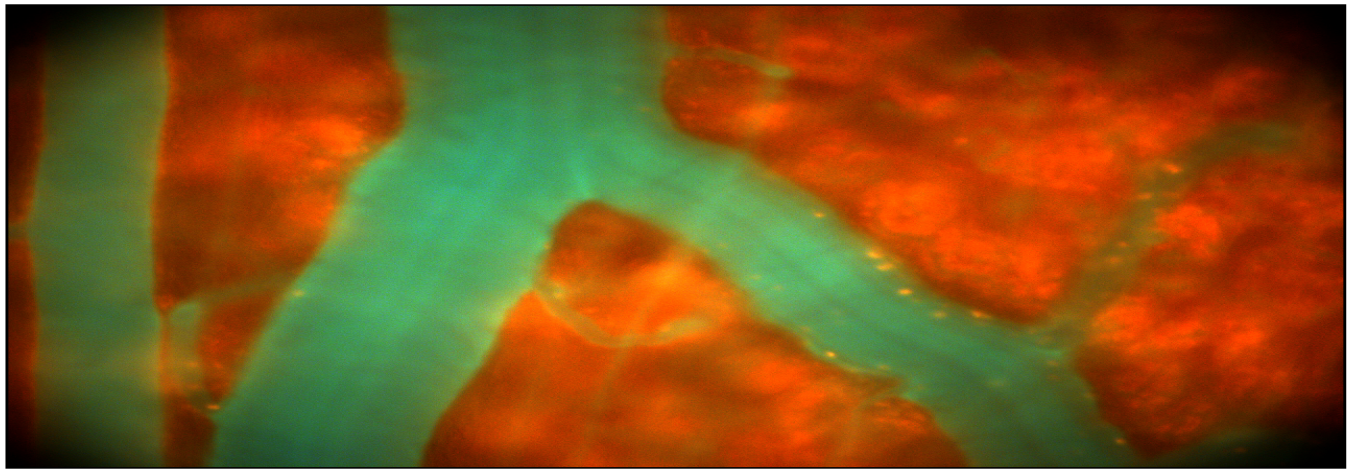
1. International **M**iDAS **M**icrocirculation **M**eeting "3**M**"

April 4, 2013

Halifax, Nova Scotia, Canada



“Seeing is believing”

1. International **M**iDAS **M**icrocirculation **M**eeting “3**M**”

Date: April 4, 2013

Venue: QE II Health Sciences Centre, Halifax Infirmary Site, Anesthesia Library, 5th floor, Halifax, NS, Canada

Organization: Prof. Dr. Ch. Lehmann, Dalhousie University Halifax, Canada

Publication: Journal “Clinical Hemorheology and Microcirculation”

Program:

1. Workshop (MiDAS only)

14:00 Round table: Guidelines for intestinal microcirculation imaging

2. Public Meeting

16:00 Reception

17:00 Opening (Shukla, Halifax)

17:05 Basics of vascular reactivity in inflammation and sepsis (Pavlovic / Paris)

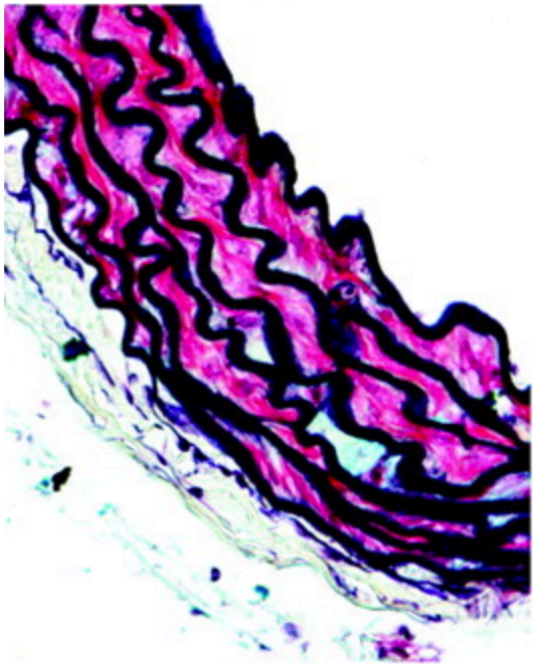
17:30 Sublingual OPS imaging in intra-abdominal hypertension patients (Maddison / Tartu, Estonia)

