JDDG Journal of the German Society of Dermatology
DOI: 10.1111/j.1610-0387.2010.07495.x

Plasma medicine: possible applications in dermatology

Julia Heinlin[1], Gregor Morfill[2], Michael Landthaler[1], Wilhelm Stolz[3], Georg Isbary[3], Julia L. Zimmermann[2], Tetsuji Shimizu[2], Sigrid Karrer[1]
(1) Department of Dermatology, University of Regensburg, Germany
(2) Max Planck Institute for Extraterrestrial Physics, Garching, Germany
(3) Department of Dermatology, Schwabing Hospital, Munich, Germany

JDDG; 2010 · 8 Submitted: 5.3.2010 | Accepted: 29.5.2010

Keywords
- plasma medicine
- plasma
- cold atmospheric plasma
- microbiology
- chronic wounds
- sterilization
- disinfection

Summary
As a result of both the better understanding of complex plasma phenomena and the development of new plasma sources in the past few years, plasma medicine has developed into an innovative field of research showing high potential. While thermal plasmas have long been used in various medical fields (for instance for cauterization and sterilization of medical instruments), current research mainly focuses on application of non-thermal plasmas.
Experiments show that cold atmospheric plasmas (CAPs) allow efficient, contact-free and painless disinfection, even in microscopic openings, without damaging healthy tissue. Plasmas influence biochemical processes and offer new possibilities for the selective application of individually designable medically active substances. In dermatology, new horizons are being opened for wound healing, tissue regeneration, therapy of skin infections, and probably many more diseases. First clinical trials show the efficacy and tolerability of plasma in treating infected chronic wounds. A major task will be the introduction of plasma into clinical medicine and, simultaneously, the further investigation of the mechanisms of action of plasma at the cellular level.

Introduction

In physics plasma is considered the fourth state of matter next to solids, liquids and gases. In 1879 the British chemist and physicist William Crookes first described it as "radiant matter " [1]. The term "plasma" itself comes from Greek ("something molded") and was introduced in 1928 by Irving Langmuir, as the multicomponent mixture of highly ionized gases reminded him of blood plasma. In technology plasmas have been established for a very long time – for example in the manufacture of television screens or fluorescent tubes. On the basis of their high bactericidal effectiveness plasmas are also used to sterilize medical devices and in packaging of food stuffs. The development of diverse, usually non-thermal atmospheric-pressure plasma sources makes its use also in the (bio)medical field possible. While in the past only the thermal properties of plasmas (> 80 °C) were utilized – cauterization, sterilization of heat-resistant instruments or for cosmetic, reconstructive procedures – current research is directed primarily at the non-thermal effects of plasma. Research ranges from investigation of the fundamental physics, study of the optimal, individual plasma composition over the interaction of plasmas with prokaryotic and eukaryotic cells, viruses, spores and fungi, cell structures such as cell membranes, DNA, lipids and proteins up to studies on plant, animal and human tissue and finally on patients. Without damaging surrounding healthy tissue, cold atmospheric-pressure plasmas at room temperature lead to diverse reactions in tissue. Numerous components of plasma such as e. g reactive oxygen or nitrogen species, charged particles, electric fields and even UV light (Figure 1) are involved in these effects. Possible uses include – among others – very rapid and gentle tissue disinfection via inactivation of diverse pathogens (gram-positive and –negative bacteria, fungi, viruses, spores and parasites), precise tissue removal and stimulation of

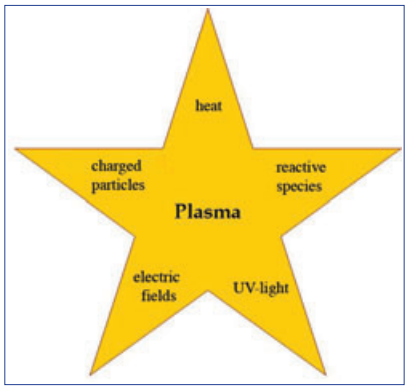

Figure 1: Relevant components of plasma. Charged particles and density of free radicals (reactive oxygen and nitrogen species) are mainly responsible for the effects of plasma.

Table 1: Comparison of UVR intensities of sunlight and MicroPlaSter β® (microwave power 100 W, main (Ar) gas flow rate 1300 sccm, z 20 mm). Data refer to an irradiation time of 5 min. Intensity of UV irradiation of sun was measured in Garching (Munich) and is averaged over one year (Data are gathered by Bernd Steffes and Dr. Tetsuji Shimizu, Max Planck Institute for Extraterrestrial Physics, Garching, 2009). Plasma treatment of 1 min with MicroPlaSter β® corresponds to 5 min sun exposure with regard to UVC, to 1 min with regard to UVB and to 10 s sun exposure with regard to UVA irradiation.

	UVC (180–280 nm)	UVB (280–320 nm)	UVA (320–400 nm)
Sunlight	1–2.5 µW/cm²	30–50 µW/cm²	~ 600 µW/cm²
MicroPlaSter β	10–16 µW/cm²	40–60 µW/cm²	< 100 µW/cm²

UVC: 1 min MicroPlaSterβ ≈ 5 min sunlight; UVB: 1 min MicroPlaSter β ≈ 1 min sunlight; UVA: 1 min MicroPlaSter β ≈ 10 s sunlight.

wound healing. Plasmas offer the possibility of a targeted application of individually composed medically active substances without requiring a carrier medium [2]. Of particular interest is the use of cold plasmas in hospital hygiene, in the treatment of diverse skin and infectious diseases, in dentistry and in the cosmetic field. A great advantage of this physical method, where according to present knowledge allergic or toxic reactions are not expected, is the contact-free, painless, self-sterilizing, non-invasive application that allows for the treatment of heat-sensitive, inhomogeneous surfaces and even live tissue.

