Plasma Medicine, 8(1):93–120 (2018)

Carbon Monoxide in Plasma Medicine and Agriculture: Just a Foe or a Potential Friend?

Emile Carbone[a,*,**] & Claire Douat[b,*,**]

[a]Max Planck Institute for Plasma Physics, Boltzmannstr. 2, 85748 Garching, Germany; [b]GREMI UMR 7344 CNRS/Université d'Orléans, Orléans, 45067, France

*Address correspondence to: Emile Carbone, Max Planck Institute for Plasma Physics, Boltzmannstr. 2, 85748 Garching, Germany; Tel.: +49 89 3299 1476; Fax: +49 89 3299 2558, E-mail: emile.carbone@ipp.mpg.de; or Claire Douat, GREMI UMR 7344 CNRS/Université d'Orléans, Orléans, 45067, France; Tel.: +33 (0) 2 38 49 46 02; Fax: +33 (0) 2 38 41 71 54, E-mail: claire.douat@univ-orleans.fr

**Both authors contributed equally to this work.

ABSTRACT: Carbon monoxide is infamously known for its toxicity when administrated in high doses. In this article, we review some of the evidence for therapeutic effects of CO used in biology, when CO is delivered in small quantities. It is argued that plasmas in this context are an attractive *in situ* source for the process of alleviating the risks related to CO storage. Moreover, synergic effects of CO with other reactive species produced by plasma may be used in the future for applications such as bacterial infection, wound healing, and cancer treatment.

KEY WORDS: carbon monoxide, plasma medicine, plasma agriculture, plasma sources

I. INTRODUCTION

Non-equilibrium, low-temperature plasmas are weakly ionized gases that have been very successfully developed for use in different fields including microelectronics,[1] lighting,[2] combustion,[3] nanoscience,[4] and spacecraft propulsion.[5] In the early 21st century, researchers first reported that plasma could potentially be used for biomedical applications. Stoffels et al.[6] were likely the first to show the potential of cold near-room-temperature plasmas in medicine by demonstrating their capability to detach mammalian cells without causing necrotic cell destruction.[6] This study sparked investigations on the potential of plasmas for medical applications, which evolved into a new research field of its own, later termed Plasma Medicine. Related research is now performed for different fields, including cancer treatment, wound healing, blood coagulation, dentistry, cosmetology, sterilization, and decontamination, among others.[7–15] Many studies have been successful, and the first clinical trials were undertaken in the last few years.[16–19] Recently, such plasmas have also been studied in regard to their use in the field of agriculture as insecticides, for destruction of bacteria and fungi, and plant-growth enhancement.[15,20] The success of plasmas has come far as a result of their versatility and capacity to generate large amounts of reactive species at low gas temperature (< 40°C), combined with electric field, photons (infrared [IR], visible, and ultraviolet [UV] light), and charged species. These represent the plasma components schematized in Fig. 1. In the case of direct plasma treatment, the interaction between gas flows and liquids needs to be taken into account as well.

Plasmas (i.e., gas electrical discharges) used in medicine are typically generated using gas mixtures based on He, Ar, O_2, N_2, or simply air. The latter is either synthetic

1947-5764/18/$35.00

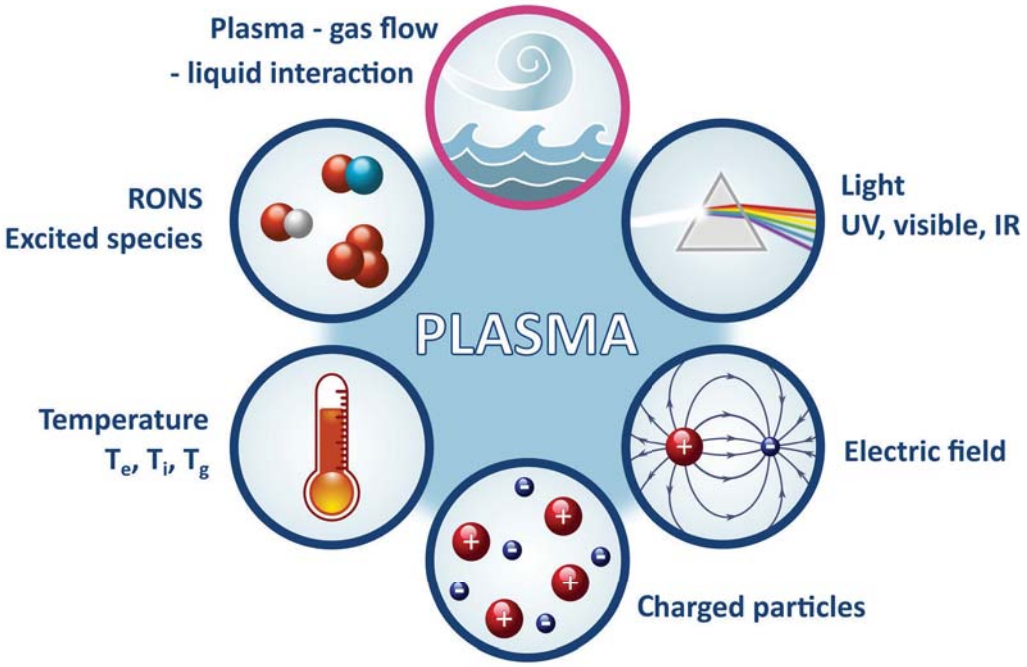

FIG. 1: Illustration of the plasma components and plasma interactions with a (biological) target. The plasma components can be separated into several categories: electric field, temperatures, electrons and ions, photons, and reactive species. Plasma-target interactions consist of gas flow–liquid interactions, dissolution of species in a liquid, and surface (and volume) reactivity. IR, Infrared; RONS, reactive oxygen and nitrogen species; UV, ultraviolet.

(~ 80% N_2 and 20% O_2) or already naturally present (N_2 78.08%, O_2 20.95%, Ar 0.934%, and CO_2 400 parts per million [ppm]) around the plasma and that can mix into the latter via convective processes. The plasma generates a lot of highly reactive neutral species, such as atomic O, N species, or He and Ar metastable states, and also rather stable neutral species such as nitric oxide (NO), NO_2, and O_3. Due to the presence of 400 ppm of CO_2 in natural air (as well as the presence of water vapor), the formation of other species such as CN, CO, OH, NH, and H_2O_2 can additionally occur.

Since Claude Bernard's discovery of carbon monoxide (CO) toxicity,[21] this molecule is mostly considered and known for its adverse effects on the human body and its reactivity with hemoglobin.[22] However, Marks et al.,[23] first suggested that CO may in fact have a physiological function as well and that, like NO, CO is an essential signaling molecule in humans.[24,25] Since then, a multitude of studies have confirmed these hypotheses, and CO has been found in many experiments to have positive effects for the treatment of several diseases.[26,27] At small doses, CO presents some beneficial effects, such as anti-inflammatory action, antiapoptotic effects, antiproliferative properties, and protective properties for tissues from hypoxia and reperfusion injury.[28]

Many studies, especially in the fields of CO_2 lasers or energy storage by CO_2 conversion, showed that CO can be easily produced with non-equilibrium plasmas.[29,30] The aims of this article are to (1) discuss the potential for using plasmas as a CO source for treating various afflictions, both in animals (humans included in that category) and plants; (2) point out that in some cases, CO molecules combined with plasmas will have some beneficial effects in medicine and agriculture, thanks to their possible synergetic effects with other species that are produced by the plasma, such as NO and reactive oxygen and nitrogen species; and (3) advocate for future studies on the development of new CO plasma sources relevant for therapeutic conditions. We also discuss some configurations that may be important for plasma medicine (i.e., direct delivery with other reactive species from the plasma, remote configurations to serve as a [pure] gaseous CO source, and plasma-activated liquids).

Because CO is highly toxic and even lethal at high doses, we start with a review of its toxicity and the mechanisms leading to its adverse effects on human physiology. We then discuss official regulations for the degrees of safe exposure to CO concentrations in the environment, based on medical investigations. In the section Benefits of CO in Medicine and Agriculture, we show that some of the evidence points to a beneficial role of CO in medicine as a signaling molecule, and we highlight some initial clinical trials. We also give a brief discussion of biochemical pathways of CO in cells and tissues, with reference to relevant works/reviews in the field. We conclude by discussing potential CO plasma sources for medicine and some of their benefits and differences compared to "traditional" CO sources.

II. TOXICITY OF THE CO MOLECULE

CO is a tasteless, odorless, and non-irritating gas that is toxic at high concentrations. It originates generally from incomplete combustion of hydrocarbons. Once in the lungs, CO binds to hemoglobin instead of O_2 and forms carboxyhemoglobin (COHb). Because the affinity of human hemoglobin for CO is 210 times greater than that for O_2 (affinity rates depend on the animal; e.g., it is only 50 times greater for mouse hemoglobin), the presence of oxygen in the blood decreases, leading to tissue hypoxia.[31,32] Due to their high metabolic rates, the brain and heart are the two first organs to show damage resulting from lack of oxygen.[31] CO is not only dangerous because of its high affinity to hemoglobin, but also because of its slow kinetics for release from hemoglobin.[31] The CO elimination half-time is ~ 150 min, whereas the recovery time (the point at which a patient feels "back to normal") can vary from hours to days.[33]

The first symptoms that a victim will experience after mild CO exposure (10%–20% COHb) are exhaustion and headache and then dizziness, nausea, and dyspnea. At moderate exposure (30%–40% COHb), signs include visual disturbances, confusion, syncope, and seizure. The victim will finally enter coma leading to death if the COHb rate rises to above 60%. Figure 2 lists CO poisoning symptoms as a function of COHb blood level. One can see that the effects of CO exposure depend very strongly on exposure time as well as CO concentration in the air. Quite interestingly, short CO exposure times to relatively high doses ($\leq$ 1000 ppm) lead to almost no adverse physiological effects because of the time necessary for CO exchange with O_2 in the lungs and fixation by hemoglobin.

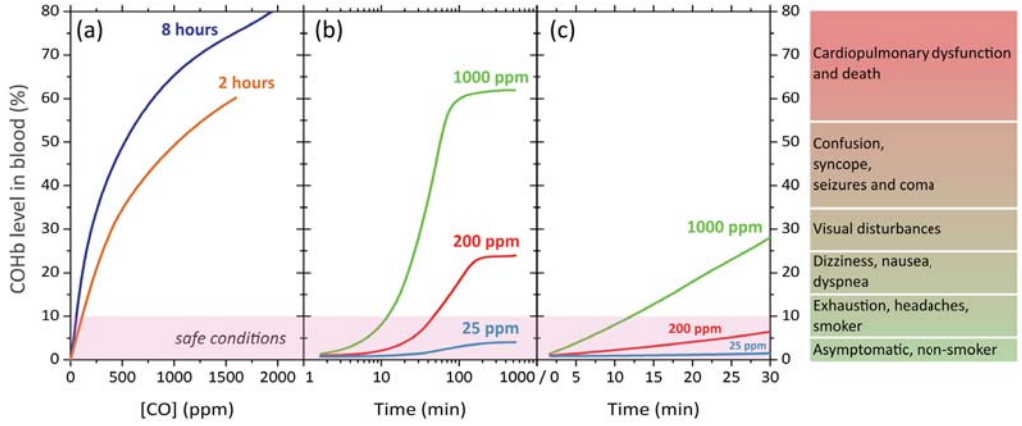

FIG. 2: CO safety. (a) COHb level in blood versus concentration of CO in air after 2 h exposure (orange line) and 8 h exposure (blue line); (b) COHb level in blood versus CO inhalation time for three different CO concentrations: 25 ppm (blue curve), 200 ppm (red curve), and 1000 ppm (green curve); (c) enlargement of (b) for short times. CO poisoning symptoms (right) are listed as a function of COHb percentage. COHb, carboxyhemoglobin; ppm, parts per million. (Adapted from Peterson and Steward, Bruce and Bruce, Omaye, Varon et al., and Raub et al.[34–39])

Exposure concentration limits in a work environment depend on the country and are listed in Table 1 for long exposure times (> 8 h). The limits are all in the safety range and do not lead to apparent symptoms, meaning that COHb in the blood is < 10%. Those CO limits can be crossed if exposure time is shorter, because the important parameter is not CO concentration, but rather, COHb blood level. One must note that heavy smokers may have as much as 10%–15% COHb in their blood.[40] The graph in Fig. 2(b) compares COHb blood level for different CO concentrations of 25, 200, and 1000 ppm and shows that 10% COHb is reached at 12 min for 1000 ppm, 50 min for 200 ppm, and never for 25 ppm, because the hemoglobin has time to liberate enough CO before the COHb level reaches 10%.

