

Carbon monoxide (CO) in plasma medicine and agriculture: just a foe or a potential friend?

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Abstract

Carbon monoxide is infamously known for its toxicity when administrated in high doses. In this paper, we review some of the evidences of therapeutic effects of carbon monoxide in biology when delivered in small quantities. It is argued that plasmas are in this context an attractive *in situ* source of CO alleviating in the process the risks related to its storage. Moreover, synergic effects of CO with other reactive species produced by the plasma can also be expected in applications such as bacterial infection, wound healing, cancer treatment but also seeds germination and plant growth.

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1 Introduction

Non-equilibrium, low temperature plasmas are weakly ionized gases which have been very successfully developed in different fields such as the micro-electronics industry [1], lighting [2], combustion [3], nanoscience [4] and spacecraft propulsion [5]. In the early 21st century, some researchers first reported that plasma could be potentially used for biomedical applications. Stoffels *et al* were probably the first to show the potential of cold, near room temperature plasmas in medicine by demonstrating their capability of detaching 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 and was coined later as “Plasma Medicine”. Research is now performed in many different topics including works on cancer treatment, wound healing, blood coagulation, dentistry, cosmetology, sterilization and decontamination, among others [7]–[15]. Many studies were successful and the first clinical trials were undertaken in the last few years [16]–[19]. Recently, those plasmas have also been studied in the field of agriculture, such as for killing insects, killing of bacterial and fungi and plant growth enhancement [15], [20]. The successes of plasmas have come so far from their versatility and their capacity of generating large amount of reactive species at low gas temperature (below 40°C) combined with electric field, photons (IR, visible and (V)UV) and charged species. They all represent the plasma components which are schematized in Figure 1. In the case of direct plasma treatment, the interaction with the gas flow and the liquid needs to be taken into account as well.

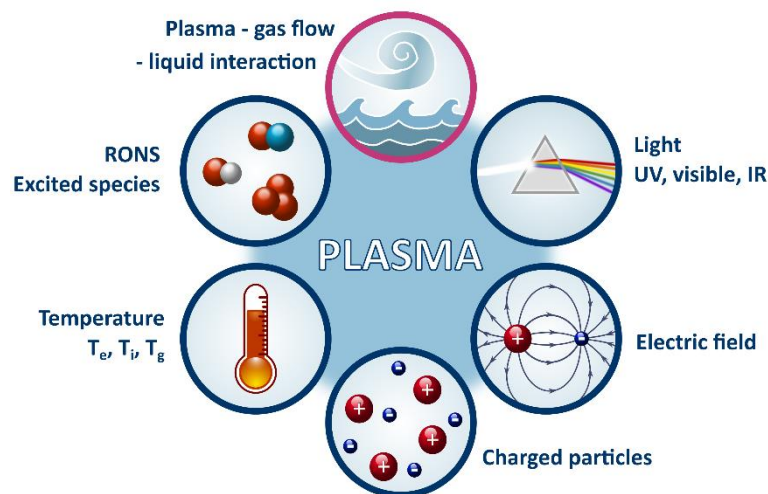


Figure 1: Illustration of the plasma components and plasma interactions with a (biological) target. The plasma components are represented with the blue circles, while the plasma-target interactions are represented by the pink circle.

Plasmas (*i.e.* gas electrical discharges) used in medicine are typically generated using gas mixtures based on He, Ar, O₂, N₂ but also simply air. The latter is either synthetic (about 80% N₂ and 20% O₂) or already naturally present (N₂ 78.08%, O₂ 20.95%, Ar 0.934%, CO₂ 400 ppm) around the plasma and mixed 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, but also rather stable neutral species such as NO, NO₂ and O₃. Due to the presence of 400 ppm of CO₂ in natural air but also water vapor, the formation of other species such as CN, CO, OH, NH and H₂O₂ can additionally occur.

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

Many studies, especially in CO₂ laser and energy storage fields, showed that CO can be easily produced with non-equilibrium plasmas [29], [30]. The aim of this perspective paper is, first, to discuss on the potentiality of using plasmas as CO source for treating various afflictions both for animals (humans being included in that category) and plants. Secondly, to point out that in some cases, CO molecules combined with plasmas will have some beneficial effects in medicine and agricultures fields, thanks to possible synergetic effects with other species produced by the plasma like NO and reactive oxygen and nitrogen species (RONS). Finally, we will advocate that new studies should be devoted in the future on the development of new CO plasma sources relevant for therapeutic conditions and we will discuss some configurations that may be relevant for in 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).

CO being highly toxic and even lethal at high doses, we will start with a review of its toxicity and the mechanisms leading to its adverse effects on human physiology. The official regulations about the degrees of safe exposure to CO concentrations in the environment are then given and discussed based on medical investigations. In section 3, some of the evidences pointing toward a beneficial role of CO in medicine as a signaling molecule are given and some initial clinical trials further highlighted. A brief discussion of the biochemical pathways of CO in cells and tissues is given with references to relevant works/reviews in the field. We finally conclude with the section 4 and 5 while discussing potential CO plasma sources for medicine and some benefits and differences that they may bring compared to “traditional” CO sources.

2 Toxicity of carbon monoxide molecule

CO is a tasteless, odorless and non-irritating gas and is toxic at high concentration. It comes generally from incomplete combustion of hydrocarbons. Once into the lungs, CO binds to hemoglobin instead of O₂ and form carboxyhemoglobin (COHb). As the affinity of human hemoglobin for CO is 210 times more than for O₂, the presence of oxygen in the blood decreases, leading to tissue hypoxia [31] (the affinity rate depends on the animal, for example, it is only 50 times more for mouse hemoglobin [32]). Due to their high metabolic rate, the brain and the heart are the two first organs to show damages from the lack of oxygen [31]. CO is not only dangerous because of its high affinity to hemoglobin, but also because of its slow kinetics for its release from hemoglobin [31]. The CO elimination half-time is about 150 minutes, while the recovery time, meaning that the patient “feels back to normal”, varies from hours to days [33].

