In conclusion, the clinical messages of this study are not clear and may create confusion among clinicians who treat patients with DMD. Many clinicians are struggling to use optimal settings when using MI-E within the goals for which this device was designed. We believe that MI-E studies must focus on assisting cough rather than improving breathing pattern and lung mechanics.

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## Effects of Mechanical Insufflation-Exsufflation on the Breathing Pattern in Stable Subjects With Duchenne Muscular Dystrophy: "A Step Into New Knowledge"

We thank Drs Toussaint, Gonçalves, and Chatwin for their interest in our paper.[1] However, we do not think that our results may in any way create confusion or change the main focus and outcomes of mechanical insufflation-exsufflation (MI-E) treatment. On the contrary, as underlined by Joshua Benditt in his editorial accompanying our paper,[2] we believe that our data add new information by analyzing "the physiologic effects on the respiratory system of the application of MI-E as a routine application and not for secretion removal" in patients with respiratory muscle weakness due to Duchenne muscular dystrophy (DMD). In addition, our data confirm that MI-E is not effective for purposes other than to assist cough, at least in late-stage, non-ambulatory DMD subjects with inefficient cough without ongoing airways infections.

Toussaint et al named two main concerns: to consider MI-E rather than other techniques or devices to assist cough, and to consider MI-E for lung recruitment. We are fully aware that the techniques to assist cough range from simple manual assistance (eg, using a manual resuscitator bag) to more expensive cough-assist devices. We are also aware that, according to the geographic area or the national health care system, patients may not have access to all of the aforementioned devices and could use less expensive techniques. In our paper,[1] we reported data collected in a tertiary care center in Italy where all DMD patients with ineffective cough have free access to MI-E devices, which are supported by the Italian National Healthcare System.

The median unassisted cough peak flow of our patients was 163.0 L/min with an interquartile range of 85.2 L/min. These values are far below the threshold of 270 L/min, which distinguishes efficient cough from inefficient cough[3,4] and is considered by all of the international guidelines for the management of patients affected by DMD.[5] This is an important point missed by Toussaint et al, who wrote in their letter, we should "remember that there is no reason to use a MI-E device in stable DMD patients

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with effective unassisted cough peak flow." They also state, "It is hard to justify to patients, families, the health care system or private health insurers that a MI-E device should be provided to maintain an unassisted cough as evaluated in this study." The unassisted cough of our subjects was far from effective, as thought by Toussaint et al. For this reason, our patients were adapted to daily use of cough-assist devices for at least 1 y. The daily use of MI-E allows patients to remain adapted to the device and to preserve lung and chest wall compliance as a result of the cyclic mobilizations, even in absence of infections or increased airway secretions. Therefore, we designed our experimental protocol in a way to replicate the MI-E treatment as applied to the patients at home using the same settings, including positive and negative pressures. Toussaint et al criticize our pressures settings for not being adequate, suggesting that insufflation pressures need to be at least 50 cm $H_2O$. They state "a normal cough expels 85-90% of total lung capacity, a volume often unattainable at insufflation pressures $<$ 50 cm $H_2O$."[6] We believe this is not supported by available data. During normal coughing, the expired volume is dependent on lung volume[7] and is not $>$ 55% of vital capacity (not total lung capacity, which is usually not available). Moreover, in the paper by Bach,[6] there is no mention regarding the values of applied pressures. It is only reported that "the insufflation and exsufflation pressures were set on each machine to the maximum comfortable levels typically used by each patient to eliminate airway secretions." This is exactly the same approach we used. Moreover, to our knowledge there are no guidelines supporting the choice of inspiratory and expiratory pressures, but only few studies in which different levels of pressures are considered, such as those of Faroux et al[8] and Winck et al,[9] who both compared the effects of the application of $\pm$ 15, $\pm$ 30 and $\pm$ 40 cm $H_2O$.

Only 2 papers in the literature report pressures of 50 cm $H_2O$: Sánchez-García et al,[11] who applied insufflation of 50 cm $H_2O$ and exsufflation of $-45$ cm $H_2O$ in subjects with an endotracheal tube or tracheostomy cannula; and Guerin et al,[10] who used this setting of MI-E in a bench study performed on a lung model with different sizes of endotracheal and tracheostomy tubes. Both studies considered the presence of endotracheal and tracheostomy tubes, which are known to offer high air-flow resistances that therefore require higher pressures. None of our subjects had endotracheal or tracheostomy tubes, so they did not meet the condition to use such high levels of pressure.