Mann has pointed out that the exposure limits given by authorities are probably overestimated.[24] Mayr et al. showed that inhalation of 500 ppm CO for 1 h did not have any significant effect on vital parameters, whereas the American Environmental Protec-

TABLE 1: CO exposure limits at work for different countries for long term exposure[41]

Country	CO (ppm)
France (Circulaire, 1985)	50
United States (ACGIH, 1991)	25
Germany (MAK)	30

Long term exposure: typically defined as a working day period of 8 hours.
MAK = Maximale Arbeitsplatz-Konzentration (in German, meaning "maximum concentration at the workplace")
ACGIH, Association Advancing Occupational and Environmental Health; ppm, parts per millions.

tion Agency gives 330 ppm as the maximum 60-min exposure and meanwhile greater exposures can possibly result in death.[42]

CO creation with plasma requires the use of CO_2 as the feed gas. As mentioned above, CO_2 is a tasteless, odorless, and irritating gas that at high concentrations (> 20%) can become lethal. Inhalation of CO_2 increases CO_2 partial pressure in blood and then induces a pH decrease due to acid–base disequilibrium, resulting in some damage to the kidneys, lungs, heart, and central nervous system. CO_2 poisoning symptoms as a function of percentage of CO_2 in air are listed in Fig. 3. The exposure limit at long term, that is, from 8 to 10 h, is fixed at 5000 ppm, whereas the short-term exposure limit depends on the country. Table 2 lists exposure limits as a function of country.

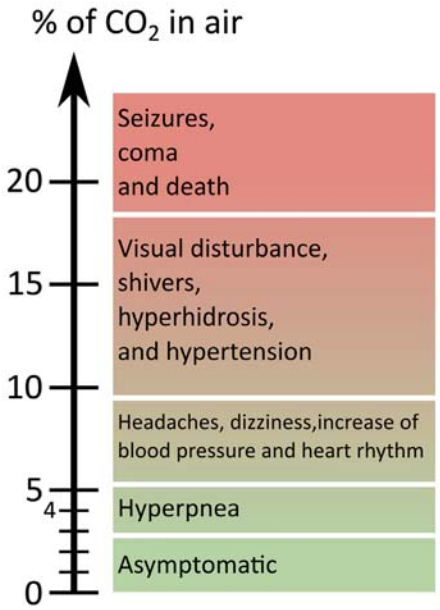

FIG. 3: CO_2 poisoning symptoms listed as a function of percentage of CO_2 in air, based on the Base de Données Fiches Toxicologiques[43]

TABLE 2: CO_2 exposure limits in the work environment for different countries[43,44]

Country	Work day exposure limit (ppm)	Short-term exposure limit (ppm/min)
United States (ACGIH, 1991)	5000	30,000/15
Germany (MAK)	5000	10,000/60
Sweden	5000	10,000/15
United Kingdom	5000	15,000/10

ACGIH, Association Advancing Occupational and Environmental Health; ppm, parts per millions.

III. BENEFITS OF CO IN MEDICINE AND AGRICULTURE

A. Roles of CO *In Vivo*

The major source of CO in mammals is the oxidation of heme (which is the name for the complexed ferrous ion Fe^{2+} with porphyrin) by the heme oxygenase (HO) enzyme. HO catalyzes the oxidation of heme to CO, Fe^{2+}, and biliverdin (bile pigment), accounting for ~ 86% of the CO produced in humans. The remaining 14% comes from a mixture of sources, including photo-oxidation, lipid peroxidation, xenobiotics, and bacteria.[25]

CO preferentially binds with heme- or transition metal–containing proteins.[45] In addition to its well-known interactions with hemoglobin, targets of CO can include cytochrome oxidase, nicotinamide adenine dinucleotide phosphate oxidase, NO synthase, and mitochondrial complexes.[25] CO is known to activate guanylyl cyclase but is about 80 times less effective than NO and leads to the formation of guanosine 3,5-monophosphate (cGMP), a secondary messenger that affects, for instance, ionic transport[46] and is involved in vasodilation. CO appears to modulate the activation state of mitogen-activated protein kinases, which are critical for cellular signal transduction in response to stress and inflammation.[47] CO also seems to be involved in down-regulation of extracellular signal-regulated kinases 1 and 2 and in c-Jun amino-terminal kinase pathways. It is important to note, however, that although the crystal structures of these proteins are still unknown, but they would not contain any metallic ion center. Considering the lack of reactivity of CO with amino acids, the mechanisms of interaction of CO with those proteins at the molecular level thus remain unclear if the absence of a metal complex is confirmed.[25]

Many potential functions of CO have been observed *in vivo*.[24] The following are a few illustrative and significant examples.

1. Anti-Inflammatory

CO inhibits the activation of monocytes, macrophages, and leukocytes *in vitro* and *in vivo* and suppresses the ability of T cells to proliferate.[45] Chronically inflamed tissue is characterized by the infiltration of mononuclear immune cells, including monocytes and macrophages, that continuously generate inflammatory mediators such as NO. CO has been shown to inhibit NO production in macrophages and reduce inflammation.[25]

2. Vasodilator

CO has been found to have important effects on vascular function. Released by vascular cells, CO regulates blood flow via inhibition of vasomotor tone (i.e., the tension in smooth muscle inside the walls of blood vessels, particularly in arteries) by way of molecular signaling with vascular smooth-muscle cells.[48]

3. Antiapoptotic

CO reduces apoptosis in renal tubular cells infected by bacterial toxins,[49] probably via inactivation of existing inducible NO synthase (iNOS) (overexpression of iNOS leads

to cytotoxic effects) via interaction with its heme iron moiety.[50] CO is also antiapoptotic for endothelial cells, hepatocytes, and cardiomyocytes and preventing in this way cell and tissue injury.[51–53]

4. Antiproliferative

CO has been shown to block cell proliferation of a number of cell types including cancer cells, T cells, and vascular smooth-muscle cells.[40]

5. Hypoxia

CO can reduce side effects of hypoxia (the deprivation of adequate oxygen supply at the tissue level). Clark showed that cardiac cells pretreated with a CO-releasing molecule (CO-RM) became more resistant to the damage caused by hypoxia reoxygenation and oxidative stress.[54]

6. Inhibitor of Human Platelet Aggregation

Platelet aggregation is inhibited in the presence of CO gas point.[55] Slow release of CO was found to be the most efficient and CO can thus be used as an anti-thrombotic drug.[56]

These specific actions at the level of tissues and organs allow the use of designing strategies for CO in treating various diseases or for circumventing side effects due to medical treatments. In the following section, a review of some of these applications shows the variety of actions that this simple gaseous molecule can have at tissue and organ levels.

B. Application of CO in Medicine

Several review articles have focused on potential applications of CO for various models of diseases. For a more extensive overview, we refer, for instance, to Mann,[24] Motterlini and Otterbein,[57] and Ling et al.[58] Various studies on the application of CO in animal models with positive results include the following cases.

1. Suppression of Organ Graft Rejection

CO as a gas (into saturated solutions) can be used as a protective adjuvant that may be added into preservation solutions before transplantation.[59] CO additionally protects against ischemia/reperfusion injury associated with transplantation.[60]

2. Cardiopulmonary Bypass Surgery

Inhaled CO provides pulmonary anti-inflammatory and anti-apoptotic effects and prevents acute lung injury and acute respiratory distress syndrome during cardiopulmonary bypass surgery.[61]

3. Pulmonary Hypertension

CO exposure can reverse established hypertension, resulting in near-normal pressures and heart weights. In addition, CO induces a remodulation of the vascular system.[62]

4. Bacterial Infection

Sepsis-induced death associated with *Enterococcus faecalis* was reversed by overexpression of HO-1; inflammatory response (i.e., the number of circulating inflammatory cells) was not reduced, but bacterial clearance was enhanced via an increase in phagocytosis and antimicrobial response.[63] A CO-RM was also observed to exert bactericidal activity on *Pseudomonas aeruginosa*.[64] Interestingly, Motterlini and Oetterbein noted that CO has no direct apparent effect on bacteria survival, but it would only enhance the killing of bacteria via macrophages.[57]

5. Wound Healing

The literature shows that HO-1 and CO exogenous application accelerated wound healing in mice due in part to their anti-inflammatory properties. In addition, an increase in vascularization was seen.[65,66]

6. Pancreatic Cancer

CO was found *in vitro* to have antiproliferative effects on human pancreatic cancer cells.[67]

The examples listed above are only a few selected cases wherein significant improvements after treatment with CO were observed. Other cases include cases of hemorrhagic shock, rheumatoid arthritis, acute liver failure, postoperative ileus, chronic colitis, and asthma.[57] Most studies showing benefits in the cases listed above were performed with either exogenous CO gas or CO-RMs in mouse or rat models and in pigs. Following successful preclinical tests, the next phase is testing humans *in vivo*, and several clinical trials are in fact now being performed, with some already in phase II or even phase III.[24,58] Bathoorn et al., for instance, observed anti-inflammatory effects of CO on patients with chronic obstructive pulmonary disease.[68] In conclusion, the results discussed here indicate that CO carries much potential as a therapeutic molecule, and its future in clinical treatments is already very promising. However, the role of its mode of delivery still needs further study.

C. Applications of CO in Agriculture

The toxicity of CO atmosphere on seed germination was studied in 1904 by Richards and MacDougal.[69] For 90% or more of CO atmosphere, these researchers observed a complete inhibition of seed growth or moderate germination followed by death.

With an atmosphere of ~ 70% of CO, germination of seeds occurred, but consequent growth and development were restricted. For pregerminated seeds, the authors found an overall inhibition of seed development. Still, in the case of wheat, they reported a comparable length of seedling compared to the control experiment in air, but with limited secondary root development. Below the circle of adventitious roots ordinarily developed in corn seedlings, a considerable number of supernumerary secondary roots arose without order.

