RATIONALE AND USE OF CYTOSORB IN PATIENTS WITH ENDOCARDITIS

PROF. DANIEL WENDT, FECTS

Disclosure

Speaker name:

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I have the following potential conflicts of interest to report:

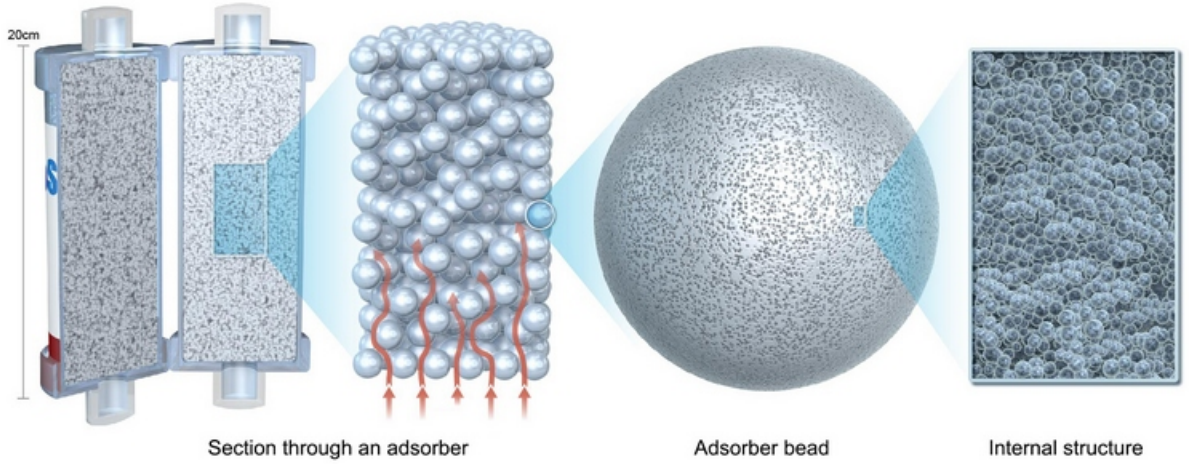
- ☐ Consulting
- ☐ Employment in industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☒ Other(s) participating in REMOVE study

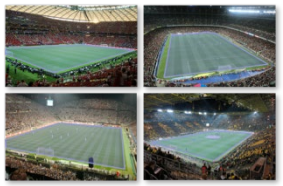
- ☐ I do not have any potential conflict of interest

Background

- Infective endocarditis (IE) is associated with high hospital mortality & morbidity
- Possible circulatory failure in patients who undergo cardiac surgery for IE
- Release of vaso-dilatatory mediators and cytokines
- Elemination may improve surgical outcomes by reducing inflammatory response

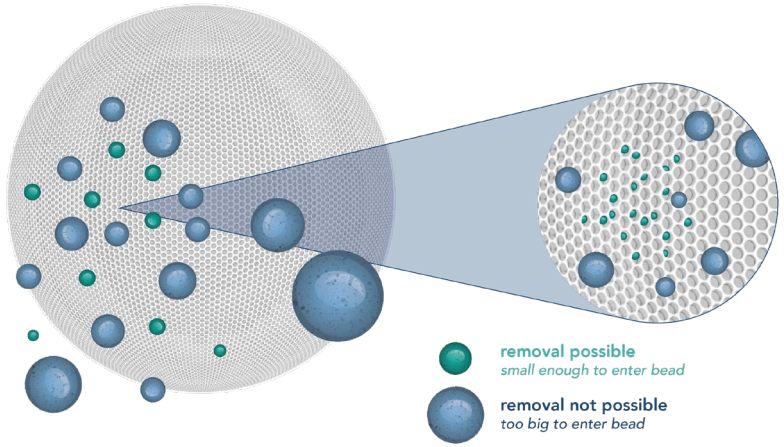
Background



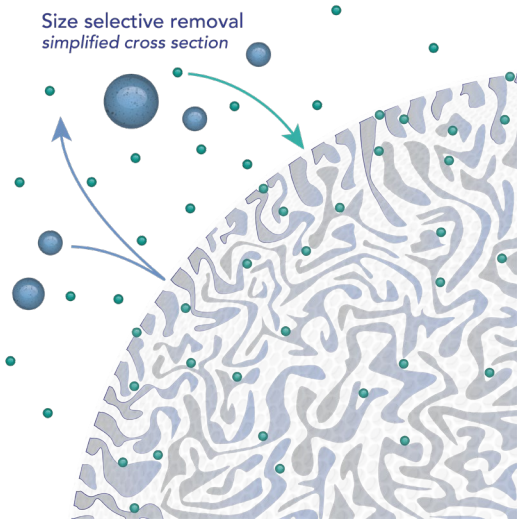


~45.000m^2

Size selective removal



Size selective removal
simplified cross section



Background

Membrane-Filter

Overall surface
≅ 2m²

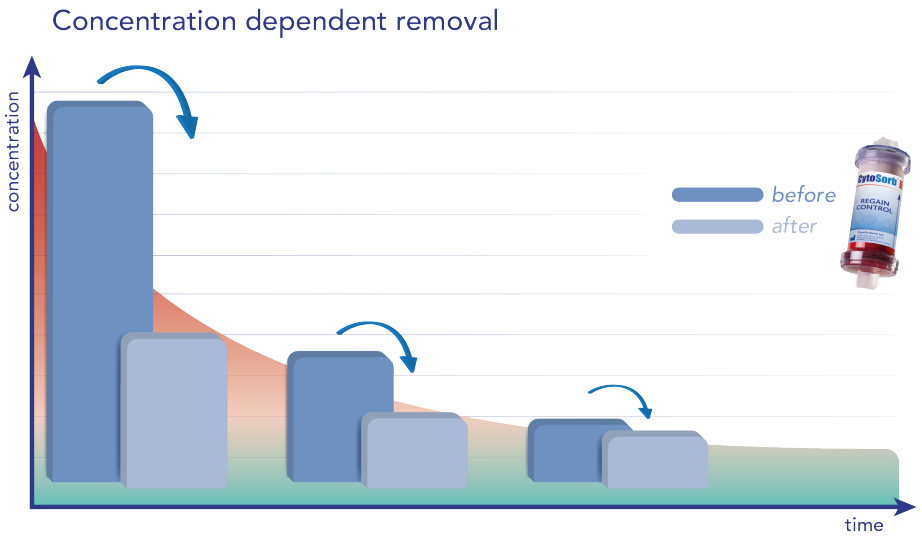
CytoSorb® – Adsorber

Overall surface
≅ 45.000m²*

Background

CytoSorb© 300 Adsorber

- Elimination of hydrophobic substances – based on pore size and physical/chemical properties
- Substances up to 55kD