The first symptoms that the victim will feel after a mild CO exposure will be exhaustion, headache and then dizziness, nausea and dyspnea (10-20% COHb). At moderate exposures (30-40% COHb), the signs will be visual disturbances, confusion, syncope, seizure and finally coma leading to death if the carboxyhemoglobin rate rises above 60%. Figure 2 lists the CO poisoning symptoms as a function of COHb level in blood. One can see that the effects of CO exposure depend very strongly on the

exposure time of the subject but also of the CO concentration in air. Quite interestingly, short exposure times to relatively high doses (≤ 1000 ppm) of CO 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.

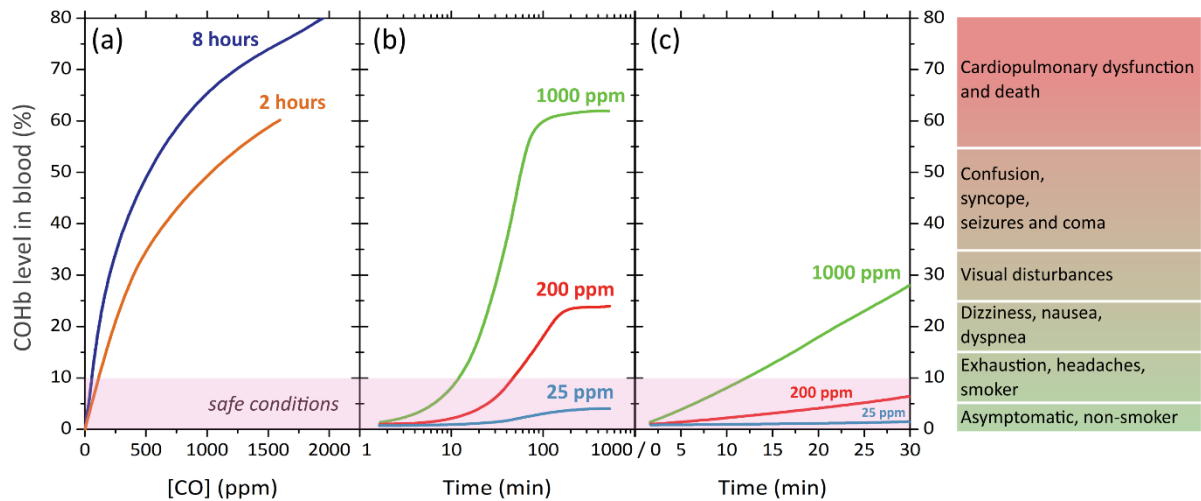


Figure 2: CO safety: (a) Carboxyhemoglobin (COHb) level in blood versus the concentration of CO in air after 2 hours exposition (orange curve) and 8 hours exposition (dark blue curve). (b) COHb level in blood versus the CO inhalation time for three different CO concentrations: 25 ppm (blue curve), 200 ppm (red curve) and 1000 ppm (green curve). (c) is a zoom in of (b) for short times. The CO poisoning symptoms are listed as a function of COHb percentage. Sources : adapted from Steward et al, Bruce et al, Omaye, Varon et al and Raub et al [34]–[39].

The exposure concentration limits at work depend on the country and are listed in Table 1 for long exposure times (longer than 8 hours). They are all in the safety range with no apparent symptoms, meaning that the COHb in blood is lower than 10%. Those CO limits can be crossed if the exposure time is shorter, since the important parameter is not the CO concentration but the COHb level in blood. One should also note that heavy smokers can have as much as 10-15% COHb in their blood [40]. The graph (b) in Figure 2 compares the COHb level in blood for different CO concentrations: 25 ppm (blue curve), 200 ppm (red curve) and 1000 ppm (green curve), and shows that 10% COHb is reached at 12 minutes for 1000 ppm, 50 minutes for 200 ppm and is never reached at 25 ppm, since the hemoglobin has time to liberate enough CO before reaching 10%.

Table 1: CO exposure limits at work for different countries (long-term exposure : higher than 8 hours) [41].

Country	[CO] (ppm)
France (circulaire – 1985)	50
USA (ACGIH - 1991)	25
Germany (MAK)	30

Mann *et al* pointed out that the exposure limits given by the authorities are probably overestimated [9]. Mayr *et al* showed that inhalation of 500 ppm CO for one hour did not have any significant effect on vital parameters, while the American Environmental Protection Agency gives 330 ppm as the maximum 60 min exposure where greater exposure could result in death [24], [42].

CO creation with plasma requires the use of CO₂ as feed gas. CO₂ is a tasteless, odorless and irritating gas. At high concentration (>20%) it can become lethal. Inhalation of CO₂ increases the CO₂ partial pressure in blood (pCO₂) and then induces a pH decrease due to an acid-base disequilibrium, leading to some damage to the kidneys, the lungs, the heart and the central nervous system. CO₂ poisoning symptoms as a function of the percentage of CO₂ in air are listed in Figure 3.

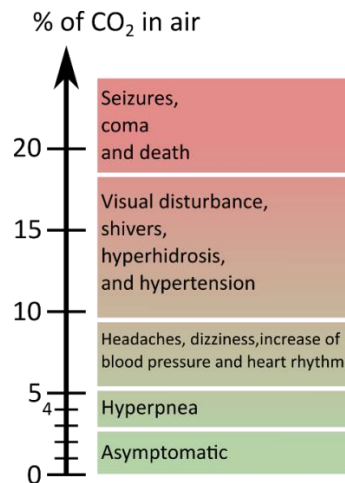


Figure 3: The CO₂ poisoning symptoms listed as a function of the percentage of CO₂ in air [43].

