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EDITORIAL COMMENT

Air Pollution and Repolarization Heterogeneity

More Impetus for Alternative Energy*

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Air pollution is associated with increased all-cause and cardiac mortality, in particular, concentrated ambient particles measuring <2.5 μm in aerodynamic diameter ($PM_{2.5}$) (1,2). Although the Environmental Protection Agency in 2006 tightened the National Ambient Air Quality Standards for acceptable levels of $PM_{2.5}$, multiple U.S. counties are not in accordance with EPA limits (2). The major source of these concentrated ambient particles (CAP) is the combustion of fossil fuels from industry, traffic, and power generation. A recent scientific statement from the American Heart Association concludes that there is "evidence for a causal relationship between $PM_{2.5}$ and cardiovascular morbidity and mortality" (2).

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Epidemiological studies and studies in patients with implantable cardioverter-defibrillators (ICDs) also suggest that arrhythmic mortality and nonfatal arrhythmias increase with increasing levels of air pollution, although the data are less consistent than for general cardiovascular mortality. In an Indianapolis study, witnessed out-of-hospital cardiac arrests increased by 12% for every 10-$\mu g/m^3$ increase in $PM_{2.5}$ (3). In a similar study in Rome, the greatest impact of air pollution on out-of-hospital cardiac death was seen in those older than 65 years of age (4). A Seattle-based study, however, failed to find an association between particulate matter and sudden cardiac arrest in the population or in any subgroup (5).

Findings of studies of patients with ICDs are mixed but predominantly confirm associations of arrhythmia with air pollution. Studies from Boston (6), St. Louis (7), and Germany (8) have shown increased likelihood of ventricular arrhythmias in the 2 h after exposure to higher levels of particulate matter. Although studies from Vancouver (9), Atlanta (10), and London (11) have not shown associations between ICD-treated arrhythmias and ambient pollution, this may be due to lower levels of air pollution (9) or differences in methodology (such as correlation with calendar days rather than shorter or rolling periods, and/or inclusion of inappropriate shocks).

The pathophysiological links by which exposure to particulate matter may increase arrhythmogenesis remain poorly described. In this issue of the *Journal*, Sivagangabalan et al. (12) advance our understanding of the mechanisms of air pollution–triggered arrhythmia, using a controlled inhalation experiment to examine the effects of CAP on measures of repolarization heterogeneity in 25 healthy volunteers. In this carefully designed study, each individual underwent 4 exposures: CAP, ozone, CAP + ozone, and a filtered-air control, in randomized order on separate days, with 12-lead electrocardiogram at the beginning and end of each exposure analyzed for measures of dispersion of repolarization, T-wave peak to end (Tp-e), and QT dispersion (QTd), and continuous ambulatory electrocardiogram analyzed for heart rate variability in the frequency domain. Although repolarization measures increased with all exposures (as did heart rate), their primary finding is that the combined exposure to CAP + ozone, a common combination of air pollutants, increased both Tp-e and QTd significantly more than did the filtered air control exposure. These findings suggest that air pollution may trigger ventricular arrhythmias via increases in repolarization heterogeneity, long known to be arrhythmogenic (13). One previous study evaluated the effects of daily-monitored $PM_{2.5}$ on multiple parameters of repolarization in ambulatory elderly individuals and found only a nonsignificant widening of the T-wave width, another measure of dispersion of repolarization (14). The authors hypothesized that daily variations of repolarization due to changes in, for example, physical activity and heart rate, may have outweighed any changes due to air pollution, underscoring the importance of controlled inhalation experiments such as that reported here, in understanding the physiological effects of air pollution.

The current study (12) further expands our understanding of the mechanisms of air pollution–triggered arrhythmias with the finding that changes in dispersion of repolarization were associated with changes in heart rate variability, with the strongest association seen with LF/HF (low frequency to high frequency) ratio, suggesting that the electrophysiological changes seen may be mediated in part by autonomic changes. Although the use of LF/HF as a marker for sympathetic-parasympathetic balance has been questioned (15), there were also less significant (inverse) associations with HF, a well-accepted marker for parasympathetic activity. It is certainly plausible that sympathetic changes induced by particle inhalation could alter repolarization heterogeneity. Other studies have also shown autonomic effects of inhalation exposures. In animal models, changes in heart rate and QT interval with inhalation exposure are

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blocked by the administration of pulmonary autonomic receptor antagonists (16). Some studies have shown that experimental exposure to inhaled pollutants decreases heart rate variability (17) , although others have shown a delayed decrease (18) or an increase in measures of vagal activity (19). Further, stress-induced increases in catecholamines similarly induce repolarization heterogeneity beyond effects of heart rate (20).

Although exciting, these findings should be considered hypothesis generating. The increases in mortality and arrhythmia due to air pollution predominantly occur in those with underlying heart disease (21), and whether these findings in normal volunteers can be extrapolated to those populations is unknown. It is likely, however, that structural abnormalities leading to baseline repolarization heterogeneity would magnify the effects seen.

Also, neither the physiological underpinnings nor the clinical implications of the 2 measured markers of repolarization are well delineated. In a left ventricular wedge preparation, the end of the T-wave corresponds to full repolarization of the action potential of mid-myocardial M cells and the peak of the T-wave to the terminal portion of the action potential of epicardial cells, suggesting Tp-e reflects transmural dispersion of repolarization (22). However, both in vivo (23) and mathematical (24) models have found that Tp-e does not reflect transmural, but rather regional dispersion of repolarization. QT dispersion, although more widely used to date than Tp-e, has not been shown mathematically (25) or experimentally (26) to correlate with directly measured dispersion of repolarization, although it may reflect other repolarization abnormalities (27).

The clinical implications of Tp-e and QTd are also in the investigative phase. Small studies have suggested that prolonged Tp-e may be associated with future ventricular arrhythmias in patients undergoing electrophysiology studies (28) and those with bradycardia (29), although other studies in cardiovascular disease populations have shown no difference (30) or a shorter Tp-e (31) in those with an adverse outcome than in survivors. Similarly, although some studies have shown QTd to predict cardiovascular mortality in population studies (32), other studies have not (30,33).

In conclusion, this study adds significantly to our understanding of the pathophysiological links between air pollution and ventricular arrhythmias and sudden death. Future studies can focus further on populations at risk as well as other indexes of repolarization heterogeneity to confirm these mechanistic pathways.

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