- No complete removal
- Overtreatment impossible
- Remained physiological immuno-response

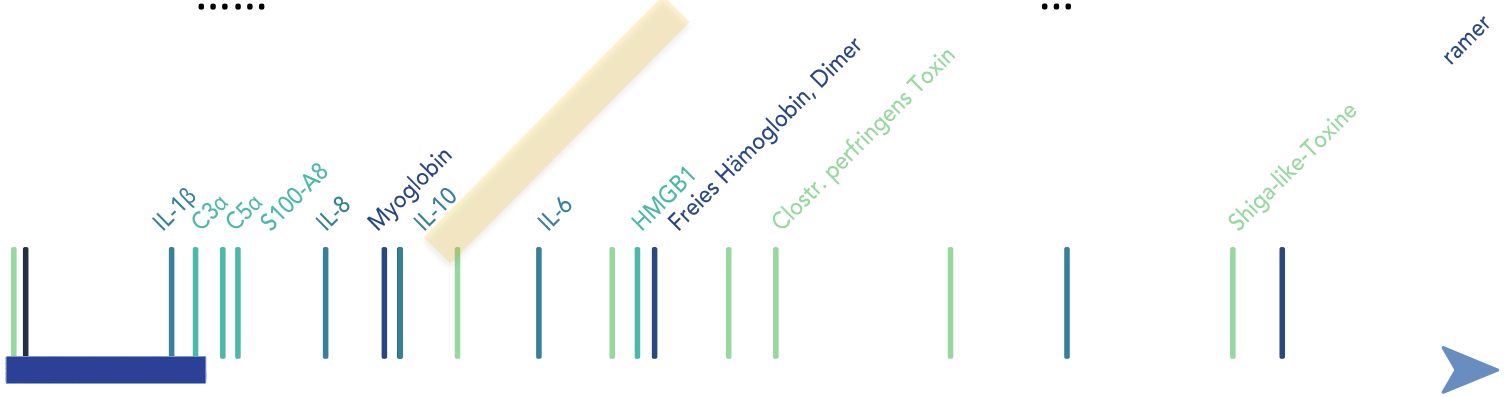
Background

Elimination

- Cytokines (IL-10, IL-6, TNFα)
- Myoglobin
- Bilirubin
- Toxins
- ……

No elimination

- Immunoglobin
- Coagulation factors
- Fibrinogen (340kD)
- AT III / Prot. C (65 / 62kD)
- Albumin (64kD)
- …



Background

Review

Open Access

Coronary artery surgery: cardiotomy suction or cell salvage?

Kelvin Lau[1], Hetul Shah[1], Andrea Kelleher[1,2] and Neil Moat*[1,2]

Address: [1]Department of Cardiac Surgery, Royal Brompton Hospital, and NHLI at Imperial College, London SW3 6NP, UK and [2]Department of Anaesthesia, Royal Brompton Hospital, and NHLI at Imperial College, London SW3 6NP, UK

Email: Kelvin Lau - kelvin.lau@uhl-tr.nhs.uk; Hetul Shah - hetul.shah@imperial.ac.uk; Andrea Kelleher - a.kelleher@rbht.nhs.uk; Neil Moat* - n.moat@rbht.nhs.uk

* Corresponding author

„We know that conventional CPB induces a systemic inflammatory response and results in microembolism to the brain and other organs.“

Postoperative Acute Kidney Injury is Associated with Hemoglobinemia and an Enhanced Oxidative Stress Response

Frederic T. Billings IV, M.D., M.S.C.I., Stephen K. Ball, M.D., L. Jackson Roberts II, M.D., and Mias Pretorius, M.B.Ch.B., M.S.C.I.
From the Department of Anesthesiology (FTB, MP), Division of Clinical Pharmacology, Department of Medicine (MP, LJR), Department of Cardiac Surgery (SKB), Department of Pharmacology (LJR), Vanderbilt University Medical School, Nashville, TN

„Acute kidney injury frequently afflicts patients undergoing CABG and independently predicts death. Release of free hemoproteins into ciculation is known to cause oxidative injury to the kidney.“

Lung Dysfunction Following Cardiopulmonary Bypass

Efstratios Apostolakis, M.D.,* Kriton S. Filos, M.D.,† Efstratios Koletsis, M.D.,* and Dimitris Dougenis, M.D.*

*Department of Cardiothoracic Surgery, University of Patras, School of Medicine, Patras, Greece; and †Department of Anesthesiology and Intensive Care Medicine, University of Patras, School of Medicine, Patras, Greece

„Therapeutic strategies should target to maintain perioperative hemodynamic stability in order to minimize postoperative intestinal ischemia. *Such an approach may reduce the* ***manifestation of SIRS, pulmonary dysfunction and multi-organ failure.“***

Journal of Cardiothoracic Surgery 2007;25:46
Free Radic Biol Med 2001;50:1480-87.
J Card Surg 2010;25:47-55.

