Plasma medicine: issues and challenges linked to the plasma/biological target interactions

J.M. Pouvesle and E. Robert

GREMI, UMR7344 CNRS/Université d'Orléans, Orléans, France

Abstract: The biological applications of plasmas are currently experiencing an impressive boom. This leads to many diagnostic experiments to better assess the role of the different components of the plasma. Many of those are made on plasmas developing freely in the air, far from the conditions of use. However, the plasma/target interactions are of considerable importance as they lead to simultaneous changes in the produced plasma and the target. After a presentation of the context, we will address this issue and give some perspectives.

Keywords: Plasma medicine, Atmospheric pressure plasmas, plasma/target interactions

1. Introduction

The last decade has seen an impressive increase of the research dedicated to the biomedical applications of low temperature plasmas, especially with plasma sources working at atmospheric pressure. In this new trend, beside decontamination/sterilization and surface treatment that have already a quite long story through low-pressure plasma research and developments, medical applications are tacking an increasing place underlined by the actual numerous clinical trials. Medical applications of low temperature plasmas now concern a very wide range of domains, including primary haemostasis and blood coagulation, dental care, skin decontamination and hygiene, wound and ulcer treatment, dermatology, cancer treatment. Biological applications are also now extended to agriculture and, more recently, to cosmetic. Despite the huge number of *in vitro* and *in vivo* experiments there are still numerous challenges to overcome linked to the nature of the encountered target (biological tissues and materials, organs and their direct environment, liquids) that have a direct effect on the produced plasma itself and on the generated species. That must therefore be taken into account in the applied treatments and complicates the definition of a "plasma dose" expected by many. It appears also very important to always take into account the complete electric circuit represented by the plasma reactor, the plasma itself and the biological target, which electrical conductivity can vary over the time, to properly adjust the plasma parameters.

2. Plasma multimodal action

The use of non-thermal atmospheric pressure plasma jet is now widely spread for a large variety of the above-mentioned applications in biology. In the use of this type of jet, expanding into the atmosphere, most attention has been paid on the role plaid by the reactive oxygen and nitrogen species, RONS, which are mainly created from the transfers of the produced energetic species of the used carrier rare gas, mostly helium and argon. The recent results obtained by different teams all around the word, especially in plasma medicine where an action of the treatment has been identify quite deeply in the tissue, tended to show that other plasma components were also playing an important role.

Focus has been recently put on the potential action of the electric field generated at the tip of the plasma plume [1] that can reach values of the same order than electric fields commonly used in the medical or industrial applications of Pulsed Electric Field (PEF). That, together with the demonstration of plasma jet induced tissue oxygenation and increase of blood flow [2], shows that the plasma action is much more complex than previously thought. Even, the action of the gas flow or on the gas flow must be considered [3, 4] (e.g. in Figure1 in case of a Plasma Gun reactor) in that it induces local changes in the environment of the treated area in *in vivo* and in *in vitro* experiments or biosurface treatment. If we add the fact that potentially the immune system can also be activated, as shown for example by V. Miller *et al* [5] or suggested by our group [6] in plasma cancer studies, this evidences that biological applications of plasma jets, and potentially all non-equilibrium cold plasma sources, must be studied taking into account the changes in the local atmosphere and tissue environments.

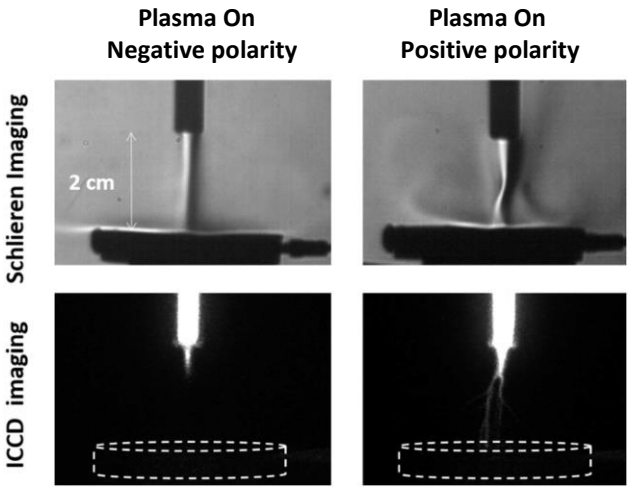

Fig. 1. Helium flow modification with "plasma on" over a grounded metallic target located 2 cm downstream of the capillary outlet of a Plasma Gun, for negative and positive polarities. Plasma plumes are imaged in corresponding configurations (integrated time: 10 μs). Applied voltage: 14 kV Pulse repetition rate: 2 kHz (figure after ref. [4]).

This includes the effective partial pressure of surrounding gases, especially oxygen and nitrogen, or the spot temperature, induced by the plasma source together with the modifications of the microenvironment (local electric field, cell membrane polarization, oxygenation and blood flow in the case of living targets).

3. Plasma/target interactions

It is clear that the extremely strong coupling between the characteristics of the plasma and those of the target, as already shown (e.g. ref. [4, 7]), will play a very important role in the results observed during the treatments. A variation in the chemical or physical characteristics of the target will involve significant differences in the gas flow, the local temperature, or the induced electric field, resulting *de facto* in variations in the production of the reactive species. It also concerns the transposition of the results between the *in vitro* and the *in vivo* experiments that are carried out under extremely different conditions, especially concerning the equivalent electric circuit of the reactor / plasma / biological target assembly. These problems directly affect the identification of the processes involved and currently limit the possibility of a definition of a "dose" in plasma treatments.

Recently, study reported in [8] led to reflections on non-sustainable tumor response. The loss of effectiveness under long-term plasma treatment of cancer tissue opens questions about plasma application and protocol. It must be considered that the treated area is morphologically and chemically changing over the time, from activated surrounding to more normal tissues that are less humid and bacteriologically cleaner. This aspect is particularly important for the development of efficient systems and protocols in plasma cancer treatment but also for any other plasma therapeutically approaches. It induce a in real-time in situ control of plasma production and at longer term a protocol adaptation taking into account the biological target evolution [9]. Some progress are already done in that domain. They concern both the control of the plasma delivery and the adjustment of treatment conditions based on the cell response [10, 11].

4. Conclusion

All the results obtained up to now concerning therapeutic and biological applications of plasmas let hope that many new applications will be develop in a near future. However, they will require major research efforts for a better understanding of the processes involved in the plasma/cell or plasma/tissue interactions, the evaluation of long-term effects and the difficult but, of course, indispensable passage from animal models to large-scale clinical trials. In this context, the proper consideration of the interactions between the plasma and the biological target is of the utmost importance and should be considered with great attention.

In this talk, after a presentation of the context of plasma biology domain, the plasma devices, and the main applications, we will focus on the different problems linked to the plasma/target interaction, including treatments of tissues and liquids. Beside the induced changes in gas flow, the radical production and the potential role of the strong electric field generated around the plasma plume of atmospheric plasma jet systems, we will discuss possible changes induced in microenvironment of living targets. Throughout this presentation, we will emphasize on the fact that plasma diagnostics must be performed in real treatment conditions. We will also tackle the main issues, challenges and opportunities linked to the control of this multimodal action of non-equilibrium cold plasmas on living organisms including electrical compensation of models from *in vitro* to *in vivo* experiments.

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