Solar UV Radiation: A Potential Modifiable Risk Factor for Hypertension

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Increased blood pressure (BP) is one of the leading risk factors for cardiovascular morbidity and mortality worldwide, eclipsing smoking and alcohol, with the lowest risk associated with a usual systolic BP (SBP) between 110 and 115 mm Hg, well within the normotensive range.[1] BP is regulated by a myriad of endogenous (eg, neural, cardiac, and endocrine) and exogenous (eg, diet and exercise) factors that can adversely serve to lead to hypertension and excess cardiovascular risk. Currently, treatment strategies to reduce BP and subsequent cardiovascular risk are underpinned by various pharmacological approaches. However, despite the availability of numerous antihypertensive agents (and easy availability of their cheap generic versions), BP control at population level seems to be elusive, even in the resource-rich western world.[2] On the other hand, public health strategies promoting diet and exercise to prevent and manage hypertension have not shown desired results either; almost all guidelines emphasize lifestyle modifications, particularly dietary and exercise-based interventions, in conjunction with antihypertensive agents.[3]

This focus on dietary and exercise-type advice is in part because of the relative ease with which these 2 interventions are amenable to design and conduct of clinical trials, although there are clearly challenges to such trials, such as blinding and adherence to intervention. However, there are protean environmental factors associated with increased BP that *may* also be amenable to modification through population strategies to lower excessive cardiovascular risk related to BP, including ambient noise and atmospheric pollution, among others.[4]

Further atmospheric conditions (namely, ambient air temperature) have long been known to be associated with seasonal variation in usual BP[5] that constitutes one of the long-term patterns of BP variability, both measured in the office and out of office.[6] The mechanisms relating to these seasonal associations of BP and ambient temperature have been proposed to include cold-induced sympathetic-induced vasoconstriction and renin-angiotensin-aldosterone system activation,[7] among others. However, interpretation of epidemiological data is confounded by daily sunlight (ie, there are longer daytime solar hours in summer). This therefore invokes the possibility that it is solar exposure rather than (or more likely, in synergy with) ambient temperature that is mechanistically important for BP regulation. Indeed, for much of the past 20 years, extensive research has been performed to determine whether vitamin D, which is produced in the skin in response to solar radiation exposure, is important in BP regulation. Large observational studies have shown that low vitamin D levels are a risk factor for hypertension,[8] although conversely meta-analysis of numerous vitamin D intervention trials has shown no overall benefit on BP.[9]

To date, no large data set combined solar radiation exposure and ambient temperature to tease out the relative importance of one or other of these mechanisms for BP regulation. In this issue of the *Journal of the American Heart Association* (*JAHA*), Weller and colleagues[10] have used an extremely large data set of 340 000 patients from >2000 hemodialysis centers in the United States, covering extremely different geographies and environmental conditions, with >45 million predialysis BP records. They used 2-stage analysis: mixed effect model for repeated measures at each center level and combining these individual center-level records using random-effects meta-analysis models, to evaluate the relative importance of UV light exposure and daily average temperature at the locality of each center.[10]

The major finding of the study is that UV radiation intensity is inversely related to predialysis SBP independent of ambient temperature, although there appeared to be an interaction

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between the 2 environmental factors, especially for patients with self-identified *white* ethnicity. The authors postulate that the mechanism of BP lowering may be caused by UV-induced mobilization of constituents of the noncanonical (or *alternative*) NO synthesis pathways. NO is a key vasoprotective molecule produced in the cardiovascular system, predominantly from canonical endothelial NO synthase in response to shear-stress or circulating agonist, such as acetylcholine or bradykinin; and tonic NO production is associated with vasorelaxation and antiatherogenic and antiplatelet phenotypes.[11] Conversely, all cardiac risk factors (including hypertension) and cardiovascular diseases, as well as chronic kidney disease, are associated with reduced NO bioavailability that is thought to be pathogenic in disease initiation and progression.[12]