Background

RESEARCH Open Access

Effect of hemoadsorption during cardiopulmonary bypass surgery – a blinded, randomized, controlled pilot study using a novel adsorbent

Martin H. Bernardi[1*], Harald Rinoesl[1], Klaus Dragosits[2], Robin Ristl[3], Friedrich Hoffelner[4], Philipp Opfermann[1], Christian Lamm[2], Falk Preißing[2], Dominik Wiedemann[4], Michael J. Hiesmayr[1] and Andreas Spittler[2,5]

- **Aim:** effect of Cytosorb hemoadsorption on changes of cytokine levels during CPB > 120 min (CABG, valve surgery)
- **Design:** RCT, 37 blinded patients (HA 19, control 18)
- **Primary outcome** was differences of cytokine levels (IL-1β, IL-6, IL-18, TNF-α, and IL-10) within the first five postoperative days

Crit Care. 2016;20:96.

Background

RESEARCH Open Access

Effect of hemoadsorption during cardiopulmonary bypass surgery – a blinded, randomized, controlled pilot study using a novel adsorbent

Martin H. Bernardi[1*], Harald Rinoesl[1], Klaus Dragosits[2], Robin Ristl[3], Friedrich Hoffelner[4], Philipp Opfermann[1], Christian Lamm[2], Falk Preißing[2], Dominik Wiedemann[4], Michael J. Hiesmayr[1] and Andreas Spittler[2,5]

- **Results:**
  - No removal of albumin
  - No serious adverse events
  - 80% lower expression of PCT
  - No influence on perioperative course
  - Inhomogenous / interindividual cytokine activation during CPB
  - After HA long lasting effect on IL-10

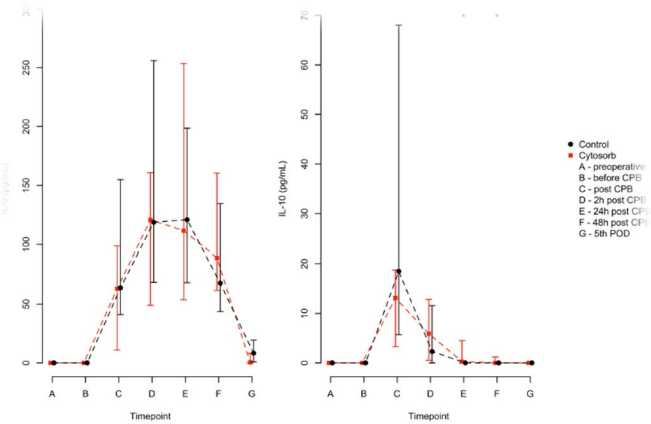
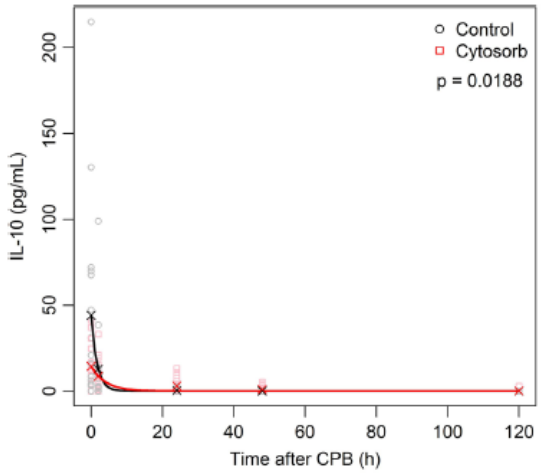
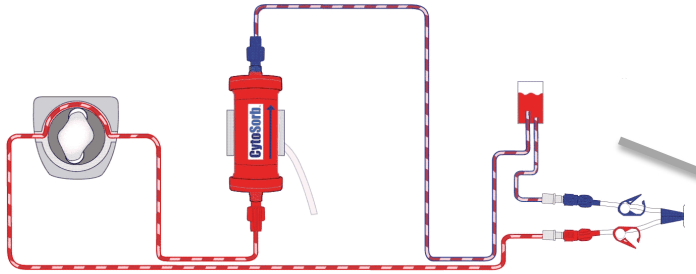


Fig. 2 Comparison of median cytokine levels in picograms per milliliter. Red lines indicate the patients in the CytoSorb™ treatment group. Black lines indicate the patients in the control group. Error bars correspond to interquartile ranges (first quartile, third quartile). Asterisks mark

