Furthermore, although ΔSVC measures were the most specific in predicting volume responsiveness they require transesophageal visualization, an approach not routinely available for repetitive measures and in nonintubated patients. Still, a continuously available minitransesophageal probe has been validated and may minimize this concern (10). So, do we really have to choose between intermittent and continuous measures? Can't we have both?

Second, different derived parameters assess right- and left-sided reserve more specifically. ΔSVC and ΔIVC assess right ventricular preload reserve, because if the right ventricle is overloaded and unable to increase flow, then volume will "back up" in the venae cavae such that they will not display collapse during positive-pressure breathing. Because venous return is the primary driving force for cardiac output, it is not surprising that ΔSVC is a more specific threshold parameter predicting volume responsiveness. In contrast, left-sided measures of $\Delta Vmax_{Ao}$, stroke volume, and pulse pressure variation require both right- and left-sided reserve, which can have their variations dampened by pulmonary vascular capacitance and arterial input impedance. Thus it is not surprising that $\Delta Vmax_{Ao}$ is more sensitive in predicting who will respond to fluids. So, do we really have to choose between right-sided ΔSVC or ΔIVC and left-sided $\Delta Vmax_{Ao}$ or pulse pressure variation measures? Can't we have both?

In the end, we are presented with an embarrassment of riches regarding monitoring tools to define volume responsiveness across large numbers of patient groups. Three take-home points can be made. First, critical care physicians need to be trained in point-of-care echocardiography and routinely use the derived hemodynamic parameters to improve the precision of their diagnoses and treatment decisions. Second, these point-of care measures should be coupled to continuous measure of volume responsiveness and vasomotor tone so as to personalize fluid and vasoactive drug therapy as the patient evolves over time. And third, these bedside tools are only as good as the craftsman who uses them. All these measures are useful in the management of acute circulatory shock only if they are coupled to a management regimen of proven efficacy, targeting restoration of tissue blood flow in a timely manner while avoiding volume overload, thus providing truly personalized precision resuscitation. ■

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The Canary in the Coal Mine Is Coughing: Electronic Cigarettes and Respiratory Symptoms in Adolescents

Since the introduction of electronic cigarettes (e-cigarettes) in the United States a decade ago, use of these devices has increased substantially. From 2010 to 2013, the prevalence of current e-cigarette use increased from 0.3 to 6.8%, with the highest prevalence (14.2%) in young adults aged 18 to 24 years (1). Perhaps most concerning is the increased use among adolescents. E-cigarettes are now the most popular tobacco product among both high school and middle school students, with a prevalence of 16 and 5.3%, respectively (2). Many e-cigarette users and some health care providers believe that e-cigarettes are safer than conventional cigarettes (3, 4), prompting some public health organizations, such as Public Health England, to strongly support the use of e-cigarettes as a harm reduction tool, despite a relative lack of data on their safety.

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Notably, although studies of the harms of e-cigarettes are limited, early reports suggest that e-cigarettes are not harmless. Cell-based and animal studies have shown that e-cigarettes are associated with a number of toxicities, including increased inflammation and oxidative stress in the lung (5, 6), endothelial dysfunction (7), and impaired pulmonary immunity (8–10). Human studies have similarly suggested that e-cigarettes may impair immunity (11), negatively affect vascular function (12), and increase peripheral airway resistance (13). Additional human studies, particularly those focusing on clinically relevant outcomes, are needed to better characterize the health effects of e-cigarettes to accurately inform regulatory bodies and public perception of these products.

In this issue of the *Journal*, McConnell and colleagues (pp. 1043–1049) report their analysis of the relationship between e-cigarette use and respiratory symptoms in the Southern California Children's Health Study (14). Children in kindergarten or first grade from 12 communities in southern California were initially enrolled in this prospective cohort from 2002 to 2003 and followed with questionnaires yearly until 2008 and every other year thereafter. The questionnaires assessed a variety of topics, including sociodemographic information, tobacco product usage, and clinical symptoms. The 2014 questionnaire was the first to assess e-cigarette use and is the focus of this report, with 2,086 subjects providing information on both e-cigarette use and respiratory symptoms, including wheezing and bronchitis. Bronchitic symptoms were defined as self-report of cough for 3 months in a row, congestion or phlegm other than when accompanied by a cold, or bronchitis in the past 12 months.

The authors found that current and past e-cigarette use were both associated with increased odds of bronchitic symptoms, both in unadjusted analyses and in a multivariable model adjusting for sociodemographic characteristics. The risk of bronchitic symptoms increased with frequency of e-cigarette usage over the prior 30 days. Notably, after additional adjustment for lifetime cigarette usage and secondhand smoke exposure, these associations were attenuated, although past e-cigarette use remained significantly associated with bronchitic symptoms. A sensitivity analysis restricted to never smokers showed similar odds of bronchitic symptoms related to past and current e-cigarette use as the overall cohort, after adjustment for sociodemographic factors and secondhand smoke exposure. These findings echo results from a cross-sectional study of Chinese adolescents, which reported an association between respiratory symptoms and e-cigarette use (15).

