Endothelium as a part of septic Multiple Organ Dysfunction Syndrome (MODS)-is endocan an answer ?

Małgorzata Lipinska-Gediga

Department of Anaesthesiology and Intensive Therapy

Medical University Wroclaw, Poland

Sepsis is a systemic, deleterious host response to infection leading to **severe sepsis** (acute organ dysfunction secondary to documented or suspected infection) and **septic shock** (severe sepsis plus hypotension not reversed with fluid resuscitation)

Intensive Care Med (2013) 39:165–228
DOI 10.1007/s00134-012-2769-8

Under resting conditions, endothelial cells exhibit a number of important physiological functions :

- **regulate** blood pressure and blood flow by modulating the tone of arterioles
- **inhibit** blood coagulation
- **express** thrombomodulin, which binds thrombin and Activated protein C (APC), with its cofactor protein S, blocks the cofactors VIIIa and Va of the clotting system.

- **release** small amount of tissue-type plasminogen activator and inhibit platelet aggregation by producing prostacyclin and nitric oxide
- **regulate** the transmigration of leukocytes by controlling the expression of adhesion molecules and the production of chemoattractants

As one of the largest “organs”, **the endothelial and capillary system occupies a central role** in the homeostasis of organ functions. However, one of the largest and most important organs, is not routinely tracked in the daily clinical routine

In **sepsis, endothelial activation** and **dysfunction** are critical determinants of the host response and represent an explanation for the complex sepsis pathophysiology (Iba et al. 2005; Shapiro et al. 2010,Paulus 2011).Given this **central place of the endothelium**, there is a strong biologic rationale for targeting markers of endothelial activation as biomarkers of sepsis. (Pierrakos and Vincent 2010, Paulus 2011, Xing 2012, De Backer 2014).

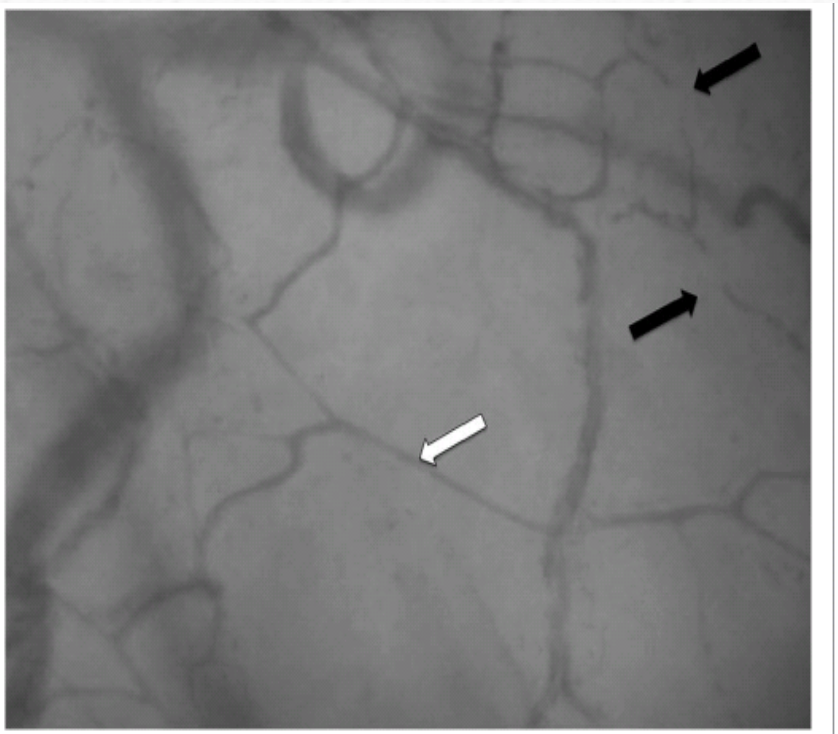


Figure 1. Sublingual microcirculation in sepsis. Photograph of the sublingual microcirculation in a patient with septic shock using a sidestream dark field (SDF) imaging device. The white arrow shows a perfused capillary, the black arrows identify a stopped flow capillary.

