Plasma Medicine in Cardiac Surgery – Treatment of the Beginning Driveline Infection with Cold Atmospheric Plasma (CAP)

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LEIBNIZ INSTITUTE FOR PLASMA SCIENCE AND TECHNOLOGY (INP GREIFSWALD), GREIFSWALD, GERMANY
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**SCORE:** 0 1 0 0
I have no relevant financial relationships within the products or services described, reviewed, evaluated or compared in this presentation.
Klinikum Karlsburg –
Heart and Diabetes Center
Mecklenburg-Vorpommern
Clinical Management of Outpatients with HVAD: The KARLA-Project

Earlier Detection:

- Beginning driveline infections
- Problems with the INR – self management
- Signs of right heart failure and decompensation
- Wounds or infections as a trigger of bacteriemia
- Hemolysis
- Cerebral deficits as signs of embolisation
- Technical problems of the equipment
- Depressive episodes

Schwester Karla mobile

LVAD-coordinator and patient with the „Schwester Karla“ mobile
5 perfusionist organizing home visits every 2-3 weeks

Equipment:
- HeartWare-monitor,
- hemodynamometer,
- Siemens-xprecia,
- dressing equipment,
- camera, cellphone
- kinPen Med pocket
Continuous Flow LVAD/BiVAD Implants: 2008 – 2013, n = 9372

Instantaneous Death Rate (Hazard) for selected causes

Cause of Death
- Infection
- Bleeding
- RHF
- Neurological
- Device Malfunction
- MSOF

Deaths/Month vs. Months post implant
Plasma: the 4th state of matter

More than 99% of all known matter is in plasma state!
First use of the term „plasma“: Langmuir (1928)

Irving Langmuir‘s coining of „plasma“ was described by H.M. Mott-Smith:

„... the discharge acted as a sort of substratum carrying particles of special kinds [...] This reminds him of the way blood plasma carries around red and white corpuscles and germs. So he proposed to call our ‘uniform discharge‘ a ‘plasma‘. Of course we all agreed.“
Plasma for biomedical applications
Plasma medicine research

Plasma Medicine:
Application of physical plasma directly on or in the human body

Basic research on the interaction of cold plasmas with physical and biological systems
Surgical plasma applications

Argon Plasma Coagulation (APC)
ERBE Elektromedizin GmbH, Tübingen, Germany

Cauterization: tissue destruction, burning
- hemostatsis
- cutting, removal of tissue

Figure 8: APC in the nasal cavity, where a probe with lateral outlet is used

Figure 3: Schematic representation of a typical APC setup. The argon flows through a tube containing the electrode wire. The discharge is ignited by a HF voltage $U_{in}$ between the wire end and the tissue. After breakdown, HF current $I_{HF}$ flows into the tissue, causing a coagulation effect, and back to the HF generator through the neutral electrode (NE).

Figure 6: Endoscopic application of APC
Surgical plasma applications

Coblation® (cold/controlled ablation)
ArthroCare Corp., Austin, TX, USA

Fig. 1 Photograph of a planar-electrode-type electrosurgical device operating in isotonic saline solution at 300 volts rms. (Online colour: www.cpp-journal.org).

Figure 1  The ReFlex Ultra® PTR Wand (ArthroCare ENT, Sunnyvale, CA). (Color version of figure is available online.)
Plasma for cosmetics

Plasma Skin Regeneration (PSR): „Portrait® PSR³ System“ (Rhytec, Inc., Waltham, MA, USA)
RF nitrogen plasma jet

Controlled thermal injury and modification:
ZTD – zone of thermal damage
ZTM – zone of thermal modification

Plasma medicine: (chronic) wound healing

Predominant focus of plasma medicine

Integrated concept for plasma-assisted wound healing

- In vivo antiseptic efficacy + inactivation of endotoxins
- Plasma debridement: necrosis + peeling of cell debris including microorganisms
- Stimulation of resorptive inflammation
- Stimulation of cell proliferation (fibroblasts, keratinocytes, capillaries)

Superficial cleaning and antiseptics + stimulation of tissue regeneration in deeper layers
Atmospheric pressure plasmas – „tool box“

