

## Potential of cold atmospheric pressure plasma (CAPP) in wound management



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In recent years, plasma medicine has become an innovative research area with great potential. Plasma — the fourth state of matter — is an ionised gas and can be produced from argon, helium, nitrogen, oxygen or air at atmospheric pressure and low temperatures. Such cold atmospheric pressure plasmas (CAPPs) consist of a mixture of reactive species that convey antimicrobial activity and affect human tissues. The development of CAPP devices has led to novel therapeutic strategies in wound healing, tissue regeneration and skin infection management. CAPPs have become an increasingly important alternative for antimicrobial treatment as bacterial resistance is unlikely due to their versatile modes of action. The greatest challenge in CAPPs introduction in clinical practice remains understanding their mechanisms of action at the cellular level for safe, targeted application.

Physical plasmas are a common natural phenomenon; about 99% of all visible matter in the universe exists in the plasma state, which refers to a partially or completely ionised gas generated by energy input. Plasmas can be artificially generated; the most common methods of gas dissociation are electricity, microwave radiation or heat (Lackmann and Bandow, 2014). The development of cold atmospheric pressure plasmas (CAPPs) for therapeutic purposes has led to the emergence of a new field of application and research called plasma medicine. 'Cold' in this case describes temperatures of around 40°C on the substrate being treated. These temperatures allow the painless treatment of human tissues (Lackmann and Bandow, 2014; Heuer et al, 2015).

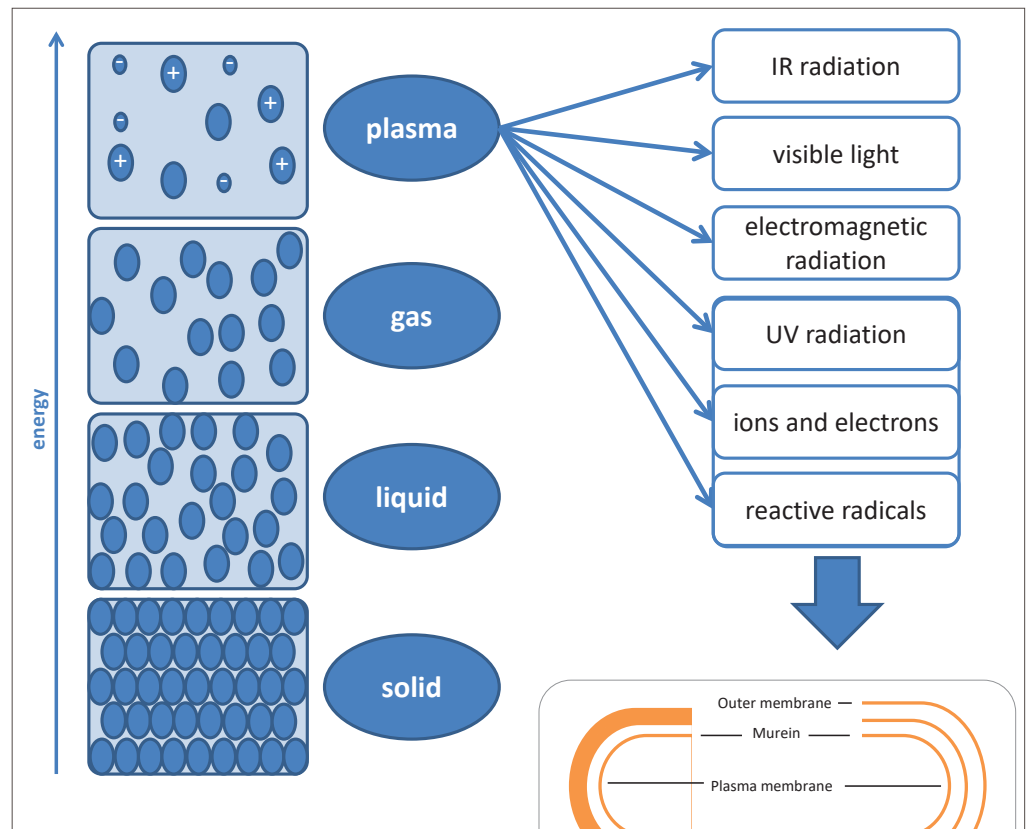
Clinical applications of CAPP range from surface decontamination to the sterilisation of medical instruments to wound healing, as well as skin disinfection, infection control for the treatment of inflammatory skin diseases and oncological applications. Wound treatment is a promising clinical application, as CAPPs have antimicrobial properties as well as stimulating skin cells and angiogenesis (Haertel et al, 2014). Different plasma devices have been shown to kill pathogens (Morfill et al, 2009; Daeschlein et al, 2015), decontaminate skin (Fridman et al, 2008) demonstrated skin and suppress bacterial growth on skin wounds (Lademann et al, 2010; Nasir et

