later". Ik hoop dat we altijd van elkaar zullen blijven houden. **Lucas**, je bent een van de mooiste geschenken die ik heb. Je enthousiasme als papa thuiskomst is een stimulans om dat ook op tijd te doen.

Tenslotte, maar vooral, dank ik **God**, Die me de kracht en de gezondheid gaf om dit proefschrift tot een goed einde te brengen. Ik geloof dat het dienen van deze Koning het leven zinvol maakt. Zijn Naam moet de eer ontvangen.



Chapter 20

List of publications and oral presentations

LIST OF PUBLICATIONS

1. Schaar JA, Mastik F, Regar E, **den Uil CA**, Gijsen FJ, Wentzel JJ, Serruys PW, van der Steen AF. Current diagnostic modalities for vulnerable plaque detection. Curr Pharm Des 2007; 13(10):995-1001.

2. **Den Uil CA,** Lagrand WK, Spronk PE, Simoons ML. Does red blood cell transfusion result in a variate microvascular response in sepsis? Crit Care Med 2007;35(10):2464-5.

3. Brugts JJ, **den Uil CA**. ACE insertion/deletion polymorphism in sepsis and acute respiratory distress syndrome. Intensive Care Med 2008;34(9):1733.

4. Brugts JJ, Danser AH, de Maat MP, **den Uil CA**, Boersma E, Ferrari R, Simoons ML. Pharmacogenetics of ACE inhibition in stable coronary artery disease: steps towards tailored drug therapy. Curr Opin Cardiol 2008;23(4):296-301

5. **Den Uil CA**, Lagrand WK, Spronk PE, van Domburg RT, Hofland J, Lüthen C, Brugts JJ, van der Ent M, Simoons ML. Impaired sublingual microvascular perfusion during surgery with cardiopulmonary bypass: a pilot study. J Thorac Cardiovasc Surg 2008;136(1):129-34.

6. **Den Uil CA,** Klijn E, Brugts JJ, Lagrand WK, Spronk PE. Monitoring of the sublingual microcirculation in cardiac surgery using two-dimensional imaging. Anesthesiology 2008;109(2):353-4.

7. **Den Uil CA**, Klijn E, Lagrand WK, Brugts JJ, Ince C, Spronk PE, Simoons ML. The microcirculation in health and critical disease. Progr Cardiovasc Dis 2008;51(2):161-70.

8. **Den Uil CA,** Lagrand WK, Brugts JJ, Spronk PE. Microcirculation and multi-organ failure in patients with sepsis. Intensive Care Med 2008;34(12):2304.

9. Brugts JJ, **den Uil CA**, Danser AH, Boersma E. The renin-angiotensin-aldosterone system: approaches to guide angiotensin-converting enzyme inhibition in patients with coronary artery disease. Cardiology 2009;112(4):303-12.

10. Klijn E, **Den Uil CA**, Bakker J, Ince C. The heterogeneity of the microcirculation in critical illness. Clin Chest Med 2008;29(4):643-54.

11. Brugts JJ, de Maat MP, **den Uil CA**, Danser JA. Angiotensinogen gene haplotypes in hypertension**.** J Hypertens 2008;26(12):2451-2.

12. **Den Uil CA**, Caliskan K. Intractable supraventricular tachycardia as first presentation of thoracic aortic dissection. Int J Cardiol 2009 **in press**

13. **Den Uil CA**, Lagrand WK, Spronk PE, van der Ent M, Jewbali LSD, Brugts JJ, Ince C, Simoons ML. Low-dose nitroglycerin improves microcirculation in hospitalized patients with acute heart failure. Eur J Heart Fail 2009;11(4):386-90.

14. **den Uil CA,** Lagrand WK, van der Ent M, Jewbali LS, Brugts JJ, Spronk PE, Simoons ML. The effects of intra-aortic balloon pump support on macrocirculation and tissue microcirculation in patients with cardiogenic shock. Cardiology 2009; 114(1):42-46.

