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AJRCCM Letter to the Editor - Research letter

Safety and histological effect of liquid nitrogen metered spray cryotherapy in the lung.

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Running Head: Safety study of Endobronchial Cryospray

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To the Editor,

Chronic bronchitis is characterized by inflammation, cough and increased mucus production. There is no cure, and current treatment options are limited to addressing symptoms [1]. The RejuvenAir® System (CSA Medical, Inc., Lexington MA, USA) is a device designed to bronchoscopically address chronic bronchitis by delivering liquid nitrogen (LN_2) as a Metered Cryospray™ (MCS). MCS is controlled by a thermocouple on the delivery catheter that feeds back real time information regarding the amount of LN_2 being delivered. That amount is tailored such that each bronchial airway receives a standardized amount of LN_2 based on airway size leading to a 10mm circular cryoablationwith a depth between 0.1mm to 0.5mm.

Based on older generations LN_2 spray interventions [2,3], it is hypothesized that LN_2 can induce an airway tissue healing effect by destroying the hyperplastic goblet cells and excess submucous glands. The extracellular matrix facilitates rapid regrowth of normal epithelium without scarring, a hallmark of cryoablation [4,5]. The healing resulting from LN_2 MCS is the basis of this proposed treatment.

To start this project, we evaluated the safety of delivering LN_2 in two small pilot studies. Two sprays were delivered into the lobar and first segmental bronchi, which would be the most distal extent of the anticipated airway treatment in chronic bronchitis, based on the significant goblet cell pathology present in these areas [6]. The primary endpoint for each study was the evaluation of device related serious adverse events (SAEs). The initial study (NCT02106143, previously reported as ATS-2016 conference abstract [7]) was conducted in subjects who were

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scheduled to undergo lobectomy or pneumonectomy immediately following MCS. The second study (NCT02483052) evaluated the same initial, plus post procedure safety as these subjects had a planned lobectomy after MCS. Both studies had evaluation of potential histologic effects of MCS as a secondary endpoint and the specimens were reviewed by an independent pathologist skilled in cryothermic tissue injuries (JC). Procedures were performed by flexible bronchoscopy under general anesthesia using an endotracheal tube with positive pressure ventilation. During the LN_2 spray, the endotracheal tube was disconnected from the ventilator with the cuff deflated, both to allow N_2 gas egress. Major inclusion criteria included FEV_1 ≥50% of predicted, no bullae >3cm, and no previous lung surgery of any sort. Both studies were approved by the local ethics committees and all patients provided informed consent.

Overall, 16 subjects were enrolled and treated at 3 sites in Europe and Canada. The initial study enrolled 11 (3F/8M) subjects, with a mean age of 65.8±8.9years [range 45.7-74.8years], a mean FEV_1 %predicted of 86.1±28.1% [range 46-132%], and a smoking history of 28.3±20.5 pack-years [range 0.02-54.0]. Mean time to the scheduled surgical resection after MCS was 37.7±21.8 minutes [range 15-80minutes]. In the delayed study, 5 subjects (4F/1M) were enrolled, with a mean age of 66.8±6.2years [range 59.2-74.0years], a mean FEV_1 %predicted of 72.8±16.5% [range 51-91%], and a smoking history of 29.8±22.4 pack-years [range 4.5-47.0]. Mean time to resection after MCS was 14±1.4 days [range 12-16 days]. Final histopathological diagnosis was non-small cell lung cancer in 15, and small cell lung cancer in one patient.

All intended thirty-two LN_2 MCS were given. The delivery of MCS was both feasible and safe with no device related (S)AEs. There were no intra-operative complications with stable vital signs and no technical difficulties preventing application of MCS. Three SAE's were reported in

each study, all determined to be unrelated to the study device, the MCS treatment or bronchoscopy as adjudicated by an independent medical monitor. The SAE's all occurred post completion of MCS and VATS: atrial fibrillation (8 days post), mucus plug (3 days post), death>30 days post LN_2 spray due to hospital acquired pneumonia after pneumonectomy in the non-treated lung, and one subject with an intra-operative bleeding during video assisted thoracoscopic surgery (VATS, 14 days post MCS), an immediate post-operative bleeding, and again 18 days after VATS.

Eight immediate resection subjects treated bronchial segments were available, with in five of them revealing presence of the intended cryothermic histologic changes. In the regions with greater epithelial changes, minimal to mild acute inflammation was present. In two specimens there was extension into the submucosa with cryothermic changes involving the submucosal glands with preservation of the underlying submucosal structure including no effect on underlying cartilage (figure 1).

