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Is There a Place for Ozone Therapy in Patients with Heart Failure?

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To the Editor,

We have read, with considerable interest, the article by Buyuklu et al. [1] regarding the beneficial effects of ozone therapy in patients with heart failure. We congratulate the authors on this timely work particularly because we have just finalized a clinical study related to this topic and we are currently developing a randomized clinical trial exploring the issues we encountered. With the prospect of improving our understanding, we wish to raise some discussion points below.

We agree with the authors in adhering to the concept "start low, go slow" [2, 3] so as to progressively stimulate the adaptive response of antioxidant systems; an adversely affected status usually observed in patients with chronic diseases. Of considerable note is that initiating treatment with final-dose concentrations to induce higher oxidative stress could be counterproductive since adaptive antioxidant capacity of patients with chronic heart failure (CHF) could be exceeded, thus reducing the beneficial effects. This occurred in the ACCLAIM trial where an appropriate immunomodulation was not achieved in patients with CHF because of the excessive oxidative stress induced by the procedures employed (blood samples were treated with ozone, ultraviolet light and heat at 42.5 °C for 20 min before re-introduction into the patient via intramuscular injection) [4, 5]. The progressive increase in ozone concentration employed by Buyuklu et al. should induce better response than initiating treatment with a high, non-variable, ozone concentration. However, because two different ranges were described, we are not sure whether the 40 or the 50 μg/ml was the preferred upper limit of ozone administration.

Although the procedure employed by Buyuklu et al. was well tolerated, the ozone therapy required 3–4 venipunctures per week for 5 weeks, and >50% of patients were receiving anti-aggregant treatment. It would be of interest to know if there were: (1) any interruptions of scheduled treatment due to hematomas at the sites of previous venous access; (2) any differences in tolerance to treatment between CHF class 2 and class 3 patients or between patients with versus without anti-aggregant treatment; and (3) differences in patient compliance with the treatment plans. Also, Buyuklu et al. noted that 5 patients did not tolerate ozone dose of 20 μg/mL. What symptoms indicated intolerance? Was the intolerance related to the ozone per se or were they related to the procedures (venous access, other nosocomial or iatrogenic reactions)? This additional information could be relevant in improving the design of future studies with ozone therapy, especially if focusing on: (1) ozone treatment >5 weeks; (2) patients

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with the most advanced CHF (classes 3 and 4); and (3) patients with anti-aggregant/anticoagulant treatments. For these potential conditions, it could be interesting to evaluate the best accuracy and control obtained by the autohemotherapy route versus the easier, well-tolerated and theoretically lower risk of the rectal administration route.

At the end of baseline characteristics in the "Results" section, Buyuklu et al. described some differences in responses compared to "healthy subjects." Were these clinically healthy subjects or were they patients from the control group (i.e., patients without heart failure and not receiving the ozone therapy)?

Buyuklu et al. describe encouraging results post-ozone therapy; several biochemical parameters improved, as did the 6-min walk test. Additionally, it would be interesting to know if patients reported a subjective improvement in quality-of-life or an improvement in NYHA functional classification. The clinical study we have just concluded (K. Eltobgy et al.; data presented at the International Congress of the European Cooperation of Medical Ozone Societies, Berlín, March 2017) was not focused in biochemical parameters. However, clinical outcomes concur with those of Buyuklu et al., i.e., with significant improvement in the 6-min walk test and in the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

In the Discussion section, Buyuklu et al. describe several ozone effects, mainly related to modulation of antioxidant and immune systems. It would be interesting to have some input on other potential beneficial effects of ozone therapy. These could include increased nitric oxide release from endothelial cells [6]; improvement of rheological properties of the blood [7] which may improve blood flow [7–9], oxygenation [10] and glucose metabolism in altered tissues [3, 9]. All these actions could be invaluable in alleviating chronically ischemic heart tissue.

Finally, many questions become evident in relation to volume, concentration and route of ozone administration. Also, the optimum schedule and duration of the treatment remain to be investigated in future studies to determine an optimized ozone therapy procedure. As the authors themselves stated, placebo-controlled studies to validate the potential role of ozone as adjuvant treatment in patients with heart failure need to be performed. Currently, our group is planning and designing just such a randomized clinical trial.

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