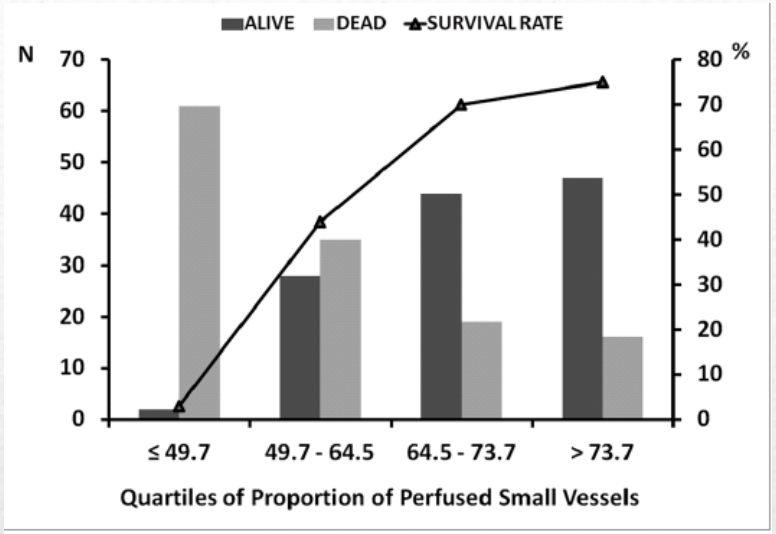
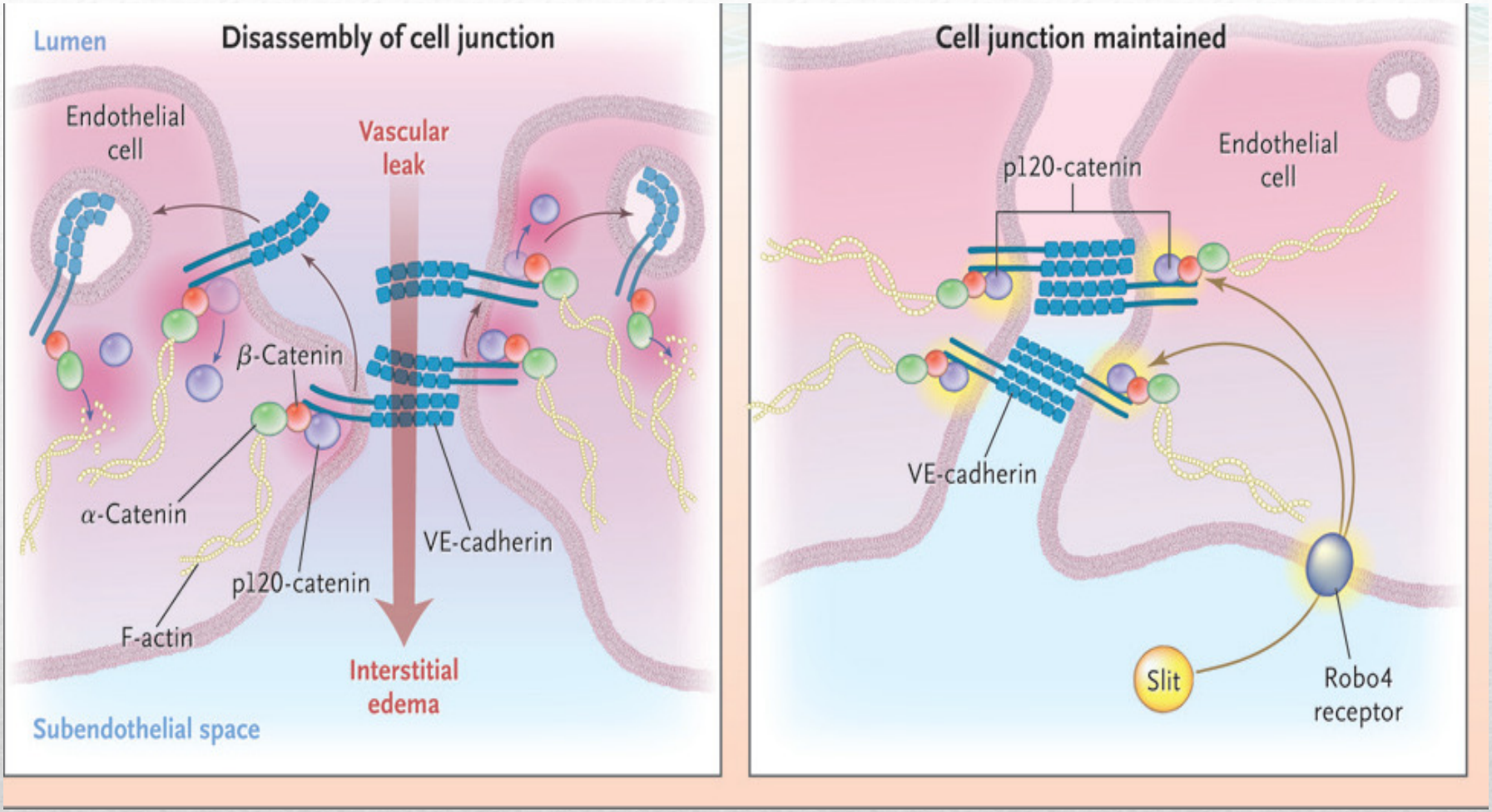