In the delayed resection study, a bronchoscopy was performed just before lung resection took place. The video of these bronchoscopies were independently reviewed by an experienced bronchoscopist (RB), with three subjects showing a slight mucosal whitening, one of which seemed to represent subtle white rings consistent with cryoablation. Airway caliber was normal and there were no signs of infection. All five subjects had bronchial segments submitted for histopathological evaluation. Due to the lack of visual mucosal changes post fixation, identification of the treatment sites represented a major limitation in the subsequent histologic evaluation. Histology findings were consistent with complete re-epithelialization at the treatment site. No persistent treatment-related epithelial erosions, acute inflammation,

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granulomatous inflammation, mucosal necrosis, fibroproliferative healing or collagenous luminal narrowing were identified (see figure 2 for a representative example). The bronchial cartilage rings primarily appeared unremarkable with one specimen showing focal cartilage ring necrosis, consistent with possible cryothermic injury or non-specific degenerative changes.

In summary, the data obtained in both clinical trials met the primary and secondary endpoints with safe delivery of MCS to the segmental and/or lobar bronchi without device related serious adverse events. Histology from immediate resection specimens documented MCS effect, and non-scarring healed tissue from the delayed resection group.

The information learned from this study is important for the future development of a bronchoscopic treatment for patients who suffer from chronic bronchitis. While the future intended indication was not specifically studied in these patients, they share some chronic bronchitis characteristics such as exposure to cigarettes, and most having COPD. Using MCS in a similar population and determining the immediate and delayed healing response has provided important information in the stepwise clinical development of the system. These results warrant further investigation in a larger clinical trial targeting chronic bronchitis patients, which is currently underway (NCT02483637).

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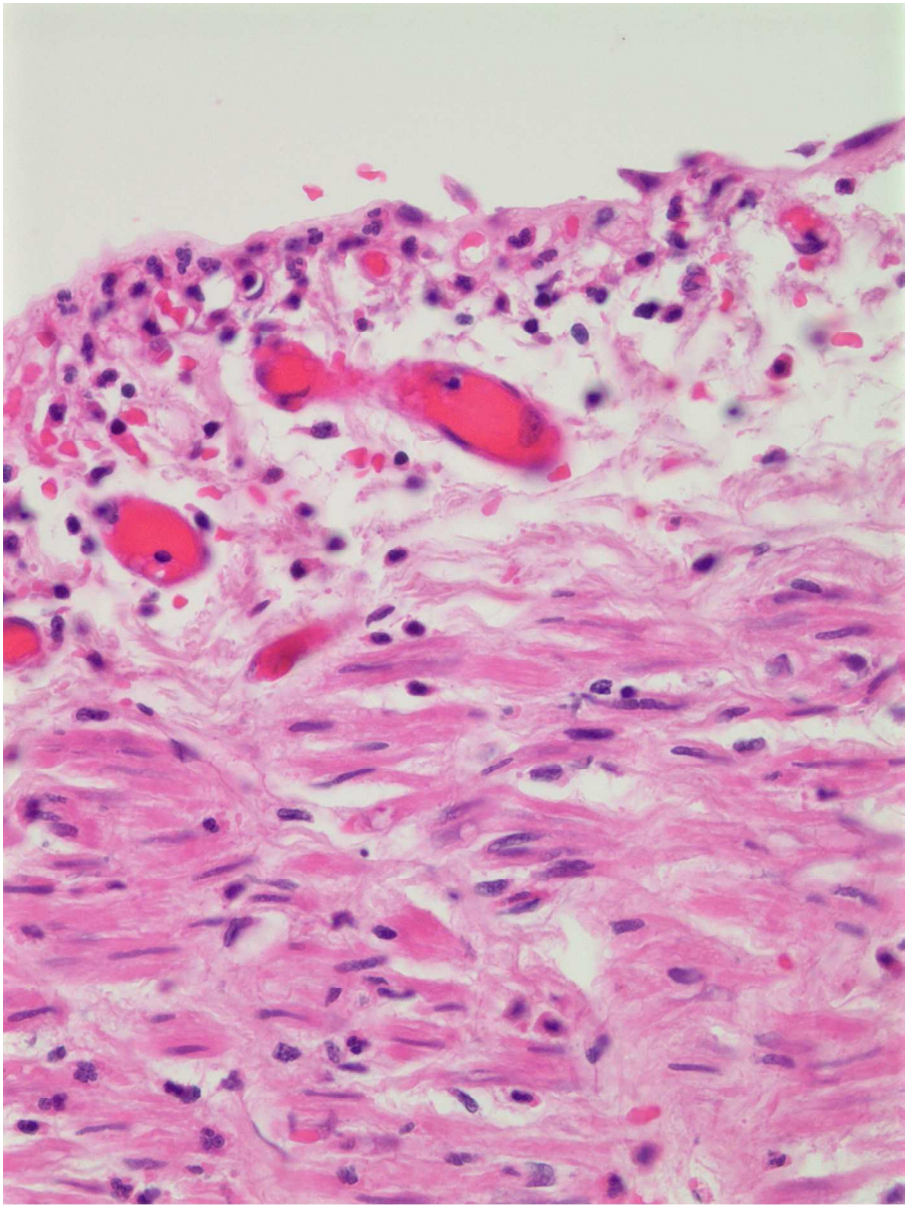
Legend to the figures