While bactericidal effects are undisputed, most mechanisms of action of plasma at a molecular level have largely remained unstudied. This review article concentrates on various medical uses of plasmas with a special focus on dermatology.

Fundamental physics

Plasma denotes a partially ionized gas that consists to a large extent of charged particles such as ions and electrons, free radicals, molecules and also of neutral atoms. In principle naturally occurring (terrestrial and astrophysical plasmas, e. g. the sun, lightning and the polar lights) and artificially produced plasmas (e. g. in screens, fluorescent tubes). It is estimated that natural plasmas constitute over 99 % of the visible material of the universe. It is important to differentiate between hot (thermal) and cold (non-thermal or low-temperature) plasma depending on the relative temperatures of electrons, ions and neutral gas. In thermal plasmas the latter have the same temperature and are thus in equilibrium with themselves and their surroundings [3], while in non-thermal plasmas – e. g. due to microwave discharge – ions and uncharged molecules are much cooler than electrons. These plasmas are "cold" because the carrier gas (argon, helium, air …) is only slightly ionized (typically 1 part in 1 billion) and therefore the ions cool down to room temperature very rapidly – in fractions of a second.

Relevant parameters of medical plasmas are the electron and ion temperatures and density, UV irradiation (Table 1), optical and infrared emission, the density of free radicals, the temperature of the neutral gas, the gas composition and the gas flow. Decisive for the action is the flow of active, charged particles (electrons, positive and negative ions, e. g. Ar^+, Ag^-) and uncharged atoms and molecules (such as O_3, OH, H_2O_2, NO, OH radicals etc.). A great advantage of low-temperature plasmas under atmospheric pressure is the possibility to chemically "design" the plasma, i. e. its composition can be varied depending on the desired effect ("chemical cocktail") [4].

Low-temperature plasmas at atmospheric pressure can in principle be classified into 3 types (Table 2):

1) In **direct plasmas** the tissue/skin itself serves as an electrode so that in this form current flows through the body [5]. A common example of this is the "dielectric barrier discharge" device (DBD) [6]. These discharges are termed barrier discharges, because the electrodes are separated by a non-conducting layer (barrier). The discharges are then not "massive" (and possibly catastrophic) as in lightning, but "gentle" – in many small microdischarges of about 100 nanoseconds duration – from the barrier to the opposite electrode. On average an almost homogeneous "carpet" of discharges results – assuming that the distances to the opposite electrode are exactly equal. Typically, the distance between the plasma device and tissue is 1 mm.
2) **Indirect plasmas** are produced between two electrodes and then transported to the target area by a gas flow [7–9]. The individual discharge can be markedly stronger here (there is no hindrance by a barrier), the transport of the charge carriers (and the produced molecules) away from the discharge region results simply from the gas flow and from diffusion. Most devices of this type produce thin (mm diameter) plasma jets, larger surfaces can be treated simultaneously by joining many such jets or by multi-electrode systems. Significantly larger surfaces can be treated than with direct plasmas. Further, the distance between the device and the skin is to a certain degree variable, as the skin is not needed as a plasma electrode, significantly simplifying use on the patient.
3) **„Hybrid" plasmas**, also termed „barrier coronal discharges", combine both techniques discussed above. They are produced just as direct plasmas,

Table 2: Characteristics of the different atmospheric low-temperature plasmas.

	Direct plasmas	Indirect plasmas	„Hybrid" plasmas
Technical examples	Dielectric barrier discharge device	Plasma needle, plasma torch	Barrier coronal discharges
Mode of production and properties	Skin or tissue functions as electrode, current flows through body	Production of plasma between 2 electrodes, transport via gas flow to target area	Mode of production of direct plasmas with properties of indirect plasmas: Due to grounded electrode net with low electrical resistance no current flows through tissue
Gas	Air	Noble gas/air	Air
Distance between device and treated object	~ mm	~ mm–cm	~ mm
Reactive species	Are produced in the plasma	Are produced by mixing plasma and air	Are primarily produced in the plasma
UV radiation	Relatively weak	Relatively strong	Relatively weak
Gas temperature	~ Room temperature	Hot at the production site	~ Room temperature
Plasma density on the treated object	High	Low	Relatively high

but due to a grounded mesh electrode no current flows through tissue anymore [10]. In contrast to DBD systems no air space exists between the barrier and the opposite electrode (in which the micro-discharges occur) and the opposite electrode must be structured (e. g. mesh). The micro discharges then occur parallel to the surface of the dielectric barrier, which is why these electrodes are also termed surface micro discharge (SMD)" electrodes. These SMD systems are also independent of the distance from the surface to be treated (within certain limits).

Universal requirements for the composition of plasmas do not exist. Most cold plasmas at atmospheric pressure are produced using helium or argon gas, but production of plasma e. g. from air or other mixtures is possible. Limits exist with regard to electric current, UV radiation (maximum allowed dose 30 µW/cm², for details see SCCP European Commission Report 0949/05) and the production of reactive species (limit for ozone 50 ppb, see CPSC Consumer Products Safety Commission – report of 09/26/2006, for NO_2 2 or 5 ppm and 25 ppm for NO over a time period of 8 hours, US National Institute for Occupational Safety and Health, NIOH). The application time depends on the purpose and the plasma composition and can therefore vary greatly. For bacterial sterilization, for example, with suitable parameters a short application time of a few seconds is sufficient.

