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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

natriuretic peptide [BNP]; and catecholamine and coagulogram); changes in exercise testing (6-min walking distance, systemic blood pressure, and heart rate [HR] response) (19); and heart rate variability (HRV) measures. Briefly, time domain measures of HRV include the mean heart rate and standard deviation of the normal interbeat intervals (SDNN), the root mean square successive difference between adjacent normal interbeat intervals (RMSSD), and the percentage of adjacent intervals that varied by greater than 50 ms (pNN50). Standard frequency domain measures of HRV include high-frequency component, low-frequency component and ratio.

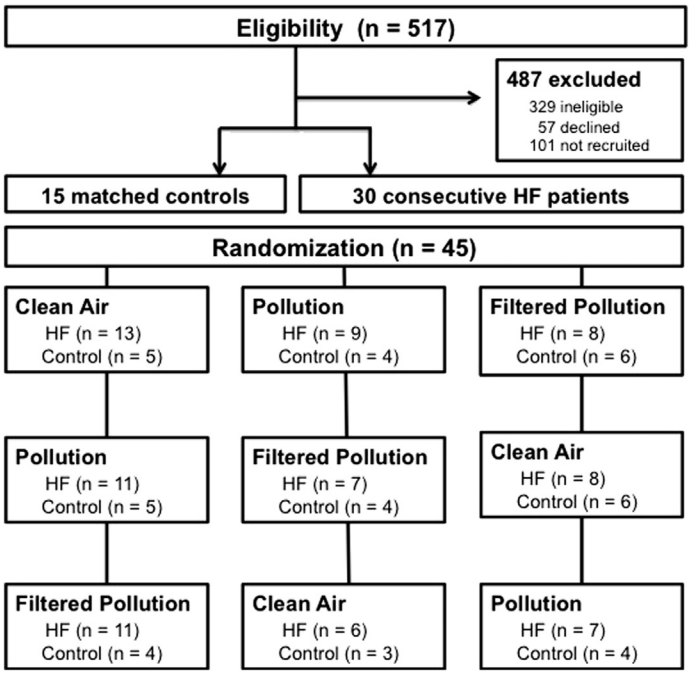
STUDY DESIGN. All participants were randomly assessed in 3 different sessions that were conducted at least 48 h apart. In each session, they were assigned to a controlled inhalation protocol in a randomized order, with an independent predetermined exposure sequence (**Figure 1**). The inhalation protocols were as follows: 1) clean air was obtained from compressed-air breathing cylinders; 2) unfiltered pollution was obtained from dilute DE, standardized by maintaining the PM2.5 concentration at 300 $\mu g/m^3$; and 3) filtration was obtained from DE that had passed through a mask filter intervention (filter).

All of the trial participants and technical staff were blinded to the exposure allocation, with the exception of the investigator responsible for the DE dilution adjustment. Each exposure session lasted 21 min, with participants evaluated at rest (for 15 min) and during a 6-min walking test. The subjects fasted overnight and throughout the rest protocols, and they ate a standardized caffeine-free meal before each exercise test. All of the endpoint measures were collected for the clean air, DE, and filter conditions.

POLLUTION SYSTEM. The DE was generated from a diesel engine (Branco BD-2500 CFE, Toyama, Sao Paulo, SP, Brazil) and conditioned through a refrigerated metal retainer (**Figure 2**). A partial DE flow was fed into a Tedlar bag (Horiba Instruments Ltda, Jundiaí, SP, Brazil) to be diluted with clean air by using a diaphragm pump (Pulsafeeder Series E, Punta Gorda, Florida). The main gaseous components of the DE were continuously monitored within a mixing tube for PM2.5 (DustTrak II Aerosol Monitor 8530, TSI, Shoreview, Minnesota), nitrogen oxides (NO_x) (Model 42i NO-NO2-NOx Analyzer, Thermo Instruments, Franklin, Massachusetts), and CO (ToxiPro CO-analyzer, Biosystems, Middletown, Connecticut) using standard real-time instruments. The diaphragm pump was adjusted by maintaining the PM2.5 concentration at approximately 300 $\mu g/m^3$. The filtered pollution was generated in an identical manner, but the exhaust was passed through a respiratory filter (Affinity Plus PFF2/ VO AF-38, MSA, Sao Paulo, SP, Brazil) that was inserted into the mixing tube. The filter promotes mechanical and electrostatic retention, protecting against fine particles (PM2.5), organic vapor, and smoke (20). The temperature and humidity in the room were controlled at 21°C to 24°C and 50%, respectively.

