Limitations of the study include the observational nature of the study and the fact that we did not confirm the spatial distribution of the inhaled cigarette smoke by using a tracer. However, OEP is an excellent noninvasive tool to determine compartmental displacement during breathing accurately and has the advantage of allowing accurate observation without complex instrument interference.

To conclude, we show for the first time that, while smoking, women mainly engage the pulmonary ribcage, whereas men mainly engage the abdominal compartment. These findings may help explain the increased susceptibility to cigarette smoke in women versus men, which underlies the increased risk of developing COPD, severe emphysema, and lung cancer in the female population. ■

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## Five-Year Follow-up after Mesenchymal Stromal Cell–based Treatment of Severe Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by uncontrolled bilateral inflammatory



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**Table 1.** Presentation of Basal Characteristics as well as Clinical Outcomes Directly and 5 Years after a Single Infusion of BM-MSCs in Two Patients with ARDS

| Characteristics | Patient 1 | Patient 2 | ARDS Survivors at 5 yr |
|---|---|---|---|
| Age at admittance and at 5-yr follow-up, yr | 58 (64) | 40 (45) | — |
| Weight, kg | 116 | 113 | — |
| Height, cm | 179 | 182 | — |
| Body mass index, kg/m$^2$ | 36 | 34 | — |
| Sex | M | M | — |
| Smoker, yes/no | No | No | — |
| Cause of ARDS | H1N1 | Chemotherapy/infection/TRALI | — |
| SOFA score | 18 | 14 | — |
| Comorbidity | | | |
| Diabetes, yes/no | No | No | — |
| COPD, yes/no | No | No | — |
| Asthma, yes/no | No | No | — |
| Hypertension, yes/no | Yes | No | — |
| Heart failure, yes/no | No | No | — |
| LVEF, % | >50 | >50 | — |
| Kidney failure, yes/no | Yes | No | — |
| Dialysis, yes/no | Yes | Yes | — |
| Liver failure, yes/no | Yes | No | — |
| Peak Bilirubin concentration, μmol/L | 306 | 199 | — |
| Coagulopathy, yes/no | Yes | Yes | — |
| Platelet count, $\times 10^9$/L | 47 | 6 | — |
| Initial clinical outcome | | | |
| Length of mechanical ventilation, d | 53 | 40 | — |
| Length of ECMO support, d | 30 | 36 | — |
| Length of mechanical ventilation after BM-MSC infusion, d | 41 | 12 | — |
| Length of ECMO support after BM-MSC infusion, d | 24 | 8 | — |
| ICU stay, d | 46 | 42 | — |
| Hospital stay, d | 69 | 79 | — |
| $FEV_1$% predicted | 103 | 95 | — |
| Median | — | — | 83 |
| Interquartile range | — | — | 69–98 |
| Distance walked in 6 min, m | 450 | 565 | |
| Median | 132 | 115 | 436 |
| Interquartile range | — | — | 324–512 |
| Percentage of predicted | — | — | 76 |
| Back to work at 1 yr and 5 yr, % | 100 and 100 | 100 and 100 | 48 and 77 |
| SF-36 score | | | |
| Physical functioning | 100 | 85 | 75 |
| Role, physical | 100 | 100 | 88 |
| Bodily pain | 100 | 90 | 74 |
| General health | 80 | 95 | 62 |
| Vitality | 95 | 85 | 55 |
| Social functioning | 100 | 100 | 75 |
| Role, emotional | 100 | 100 | 100 |
| Mental health | 100 | 96 | 76 |

*Definition of abbreviations*: ARDS = acute respiratory distress syndrome; BM-MSC = bone marrow mesenchymal stromal cells; COPD = chronic obstructive pulmonary disease; ECMO = extracorporeal membrane oxygenation; LVEF = left ventricular ejection fraction; SF-36 = Short Form 36-Item Health Survey; SOFA = Sequential Organ Failure Assessment; TRALI = transfusion-related acute lung injury.
Our 5-year clinical data are presented as a comparison to previously reported 5-year follow-up of conventionally treated patients with ARDS by Herridge and colleagues (4). The SF-36 scores range from 0 to 100, with higher scores indicating better health status.