In medical use on patients safety comes first, so that a risk evaluation of the respective plasma device must take place. Potential risk factors such as electric current, thermal damage of tissue and the intensity of UV emission as well as optimal duration and intensity of application and gas composition must be checked exactly. Lademann et al. [11] in studies on pig's ears and tape stripping of volunteers demonstrated that in treatment with a CE-certified plasma jet with argon as carrier gas and optimal treatment parameters practically no UV light reached living skin cells (< 1 % at 200 µm skin thickness, maximum UV emission in this case at 310 nm, small bands between 325 and 450 nm), as each individual of the 15 to 25 corneocyte layers in human skin absorbs about 25 % of the radiation. Temperature effects also were negligible, so that no risk potential is expected for this device in vivo.

Disinfection and sterilization of inert materials and vital tissue

It has been known for a long time that ionized gases have biocidal effects, but only in 1996 successful killing of bacteria with plasma was reported [12]. In contrast to conventional methods which usually require high temperatures or high concentrations of chemical substances such as ethylene oxide, ozone or chlorine, cold plasma can also be used on heat-sensitive and chemically reactive surfaces. Plasma acts rapidly and very effectively and penetrates the smallest openings and hollow spaces. How plasma actually achieves disinfection or sterilization is not yet fully understood. According to current knowledge both physical mechanisms (caused by reactive species, free radicals, UV photons) and biological mechanisms (cellular processes such as DNA and cell membrane damage) appear to be responsible for the inactivation of bacteria [13]. UV radiation via energy absorption directly damages cellular macromolecules on the one hand, on the other, DNA proteins and lipids are irreparably harmed by oxidative stress.

Numerous studies using varying treatment parameters prove in vitro the efficacy of low-temperature plasmas towards gram-negative and gram-positive bacteria, spores, biofilm-producing bacteria, viruses and fungi. In a phase I study performed by our working group [7, 14] in which low-temperature plasma at atmospheric pressure was employed (MicroPlaSter®, a plasma torch with

Figure 2: The plasma torch (MicroPlaSter β®; 2.45 GHz, 86 W, Ar 2.2 slm) as an example of an indirect plasma source: Plasma is generated at the 6 electrodes and then transported to the target area via gas flow. The torch itself has to be cooled by air flow.

6 electrodes, 110 W microwave output power, argon gas, Figure 2) a reduction of bacterial load on agar plates after 2 min by 6 log steps that lasted for at least 2 days was achieved. Plasma proved to be effective towards gram-positive and gram-negative bacteria, multiresistant bacteria such as MRSA and fungi such as *Candida albicans*. Studies of our working group up to now suggest that there is no primary as well as no secondary resistance of the pathogens towards plasma (unpublished data).

Kamgang-Youbi et al. demonstrated that even plasma-treated distilled water (5 min non-thermal atmospheric-pressure plasma with air as carrier gas) has in vitro significant antimicrobial effects on diverse pathogens and can in the future be used in treating contaminated materials/ tissue [15]. The proof that the infectiosity of prions is reduced significantly must still be provided, even though a reduction was shown in prion-protein models [16]. Low-temperature plasmas also make a dissolution or removal of biofilms, often found on catheters, medical implants and teeth, possible. Biofilms are three-dimensional accumulations of microorganisms that adhere to a surface and are enclosed by polymeric substances and can, for example, effectively protect yeasts from attacks out of the environment or the immune system. This markedly increases resistance towards antifungal agents. Lee et al., among others, were able to show that biofilms (produced both by gram-negative and gram-positive bacteria) could be removed in less than 20 s and the growth of planktonic bacteria in biofilms could be inhibited within 5 s [17]. Further possible results were found with respect to protein removal from surfaces of medical devices with helium-oxygen plasma, probably due to the effects of reactive oxygen species [16].

Effects of low-temperature plasmas on mammalian cells

To study the effects and potential toxicities of cold plasmas on mammalian cells diverse studies have been performed. In vitro experiments on fibroblasts, endothelial and muscle cells have shown that effects of low-temperature plasmas are dose- and time-dependent [18]. While a longer treatment duration or greater treatment intensity (DBD plasma, 0.1 W/cm², > 60 s) result in apoptosis or necrosis of the cells, shorter treatment time (30 s) or lower intensity lead to a reversible loss of cell adhesion, temporary increase in cell membrane permeability, an inhibition of migration or a stimulation of cell proliferation (probably due to growth factors such as e. g. FGF2 [19]). For plasma-induced cell apoptosis or also cell proliferation most likely reactive species, such as oxygen and nitrogen species, are responsible.

Low doses that would already be sufficient to kill bacteria effectively are harmless for human and animal cells [14, 20]. Trials on human or animal skin support this theory. Short treatment times already lead to a significant reduction of the bacterial load, but do not cause macro- or microscopic alterations in vivo or ex vivo (Pompl et al. [14]: 95 W, 2.45 GHz, argon as carrier gas, ~ 36 °C, few eV; Daeschlein et al. [21]: 1–5 kV, 1.5 MHz, argon). Only after a 10-minute treatment with the FE-DBD device vacuolization of keratinocytes in human skin was detectable histologically.