al, 2016; Kubinova et al, 2017). In a study using the MicroPlaSter® on infected chronic wounds, once daily CAPP application for 2–5 minutes significantly reduced the number of bacteria in the wounds compared to untreated controls (Isbary et al, 2012). A clinical trial that used a dielectric barrier discharge (DBD) plasma source (PlasmaDerm® VU-2010) as adjunctive therapy for chronic venous leg ulcers showed that treatment is safe, generally well tolerated and effectively reduces bacterial load (Brehmer et al, 2015). Additional studies have shown improved wound healing using a CAPP jet device (Hilker et al, 2017) and following pretreatment with octenidine dihydrochloride (Hartwig et al, 2017a) in cases of infection.

CAPP stimulates the migration and proliferation of keratinocytes and fibroblasts (Arndt et al, 2013; Schmidt et al, 2017). Clinically-accelerated wound healing was observed in chronic wounds (Isbary et al, 2013; Brehmer et al, 2015) and at skin graft donor sites treated with CAPP (Heinlin et al, 2013). In addition to faster wound closure, Heinlin et al (2010) observed significant pain reduction within 5 days of CAPP treatment compared to the untreated control group. Kisch et al (2016a) studied changes in the intact skin of healthy volunteers after CAPP and demonstrated that CAPP probably works by influencing microcirculation. Plasma application *in vivo* led to a fast increase in dermal microcirculation parameters such as capillary–venous oxygen saturation, relative haemoglobin,

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**Figure 1.** Plasma is the fourth state of matter, a partially or completely ionised gas that is generated by energy input. Plasmas can be artificially generated through gas dissociation by electricity, microwave radiation or heat under ambient conditions. If the ejection of the normal pressure plasma is very fast, the electrons and heavy particles are not in thermal equilibrium and the resulting temperature is only between 25°C and 45°C. These plasmas are called cold atmospheric plasmas (CAPP). They consist of electrons, negative and positive ions, free radicals and reactive molecules as well as UV and other radiation.

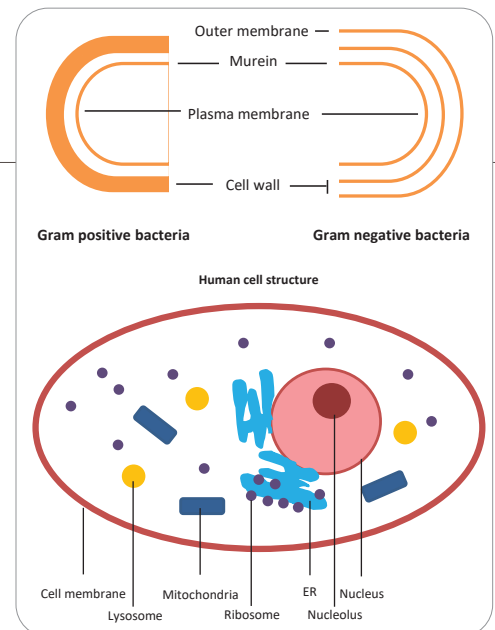


blood flow and velocity lasting at least 1 hour (Heuer et al, 2015), which could be of particular interest in diabetic wounds.