15. **den Uil CA,** Valk SD, Cheng JM, Kappetein AP, Bogers AJ, van Domburg RT, Simoons ML. Prognosis of patients undergoing cardiac surgery and treated with intra-aortic balloon pump counterpulsation prior to surgery: a long-term follow-up study. Interact Cardiovasc Thorac Surg 2009; 9(2):227-31

16. Cheng JM, Valk SD, **den Uil CA**, van der Ent M, Lagrand WK, van de Sande M, van Domburg RT, Simoons ML. Usefulness of intra-aortic balloon pump counterpulsation in patients with cardiogenic shock from acute myocardial infarction. Am J Cardiol 2009; 104(3):327-32

17. **den Uil CA**, Lagrand WK, Valk SD, Spronk PE, Simoons ML. Management of cardiogenic shock: Focus on tissue perfusion. Curr Probl Cardiol 2009; 34(8):330-49.

18. **den Uil CA,** Maat AP, Lagrand WK, van der Ent M, Jewbali LS, van Thiel RJ, Spronk PE, Simoons ML. Mechanical circulatory support devices improve tissue perfusion in patients with end-stage heart failure or cardiogenic shock**.** J Heart Lung Transpl 2009; 28(9):906-11

19. **den Uil CA**, Bezemer R, Miranda DR, Ince C, Lagrand WK, Hartman JM, Bogers AJ, Spronk PE, Simoons ML. Intra-operative assessment of human pulmonary alveoli in vivo using Sidestream Dark Field imaging: a feasibility study. Med Sci Monit 2009 **in press**.

20. Cheng JM, **den Uil CA**, Hoeks SE, van der Ent M, Jewbali LS, van Domburg RT, Serruys PW. Percutaneous left ventricular assist devices versus intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. Eur Heart J 2009; 30(17):2102-8

21. **Den Uil CA**, Caliskan K, Lagrand WK, van der Ent M, Jewbali LS, Spronk PE, Simoons ML. Dose-dependent benefit of nitroglycerin on microcirculation of patients with severe heart failure. Intensive Care Med 2009 **in press**

22. van Kuijk JP, Schouten O, Flu WJ, **den Uil CA**, Bax JJ, Poldermans D. Perioperative blood glucose monitoring and control in major vascular surgery patients. Eur J Vasc Endovasc Surg 2009 **in press**

23. **den Uil CA**, Caliskan K, Balk AHMM. Abdominal complaints: consider heart failure. Ned Tijdschr Geneeskd. 2009; 153:A238

LIST OF ORAL PRESENTATIONS AT INTERNATIONAL CONGRESSES

1. **Sublingual microcirculation is impaired during cardiopulmonary bypass in cardiac surgery.** European Society of Intensive Care Medicine, Berlin, 2007

2. **Visualization of human alveoli with Sidestream Dark Field imaging.** American Thoracic Society, Toronto, 2008

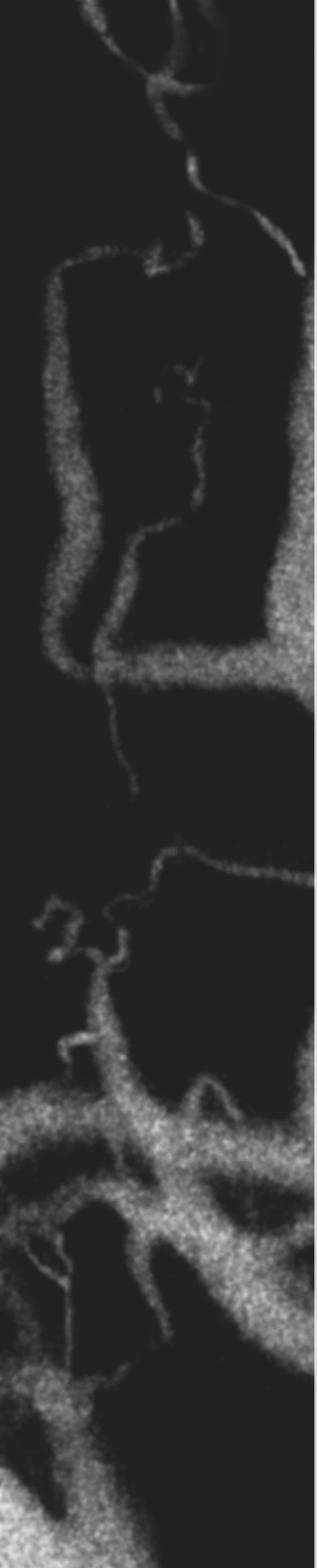
3. **Sublingual functional capillary density is associated with lactate level in patients with acute heart failure.** European Society of Intensive Care Medicine, Lisbon, 2008