Despite the earlier overall negative effects of CO on plants, its role at low doses and more particularly in saturated solutions has been more recently investigated. Several studies indicate that CO is involved in several physiological processes and is generated as a signaling molecule in response to abiotic and oxidative stresses. Abiotic stress includes excessive salinity, heavy metals, drought, and UV radiation (see He and He[70] and Jin et al.[71] and references therein).

Liu et al. showed that exogenous CO aqueous solution can alleviate salt-induced inhibition of rice seed germination.[72] Ling et al.[73] showed similarly that CO aqueous solution mitigates salt-induced inhibition of wheat root growth and suppresses programmed cell death by inhibiting superoxide anion overproduction. Siegel et al.[74] were the first to report that CO can promote seed germination. CO has been also found to induce an increase in lateral root formation in several types of seeds.[75–79] The direct role of CO was confirmed by Guo et al.,[80] who observed delayed root hair development for the tomato HO-1 mutant *yg-2*, which is defective in CO generation. Cao et al.[76] additionally showed that for rapeseed, CO is directly involved in the endogenous production of NO by adding specific scavengers for the CO molecule and an inhibitor of the NO synthase when measuring NO. They concluded that CO-induced lateral root development in rapeseed seedlings is NO dependent and that CO intervenes as a trigger for NO endogenous production.

Yannarelli et al.[81] showed an increase of HO-1 expression in soybean plants following exposure to UV-B radiation. They related HO-1 expression as a response to the formation of reactive oxygen species to protect the cell against oxidative damage. Xie et al.[82] studied the *Arabidopsis* HY1 mutant (deficient in HO-1) and found UV-C hypersensitivity and down-regulation of antioxidant defenses. Another example of the role of CO in plants is the observation that CO can alleviate cadmium-induced stress in *Medicago sativa* seedlings by activating gluthatione metabolism.[83] Similarly, the administration of a CO solution rescued mercury (Hg)-induced lipid peroxidation and root growth inhibition in alfalfa.[84]

Many more studies on the potential effects of CO have been reported in the literature, and we do not to list them all here (more detail may be found in Jin et al.,[71] for instance). The examples cited above give only a flavor of the surprisingly wide range of applications for which CO was tested with apparent positive results. However, the biochemical pathways of CO in plants appear to be (much) less understood than the process in animals; the same holds true for the NO molecule.[85] However, although only phenomenological and in an early stage, the current understanding of CO biochemistry in plants highlights CO as a molecule having similar roles as those in animals and with similar importance.[86]

IV. CO SOURCES

A. Current Production and Delivery Modes of CO in Medicine

Nowadays, the two main systems of delivering CO in medicine are through inhalation and CO-RMs. Inhalation of a small amount of CO has already proven its efficiency and has been used in clinical applications.[28,87] However, this technique is difficult because of the lack of control for CO local delivery and its toxicity at high concentrations, both of which depend on the patient.[88] Delivery is not local and thus affects the entire human body because of CO fixation on hemoglobin and transport in the blood. To overcome those issues, CO-RMs are being developed to target specific tissues and organs. This technique can liberate CO locally and avoid inducing elevation in CO absorption by hemoglobin. In principle, there would be no risk of CO poisoning with this technique. However, despite their promising features, CO-RMs are far from being used in clinical application and must be scrutinized. Indeed, the safety and toxicity of these molecules and their by-products are still not fully understood.[87–89]

Other existing techniques that are currently being developed and/or investigated include hemoglobin-based CO carriers, CO-saturated red blood cells, and liquid solution presaturated with CO injection.[89] However all such techniques suffer from the unknown adverse or synergic effects of the transport/delivery process, their by-products, and elevated CO absorption by hemoglobin. As mentioned by Foresti et al., clinicians do not yet know whether these techniques will ever be used as therapeutic strategic approaches.[87] Because of that, some authors in fact believe that the future still lies in CO gaseous administration. For such a purpose, only one device, called the Covox Delivery System (DS), has been approved for hospital use.[57] The Covox DS ensures that the delivery of CO, with a rate measured in milligrams per hour, is maintained on a breath-by-breath basis. Finally, in botany, we note that in addition to using compressed CO gas bottles (that are not easily transported in hospitals for obvious safety reasons), CO is usually produced via a chemical route. For instance, Cao et al.[76] prepared CO gas by heating formic acid (HCOOH) with concentrated sulfuric acid (H_2SO_4). The aqueous CO solution was obtained by bubbling the CO gas for at least 15 min to saturate the solution. The use of concentrated acids and highly irritating species such as formic acid will not likely be very welcomed into a hospital environment. This leads us to the conclusion that room still exists for new technologies for local gaseous CO production and delivery to specific organs/parts.

B. Plasmas as CO Sources

As mentioned previously, the two main drawbacks of current CO delivery methods are the increase in COHb level and/or the uncertainties on the toxicity of the molecules used.[24,89] The pharmacodynamics and pharmacokinetics of gaseous CO are well known, but for CO-RMs this is not the case.[45] To the best of our knowledge, one patented device has been approved for use in a hospital setting.[57] Thus, the development of new devices

would be helpful for delivery of CO alone or with other species relevant for medicinal therapy. In this section, we present some plasma devices as potential CO sources (based on atmospheric pressure plasma sources with a CO_2 admixture) that may offer alternative, flexible solutions (e.g., for external application on wounds, for instance). In addition, because of the intrinsic properties of plasmas, synergic effects can be expected in addition to the sole delivery of the CO molecule to the target (see the Conclusion, below).

1. Geometries and Delivery Modes

Plasmas have been studied for biological and medical application for almost two decades. This ionized gas has demonstrated its ability to generate a multitude of components (such as reactive species, electric field, light, and charged particles [see Fig. 1]) that can interact with living tissue. But as far as we know, plasmas have not yet specifically been used as a CO source for biomedical applications, although for several decades it has been well known that plasma can produce CO molecules. Many studies have been performed on plasma, especially for the fields of CO_2 lasers and energy storage.[29,30] Those studies reveal that, depending on the plasma source, the amount of CO can be controlled and tuned to a very broad range, from less than 1 ppm to several 10s of percent.

Figure 4 presents a schematic of some plasma discharge reactors that could be used as CO sources. They are classified into two categories: direct and indirect plasma sources.[90,91] A reactor is called a "direct plasma source," if the plasma components

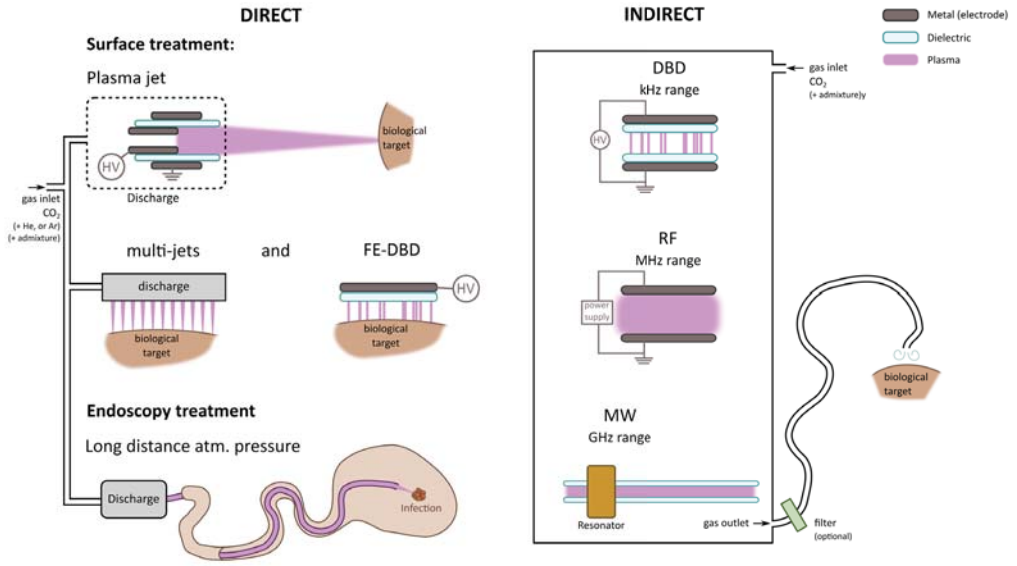

FIG. 4: Scheme of different potential plasma sources as CO sources. atm, atmospheric; DBD, dielectric barrier discharge; FE-DBD, floating electrode–dielectric barrier discharge; HV, high voltage; RF, radio frequency; MW, microwave.

(light, electric field, charged particles and reactive species [Fig. 1]) can interact with the biological target. A synergistic effect can occur with the combination of those components (discussed more in detail in the Conclusion, below). In contrast, if reactive species are the only plasma components able to interact with the target, the source is indirect. A third configuration is a hybrid source, wherein the plasma is not in direct contact with the target, but components other than reactive species, such as charged particles and light, can interact with the target. This configuration is not discussed here, but details may be found in the review of Isbary et al.[91]

Direct plasma source treatments can be classified into two types: at the surface or via endoscopy. Surface treatment allows treating external tissues or targeted organs after surgical protocol provides the access, whereas endoscopy treatment reaches some organs without (invasive) surgery. For instance, floating electrode–dielectric barrier discharge (FE-DBD) provides nonthermal plasma and is generated in air.[92] Naturally, 400 ppm of CO_2 is present in air and can potentially be converted into CO, and even if conversion is complete, the concentration of CO does not exceed 400 ppm. As the treatment time range is typically from seconds to several minutes, COHb levels will not exceed 10%, meaning that conditions are safe.

Plasma jets are devices that deliver a non-thermal plasma outside the confinement of electrodes. The plasma propagates in the surrounding air and can reach very long distances (up to 10 cm).[93,94] Contrary to FE-DBD, the feed gas is generally a noble gas such as helium or argon. Because the plasma propagates in air, it can convert a small part of the CO_2 present into CO. The amount of CO produced can be easily increased and controlled by adding a small percentage of CO_2 through the discharge. The plasma diameter is very small, from some hundreds of micrometers to a few millimeters, and allows tissues to be treated locally. The geometry of the plasma jet represented in Fig. 4 is a coaxial DBD,[93,95] but this is only one example among numerous existing configurations.[96]

If wider treatment surfaces are required, one can use a multi-jet. This device generates several plasma jets that form a pattern. The latter pattern can be modified according to the application to form, for instance, a line, matrix, or circle.[97–100] In addition, other plasma devices may be used, such as the atmospheric pressure plasma radio frequency (RF) torch in a "shower-head" configuration that can operate in argon with small admixtures of molecular gases in the < 1% range.[101,102]

To avoid surgery for a patient, an endoscopic method may be used. Some devices, generally based on the plasma jet configuration, can propagate the plasma in a capillary tube for several meters.[103,104] These devices are fed with noble gas and in the body can result in He or Ar gas accumulation and then to an arc formation (because of the low potential threshold for electrical breakdown). Winter et al. showed recently that CO_2 or air shielding avoids this effect.[104] Even if gas shielding is not required for plasma jets in an open environment, it is worth noting that gas shielding offers an additional tool for controlling plasma chemistry (in addition to adding gases directly through the plasma). In any case, CO_2 gas shielding locally increases the amount of CO, and its biological relevance should be studied in the future.