18:00 Coffee break

18:15 Intestinal SDF imaging in critical ill patients (Cerny, Abdo / Prague)

18:40 Clinical perspectives for micro-circulation monitoring (Kern / Berlin)

19:00 Closing remarks (Lehmann / Halifax)



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Basics of vascular reactivity in inflammation and sepsis

It is a feature peculiar to sepsis, that apart from compromised microcirculation, the vascular system is little if at all responsive to the constricting agents - a condition known as the arterial hyporeactivity of sepsis. In patients it could be observed that the increased doses of catecholamines or other vasoconstricting agents are needed to achieve some increase of peripheral resistance. In animal models and in vitro experiments it is observed that following challenge with the endotoxin (LPS), the response to vasoconstricting agents is diminished or almost absent. The exact mechanisms behind this phenomenon are not known. Tone of the vascular smooth muscle is a result of a fine balance between constricting and relaxing mechanisms. It is believed that increased activity on the side of the relaxing mechanisms would contribute to the insensitivity of the arterial smooth muscle to the constricting agents. It is possible that at least partially an increased production of nitric oxide (NO) that is present in sepsis, prevents smooth muscle to respond adequately when stimulated pharmacologically with a constricting agent. Various other mechanisms that involve local cotransmission probably play an important role in this quite unspecific hyporeactivity of the vascular smooth muscle. Various strategies to increase smooth muscle reactivity have been tried, like increasing excitability of the smooth muscle cell membrane, diminishing Ca^{++} extrusion, increasing intracellular Ca^{++} content or increase of Ca^{++} sensitivity of contraction, favoring myosin phosphorylation or other mechanisms that promote these effects and which could theoretically promote arterial reactivity. If a correction of vascular hyposensitivity would be achieved this would permit to better design therapy for such patients. If such a therapy would also be vascular bed specific, it would permit better control of the local perfusion of some critical regions, like intestinal vascular bed.

Sublingual microcirculation in patients with intra-abdominal hypertension

Background: Intra-abdominal hypertension (IAH) – abdominal pressures equal to or above 12 mmHg – affects approximately one third of intensive care patients. Epidemiological studies have repeatedly shown that patients with IAH have impaired outcomes. Microvascular alterations are associated with the development of organ failure and death, especially in sepsis. It is not known whether increased intra-abdominal pressure (IAP) is associated with microcirculatory perfusion derangements. Our hypothesis was that increased IAP is related to microcirculatory alterations. Sublingual microcirculation has been shown to correlate well with splanchnic perfusion, therefore we used sublingual OPS imaging to test this hypothesis.

Methods: Two prospective observational studies were performed. First, effect of mild and short-term IAP increase was investigated in 16 patients undergoing elective laparoscopic surgery. Second, to assess the impact of moderate and prolonged IAH fifteen intensive care patients with IAP ≥12 mmHg for at least 12 hours were enrolled and followed for next 72 hours as minimum.

Results: Laparoscopic patients had baseline (before anaesthesia) median (IQR) total vascular density of 19.4 (17.0 – 21.1) and perfused vessel density 13.3 (10.9 – 15.2) per mm^2. Proportion of perfused vessels was 61(50– 69) %, microvascular flow index 2.4 (2.0 – 2.5), heterogeneity index 0.8 (0 – 0.9) and De Backer score 13.4 (11.7 – 14.9). IAP of 12-13 mmHg induced by pneumoperitoneum did not caused significant changes in these parameters if assessed 15 minutes after gas insufflation.

Intensive care patients were enrolled median 36 (26 - 45) hours after admission, their baseline median IAP was 14.5 (12.5 – 16.0) mmHg. Significant decrease of IAP over the time was observed with near to normal values 24-36 hours after enrolment. The total vascular density of small vessels was 13.1 (11.0 – 15.1) per mm^2 at the baseline, and perfused vessel density 12.2 (10.7 – 14.1) per mm^2. Proportion of perfused vessels was 80.3% (68.2 – 86.9%), De Backer Score 9.1 (8.1 – 10.3) and a microvascular blood flow of 3 (3 - 3). Blood flow heterogeneity index was 0 (0 - 0.3) at the study entry. No significant changes were observed through the study period. Correlation-analysis revealed slightly impaired microvascular blood flow at lower levels of abdominal perfusion pressure.