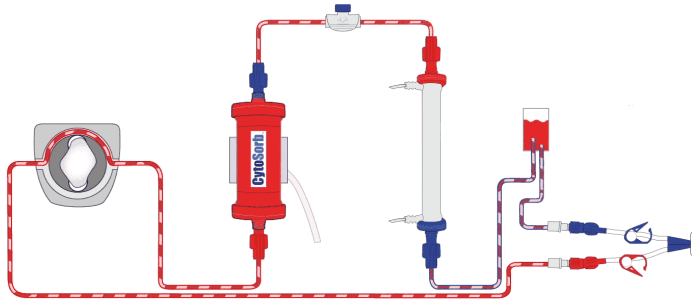


Background



hemoperfusion

ECC

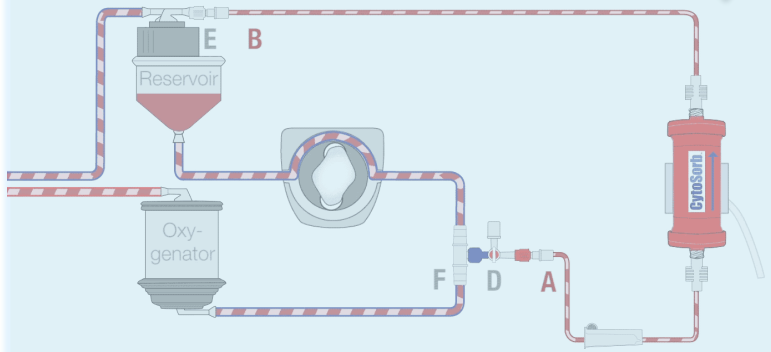


dialysis

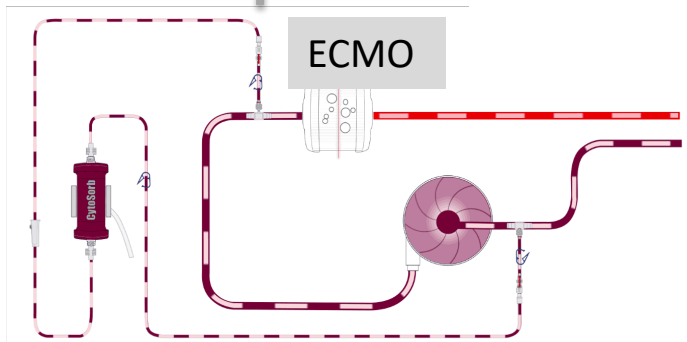
Pre-filter

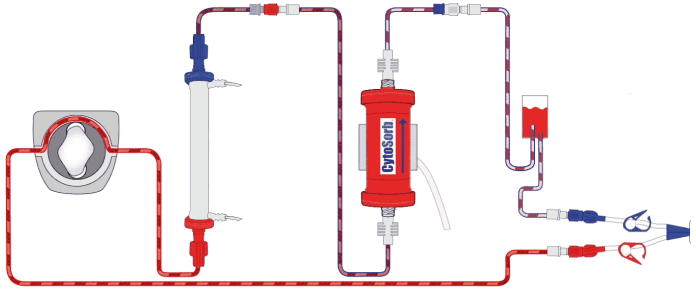
Post-filter

CPB



ECMO





Background

Hemoadsorption treatment of patients with acute infective endocarditis during surgery with cardiopulmonary bypass - a case series

Karl Träger[1], Christian Skrabal[2], Guenther Fischer[1], Thomas Datzmann[1], Janpeter Schroeder[1], Daniel Fritzler[1], Jan Hartmann[1], Andreas Liebold[2], Helmut Reinelt[1]

- **39 patients with proven IE undergoing valve replacement with CytoSorb (HA)**
- **Compared to a historical group of 28 patients without intraoperative hemoadsorption**
- **All types of endocarditis (AV, MV, TV) included → *potpourri***

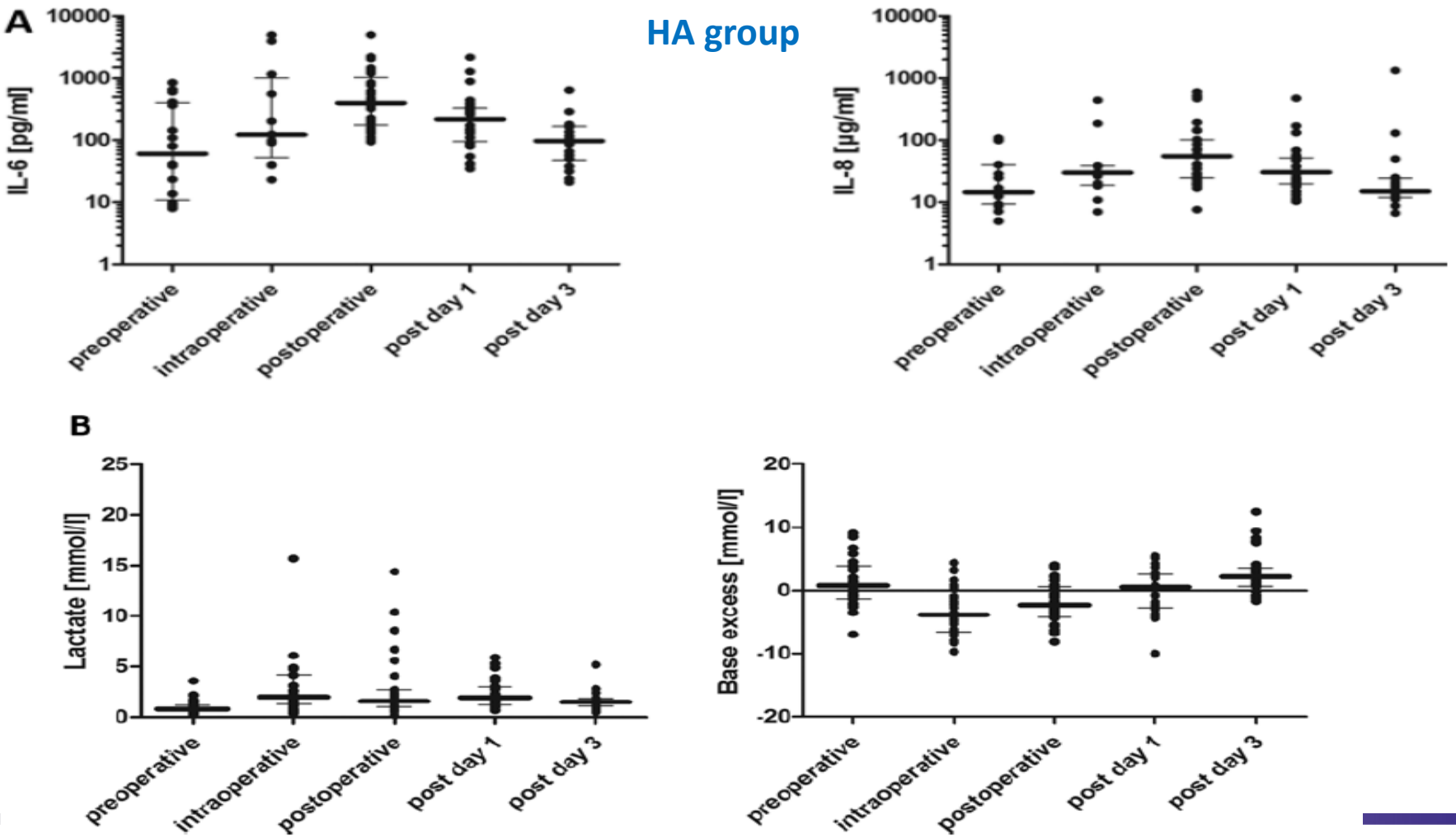
Int J Artif Organs 2017;40:240-49

Background

Course of IL-6 and IL-8

Course of Lactate & BE

Course of Lactate & BE
Historical control



Int J Artif Organs 2017;40:240-49

Essen results

- Effect of intraoperative hemoadsorption in patients with ***native isolated mitral valve infective endocarditis***
- Between January 2014 und July 2018, 58 consecutive patients with acute infective endocarditis of the mitral valve were operated
- Intraoperative hemoadsorption (HA) was applied in 30 patients (group A); in group B (n=28 patients), no hemoadsorption was used
- Primary endpoint: occurrence of postoperative sepsis as defined by The Third International Consensus Definitions for Sepsis and Septic Shock and sepsis-related death (SEPSIS-3)[1]
- Secondary endpoints: overall in-hospital mortality, need for postoperative vasopressors and ICU-stay