4. **Outcome among patients with cardiogenic shock treated with intra-aortic balloon pump counterpulsation: a long-term follow-up study of 386 patients.** European Society of Cardiology, Barcelona, 2009

5. **Inverse correlation between nitroglycerin-induced changes in central-peripheral temperature gradient and changes in sublingual perfused capillary density in patients with cardiogenic shock or end-stage chronic heart failure.** European Society of Intensive Care Medicine, Vienna, 2009

6. **Percutaneous left ventricular assist devices versus intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials.** European Society of Intensive Care Medicine, Vienna, 2009

7. **Mechanical circulatory support devices improve tissue perfusion in patients with end-stage heart failure or cardiogenic shock.** European Society of Intensive Care Medicine, Vienna, 2009



Chapter 21

PhD portfolio

Name PhD student: CA den Uil
Erasmus MC, Thoraxcenter, Department of Cardiology
Research School: COEUR

	Year	Workload (ECTS)
1. PhD TRAINING		
General academic skills		
Course in Biomedical English Writing and Communication	2007	3
Course in Statistics in Intensive Care – professor E. Lesaffre	2009	1
Reviewer for American Journal of Cardiology, Expert Review of Medical Devices, Netherlands Heart Foundation, and NHS Blood and Transplant	2008-2009	1
In-depth COEUR courses		
Cardiovascular Medicine	2007	1.5
Pathophysiology of ischemic heart disease	2007	1.5
Heart Failure Research	2006	1.5
COEUR Research seminars (Friday afternoon)	2006-2009	2.0
Other courses		
Cursus Moleculaire Biologie, Rotterdam	2003	1
24th European Conference on Microcirculation, Amsterdam	2006	1.5
Advanced Cardiac Life Support, Houten	2006	1.5
Symposium coronairlijden en cardiomyopathie, Scheveningen	2006	1
Symposium Cardiorenaal Falen, Utrecht	2006	1
Cardiology and Vascular Medicine, Rotterdam	2006	1
Cardiology and Vascular Medicine, Rotterdam	2007	1
Najaarscongres Nederlandse Vereniging Voor Cardiologie, Ermelo	2007	1
Quantification of microcirculation using MAS software, Amsterdam	2007	1
Symposium Let it Flow, Leeuwarden	2009	0.5
Conferences – participation and presentations		
International Symposium on Intensive Care, Brussels *Poster presentation*	2007	1
International Symposium on Intensive Care, Brussels *Two poster presentations*	2008	1
European Society of Cardiology, Annual Congress, Vienna *Poster presentation*	2007	1
European Society of Cardiology, Annual Congress, Munich *Poster presentation*	2008	1
European Society of Cardiology, Annual Congress, Barcelona *Oral presentation*	2009	1
European Society of Intensive Care Medicine, Berlin *Poster presentation and oral presentation*	2007	1
European Society of Intensive Care Medicine, Lisbon *Poster presentation and oral presentation*	2008	1
European Society of Intensive Care Medicine, Vienna *Three oral presentations and three poster presentations*	2009	1
American Thoracic Society, Toronto *Moderated poster presentation*	2008	1

Voorjaarscongres Nederlandse Vereniging Voor Cardiologie, Amsterdam *Two poster presentations*	2008	1
Congres Venticare, Utrecht *Oral presentation*	2009	0.5
Meeting HERMES critical care group "Over the fence", Apeldoorn *Oral presentation*	2009	0.5