Over the past 25 years, there has been the discovery of an alternative pathway for NO generation involving the sequential reduction of inorganic nitrate and thence nitrite to bioactive NO.[13] Increase in circulating nitrite levels, whether through infusion of sodium nitrite[14] or through provision of fixed doses of either oral inorganic nitrate salts or dietary nitrate (usually in the form of beet juice),[15,16] is associated with robust and reproducible reductions in BP in healthy volunteers and hypertensive patients that is associated with elevations of downstream canonical NO secondary messengers, confirming the production of bioactive NO.[15,16] More important, for the hypothesis postulated within the linked article, both the authors and others have directly demonstrated that UV light exposure to human skin mobilizes nitrite (and other NO storage forms) into the circulation[17–19] and that this is associated with short-lived (<1-hour) BP reduction.[18,19]

Weller and the colleagues[10] are to be congratulated for putting together such diverse data sets in an innovative manner to try to determine the independent effects of light versus temperature. Although the enormity of the data set can overcome some imprecision of measure in exposure, there are some potential systematic confounders that are not addressed in these data and although mentioned in the article are worth pointing out, such as physical activity and lack of information on diastolic BP and concomitant antihypertensive therapy. One cannot also discount a possibility of some residual confounding, although it is unlikely to have affected the findings in this big database.

Of paramount importance, when it comes to exposure to either of the 2 main variables of interest, the estimates taken from the US national agencies are far from personal exposures. In particular, temperature exposure in the (cold) winter months is more closely related to internal temperature and the association of temperature to BP is stronger for internal versus external temperature.[20] Similarly, although the data set on UV exposure estimated hourly UV irradiance at all >2000 hemodialysis centers, the lack of granularity of personal exposure taking into account cultural, environmental (other than simply ambient temperature), and outdoor time factors influences these results. Although it may be tempting to consider that in warmer areas of the continental United States, people are more likely to be outdoor and wear clothes that reveal more skin to solar radiation, patients with end-stage renal disease are known to be more frail than the average population, as the authors themselves contend, and therefore these concepts may not hold true and may cloud the strength of associations. Another limitation of critical importance is the lack of information on the skin color, which itself would influence the absorption and the impact of the UV radiation. However, this limitation was somewhat mitigated by the stratified analysis using self-defined white and black ethnicity. Indeed, the strong effect of skin pigmentation on these relationships is apparent in these analyses, when self-defined blacks had a higher baseline SBP and with lower decrease in SBP with the increase in the strength of UV radiation.

In considering the importance of these data, there are at least 2 different levels to consider. More important, these appear to be the first data to try to tease out the effect of sunlight versus ambient temperature on BP, albeit in an end-stage kidney disease population, and the interesting finding of a sunlight-independent effect is noteworthy and novel. However, these findings should not detract from the fact that the relationship between the ambient temperature and the SBP was significant and substantial. Indeed, the synergy between the 2 was apparent, with larger SBP reduction associated with UV radiation for each higher quartile of the temperature range. Unfortunately, whether UV radiation can be used therapeutically to lower BP chronically (given the <1-hour BP-lowering effect seen with short-term exposure[18,19]) is not currently known, and a randomized controlled trial by the same authors to determine this in drug-naïve volunteers exposed to twice-daily UV lamp irradiation has recently terminated because of poor recruitment (NCT02621866).

Second, the question follows how best to use such information to improve public or individual patient health. On this second point, it is simple to envisage a future guideline recommending a set amount of natural sun exposure per day, but how to determine to optimal amount and to balance the real carcinogenic risks of sun exposure will not be simple. Perhaps if the mechanism postulated is correct, one could simply eat an extra beet daily!

However, as in other cases, there appear to be more complexities, including the synergy between the UV radiation and temperature and their differential impact as per skin color or, perhaps, salt sensitivities. The fact that those living in the areas with a warmer climate and higher incident sunshine had a higher baseline SBP suggests the presence of these complex factors interplay with other factors that at times

outweigh the hypotensive effect of the sun and warmth. It is possible that the next phase of research on these novel and modifiable risk factors may potentially uncover further modifiable mechanisms, and may as yet help reduce the immense burden of hypertension and possibly cardiovascular disease.

Disclosures

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