Various hypotheses for the observed selectivity of plasma for prokaryotic as opposed to eukaryotic cells, which are also supported by other authors, were summarized by Dobrynin et al. [22]: Eukaryotic cells due to a different cell metabolism and higher cell organization are better protected from external stress and further have a more favorable surface-volume ratio, so that they are damaged only by a distinctly higher dose of poison.

The effect of targeted apoptosis can be used in the treatment of malignant cells which was demonstrated by Fridman et al. in vitro on ATCC A2058 melanoma cells (FE-DBD plasma treatment) and Lee et al. on G361 melanoma cells (helium plasma needle, 13.56 MHz, 15 s at 4 W, 0.5–5 slm) [23, 24].

Further pilot studies – also on other cancer cells – confirm the apoptotic effect [25–27].

Low-temperature plasmas and wound healing

Already in 1970 Robson and coworkers recognized that more than 10^5 colony-forming units of β-hemolytic streptococci, *Staphylococcus aureus* and *Pseudomonas aeruginosa* on a wound suffice to disturb wound healing [28]. Wound healing is also delayed if more than four different bacteria species are found on a wound [19, 28]. Resistant pathogens, especially methicillin-resistant *Staphylococcus aureus* strains (MRSA), which can become a global threat, are occurring with increasing frequency in chronic wounds [30, 31].

Studies on cell cultures prove that a plasma treatment can influence wound healing not only by a reduction of bacterial colonization but also by direct effects on epidermal and dermal cells [19, 32]. An interim analysis of the worldwide first randomized clinical trial with MicroPlaSter® (parameters see above) in which in the meantime already over

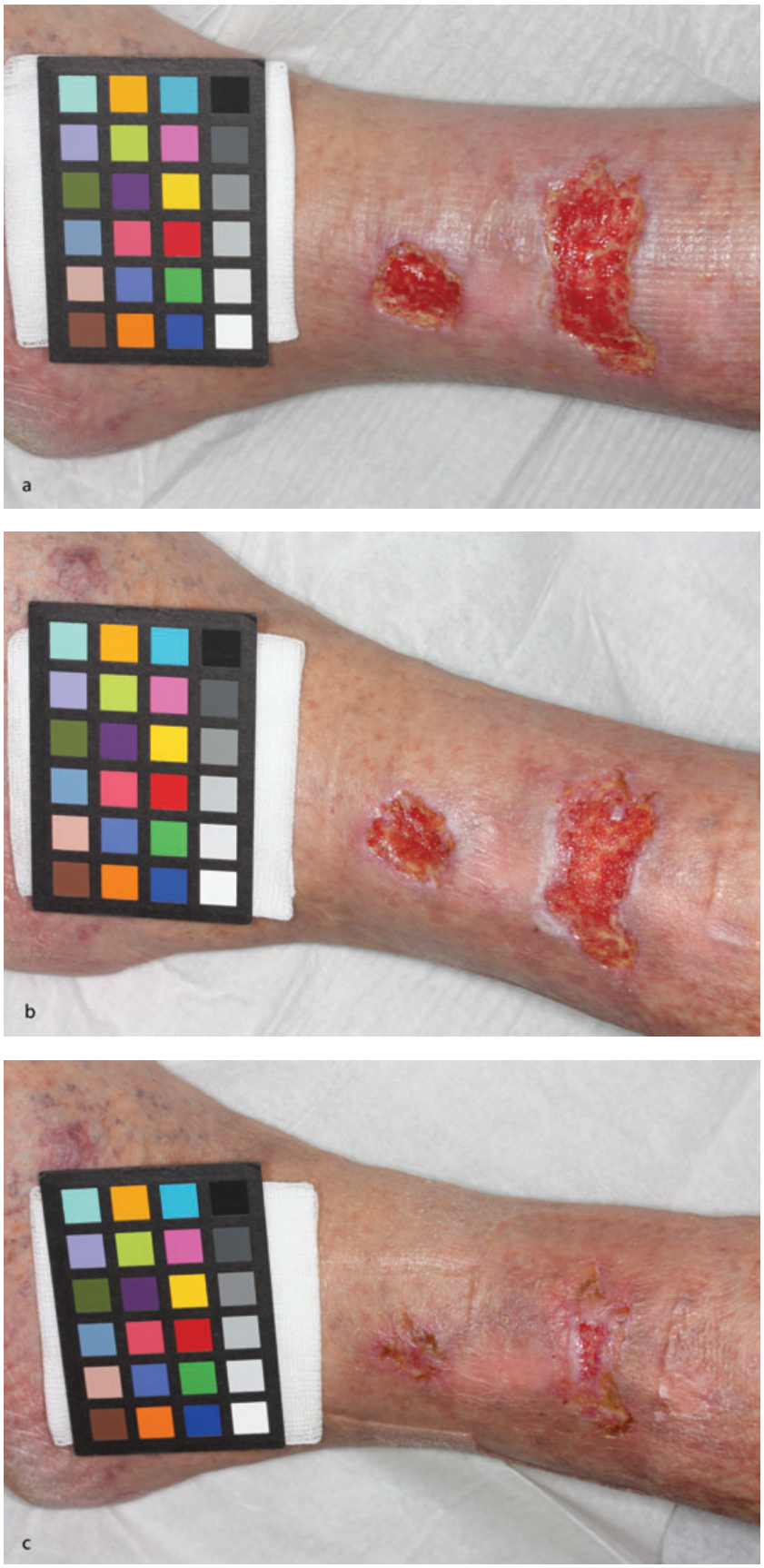

Figure 3: A 61-year-old patient with venous ulcers: wounds before plasma treatment (a), after 7 (b) and after 11 treatments (c). For the daily therapy of 2 min MicroPlaSter® was used. At the beginning of plasma treatment *Klebsiella oxytoca* and *Enterobacter cloacae* were detectable, after 11th treatment (23 days later) swabs were sterile.

