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AIR QUALITY, OUTDOOR RUNNING AND VASCULAR DYSFUNCTION: A SYSTEMATIC REVIEW

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ABSTRACT
Cardiovascular disease (CVD) is the leading cause of death in industrialized countries and air pollution exposure is believed to be a key modifiable risk factor. Although explanations by which pollution leads to CVD remain inconsistent, recent studies suggest that compromise to vascular function are potential pathophysiological mechanisms. The inhalation of ambient particulate matter (PM) is linked to an increased inflammatory status and adverse myocardial and vascular functions. Notably, physical exercise improves the CV risk profile. However, studies indicate that the forceful inhalation, as in intense exercise, of small environmental particles may directly or indirectly result in vascular damage, an early feature of the atherogenic process. The mechanisms responsible for this vascular dysfunction remain unknown. Therefore, a systematic review on vascular dysfunction markers in the setting of outdoor running in poor air quality environment was performed. Inflammatory, thrombotic, oxidative stress and endothelial markers were emphasized. These markers are adversely affected among high-volume runners exposed to an increased inhaled dose of air pollution. This adverse effect may induce vascular dysfunction and stimulate CVD.

KEY POINTS
- Atherosclerotic coronary artery disease has long been considered a chronic low-grade subclinical systemic inflammatory disease.
- Coronary atherosclerosis is the main underlying cause of exercise-related coronary events not only among elderly persons unaccustomed to exercise, but also in adult athletes including marathon runners.
- Vascular dysfunction markers are adversely affected among high-volume runners exposed to an increased inhaled dose of air pollution.

KEYWORDS: Air quality; outdoor running; marathon; vascular dysfunction markers; atherosclerosis; coronary artery disease.

BACKGROUND
Air pollution and cardiovascular disease. Cardiovascular disease (CVD) is the leading cause of death in developed countries.[1] In these countries, air pollution, has become a major public health concern in the last years, specially because of its association as a risk factor of many kind of common diseases, such as respiratory and CVD. Although explanations by which pollution leads to CVD remain unclear, recent studies suggest that compromise to vascular function are potential pathophysiological mechanisms.[2,3]

In a recent review of pollutant exposure impacts on healthy individuals, Cutrufello et al.[4] note that, while some detrimental effects are still in question, the inhalation of ambient particulate matter air pollution (PM) is linked to an increased inflammatory status and adverse myocardial and vascular functions. Consequently, onset of higher blood pressure levels, decreased heart rate variability and myocardial ischemia follow, which contribute to higher morbidity and mortality. Oxidative stress, through endothelial dysfunction, seems to be one of the most important mechanisms by which pollutants affect CV performance.[5] Despite compensatory mechanisms, chronic exposure to air pollution still leads to decreased pulmonary and cardiovascular function and increased

mortality, as it is shown in traffic[6] and pneumonia[7] related air-pollution studies.

Atherosclerotic coronary artery disease (CAD) has long been shown to represent a chronic low-grade subclinical systemic inflammatory disease. Numerous pathways and markers have been studied in order to detect the presence and evolution of this disease.[8,9] Among markers of inflammation involved in atherosclerosis, increasing importance has been given to circulating blood components as indicators of the risk of future cardiovascular events in healthy subjects.[10,11] In a recent published meta-analysis, Luo et al.[12] have speculated an association between short-term exposure to PM10, PM2.5 (particulate matter $\leq$ 10µm, 2.5µm in diameter) and risk of specific atherosclerotic events, such as myocardial infarction. Thirty-one published observational epidemiological studies were identified. Risk of myocardial infarction was significantly associated with per 10µg/m^3 increment in PM10 and PM2.5.