### Mode of action

CAPPs are electrically conductive, quasi-neutral gases consisting of electrons, negative and positive ions, free radicals, reactive molecules, and ultraviolet (UV) radiation [Figure 1]. They generate visible light, heat and electromagnetic radiation (O'Connor et al, 2014). As CAPP sources are operated at ambient pressure in contact with air, large amounts of reactive oxygen and nitrogen radicals are generated. These exert antimicrobial effects and have a strong influence on cellular biochemistry (Gay-Mimbrera et al, 2016; Szili et al, 2018). For example, atomic oxygen, ozone, superoxide, hydroxyl radicals, nitric oxide and hydrogen peroxide are all known to kill microorganisms by attacking microbial structures in various ways (Laroussi, 2005; Lackmann and Bandow, 2014). Reactive oxygen components etch the outer cell capsule exposing the cellular membrane (Laroussi, 2002), which makes the unsaturated fatty acids in the phospholipid bilayer susceptible to more plasma-induced radicals (Stoffels et al, 2008).

Further oxidation of the cellular protein components and DNA alters their structure and causes functional changes, disrupting cell



metabolism and preventing cell replication (Sharma et al, 2009; O'Connor et al, 2014).

CAPPs effectively inactivate microorganisms (Hong et al, 2009; Hähnel et al, 2010; Kim et al, 2011; Zimmermann et al, 2011; Matthes et al, 2012; Daeschlein et al, 2012b; Li et al, 2013; Wiegand et al, 2014), successfully eliminate antibiotic-resistant pathogens (Maisch et al, 2012; Daeschlein et al, 2014; Alkawareek et al, 2014) and remove microbial biofilms (Joshi et al, 2010; Alkawareek et al, 2012; Fricke et al, 2012; Julak and Scholtz, 2013; Matthes et al, 2013), as well as killing bacterial and fungal spores (Trompeter et al, 2002; Klämpfl et al, 2012). However, differences in efficacies have to be noted. Gram-positive bacteria possess a thick cell wall, which conveys higher tolerance to CAPP,

while the outer membrane of Gram-negative bacteria is highly sensitive to peroxidation and prone to electrostatic disruption by CAPP treatment (Mai-Prochnow et al, 2016; Nishime et al, 2017) [Figure 1]. Furthermore, individual bacteria differ in (Mahadevan, 2009; Furchtgott et al, 2011):

- Cell wall composition
- Cell shape
- Physical properties (cell wall)
- Synthesis and remodelling processes
- Cell wall extension force and turgor pressure balance.

Electrostatic disruption occurs when CAPP components strike the microbe surface, triggering cell wall tension leading to mechanical rupture and subsequent leakage of cell content (Laroussi et al, 2003). The mechanism by which CAPP inactivates filamentous fungi resembles that described for bacteria, and fungal death is preceded by structural damage to the cell envelope and the oxidation of cell macromolecules (Šimončicová et al, 2018).

As with microorganisms, the effects of CAPP on human cells can be observed at different levels [Figure 1]. The first target structure is the cell membrane, with its lipids, embedded receptor proteins and enzymes. Lipid peroxidation and modification of cell adhesion molecules alter cell migration and signal transduction (Haertel et al, 2011). UV radiation and free radicals continue to affect DNA and thus precede changes in cell proliferation or the induction of apoptosis. (Cao and Wan, 2009). All effects depend on the plasma dose/treatment time. Accordingly, both stimulatory and damaging effects are possible (Haertel et al, 2014). CAPP is well tolerated if treatment times are short (Stoffels et al, 2008; Wiegand et al, 2016). Moreover, CAPP treatment can stimulate eukaryotic cells, resulting in faster cell proliferation and enhanced angiogenesis, which can shorten the wound healing process (Lackmann and Bandow, 2014). Plasma-dependent activation of cytokines and growth factors has also been reported (Arndt et al, 2013).

### CAPP treatment devices

There is a long history of plasma use in medical treatment. The mid 19th century saw the introduction of electrotherapy and the use of spark discharges to treat various diseases (Gay-Mimbrera et al, 2016). Later, electrosurgical techniques were developed based on plasma applications. Argon plasma coagulation was introduced in the 1970s; this well-established endoscopic procedure is used in gastroenterology, general and visceral surgery, urology and gynaecology to control

bleeding and debulk tumours (Raiser and Zenker, 2006). The more recent PlasmaJet Surgery System is commonly used to cut or coagulate tissue. In electrosurgery, the plasma interacts with the tissue, denaturing proteins, destroying cells and devitalising (sealing) local tissue (von Woedtke et al, 2013; Gay-Mimbrera et al, 2016).