[1] JAMA 2016;315:801-10

Essen results, preoperative

	All patients N=58	With HA N=30	Without HA N=28	*P-Value*
Age, years	60±14	59±14	61±14	0.489
BMI, kg/m²	25±6	25±5	25±7	0.781
Gender, male	37 (64)	21 (70)	16 (57)	0.309
Drug abuse	3 (5)	2 (7)	1 (4)	0.595
Hypertension	30 (52)	16 (53)	14 (50)	0.800
Coronary artery disease	18 (31)	9 (30)	9 (32)	0.860
Previous CABG	2 (3)	-	2 (7)	0.136
Previous valve operation	2 (3)	-	2 (7)	0.136
Pulmonary disease	4 (7)	2 (7)	2 (7)	0.943
Dialysis	3 (5)	1 (3)	2 (7)	0.513
Liver disease	3 (5)	2 (7)	1 (4)	0.595
Peripheral vascular disease	9 (16)	5 (17)	4 (14)	0.802
Endocarditis related stroke	20 (35)	11 (37)	9 (32)	0.717
Neurological deficit	17 (29)	10 (33)	7 (25)	0.486
Endocarditis related peripheral embolism	17 (29)	11 (37)	6 (21)	0.203
EuroSCORE I (logistic), %	17 (10-30)	14 (9-24)	14 (9-24)	0.599
EuroSCORE II, %	4 (2-12)	3 (2-8)	3 (2-8)	0.115

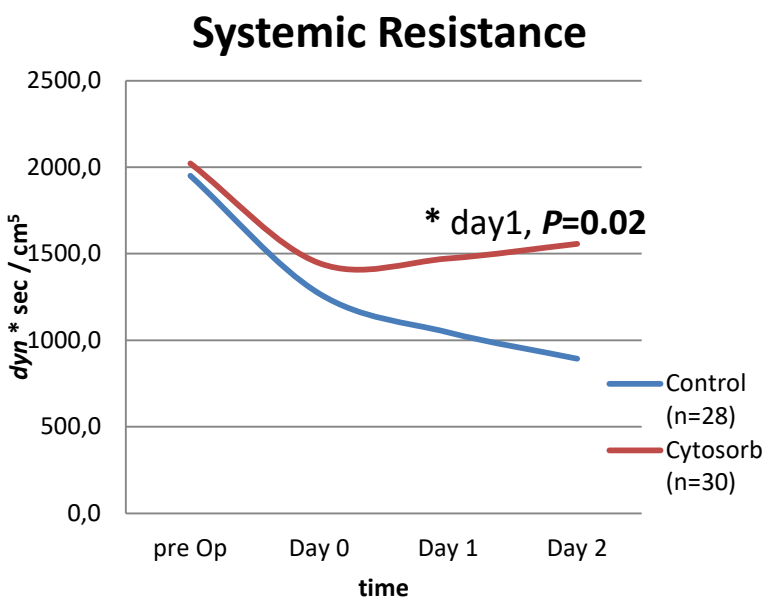
Essen results, endocarditis characteristics

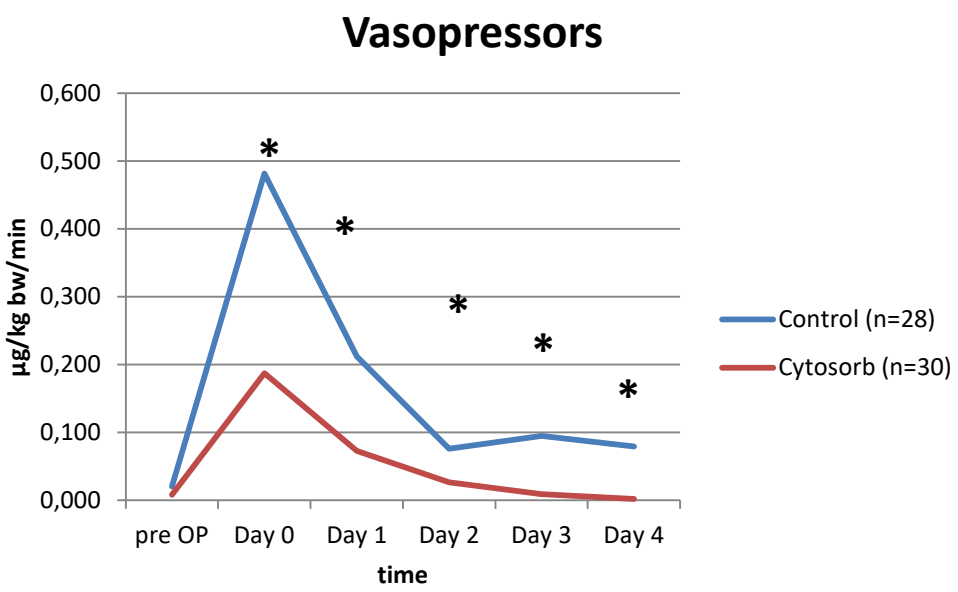
	All patients N=58	With HA N=30	Without HA N=28	*P-Value*
Clinical status				
NYHA* III-IV	31 (53.4)	15 (50.0)	16 (57.1)	0.586
Preoperative intubated	9 (15.5)	5 (16.7)	4 (14.3)	0.802
Preoperative vasopressor	7 (12.1)	3 (10.0)	4 (14.3)	0.617
Identified pathogens				
Staphylococcus aureus	**15**	**10**	**5**	**0.205**
MSSA	14/15	9/10	5/5	0.280
MRSA	1/15	1/10	-	0.330
Streptococcus species	11 (19.0)	8 (26.6)	3 (10.7)	0.121
Enterococcus species	4 (6.9)	-	4 (14.3)	0.032
Other	6 (10.3)	3 (10.0)	3 (10.7)	0.939
Negative culture	**17**	**5**	**12**	**0.029**
Echocardiographic data				
Good LVF (LVEF >50%)	48 (82.8)	24 (80.0)	24 (85.7)	0.565
Poor LVF (LVEF <35%)	1 (1.7)	-	1 (3.6)	0.296
Severe mitral regurgitation	40 (69.0)	19 (63.3)	21 (75.0)	0.337
Concomitant aortic/tricuspid valve disease	14 (24.1)	5 (16.7)	9 (32.1)	0.169