Unlike direct plasma sources, any kind of (non)equilibrium plasma can be used as an indirect source as long as the reactive species are the only plasma components that interact with the target. The gas temperature in the enclosures does not need to be at room temperature, because temperature will cool down during transport to the target via the gas flow. CO is produced by plasma in its conversion of the CO_2 gas initially injected through the reactor. CO, which reacts very slowly with other species in the atmosphere,[105] is essentially chemically inert in water due to the large activation energy needed for the water–gas shift reaction at room temperature.[106] Because CO is a stable molecule, it can be transported for long distances to a biological target. A direct correlation between fluxes from the plasma and doses delivered to the tissues can then, in principle, be made in a straightforward fashion, independently of the exact production mode.

Indirect sources can be classified based on the frequency of the applied voltage: DBD (single shots to several kilohertz), RF discharge (some megahertz), and microwave discharge (some gigahertz). The feed gas can be pure CO_2 or CO_2 with some admixture. Noble gases dilute the amount of CO produced, whereas molecular gases including oxygen and nitrogen allow for the production of other species, such as NO or O_3, that will additionally affect a biological target.[8,107] According to the reactor, gas mixture, and plasma parameters, the concentration of CO can be tuned from some parts per million to 10s of percents. For instance, a small DBD in pure CO_2 that generates only one or two filaments produces some hundreds ppm of CO,[108–110] and the conversion rate with a microwave plasma can rise to > 60%.[111,112]

As explained in a previous subsection, CO-saturated solutions are among the current methods used for CO delivery in medicine.[113,114] One drawback of this method, however, is the use of a CO tank, which can be dangerous in a medical environment if a leak should occur. Plasmas may be used as a local, inline CO source instead of being used with a CO tank. An indirect plasma source in pure CO_2 can provide a very large amount of CO (> 60%).[112] In the afterglow of the plasma, CO can be separated from the other species present in the gas phase using membranes or reactive absorption processes.[115–117] The gas is then bubbled into a liquid, or the plasma can be generated directly in contact with the solution, as shown in Fig. 5. Such a system would be safer than using compressed CO gas bottles or high-temperature processes.

The combination of CO-saturated solution with plasma-activated water (PAW) may be beneficial for medical or plant treatments as well. For instance, CO may reduce an inflammatory response, whereas PAW would disinfect the tissue thanks to its antibacterial properties.[118,119] PAW is produced by the interaction of a plasma source with a liquid. Its low pH and the presence of NO_2^- and H_2O_2 are usually invoked to explain its bactericidal effect.[118] Figure 5 presents an example of such a system, wherein a discharge is in contact with the water surface,[118] but it exists among other configurations.[120] Generally, water is treated by the plasma, but other types of liquid, such as phosphate-buffered saline (PBS) solution, can also be activated by the plasma.[119]

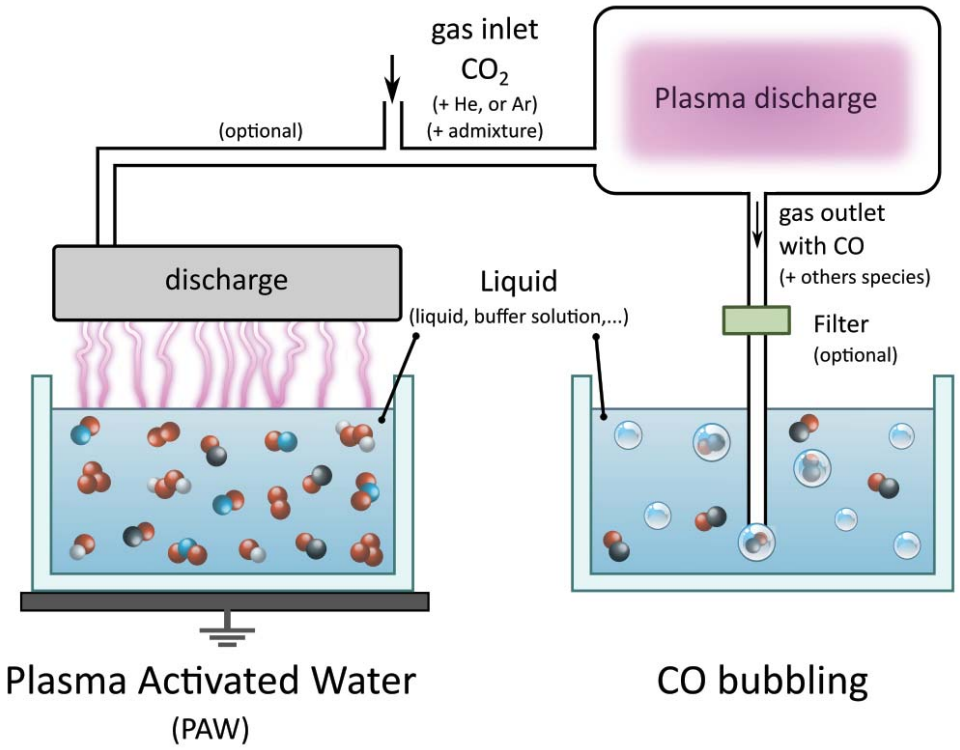

FIG. 5: Scheme of plasma-activated water and CO bubbling

We have briefly discussed several plasma reactors that can generate CO (and other species) in various configurations. This non-exhaustive list demonstrates their flexibility, and it is important to mention that almost all of these devices are already being investigated for specific applications in plasma medicine. It is hoped that using these plasmas with CO for *in vitro* or *in vivo* experiments will then require only minimal changes.

2. *Plasma Diagnostics*

Measuring CO can be challenging, especially when performing local non-invasive measurements on plasmas at atmospheric pressure. Such plasmas are generally non-homogenous and have a filamentary structure that render them difficult to diagnose *in situ*. Moreover, plasma dimensions can be very small, ranging from some hundreds of micrometers (the typical diameter of a filament) to centimeters, and they are influenced by the presence of any metal or dielectric surfaces that are within close range. However, the CO molecule has the advantage of stability at atmospheric pressure and room temperature and can therefore be easily measured *ex situ*. Listed in Table 3 are different types of diagnostics and their characteristics. Below, we discuss these techniques in some more detail.

TABLE 3: Characteristics of various diagnostic techniques for CO density measurements

Techniques	*In situ*	Absolute density	Sensitivity	Time resolution
FTIR	No	Yes	Medium	s to min
Laser absorption	Difficult	Yes	High	100 ns to ms
MS	No	Yes	Low	s to min
TALIF	Yes	Complicated	High	ns to min
GC	No	Yes	High	min
Solid sensors	No	Yes	High	s to min

FTIR, Fourier-transform infrared (spectroscopy); GC, gas chromatograph; MS, mass spectrometry; TALIF, two-photon absorption laser-induced fluorescence.

a. Residual Gas Analyzers

For plasma diagnostics, residual gas analyzers can be subdivided into mass spectrometers and gas chromatographs (GCs), based on their separation techniques. These devices usually operate on the principle that a small fraction of gas that is sampled from the volume is then sent to an analyzer. The chemical composition of reactive plasmas can be investigated by mass spectrometry using a capillary sampling orifice[121–123] or a differentially, double-pumped micro-orifice in a molecular beam configuration.[124] Both can determine densities of stable species, but the latter can sample additional radicals. In the case of CO, which has 28 atomic mass units of molecular mass, its detection is complicated by the fact that N_2, which is naturally present in air, has the same mass. The shape of the cross sections for electron impact ionization can in theory discriminate among different species having the same mass by measuring the ionic signal for several electron energies and then distinguishing the parent ion from dissociative ionization processes.[125] CO has an ionization potential of 14 eV, whereas N_2 has an appearance ionization potential of 15.6 eV.[126] In principle then, these two species can be differentiated. However, the targeted densities of CO to be measured (< 1000 ppm) for any practical application in plasma medicine makes its signal discrimination from noise highly difficult. Thus, this technique appears to be unsuitable.[127]

GCs are routinely used in medicine for measuring the quantity of CO in blood (see Sundin and Larsson,[128] for instance). In the gas phase, various GCs can detect CO with high sensitivity.[129] The downside of GCs is usually their very slow response time (several minutes). In the category of residual gas analyzers, we may also add solid-state gas sensors that also detect CO remotely. They have limited, but usually low, detection ranges and can give absolute densities following proper calibration procedures for given temperature ranges.[130] Their response time is slow as well.

b. Absorption Spectroscopy

IR light can interact with the CO molecule and therefore be measured by means of an absorption method that is based on the Beer–Lambert law.[131–133] Fourier-transform IR

(FTIR) absorption spectroscopy and laser absorption, both based on this law, use, respectively, a broadband light and a laser as light source. FTIR absorption yields broad absorption spectra with low sensitivity,[132] whereas laser absorption can measure a very small amount of CO (< 1 ppm) on a very narrow spectral range. A quantum cascade laser is generally used instead of its ancestor, the lead salt laser,[131] and a temporal resolution down to 100 ns is, in principle, feasible.

Usually, it is hardly possible to use these methods *in situ* to measure CO density due to the small dimensions and the nonhomogeneity of atmospheric pressure plasmas. For low CO concentrations, a multipass cell is needed to allow increases in absorption length and method sensitivity. The diagnostic can then be remote and deliver similar results to those of gas analyzers.

c. Two-Photon Absorption Laser-Induced Fluorescence

Two-photon absorption laser-induced fluorescence (TALIF) of the CO molecule in the $B^1\Sigma^+$ state was first demonstrated by Loge et al.[134] and has since been developed to detect CO.[135] In atmospheric pressure gases, sub-ppm detection levels were reported by Aldén et al.[136] Planar laser-induced fluorescence, first developed by Haumann et al., allows two-dimensional CO density distribution mapping.[137] At high pressure, collisional quenching (mainly by CO_2 and O_2, but also by CO itself) limits the detection of CO when using nanosecond pulsed lasers,[138] and picosecond lasers are necessary at atmospheric pressure.[139] Femtosecond lasers have been recently developed in the field of TALIF diagnostics, allowing faster measurements and alleviating laser disturbance including photolytic effects.[140] The determination of the effective collisional quenching rate (which depends on the species present in the gas phase and on the gas temperature) makes this technique relatively difficult to use for quantitative measurements *in situ* in the plasma phase. However, both spatial and temporal resolution are excellent.

In summary, several diagnostic methods are available to measure CO concentration at various ranges, allowing control of the amount of CO produced by the plasma. Table 3 summarizes and sorts these methods as a function of their advantages and disadvantages. Local absolute-density measurements in the plasma (i.e., mapping) is complicated to achieve, due to the filamentary structure. But because the dimension of the plasma is much smaller than the dimensions of the biological target, local absolute density in plasma may not be an important criterion but nevertheless can still be obtained using TALIF. The parameter of primary biological relevance is the total amount of CO produced by the plasma. Depending on conditions, the amount can be measured with the techniques listed previously. It is important to note that those measurements are hardly feasible during treatment of an animal, because the techniques are very sensitive and must be performed in motionless conditions. However, the plasma can be calibrated ahead of time by measuring CO concentration in conditions with a similar setup, during

which every component is stabilized. On a final note, it is worth noting that despite the fact that CO is a species that is naturally present in air, no easy, straightforward method for its detection is available, and dedicated measurements are required. Considering that plasma jets or discharges in air affect the CO/CO_2 ratio at the tissue level, it will be interesting to characterize the existing sources and correlate their biological impact with other reactive species such as H_2O_2 or NO.