The exposure limit at long term, which means from 8 to 10 hours exposure, is fixed at 5000 ppm, while the short-term exposure limit depends on the country. Table 2 lists the exposure limits as a function of countries.

Table 2: CO₂ exposure limits at work for different countries [43], [44].

Country	Work day exposure limit	Short-term exposure limit
USA (ACGIH - 1991)	5000 ppm	30 000 ppm for 15 minutes
Germany (MAK)	5000 ppm	10 000 ppm for 60 minutes
Sweden	5000 ppm	10 000 ppm for 15 minutes
UK	5000 ppm	15 000 ppm for 10 minutes

3 Benefits of CO in medicine and agriculture

3.1 Roles of CO in vivo

The major source of CO in mammals is from the oxidation of heme (which is the name for the complexed ferrous ion Fe²⁺ with porphyrin) by heme oxygenase enzyme. Heme oxygenase catalyzes the oxidation of the heme to CO, Fe²⁺ and biliverdin (bile pigment) and accounts for about 86% of the CO produced in humans, with the remaining 14% of the CO generated 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]. Besides its well-known interactions with hemoglobin, targets of CO include potentially cytochrome oxidase, NADPH oxidase, nitric oxide synthase and mitochondrial complexes [25]. For instance, CO is known to

activate guanylyl cyclase but is about eighty times less effective than NO and lead to the formation of guanosine 3,5-monophosphate (cGMP which is a secondary messenger affecting for instance ionic transport [46]) and is involved in vasodilation. CO appears to modulate the activation state of mitogen-activated protein kinases (MAPK) which are critical for cellular signal transduction in response to stress and inflammation [47]. CO seems to be involved in the downregulation of ERK1-2 (extra cellular signal regulated kinases) and in the JNK pathways. One should note however that, 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 remain then unclear if the absence of a metal complex is confirmed [25].

Many potential functions of CO were observed *in vivo* [24]. Here we give a few illustrative and significant examples:

- **Anti-inflammatory:** CO inhibits the activation of monocytes, macrophages, and leukocytes *in vitro* as well as *in vivo* while it 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, which continuously generate inflammatory mediators such as NO. CO has been shown to inhibit NO production in macrophages and reduces inflammation [25].
- **Vasodilation:** CO has been found to have important effects on vascular function. It is released by vascular cells and regulates blood flow via inhibition of the vasomotor tone (*i.e.* the tension in the smooth muscle inside the walls of blood vessels, particularly in arteries) via molecular signaling with the vascular smooth muscle cells [48].
- **Anti-apoptotic:** CO reduces apoptosis in renal tubular cells infected by bacteria toxins [49] probably via inactivation of existing inducible nitric oxide synthase (iNOS) (over-expression of iNOS leading to cytotoxic effects) while interacting with its heme iron moiety [50] CO is also anti-apoptotic for endothelial cells, hepatocytes and cardiomyocytes preventing in this way cell and tissue injury [51]–[53].
- **Anti-proliferative:** 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].
- **Anti-hypoxia:** CO can reduce hypoxia (deprivation of adequate oxygen supply at the tissue level). Clark *et al* showed that cardiac cells pretreated with CO releasing molecule become more resistant to the damage caused by hypoxia-reoxygenation and oxidative stress [54].
- Human **platelet aggregation** is inhibited by the presence of CO gas [55]. Slow release of CO was found to be the most efficient and can be used as an anti-thrombotic drug [56].

These specific actions at the level of tissues and organs allowed designing strategies using CO for treating various diseases or for circumventing side effects due to medical treatments. In the next section, some of these applications will be reviewed showing the variety of actions that this simple gaseous molecule can have at the tissues and organs levels.

3.2 Application of CO in medicine

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

- **Suppression of organ graft rejection:** CO as a gas (into saturated solutions) can be used as a protective adjuvant into preservation solutions before transplantation [59]. CO additionally protects against ischemia/reperfusion (I/R) injury associating with transplantation [60].
- **Cardiopulmonary bypass (CPB) surgery:** inhaled carbon monoxide provides pulmonary anti-inflammatory and anti-apoptotic effects and prevent acute lung injury and acute respiratory distress syndrome during CPB [61].
- **Pulmonary hypertension:** CO exposure can reverse established hypertension, resulting in near normal pressures and heart weights and induces a re-modulation of the vascular system [62].
- **Bacterial infection:** sepsis-induced death associated with *Enterococcus faecalis* was reversed by over-expression of Heme Oxygenase-1 (HO-1); inflammatory response (*i.e.* number of circulating inflammatory cells) was not reduced but bacterial clearance was enhanced via an increase of phagocytosis and antimicrobial response [63]; a CO releasing molecule (CORM) was also observed to have bactericidal activity on *Pseudomonas Aeruginosa* [64]. Interestingly, Motterlini and Oetterbein noted that CO has no direct apparent effect on bacteria survival but would only enhance bacteria killing via macrophages [57].
- **Wound healing:** In a study, heme Oxygenase-1 and CO exogenous application accelerated wound healing in mice due in part to their anti-inflammatory properties but also an increase in vascularisation could be seen [65], [66].
- **Pancreatic cancer:** CO was found *in vitro* to have anti-proliferative effects on human pancreatic cancer cells [67].