150 patients with chronic infected wounds received low-temperature argon plasma once daily over 2 to 5 minutes as an add-on therapy demonstrated in 291 treatments of 36 patients – independent of the species of bacteria including MRSA – a highly significant reduction of bacterial load (34 %, $p < 10^{-6}$) in wounds treated with plasma in comparison to the control wounds without plasma [33]. Side effects did not occur at any time, treatment was well-tolerated by the patients (Figures 3a, b, c). In an uncontrolled study on 48 patients with diabetic foot syndrome Fetykov et al. using the "Plasmafon", a low-temperature plasma source with a large share of UV radiation, double as rapid complete wound healing and pain reduction within 5 days in comparison to the control group [34].

Of additional benefit to wound healing and regenerative processes are elevated concentrations of nitric oxide (NO) which can be generated exogenously by plasma [35, 36]. Among others vasodilation and normalized microcirculation, direct bactericidal effects, improvement of nerve conduction velocity, stimulation of fibroblasts and vessel growth are attributed to the induction of cytokines and growth factors. In animal models after application of NO generated exogenously in plasma wounds healed on average about 24.6 % more rapidly than in the control group. In an uncontrolled study on 65 diabetes patients with purulent or necrotic wounds on the legs the treatment with the "Plazon", a plasma device where hot plasma with high NO concentrations is very rapidly cooled to 20–40 °C, leads to accelerated wound healing [37]. This fact was confirmed by Lipatov et al. on 40 patients [36]. Despite the fact that the "Plazon" system has been in medical use for 9 years on thousands of patients, no controlled, randomized studies exist yet.

Cold plasmas in atopic dermatitis and other pruritic diseases

Skin colonization with facultatively pathogenic microorganisms can trigger various skin diseases including atopic dermatitis. To verify this effect of cold plasmas on bacterial colonization Daeschlein and coworkers treated a patient with pronounced *Staphylococcus aureus* colonization for 3 minutes with a low-temperature atmospheric-pressure

Figure 4: Treatment of a forearm of a patient with hepatogenic pruritus with argon plasma (MicroPlaSter β®). Therapy was also performed daily over 2 min.

plasma jet (1–5 kV; 1.5 MHz, argon gas), which led to a selective eradication of this pathogen, while the physiological skin flora with *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* remained undamaged and was mobilized to the skin surface from deeper skin layers (observable by confocal scanning laser microscopy) [38]. Mertens et al. also demonstrated a reduction of *Staphylococcus aureus* by more than tenfold within 2 days in a patient with atopic dermatitis (with a direct DBD device at a frequency of 90–700 Hz at 3–7.8 kV). Further, distinct improvement of erythema and a reduction of pruritus for hours were observed [39].

Possibly low-pressure plasmas will in the future represent therapy options for the treatment of diverse pruritic disorder, even though no controlled studies have yet been published on this (Figure 4) and the exact pathomechanism or mechanism of action are still unknown.

Cosmetic applications

In 2005 the UF Food and Drug Administration licensed plasma skin regeneration technology (PSR) for skin rejuvenation and for treatment of wrinkles.

Here a hot, but rapidly cooling plasma, that is produced by a radiofrequency plasma jet with nitrogen as carrier gas, is employed. The heat application induces controlled thermal damage in the skin which results in the new production of collagen, a reduction of elastic fibers and a restructuring of dermal architecture that can be confirmed histologically [40–42]. In addition to wrinkle treatment the method can also be used in the therapy of, among others, actinic keratoses, seborrheic keratoses, viral papillomas, scars and sun-damaged skin including pigmentary disturbance or in combination with aesthetic-surgical procedures. During treatment local or systemic anesthesia is required. Several studies confirm the method's success with a reduction of wrinkles by up to 50 % [43, 44].

Blood coagulation

Local application of high-temperature plasma for hemostasis and for sclerosing angiodysplasias and ablation of tumors has been used since about 30 years, e. g. in the form of the argon plasma coagulator (APC) [45, 46] in many surgical disciplines including endoscopic procedures (40–75 W in the MHz range, 1–10 l gas flow rate, ~ 120 °C, ~ 3 eV). The effect of ionized gas applied without tissue contact is thermal and is based on protein denaturation and desiccation. In dermatology the technique was first employed in 1997 by Katsch et al. for the treatment of intraepithelial disorders (e. g. actinic keratoses, condylomata acuminata etc) [47]. The depth of penetration is only 2–3 mm, making the method relatively free of side effects. Nevertheless, depending on site of application diverse complications such as pain, bleeding, perforation, strictures, disturbances in swallowing, the development of gas emphysema of the mucosa, neuromuscular stimulation and even gas explosions have been reported [48].