The effect of exercise on cardiovascular risk. Regular physical exercise improves the CV risk profile and is a robust recommendation for primary and secondary prevention, according to current guidelines.[13,14] In addition, low-to-moderate running reduces levels of the inflammatory markers.[15]

On the other hand, vigorous exercise, such as marathon running, may increase the short-term risk of coronary events.[16] Coronary atherosclerosis is the main underlying cause of exercise-related coronary events not only among elderly people unaccustomed to exercise[17], but also in adult athletes including marathon runners.[18,19] Over the past decades, the number of recreational marathon runners, including those at older age, has constantly risen.

Intense exercise, air quality and atherosclerosis. Forceful inhalation, as in intense exercise, of small environmental particles may directly or indirectly result in vascular damage, an early feature of the atherogenic process.[20,21] The mechanisms responsible for this vascular dysfunction remain unknown. One hypothesis is that the amplification of shear and oxidative stresses, present during vigorous running in air-polluted surroundings, promote the activation of inflammatory and thrombotic mediators as well as endothelial injury.[22,23,24] Inflammatory, thrombotic, oxidative stress and endothelial markers characterize vascular dysfunction are denoted as follows. These markers can affect vascular function independently or manifest through overlapping pathways.

To date, little is known about genetic responses to human exercise.[25] Exercise training induces numerous cardiovascular changes in the cellular and molecular level, including mitochondrial synthesis[26], myocardial remodeling[27], and angiogenesis.[28] Although such adaptations and their attendant impact on exercise capacity and health outcomes have been well documented, the genetic mechanisms leading to these changes remain incompletely understood. In addition, it is important to point out that genetic susceptibility is likely to play a role in response to air pollution.[29] Hence, gene-environment interaction studies can be a tool for exploring the mechanisms and the importance of pathways in the association between exercise, air pollution and a cardiovascular outcome.[30]

Since the Los Angeles Olympics in 1984, this issue has become a frequent global concern, attracting media attention. Several studies were designed to correlate exposure to PM and other gases (i.e., O3, CO and NOx) to their effects on an athlete's performance. This particular population may have higher risk of inhaling pollutants because of vigorous breathing.[31] Rundell, in his 2012 review[32] on effect of air pollution on athlete health and performance, established that vascular dysfunction related to pollution inhalation can detract from performance. However, he emphatically says that there has been no research into the effects of long-term exposure to air pollution on athletic performance and very few studies exist that describe the effects of acute exposure on exercise performance.

Many scientists around the world have restricted their studies to the harmful effects of pollutant inhalation in their own cities or countries, demonstrating that training or living close to major roads or to industrial centers may increase CV risks and reduce exercise performance. This dearth of multinational data has left important questions unanswered. Is the burden of CVD attributed to outdoor air pollution similar among different running volumes (e.g., weekly training mileage)? Has air pollution exposure any implication on international competitions, as training programs are developed in different cities and countries?

Sao Paulo vs Toronto: opposite examples for outdoor running. Air pollutant concentrations during marathon running and their effect on performance have not been reported.

According to official databases of Sao Paulo in 2012 and 2013 and at Ontario in 2011[33,34], Sao Paulo (Brazil) is one of most populated and industrialized cities in the world and its average pollution index is markedly higher than other major cities such as Toronto (Canada), respectively: PM2.5 levels of 24.9µg/m3 *vs* 6.0µg/m3 for the following years 2014, 2015 and 2016. Figure 1 illustrates PM2.5 measurements during the 3 months prior to major marathon competitions in each city. These 3 months are periods during which runners intensify their exercise training before the marathon competition. Disparities in air quality between these two cities may affect vascular function differently among marathon runners.

Air quality, outdoor running and vascular dysfunction markers. In this present review, we dedicate our efforts to explore the importance of air quality on vascular dysfunction markers, denoted as inflammatory, thrombotic, endothelial and oxidative mediators, among outdoor training athletes. Our hypothesis is that these markers are adversely affected among high-volume runners exposed to an increased inhaled dose of air pollution.