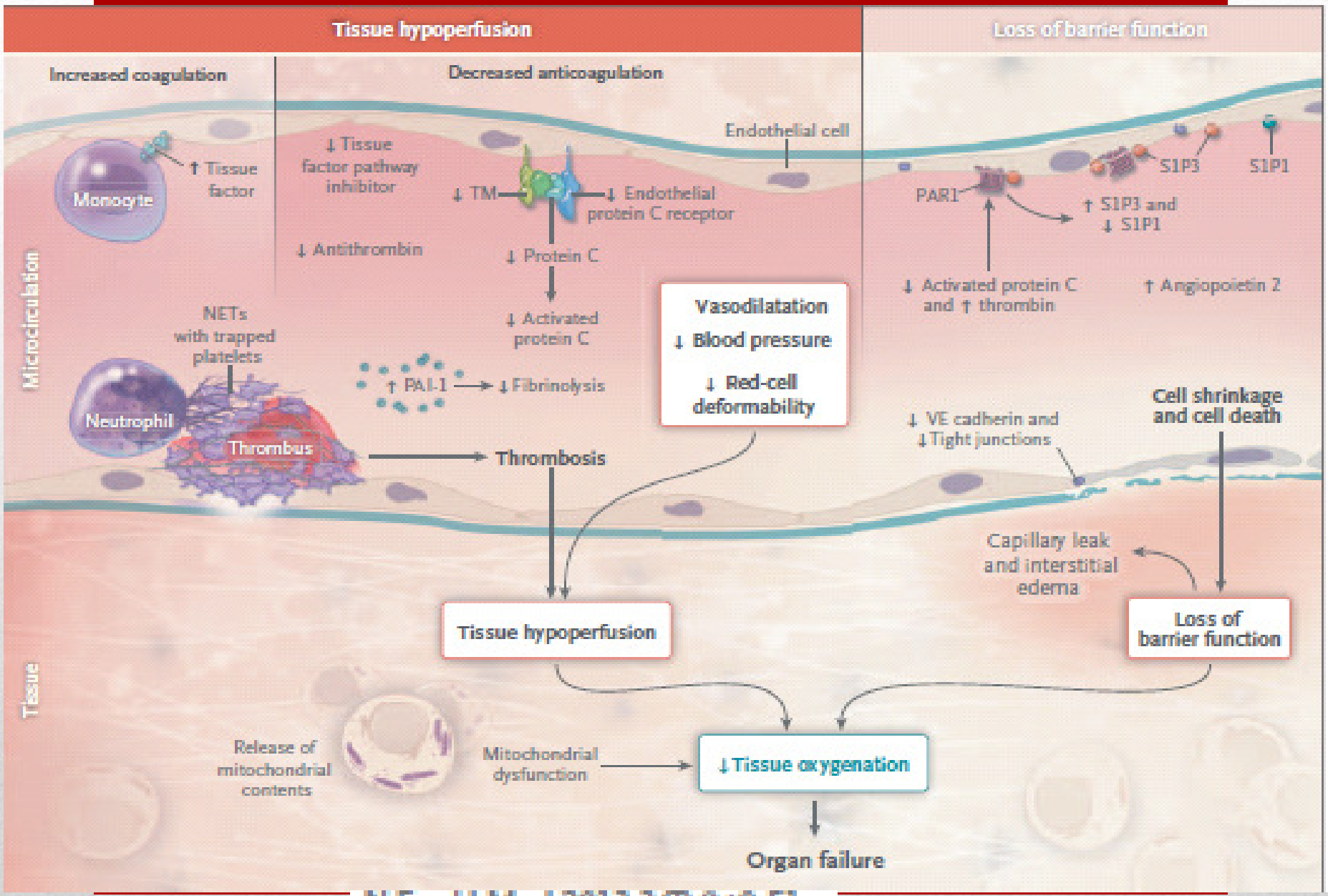