Generally, the CAPP discharge is created and maintained by applying high voltage to gas flowing between two dielectric-covered electrodes (O'Connor et al, 2014). The properties of the plasma depend on parameters such as gas flow and the type of gas used, as well as discharge geometry (Heuer et al, 2015). A mixture of active agents is created, the composition and concentration of which result in different biological responses (Gan et al, 2018).

There are two main approaches to generating CAPP: indirect and direct systems (Yan et al, 2017). Indirect plasma sources are characterised by self-contained systems. The plasma is ignited in a tube through which gas — usually helium or argon — flows between two electrodes (Stoffels et al, 2002; Weltmann et al, 2009; Mai-Prochnow et al, 2014; Yan et al, 2017). The active species are then transported as effluent within the gas stream, ensuring that the treated surface does not come into direct contact with the plasma (Stoffels et al, 2002; Weltmann et al, 2009; Mai-Prochnow et al, 2014; Gay-Mimbrera et al, 2016).

Plasma is generated between the electrode and the biological sample — which serves as the counter-electrode — in direct systems (Heuer et al, 2015; Gay-Mimbrera et al, 2016). The plasma therefore comes into direct contact with the surface being treated (Mai-Prochnow et al, 2014). DBD sources directly generate plasma in air. In some applications, oxygen and nitrogen are added to produce a specific chemical CAPP composition (Yan et al, 2017). The continuous flow of carrier gas creates a 'flame' in the plasma jet while the DBD source provides a short but wide plasma; therefore, the former may be more suitable for the treatment of small areas and the latter more appropriate for large areas (Yan et al, 2017).

The development of new devices optimised for specific clinical applications is well under way. Several CAPP devices are CE-certified and available for use in wound treatment (Karrer and Arndt, 2015), the most prominent being (Boehm and Bourke, 2019):

- MicroPlaSter (Adtec Plasma Technology Co. Ltd, Fukuyama, Japan)
- kINPen® Med (neoplas tools GmbH, Greifswald, Germany)
- PlasmaDerm (CYNODY GmbH, Duderstadt, Germany).

### MicroPlaSter

MicroPlaSter was developed by the Max Planck Institute for Extraterrestrial Physics in cooperation with Adtec Plasma Technology and is currently marketed as Adtec SteriPlas (ADTEC Healthcare, Hounslow, UK).

Isbary et al (2012) conducted a number of trials on *in vivo* human skin, demonstrating that 2 minutes of treatment with the MicroPlaSter  $\alpha$  or  $\beta$  plasma devices was safe, painless and effectively decreased bacterial load in chronic wounds without causing side-effects. Further studies by the same group demonstrated good treatment tolerability without pain, heat or discomfort (Li et al, 2013). Adtec SteriPlas consists of a plasma torch with six electrodes and has a 3.5 cm diameter. Plasma is produced by microwave-induced discharge and argon is used as the carrier gas. The recommended distance from the target tissue is 2 cm; this is ensured by using disposable plastic spacers. Treatment times of 2–5 minutes are suggested (Karrer and Arndt, 2015).

### kINPen Med

In 2013, kINPen Med was certified as a medical device in Germany (Karrer and Arndt, 2015). It was developed in cooperation between Leibniz Institute for Plasma Science and Technology, University Medical Center Greifswald and Charité Universitätsmedizin Berlin (Karrer and Arndt, 2015).

This device can be used to treat small chronic wounds. The pen-like tool is held perpendicular to the affected area of skin and is moved in a uniform motion at a speed of about 5 mm per second.

Studies on the skin of healthy human volunteers showed treatment with kINPen Med to be well tolerated in terms of paraesthesia, pain and heat, and did not damage the skin barrier or cause dry skin (Daeschlein et al, 2012a; 2012b). No side-effects or inflammatory reactions were observed in clinical trials of patients with chronic leg ulcers (Ulrich et al, 2015) and wound healing disorders (Hartwig et al, 2017b) or when employed as an adjuvant to oral antifungal treatment (Preissner et al, 2016). *In vivo* risk assessments indicated that UV radiation from the plasma jet was an order of magnitude below the dose inducing sunburn and did not result in thermal tissue damage (Lademann et al, 2009).

