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The Environmental Epidemiology of Atrial Arrhythmogenesis: A Research Agenda

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia seen in clinical practice and as a potent risk factor for heart failure and stroke, it makes an important contribution to cardiovascular disease (CVD) and all-cause mortality. Its large and increasing population burden has prompted a recent shift in the focus of AF research, from that concentrating on its treatments and complications, to the evaluation of its putative risk factors including ambient air pollution, the topic of this review. Although the review pertains specifically to AF, much of its content is drawn from and therefore applicable to the study of other arrhythmias, the conduct of which is confronted by many of the same challenges. Meeting these challenges involves recognizing the collective importance of 1) large, ethnically and geographically diverse, clinically well-characterized populations; 2) methods for reducing uncertainty in outcome ascertainment, distinguishing effects of pervasive environmental exposures, and improving their estimation; 3) approaches to evaluation of susceptibility; as well as 4) strategies for informing regulatory policies designed to help control population-level risks for CVD.

Keywords

Air Pollution; Epidemiology; Electrocardiography; Arrhythmia; Atrial Fibrillation

State of the Science

Atrial fibrillation is a common cardiac arrhythmia in which disorganized electrical impulses in the atria or pulmonary veins overwhelm those in the sinoatrial node, leading to chaotic and continuous electrical activity of the atria, loss of rate control, and an irregularly irregular pulse. Available estimates suggest that approximately four percent of U.S. adults aged sixty

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or more years have been diagnosed with this disease [1] and similar estimates have been reported in European populations [2, 3]. However, the prevalence of AF is likely to be much higher, reflecting the large proportion of cases that are either intermittent, asymptomatic, or undetected by the resting, supine, standard twelve-lead electrocardiogram (ECG), an insensitive clinical tool often used in initial attempts to diagnose it [4]. Despite being common, clinical and sub-clinical forms of AF are associated with reduced cardiac performance, functional status and quality of life. Moreover, the arrhythmia accounts for fifteen percent of ischemic strokes [5], is a potent risk factor for heart failure [6], and thereby contributes to both the burden of cardiovascular disease (CVD) and all-cause mortality [5].

The majority of AF research to date has focused on treatments for and complications of this disease [7]. Although several AF risk factors have been described (including age; male sex; race; family history[8, 9]; single nucleotide polymorphisms on chromosomes 1q21, 4q25 and 16q22 [7, 10-13]; myocardial infarction; valvular heart disease; hyperthyroidism; hypertension; diabetes; obesity; and smoking), AF prevention has been studied much less extensively despite projections suggesting that the prevalence will increase 2.5-fold by 2050 [1]. Indeed, the cumulative risk of incident AF at age 80 is 19% in whites and 11% in African-Americans, a paradox inconsistent with the relative preponderance of AF risk factors in the latter race group, but one also observed in other contexts [14]. Research focused on AF prevention, including the identification of modifiable, pervasive risk factors that have potential to help elucidate and eliminate these disparities, is therefore needed [7].

Ambient air pollution exposure is an established cardiovascular disease risk factor [15, 16] that may trigger AF paroxysms via direct and / or indirect effects on the atrial myocardium. Direct effects may be due to the actions on membrane ion currents of inhaled particles hematogenously translocated from the lungs to the atria and pulmonary veins [17-19]. Indeed, the chemical components of ambient particulate matter (PM) air pollution include noxious fossil fuel combustion species, as well as non-metallic and metallic cations capable of affecting how sodium, potassium, calcium, and magnesium are transported by channel proteins that maintain resting trans-membrane voltages critical to the generation and conduction of action potentials in the atrial myocardium [20]. Indirect effects may depend on autonomic, inflammatory and / or ischemic mechanisms [7]. Such initiating mechanisms may include 1) reflexive responses of the cardiac autonomic nervous system to particulate activation of chemosensitive pulmonary afferents; 2) stimulus-evoked production and release of inflammatory cytokines from pulmonary macrophages, epithelial cells, and fibroblasts; or 3) inhibition of endogenous fibrinolytic capacity, subclinical coronary thrombosis and ischemia, as suggested by experimental, clinical and epidemiologic evidence [21-26].

Although several studies have examined how mass concentrations of PM less than 2.5 and 10 μm in aerodynamic diameter ($PM_{2.5}$; PM_{10}) affect atrial and ventricular arrhythmogenesis [16, 27-39], relatively few have done so in large, multi-city, racially diverse, gender-balanced populations without implantable cardioverter-defibrillators (ICDs) [40], and to our knowledge, none have evaluated the association between exposures to PM chemical components and AF or interval-scale, i.e. “continuous” ECG measures that have been associated with incident AF (PR interval; P wave duration, amplitude, area, terminal

force) [4]. It therefore remains unclear whether air pollution-AF associations observed in small, geographically homogeneous, majority-male, CVD-burdened convenience samples are generalizable to other populations. It also remains unclear how the associations vary by subpopulation characteristics. Moreover, how reliance on unvalidated arrhythmic causes of death, assignment of air pollution exposures with little consideration of exposure measurement error, and failure to assess effects of multiple co-pollutants influences the validity of extant inferences regarding air pollution-AF associations is unknown.