More recent studies show that even low-temperature plasmas accelerate blood coagulation [49], both in vitro and in vivo in animal models. After treatment with FE-DBD significant alterations in the protein composition and coagulation factors in blood, even in anticoagulated patients and patients with hemophilia were observed. The detailed biochemical basis for accelerated coagulation is still largely unknown. It is known that the natural blood coagulation is triggered by selective effects on certain blood proteins, but that the release of calcium ions or pH changes are not of significance and that the effect is independent of the gas temperature or the temperature on the surface of blood [50].

Further applications

A further possible indication in dermatology is the treatment of cutaneous leishmaniasis. Fridman and colleagues demonstrated in a cell culture a successful 100 % inactivation of *Leishmania major* promastigotes within 20 s, while for inactivation of human macrophages in contrast a two-minute treatment was required to inactivate 20–30 % [51].

Many bacterial skin diseases such as impetigo contagiosa, folliculitis or ecthyma, fungal infections such as tinea pedis or even viral diseases might profit from a treatment with cold plasma in the future. The ability to penetrate textiles (e. g. socks) makes the use of plasma e. g. in the prevention or therapy of tinea pedis an interesting alternative. Besides large devices for clinics and medical offices small devices for home use are under development. A further revolution might also take place in (hospital) hygiene: The HandPlaSter®, a low-temperature plasma device using barrier coronal discharge (BCD) technology (≤ 0.5 W/cm², 18 kV_{pp}, 12.5 kHz) that was developed for potential use for hand disinfection allows for in vitro a reduction of the bacterial load by over 5 log steps within few seconds (< 10 s) [10]. Here even multiresistant pathogens such as MRSA are effectively destroyed. This new form of (hand) disinfection has some advantages over conventional liquid disinfectants, which must be applied

for several minutes and irritate the skin, while at the same time remaining distinctly below WHO limits for UV, toxic gases and electric current [10]. Naturally, not only clinics but also public establishments, nursing homes etc. could profit. Cold plasmas may also find applications in dentistry in the future. Due to the ability to enter microscopically small openings, theoretically therapeutic measures against periodontitis, chronic gingivitis and in the treatment of infected root canals are possible. Clinical evidence for this must still be gathered. Further, in vivo the combination with H_2O_2 showed an increase in the bleaching effect as well as protein removal on the surface of plasma-treated teeth [52, 53].

Conclusions

Thanks to interdisciplinary cooperation in medicine, physics, chemistry, biology and microbiology plasma medicine has developed into an innovative and dynamic field of research in recent years. Even if many questions remain unanswered – especially the mechanism of interaction between plasma and living cells/ tissues and the optimization of plasma composition depending on the desired effect – studies to date illustrate the great potential of plasma medicine. Cold plasmas will surely be available in the near future to an increasing extent both for therapy and prevention of diverse, particularly infectious diseases. There does exist a vision of a breakthrough in medicine comparable to the introduction of antibiotics. The superiority of plasmas in comparison to previous medical standards remains to be clarified, especially in economic terms.

Conflicts of interest

Some members of our working group hold patents on diverse plasma devices and techniques. A phase II study on the treatment of infected wounds with cold atmospheric plasma (MicroPlaSter®) is being financed by the Max Planck Institute for Extraterrestrial Physics, Munich, Germany. <<<

Abbreviations

APC: argon plasma coagulator
CAP: cold atmospheric plasma
DBD: dielectric barrier discharge
FE-DBD: floating-electrode dielectric barrier discharge
MRSA: methicillin-resistant *Staphylococcus aureus*
PSR: plasma skin regeneration
SMD: surface micro discharge
SSCP: Scientific Committee on Consumer Products

Julia Heinlin

Correspondence to

Prof. Dr. Sigrid Karrer
Department of Dermatology
University of Regensburg
Franz-Josef-Strauß-Allee 11
D-93053 Regensburg, Germany
Tel.: +49-941-944-9656
Fax: +49-941-944-9657
E-mail:
sigrid.karrer@klinik.uni-regensburg.de

References

1 Crookes W. On Radiant Matter Spectroscopy: A New Method of Spectrum Analysis. Proc Roy Soc 1883; 35: 262–71.
2 Morfill G, Kong MG, Zimmermann JL. Focus on Plasma Medicine. New Journal of Physics 2009; 11: 115011.
3 Fridman A, Chirokov A, Gutsol A. Non-thermal atmospheric pressure discharges. J Phys D: Applied Physics 2005; 38: R1–R24.
4 Nosenko T, Shimizu T, Morfill GE. Designing plasmas for chronic wound disinfection. New Journal of Physics 2009; 11: 115013.
5 Fridman G, Friedman G, Gutsol A, Shekhter AB, Vasilets VN, Fridman A. Applied Plasma Medicine. Plasma Process Polym 2008; 5: 503–33.
6 Fridman G, Brooks AD, Balasubramanian M, Fridman A, Gutsol A, Vasilets VN, Ayan H, Friedman G. Comparison of direct and indirect effects of non-thermal atmospheric-pressure plasma on bacteria. Plasma Process Polym 2007; 4: 370–5.
7 Shimizu T, Steffes B, Pompl R, Jamitzky F, Bunk W, Ramrath K, Georgi M, Stolz W, Schmidt HU, Urayama T, Fujii S, Morfill GE. Characterization of microwave plasma torch for decontamination. Plasma Process Polym 2008; 5: 577–82.
8 Sladek RE, Stoffels E. Deactivation of *Escherichia coli* by the plasma needle. J Phys D: Applied Physics 2005; 38: 1716–21.
9 Cao Z, Walsh JL, Kong MG. Atmospheric plasma jet array in parallel electric and gas flow fields for three-dimensional surface treatment. Appl Phys Lett 2009; 94: 021501.
10 Morfill GE, Shimizu T, Steffes B, Schmidt HU. Nosocomial infections – a new approach towards preventive medicine using plasmas. New Journal of Physics 2009; 11: 115019.
11 Lademann J, Richter H, Alborova A, Humme D, Patzelt A, Kramer A, Weltmann KD, Hartmann B, Ottomann C, Fluhr JW, Hinz P, Hubner G, Lademann O. Risk assessment of the application of a plasma jet in dermatology. J Biomed Opt 2009; 14: 054025.
12 Laroussi M. Sterilization of Contaminated Matter with an Atmospheric Pressure Plasma. IEEE Trans Plasma Sci 1996; 24: 1188–91.
13 Kong MG, Kroesen J, Morfill G, Nosenko T, Shimizu T, van Dijk J, Zimmermann JL. Plasma medicine: an introductory review. New Journal of Physics 2009; 11: 115012.
14 Pompl R, Shimizu T, Schmidt HU, Bunk W, Jamitzky F, Steffes B, Ramrath K, Peters B, Stolz W, Urayama T, Ramasamy R, Fujii S, Morfill GE. Efficiency and medical compatibility of low-temperature plasma sterilization. 6th International Conference on Reactive Plasmas. Matsushima, Japan, 2006.
15 Kamgang-Youbi G, Herry JM, Meylheuc T, Brisset JL, Bellon-Fontaine MN, Doubla A, Naitali M.

