Air Pollution in Patients With Heart Failure
Lessons From a Mechanistic Pilot Study of a Filter Intervention*

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Despite recent advances in the treatment of heart failure with reduced ejection fraction (HFrEF), adverse event rates remain high with >50% mortality at 5 years (1). The progressive nature of HFrEF coupled with high mortality and rehospitalization rates (2) mandates greater attention to previously underappreciated etiologies of heart failure (HF) exacerbation, including environmental exposures. The adverse cardiovascular effects of air pollution have been described in a series of epidemiological studies (3,4). Potential mechanisms for the association include endothelial dysfunction, systemic inflammation, increased blood pressure, altered coagulation, arrhythmia, and ischemia (3). HF patients appear to experience stronger negative effects of air pollution than do those with other cardiovascular conditions (5). Short-term air pollution exposure, specifically particulate matter <2.5 μm (PM2.5), is associated with increased HF hospitalization and mortality (6,7). However, the majority of studies to date investigating air pollution in HF patients have been limited by retrospective and noninterventional designs.

In this context, Vieira et al. (8) present their prospective assessment of the effects of air pollution on surrogate markers in HFrEF patients and explore the utility of a respiratory filter intervention in a controlled experimental setting. The investigators performed a single-center, double-blind, crossover trial of 26 HFrEF patients and 15 matched control subjects. Participants were exposed in random order to 3 study environments: clean air, unfiltered diesel exhaust, and mask-filtered diesel exhaust each for 21 min (15 min at rest and 6 min walking). The diesel exhaust was standardized to a PM2.5 of 300 μg/m³. For context, World Health Organization Guidelines target 24-h PM2.5 <25 μg/m³ (9) and on November 13, 2015, the PM2.5 in Durham, North Carolina; São Paulo, Brazil; and Beijing, China were 25 μg/m³, 127 μg/m³, and 279 μg/m³, respectively (10–12).

Participants underwent testing for endothelial function, arterial stiffness, serum biomarkers, and 6-min walk distance immediately after each exposure. The primary endpoint was change in endothelial function (quantified by digital peripheral-arterial tonometry after arm ischemia) and presented as the reactive hyperemic index (RHi).

Diesel exhaust exposure in HF patients (but not control subjects) resulted in significant worsening of the RHi compared with clean air, and this was mitigated by the filter intervention. Interestingly, exposure to diesel exhaust decreased a measure of arterial stiffness (the augmentation index) in both the HF and control groups with no significant alteration in response observed with filtration. The 6-min walk distance decreased by a mean of 22.5 m with exhaust exposure (compared with clean air in HF patients), and this was attenuated with the filter. Of a large panel of biomarkers, only B-type natriuretic peptide (BNP) significantly increased in HF patients with air pollution exposure, and this effect was mitigated with the intervention. Based on these results, the authors conclude that a mask filter can reduce endothelial dysfunction and BNP rise in HF patients exposed to traffic-derived air pollution.

This is an interesting pilot study that explored underlying mechanisms for the adverse effects of air pollution.

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pollution in HFrEF patients and demonstrated the potential utility of a mask-filter to reduce these detrimental effects. Notably, the filter attenuated the effects of air pollution on endothelial dysfunction and BNP but not on 6-min walk distance. The strengths of the study include the double-blind design, controlled air pollution exposure, comprehensive assessment of biomarkers and functional status, and use of a control group.

These data should be interpreted in the context of several methodological considerations. The primary endpoint was the effect on endothelial dysfunction as characterized by the RHi quantified with the EndoPAT system (Itamar Medical Ltd., Caesarea, Israel). The semiautomated device offers advantages over the operator dependence seen with flow-mediated brachial artery dilation via the conventional technique of high-resolution ultrasound (13). However, previous studies questioned the utility of the EndoPAT device in early-phase clinical studies. Moerland et al. (14) showed that the device did not distinguish baseline differences in endothelial function between healthy volunteers and those with renal impairment or diabetes mellitus and did not detect changes with glucose loading or smoking. This previous analysis also showed substantial intra-individual variability in the augmentation index (coefficient of variation, 37%). These diagnostic test characteristics may explain, in part, the unexpected observations in the current study of a reduction in the augmentation index with air pollution exposure and a nominally greater reduction when combined with the filter. Thus, although the study results support the primary hypothesis that a filter could reduce endothelial dysfunction due to air pollution, these observations require validation in a larger population and potentially also with conventional diagnostic techniques in combination with assessment of clinical outcomes.

Furthermore, the statistical approach involved multiple comparisons, which increase the likelihood of a type I error. In the Methods section, the authors reference a Bonferroni test, but a corrected statistical significance level (α) is not presented. Given the stated α level of 0.05, the standard Bonferroni correction is calculated as 0.05/m, where m is equal to the number of hypotheses tested. Even with a conservative estimate of 10 hypotheses tested, the corrected threshold for statistical significance is p = 0.005, far below the p value of 0.019 reported for the “significant” effect of filtered pollution versus air pollution on the RHi. Caution should be exerted when making conclusions based on a single p-value in the context of dozens of other comparisons that do not reach pre-specified thresholds.

The implications of the BNP observations should also not be overextended. Specifically, the investigators found that in the HF group, BNP increased from a median of 47.0 pg/ml to 66.5 pg/ml with diesel exhaust exposure. The authors highlight the 41.5% increase in BNP, yet the absolute magnitude of the change is modest (<20 pg/ml). Moreover, BNP was the only serum biomarker of the 13 evaluated that demonstrated a statistically significant increase with exhaust exposure. On the one hand, BNP is consistently associated with clinical outcomes in HF (15,16). Alternatively, these observations may be due to statistical chance, and the clinical significance of this modest short-term change in BNP is uncertain.

These observations provide important exploratory data to support further investigation into the mechanisms by which air pollution affects HF patients. Future studies from other regions of the world are needed to validate these findings and assess generalizability, particularly given the likelihood of type I error. The HFrEF population in the analysis tended to be younger with more nonischemic etiologies compared with U.S. HFrEF patients (1). Future studies are also needed to assess the subpopulations that are at greatest risk of air pollution exposure (17). If the present findings are validated and extended, patient-directed air pollution interventions may represent a novel therapeutic strategy to improve outcomes and quality of life. One could envision an approach where HF patients at increased risk could use filter interventions in home air systems and/or mask filters in the community during high-risk exposure periods. Importantly, the observed adverse effects related to short-term air pollution exposure may also provide broader insights into the overall pathophysiological abnormalities in HF (e.g., acute alteration in endothelial function). Further research investigating the effects of environmental stressors on HF patients is warranted to improve scientific understanding and promote population health.

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KEY WORDS air pollution, endothelium, heart failure