### PlasmaDerm

The PlasmaDerm product family includes a variety of DBD sources designed to cover areas

from 1 cm<sup>2</sup> to 22.5 cm<sup>2</sup> (Karrer and Arndt, 2015). These medical devices use ambient air to generate the CAPP.

Studies of the effects of plasma on skin microcirculation and bacterial levels in chronic leg ulcers found PlasmaDerm to be well tolerated by patients, with no pain or adverse effects reported (Brehmer et al, 2015; Kisch et al, 2016a; 2010b). In addition to chronic leg ulcers, PlasmaDerm can be used in the management of arterial ulcers, pressure (decubitus) ulcers and diabetic foot ulcers (Karrer and Arndt, 2015).

### Future potential

CAPP is a safe treatment option in wound care, enhancing the healing process by reducing bioburden and stimulating the production of skin cells and blood vessels. It is currently used as an add-on to standard wound care, usually three times a week. CAPP should be applied after debridement and the removal of any dressings. The overall duration of treatment is variable, since it depends on the wound size and plasma device used.

Despite differences in application, CAPP effectively supports re-epithelialisation, angiogenesis, the formation of new hair follicles and collagen fibres, while controlling inflammation (Chatraie et al, 2018). Moreover, mechanical analysis has demonstrated improved mechanical strength and tissue tolerance to tensile load following CAPP treatment (Chatraie et al, 2018).

CAPP has become increasingly important as an alternative to topical antibiotics in non-systemic infections. Due to its versatile modes of action, the development of bacterial resistance is unlikely. The active components of CAPP — reactive oxygen and reactive nitrogen species, UV radiation, positive and negative charge particles, excited-state and metastable particles — affect the biochemical processes of the organism. Different discharge parameters, including plasma device geometry, working gas species, gas flow and treatment time, affect the mixture of active agents resulting in different compositions with varying biological responses that have yet to be fully characterised (Gan et al, 2018). Future research needs to fill this gap and ensure the long-lasting, successful application of new CAPP intervention options. **WINT**

### References

- Alkawareek MY, Algwari QT, Laverty G et al (2012) Eradication of *Pseudomonas aeruginosa* biofilms by atmospheric pressure nonthermal plasma. *PLoS One* 7(8): e44289