Microbial inactivation using plasma-activated water obtained by gliding electric discharges. Lett Appl Microbiol. 2009; 48: 13–8.
16 Deng X, Shi JJ, Kong MG. Protein destruction by a helium atmospheric pressure glow discharge: Capability and mechanisms. J Appl Phys 2007; 101: 074701.
17 Lee MH, Park BJ, Jin SC, Kim D, Han I, Kim J, Hyun SO, Chung KH, Park JC. Removal and sterilization of biofilms and planktonic bacteria by microwave-induced argon plasma at atmospheric pressure. New Journal of Physics 2009; 11: 115022.
18 Shashurin A, Keidar M, Bronnikov S, Jurjus RA, Stepp MA. Living tissue under treatment of cold plasma atmospheric jet. Appl Phys Lett 2008; 93: 181501.
19 Kalghatgi S, Fridman A, Friedman G, Clyne AM. Non-thermal plasma treatment enhances proliferation of endothelial cells. Second International Conference on Plasma Medicine. San Antonio, Texas, USA, 2009.
20 Sosnin EA, Stoffels E, Erofeev MV, Kieft IE, Kunts SE. The effects of UV irradiation and gas plasma treatment on living mammalian cells and bacteria: a comparative approach. IEEE Transact Plasma Sci 2004; 32: 1544–50.
21 Daeschlein G, Darm K, Majunke S, Kindel E, Weltmann KD, Juenger M. In vivo monitoring of atmospheric pressure plasma jet (APPJ) skin therapy by confocal laserscan microscopy (CLSM). Second International Conference on Plasma Medicine. San Antonio, Texas, USA, 2009.
22 Dobrynin D, Fridman G, Friedman G, Fridman A. Physical and biological mechanisms of direct plasma interaction with living tissue. New Journal of Physics 2009; 11: 115020.
23 Lee HJ, Shon CH, Kim YS, Kim S, Kim GC, Kong MG. Degradation of adhesion molecules of G361 melanoma cells by a non-thermal atmospheric pressure microplasma. New Journal of Physics. 2009; 11: 115026.
24 Fridman G, Shereshevsky A, Jost M, Brooks A, Fridman A, Gutsol A, Vasilets V, Friedman G. Floating electrode dielectric barrier discharge plasma in air promoting apoptotic behavior in melanoma skin cancer cell lines. Plasma Chem Plasma Process 2007; 27: 163–76.
25 Kim D, Gweon B, Kim DB, Choe W, Shin JH. A feasibility study for the cancer therapy using cold plasma. 13th International Conference on Biomedical Engineering. Singapore: ICBME, 2008: 355–57.
26 Kim G, Lee H, Shon C. The effect of a micro plasma on melanoma (G361) cancer cells. J Korean Physical Society 2009; 54: 628–32.
27 Zang X, Li M, Zhou R, Feng K, Yang S. Ablation of liver cancer cells in vitro by a plasma needle. Appl Phys Lett 2008; 93: 021502.
28 Robson MC, Heggers JP. Delayed wound closure based on bacterial counts. J Surg Oncol 1970; 2: 379–83.
29 Trengove NJ, Stacey MC, McGechie DF, Mata S. Qualitative bacteriology and leg ulcer healing. J Wound Care 1996; 5: 277–80.
30 Grundmann H, Aires-de-Sousa M, Boyce J, Tiemersma E. Emergence and resurgence of meticillin-resistant Staphylococcus aureus as a public-health threat. Lancet 2006; 368: 874–85.
31 Klein E, Smith DL, Laxminarayan R. Hospitalizations and deaths caused by methicillin-resistant Staphylococcus aureus, United States, 1999–2005. Emerg Infect Dis 2007; 13: 1840–6.
32 Wende K, Landsberg K, Lindequist U, Weltmann KD, v. Woedtke T. Microorganisms, human cells and cold atmospheric plasma – looking for an intersection. 2nd International Workshop on Plasma-Tissue Interactions. Greifswald, Germany, 2009.
33 Isbary G, Morfill G, Schmidt HU, Georgi M, Ramrath K, Heinlin J, Karrer S, Landthaler M, Shimizu T, Steffes B, Bunk W, Monetti R, Zimmermann JL, Pompl R, Stolz W. A first prospective randomized controlled trial to decrease bacterial load using cold atmospheric argon plasma on chronic wounds in patients. Br J Dermatol 2010 Mar 5. [Epub ahead of print].
34 Fetykov AI, Avdeeva EA, Fulton J, Ferrel J, Gotsev VA, Galov AA. The effectiveness of cold plasma treatment of diabetic feet syndrome, complicated by purulonecrotic process. Second International Conference on Plasma. San Antonio, Texas, USA, 2009.
35 Shekhter AB, Kabisov RK, Pekshev AV, Kozlov NP, Perov YL. Experimental and clinical validation of plasmadynamic therapy of wounds with nitric oxide. Bulletin of Experimental Biology and Medicine 1998; 126: 829–34.
36 Lipatov KV, Sopromadze MA, Shekhter AB, Emel'ianov A, Grachev SV. [Use of gas flow with nitrogen oxide (NO-therapy) in combined treatment of purulent wounds]. Khirurgiia (Mosk) 2002: 41–3.
37 Shulutko AM, Antropova NV, Kriuger Iu A. [NO-therapy in the treatment of purulent and necrotic lesions of lower extremities in diabetic patients]. Khirurgiia (Mosk) 2004: 43-6.
38 Daeschlein G, Darm K, Niggemeier M, Majunke S, von Woedtke T, Kindel E, Weltmann KD, Juenger M. Selective antistaphylococcal activity of atmospheric pressure plasma jet (APPJ) on human skin. Second International Conference on Plasma Medicine. San Antonio, Texas, USA, 2009.
39 Mertens N, Helmke A, Goppold A, Emmert S, Kaemling A, Wandke D, Vioel W. Low temperature plasma treatment of human tissue. Second International Conference on Plasma Medicine. San Antonio, Texas, USA, 2009.
40 Bogle MA, Arndt KA, Dover JS. Evaluation of plasma skin regeneration technology in low-energy full-facial rejuvenation. Arch Dermatol 2007; 143: 168-74.
41 Fitzpatrick R, Bernstein E, Iyer S, Brown D, Andrews P, Penny K. A histopathologic evaluation of the Plasma Skin Regeneration System (PSR) versus a standard carbon dioxide resurfacing laser in an animal model. Lasers Surg Med 2008; 40: 93–9.
42 Foster KW, Moy RL, Fincher EF. Advances in plasma skin regeneration. J Cosmet Dermatol 2008; 7: 169–79.
43 Kilmer S, Semchyshyn N, Shah G, Fitzpatrick R. A pilot study on the use of a plasma skin regeneration device (Portrait PSR3) in full facial rejuvenation procedures. Lasers Med Sci 2007; 22: 101–9.
44 Kilmer S, Fitzpatrick R, Bernstein E, Brown D. Long term follow-up on the use of plasma skin regeneration (PSR) in full facial rejuvenation procedures. Lasers Surg Med 2005; 36: 22.
45 Morrison JCF. Electrosurgical method and apparatus for initiating an electrical discharge in an inert gas flow. US Patent. 1977; 4,040,426.
46 Ginsberg GG, Barkun AN, Bosco JJ, Burdick JS, Isenberg GA, Nakao NL, Petersen BT, Silverman WB, Slivka A,