The examples listed above are only a few selected cases where significant improvements after treatment with CO were observed. Other cases include haemorrhagic shock, rheumatoid arthritis, acute liver failure, postoperative ileus, chronic colitis and asthma [57]. Most studies showing benefits in the cases listed above were studied either with exogenous CO gas or CO-releasing molecules on mouse or rat models but also pigs. Following successful preclinical tests, the next phase is testing *in vivo* on humans and several clinical trials are, in fact, now being performed. Some of them are already in phase II or even 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 shortly discussed here indicate that CO carries a lot of potential as a therapeutic molecule and that its future in clinical treatments is already very promising. The role of the mode of its delivery still need however to be studied further (cf. section 4).

3.3 Applications of CO in agriculture

The toxicity of pure CO atmosphere on seed germination was already studied in 1904 by Richards and MacDougal [69]. For 90% or more of CO atmosphere, they observed a complete inhibition of seeds growth or moderate germination followed by death. With an atmosphere of about 70% of CO they observed germination of seeds but their consequent growth and development were restricted. For pre-germinated seeds they observed also an overall inhibition of the development of the seeds. Still in the case of wheat they reported comparable length of the seedling compared to the control experiment in air but with limited secondary roots development. They also observed below the circle of adventitious roots ordinarily developed in corn seedlings a considerable number of supernumerary secondary roots which arose without order.

Despite the earlier overall negative effects of CO on plants, the role of CO at low doses, and more particularly in saturated solutions has been more recently investigated. Several studies indicate now that CO is involved in several physiological processes and that it is generated as a signaling molecule

in response to abiotic and oxidative stresses. Abiotic stresses include excessive salinity, heavy metals, drought and UV radiation (see [70], [71] and references therein).

Liu *et al* showed that exogenous CO aqueous solution is able to alleviate salt-induced inhibition of rice seed germination [72]. Ling *et al* [73] showed similarly that CO aqueous solution mitigate salt-induced inhibition of wheat root growth and suppress 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 of lateral root formation in several types of seeds [75]–[79]. The direct role of CO was confirmed by Guo *et al* [80] who observed a delayed root hair development for the tomato HO-1 mutant *yg-2* which is defective in CO generation. Cao *et al* [76] additionally showed for rapeseed that CO is directly involved in the endogenous production of NO by adding specific scavengers for the CO molecule and an inhibitor of the nitric oxide synthase while measuring NO. They concluded that CO-induced lateral root development in rapeseed seedlings is nitric oxide (NO) dependent and that CO intervenes as a trigger for NO endogenous production.

Yanarelli *et al* [81] showed an increase of Heme Oxygenase-1 (HO-1) expression in soybean plants following exposition to UV-B radiation. They related the HO-1 expression as a response to the formation of ROS to protect the cell against oxidative damage. Xie *et al* 2012 [82] studied Arabidopsis HY1 mutant (deficient in HO-1) and showed a UV-C hypersensitivity and down regulation of antioxidant defense.

Finally, 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 glutathione metabolism [83]. Similarly, the administration of a CO solution was able to rescue 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 aim to discuss nor even list all of them here (more detail can be found in Ref. [71] for instance). The examples cited above give only a flavor of the surprisingly wide range of applications where CO was tested with apparent positive results. The biochemical pathways of CO in plants appear however to be (much) less understood than in animals like-wise the NO molecule [85]. Even if only phenomenological and only in its early stage, the current understanding of CO biochemistry in plants highlights CO as a molecule playing similar roles as in animals with similar importance as in animals [86].

4 CO sources

4.1 Current production and delivery modes of CO in medicine

Nowadays, the two main systems to deliver CO in medicine are CO inhalation and CO-releasing molecules (CO-RMs). Inhalation of small amount of CO has already proved its efficiency in medicine and has been used in clinical applications [28], [87]. This technique is however difficult to handle because of the lack of control on CO local delivery and toxicity at high concentrations, which depend on the patient [88]. The delivery is not local and affects the whole human body via its fixation on hemoglobin and transport in the blood. To overcome those issues, CO-RMs are being developed and studied with the aim to target specific tissues and organs. This technique has the advantages to

liberate CO locally and not to induce an elevation of CO absorption by hemoglobin. Therefore, there are in principle no risk of CO poisoning with this technique. Despite its promising features, this technique is far to be used into clinical applications and needs to be under scrutiny. Indeed, the safety and the toxicity of these molecules and their by-products are still not fully known [87]–[89]. There are other existing (or under development) techniques such as hemoglobin-based CO carrier, CO-saturated red blood cells and liquid solution pre-saturated with CO injection [89]. However all those techniques suffer from the unknown adverse or synergic effects of the transport/delivery process, their byproducts and by an elevation of CO absorption by hemoglobin. As mentioned by Foresti *et al*, clinicians have no idea yet if those techniques will ever be utilized as therapeutic strategic approaches [87]. Because of that, some clinicians in fact believe that the future still lay in the CO gaseous administration. For such purpose, only one device has been developed till now and being approved for use in hospital, it is the Covox device [57]. This device ensures the delivery of CO with a rate (mg per hour) maintained on a breath-by-breath basis. Finally, in botany we note that besides using compressed CO gas bottles (which cannot easily be transported in hospital for obvious safety reasons), CO is usually produced via a chemical route. For instance, Cao *et al* [76] prepared carbon monoxide gas by heating formic acid HCOOH with concentrated sulfuric acid H₂O₄. Their aqueous solution of CO was further obtained by bubbling the CO gas for at least 15 min in order to saturate the solution with CO. The use of concentrated acids and highly irritant species like formic acid is however probably not very welcome in hospital environment. This leads us to the conclusion that room for new technologies for local gaseous CO production and delivery to specific organs/parts exists yet.

