MAYO CLINIC

Environmental Factors Impact Clinical Outcomes in Atrial Fibrillation

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ATRIAL FIBRILLATION AS A WORLDWIDE EPIDEMIC

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the world with a lifetime risk of 26% for men and 23% for women. The global prevalence was estimated at 20.9 million males and 12.6 million females in 2010, with as many as 4.7 million total new cases per year.[1] AF carries significant comorbidities such as stroke, leading to over 467,000 hospitalizations and over 99,000 deaths per year in the US.[2] AF has repeatedly been shown to be associated with poorer quality of life.[3] The underlying mechanisms of AF are extremely complex with an integral part involving a systemic inflammatory syndrome.[4] This has led to interest in examining and intervening on traditional risk factors, such as obesity, obstructive sleep apnea, hypertension, and diabetes mellitus as modifiable targets in AF.[5] Our understanding of this syndromic disease remains incomplete, and further examination of additional risk factors and their influence on AF is paramount to improving therapies and outcomes.

ENVIRONMENTAL FACTORS AND POSSIBLE LINK TO AF

Environmental factors are well-established in playing a role in an assortment of chronic diseases, in particular cardiovascular disease (CVD). An estimated 21% of all cardiovascular-related mortality worldwide is thought to be correlated to various forms of pollution.[6] Air pollution, specifically particulate matter (PM), has been linked to myocardial infarction, congestive heart failure, hypertension, and arrhythmias. Beyond CVD, causal associations exist between PM and chronic diseases such as chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), and increased oxidative stress.[6] While these associations are not fully understood, emerging theories suggest that increased exposure to PM can lead to increased inflammation. Thus, as a trigger of inflammation, increased PM may incite or exacerbate AF.

Several environmental factors drive outcomes in CVD, including air temperature and its seasonal fluctuation. Seasonal variation correlates with cardiovascular outcomes such as mortality, with a peak occurrence in winter months as compared with summer. This is consistent irrespective of which hemisphere patients live in.[7] Colder temperatures have been suggested to have an impact on microvascular function, vasospasm, and vascular resistance, with resultant strain on the cardiovascular system. Interestingly, both human and animal studies have suggested that lipoprotein metabolism may be altered by seasonal change.[7] Despite these observations, the underlying mechanism of seasonal variation remains incompletely defined, and another theory is that sunlight and vitamin D levels may play a role.[7]

PARTICULATE MATTER AND AIR TEMPERATURE: EFFECT ON OUTCOMES IN AF PATIENTS

The work by Rivera-Caravaca *et al* in this issue of *Mayo Clinic Proceedings* enhances our understanding of contributors to AF and adds to the paradigm that certain aspects of patients' environments, in particular air pollution and temperature, may contribute to worse outcomes.[8] The authors studied a well-defined and robust cohort of 1361 consecutive AF patients with long-term follow up from a single tertiary hospital center in Spain. The investigators only included patients who were already on vitamin K antagonist (VKA) therapy and exhibited stable, therapeutic INR levels for further study. Clinically relevant outcomes included ischemic stroke, major bleeds, adverse cardiovascular events, and mortality.

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These outcomes were stratified in the context of ambient air temperature and PM_{10} (PM with aerodynamic diameter <10 μm). This was meticulously studied and involved the use of data derived from local weather stations and an air pollution monitoring center responsible for recording these measurements. The environmental data used were collected and verified by the local government. Patients were followed with personal interviews during routine presentation to the anticoagulation clinic and through chart review. Impressively, not a single patient was lost to follow-up.

