not measurable, but the clinicians felt the patient benefited from parental presence.

There were a small but real percentage of responses that expressed concern regarding difficulties in carrying out the procedure (4%), ability to teach (9%), or clinical decision making (5%) while the parent was present. This highlights the importance of having processes in place to address the concerns. These difficulties were more marked with increasing complexity of the procedure and during resuscitation. This reinforces the point of not providing such choices unless the clinician performing the procedure is willing for the parent to be present. It is these scenarios where the parent facilitators could potentially have a bigger role.

The patient population in the cohort was from the younger pediatric age group, and the authors acknowledge the limitation of feedback from the patient. The data do not cover all resuscitation scenarios, as parents were not surveyed if the resuscitation was unsuccessful. The work presented is from a single institution, and how it translates to other centers and different cultures is unknown as yet. The process outlined reports a culture of inclusivity of families and strong institutional ethos with champions to promote the cause. For other centers to follow on this model will need a heavy investment in training and education. However, this work can provide a template on which other institutions could implement their tailored program in relation to procedures.

Family presence during procedures and resuscitation requires guidelines and a structured approach to ensure success. Curley and colleagues have taken a step in the right direction. They have implemented an education intervention for staff and followed it with evaluating both the parent and the clinical team. The importance of having a designated staff member who has the skill set to emotionally support and continue to assess the parent, as well as to inform and educate, and even to “control” parental movement and behavior should not be underestimated in the success of such an intervention.

The clinicians’ ability to perform the procedure and exercise clinical decision-making skills is of paramount importance for the quality of care. This issue is also relevant when highly invasive, low-frequency procedures are performed at teaching institutions that are responsible for training clinicians. Having a policy in place assists in addressing these concerns.

The policy makers and planners have acknowledged shift from research for the researchers to research for the patient (8), and this article addresses this new focus of patient-centered intervention. Dr. Edward Trudeau’s aphorism “To cure sometimes, to relieve often, to comfort always” remains relevant two centuries later.

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Lipid Overload: Trigger or Consequence of Mitochondrial Oxidative Stress in Ventilator-induced Diaphragmatic Dysfunction?

Invasive mechanical ventilation (MV) is a life-saving measure applied to critically ill patients to achieve adequate pulmonary gas exchange and unload excessive respiratory muscle work. However, both animal (1) and recent human (2) studies have

demonstrated that complete diaphragm muscle unloading or inactivity during invasive MV induces a rapid and profound loss of diaphragm muscle force-generating capacity. In 2004, the loss of diaphragmatic force in the course of MV was termed ventilator-induced diaphragmatic dysfunction (VIDD) (3). In 2008, Levine and colleagues (4) demonstrated that VIDD occurs in critically ill patients and is characterized by marked diaphragm atrophy of both slow-twitch and fast-twitch fibers, with evidence of both oxidative stress and proteolysis. In several

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recent studies using animal models (5, 6), investigators have reported that redox disturbances in diaphragmatic fibers play a key role in VIDD. In particular, diaphragmatic inactivity promotes the production of reactive oxygen species (ROS) from the mitochondria, and importantly, the administration of mitochondrially targeted antioxidants protects against VIDD.