response with infiltrations in the lungs followed by noncardiac hypoxemic respiratory failure (1). Even though major advancements in the management of patients with ARDS have improved survival, this syndrome still accounts for more than 10% of ICU admissions worldwide and has a mortality exceeding 40% in the most severe cases (2). Extracorporeal membrane oxygenation (ECMO) might be considered to stabilize patients with extreme hypoxemia (3) but has not proven superior to conventional therapy for decreasing 60-day mortality (3).

Another growing need is to prevent the long-term neuromuscular, mental, and respiratory complications of the syndrome, which have major socioeconomic consequences (2, 4).

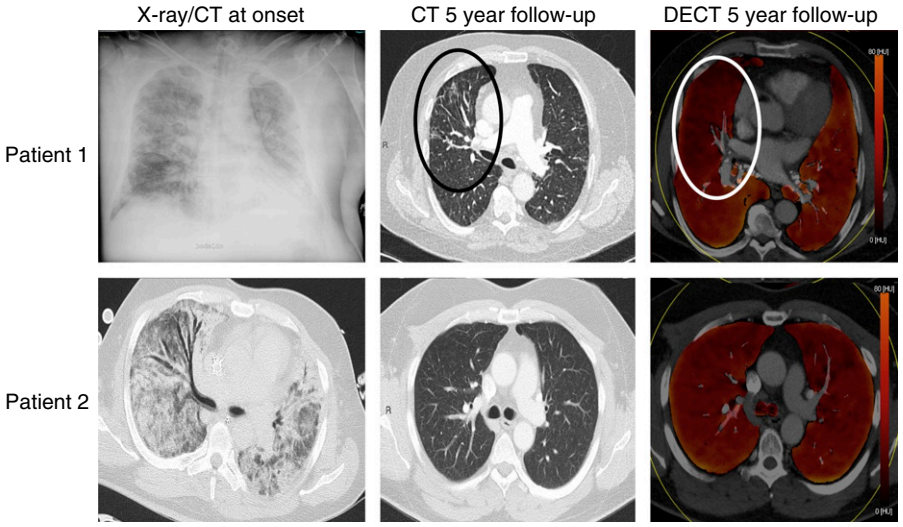


**Figure 1.** (Top row) Patient 1: 58-year-old man with influenza A H1N1–induced acute respiratory distress syndrome (ARDS). (Left) A supine conventional X-ray on admission with bilateral opacifications. No computed tomography (CT) was performed. (Middle) Five-year follow-up CT, in which the axial morphological image reveals signs of pulmonary injury with traction bronchiectasis and linear strands in the anterior parts of the right upper lobe, marked with black oval. (Right) Axial color-coded perfusion map (DECT) with deficits corresponding with the morphological findings marked with a white circle. (Bottom row) Patient 2: 40-year-old man, in whom a combination of cytokine release after intensive chemotherapy because of acute myeloid leukemia, infection, and massive transfusions most probably caused the ARDS. (Left) Signs of ARDS on CT at admission with bilateral ground glass opacities and consolidations without pleural fluid. (Middle) Axial section demonstrating no pathological findings on the five-year follow-up CT. (Right) Normal-appearing axial color-coded perfusion map (DECT). DECT = dual-energy computed tomography.

In 2015, we reported the successful use of systemic administration of a single dose of minimally expanded allogeneic bone-marrow (BM) mesenchymal stromal cells (MSCs) from one donor on two patients with severe ARDS on ECMO support (5). In this study, we describe the 5-year follow-up of these two patients regarding health-related quality of life (HRQoL), physical capacity, and pulmonary morphology and function.