4.2 Plasmas as CO sources

The two main drawbacks of the current CO delivery methods are the increase of COHb level and/or the uncertainty on the toxicity of the molecules used [24], [89]. The pharmacodynamics and pharmacokinetics of gaseous CO are well known while for CO-RMs there are still not well described [45]. To the best of our knowledge, there is only one patented device which has been approved yet for use in hospital environment [57]. There is then still plenty of room for new devices to be developed for delivery of CO alone or together with other species relevant for medicinal therapy. In this section, we will present some plasma devices as potential CO sources based on atmospheric pressure plasma sources with CO₂ admixture that may offer alternative and more flexible solutions (e.g. for external application on wounds for instance). Also due to their intrinsic nature, synergic effects can be expected in addition to the sole delivery of the CO molecule to the target (see section 5).

4.2.1 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 that can interact with living tissue such as reactive species, electric field, light and charged particles (*cf* Figure 1). But as far as we know, plasmas have never been used yet specifically as CO source for biomedical applications, whereas for several decades it is well known that plasma can produce CO molecules. Many studies were performed on it, especially in the fields of CO₂ lasers and energy storage [29], [30]. Those studies reveal that, depending on the plasma source, the amount of CO can be controlled and tuned in a very broad range from less than ppm to several 10's %.

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 (light, electric field, charged particles and reactive species, (cf Figure 1)) can interact with the biological target. A synergetic effect can occurred with the combination of those components, but this will be discussed more in detail in section 5. On the contrary, if reactive species are the only plasma components able to interact with the target, the source is called an “indirect plasma source”. A third configuration exists and is called hybrid source. The plasma is not in direct contact with the target but others plasma components than reactive species, like charged particles and light, can interact with the target. This configuration will not be discussed here and more details can be found in the review of Isbary *et al* [91].

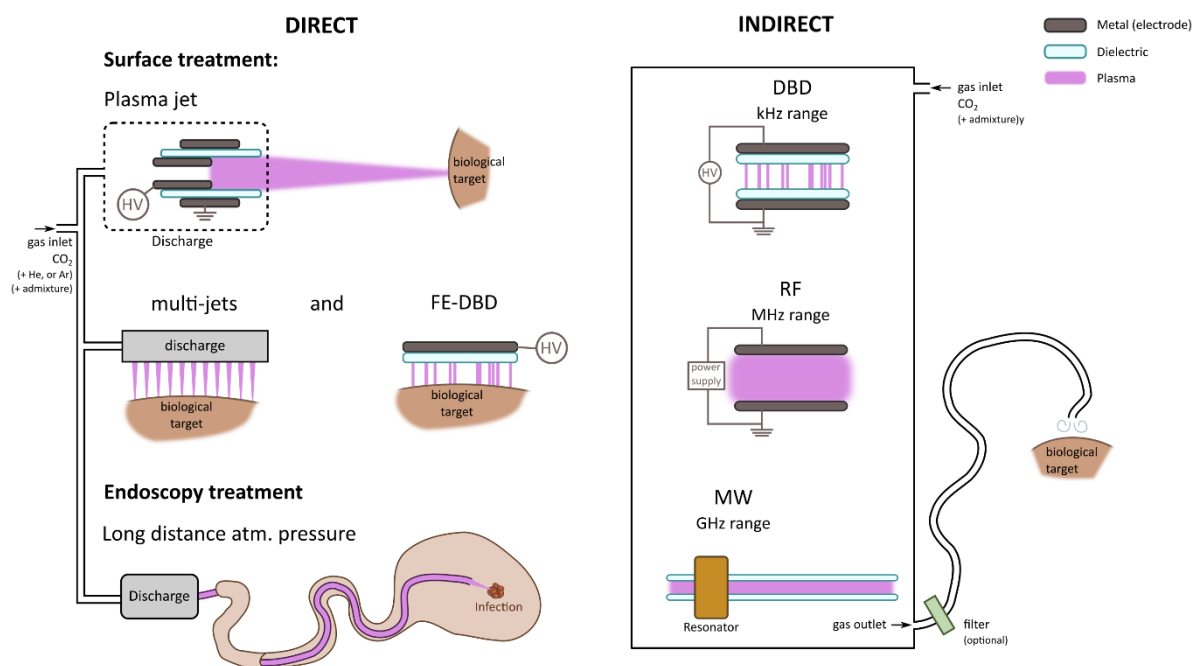


Figure 4: Schema of the different potential plasma sources as CO sources.

Direct plasma sources can be classified into two types: surface and endoscopy treatment. Surface treatment allows treating external tissues or targeted organs after surgical protocol providing the access, while endoscopy treatment allows reaching some organs without (invasive) surgery.

For instance, the floating electrode dielectric barrier discharge (FE-DBD) provides a non-thermal plasma and is generated in air [92]. Naturally, 400 ppm of CO₂ is present in air and could be potentially converted into CO. Even if the conversion is complete, the concentration of CO will not exceed 400 ppm. As the treatment time is typically from some seconds to several minutes, the COHb level will not exceed 10% meaning that the 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]. Instead of FE-DBD, the feed gas is generally a noble gas such as helium or argon. As the plasma propagates in air, it can convert a small part of the CO₂ present into CO. The amount of CO produced can be easily increased¹ and controlled by adding a small percentage of CO₂ through the discharge.

¹ One should note that in the presence of water, the chemistry of CO₂ dissociation is however not simple and small addition of H₂ or H₂O have been demonstrated to reduce the degree of degradation in time of CO₂ gas lasers [29].

The plasma diameter is really small, from some hundreds of μm to a couple of mm, and allows treating locally the tissues. The geometry of the plasma jet represented in Figure 4, is a coaxial DBD [93], [95], but it is only one example among numerous existing configurations [96].