Kelsey PB. The argon plasma coagulator: February 2002. Gastrointest Endosc 2002; 55: 807–10.
47 Katsch J, Müller RPA, Mailänder W. Argon-Plasma-Koagulation (APC) in der Dermatologie – Eine Standortbestimmung. VOD Dialog Beilage in Der Deutsche Dermatologe 1997; 45: 2–6.
48 Manner H, Enderle MD, Pech O, May A, Plum N, Riemann JF, Ell C, Eickhoff A. Second-generation argon plasma coagulation: two-center experience with 600 patients. J Gastroenterol Hepatol 2008; 23: 872–8.
49 Fridman G, Peddinghaus M, Ayan H, Fridman A, Balasubramanian M, Gutsol A, Brooks A, Friedman G. Blood coagulation and living tissue sterilization by floating-electrode dielectric barrier discharge in air. Plasma Chem Plasma Process 2006; 26: 425–42.
50 Fridman A. Non-thermal plasma assisted blood coagulation. Cambridge University Press, New York, 2008.
51 Fridman G, Shereshevsky A, Peddinghaus M, Gutsol A, Vasilets V, Brooks A, Balasubramanian M, Friedman G, Fridman A. Bio-medical applications of non-thermal atmospheric pressure plasma. 37th AIAA Plasmadynamics and Lasers Conference. San Francisco, California, USA, 2006.
52 Sun P, Wang R, Tong G, Zhang J, Fang J. Teeth whitening with dental gel assisted by an atmospheric pressure non-thermal plasma. Second International Conference on Plasma Medicine. San Antonio, Texas, USA, 2009.
53 Lee HW, Kim GJ, Kim JM, Park JK, Lee JK, Kim GC. Tooth bleaching with nonthermal atmospheric pressure plasma. J Endod 2009; 35: 587–91.