## Methods

***Patients and study design.*** The regional ethic review board at Uppsala, Sweden (Dnr:2017/255) has approved this 5-year follow-up study of two patients with severe ARDS treated on a compassionate use basis with a single intravenous infusion of thawed, cryopreserved, minimally expanded, HLA-mismatched, allogeneic BM-MSCs ($2 \times 10^6$ cells/kg body weight) from the same donor (5).

The follow-up evaluation consisted of an in-depth review of the patients' medical records, a self-assessment test of mental and physical health (the Short Form 36-item health survey [SF-36]), a physical examination, a high-resolution dual-energy computed tomography (DECT) of the lungs, static and dynamic spirometry, and a 6-minute-walk test. All examinations were performed by accredited personnel at Uppsala University Hospital.

## Results

***Baseline characteristics and initial clinical outcomes.*** The descriptive data for the two patients at the time of BM-MSC infusion are summarized in Table 1. Despite different etiologies of ARDS, after BM-MSC infusion, there was a subsequent resolution of respiratory and multiorgan failure, leading to weaning off the ECMO system after 24 and 8 days and from mechanical ventilation after 41 and 12 days for patient 1 and 2, respectively.

The Sequential Organ Failure Assessment (SOFA) score is an ICU mortality prediction scoring system and is useful in predicting the clinical outcome of critically ill patients (6). The patients in our study had SOFA scores of 18 and 14 (patient 1 and 2, respectively), in which a SOFA score of greater than 12 has a predicted mortality of 95.2% (6).

***Physical capacity, HRQoL, and respiratory function.*** At 5 years, both patients demonstrated normal physical capacity on the 6-minute walk test (Table 1), with the longest recorded distances of 450 m and 565 m, corresponding to 132% and 115% of predicted values based on established norms (7) for patient 1 and 2, respectively. The distance walked in 6 minutes correlated well with the physical component score of the SF-36 and the normalized lung functions on spirometry (Table 1). The two patients also scored highly on the mental health and vitality components of the SF-36 (range 85–100). Both patients were back to 100% work without modification of work schedule within 1 year after the BM-MSC treatment.

***Lung parenchymal findings on DECT.*** Patient 1 had bilateral infiltrates at admission to the hospital (Figure 1). At the 5-year follow-up, the distribution of deficits in the color-coded perfusion map corresponded with the signs of parenchymal fibrosis, such as segmental traction bronchiectasis and linear stranding of the anterior parts of the right upper lobe. In contrast, although patient 2 had been on ECMO for 28 days before BM-MSC infusion and at that time had massive bilateral pulmonary infiltrates (Figure 1), at the 5-year follow-up, DECT perfusion images were homogeneous without indication of any perfusion deficits or parenchymal

fibrosis. No sign of pulmonary embolism was detected in either of the two patients.

## Discussion

To our knowledge, this is the first long-term follow-up of patients with the most severe form of ARDS that needed ECMO support in combination with mechanical ventilation in the acute phase and who, at the same time, were treated with a single systemic infusion of allogeneic BM-MSCs (5).

Our main finding is that 5 years after the treatment, both patients have fully recovered their physical and mental capacities, which is unusual for survivors of ARDS (2, 4, 8). Another important finding is that the second patient (patient 2), who had the most severe form of ARDS and was on ECMO support for 28 days before the MSC infusion, had no signs of pulmonary fibrosis 5 years after the MSC treatment, as demonstrated using DECT. Furthermore, because of the immediate response of the MSC infusion in the acute phase, patient 2 could complete treatment for his acute myeloid leukemia and is still in remission 5 years later.

Patient 1, with influenza A H1N1–induced ARDS, exhibited signs of only mild pulmonary injury in the anterior part of the right upper lobe. Such resolutions of severe lung parenchymal injury are rarely seen in long-term follow-up studies of conventionally treated patients with ARDS, in whom computed tomography scans demonstrate residual signs of anterior interstitial fibrosis (4, 9).

The normalization of lung function in the two MSC-treated patients is in line with follow-up reports on patients with conventionally treated ARDS without ECMO support, in whom the lung function usually is described as normal or near normal (2, 4, 8).