Figure 2. Relationship between sublingual microcirculation and ICU mortality in patients with severe sepsis. In this series of 252 patients with severe sepsis, the sublingual microcirculation was assessed either with an orthogonal polarization spectral (OPS) or a sidestream dark field (SDF) imaging device. The patients were grouped into quartiles of proportion of perfused capillaries. From reference 3 with permission.



N Engl J Med 363;7 nejm.org August 12, 2010



N Engl J Med 2013;368:840-51.
DOI: 10.1056/NEJMra1208623

Endocan, also called endothelial cell-specific molecule-1, is a soluble 50 kDa **dermatan sulfate proteoglycan** that is secreted from pulmonary and kidney vascular endothelial cells [Bechard et al. 2001, Lassalle et al.1996]. Endocan is stable at low levels in the blood and was detected in the serum of healthy subjects at an average concentration of 1.08 ng/ml**. ESM-1 mRNA** is regulated by the cytokines, TNFα induced accumulation of ESM-1 mRNA early;(Berchard et al. 2000), it was detectable at the second hour and peaked at the 18th hour of TNF incubation. The spontaneous as well as TNFα-induced secretion of ESM-1 is strongly inhibited by IFNγ. **Endocan** was shown to inhibit the interaction between intercellular adhesion molecule-1 **(ICAM-1**) and the integrin (lymphocyte function-associated antigen-1) **LFA-1** on leukocytes, and can modulate LFA-1 mediated leukocyte functions, such as the firm adhesion of leukocytes to the endothelium and the leukocytes transmigration (Bechard et al. 2000)

Study group comprised twenty two patients with septic shock, admitted to the Department of Anesthesiology and Intensive Therapy of Wroclaw Medical University, Poland. Patients with cardiogenic shock and other acute circulatory failure not induced by infection were excluded from the study. The study group patients were retrospectively divided into the **survivors** (n = 15) and **non-survivors** (n = 7) subgroups. The diagnosis of septic shock was performed according to the 2001 Consensus Conference Criteria .This study is observational and prospective. The status of clinical patients was assessed with the **Acute Physiology and Chronic Health Evaluation II** (**APACHE II**) score [Knaus et al. 1985] on admission to the ICU, and the extent of multiple organ failure was evaluated using the **Sequential Organ Failure Assessment** (**SOFA**) score [Vincent et al.1996] on admission, and on the 2nd, 3rd, and 5th days. Blood was drawn on admission, and on the 2nd, 3rd, and 5th days.