V. POTENTIAL SYNERGIC EFFECTS OF CO AND PLASMAS: DISCUSSION

Usual CO-based treatments now occur via inhalation of gaseous[†] CO that is then fixed in large quantities as COHb. Quite interestingly, it has been reported that CO can mediate HO-1 induction in hepatoma cells.[45,141] Local delivery of controlled CO amounts (see Section IV.A. Plasmas as CO Sources) has the potential to activate locally the CO signaling pathways and avoid using large amounts of CO that will impact the whole organism.

Reviewing some of the clinical investigations of the CO molecule as a therapeutic species reveals its high potential. Because plasmas have proven effects in treating some afflictions, it is very likely that beneficial effects of adding CO_2 to the plasma discharge (and so producing CO) will also be observed. However, considering the large number of species that a plasma produces, we must caution that any new positive results due to the addition of CO_2 (and consequently the production of CO) shall not be by default associated with a therapeutic effect of CO. Adding an extra molecule to the discharge can lead to strong modulation of all reactive species present in the plasma and its afterglow.

HO-1 is also often referred as heat shock protein (i.e., a protein that is produced in response to a thermal stress of the tissue).[142] Because cold atmospheric pressure plasmas can sometimes be a moderate source of heat, it can be expected that heat and exogenous CO (both delivered by the plasma) may induce cumulative effects in cellular response. Plasmas would then offer the possibility of limiting the effects of excessive exposure to gaseous CO and accelerating CO induction of transcription processes at lower exogenous doses of CO.[‡]

The potential benefits of plasmas have been recently studied in cases of seed germination and growth in plants.[20] Some positive results have been observed, but UV radiation (from the plasma) may also eliminate some/most of the beneficial effects.[82] The observation that in most cases exposure to CO can mimic the protective effects of HO-1[47,143] suggests that HO-1 acts in a protective manner via the generation of CO. In that respect, the observation that the up-regulation of HO-1 procures protection against UV radiation indicates that CO could have a direct protective role.[81]

[†]A promising field is also the administration of CO-RMs, but molecular carriers continue to be tested for potential pathological effects. The amounts of CO delivered to target tissues are complex to predict because of the relatively limited knowledge about equilibrium dissociation constants of the complexes *in vivo*.

[‡]However, there appears to be conflicting evidence and/or interpretation about the direct induction of HO-1 protein transcription by heat shock.[144,145]

NO has been very much discussed in the field of plasma medicine for its role in various processes such as wound healing and cancer therapy.[146] Similarly to CO, NO increases activation of guanylyl cyclase (one of the main receptors for NO itself, as a signaling molecule)[147] to produce cGMP, acts as a neurotransmitter in the brain, decreases vascular tone, and inhibits platelet aggregation.[148] However, it is not expected that CO and NO are redundant messenger molecules. Durante and Schafer[48] point out that important differences in the specific inducers and regulators of the enzymes lead to their production, and they have different reactivity with biomolecules such as hemoproteins. The lack of CO reactivity when compared to NO has in fact been proposed to be an advantage in stress conditions, where NO bioavailability is compromised, but CO can still exert its signaling properties.[25] NO has also been determined to be a regulator of HO-1 gene expression in vascular smooth-muscle cells.[149] However, CO can also act as a regulator of the effects of NO at the cellular level. For instance, Kostoglou-Athanassiou et al. reported that endotoxin stimulates both NO and CO generation, but the two gases have counter-regulatory effects on the activation of endocrine glands.[150] In some conditions, CO can also bind and activate NO synthase to stimulate NO production.[151] Ingi et al. showed that cerebellar granules produce significant amounts of CO in culture. In this system, NO acts as the major regulator of cGMP production, whereas endogenous CO apparently down-regulates the response to NO.[152]

More generally, chronically inflamed tissue is characterized by the infiltration of immune cells including macrophages that continuously generate inflammatory mediators such as NO. CO has been shown to inhibit NO production in macrophages and reduce inflammation.[25] NO exerts multiple modulating effects on inflammation and has a key role in the regulation of immune responses. However, large amounts of NO, usually produced endogenously by iNOS, can be toxic and proinflammatory.[153] Thom et al.[154] reported that CO stimulates the release of NO and the production of the strong oxidant peroxynitrite (e.g., in blood platelets and vascular cells). Piantadosi remarked that NO is the most reactive physiological gas and it may be converted to the toxic NO_2 molecule at high concentrations.[22] Additionally, both NO and CO interact with the Fe^{2+} of hemoglobin, with an association rate constant in favor of NO compared to CO. However, the dissociation rate of CO bound to hemoglobin is much slower. Piantadosi concluded that CO will likely influence the bioactivity of newly synthesized NO in response to physiological stimulation or pathological events.[22] Motterlini and Otterbein[57] argued that both molecules are closely related and necessary for the expression/production of one another. Actually, it was proposed that the activation of HO-1 may defend against NO-mediated toxicity by negatively modulating iNOS expression or activity. CO released in the process of heme catabolism can inactivate existing iNOS by interacting with its iron moiety.[49,155]

From the discussion throughout this article, it may appear that NO is usually a molecule (that is currently widely studied in plasma medicine) with often the same effects as those tentatively attributed to CO. However, one should note that during treatment, a limit of 80 ppm of exogenous gaseous NO is followed in clinical therapies.[156] Plasma

jets typically produce NO densities in the range of 1–100 ppm.[133,157–159] Graves[144] also notes also that creams used for wound healing usually use NO-releasing species, but discussions about their use cite the fact that they can cause skin irritation/inflammation. Due to its overall complete chemical inertness (which only forms complexes with transition metals, the latter being weak, nonchemical bounds in a reversible manner), CO clearly shows the potential to be a substitute (of exogenous NO) and/or complementary molecule in the plasma cocktail delivered to solutions, cells, and tissues. Adding CO to the mix is expected to offer extra cell protection and enhance positive cellular responses to the plasma.

High concentrations of CO increase intracellular hydrogen peroxide (H_2O_2) production[§] in the brain, accompanied by increases in hydroxyl radical ($^{\bullet}OH$) production. This consequently affects the redox balance of glutathione in mitochondria.[160] High doses of exogenous CO produced by plasmas may then trigger $^{\bullet}OH$ and H_2O_2 production inside cells in addition to delivering them at their surface. Adding CO to the cocktail of reactive molecules may then help achieve similar effects at the cellular level, maintain reduced oxidation levels of the membrane, and increase survival.

Finally, we note that plasmas with CO_2 admixture also produce significant amounts of other species including O atoms, O_3, and $^1O_2$ molecules that are also active in medicine. Adding CO_2 to the gas discharge is an additional way to tune the flux of those species to the target and provide an alternative to the O_2 admixture into the plasma jet (e.g., and provide less oxidizing conditions).

VI. CONCLUSIONS

From this review of the literature, it appears that the CO molecule has a surprisingly large range of therapeutic actions including anti-inflammatory, antihypoxia, and antiapoptotic effects; vasodilation; and inhibition of platelet aggregation. In plants, CO promotes cell germination and lateral root formation and is involved in protective mechanisms against UV radiation and abiotic stresses due to metals, salinity, or drought. Importantly, the ranges wherein therapeutic effects can be observed are below levels of either short- or long-term toxicity.

There may be a significant but yet unexplored opportunity for CO_2 plasma discharges that have been previously analyzed to come to a fundamental understanding of the dissociation process of the CO_2 molecule into CO to be reused in the field of plasma medicine. In this article, we reviewed several studies that show the beneficial effects of CO at low doses (both in medicine and agriculture), with some discussion on the molecular pathways involved with CO. In that respect, CO's interplay with the NO molecule appears to be critical. This may produce general implications on the use of NO generating plasma sources in medicine. Fundamental understanding of CO's effects on tissues may not directly increase from trial results using plasmas because of

[§]Note that NO also triggers H_2O_2 production.[144]

their high intrinsic complexity. However, it appears that sufficient evidence and a good understanding exist already in the literature about CO pharmacology. These previous studies will help clarify any new effect that may be observed using (well-characterized) plasmas with and without CO production. It is even tempting to consider that CO may already be responsible for some of the effects observed in plasma medicine because of the natural CO_2 presence in the atmosphere. It will be interesting to experimentally measure CO densities in the effluent of plasma jets to verify its presence. To the best of our knowledge, such measurements have not been reported in the literature yet for any plasma source used in biomedical applications. We provided a review of potential (plasma) diagnostic techniques that could be used for that purpose and included their respective advantages and disadvantages.

An overview of the recent literature on CO and NO molecules shows them to be strongly related both in their effects and their mutual regulation of endogenous expression. In that respect, the addition of exogenous CO may be particularly beneficial for counterbalancing the potential irritation/inflammatory effects of exogenous NO produced by the plasma. In the case of (chronic) wounds, CO-based plasmas may be of particular use in combining sterilization and anti-inflammatory effects.

Following this overview of the related literature, we make a compelling case for the importance of the CO molecule in the treatment of various afflictions and for process stimulation. Potential applications both in medicine agriculture were underlined. We believe that CO_2 plasmas should be tested for use in plasma medicine and agriculture in the future. The fact that the CO molecule has positive biological effects was discovered less than 20 years ago; thus, potential biomedical CO use is still in its infancy compared to other pharmacological active species. However, this relatively recent discovery does not diminish its potential, but instead opens a window of opportunity for plasmas with CO_2 admixture. The possibility of synergic effects of the CO molecule with other components of plasma such as charged and neutral species, UV radiation, or heat are very exciting.

REFERENCES

1. Economou DJ. Pulsed plasma etching for semiconductor manufacturing. J Phys D Appl Phys. 2014;47(30):303001.
2. Zissis G, Kitsinelis S. State of art on the science and technology of electrical light sources: From the past to the future. J Phys D Appl Phys. 2009;42(17):173001.
3. Starikovskaia SM. Plasma assisted ignition and combustion. J Phys D Appl Phys. 2006;39(16):R265–99.
4. Ostrikov K, Cvelbar U, Murphy AB. Plasma nanoscience: Setting directions, tackling grand challenges. J Phys D Appl Phys. 2011;44(17):174001.
5. Charles C. Plasmas for spacecraft propulsion. J Phys D Appl Phys. 2009;42(16):163001.
6. Stoffels E, Flikweert AJ, Stoffels WW, Kroesen GMW. Plasma needle: A non-destructive atmospheric plasma source for fine surface treatment of (bio)materials. Plasma Sources Sci Technol. 2002;11(4):383–8.
7. Yan D, Sherman JH, Keidar M. Cold atmospheric plasma, a novel promising anti-cancer treatment modality. Oncotarget. 2017;8(9):15977–95.