MSCs have inborn immunomodulatory and reparative properties that, in preclinical studies, have been demonstrated to affect the different pathological mechanisms involved in ARDS progression (2). In the randomized, multicenter phase IIa START study (10), a single infusion of allogeneic BM-MSCs was demonstrated to be safe in the treatment of patients with moderate to severe ARDS. The efficacy of the treatment was dependent on the viability of MSCs at the time of infusion (10).

In the future, adequately powered randomized trials, with particular attention to quality and viability of MSCs, need to be performed to determine the potential efficacy of BM-MSC treatment of ARDS. ■

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## Does Vaping Increase Susceptibility to COVID-19?

*To the Editor*:

We read with much interest the study by Zhang and colleagues (1) in which they show that ACE2, the gene encoding the receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is expressed throughout the human airway epithelium. They also show a relative increase in the expression of ACE2 in airway epithelial cells derived from smokers. In addition, men who smoke have a higher expression of ACE2 than women. TMPRSS2, a cellular protease that facilitates viral entry, is also increased in the small airways of smokers. These data support the notion that smoking may pose a greater risk of SARS-CoV-2 respiratory infection and subsequent development of coronavirus disease (COVID-19). However, whether this explains the higher male susceptibility to COVID-19 is not yet clear (1).

As of June 1, 2020, the COVID-19 pandemic has now spread to more than 180 countries, infecting 6 million people globally and resulting in more than 360,000 deaths (2). SARS-CoV-2 is highly transmissible and can spread readily from human-to-human, causing acute and severe respiratory failure, often followed by death. This scenario appears to be even more likely in patients with preexisting health conditions and other comorbidities, including diabetes and cardiopulmonary diseases.

We know that active smokers have an increased risk of respiratory tract viral infections and virus-related exacerbations in chronic obstructive pulmonary disease. Emerging research also suggests that current smokers and patients with chronic obstructive pulmonary disease have higher expression of ACE2 in the airway epithelium, type 2 pneumocytes, tissue macrophages, and ciliated airway epithelial cells (3, 4) and that this ACE2 expression may vary with sex and age (5).

Zhang and colleagues have further confirmed and extended these findings, showing that both ACE2 and TMPRSS2 expression are increased with smoking, and have provided new evidence that ACE2 expression is greater in the male population (1). Although new data are still emerging, earlier reports have suggested that COVID-19 mortality rates are higher in the male population (6). Of note, the upregulation of ACE2 may be useful in protecting the host against acute lung injury by producing proresolution peptides such as angiotensin 1–7; however, chronically elevated ACE2 in the lungs may predispose individuals to an increased risk of developing COVID-19.

Although it is becoming increasingly clear that ACE2 expression is induced by active smoking (1, 3), we are not aware of any studies that have evaluated exposure to electronic cigarettes (e-cigarettes), heat-not-burn devices (IQOS), or other electronic nicotine-delivery systems. Cigarette smoking appears to be an important risk factor that could further exacerbate this pandemic. We believe that new data on e-cigarette exposure both with and without nicotine may shed light on the nicotine-dependent effect, as suggested by Leung and colleagues (3), and the nicotine-independent effect, which we believe may also influence ACE2 expression in the airways. If there is a connection between such an exposure (i.e., electronic nicotine-delivery devices) and the risk of succumbing to COVID-19, then this risk extends to not only cigarette smoking but possibly also vaping via e-cigarette use.

Long-term safety studies with e-cigarette devices on humans are still lacking. However, the 2019 e-cigarette or vaping use–associated lung injury epidemic revealed the serious ill effects of vaping. Although many researchers have now shown the harmful effects of vaping, we first reported the deleterious effects of IQOS on human airway cells as compared with e-cigarettes and traditional cigarettes (7). Additional research is needed to investigate the relationship between smoking, other electronic delivery devices, and SARS-CoV-2 infection as well as its transmission and progression. This understanding will not only affect public health policies but may also shed light on important new therapeutic approaches. ■

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