<table>
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<tr>
<th>Non-Thermal (NT) Plasmas</th>
<th>Translational (&quot;Hot NT&quot;) Plasmas</th>
<th>Thermal Plasmas</th>
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<tr>
<td>&quot;Cold&quot; Non-Thermal Plasmas</td>
<td>$T_i \ll T_e &lt; 10^5 \text{ K}$</td>
<td>$T_i = T_g = T_e$</td>
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<td>$T_i \approx T_g \approx 300 \ldots 400 \text{ K}$</td>
<td>$T_i \ll T_e \leq 10^4 \ldots 10^5 \text{ K}$</td>
<td>$T_x &lt; 5 \times 10^3 \ldots 10^4 \text{ K}$</td>
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<td>$T_i \ll T_e &lt; 10^5 \text{ K} (10 \text{ eV})$</td>
<td>$T_i \approx T_g \leq 4 \times 10^3 \text{ K}$</td>
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[1] Barrier discharges
[2] Coronas
[4] Plasma jets
[7] Plasma Torch
[8] Arc

picture: R. Brandenburg
Before application: Characterization of plasma sources – plasma physics

- **UV radiation (UVB, UVC)**
  Parameters: distance [mm], irradiance [mW/cm²], operation mode (e.g. continuous, pulsed, burst)

- **Temperature**
  Parameters: distance [mm], power [W], operation mode (e.g. continuous, pulsed, burst)

- **Radicals and chemical products (ROS, RNS)**
  Parameters: distance [mm], power [W], operation mode (e.g. continuous, pulsed, burst), admixture of H₂O, O₂, air
  - Ozone (O₃)
  - Nitric oxide (NO), Nitrogen dioxide (NO₂)
  - Hydroxyl radical (OH)

Methods: Spectroscopy (OES, FT-IR, TDLAS), Dräger tubes, Fiber-optical temperature measurement
Atmospheric pressure plasma sources for medical applications – global R&D activities

(1) Drexel University (USA)
(2) Cinogy GmbH (GER)
(3) Old Dominion University (USA)
(4) IOM Leipzig (GER)
(5) Eindhoven Univ. of Techn. (NED)
(6) New York University (USA)
(7) MPE Garching (GER)
(8) University of Orléans (FRA)
(9) McGill University, Montreal (CAN)
(10) Loughborough University (UK)
(11) INP Greifswald (GER)
Atmospheric pressure plasma jet (kINPen MED)

Plasma source for medical application

Certified as **medical device class IIa** (June 2013) according to European Council Directive 93/42/EEC

**Purpose:** Treatment of chronic wounds as well as pathogen-based diseases of skin, skin appendages, extremities and body

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Normothermic atmospheric plasmajet

- **Dimension:** $L = 155\, \text{mm}$, $\varnothing = 20\, \text{mm}$
- **Gewicht:** 170 g
- **HF-Voltage:** 1.1 MHz; 2…6 $kV_{pp}$
- **Gastemp.:** 30°C …150°C
- **Trärgas:** Argon
- **Gasfluß:** 1…5 sl

Bedside application
kINPen Med mobile pocket
H.V., 72 years, CHD, IDDM II, PAVD IV, amputation of right lower limb, dialysis, cross-over bypass, DI 0,58
CAP and intertriginous mycosis

R.R., 77 years, AVS, CHD, pre-TAVI
S.T., 66 years, CABG 28.02.2014, mediastinitis, closure of the thorax 31.03.2014, 09.04.2014 sternal fistula with MRSA colonisation

13.05.15 recurrence, 15.05.15 excision, VAC
D.S., 75 years, ICM, CABG 1996, CRT-ICD, TAVI 23.09.2015, lymphatic fistula, wound revision 10.10.2015, intraoperative swab: Serratia species, clindamycin, postoperative CAP
CAP and surgical wounds II


22.02.2016

27.02.2016 5xCAP

04.04.2016
CAP – critical ill patients with wounds I

R.F., 78 years, AVR (stenosis) 23.10.2015, Re-Re-Re-Thorax, 30.10.2015

17.11.2015 after conservative therapy

23.11.2015 3xCAP

02.12.2015 8xCAP
CAP – critical ill patients with wounds II

H.W., 74 years, CABG 20.08.14, COPD, mediastinitis, failed weaning
15.12.2014

27.12.2014 3xCAP
←Only under the right breast

11.01.2015 4xCAP
Only under the left breast →
Impact on the pump function?
Interference with the driveline isolation?
Plasma application
CAP and DI I