2. TEACHING ACTIVITIES

Lecturing

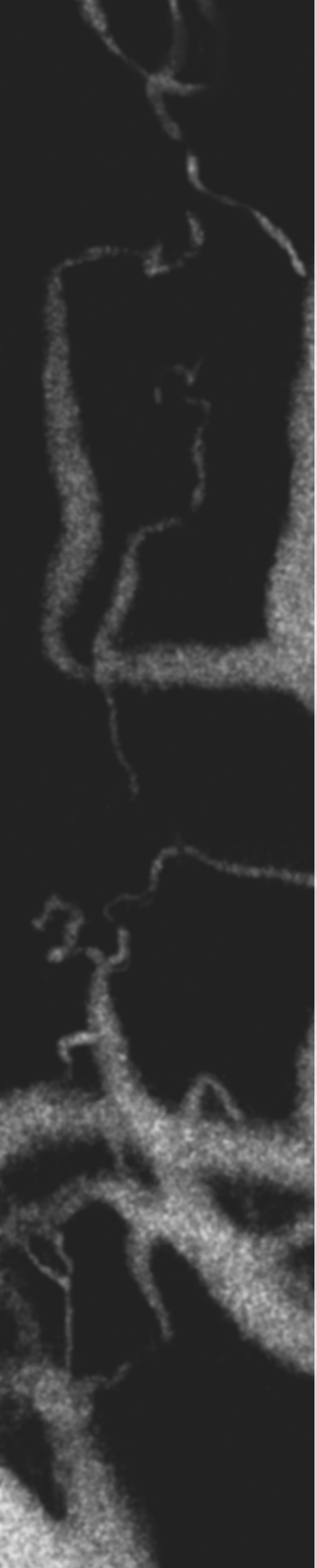
ECG course for 4th year medical students	2007-2009	2
Information talks for patients undergoing cardiac rehabilitation	2006-2009	2

Supervising of medical students

Supervising practicals on how to write a medical review	2007-2008	2
Supervising Masters thesis of Jin Ming Cheng	2008-2009	1

Writing

Author for "Cordiaal", the journal for cardiac care nurses *Contributions: 1. Zin en onzin van inotropica* *2. Harttamponade*		2
Author for "Intensive Care Capita Selecta" *Contribution: 1. Laboratoriumdiagnostiek in de acute cardiologie*		1
	Total	43



Chapter 22

Curriculum vitae

The author of this thesis, Cornelis Adrianus (Corstiaan) den Uil, was born on September 19, 1981 in Sliedrecht, the Netherlands. He attended secondary school at Wartburg College, site Guido de Brès, in Rotterdam, where he graduated in 1999. He obtained his medical degree in 2005 at Erasmus University Rotterdam. Next, he worked for one year as junior house officer at the Intensive Cardiac Care Unit of the Thoraxcenter, Erasmus Medical Center in Rotterdam. At the end of the year 2006, he started a Ph.D.-project at the Erasmus Medical Center (supervisors: Prof.dr. Maarten L. Simoons (Erasmus Medical Center, Rotterdam), Dr. Wim K. Lagrand (Academic Medical Center, Amsterdam), and Dr. Peter E. Spronk (Gelre Hospitals, Apeldoorn)). As of July, 2009, he has started his training as a cardiologist at the Thoraxcenter (head: Prof. dr. Maarten L. Simoons), which includes a two years residency at the department of Internal Medicine of the Albert Schweitzer Hospital in Dordrecht (supervisor: Dr. Eric F.H. van Bommel, internist-nephrologist). The author is a member of the Working Group "Acute Cardiac Care" of the European Society of Cardiology. He is married to Therése van Wijngaarden. They have a son, Lucas.

De auteur van dit proefschrift, Cornelis Adrianus (Corstiaan) den Uil, werd op 19 september 1981 geboren te Sliedrecht. In 1999 slaagde hij voor het eindexamen Voorbereidend Wetenschappelijk Onderwijs aan het Wartburg College, locatie Guido de Brès, te Rotterdam. Aansluitend studeerde hij Geneeskunde aan de Erasmus Universiteit Rotterdam. In 2005 werd het artsexamen behaald. Vervolgens werkte hij als arts niet in opleiding tot specialist (anios) op de Intensive Cardiac Care Unit van het Thoraxcentrum, Erasmus MC te Rotterdam. Aan het einde van 2006 startte hij zijn promotieonderzoek in het kader van een assistent-geneeskundige in opleiding tot klinisch onderzoeker (agiko) project (promotor: Prof.dr. Maarten L. Simoons (Erasmus MC, Rotterdam); co-promotoren: Dr. Wim K. Lagrand (Academisch Medisch Centrum, Amsterdam) en Dr. Peter E. Spronk (Gelre Ziekenhuizen, Apeldoorn)). Per 1 juli 2009 is hij gestart met het klinische gedeelte van de opleiding tot cardioloog, te beginnen met de vooropleiding Interne Geneeskunde in het Albert Schweitzer Ziekenhuis te Dordrecht (opleider: Dr. Eric F.H. van Bommel, internist-nefroloog). De auteur is lid van de werkgroep "Acute Cardiale Zorg" van de Europese Vereniging voor Cardiologie. Hij is getrouwd met Therése van Wijngaarden. Zij hebben een zoon, Lucas.

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