The data were analyzed with non-parametric test (Mann–Whitney U-test) to compare the two groups. The APACHE II and SOFA score values are presented as the mean ± standard deviation (SD). A P value ≤ 0.05 was considered to be statistically significant. Correlation analysis with continuous data was conducted using Pearson's correlation test (r). All analyses were performed using the *STATISTICA data analysis software system, version 10. StatSoft, Inc. (2011). www.statsoft.com*

Control group-adult patients undergoing valve replacement or coronary artery bypass grafting under **cardiopulmonary bypass (ECC)** were consecutively included in the study. Endocan levels were measured before and directly after surgery, next on the 1st and 2nd postoperative day at the ICU. The control group consisted of 19 patients (12 men, 7 women, mean age 67 years), this group presented no multiple organ failure in postoperative period and the ICU stay didn't exceed 2 days.

	Cardio (ECC) group n=19	**Septic group n=22**	**P value**
Endocan $_{1st}$	2,10 (0,64÷7,9)	5,25 (0,58÷13,0)	0,0009
Endocan $_{2nd}$	5,06 (0,97÷6,9)	5,09 (0,58÷12,0)	0,24
Endocan $_{3rd}$	4,80 (1,09÷11,0)	2,36 (0,65÷10,0)	0,08
Endocan $_{4th}$	3,1 (1,0÷10,7)	2,01 (0,58÷12,0)	0,68

APACHE II and SOFA score in septic shock group

	Survivors N=15	Non-survivors N=7	P value
APACHE II 1st day	21,5 ± 5,41	28,66± 7,36	0,025
SOFA 1st day	10,85 ± 2,53	13,66 ± 3,07	0,048
SOFA 2nd day	8,14 ± 1,87	12,16 ± 3,18	0,002
SOFA 3rd day	6,07 ±3 ,19	11,00 ± 6,27	0,04
SOFA 5th day	4,33 ± 3,04	12,00 ± 5,29	0,009

Endocan (ng/ml) in septic shock group

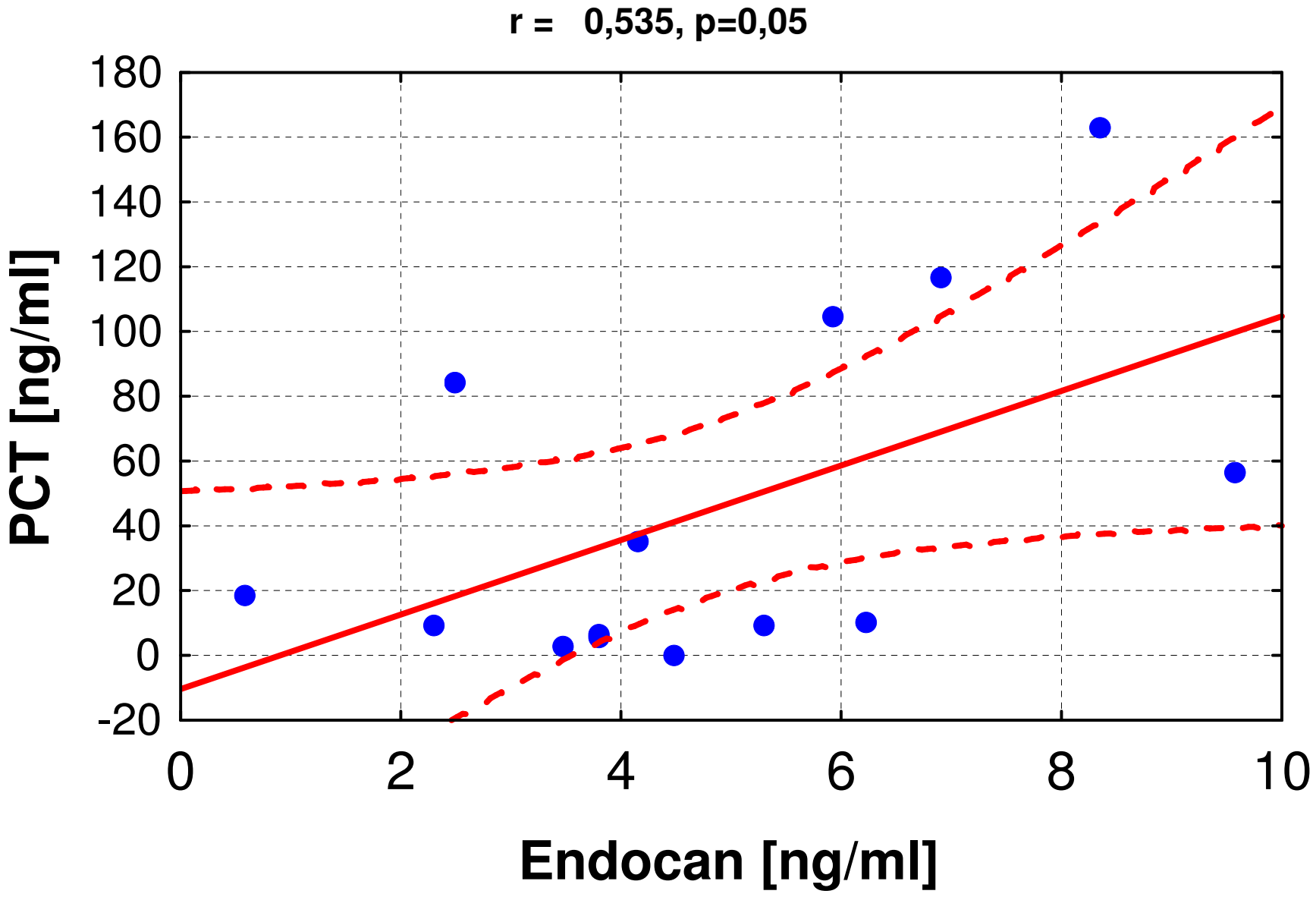
	Survivors N=15	Non-survivors N=7	P value
Endocan 1st day	4,46 (0,58÷9,57)	7,15 (2,8÷13,0)	0,13
Endocan 2nd day	5,34 (0,58÷10,8)	4,85 (2,6÷12,0)	0,52
Endocan 3rd day	2,26 (0,65÷10,0)	4,0 (2,34÷10,0)	0,19
Endocan 5th day	1,76 (0,58÷8,00)	10,8 (1,56÷12,0)	0,03