W.H. 67 years, LVAD HW
25.03.2013, ICM
CAP an DI II

Before AgNO3

19xCAP

25xCAP

20.04.2016

W.H. 67 years,
LVAD HW
25.03.2013, ICM
3 month`s later
CAP and DI III

K.S., 68 years, ICM, HW-LVAD
11.09.2014, always wet DL-wound-dressing

23.09.2014
07.10.2014 6xCAP
08.10.2014
13.10.2014 9xCAP
07.11.2014 14xCAP
21.11.2014 23xCAP
05.01.2015 25xCAP
07.06.2015
D.R., 68 years, HW-LVAD 08.07.2015, ICM, Adipositas, 24.02.2016 putrid secretion and rubor, swab with MRSA, CT without abscess, CAP (13 applications), treatment with linezolid and clindamycin over 4 weeks, signs of bone marrow suppression. Now no signs of inflammation (CRP 12.5 mg/l, Leuco 5.6 Gpt/l)
CAP and DI V

D.M., 53 years, HW-LVAD, TVR, PFOC 29.10.2014, ICM, wet DI-exit, 28.04.2015 1.operative DL-Revision / Ampicillin-Sulbactam, 23.11.2015 2.operative DL-Revision /Clindamycin, in the follow up CAP once a week
H.P., 55 years, HW-LVAD 12.10.2014, January 2016 progredient dyspnoe, catheter with RCA-spasm, TEE AI I, April 2016 accidental tug to the DL, pain syndrom, analgetics inclusive carbamazepin with short effect, in May readmission, now fistula (Staph. epi.), 06.05.2016 operative DL-exit-revision. intraop. CAP, 26.05.2016 readmission with progredient dyspnoe, TEE no endokarditis AI II, TI II-III, HU-TX?

**Makroskopischer Befund:**
2,7 x 1,7 x 0,7 cm großes Hautexsudat.

**Mikroskopischer Befund:**

**Diagnose:**

Prof. Dr. med. Klaus Hamper
CAP and DI IV

11.03.2016


04.05.2016 AgNO₃, 7xCAP

06.05.2016

07.05.2016

12.05.2016 +5xCAP

19.05.2016 +6x CAP

31.05.2016 +7xCAP

03.06.2016 +12xCAP
Studienprotokoll

< KBGWZP 1/2015 >

Plasma in Superficial Driveline Infections Trial

Prospektive multizentrische Anwendungsbeobachtung zur Therapieoptimierung oberflächlicher Infektionen der Austrittstellen von Drivelines bei LVAD-Patienten mittels Atmosphärendruck-Plasma

Kurztitel: PLASDIT

Herkömmliches Wund Management unter Antibiotikatherapie gegenüber gleicher Therapie + lokaler Anwendung von Atmosphärendruck-Plasma unter Nutzung des Kinpen Med

Sponsor: Fa. HeartWare, Fa. neoplas tools GmbH

Studienleiter:

Studienkoordinator: ........
State of knowledge: Plasma-cell interactions

1. Biological plasma effects are significantly caused by plasma induced changes of the **liquid environment** of cells

2. Dominating role of (non-charged, stable) **oxidizing** species
   - transferred and/or generated into/in the liquid environment of cells
   - being able to act inside the cells

3. Active agents (mammalian cells): plasma-generated **ROS**
   - low ROS doses: stimulation of cellular functions
   - high ROS doses: apoptosis

4. Active agents (microorganisms): plasma-generated **RNS/RONS** and acidification
ROS and RNS in cell physiology

Wound healing

Redox-based wound therapy


Scientific basis of plasma-supplemented wound healing

Picture source: W. Probst, A. Vasel-Biergans, Wundmanagement, Stuttgart 2004
ROS and RNS in cell physiology

Regulatory events and their dysregulation depend on the magnitude and duration of the change in ROS and/or RNS concentration.

- **I)** Baseline level
- **II)** Regulatory imbalances
- **III)** Dysregulation by chronic oxidative stress

Because its localized and short-term generation by local plasma treatment these substances can be detoxified by processes of regular cell metabolism.

The risk of plasma application is assessable and managable.

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*W. Dröge: Free radicals in the physiological control of cell function. Physiol. Rev. 82 (2002) 47-95*
Plasma application: main advantages

- active components are generated locally and only for the required duration of the application by powering a not directly effective gas (argon, helium, oxygen, nitrogen, air, or mixtures thereof, respectively) using electric energy.