In this issue of the *Journal*, Picard and colleagues (pp. 1140–1149) provide a novel, in-depth study of the role of mitochondrial dysfunction in humans subjected to diaphragm inactivity during the course of invasive MV (7). They obtained diaphragmatic muscle fibers from brain-dead organ donors who had been mechanically ventilated for 15–176 hours and compared them with control patients who were mechanically ventilated for 2–3 hours during thoracotomy. They found that diaphragms from subjects receiving prolonged mechanical ventilation had reduced levels of respiratory chain enzymes and impaired mitochondrial biogenesis. These changes were associated with mitochondrial DNA deletions and decreased levels of peroxiredoxin-3, a mitochondrial scavenger of peroxides. These findings suggest that mitochondrial-generated oxidative stress plays a key role in the development of VIDD. What, then, is the trigger for mitochondrial-generated ROS production? The authors suggested a model of metabolic oversupply as the trigger for mitochondrial-generated ROS production. They hypothesized that in mechanically ventilated subjects, a state of energetic substrate oversupply develops in diaphragm muscle fibers when the workload is taken over by the ventilator. In support of this hypothesis, they showed excess lipid accumulation in the diaphragm muscle of mechanically ventilated subjects. They also found that two important proteins regulated by energy imbalances were down-regulated: AMPK and Sirtuin-1, both known to regulate mitochondrial metabolism and biogenesis (8). Based on these data, the authors suggest that MV induces a state of energy imbalance in the diaphragm that leads to lipid accumulation, increased mitochondrial oxidative stress, and decreased AMPK and Sirtuin activities, resulting in mitochondrial dysfunction and reduced mitochondrial biogenesis. However, this hypothesis was not supported by their murine model of lipid oversupply and mechanical ventilation, as they did not find a significant reduction in diaphragmatic force when compared with MV alone.

As a matter of fact, the relationship between lipid accumulation and mitochondrial dysfunction is controversial. In other models of lipid overload (e.g., models of insulin resistance in skeletal muscle), it has been postulated that mitochondrial abnormalities lead to the accumulation of ectopic lipids (9), in contrast to the hypothesis presented by Picard and coworkers, in which lipid accumulation seems to precede mitochondrial dysfunction in the animal model. Further limitations of the study include the lack of information with respect to body composition, the presence of metabolic syndrome, and the mode of mechanical ventilation. Similar to previous studies (2, 4), the subjects consisted of brain-dead organ donors—a population that differs from typical critically ill patients receiving prolonged MV in the intensive care unit. This poses the question of whether, in those patients, diaphragm muscle metabolism including redox balance and mitochondrial function might result from the loss of central nervous system input. Nevertheless, it must be acknowledged that biopsies from the diaphragm, the primary respiratory muscle, can only be obtained from brain-dead organ donors.

The findings by Picard and colleagues are clinically relevant, but they will require validation and further investigation before they can be translated to the care of critically ill patients receiving MV. Diaphragm muscle weakness due to mitochondrial dysfunction stimulated by energy oversupply might contribute to weaning failure, which if prolonged to more than 7 days, is

associated with an increased risk of death (10, 11). Further research will be required to assess whether the concept of lipid/energy oversupply is associated with other cellular mechanisms such as autophagy (12), apoptosis (13), and enhanced protein catabolism (4), which were shown to be major contributors to VIDD. Finally, new studies should also aim to shed light on whether scavengers of reactive oxygen species and antioxidants may offer novel therapeutic strategies to the critically ill patients with VIDD.

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From Olympians to Mere Mortals The Indiscriminate, Global Challenges of Air Pollution

Beijing won its bid to host the 2008 Olympics while promising to substantially improve its air quality, spending in excess of 10 billion dollars to implement pollution control measures (1). Based on substantial and growing evidence that air pollution impacts cardiac and respiratory health (2), Olympic athletes and the public were concerned that notoriously poor air quality in Beijing might have detrimental impacts on athletes. Even after substantive (13–60%) reductions in individual air pollutant concentrations during the 2008 Games as reported in this issue of the *Journal* (pp. 1150–1159) by Huang and colleagues (3), daily average levels of pollutants such as fine particulate matter in Beijing remained four to nine times higher than in large metropolitan cities in the United States during the same time period (4). Athletes remained concerned about potential health impacts, some deferred competing in the Games (5), and Olympic teams set up training camps away from Beijing to avoid intense air pollution exposures (6).