Essen results, operative characteristics

	All patients N=58	With HA N=30	Without HA N=28	*P-value*
Days between diagnosis and surgery	9 (3-21)	12 (6-22)	6 (1-20)	0.064
Indication for surgery:				
Large/embolic vegetation	**35**	**23**	**12**	**0.009**
Heart failure	**14**	**3**	**11**	**0.009**
Severe mitral regurgitation	6 (10.3)	4 (13.3)	2 (7.1)	0.439
Sepsis	3 (5.2)	-	3 (10.7)	0.066
Isolated mitral valve	[illegible]	[illegible]	[illegible]	[illegible]
Mitral valve repair	**35**	**23**	**12**	**0.009**
Mitral valve replacement	**23**	**7**	**16**	**0.009**
Concomitant CABG	13 (22.4)	6 (20.0)	7 (25.0)	0.648
Concomitant AV/TV procedure	14 (24.1)	5 (16.7)	9 (32.1)	0.169
CPB time, minutes	101 (76-127)	85 (74-106)	116 (79-149)	0.115
ACC time, minutes	61 (46-83)	59 (45-78)	74 (49-106)	0.067

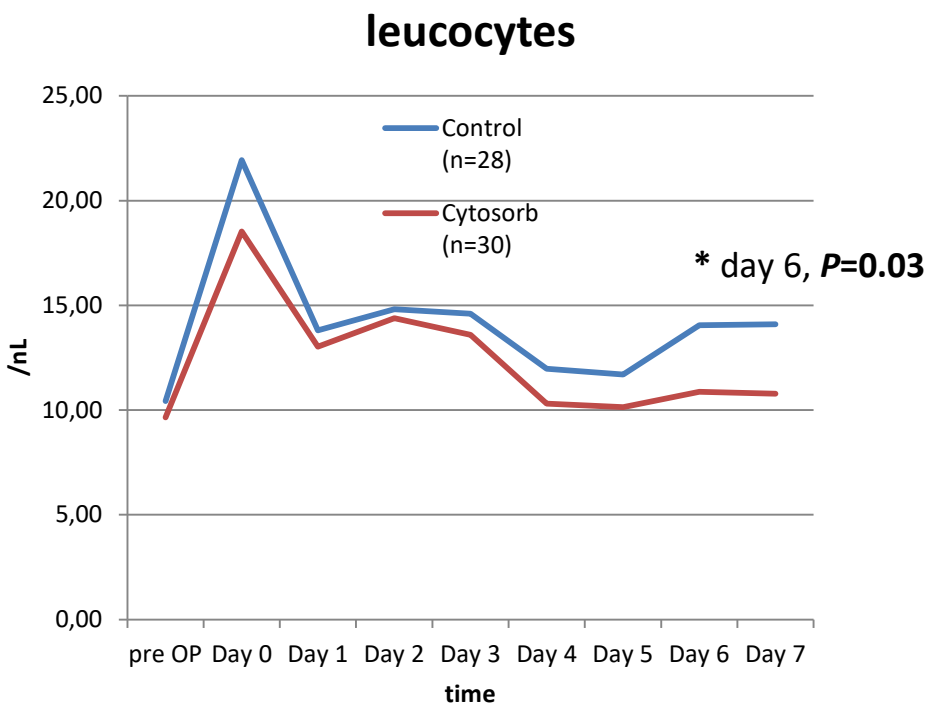