Vascular dysfunction markers related to atherosclerosis, exercise and air pollution

For means of didactic presentation, the vascular dysfunction markers were organized as inflammatory, thrombotic, endothelial and oxidative stress markers. Each set of markers is described in the trinomial association of "atherosclerosis, exercise and air pollution". Regarding exercise, data is centered on outdoor running, mainly marathon running.

Inflammatory markers related to atherosclerosis, exercise and air pollution. Inflammation has been implicated in the development and progression of atherosclerosis. Physical activity has been associated with lower levels of several inflammatory markers. However, the anti-atherosclerotic effects of intense outdoor physical activity with poor air quality remain controversial. Table 1 summarizes the role of inflammatory markers in this scenery.

Thrombotic markers related to atherosclerosis, exercise and air pollution. Activation markers of coagulation and fibrinolysis are increased in individuals at risk of CAD. Air pollution exacerbates this prothrombotic condition. Table 2 reviews the evidence of thrombotic disorders in this setting.

Endothelial dysfunction markers related to atherosclerosis, exercise and air pollution. It is well understood that exercise augments coronary blood flow through direct actions on the vasculature that improve endothelial function, enhancing coronary vasodilation. However, as seen in Table 3, outdoor running in an air pollution environment can provoke endothelial dysfunction and coronary atherosclerotic progression.

Oxidative stress markers related to atherosclerosis, exercise and air pollution. Support that ambient air pollution exposure during intense outdoor running can provoke cellular oxidative imbalances and favor vascular dysfunction is displayed in Table 4.

CONCLUSION

Our understanding of the role of vascular dysfunction in the development of CVD in the setting of exercise training in an air-polluted environment has been profoundly considered. Exposure to air pollution negatively impacts cardiovascular health. Studies show that increased exposure to a number of airborne pollutants increases the risk for CVD progression, myocardial events, and cardiovascular mortality. A hypothesized mechanism linking air pollution and CVD is the development of vascular dysfunction. Additional studies are also needed to determine what role pollution exposure plays in the levels of vascular dysfunction markers in healthy versus diseased individuals, with and without exercise.

Tables and figures

Figure 1. PM2.5 measurements during 3 time periods (a, b and c) within the 3 previous months (1, 2 and 3) of a major marathon competition in Sao Paulo (Ibirapuera Park) and Toronto (downtown) for 2014, 2015 and 2016.

Table 1. Inflammatory markers related to atherosclerosis, exercise and air pollution.

Table 2. Thrombotic markers related to atherosclerosis, exercise and air pollution.

Table 3. Endothelial dysfunction markers related to atherosclerosis, exercise and air pollution.

Table 4. Oxidative stress markers related to atherosclerosis, exercise and air pollution.

Abbreviations

CVD, cardiovascular disease
WBC, white blood cell
IL, interleukin
TNF, tumoral necrosis factor-α
CRP, high-sensitivity C-reactive protein
PAI-1,
oxLDL, oxidized LDL
vWF, von Willebrand factor
EPC, endothelial progenitor cell
F2-Isop, F2-isoprostanes
ADMA, asymmetric dimethylarginine
MPO, myeloperoxidase
Oxidized/reduced glutathione, GSH/GSSG

Declarations

Ethical Approval and Consent to participate. Not applicable.

Consent for publication. The authors have approved the manuscript and would like to emphasize that (1) are in consent for publication in this Journal, (2) the paper is not under consideration elsewhere, (3) none of the paper's contents have been previously published, and (4) no potential conflict of interest exists.

Availability of supporting data. The clinical and laboratorial data used to support the findings of this study are included within the article.

Competing interestings. The authors have no conflicts of interest.

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Authors' contributions. CVSJr, CLG, EGL and LDNJM developed the literature search strategy. FGP and LCG directed the literature exploration. MEF and GJE reviewed the included papers, and abstracted them for the detailed tables prepared for this paper. CVSJr wrote the initial draft of the manuscript, and the other authors all contributed to its development, particularly the discussion. All authors reviewed and approved the final manuscript.

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