8. Graves DB. Reactive species from cold atmospheric plasma: Implications for cancer therapy. Plasma Process Polym. 2014;11(12):1120–7.
9. Heinlin J, Isbary G, Stolz W, Morfill G, Landthaler M, Shimizu T, Steffes B, Nosenko T, Zimmerman J, Karrer S. Plasma applications in medicine with a special focus on dermatology. J Eur Acad Dermatol Venereol. 2011;25:1–11.
10. Kong MG, Kroesen G, Morfill G, Nosenko T, Shimizu T, van Dijk J, Zimmermann JL. Plasma medicine: An introductory review. New J Phys. 2009;11(11):115012.
11. Laroussi M. Low-temperature plasmas for medicine? IEEE Trans Plasma Sci. 2009;37(6):714–25.
12. Morfill GE, Kong MG, Zimmermann JL. Focus on plasma medicine. New J Phys. 2009;11(11):115011.
13. Chunqi J, Chen M-T, Schaudinn C, Gorur A, Vernier PT, Costerton JW, Jaramilo DE, Sedghizadeh PP, Gunderson MA. Pulsed atmospheric-pressure cold plasma for endodontic disinfection. IEEE Trans Plasma Sci. 2009;37(7):1190–5.
14. Vandamme M, Robert E, Pesnel S, Barbosa E, Dozias S, Sobilo J, Lerondel S, Le Pape A, Pouvesle J-H. Antitumor effect of plasma treatment on U87 glioma xenografts: Preliminary results. Plasma Process Polym. 2010;7(3–4):264–73.
15. Tanaka H, Ishikawa K, Mizuno M, Toyokuni S, Kajiyama H, Kikkawa F, Metelmann H-R, Masaru H. State of the art in medical applications using non-thermal atmospheric pressure plasma. Rev Mod Plasma Phys. 2017;1(1):3.
16. 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;163(1):78–82.
17. Kolb JF, Mohamed A-H, Price RO, Swanson RJ, Bowman A, Chiavarini RL, Stacey MW. Cold atmospheric pressure air plasma jet for medical applications. Appl Phys Lett. 2008;92(24):241501.
18. Isbary G, Heinlin J, Shimizu T, Zimmermann JL, Morfill G, Schmidt H-U, Monetti R, Steffes B, Bunk W, Li Y, Klaempfl T, Karrer S, Landthaler M, Stolz W. Successful and safe use of 2 min cold atmospheric argon plasma in chronic wounds: Results of a randomized controlled trial. Br J Dermatol. 2012;167(2):404–10.
19. Metelmann H-R, Nedrelow DS, Seebauer C, Schuster M, von Woedtke T, Weltmann K-D, Kindler S, Metelmann PH, Finkelstein SE, Von Hoff DD, Podmelle F. Head and neck cancer treatment and physical plasma. Clin Plasma Med. 2015;3(1):17–23.
20. Ito M, Ohta T, Hori M. Plasma agriculture. J Korean Phys Soc. 2012;60(6):937–43.
21. Bernard C. Lecons sur les effets des substances toxiques et medicamenteuses. Paris: J-B. Baillire et Fils, Librairie de l'Académie Impériale de Médecine; 1857.
22. Piantadosi CA. Biological chemistry of carbon monoxide. Antioxid Redox Signal. 2002 Apr;4(2):259–70.
23. Marks GS, Brien JF, Nakatsu K, McLaughlin BE. Does carbon monoxide have a physiological function? Trends Pharmacol Sci. 1991;12:185–8.
24. Mann BE. Carbon monoxide: An essential signalling molecule. In: Jaouen G, Metzler-Nolte N, editors. Berlin, Heidelberg: Springer; 2010. p. 247–85.
25. Mann BE, Motterlini R. CO and NO in medicine. Chem Commun. 2007;41:4197.
26. Olas B. Carbon monoxide is not always a poison gas for human organism: Physiological and pharmacological features of CO. Chem Biol Interact. 2014;222:37–43.
27. Wu L, Wang R. Carbon monoxide: Endogenous production, physiological functions, and pharmacological applications. Pharmacol Rev. 2005;57(4):585–630.
28. Otterbein LE, Bach FH, Alam J, Soares MP, Lu H-T, Wysk MA, Davis RJ, Flavell RA, Chor AM. Carbon monoxide has anti-inflammatory effects involving the mitogen-activated protein kinase pathway. Nat Med. 2000;6(4):422–8.
29. Hokazono H, Fujimoto H. Theoretical analysis of the CO_2 molecule decomposition and contaminants yield in transversely excited atmospheric CO_2 laser discharge. J Appl Phys. 1987;62(5):1585–94.

30. Lebouvier A, Iwarere SA, D'Argenlieu P, Ramjugernath D, Fulcheri L. Assessment of carbon dioxide dissociation as a new route for syngas production: A comparative review and potential of plasma-based technologies. Energy Fuels. 2013;27(5):2712–22.
31. Prockop LD, Chichkova RI. Carbon monoxide intoxication: An updated review. J Neurol Sci. 2007;262(1–2):122–30.
32. Brittain T, Sutherland J, Greenwood C. A study of the kinetics of the reaction of ligands with the liganded states of mouse embryonic haemoglobins. Biochem J. 1986;234(1):151–5.
33. Burney RE, Wu S-C, Nemiroff MJ. Mass carbon monoxide poisoning: Clinical effects and results of treatment in 184 victims. Ann Emerg Med. 1982;11(8):394–9.
34. Peterson JE, Stewart RD. Absorption and elimination of carbon monoxide by inactive young men. Arch Environ Health. 1970;21(2):165–71.
35. Bruce EN, Bruce MC. A multicompartment model of carboxyhemoglobin and carboxymyoglobin responses to inhalation of carbon monoxide. J Appl Physiol. 2003;95(3):1235–47.
36. Omaye ST. Metabolic modulation of carbon monoxide toxicity. Toxicology. 2002;180(2):139–50.
37. Varon J, Marik PE, Fromm Jr. RE, Gueler A. Carbon monoxide poisoning: A review for clinicians. J Emerg Med. 1999;17(1):87–93.
38. Raub JA, Mathieu-Nolf M, Hampson NB, Thom SR. Carbon monoxide poisoning—A public health perspective. Toxicology. 2000;145(1):1–14.
39. Fiche technique monoxyde de carbone, Région de la Mauricie et du Centre-du-Québec Santé au travail. Available from: http://www.santeautravail.qc.ca/c/document_library/get_file?uuid=a0220f6a-b9f2-4686-86f7-31831af0a203&groupId=67467.
40. Ryter SW, Otterbein LE. Carbon monoxide in biology and medicine. BioEssays. 2004;26(3):270–80.
41. Base de données fiches toxicologiques: Monoxyde de carbone. INRS. 2016; p. 1–3. Available from: http://www.inrs.fr/publications/bdd/fichetox.html.
42. Mayr FB, Spiel A, Leitner J, Marsik C, Germann P, Ullrich R, Wagner O, Jilma B. Effects of carbon monoxide inhalation during experimental endotoxemia in humans. Am J Respir Crit Care Med. 2005;171(4):354–60.
43. Base de données fiches toxicologiques: Dioxyde de carbone. INRS. 2016; p. 1–8.
44. ethanolrfa.org [homepage on the Internet]. Washington DC: Renewable Fuels Association. Available from: http://www.ethanolrfa.org/producers/safety/carbon-dioxide-co2-safety-program/.
45. Rochette L, Cottin Y, Zeller M, Vergely C. Carbon monoxide: Mechanisms of action and potential clinical implications. Pharmacol Ther. 2013;137(2):133–52.
46. Nelson DL, Cox MM. Lehninger principles of biochemistry. 7th edition. New York: Macmillan Learning; 2017.
47. Kim HP, Ryter SW, Choi AMK. CO as a cellular signaling molecule. Annu Rev Pharmacol Toxicol. 2006;46(1):411–49.
48. Durante W, Schafer AI. Carbon monoxide and vascular cell function (review). Int J Mol Med. 1998;2(3):255-317.
49. Chen M, Tofighi R, Bao W, Aspevall O, Jahnukainen T, Gustafsson LE, Ceccatelli S, Celsi G. Carbon monoxide prevents apoptosis induced by uropathogenic Escherichia coli toxins. Ped Nephrol. 2006;1:382–9.
50. McMillan K, Bredt DS, Hirsch DJ, Snyder SH, Clark JE, Masters BS. Cloned, expressed rat cerebellar nitric oxide synthase contains stoichiometric amounts of heme, which binds carbon monoxide. Proc Natl Acad Sci USA. 1992;89(23):11141–5.
51. Sato K, Balla J, Otterbein L, Smith RN, Brouard S, Lin Y, Csizmadia E, Sevigny J, Robson SC, Vercellotti G, Choi AM, Bach FH, Soares MP. Carbon monoxide generated by heme oxygenase-1 suppresses the rejection of mouse-to-rat cardiac transplants. J Immunol. 2001;166(6):4185–94.
52. Kim KM, Pae H-O, Zheng M, Park R, Kim Y-M, Chung H-T. Carbon monoxide induces heme oxygenase-1 via activation of protein kinase R-like endoplasmic reticulum kinase and inhibits endothelial cell apoptosis triggered by endoplasmic reticulum stress. Circ Res. 2007;101(9):919–27.

53. Kim HS, Loughran PA, Rao J, Billiar TR, Zuckerbraun BS. Carbon monoxide activates NF-κB via ROS generation and Akt pathways to protect against cell death of hepatocytes. Gastrointest Liver Physiol. 2008;295(1):G146–52.
54. Clark JE. Cardioprotective actions by a water-soluble carbon monoxide-releasing molecule. Circ Res. 2003;93:e2–8.
55. Brüne B, Ullrich V. Inhibition of platelet aggregation by carbon monoxide is mediated by activation of guanylate cyclase. Mol Pharmacol. 1987;32(4):497–504.
56. Chlopicki S, Lomnicka M, Fedorowicz A, Grochal E, Kramkowski K, Mogielnicki A, Buczko W, Motterlini R. Inhibition of platelet aggregation by carbon monoxide-releasing molecules (CO-RMs): Comparison with NO donors. Naunyn Schmiedebergs Arch Pharmacol. 2012;385(6):641–50.
57. Motterlini R, Otterbein LE. The therapeutic potential of carbon monoxide. Nat Rev Drug Discov. 2010;9(9):728–43.
58. Ling K, Men F, Wang W-C, Zhou Y-Q, Zhang H-W, Ye D-W. Carbon monoxide and its controlled release: Therapeutic application, detection, and development of carbon monoxide releasing molecules (CORMs). J Med Chem. 2018;61(7):2611–35. DOI: 10.1021/acs.jmedchem.6b01153.
59. Nakao A, Choi AMK, Murase N. Protective effect of carbon monoxide in transplantation. J Cell Mol Med. 2006;10(3):650–71.
60. Amersi F, Shen X-D, Anselmo D, Melinek J, Iyer S, Southard DJ, Katori M, Volk H-D, Busuttil RW, Buelow R, Kupiec-Weglinski JW. Ex vivo exposure to carbon monoxide prevents hepatic ischemia/reperfusion injury through p38 MAP kinase pathway. Hepatology. 2002;35(4):815–23.
61. Goebel U, Siepe M, Mecklenburg A, Stein P, Roesslein M, Schwer CI, Schmidt R, Doenst T, Geiger KK, Pahl HL, Schlensak C, Loop T. Carbon monoxide inhalation reduces pulmonary inflammatory response during cardiopulmonary bypass in pigs. Anesthesiology. 2008;108(6):1025–36.
62. Zuckerbraun BS, Chin BY, Wegiel B, Billiar TR, Czsimadia E, Rao J, Shimoda L, Ifedigbo E, Kanno S, Otternein LE. Carbon monoxide reverses established pulmonary hypertension. J Exp Med. 2006;203(9):2109–19.
63. Chung SW, Liu X, Macias AA, Baron RM, Perrella MA. Heme oxygenase-1–derived carbon monoxide enhances the host defense response to microbial sepsis in mice. J Clin Invest. 2008;118(1):239–47.
64. Desmard M, Davidge KS, Bouvet O, Morin D, Roux D, Foresti R, Ricard JD, Denamur E, Poole RK, Montravers P, Motterlini R, Boczkowski J. A carbon monoxide-releasing molecule (CORM-3) exerts bactericidal activity against Pseudomonas aeruginosa and improves survival in an animal model of bacteraemia. FASEB J. 2009;23(4):1023–31.
65. Grochot-Przeczek A, Lach R, Mis J, Skrzypek K, Gozdecka M, Sroczynska P, Dubiel M, Rutkowski A, Kozakowska M, Zagorska A, Walczynski J, Was H, Kotlinowski J, Drukala J, Kurowski K, Kieda C, Herault Y, Dulak J, Jozkowicz A. Heme oxygenase-1 accelerates cutaneous wound healing in mice. PLoS ONE. 2009;4(6):e5803.
66. Ahanger AA, Prawez S, Kumar D, Prasad R, Amarpal, Tandan SK, Kumar D. Wound healing activity of carbon monoxide liberated from CO-releasing molecule (CO-RM). Naunyn Schmiedebergs Arch Pharmacol. 2011;384(1):93–102.
67. Vítek L, Gbelcová H, Muchová L, Váňová K, Zelenka J, Koníčková R, Suk J, Zadinova M, Knejzlík Z, Ahmad S, Fujisawa T, Ahmed A, Ruml T. Antiproliferative effects of carbon monoxide on pancreatic cancer. Digest Liver Dis. 2014;46(4):369–75.
68. Bathoorn E, Slebos D-J, Postma DS, Koeter GH, van Oosterhout AJM, van der Toorn M, Boesen HM, Kerstjens HA. Anti-inflammatory effects of inhaled carbon monoxide in patients with COPD: A pilot study. Eur Respir J. 2007;30(6):1131–7.
69. Richards HM, MacDougal DT. The influence of carbon monoxide and other gases upon plants. Bulletin Torrey Botany Club. 1904;31(2):57.
70. He H, He L. The role of carbon monoxide signaling in the responses of plants to abiotic stresses. Nitric Oxide. 2014;42:40–3.