- Alkawareek MY, Gorman SP, Graham WG et al (2014) Potential cellular targets and antibacterial efficacy of atmospheric pressure non-thermal plasma. *Int J Antimicrob Agents* 43(2): 154–60
- Arndt S, Unger P, Wacker E et al (2013) Cold atmospheric plasma (CAP) changes gene expression of key molecules of the wound healing machinery and improves wound healing in vitro and in vivo. *PLoS One* 8(11): e79325
- Boehm D, Bourke P (2019) Safety implications of plasma-induced effects in living cells - a review of in vitro and in vivo findings. *Biol Chem* 400(1): 3–17
- Brehmer F, Haenssle HA, Daeschlein G et al (2015) Alleviation of chronic venous leg ulcers with a handheld dielectric barrier discharge plasma generator (PlasmaDerm® VU-2010): results of a monocentric, two armed, open, prospective, randomized and controlled trial (NCT01415622). *J Eur Acad Dermatol Venerol* 29(1): 148–55
- Campas O, Mahadevan L (2009) Report shape and dynamics of tip-growing cells. *Curr Biol* 19(24): 2102–7
- Cao C, Wan Y (2009) Parameters of protection against ultraviolet radiation-induced skin cell damage. *J Cell Physiol* 220(2): 277–84
- Chatraie M, Torkaman G, Khani M et al (2018) In vivo study of non-invasive effects of non-thermal plasma in pressure ulcer treatment. *Sci Rep* 8(1): 5621
- Daeschlein G, Scholz S, Ahmed R et al (2012a) Cold plasma is well-tolerated and does not disturb skin barrier or reduce skin moisture. *J Dtsch Dermatol Ges* 10(7): 509–15
- Daeschlein G, Scholz S, Ahmed R et al (2012b) Skin decontamination by low-temperature atmospheric pressure plasma jet and dielectric barrier discharge plasma. *J Hosp Infect* 81(3): 177–83
- Daeschlein G, Napp M, von Podewils S et al (2014) In vitro susceptibility of multidrug resistant skin and wound pathogens against low temperature atmospheric pressure plasma jet (APPJ) and dielectric barrier discharge plasma (DBD). *Plasma Process Polym* 11(2): 175–83
- Daeschlein G, Napp M, Lutze S et al (2015) Skin and wound decontamination of multidrug-resistant bacteria by cold atmospheric plasma coagulation. *J Dtsch Dermatol Ges* 13(2): 143–50
- Fricke K, Koban I, Tresp H et al (2012) Atmospheric pressure plasma: a high-performance tool for the efficient removal of biofilms. *PLoS One* 7: e42539
- Fridman G, Friedman G, Gutsol A et al (2008) Applied plasma medicine. *Plasma Process Polym* 5(6): 503–33
- Furchtgott L, Wingreen NS, Huang KC (2011) Mechanisms for maintaining cell shape in rod-shaped Gram-negative bacteria. *Mol Microbiol* 81(2): 340–53
- Gan L, Zhang S, Poorun D et al (2018) Medical applications of nonthermal atmospheric pressure plasma in dermatology. *J Dtsch Dermatol Ges* 16(1): 7–13
- Gay-Mimbrera J, García MC, Isla-Tejera B et al (2016) Clinical and biological principles of cold atmospheric plasma application in skin cancer. *Adv Ther* 33(6): 894–909
- Hähnel M, von Woedtke T, Weltmann KD (2010) Influence of the air humidity on the reduction of bacillus spores in a defined environment at atmospheric pressure using a dielectric barrier surface discharge. *Plasma Process Polym* 7(3–4): 244–9
- Haertel B, Wende K, von Woedtke T (2011) Non-thermal atmospheric-pressure plasma can influence cell adhesion molecules on HaCaT-keratinocytes. *Exp Dermatol* 20(3): 282–4