Multi-variable Cox regression analyses were performed to delineate the impact of temperature and PM_{10} on the pre-stated outcomes. The main findings of the study were striking, noting that a high ambient PM_{10} was associated with an increased risk of ischemic stroke (aHR 1.64, 95% CI, 1.28 to 2.09). In fact, patients suffering an ischemic stroke had a higher median exposure to PM_{10} levels (29.3 $\mu g/m^3$) compared with those who did not (27.2 $\mu g/m^3$, P=.001). Second, lower air temperature was associated with an increase in cardiovascular events (aHR 1.06, 95% CI, 1.03 to 1.1). This relationship held across seasons with the highest number of events occurring in winter months (coldest on average) and the lowest number of events occurring in summer months (warmest on average). Third, both high PM_{10} and low temperature were associated with major bleeding (aHR 1.44 and aHR 1.03, respectively) and mortality (aHR 1.50 and aHR 1.04, respectively). These findings remained consistent, even when factoring in CHA_2DS_2-VASc and HAS-BLED scores. It should be noted that the authors did not investigate repeated events. However, one could speculate that this makes these data all the more intriguing, as the HRs would likely have been much higher.

PARTICULATE MATTER AND AIR TEMPERATURE: BIOLOGIC PLAUSIBILITY AND BIOLOGICAL VARIATIONS

These findings are plausible in the context of previous research and add to the growing literature surrounding the impact of pollution on CVD. Prior studies have implicated fine PM (defined by an aerodynamic diameter 1.0-2.5 μm) in accelerating or exacerbating CVD through a multitude of mediators, including endothelial dysfunction, inflammation, and pro-thrombotic pathways.[9] While only PM_{10} levels were available to the researchers, it is reasonable to expect similar effects could lead to increased risk of ischemic stroke in the AF population. To put the levels seen into context, the mean PM_{10} level of around 30 $\mu g/m^3$ experienced by this patient population during winter months (highest level during this study) was well below the European recommended annual safety standards (<40 $\mu g/m^3$); however, this was also well below the average levels seen in many parts of Asia. Regardless, what remains unclear is how comorbid conditions, such as COPD or DM, and the impact of PM_{10} levels on their disease control might impact AF outcomes. For example, increased PM may lead to COPD exacerbations. Also, dietary habits in the setting of seasonal changes may lead to fluctuations in blood sugar levels and thus DM control may have been sub-optimal.

The general association of low temperature and cardiovascular events is consistent with prior data. In the region of Spain where this population resided, the average daily high temperature ranges from around 34°C (94°F) in the hottest months to 17°C (63°F) in the coldest. Compared with many parts of the world, this range is relatively modest. Furthermore, it is unknown how even colder average temperatures might influence outcomes, which might limit extrapolation. Additionally, previous studies have shown that heat waves or large fluctuations in daily temperature were associated with adverse outcomes.[7] Thus, a more granular analysis looking at day-to-day variation and outcomes may not exhibit similar findings as seen in this cohort, but find clusters of correlations. Given the observational nature of the study, there could be multiple confounders to the seasonal variation of outcomes, including not only sunlight and Vitamin D levels, but also activity level or even exposure to outside temperatures. One could imagine that during the winter

months, patients are likely more sedentary, with attendant increased dietary consumption and weight gain.

EXTRAPOLATION TO THE CLINICAL ARENA FOR AF PATIENTS

Overall, these data support the notion that AF endpoints are impacted by more than what clinicians traditionally try to modify in order to reduce patients' risk. However, there are still several limitations and difficulties in attempting to extrapolate these findings to routine patient care. First, all patients were on vitamin K antagonists. Since the advent of direct oral anticoagulants (DOAC), given the efficacy, safety profiles, and ease of use compared with VKA, there has been a significant shift towards use of these agents. Whether the results would be similar in the setting of DOACs remains to be seen. Second, how should we risk stratify and counsel patients? Given the fluctuation of PM and air temperature, it is hard to incorporate these risks in the traditional point-based scoring systems. Third, socioeconomic factors will undoubtedly play a role in how we counsel patients. Do we advise those who might be thought of as particularly high risk to avoid high air pollution areas or colder temperatures, with recommendations of moving to a different area or climate? Should these patients stay inside during winter months or wear masks when traveling to cities with high PM levels?

The authors should be congratulated on a well-done and welcome addition to the AF literature. We hope future consideration will be given to performing similar study in different parts of the world with varied environmental factors to see if these results can be replicated. Such future studies would be informative given the strong use of DOACs and ubiquity of AF.

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