71. Jin Q, Cui W, Xie Y, Shen W. Carbon monoxide: A ubiquitous gaseous signaling molecule in plants. In: Gasotransmitters in Plants, eds: L. Lamattina, C. García-Mata; Springer; 2016.
72. Liu K, Xu S, Xuan W, Ling T, Cao Z, Huang B, Sun Y, Liu Z, Zhao N, Shen W. Carbon monoxide counteracts the inhibition of seed germination and alleviates oxidative damage caused by salt stress in Oryza sativa. Plant Sci. 2007;172(3):544–55.
73. Ling T, Zhang B, Cui W, Wu M, Lin J, Zhou W, Huang J, Shen W. Carbon monoxide mitigates salt-induced inhibition of root growth and suppresses programmed cell death in wheat primary roots by inhibiting superoxide anion overproduction. Plant Sci. 2009;177(4):331–40.
74. Siegel SM, Renwick G, Rosen LA. Formation of carbon monoxide during seed germination and seedling growth. Science. 1962;137(3531):683–4.
75. Xu J, Xuan W, Huang B, Zhou Y, Ling T, Xu S, Shen W. Carbon monoxide-induced adventitious rooting of hypocotyl cuttings from mung bean seedling. Chinese Sci Bull. 2006;51(6):668–74.
76. Cao Z-Y, Xuan W, Liu Z-Y, Li X-N, Zhao N, Xu P, Wang Z, Guan R-Z, Shen W-B. Carbon monoxide promotes lateral root formation in rapeseed. J Integr Plant Biol. 2007;49(7):1070–9.
77. Xuan W, Zhu F-Y, Xu S, Huang B-K, Ling T-F, Qi J-Y, Ye MB, Shen WB. The heme oxygenase/carbon monoxide system is involved in the auxin-induced cucumber adventitious rooting process. Plant Physiol. 2008;148(2):881–93.
78. Guo K, Xia K, Yang Z-M. Regulation of tomato lateral root development by carbon monoxide and involvement in auxin and nitric oxide. J Exp Bot. 2008;59(12):3443–52.
79. Chen Y-H, Chao Y-Y, Hsu YY, Kao CH. Heme oxygenase is involved in H_2O_2-induced lateral root formation in apocynin-treated rice. Plant Cell Rep. 2013;32(2):219–26.
80. Guo K, Kong WW, Yang ZM. Carbon monoxide promotes root hair development in tomato. Plant Cell Environ. 2009;32(8):1033–45.
81. Yannarelli GG, Noriega GO, Batlle A, Tomaro ML. Heme oxygenase up-regulation in ultraviolet-B irradiated soybean plants involves reactive oxygen species. Planta. 2006;224(5):1154–62.
82. Xie Y, Xu D, Cui W, Shen W. Mutation of Arabidopsis HY1 causes UV-C hypersensitivity by impairing carotenoid and flavonoid biosynthesis and the down-regulation of antioxidant defence. J Exp Bot. 2012;63(10):3869–83.
83. Han Y, Zhang J, Chen X, Gao Z, Xuan W, Xu S, Ding X, Shen W. Carbon monoxide alleviates cadmium-induced oxidative damage by modulating glutathione metabolism in the roots of Medicago sativa. New Phytol. 2008;177:155–66.
84. Han Y, Xuan W, Yu T, Fang W-B, Lou T-L, Gao Y, Chen X-Y, Xiao X, Shen W-S. Exogenous hematin alleviates mercury-induced oxidative damage in the roots of Medicago sativa. J Integr Plant Biol. 2007;49(12):1703–13.
85. Domingos P, Prado AM, Wong A, Gehring C, Feijo JA. Nitric oxide: A multitasked signaling gas in plants. Mol Plant. 2015;8(4):506–20.
86. Wang M, Liao W. Carbon monoxide as a signaling molecule in plants. Front Plant Sci. 2016;7:572.
87. Foresti R, Bani-Hani MG, Motterlini R. Use of carbon monoxide as a therapeutic agent: Promises and challenges. Intensive Care Med. 2008;34(4):649–58.
88. García-Gallego S, Bernardes GJL. Carbon-monoxide-releasing molecules for the delivery of therapeutic CO in vivo. Angew Chemie Int Ed. 2014;53(37):9712–21.
89. Hu H-J, Sun Q, Ye Z-H, Sun X-J. Characteristics of exogenous carbon monoxide deliveries. Med Gas Res. 2016;6(2):96.
90. Kong MG, Kroesen G, Morfill G, Nosenko T, Shimizu T, van Dijk J, Zimmermann JL. Plasma medicine: An introductory review. New J Phys. 2009;11(11):115012.
91. Isbary G, Shimizu T, Li Y-F, Stolz W, Thomas HM, Morfill GE, Zimmermann JL. Cold atmospheric plasma devices for medical issues. Expert Rev Med Devices. 2013;10(3):367.
92. Fridman G, Peddinghaus M, Balasubramanian M, Ayan H, Fridman A, Gutsol A, Brooks A. Blood coagulation and living tissue sterilization by floating-electrode dielectric barrier discharge in air. Plasma Chem Plasma Process. 2006;26(4):425–42.

93. Robert E, Sarron V, Riès D, Dozias S, Vandamme M, Pouvesle J-M. Characterization of pulsed atmospheric-pressure plasma streams (PAPS) generated by a plasma gun. Plasma Sources Sci Technol. 2012;21:34017.
94. Mericam-Bourdet N, Laroussi M, Begum A, Karakas E. Experimental investigations of plasma bullets. J Phys D Appl Phys. 2009;42(5):55207.
95. Douat C, Kacem I, Sadeghi N, Bauville G, Fleury M, Puech V. Space-time resolved density of helium metastable atoms in a nanosecond pulsed plasma jet: Influence of high voltage and pulse frequency. J Phys D Appl Phys. 2016;49(28):285204.
96. Lu X, Laroussi M, Puech V. On atmospheric-pressure non-equilibrium plasma jets and plasma bullets. Plasma Sources Sci Technol. 2012;21(3):34005.
97. Robert E, Darny T, Dozias S, Iseni S, Pouvesle JM. New insights on the propagation of pulsed atmospheric plasma streams: From single jet to multi jet arrays. Phys Plasmas. 2015;22(12):122007.
98. Cao Z, Nie Q, Bayliss DL, Walsh JL, Ren CS, Wang DZ, Kong MG. Spatially extended atmospheric plasma arrays. Plasma Sources Sci Technol. 2010;19(2):25003.
99. Weltmann K-D, Brandenburg R, von Woedtke T, Ehlbeck J, Foest R, Stieber M, Kindel E. Antimicrobial treatment of heat sensitive products by miniaturized atmospheric pressure plasma jets (APPJs). J Phys D Appl Phys. 2008;41(19):194008.
100. Nie Q, Cao Z, Ren CS, Wang DZ, Kong MG. A two-dimensional cold atmospheric plasma jet array for uniform treatment of large-area surfaces for plasma medicine. New J Phys. 2009;11(11):115015.
101. Carbone EAD, Boucher N, Sferrazza M, Reniers F. How to increase the hydrophobicity of PTFE surfaces using an R.F. atmospheric-pressure plasma torch. Surf Interface Anal. 2010;42(6–7):1014–8.
102. Atanasova M, Carbone EAD, Mihailova D, Benova E, Degrez G, van der Mullen JJAM. Modelling of an RF plasma shower. J Phys D Appl Phys. 2012;45(14):145202.
103. Robert E, Vandamme M, Brullé L, Lerondel S, Le Pape A, Sarron V, Riés D, Darny T, Dozias S, Collet G, Kieda C, Pouvesle JM. Perspectives of endoscopic plasma applications. Clin Plasma Med. 2013;1(2):8–16.
104. Winter J, Glitsch S, Lühder H, Bansemer R, Wende K. On the application of atmospheric pressure plasma jets in endoscopy. Conference proceedings of the 23rd International Symposium on Plasma Chemistry, ISPC-23, 2017, pp 852–54.
105. Jaffe LS. Ambient carbon monoxide and its fate in the atmosphere. J Air Pollut Control Assoc. 1968;18(8):534–40.
106. Bustamante F, Enick RM, Cugini AV, Killmeyer RP, Howard BH, Rothenberger KS, Ciocco MV, Morreale BD, Chattopadhyay S, Shi S. High-temperature kinetics of the homogeneous reverse water-gas shift reaction. Am Inst Chem Eng. 2004;50(5):1028–41.
107. Graves DB. The emerging role of reactive oxygen and nitrogen species in redox biology and some implications for plasma applications to medicine and biology. J Phys D Appl Phys. 2012;45(26):263001.
108. Douat C, Guaitella O, Ponduri S, Boumans T, Welzel S, Engeln R. Effects of the addition of oxygen and nitrogen on the dissociation of CO_2 in a dielectric barrier discharge. Conference proceedings of the 22nd International Symposium on Plasma Chemistry, ISPC-22, 2015, IN-01, pp 1–3.
109. Ponduri S, Becker MM, Welzel S, Sanden MCM Van De, Loffhagen D, Engeln R. Fluid modelling of CO_2 dissociation in a dielectric barrier discharge. J Appl Phys. 2016;119:093301.
110. Ramakers M, Michielsen I, Aerts R, Meynen V, Bogaerts A. Effect of argon or helium on the CO_2 conversion in a dielectric barrier discharge. Plasma Process Polym. 2015;12(8):755–63.
111. Fridman A. Plasma chemistry. New York: Cambridge University Press; 2008.
112. Bongers W, Bouwmeester H, Wolf B, Peeters F, Welzel S, van den Bekerom D, den Harder N, Goede A, Graswinckel M, Groen PW, Kopecki J, Leins M, van Rooij G, Schulz A, Walker M, van de Sanden R. Plasma-driven dissociation of CO_2 for fuel synthesis. Plasma Process Polym. 2017;14(6):1600126.
113. Hangai-Hoger N, Tsai AG, Cabrales P, Suematsu M, Intaglietta M. Microvascular and systemic effects following top load administration of saturated carbon monoxide-saline solution. Crit Care Med. 2007;35(4):1123–32.