Figure 1

Representative 2 hour post liquid nitrogen metered cryospray treated bronchial micrograph demonstrating surface and superficial ductal epithelial removal to a depth up to 500 microns (Hematoxylin and eosin stained, 400x magnification). The submucosal extracellular matrix remains intact (non-denatured) with mild capillary congestion and minimal luminal-oriented acute inflammation and edema.

Figure 2

Representative 14 days post liquid nitrogen metered cryospray treated bronchial micrograph demonstrating complete rejuvenative healing characterized by pseudostratified respiratory epithelium with occasional goblet cells, preservation of the submucosa and cartilage, and absence of inflammation and fibrosis (Hematoxylin and eosin stained, 400x magnification).



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133x177mm (300 x 300 DPI)

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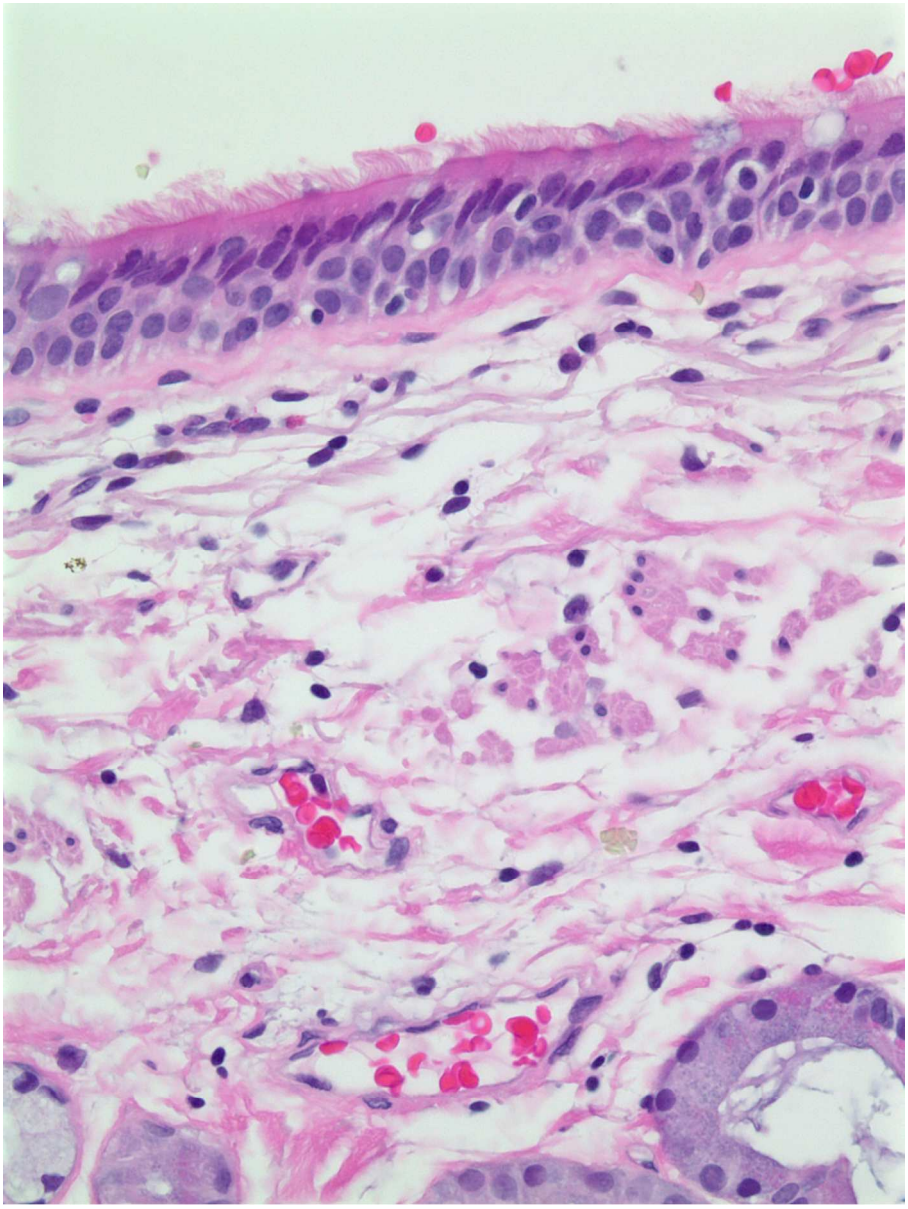

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