A Research Agenda

Research addressing these criticisms is therefore a priority. Ancillary studies of previously well-characterized populations provide resource-efficient opportunities for such research, especially those that have or will be undertaking systematic collection of 24-48 hour Holter ECGs using standardized protocols or central adjudication of in- and outpatient AF by trained and certified physician reviewers. These strategies represent substantial improvements over ascertainment of AF using standard 10-second ECGs, unvalidated self-reports, hospital discharge diagnoses, and death certificates with no concomitant effort dedicated to distinguishing between AF as an immediate, contributing or underlying cause of heart failure and stroke deaths.

Although physician adjudication and Holter electrocardiography will improve AF ascertainment, others have argued that paroxysmal arrhythmias frequent enough to be captured by insensitive, but highly specific, short recordings may carry more prognostic significance than those so infrequent that they require long recordings to capture them [40]. In addition, potential for bias in air pollution-AF associations related to diagnostic insensitivity will not be completely eliminated by longer ECG recordings. Several forms of exposure measurement error—one of which is associated with the use of geocoded residential addresses—may well compound such biases. Indeed, the ability to reliably and accurately link residential addresses with spatial coordinates and statistical tabulation areas using geographic information systems software may be critically important because geocoding error has the potential to distort downstream interpolation of residence-specific ambient pollution exposures and definition of socioeconomic contexts within which pollution exposures occur. These distortions may, in turn, lead to biased estimates of association and contextual effect modification [41, 42].

An additional, and in this setting, arguably more important form of exposure measurement error is related to the use of ambient concentrations as surrogates for personal exposure. The potential importance of this uncertainty is underscored by evidence of the so-called “personal cloud”; findings that ambient, residential-outdoor, and personal PM exposures appear to be more weakly correlated than originally suspected; and that characteristics of participants, studies and the environments in which they are conducted may affect the accuracy of this proxy [43-45]. Use of spatially interpolated, residence-specific ambient pollution concentrations as proxies for monitored exposures is also associated with other forms of measurement error, one example of which can be estimated via Kriging—a spatial interpolation method that predicts exposures and their prediction variances at unmonitored

residential locations [46]. A related form of uncertainty is that due to correlation between co-pollutants and PM chemical components measured with error.

A unified statistical framework that can effectively extend conceptually simple analyses by incorporating the effect of diagnostic insensitivity as well as correlated exposures and measurement errors is therefore needed [47, 48]. A fully Bayesian hierarchical framework in which site-specific regression parameters are represented as random effects with prior distributions reflecting anticipated variation among sites meets this need [49]. The advantage of this framework is that uncertainty in exposure measurements can be represented within it by prior distributions derived from the above-referenced participant address geocoding analyses, kriging analyses, and random-effects meta-analyses of the bivariate association between personal and ambient pollution concentrations [41-44, 46]. Additional sources of uncertainty—namely those associated with co-pollutants and PM chemical components—can be incorporated in a similar manner.

Modeling efforts of this nature would be misleading if factors associated with the ambient-personal correlation were to differ substantially among participants and the studies in which they are enrolled. They also would be of questionable utility if the studies on which they are based were unable to provide the spatiotemporal variation in exposures absent in available cross-sectional examinations of single-city populations. Future studies would therefore benefit from being geographically diverse, longitudinally designed, and open to trans-disciplinary, cross-study collaboration, the facilitation of which is a goal of e.g. the PhenX Project [50]. Future studies would also benefit from being gender, race and health inclusive such that comparisons of air pollution-AF associations across subpopulations are possible. This is an especially important issue from the regulatory perspective, which is concerned with the identification of subpopulations susceptible to the adverse effects of ambient air pollution so that population-wide pollution control strategies with an adequate margin of safety can be devised, regardless of whether susceptibility is acquired or innate [51, 52].

To this end, availability of single nucleotide polymorphisms typed on genome-wide arrays would allow researchers to investigate interactions between relevant, but previously unconsidered genetic and environmental exposures in studies of AF and its ECG predictors. The value of such studies is usually viewed in terms of their promise for improved understanding of pathophysiological mechanisms underlying genetic and environmental susceptibility—insight that has not been provided by published genome-wide association studies of AF [10-13]. However, this view overlooks the potential public health and regulatory importance of gene-environment interactions in the study of air pollution-AF associations [53]. The size of genetically susceptible populations as well as the likelihood and severity of the adverse PM effects they experience are both pertinent in this regard.

To further increase their pertinence and regulatory utility, effects of population-wide reductions in air pollution concentrations on AF can be estimated using epidemiologic measures of population burden. Such measures might include expected proportional changes in the exposure-weighted relative risks associated with shifts in exposure distributions accompanying a range of potential changes in regulatory standards and numbers of participants with exposures above a given regulatory standard among whom one excess case

of AF can be attributed to exposure [54, 55]. Collectively, the measures would be capable of providing quantitative insight into the proportion of exposure-attributable AF that could be reduced by establishing and complying with stricter standards.

Summary

Studies examining the environmental epidemiology of atrial arrhythmogenesis have begun to provide insight into the epidemiology of atrial fibrillation. However, a research agenda focused on reducing uncertainty in outcomes and exposures; distinguishing effects of pervasive and correlated environmental exposures; evaluating susceptibility factors in subpopulations defined by sociodemographic, clinical and genetic characteristics; and informing regulatory policies in large, ethnically and geographically diverse, clinically well-characterized populations is needed. These investments have the capacity to increase our understanding of the pathophysiological mechanisms underlying atrial fibrillation and its clinical sequelae, inform environmental policy, and in doing so, improve public health.

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