This study has several strengths that make it a significant addition to the small but rapidly growing body of literature on the potential harms of e-cigarettes. First, this study assesses a large population of adolescents, in whom e-cigarette use is increasing rapidly. Notably, nearly half of current or past e-cigarette users in this study were never smokers, emphasizing the concern that this age group may be particularly vulnerable to trying these products. Furthermore, although e-cigarette use was only assessed in the 2014 survey, subjects had been followed over many years, allowing for a thorough evaluation of potential confounders in multivariate models. The inclusion of sensitivity analyses adjusting for bronchitic symptoms reported in previous questionnaires makes it more likely that the newly reported symptoms are related to e-cigarette use.

Although this study represents an important contribution to the literature on the potential harms of e-cigarettes, areas of uncertainty remain. First, this study was based on self-report, and the symptoms described are fairly nonspecific. Future human studies will need more objective and detailed quantification of the effects of e-cigarettes on lung physiology, biology, and pathology.

Second, given the heterogeneity in e-cigarette devices and products, it remains unclear whether particular device types, usage patterns, or flavors are more likely to produce harm. Future studies in both animal models and humans need to assess e-cigarette device components, usage patterns, and flavors to address critical gaps in our understanding of these relatively new products, particularly in light of the Food and Drug Administration's recently asserted regulatory authority over product and device characteristics.

Third, as illustrated by this study, studies of e-cigarettes must account for potential confounding effects of conventional cigarettes, given the high prevalence of dual use. In this study, inclusion of lifetime cigarettes smoked and secondhand smoke exposure in multivariate models significantly attenuated associations between e-cigarette usage and respiratory symptoms. Although the authors did assess for exposure to cigarette smoke, passive smoking by self-report is relatively crude, may miss biologically significant lower levels of exposure, and is prone to recall bias (16). The inclusion of biomarkers of conventional cigarette exposure in future studies may be helpful, particularly in accounting for passive smoke exposure.

Last, although beyond the scope of the study at hand, it will be critical to assess how e-cigarette use compares to and affects the risk of using other tobacco products with known harms. Some studies have suggested that e-cigarettes may increase the risk of conventional cigarette or cigar use in adolescents (17, 18), and initial hopes that they would be highly effective for smoking cessation have not been borne out (19). If e-cigarettes are ultimately found to increase nicotine addiction and/or promote use of combustible tobacco products, they may prove more harmful than isolated studies of their physiologic toxicities suggest. We also need additional studies directly comparing the physiologic and biologic toxicities of e-cigarettes to those of combustible tobacco products, to fully compare the risks of these devices to any potential benefit via harm reduction.

It has taken decades to understand much of the harm caused by conventional cigarettes and years to reshape public perceptions of these harms. With lessons learned from the tobacco epidemic, we should be able to expedite our investigations of e-cigarettes, with a focus on their potential toxicities as well as their impact on addiction and use of combustible tobacco products. Regarding toxicity specifically, the scientific community should prioritize the evaluation of e-cigarettes through human studies as well as laboratory models, using endpoints that reflect both short-term toxicity and potential long-term harms, to ultimately improve our understanding of these increasingly popular devices and to inform regulation. ■

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The Evolving Role of the Indwelling Tunneled Pleural Catheter
A Means to an End

Malignant pleural effusions portend a poor prognosis and lead to symptoms such as dyspnea, cough, chest pain, and fatigue (1). Palliation is critical to optimize the quality of life and candidacy for further treatment for these patients. For many years, chemical or mechanical pleurodesis was the dominant modality by which palliative control of a recurrent symptomatic malignant pleural effusion could be achieved. Many different types of sclerosants and delivery systems have been tried, with talc slurry or poudrage remaining most popular, because of high efficiency and low cost (2, 3). For many patients, chemical pleurodesis is associated with significant pain and hospitalization time. When successful, pleurodesis is able to control fluid accumulation without the added patient or family responsibility for ongoing management. However, for a subset of patients, especially those with lung entrapment, pleurodesis is not likely to be successful and, for the most part, is avoided.

With the advent of the indwelling tunneled pleural catheter (IPC), clinicians were provided with another viable, minimally invasive option. After several reports described effective outpatient management of malignant effusions with an indwelling pleural catheter (4–6), the U.S. Food and Drug Administration granted marketing approval to Denver Biomaterials (Denver, CO) for its