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

Author: *Cornelia Wiegand*

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,

Cornelia Wiegand *is Biochemist, Scientific Associate, Department of Dermatology, University Hospital Jena, Germany*

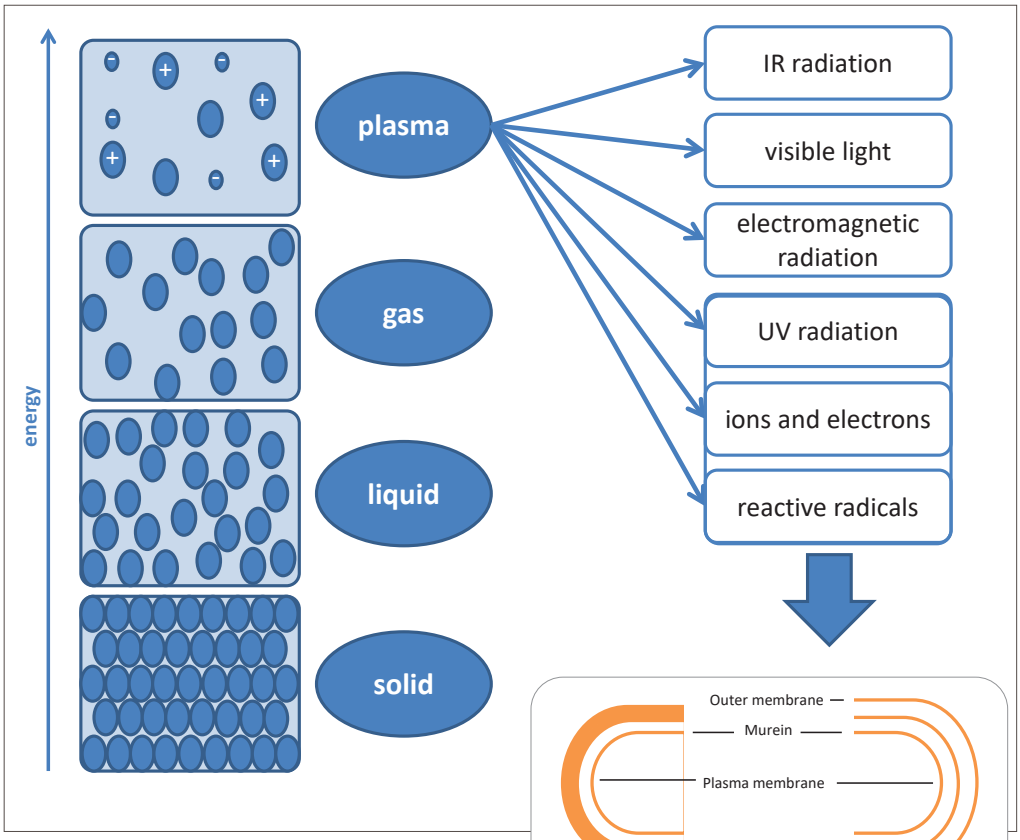

Figure 1. Plasma is the fourth state of matter, a partially or completely ionised gas that is generated by energy input. Plasmas can be artificially generated through gas dissociation by electricity, microwave radiation or heat under ambient conditions. If the ejection of the normal pressure plasma is 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 (CYNOGY 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 α or β 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^2 to 22.5 cm^2 (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

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