	Cardio (ECC) group n=19	Septic survivors n=15	P value
Endocan $_{1st}$	2,10 (0,64÷7,9)	4,46 (0,58÷9,57)	0,006
Endocan $_{2nd}$	5,06 (0,97÷6,9)	5,34 (0,58÷10,8)	0,6
Endocan $_{3rd}$	4,80 (1,09÷11,0)	2,26 (0,65÷10,0)	0,005
Endocan $_{4th}$	3,1 (1,0÷10,7)	1,76 (0,58÷8,00)	0,25

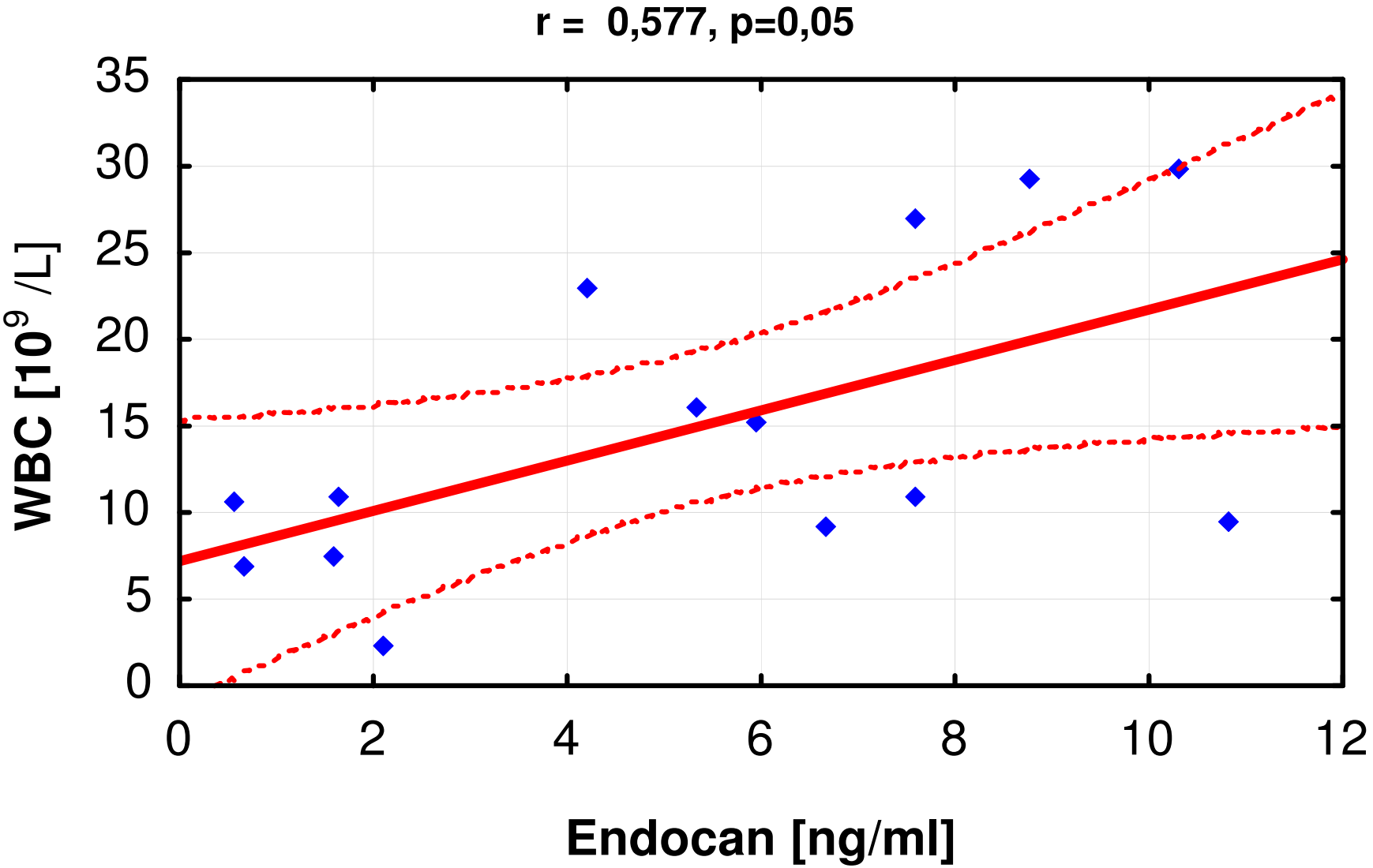
	Cardio (ECC) group n=19	Septic non-survivors n=7	P value
Endocan $_{1st}$	2,10 (0,64÷7,9)	7,15 (2,8÷13,0)	0,002
Endocan $_{2nd}$	5,06 (0,97÷6,9)	4,85 (2,6÷12,0)	0,38
Endocan $_{3rd}$	4,80 (1,09÷11,0)	4,0 (2,34÷10,0)	0,88
Endocan $_{4th}$	3,1 (1,0÷10,7)	10,8 (1,56÷12,0)	0,20

Procalcitonin (PCT) is a prohormone of calcitonin consisting of 114 to 116 amino acid, PCT originates from the calcitonin-I (CALC-I) gene on chromosome 11.Under physiological conditions serum levels are below 0.5 ng/ml. A microbial infection induces an ubiquitous increase in CALC-I gene expression and a significant release of **CTpr** from all tissues and cell types (Müller, 2001) . Whang and et. al considers that PCT is a secondary mediator intensifying, rather than initiating, the septic response (Whang, 2000). According to **SSCIG 2013** (Dellinger 2013) **PCT** is used as a diagnostic marker of **sepsis,** monitoring its course and therapeutical efficacy.

Correlation between the procalcitonin (PCT) and endocan levels o admission in septic survivors group



Correlation between the endocan and WBC on 2-nd day after research in septic survivors group



Based on the preliminary results, the serum endocan is usually only slightly induced in the course of the time-limited inflammatory response (cardiac surgery)

The highest values of endocan were observed in non-survivors (n=7) and was directly associated with the highest APACHE II and SOFA score results, reflecting the clinical status and progress of multiple organ failure in this group

Prognostic value ?

Correlations?

The research is ongoing