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CLINICAL RESEARCH

Respiratory Filter Reduces the Cardiovascular Effects Associated With Diesel Exhaust Exposure

A Randomized, Prospective, Double-Blind, Controlled Study of Heart Failure: The FILTER-HF Trial

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ABSTRACT

OBJECTIVES The goal of this study was to test the effects of a respiratory filter intervention (filter) during controlled pollution exposure.

BACKGROUND Air pollution is considered a risk factor for heart failure (HF) decompensation and mortality.

METHODS This study was a double-blind, randomized to order, controlled, 3-way crossover, single-center clinical trial. It enrolled 26 patients with HF and 15 control volunteers. Participants were exposed in 3 separate sessions to clean air, unfiltered diesel exhaust exposure (DE), or filtered DE. Endpoints were endothelial function assessed by using the reactive hyperemia index (RHi), arterial stiffness, serum biomarkers, 6-min walking distance, and heart rate variability.

RESULTS In patients with HF, DE was associated with a worsening in RHi from 2.17 (interquartile range [IQR]: 1.8 to 2.5) to 1.72 (IQR: 1.5 to 2.2; $p = 0.002$) and an increase in B-type natriuretic peptide (BNP) from 47.0 pg/ml (IQR: 17.3 to 118.0 pg/ml) to 66.5 pg/ml (IQR: 26.5 to 155.5 pg/ml; $p = 0.004$). Filtration reduced the particulate concentration (325 ± 31 μg/m^3 vs. 25 ± 6 μg/m^3; $p < 0.001$); in the group with HF, filter was associated with an improvement in RHi from 1.72 (IQR: 1.5 to 2.2) to 2.06 (IQR: 1.5 to 2.6; $p = 0.019$) and a decrease in BNP from 66.5 pg/ml (IQR: 26.5 to 155.5 pg/ml) to 44.0 pg/ml (IQR: 20.0 to 110.0 pg/ml; $p = 0.015$) compared with DE. In both groups, DE decreased the 6-min walking distance and arterial stiffness, although filter did not change these responses. DE had no effect on heart rate variability or exercise testing.

CONCLUSIONS To our knowledge, this trial is the first to show that a filter can reduce both endothelial dysfunction and BNP increases in patients with HF during DE. Given these potential benefits, the widespread use of filters in patients with HF exposed to traffic-derived air pollution may have beneficial public health effects and reduce the burden of HF. (Effects of Air Pollution Exposure Reduction by Filter Mask on Heart Failure; NCT01960920) (J Am Coll Cardiol HF 2016;4:55–64) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

Aix = augmentation index

CO = carbon monoxide

CRP = C-reactive protein

DE = dilute diesel exhaust exposure

HF = heart failure

HFc = high-frequency component

HRV = heart rate variability

IQR = interquartile range

LFc = low-frequency component

NO_2 = nitrogen dioxide

NO_x = nitrogen oxides

PM = particulate matter

PM2.5 = particulate matter <2.5 μm in aerodynamic diameter

RHi = reactive hyperemia index

The World Health Organization estimates that air pollution was responsible for 3.7 million premature deaths worldwide in 2012 (1). Air pollution consists of a heterogeneous mixture of gases, liquids, and particulate matter (PM) (2). Adverse cardiovascular events are most strongly associated with fine particulate pollutants (particulate matter <2.5 μm in aerodynamic diameter [PM2.5]), of which the combustion-derived particulate in diesel exhaust exposure (DE) is the principal source (3,4). Every 10 $\mu g/m^3$ elevation in PM2.5 is associated with 11% increases in cardiovascular mortality risk (5,6).

Although most attention has focused on the association of air pollution with myocardial infarction, the effects of PM on other cardiovascular conditions, such as heart failure (HF), have been less well described. HF imposes one of the highest clinical and economic burdens of any medical condition in the United States (7,8) and is often marked by recurrent episodes of decompensation and multiple hospitalizations (9). Air pollution is linked to an increased risk of HF decompensation (10,11), and it has been estimated that reducing median daily PM2.5 concentrations by a mean of 3.9 $\mu g/m^3$ would prevent approximately 8,000 HF hospitalizations in the United States (10).

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Epidemiological and observational clinical studies are limited by imprecise measurements of pollution exposure, potential environmental and social factor confounders, and the lack of mechanistic data. Experimental studies with DE can provide a precisely defined PM2.5 concentration in a regulated environment that facilitates investigation with validated measures of cardiovascular health (12), such as endothelial function. Previous studies with controlled human exposure to air pollution have shown an immediate impairment of endothelial function and vasoconstriction associated with DE in healthy adults (13,14). Endothelial dysfunction is an early and independent predictor of clinical deterioration and death in patients with HF (15); the effects of DE on the endothelial function of patients with HF have never been studied in a controlled exposure setting, however.

Reduction of traffic emissions involves economic and political difficulties. In an open-label study, use of a polypropylene filter face mask reduced the adverse effects of particle inhalations on blood pressure and heart rate variability (HRV) in healthy volunteers (16). The potential cardiovascular benefits of individual filters for patients with HF exposed to urban air pollution have not been established. The present superiority trial tested whether a filter could reduce endothelial dysfunction and other adverse cardiovascular effects related to DE compared with unfiltered DE in patients with HF.

METHODS

This study was a double-blind, randomized to order, controlled, 3-way crossover, single-center clinical trial conducted in the heart failure department of a tertiary teaching hospital in São Paulo, Brazil. According to the State Basic Sanitation Engineering Company, air quality in São Paulo is considered unfit during most of the year, with reports of PM2.5 concentrations reaching 750 $\mu g/m^3$ (17), which is 30 times the recommended daily limit according to the World Health Organization. Environmental quality reports in 2013 reported co-pollutant daily concentrations of 7.9 ppb nitrogen dioxide (NO_2), 19 $\mu g/m^3$ sulfur dioxide, and 8.1 ppm carbon monoxide (CO).

ELIGIBILITY CRITERIA. Eligibility requirements included patients with HF aged >18 years who met the Framingham criteria for HF with New York Heart Association functional class I, II, or III symptoms, had an ejection fraction ≤40% as assessed by any method before enrollment, and were under guideline-oriented treatment. Subjects were excluded if they had the following: unstable coronary disease 6 months before enrollment; decompensated HF; uncontrolled arrhythmia or hypertension; or renal, hepatic, or respiratory failure. Also excluded were patients weighing >265 lb (because of the treadmill restrictions) and those with musculoskeletal limitations for exercise. We also rescheduled patients who reported symptoms of upper respiratory tract infections. Matched control subjects were recruited from the same locality as the patients with HF.

The study was performed with the approval of the local research ethics committee in accordance with the Declaration of Helsinki. Written informed consent was obtained for all of the participants.

STUDY ENDPOINTS. The primary endpoint was a shift in endothelial function as assessed by repeated noninvasive measures of the reactive hyperemia index (RHi) (18). Secondary endpoints included arterial stiffness as assessed by using the augmentation index (Aix); blood biomarker analysis (complete blood cell count; troponin; C-reactive protein [CRP]; B-type