The pressure of 34 $\pm$ 5 cm $H_2O$ that we used both for positive and negative phases therefore are in line with those reported by other studies dealing with MI-E,[12-16] and the pressure was enough to clear secretions effectively in our patients. In addition, 50 cm $H_2O$ is a very high level of pressure for cyclic repetitive opening and closing of small airways and alveoli. This may induce alveolar overdistention or mechanical shear stress on airways and alveolar epithelial cells, with the potential for cell and tissue damage.[17]

We have considered MI-E because it was the device available for our subjects. They were adapted to use it and not other devices. In our paper, we do not encourage the use of MI-E instead of other techniques or devices. In addition, the effectiveness of all these different techniques to assist cough was already investigated by different studies and was not the purpose of our study. As Toussaint et al wrote in their letter, "MI-E is an ideal, although expensive, technique to assist cough in the severely affected DMD patients"; in fact, it was already proven to be more effective than other techniques to improve cough.[6,13,18]

Our patients with DMD and ineffective cough are encouraged to use MI-E daily, even when they are stable, as suggested by the newest international guidelines for the management of DMD, recently written by a steering committee of experts from a wide range of disciplines in DMD.[5] The daily use of lung volume-recruitment techniques is herein highly recommended: "as their vital capacity decreases, patients with DMD develop stiff, non-compliant chest walls and lung volume restriction. To preserve lung compliance, lung volume recruitment is indicated when FVC is 60% predicted or less, achieved with a self-inflating manual ventilation bag or mechanical insufflation–exsufflation device to provide deep lung inflation once or twice daily."[5] MI-E, therefore, like other less expensive techniques for cough assistance, also could be used for this purpose in the absence of respiratory tract infections. The association of MI-E and lung recruitment, therefore, was supported by the international consensus of a highly expert group on DMD and neuromuscular diseases. This was furthermore supported and underlined by Toussaint et al themselves, who affirmed that they "agree that patients with DMD who are living in areas where MI-E is available can have multiple long-term goals of cough augmentation, chest-wall stretching and lung-volume recruitment." On the other hand, they also stated, "We understand that positive pressure may recruit volumes. However, there is little physiological explanation to argue that negative pressures will help to maintain lung compliance and volumes." These two sentences seem to be in conflict and opposition between each other. It is not clear what the position of Toussaint et al is regarding the possible role of a MI-E device for lung-volume recruitment.

As correctly underlined by Joshua Benditt in his editorial,[2] in our paper "MI-E was not used for the purpose of removing secretions from the airways, which is the accepted clinical indication for the device, but rather to measure the physiologic effects of cycling on the lung and chest wall through volumes above and below those normally seen during tidal or even maximal voluntary ventilation maneuvers in patients with neuromuscular weakness due to DMD. . . . However, the physiologic effects on the respiratory system of the application of MI-E as a routine application and not for secretion removal has not been well studied, particularly in the non-pediatric population."

For this reason, we have not provided the values of assisted versus unassisted cough peak flow before and after MI-E. We thought it was more important to better understand its acute effects on breathing pattern and lung recruitment. This was achieved by studying MI-E with optoelectronic plethysmography, which allows the measurement of the complete ventilatory pattern, including total and compartmental (ie, rib cage and abdominal) tidal volumes and operating (end-expiratory and end-inspiratory) chest wall volumes.[19] Variations of end-expiratory volumes of the chest wall accurately reflect the changes of end-expiratory lung volume.[20] No other technique, other than optoelectronic plethysmography, allows obtaining this information noninvasively and on a breath-by-breath basis, therefore allowing the quantitative assessment of any possible recruitment effect.

In this way, we were able to investigate the effects of a single treatment of MI-E on lung and chest wall recruitment, and on breathing and thoraco-abdominal patterns beyond those on unassisted cough. We wanted to verify whether there were impor-

tant detectable effects on the short-term; as we have shown, there are not such detectable effects. We have provided a comprehensive description of the ventilatory and thoraco-abdominal pattern, operational volumes, and unassisted cough peak flow before and immediately after a single MI-E treatment.

We found no improvement effects on operational volumes or unassisted cough peak flow, only on breathing frequency. We do not think that our study provides misconceptions about the objective intended use of MI-E devices. It simply provides new and original insights. We have shown that, immediately after treatment, MI-E does not provide lung recruitment, does not affect thoraco-abdominal volume variations (and therefore respiratory muscle action and control), and does not improve unassisted cough peak flow and vital capacity. In contrast, the significant short-term effect is on breathing frequency, which remains significantly lower for 6.2 ± 1.8 min after MI-E treatment, which is a too short period to recommend MI-E to reverse rapid and shallow breathing patterns or to prefer MI-E over other, less expensive techniques. For this reason, we have not encouraged the use of MI-E to reduce breathing frequency and thereby improve dyspnea, and we have underlined in the discussion the need for further studies aimed to investigate the long-term effects of MI-E on breathing pattern.

In conclusion, we do not believe that our paper provides any "miscommunication," "doubtful clinical message," or improper recommendations of a preferred device. Actually, our study confirms that "there is no reason to use a MI-E device in stable DMD patients with not effective (as written by Toussaint et al) unassisted cough peak flow to specifically target lung volume recruitment." Conversely, we fully agree with Joshua Benditt, who observed that our study "supports the very important and growing notion that respiratory support for patients with neuromuscular weakness is much more than just a focus on the noninvasive ventilator and actually requires a holistic approach to ventilation, cough function, and maintenance of the mechanical properties of the lung and chest wall in a way that is as close to normal as possible."

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## Assessment of Peripheral Muscle Function in Cystic Fibrosis: Why and How?

There is a growing body of evidence, in people with cystic fibrosis, to support pe-