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

In order to avoid any surgery, an endoscopic method can be used. Some devices, generally based on plasma jet configuration, are able to propagate the plasma in capillary tube on several meters [103], [104]. Those devices are fed with noble gas and can lead in the body to He or Ar gas accumulation and then to an arc formation (because of their 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 open environment, one shall note that it offers an additional tool for controlling the plasma chemistry (besides adding gases directly through the plasma). CO_2 gas shielding will in any case increase locally the amount of CO and its biological relevance shall be studied in the future.

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

Indirect sources can be classified based on the frequency of the applied voltage: dielectric barrier discharges (DBD) (single shot to several kHz), radio frequency discharge (RF) (some MHz) and microwave discharge (some GHz). The feed gas can be pure CO_2 or with some admixture. Noble gases dilute the amount of CO produced, while molecular gases such as oxygen and nitrogen allow the production of other species, like NO or O_3 , which will have additional effects on the biological target [8], [107]. According to the reactor, the gas mixture and the plasma parameters, the concentration of CO can be tuned from some ppm to tens of percent's. For instance, a small DBD in pure CO_2 which generates only one or two filaments, produces some hundreds ppm of CO [108]–[110], while the conversion rate with a microwave plasma can rise to more than 60% [111], [112].

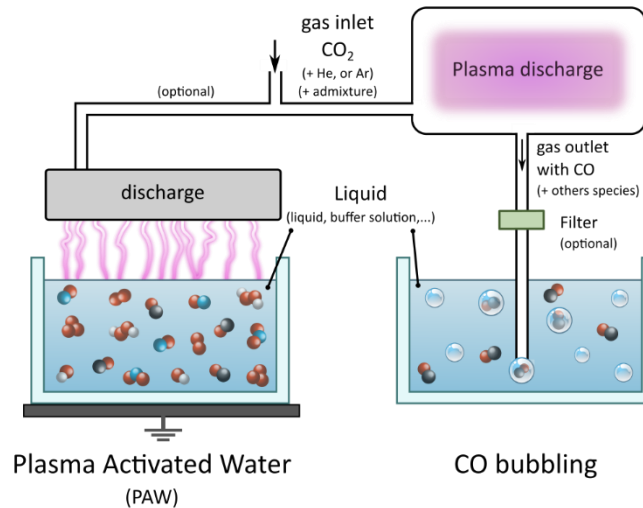


Figure 5: Schema of Plasma Activated Water and CO bubbling.

As explained in the previous sub-section, CO saturated solutions are one of the current methods used as CO delivery methods in medicine [113], [114]. One drawback of this method is the use of a CO tank, which can be dangerous in a medical environment if there is any leak. Plasmas could be used as a local, inline CO source instead of a CO tank. Indirect plasma sources in pure CO₂ can provide a very large amount of CO (more than 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 Figure 5. Such a system would be safer than using compressed CO gas bottles or high temperature processes.

The combination of CO-saturated solutions with plasma-activated water (PAW) may have some benefits for medical or plant treatments as well. For instance, CO may reduce an inflammatory response while PAW would disinfect the tissue thanks to its antibacterial properties [118], [119]. Plasma-activated water (PAW) is produced by the interaction of a plasma source with a liquid. Its low pH, the presence of NO₂⁻ and H₂O₂ are usually invoked to explain its bactericidal effect [118]. Figure 5 presents an example of such a system, where a discharge is in contact with the water surface [118], but it exists 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].

In conclusion, we have discussed here briefly 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 these devices are already being investigated for specific applications in plasma medicine. Using these plasmas with CO for *in vitro* or *in vivo* experiments will then require minimal changes.

4.2.2 Plasma diagnostics

Measuring CO can be challenging, especially when trying to perform local non-invasive measurements on plasmas at atmospheric pressure. Those plasmas are generally non-homogeneous and have a filamentary structure, which makes them difficult to diagnose *in situ*. Moreover, the plasma dimensions can be really small, from some hundreds of micrometers (typical diameter of a filament) to centimeters and they are influenced by the presence in their vicinity of any metal or

dielectric surfaces. However the CO molecule has the advantage to be stable at atmospheric pressure and room temperature and can therefore be easily measured *ex situ*. Different types of diagnostics exist and are listed in Table 3 with some of their characteristics. In the following, we will discuss these techniques in a little bit more detail.

Residual gas analyzers

For plasma diagnostics, residual gas analyzers can be sub-divided into two main categories that are mass spectrometers and gas chromatographs based their separation techniques. They usually operate on the principle that a small fraction of gas is sampled from the volume and sent to an analyzer.

The chemical composition of a reactive plasmas can be investigated by **mass spectrometry** using a capillary sampling orifice [121]–[123] or a differentially double pumped micro-orifice in molecular beam configuration [124]. They both allow determining the densities of stable species while the latter can sample additionally radicals. In the case of CO which has 28 a.m.u. molecular mass, its detection is made complicated by the fact that N₂ which is naturally present in air has the same mass. The shape of the cross sections for electron impact ionization can in theory allow discriminating different species having the same mass by measuring the ionic signal for several electron energies and distinguishing the parent ion from dissociative ionization processes [125]. CO has an ionization potential of 14 eV while N₂ has an appearance ionization potential of 15.6 eV [126]. These two species can then in principle 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 and this technique appears then non-suitable [127].

Gas chromatographs (GCs) are routinely used in medicine for measuring the quantity of carbon monoxide in blood (see for instance [128]). In the gas phase, various GCs exist that can be used for detecting 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** which allow detecting CO remotely as well. They have limited but usually low detection ranges and can give absolute densities following proper calibration procedures and for given temperature ranges [130]. Their response time is however slow as well.