- Haertel B, von Woedtke T, Weltmann KD et al (2014) Non-thermal atmospheric-pressure plasma possible application in wound healing. *Biomol Ther* 22(6): 477–90
- Hartwig S, Preissner S, Voss JO et al (2017a) The feasibility of cold atmospheric plasma in the treatment of complicated wounds in craniomaxillo-facial surgery. *J Craniomaxillofac Surg* 45(10): 1724–30
- Hartwig S, Doll C, Voss JO et al (2017b) Treatment of wound healing disorders of radial forearm free flap donor sites using cold atmospheric plasma: a proof of concept. *J Oral Maxillofac Surg* 75(2): 429–35
- Heinlin J, Morfill G, Landthaler M et al (2010) Plasma medicine: possible applications in dermatology. *J Dtsch Dermatol Ges* 8(12): 968–76
- Heinlin J, Zimmermann JL, Zeman F et al (2013) Randomized placebo-controlled human pilot study of cold atmospheric argon plasma on skin graft donor sites. *Wound Rep Reg* 21(6): 800–7
- Heuer K, Hoffmanns MA, Demir E et al (2015) The topical use of non-thermal dielectric barrier discharge (DBD): nitric oxide related effects on human skin. *Nitric Oxide* 44: 52–60
- Hilker L, von Woedtke T, Weltmann KD, Wollert HG (2017) Cold atmospheric plasma: a new tool for the treatment of superficial driveline infections. *Eur J Cardiothorac Surg* 51(1): 186–7
- Hong YF, Kang JG, Lee HY et al (2009) Sterilization effect of atmospheric plasma on *Escherichia coli* and *Bacillus subtilis* endospores. *Lett Appl Microbiol* 48(1): 33–7
- Isbary G, Heinlin J, Shimizu T et al (2012) Successful and safe use of 2 min cold atmospheric argon plasma in chronic wounds: results of a randomized controlled trial. *Br J Dermatol* 167(2): 404–10
- Isbary G, Stolz W, Shimizu T et al (2013) Cold atmospheric argon plasma treatment may accelerate wound healing in chronic wounds: results of an open retrospective randomized controlled study in vivo. *Clin Plasma Med* 1(2): 25–30
- Joshi SG, Paff M, Friedman G et al (2010) Control of methicillin-resistant *Staphylococcus aureus* in planktonic form and biofilms: A biocidal efficacy study of non-thermal dielectric-barrier discharge plasma. *Am J Infect Control* 38(4): 293–301
- Julak J, Scholtz V (2013) Decontamination of human skin by low-temperature plasma produced by cometary discharge. *Clin Plasma Med* 1(2): 31–4
- Karrer S, Arndt S (2015) [Plasma medicine in dermatology: Mechanisms of action and clinical applications]. *Hautarzt* 66(11): 819–28 [in German]
- Kim PY, Kim YS, Koo I G et al (2011) Bacterial inactivation of wound infection in a human skin model by liquid-phase discharge plasma. *PLoS One* 6(8): e24104
- Kisch T, Helmke A, Schleusser S et al (2016a) Improvement of cutaneous microcirculation by cold atmospheric plasma (CAP): Results of a controlled, prospective cohort study. *Microvasc Res* 104: 55–62
- Kisch T, Schleusser S, Helmke A et al (2016b) The repetitive use of non-thermal dielectric barrier discharge plasma boosts cutaneous microcirculatory effects. *Microvasc Res* 106: 8–13
- Klämpfl TG, Isbary G, Shimizu T et al (2012) Cold atmospheric air plasma sterilization against spores and other microorganisms of clinical interest. *Appl Environ Microbiol* 78(15): 5077–82