Essen results I

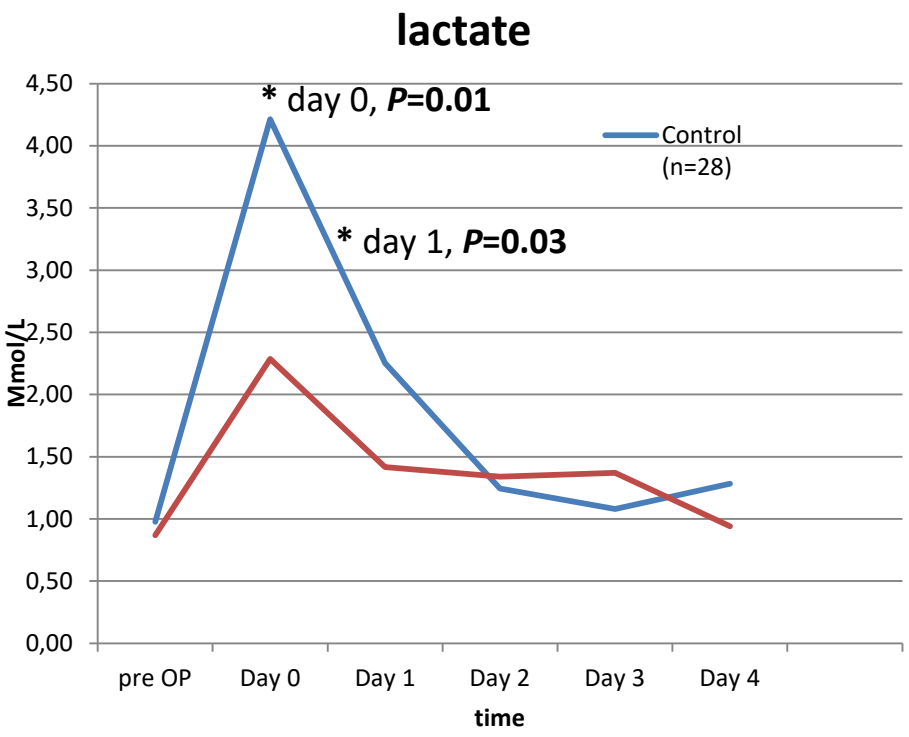




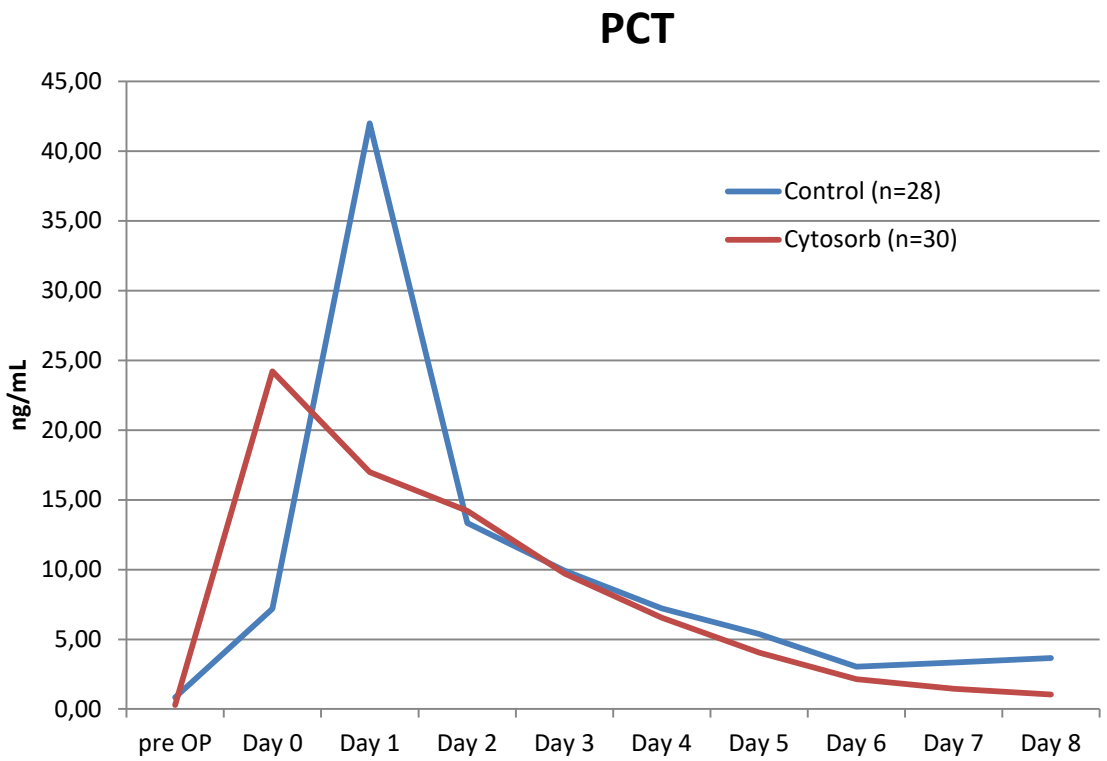
Systemic resistcance measured by SGK

Essen results II





Essen results III



REMOVE study (NCT03266302)

Revealing mechanisms and investigating efficacy of hemoadsorption for prevention of vasodilatory shock in cardiac surgery patients with infective endocarditis – a multicentric randomized controlled trial

Aim: to examine the efficacy and safety of a hemoadsorption filter, which is approved for the reduction of the concentration of cytokines in the bloodstream

Collaborators:

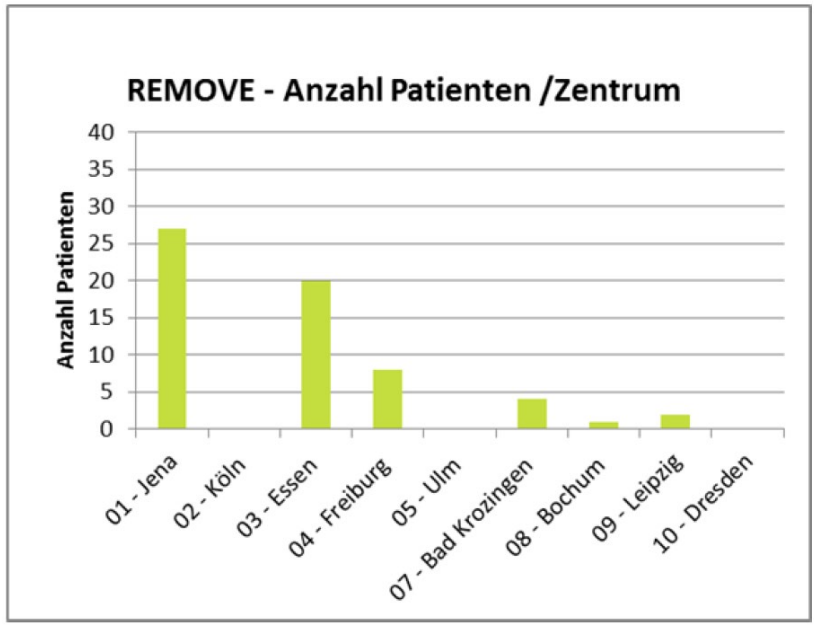
- CytoSorbents, Inc.
- B.R.A.H.M.S. (part of ThermoFisher Scientific)
- Fraunhofer Institute for Interfacial Engineering and Biotechnology
- German Federal Ministry of Education and Research (BMBF)