Over several years just prior to the 2008 Olympics, epidemiological studies reported that patterns of associations between fine particulate air pollution and cause-specific mortality were consistent with the hypothesis that air pollution exposure contributes to pulmonary and systemic oxidative stress, inflammation, and associated increased risk of atherosclerosis and ischemic cardiovascular and obstructive pulmonary diseases (2, 7). Recent reviews of the expanding literature (8) and emerging evidence from the Multi-Ethnic Study of Atherosclerosis (9) suggest that there are likely multiple, complex, interdependent mechanistic pathways linking air pollution to cardiopulmonary disease, but also provide growing evidence that pulmonary and systemic oxidative stress and inflammation play important roles.

Against this backdrop, in this issue of the *Journal*, Huang and coworkers (pp. 1150–1159) report results of a Beijing Olympics-based study investigating the relationship between air pollution and exhaled breath and urinary biomarkers of pulmonary and systemic oxidative stress and inflammation (3). This quasiexperimental study evaluated 125 young and healthy medical students before, during, and after the 2008 Beijing Olympics. Huang and colleagues demonstrated substantial decreases in these biomarkers tracking with reductions in air pollution, followed by subsequent increases in these biomarkers after return toward typical levels of air pollution in Beijing. These results add to previously reported evidence, from the same research team, that these Olympics-related changes in air pollution in Beijing were also associated with changes in systemic inflammation, thrombosis, blood pressure, and heart rate (10). Also, a third study using the Beijing Olympics-related changes in air pollution (with a focus on black carbon) found that the reductions in air pollution were also associated with exhaled nitric oxide, a biomarker of acute respiratory inflammation (11).

These studies have several important strengths. For example, Huang and colleagues (3) took advantage of the sharp reductions in pollutant levels achieved through intense restrictions on industrial

operations and traffic in the Beijing area during the Olympics, followed by a rapid return to usual practices and more typical pre-Olympic pollutant concentrations after the Games. The use of quasiexperimental design in this panel study to estimate the effect of air pollution on the outcomes reduces the potential for confounding by long-term trends in health. Such confounding by trends in both the health outcomes of interest and air pollution levels over time has been a common challenge in air pollution health effects research.

Furthermore, quasiexperimental studies of air pollution health effects are relatively unique, with a few notable exceptions. In the 1980s in Utah Valley, a labor dispute resulted in the intermittent operation of the local steel mill, the primary single source of air pollution in the valley, demonstrating significant associations between air pollution and hospital admissions for respiratory disease (12). A ban on coal sales in Dublin Ireland in 1990 resulted in an immediate and large reduction in particulate matter air pollution and corresponding significant reductions in respiratory and cardiovascular death rates (13). An initial analysis of the 1996 Atlanta Olympics took advantage of transiently reduced traffic levels and found some evidence of associations between changes in ozone and childhood asthma emergency room visits (14). However, compared with conditions in 2008 Beijing, the changes in air pollution were very small, and subsequent analyses were unable to disentangle the combined effects of meteorological conditions, reduced traffic, and intervention-related health effects (15). Related natural experiment studies also include studies of public smoking bans and evidence of related reductions in cardiovascular disease (16).

Randomized experimental designs (including controlled exposure human studies) conceptually may be ideal for understanding the underlying mechanisms of air pollution-induced cardiac and pulmonary disease in humans, but obvious practical and ethical concerns significantly limit who can be exposed and the duration and intensity of exposure in such studies. Quasiexperimental designs with high pollution variability, such as the study in this issue of the *Journal*, allow important mechanistic inferences to be made about longer-term exposures under “real-world” conditions.

Collectively, these recent Beijing Olympics studies lend support to the hypothesis that exposure to particulate matter induces inflammation and oxidative stress in the lungs and perhaps other tissues, which increases the tendency toward thrombosis and activates the sympathetic nervous system to increase the risk of cardiovascular death. These studies also suggest that even young and healthy individuals without pulmonary or cardiac disease may be susceptible to these effects of particulate matter, and provide additional promising novel biomarkers for investigating the mechanisms of air pollution-induced disease.

Although this study measured multiple pollutants in an effort to understand how individual components of the complex air