114. Nakao A, Schmidt J, Harada T, Tsung A, Stoffels B, Cruz RJ, Kohmoto J, Peng X, Tomiyama K, Murase N, Bauer AJ, Fink MP. A single intraperitoneal dose of carbon monoxide-saturated ringer's lactate solution ameliorates postoperative ileus in mice. J Pharmacol Exp Ther. 2006;319(3):1265–75.
115. Dutta NN, Patil GS. Developments in CO separation. Gas Sep Purif. 1995;9(4):277–83.
116. David OC, Zarca G, Gorri D, Urtiaga A, Ortiz I. On the improved absorption of carbon monoxide in the ionic liquid 1-hexyl-3-methylimidazolium chlorocuprate. Sep Purif Technol. 2012;97:65–72.
117. Reed DA, Xiao DJ, Gonzalez MI, Darago LE, Herm ZR, Grandjean F, Long JR. Reversible CO scavenging via adsorbate-dependent spin state transitions in an iron(II)–triazolate metal–organic framework. J Am Chem Soc. 2016;138(17):5594–602.
118. Lukes P, Dolezalova E, Sisrova I, Clupek M. Aqueous-phase chemistry and bactericidal effects from an air discharge plasma in contact with water: Evidence for the formation of peroxynitrite through a pseudo-second-order post-discharge reaction of H_2O_2 and HNO_2. Plasma Sources Sci Technol. 2014;23(1):15019.
119. Traylor MJ, Pavlovich MJ, Karim S, Hait P, Sakiyama Y, Clark DS, Graves DB. Long-term antibacterial efficacy of air plasma-activated water. J Phys D Appl Phys. 2011;44(47):472001.
120. Bruggeman PJ, Kushner MJ, Locke BR, Gardeniers JGE, Graham WG, Graves DB, Hofman-Caris RCHM, Mario D, Reid JP, Ceriani E, Fernandez Rivas D, Foster JE, Garrick SC, Gorbanev Y, Hamaguchi S, Iza F, Jablonowski H, Klimova E, Kolb J, Kroma F, Lukes P, Machala Z, Marinov I, Mariotti D, Mededovic Thagard S, Minakata D, Neyts EC, Pawlat J, Petrovic ZLJ, Pflieger R, Reuter S, Schram DC, Schroter S, Shiraiwa M, Tarabova B, Tsai PA, Verlet JRR, von Woedtke T, Wilson KR, Yasui K, Zvereva G. Plasma–liquid interactions: A review and roadmap. Plasma Sources Sci Technol. 2016;25(5):53002.
121. Halsted RE, Nier AO. Gas flow through the mass spectrometer viscous leak. Rev Sci Instrum. 1950;21(12):1019–21.
122. Grob K, Jaeggi H. Direct coupling of capillary columns to a mass spectrometer. Technique allowing rapid column interchange. Anal Chem. 1973;45(9):1788–90.
123. Hatch FW, Parrish ME. Vacuum gas chromatography using short glass capillary columns combined with mass spectrometry. Anal Chem. 1978;50(8):1164–8.
124. Große-Kreul S, Hübner S, Schneider S, Ellerweg D, von Keudell A, Matejčík S, Benedikt J. Mass spectrometry of atmospheric pressure plasmas. Plasma Sources Sci Technol. 2015;24(4):44008.
125. Singh H, Coburn JW, Graves DB. Appearance potential mass spectrometry: Discrimination of dissociative ionization products. J Vac Sci Technol A. 2000;18(2):299–305.
126. Kambara H, Ogawa Y, Mitsui Y, Kanomata I. Carbon monoxide detection in nitrogen gas by atmospheric pressure ionization mass spectrometry. Anal Chem. 1980;52(9):1500–3.
127. Singh H, Coburn JW, Graves DB. Mass spectrometric detection of reactive neutral species: Beam-to-background ratio. J Vac Sci Technol A. 1999;17(5):2447–55.
128. Sundin A-M, Larsson JE. Rapid and sensitive method for the analysis of carbon monoxide in blood using gas chromatography with flame ionisation detection. J Chromatogr B. 2002;766(1):115–21.
129. Berezkin V, Drugov Y. Gas chromatography in air pollution analysis. Amsterdam: Elsevier; 1991.
130. Azad AM. Solid-state gas sensors: A review. J Electrochem Soc. 1992;139(12):3690.
131. Röpcke J, Davies P, Hamann S, Hannemann M, Lang N, van Helden J-P. Applying quantum cascade laser spectroscopy in plasma diagnostics. Photonics. 2016;3(3):45.
132. Liu Y, Welzel S, Starostin SA, van de Sanden MCM, Engeln R, de Vries HW. Infrared gas phase study on plasma-polymer interactions in high-current diffuse dielectric barrier discharge. J Appl Phys. 2017;121(24):243301.
133. Douat C, Hübner S, Engeln R, Benedikt J. Production of nitric/nitrous oxide by an atmospheric pressure plasma jet. Plasma Sources Sci Technol. 2016;25(2):25027.
134. Loge GW, Tiee JJ, Wampler FB. Multiphoton induced fluorescence and ionization of carbon monoxide ($B^1\Sigma^+$). J Chem Phys. 1983;79(1):196–202.

135. Seitzman JM, Haumann J, Hanson RK. Quantitative two-photon LIF imaging of carbon monoxide in combustion gases. Appl Opt. 1987;26(14):2892.
136. Aldén M, Wallin S, Wendt W. Applications of two-photon absorption for detection of CO in combustion gases. Appl Phys B Photophysics Laser Chem. 1984;33(4):205–8.
137. Haumann J, Seitzman JM, Hanson RK. Two-photon digital imaging of CO in combustion flows using planar laser-induced fluorescence. Opt Lett. 1986;11(12):776.
138. Settersten TB, Dreizler A, Farrow RL. Temperature- and species-dependent quenching of CO B probed by two-photon laser-induced fluorescence using a picosecond laser. J Chem Phys. 2002;117(7):3173–9.
139. Agrup S, Aldén M. Measurement of the collision-quenched lifetime of CO molecules in a flame at atmospheric pressure. Chem Phys Lett. 1992;189(3):211–6.
140. Richardson DR, Roy S, Gord JR. Femtosecond, two-photon, planar laser-induced fluorescence of carbon monoxide in flames. Opt Lett. 2017;42(4):875.
141. Lee B-S, Heo J, Kim Y-M, Shim SM, Pae H-O, Kim Y-M, Chung HT. Carbon monoxide mediates heme oxygenase 1 induction via Nrf2 activation in hepatoma cells. Biochem Biophys Res Commun. 2006;343(3):965–72.
142. Graves DB. Mechanisms of plasma medicine: Coupling plasma physics, biochemistry, and biology. IEEE Trans Radiat Plasma Med Sci. 2017;1(4):281–92.
143. Otterbein LE, Soares MP, Yamashita K, Bach FH. Heme oxygenase-1: Unleashing the protective properties of heme. Trends Immunol. 2003;24(8):449–55.
144. Ewing JF, Maines MD. Rapid induction of heme oxygenase 1 mRNA and protein by hyperthermia in rat brain: Heme oxygenase 2 is not a heat shock protein. Proc Natl Acad Sci. 1991;88(12):5364–8.
145. Dwyer BE, Nishimura RN, De Vellis J, Yoshida T. Heme oxygenase is a heat shock protein and PEST protein in rat astroglial cells. Glia. 1992;5(4):300–5.
146. Graves DB. The emerging role of reactive oxygen and nitrogen species in redox biology and some implications for plasma applications to medicine and biology. J Phys D Appl Phys. 2012;45(26):263001.
147. Russwurm M, Koesling D. NO activation of guanylyl cyclase. EMBO J. 2004;23(22):4443–50.
148. Hartsfield CL. Cross talk between carbon monoxide and nitric oxide. Antioxid Redox Signal. 2002;4(2):301–7.
149. Hartsfield CL, Alam J, Cook JL, Choi AM. Regulation of heme oxygenase-1 gene expression in vascular smooth muscle cells by nitric oxide. Am J Physiol. 1997;273(5 Pt 1):L980–8.
150. Kostoglou-Athanassiou I, Costa A, Navarra P, Nappi G, Forsling ML, Grossman AB. Endotoxin stimulates an endogenous pathway regulating corticotropin-releasing hormone and vasopressin release involving the generation of nitric oxide and carbon monoxide. J Neuroimmunol. 1998;86(1):104–9.
151. Lim I, Gibbons SJ, Lyford GL, Miller SM, Strege PR, Sarr MG, Chatterjee S, Szurszewski JH, Shah VH, Farrugia G. Carbon monoxide activates human intestinal smooth muscle L-type Ca^{2+} channels through a nitric oxide-dependent mechanism. Gastrointest Liver Physiol. 2005;288(1):G7–14.
152. Ingi T, Cheng J, Ronnett GV. Carbon monoxide: An endogenous modulator of the nitric oxide–cyclic GMP signaling system. Neuron. 1996;16(4):835–42.
153. Guzik TJ, Korbut R, Adamek-Guzik T. Nitric oxide and superoxide in inflammation and immune regulation. J Physiol Pharmacol. 2003;54(4):469–87.
154. Thom SR, Xu YA, Ischiropoulos H. Vascular endothelial cells generate peroxynitrite in response to carbon monoxide exposure. Chem Res Toxicol. 1997;10(9):1023–31.
155. Maines MD. The heme oxygenase system: A regulator of second messenger gases. Annu Rev Pharmacol Toxicol. 1997;37(1):517–54.
156. Kinsella J. Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. Lancet. 1992;340(8823):819–20.

157. Iseni S, Zhang S, van Gessel AFH, Hofmann S, van Ham BTJ, Reuter S, Weltmann K-D, Bruggeman PJ. Nitric oxide density distributions in the effluent of an RF argon APPJ: Effect of gas flow rate and substrate. New J Phys. 2014;16(12):123011.
158. van Gessel AFH, Alards KMJ, Bruggeman PJ. NO production in an RF plasma jet at atmospheric pressure. J Phys D Appl Phys. 2013;46(26):265202.
159. van Gessel AFH, Hrycak B, Jasiński M, Mizeraczyk J, van der Mullen JJAM, Bruggeman PJ. Temperature and NO density measurements by LIF and OES on an atmospheric pressure plasma jet. J Phys D Appl Phys. 2013;46(9):95201.
160. Piantadosi CA, Tatro L, Zhang J. Hydroxyl radical production in the brain after CO hypoxia in rats. Free Radic Biol Med. 1995;18(3):603–9.