- Kubinova S, Zaviskova K, Uherkova L et al (2017) Non-thermal air plasma promotes the healing of acute skin wounds in rats. *Sci Rep* 7: 45183
- Lackmann JW, Bandow JE (2014) Inactivation of microbes and macromolecules by atmospheric-pressure plasma jets. *Appl Microbiol Biotechnol* 98(14): 6205–13
- Lademann J, Richter H, Alborova A et al (2009) Risk assessment of the application of a plasma jet in dermatology. *J Biomed Opt* 14(5): 054025
- Lademann O, Richter H, Patzelt A et al (2010) Application of a plasma-jet for skin antiseptics: analysis of the thermal action of the plasma by laser scanning microscopy. *Laser Phys Lett* 7(6): 458–62
- Laroussi M (2002) Nonthermal decontamination of biological media by atmospheric pressure plasmas: review, analysis, and prospects. *IEEE Trans Plasma Sci* 30(4):1409–15
- Laroussi M (2005) Low temperature plasma-based sterilization: Overview and state-of-the-art. *Plasma Process Polym* 2(5): 391–400
- Laroussi M, Mendis DA, Rosenberg M (2003) Plasma interaction with microbes. *New J Phys* 5: 41
- Li YF, Taylor D, Zimmermann JL et al (2013) In vivo skin treatment using two portable plasma devices: Comparison of a direct and an indirect cold atmospheric plasma treatment. *Clin Plasma Med* 1(2): 35–9
- Mai-Prochnow A, Murphy AB, McLeanb KM et al (2014) Atmospheric pressure plasmas: Infection control and bacterial responses. *Int J Antimicrob Agents* 43(6): 508–17
- Mai-Prochnow A, Clauson M, Hong J, Murphy AB (2016) Gram positive and Gram negative bacteria differ in their sensitivity to cold plasma. *Sci Rep* 6: 38610
- Maisch T, Shimizu T, Li YF et al (2012) Decolonisation of MRSA, *S. aureus* and *E. coli* by cold-atmospheric plasma using a porcine skin model in vitro. *PLoS One* 7(4): e34610
- Matthes R, Bekeschus S, Bender C et al (2012) Pilot-study on the influence of carrier gas and plasma application (open resp. delimited) modifications on physical plasma and its antimicrobial effect against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. *GMS Krankenhaushyg Interdisziplin* 7(1): Doc02
- Matthes R, Bender C, Schlüter R et al (2013) Antimicrobial efficacy of two surface barrier discharges with air plasma against in vitro biofilms. *PLoS One* 8(7): e70462
- Morfill GE, Shimizu T, Steffes B et al (2009) Nosocomial infections: a new approach towards preventive medicine using plasmas. *New J Phys* 11: 115019
- Nasir NM, Lee BK, Yap SS et al (2016) Cold plasma inactivation of chronic wound bacteria. *Arch Biochem Biophys* 605: 76–85
- Nishime TMCC, Borges AC, Koga-ito CY, et al (2017) Non-thermal atmospheric pressure plasma jet applied to inactivation of different microorganisms. *Surf Coat Technol* 312: 19–24
- O'Connor N, Cahill O, Daniels S et al (2014) Cold atmospheric pressure plasma and decontamination. Can it contribute to preventing hospital-acquired infections? *J Hosp Infect* 88(2): 59–65
- Preissner S, Kastner I, Schutte E et al (2016) Adjuvant antifungal therapy using tissue tolerable plasma on oral mucosa and removable dentures in oral candidiasis patients: A randomised double-blinded split-mouth pilot study. *Mycoses* 59(7): 467–75
- Raiser J, Zenker M (2006) Argon plasma coagulation for open surgical and endoscopic applications: state of the art. *J Phys D Appl Phys* 39(16): 3520–3
- Schmidt A, Bekeschus S, Wende K et al (2017) A cold plasma jet accelerates wound healing in a murine model of full-thickness skin wounds. *Exp Dermatol* 26(2): 156–62
- Sharma A, Collins G, Pruden A (2009) Differential gene expression in *Escherichia coli* following exposure to nonthermal atmospheric pressure plasma. *J Appl Microbiol* 107(5): 1440–9
- Šimončicová J, Kaliňáková B, Medvecká V et al (2018) Cold plasma treatment triggers antioxidative defense system and induces changes in hyphal surface and subcellular structures of *Aspergillus flavus*. *Appl Microbiol Biotechnol* 102(15): 6647–58
- Stoffels E, Flikeweert AJ, Stoffels WW, Kroesen GMW (2002) Plasma needle: a non-destructive atmospheric plasma source for fine surface treatment of (bio)materials. *Plasma Sources Sci Technol* 11(4): 383–8
- Stoffels E, Sakiyama Y, Graves DB (2008) Cold atmospheric plasma: charged species and their interactions with cells and tissues. *IEEE Trans Plasma Sci* 36(4): 1441–57
- Szili EJ, Hong SH, Oh JS, et al (2018) Tracking the penetration of plasma reactive species in tissue models. *Trends Biotechnol* 36(6): 594–602
- Trompeter F, Neff W, Franken O et al (2002) Reduction of *Bacillus subtilis* and *Aspergillus niger* spores using nonthermal atmospheric gas discharges. *IEEE Trans Plasma Sci* 30(4): 1416–23
- Ulrich C, Kluschke F, Patzelt A et al (2015) Clinical use of cold atmospheric pressure argon plasma in chronic leg ulcers: a pilot study. *J Wound Care* 24(5): 196–203
- von Woedtke T, Reuter S, Masur K et al (2013) Plasmas for medicine. *Phys Rep* 530: 291–320
- Weltmann KD, Kindel E, Brandenburg R et al (2009) Atmospheric pressure plasma jet for medical therapy: plasma parameters and risk estimation. *Contrib Plasma Phys* 49(9): 631–40
- Wiegand C, Beier O, Horn K et al (2014) Antimicrobial impact of cold atmospheric pressure plasma on medical critical yeasts and bacteria cultures. *Skin Pharmacol Physiol* 27(1): 25–35
- Wiegand C, Fink S, Beier O et al (2016) Dose- and time-dependent cellular effects of cold atmospheric pressure plasma evaluated in 3D skin models. *Skin Pharmacol Physiol* 29(5): 257–65
- Yan D, Sherman JH, Keidar M (2017) Cold atmospheric plasma, a novel promising anti-cancer treatment modality. *Oncotarget* 8(9): 15977–95
- Zimmermann JL, Dumler K, Shimizu T et al (2011) Effects of cold atmospheric plasmas on adenoviruses in solution. *J Phys D Appl Phys* 44(50): 505201