Conclusions: IAH at grades I and II (IAP from 12 to 18 mmHg) lasting up to 24 hour has only negligible influence upon sublingual microcirculation in elective surgical patients or in fluid resuscitated critically ill patients.

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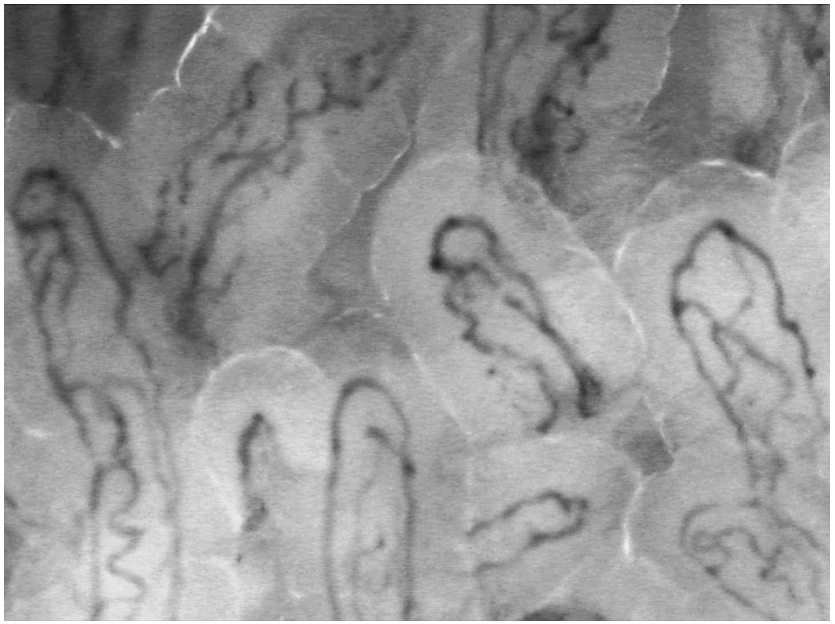
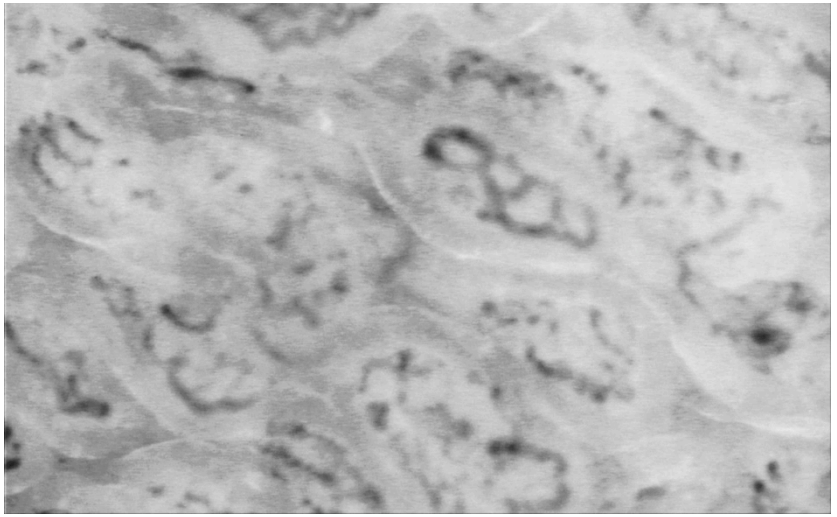
Intestinal SDF imaging in critically ill patients

The microcirculation plays a crucial role in the interaction between blood and tissue both in the physiological and pathophysiological states. In the last few years, an important body of knowledge has been developed to show the pathophysiological relevance of the microcirculation in the development of multiorgan failure associated with sepsis. In addition to the compelling experimental evidence, the development of new videomicroscopic techniques allows now the evaluation of the microcirculation in critically ill patients. The introduction of the Sidestream Dark Field imaging technology (originally designed to study the sublingual microcirculation) offered a possible window for researchers to study the microcirculatory alterations related to sepsis in various organs and tissues, intestinal mucosa represents one of them. The intact intestinal villi play an important role against bacterial translocation; nevertheless, such unique protecting function could be compromised during septic shock as alteration in the intestinal microcirculation lead to the loss of villi wall integrity. Patients with ileostomies offer a unique window to intestinal microcirculation. The MiDAS group carried an observational prospective study investigating alterations in the intestinal microcirculation in the critically ill patient. The SDF technology proved to be a feasible method in studying the intestinal microcirculation. Furthermore, the MiDAS group concluded the necessity for the development of new guidelines directed towards the capturing and analysis of intestinal microcirculation. The intestinal microcirculation could rise as a new more clinically related target in the treatment of patients with sepsis and septic shock. Key points covered by lecture:

1) Current scientific evidence on the clinical importance of intestinal microcirculation in sepsis
2) Describing the method of SDF intestinal imaging
3) Highlighting the challenges and obstacles
4) Demonstrating results and most interesting findings





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Clinical perspectives for microcirculation monitoring

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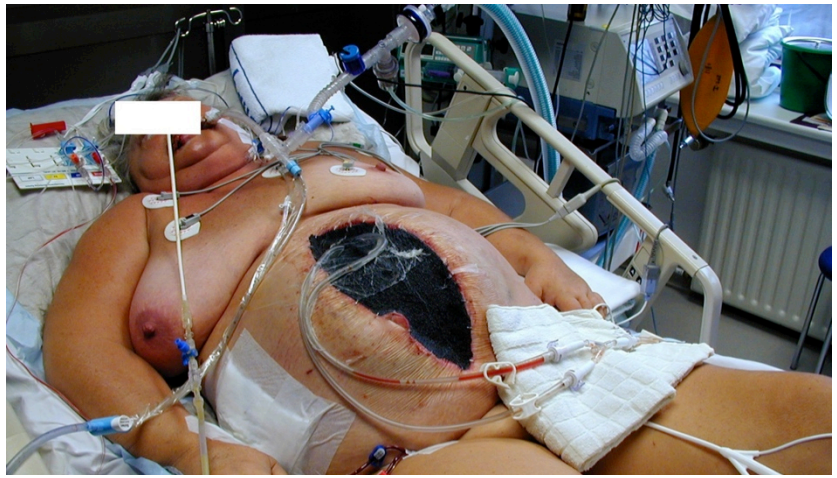
Early goal-directed therapy (EGDT) is a term used by Rivers et al. (1) in 2001 to describe the use of certain parameters to guide intravenous fluid and inotropic therapy in severe sepsis and in septic shock patients already in the emergency department. He could demonstrate an incredible 16 % mortality benefit by this way patients were cared for. These results of EGDT in septic patients were successfully transformed into clinical practice in different countries (2).

The transformation of the technique of goal-directed therapy (GDT) in the preoperative setting of high-risk general surgical patients has been shown to improve outcome as well (3,4).Pearse et al. (5) suggested that postoperative goal-directed therapy in high risk general surgical patients was effective without requiring additional intensive care resources. However, only global haemodynamic changes were focussed on. The technique of cardiac output measurement by lithium indicator dilution and pulse power analysis has widely been demonstrated to create similar results (4-6).

The question with fortcoming interest however was, if the goal to achieve global haemodynamics represented really regional perfusion (7). Instead of that, growing evidence has been shown that there exists at least an heterogeneity of microcirculation in different states of haemodynamic instability and critical illness (8).

Due to ongoing technological development, microcirculation could be directly measured sublingually and enterostomically in an experimental setting by Orthogonal-Polarisations-Spectral(OPS) –Imaging (9-10). Recently, a device even easier to handle has been developed: the Sidestream dark-field technology (SDF) bringing microcirculation diagnostics from the bench to the bedside (11).



This new technique opens wide clinical perspectives: SDF imaging may permit a real-time diagnosis of early changes in the microcirculation as a reflection of fluid loss and administration during the conduct of surgery in different perioperative settings. In critical care patients, this technique may permit a real-time diagnosis of early changes in the microcirculation as a reflection of fluid therapy and administration of vasoactive drugs during different states of circulatory shock.

However, certain requirements have to be solved before this technique may be used worldwide in clinical practice.

Notes

Microcirculation Diagnostics and Applied Studies (MiDAS)
Halifax, Prague, Berlin, Greifswald, Tartu

Supported by the Department of Anesthesia, Pain Management and Perioperative Medicine, Dalhousie University Halifax and the Nova Scotia Health Research Foundation, Canada

http://microcirculation.medicine.dal.ca