Absorption spectroscopy

Infrared light can interact with the CO molecule and therefore can be measured by means of an absorption method, which is based on the Beer Lambert law [131]–[133]. Fourier Transform Infrared (FTIR) absorption spectroscopy and laser absorption are both based on this law, and use respectively a broadband light and a laser as light source. FTIR method allows to get a broad absorption spectra with a low sensitivity [132] while laser absorption can measure very small amount of CO (under 1 ppm) on a very narrow spectral range. A quantum cascade laser (QCL) 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 those methods *in situ* to measure CO density due to the small dimensions and the non-homogeneity of atmospheric pressure plasmas. For low CO concentrations, a multi-pass cell is needed allowing to increase the absorption length and the sensitivity of the method. The diagnostic will be then remote and deliver similar results as gas analyzers.

Two photons absorption laser induced fluorescence

Two photons absorption laser induced fluorescence (TALIF) in the $B^1\Sigma^+$ state was first demonstrated by Loge *et al* [134] and has been developed since for the detection of CO [135]. In atmospheric pressure gases, sub ppm detection levels were reported by Aldén *et al* [136]. Planar laser induced

fluorescence allows two dimensional CO density distribution mapping and was first made by Haumann *et al* [137]. At high pressure, collisional quenching (mainly by CO₂, O₂ but also CO itself) limits the detection of CO while using nanosecond pulsed lasers [138] and picosecond laser are necessary at atmospheric pressure [139]. Femtosecond lasers have been recently developed in the field of TALIF diagnostics and they allow faster measurements while alleviating laser disturbance like photolytic effects [140]. The determination of the effective collisional quenching rate (which depends of the species present in gas phase and of the gas temperature) makes still this technique relatively difficult to use for quantitative measurements *in situ* in the plasma phase. Spatial and temporal resolution are however both excellent.

Techniques	In situ	Abs. density	Sensitivity	Time resolution
FTIR	No	yes	Medium	s ... min
Laser abs.	Difficult	yes	High	100ns ... ms
MS	No	yes	Low	s ... min
TALIF	Yes	complicated	High	ns ... min
GC	No	yes	High	min
Solid sensors	No	yes	High	s...min

Table 3 : Characteristics of various diagnostic techniques for CO density measurements.

In summary, several diagnostics methods exist to measure CO concentration at various ranges, which allows controlling the amount of CO produced by the plasma. Table 3 summarizes those methods and they are sorted 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 as the dimension of the plasma is much smaller than the dimensions of the biological target, local absolute density in the plasma may not be an important criterium and can still be obtained by TALIF. The parameter of biological relevance will first be the total amount of CO produced by the plasma. Depending of the conditions, it can be measured with the other listed techniques previously. It must be pointed out that those measurements are hardly feasible during treatment on an animal or a human, since those techniques are very sensitive and must be perform in no motion conditions. However, the plasma can be calibrated ahead by measuring the CO concentration with a setup in similar conditions where every component is stabilized. One may finally note that, despite CO being a species naturally present in air, there are no, easy, straightforward method of detecting it and dedicated measurements are required. Considering that plasma jets or discharges in air will affect the CO/CO₂ ratio at the level of the tissues, it will be interesting to characterize those existing sources and correlate their biological impact with other reactive species such as H₂O₂ or NO.

5 Potential synergic effects of CO and plasmas: discussion

Usual CO based treatments are now via inhalation of gaseous² CO which is then fixed in large quantities as COHb. Quite interestingly, it was reported that CO can mediate HO-1 induction in hepatoma cells [45], [141]. Local delivery of controlled CO amounts (see section 4.2) has then the

² A promising field is also the administration of CO-RMs but the molecular carriers are still being tested for potential pathological effects. The amounts of CO delivered at the target tissues is in any case complex to predict because of a relatively limited knowledge about equilibrium dissociation constants of the complexes *in vivo*.

potential of activating locally the CO signaling pathways while avoiding to use large amounts of CO that will impact the whole organism.

Reviewing some of the clinical investigations of the CO molecule as a therapeutic species shows its high potential. As plasmas have also proven effects for the treatment of some afflictions, it is very likely that beneficial effects of adding CO₂ to the plasma discharge (and so producing CO) will be observed. Considering the large number of species that a plasma produces, we may however caution that any new positive results due to the addition of CO₂ (and consequently the production of CO) shall not be by default associated to 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.

Heme Oxygenase-1 (HO-1) is also often referred as heat shock protein (*i.e.* a protein that is being produced in response to a thermal stress of the tissue) [142]. As cold atmospheric pressure plasmas can be in some cases 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 CO³.

The potential beneficial effects of plasmas have been recently studied in the case of plants seeds germination and growth [20]. Some positive results using plasmas have been already observed but UV radiation (from the plasma) may also alleviate some/most of the beneficial effects [82]. The observation that in most cases, exposure to CO can mimic the protective effects of HO-1 (see [47], [143]) would suggest 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 play a direct protective role [81].

NO has been already much discussed in the field of plasma medicine for its role in various processes like wound healing and cancer therapy [144]. Similar to CO, NO increases activates guanylyl cyclase (which is one of the main receptor for NO itself as a signaling molecule [145]) to produce cyclic guanosine monophosphate, acts as a neurotransmitter in the brain, decreases vascular tone, and inhibits platelet aggregation [146]. However it is not expected that CO and NO are redundant messenger molecules. Durante and Schafer [48] pointed out there are important differences in the specific inducers and regulators of the enzymes that lead to their production and that they have different reactivity with biomolecules such as hemoproteins. The lack of reactivity of CO compared to NO has been in fact proposed as an advantage in stress conditions where the NO bioavailability will be compromised while CO can still exert its signaling properties [25]. NO has also been determined as a regulator of heme oxygenase-1 gene expression in vascular smooth muscle cells [147]. 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 that the two gases have counter-regulatory effects on the activation of endocrine glands [148]. CO can also in some conditions bind and activate NOS to stimulate NO production [149]. Ingi *et al* showed that cerebellar granules produced significant amounts of CO in culture. In this system, NO acted as the major regulator of cGMP production, while endogenous CO apparently downregulates the response to NO [150].