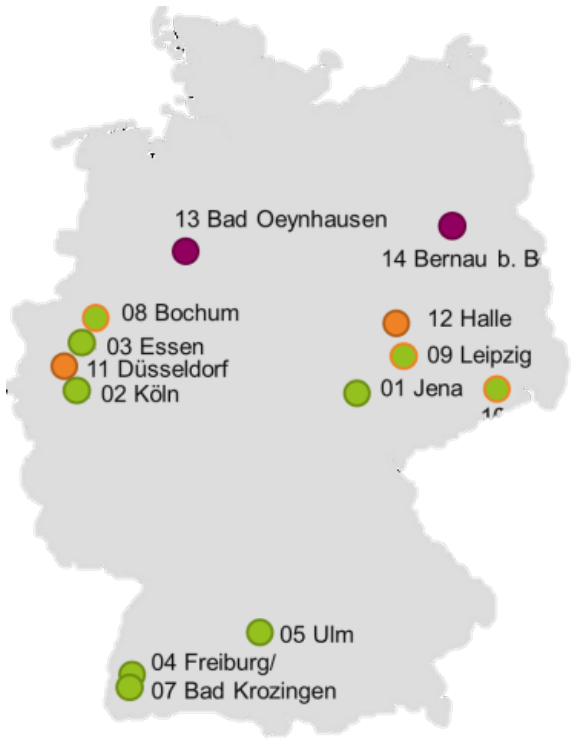
UNIVERSITÄTS KLINIKUM jena | Center for Sepsis Control & Care

WHGZ Westdeutsches Herz- und Gefäßzentrum

REMOVE study (NCT03266302)

- Randomized trial
- 250 patients
- Interim analysis after first 50 patients

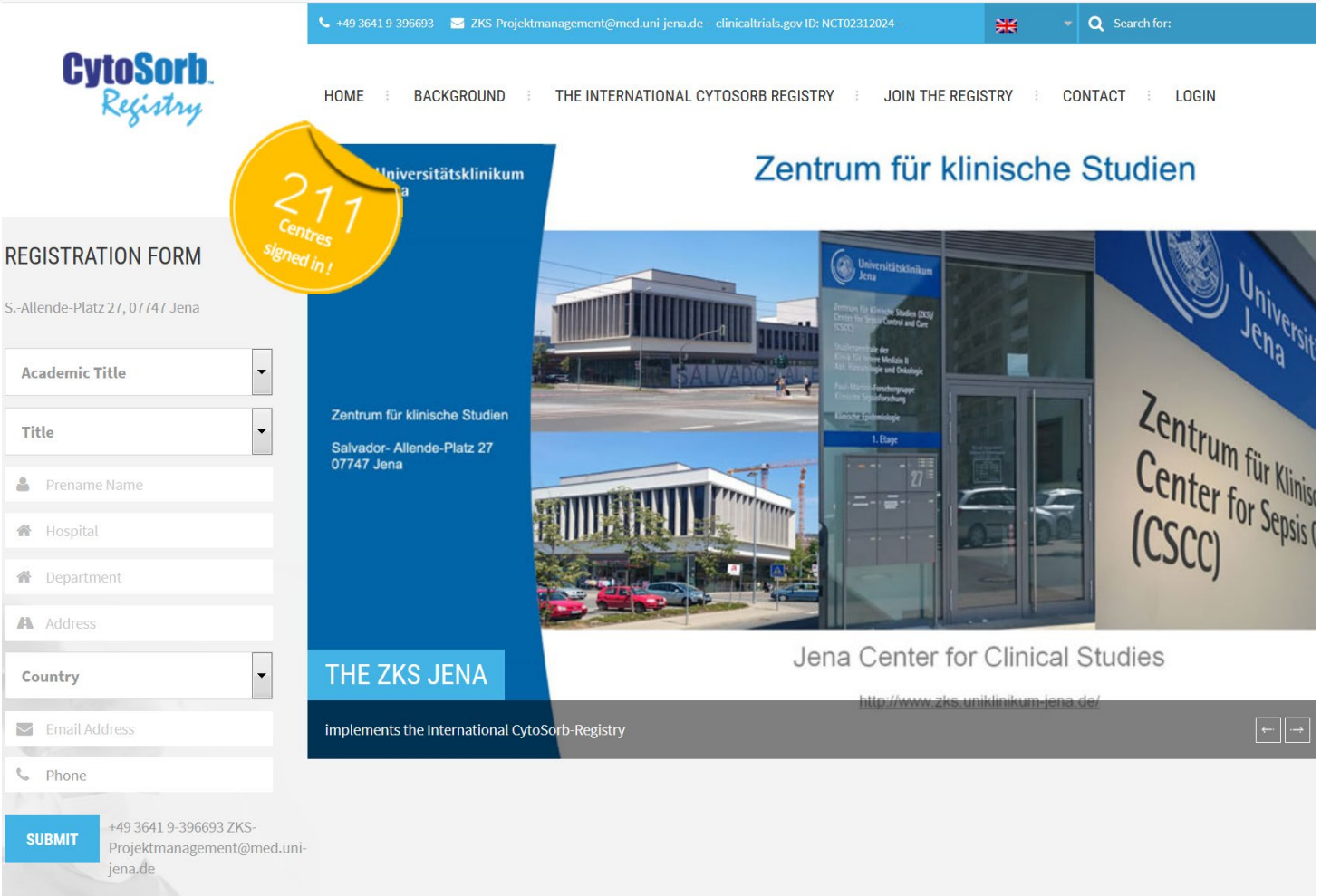




..as of 26th October 2018

Conclusion

- Most studies retrospective and small
- First beneficial hints in endocarditis
- Easy to use, no device-related SAEs
- Further investigation / larger RCTs needed
- ……guidelines?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