- the individual physical and transient chemical active components not only complement and strengthen one another through synergistic activities, but can partly replace each other.
Summary and Outlook

- An increasing number of (prototype) plasma sources for life science is available from various research institutes and universities.
- The level of physical and biological characterization of the plasma sources is very different.
- For a successful market introduction a minimum set of investigations has to be done before one can state „….also useful for medical applications“.

- Up to now, there is no big player on the (plasma-medicine) market.
- Small companies entering the market often within the field of cosmetics.

- Three companies in Germany meanwhile with certified medical product.
- Each medical indication needs a special tailored plasmasource.

- Food decontamination by plasma seems to become another field of growing interest besides plasma-pharmacy, plasma-biology…..
Medical applications of plasma

The status quo of plasma medicine foresees the following medical application areas for cold plasmas at atmospheric pressure:

- (external) plasma applications on body surfaces (skin, mucous membrane, wounds, teeth)
- plasma applications at open surgical treatment
- plasma applications in visceral cavities (endoscopic)
Plasma Medicine: Future prospects

- Application-adapted plasma sources

- Basic research on plasma-cell and plasma-tissue interaction with focus on safety of plasma application

- Clinical trials with focus on safety of plasma application as well as proof and consolidation of therapeutic applications

- Development of further fields of medical plasma use:
  - New targets: cancer treatment
  - New sites: teeth, lung, gastrointestinal tract, eyes, ...
What is the problem?

Until now no reimbursement
What is in the Pipeline?

- Plasma Plaster
CAP Plaster – biological efficiency

approximate cell count given to the plate

5x 10^8  5x 10^7  5x 10^6  5x 10^5  5x 10^4  5x 10^3  500  50  5

S. aureus
MRSA

COLDPLASMATECH
EINLADUNG

Workshop
Vorstellung klinischer Erfahrungen in der Plasmamedizin


In diesem Workshop wollen wir einen Überblick über die bisherigen klinischen Erfahrungen innerhalb der Plasmamedizin geben und diese mit Vertretern aus Praxis, Industrie und Forschung diskutieren.

Dazu sind Sie herzlich eingeladen!

Ort: Vertretung des Landes Mecklenburg-Vorpommern beim Bund
In den Mietstädten 3 // 10117 Berlin

Die Veranstaltung ist für Mitglieder kostenfrei.

Nicht-Mitglieder des NZPM zahlen einen Kostenbeitrag von 40,- € (Mittagsbuffet inbegriffen).

10.–11. Mai 2017 in Hamburg
26. Workshop
Oberflächenfunktionalisierung von starren und flexiblen Materialien
13.–14. September 2017
in Rostock/Meklenburg-Vorpommern
29. Workshop
5. Plasmamedizin–Workshop
Therapeutischer Einsatz von
physikalischen Plasmen
15.–16. November 2017
in Jena/Thüringen
30. Workshop
Verbesserte Haftung durch Plasma(vor)behandlung

Weitere Informationen und Anmeldung:
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Telefon: 0 190 28 15 14
E-Mail: info@ak-adp.de

www.ak-adp.de

6th International Conference on Plasma Medicine
icpm6
September 4-9, 2016 - Bratislava, Slovakia

Welcome

On behalf of the International Society for Plasma Medicine (ISPM), we are delighted to welcome you to the full-week 6th International Conference on Plasma Medicine (ICPM6), which will be held in Bratislava, Slovakia, from September 4 to 9, 2016.

Plasma Medicine is a rapidly growing field that faces many technological challenges and brings to the forefront fundamental questions on the mechanisms of interaction between living organisms and gas plasmas. The conference creates a multidisciplinary forum bringing together professionals from the fields of plasma physics, medicine, biology, biochemistry, pharmacy, agriculture, and food science and industry in order to develop a common language, better define key challenges and open questions, to further development of international collaborations, and to move toward effective solutions.

This time, the ICPM6 will be preceded by the ISPM Summer School on Plasma Medicine.

We hope to see you all in Bratislava, one of the pearls on the Danube river and quickly developing metropolis in the Central Europe.

Zdenko MACIHA and Karl HENSSEL
Organizers of ICPM6
CAP – further clinical research

- 22.02.2016 start-up of the Diabetes Innovation Center Karlsburg - clinical treatment and applied research
Coming soon
Acknowledgement & contact

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