³ It appears however to be conflicting evidences and/or interpretations about the direct induction of transcription of HO-1 protein by a heat shock [159], [160].

More generally, chronically inflamed tissue is characterized by the infiltration of immune cells such as macrophages, which continuously generate inflammatory mediators such as NO. CO has been shown to inhibit NO production in macrophages and reduce inflammation [25]. Nitric oxide (NO) exerts multiple modulating effects on inflammation and plays a key role in the regulation of immune responses. However large amounts of NO, usually produced endogenously by iNOS (inducible nitric oxide synthase) can be toxic and pro-inflammatory [151]. Thom *et al* [152] 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 that it may be converted into the toxic NO₂ molecule at high concentration [22]. Additionally both NO and CO interact with Fe²⁺ 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 then concludes that CO will likely influence the bioactivity of newly synthesized NO in response to physiological stimulation or pathological events. Motterlini and Otterbein [57] argued that both molecules are closely interrelated and necessary for the expression/production of each other. It has been proposed actually 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], [153].

From the discussion throughout this paper, it appeared several times that NO is usually a molecule (currently being widely studied in plasma medicine) that has often the same effects as the one that are tentatively attributed to CO as well. However, one should note that a limit during treatment of 80 ppm of exogenous gaseous NO is followed in clinical therapies [154]⁴. Plasma jets produce typically densities of NO in the range of 1-100 ppm [133], [155]–[157]. Graves [144] notes also that creams used for wound healing usually uses NO releasing species but there have been discussions about it for causing skin irritation/inflammation. CO due to its overall complete chemical inertness (which forms only complexes with transition metals, the latter being only weak, non-chemical bounds in a reversible manner) has then clearly 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 in the mix is expected then to offer extra protection to the cells and enhance positive cellular responses to the plasma.

High concentrations of CO increase intracellular hydrogen peroxide (H₂O₂) production⁵ in the brain accompanied by increases in hydroxyl radical ([•]OH) production which affects consequently the redox balance of glutathione in mitochondria [158]. High doses of exogenous CO produced by plasmas may then trigger [•]OH and H₂O₂ production inside the cells in addition to delivering them at their surface. Adding CO to the cocktail of reactive molecules may then help getting similar effects at the cellular level while keeping lower oxidation levels of the membrane and increasing survival rates.

We should finally note that plasmas with CO₂ admixture produce also significant amounts of other species such as, O atoms, O₃ and ¹O₂ molecules which are also active in medicine. Adding some CO₂ in the gas discharge is an additional way to tune the flux of those species to the target and provide an alternative to O₂ admixture into the plasma jet (*e.g.* while providing less oxidizing conditions).

⁴ Indeed, at higher concentrations, there would be the risk of NO₂ formation which is a strong irritant for the lungs [144].

⁵ Note that NO triggers also H₂O₂ production [144].

6 Conclusions

From this short review of the literature, it appears that the CO molecule has a surprisingly large range of therapeutic actions including anti-inflammatory, anti-hypoxia and anti-apoptotic effects, vasodilation and inhibition of platelets aggregation. In plants, CO promote cell germination, lateral root formation, is involved in the protection mechanisms against UV radiation and abiotic stresses due to metals, salinity or drought. Most importantly, the ranges where 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 CO₂ plasma discharges previously analyzed for a fundamental understanding of the dissociation process of the CO₂ molecule into CO to be re-used in the field of plasma medicine. In this paper, several experimental evidences showing the beneficial effects of CO at low doses, both in medicine and agriculture, have been reviewed and discussed with some hints on the molecular pathways involved with CO. In that respect, its interplay with the NO molecule appears to be critical. This may have more general implications with the use of NO generating plasma sources in medicine. Fundamental studies/understanding of CO effects on tissues may not directly benefit from trials using plasmas because of their high intrinsic complexity. However, it appears that sufficient evidence and good understanding exist already in the literature about CO pharmacology. These previous studies will help understanding any new effect that may be observed using (well characterized) plasmas with and without CO production. It is even tempting to think that CO may have been already responsible of some effects observed in plasma medicine because of the natural presence of CO₂ in the atmosphere. It will be interesting to measure experimentally CO densities in the effluent of plasma jets to verify its presence or absence. To the best of our knowledge, such measurements have not been reported in the literature yet for any plasma source used in biomedical applications. A review of potential (plasma) diagnostic techniques that could be used for that purpose was given with some of their respective advantages and disadvantages.

An overview of the recent literature about CO and NO molecules shows that those two molecules are strongly related both in their effects but also in their mutual regulation of endogenous expression. In that respect, the addition of exogenous CO may appear particularly beneficial for counter-balancing 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 interest to combine sterilization and anti-inflammatory effects.

Following this brief overview of biology and medicine literatures, a compelling case for the importance of the CO molecule was made for the treatment of various afflictions and stimulation of processes. Potential applications both in medicine but also agriculture were underlined. A strong case is made for CO₂ plasmas to be tested and used in plasma medicine and agriculture in the future. The fact that the CO molecule has also positive biological effects was discovered less than 20 years ago. Potential biomedical uses of CO are then still in their infancy compared to other pharmacological active species. This relative recent discovery does not diminish its potential but opens a window of opportunity for plasmas with CO₂ admixture. The possibility of synergic effects of the CO molecule with other components of the plasma such as charged and neutral species, UV radiation or heat are very exciting.

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