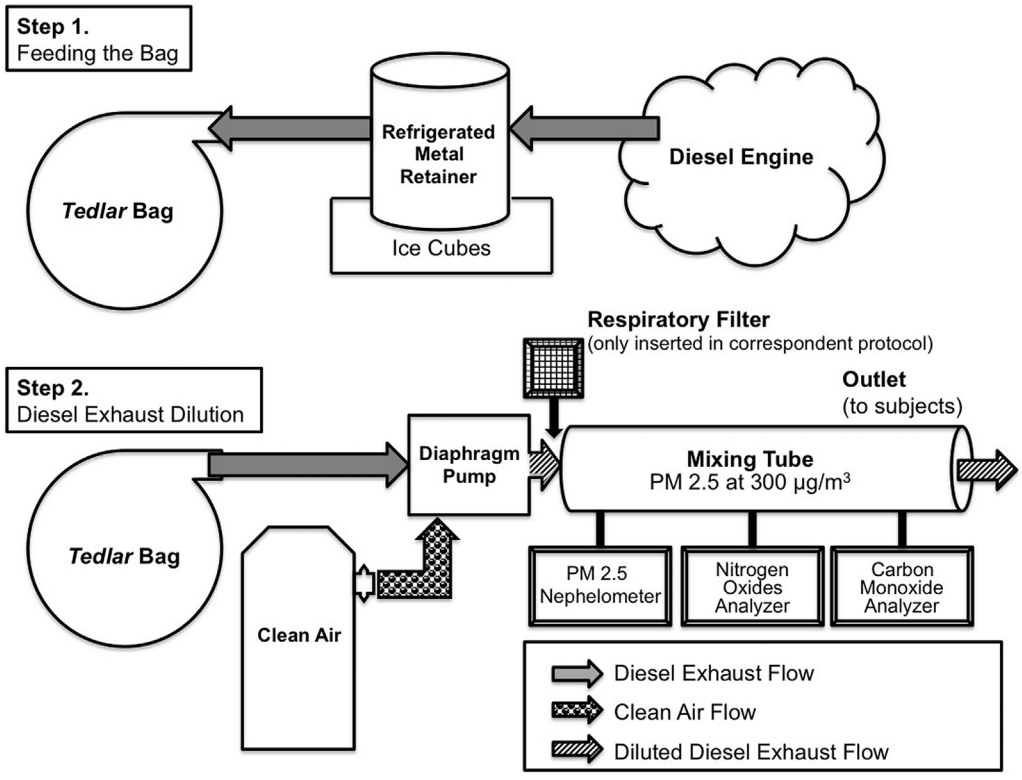
ENDOTHELIAL FUNCTION. Endothelial function was measured noninvasively by using digital peripheral artery tonometry after arm ischemia (EndoPAT2000, Itamar Medical Ltd, Caesarea, Israel), as described elsewhere (18,21). The test consisted of 3 stages: baseline, brachial arterial occlusion, and a post-occlusion recording of the induced reactive hyperemia response (RHi). RHi values <2.0 were categorized as endothelial dysfunction (22); higher values were considered normal or improved endothelial function. The Aix is defined as the difference between the first and the second peaks of the arterial waveform, and this

FIGURE 1 CONSORT Diagram



Flow diagram shows a unicenter clinical trial with a randomized, double-blind, 3-way crossover design. Participants were exposed to clean air, unfiltered dilute diesel engine exhaust (pollution), and dilute diesel engine exhaust that had passed through a respiratory filter (filtered pollution). The order of the exposures was randomized, with an independent predetermined exposure sequence. CONSORT = Consolidated Standards of Reporting Trials; HF = heart failure.

FIGURE 2 Schematic Diagram



Diesel exhaust (DE) is generated from a diesel engine connected to a refrigerated metal retainer before being fed into a Tedlar bag. Exhaust flows from the bag into a mixing tube, which is regulated by a diaphragm pump, to be diluted with clean air. The air is continuously monitored for particulate matter <2.5 μm in aerodynamic diameter (PM 2.5), nitrogen oxides, and carbon monoxide. The diaphragm pump is adjusted to keep the PM 2.5 concentration at 300 μg/m^3. The filtered pollution is generated in an identical manner, but the exhaust passes through a personal protective equipment polypropylene particulate filter respirator, which is only inserted into the mixing tube during the corresponding protocol.

metric has been proposed as an index of "arterial stiffness."

6-MIN WALK TEST. We applied the 6-min walk test aligned to the Borg Rating of Perceived Exertion scale to ensure that the subjects underwent a submaximal test, as previously described (19).

HEART RATE VARIABILITY. To assess the acute effects of DE on HRV, data were collected on a frequency counter watch and chest strap (Polar RS800, Polar Electro Oy, Kempele, Finland) and then transferred to Kubios HRV analysis (Version 2.0, Biomedical Signal and Medical Imaging Analysis Group, University of Kuopio, Finland) (23).

SERUM BIOMARKERS. Peripheral blood samples were taken at the end of each session to avoid interference with the RHi measure. An autoanalyzer was used to assess total and differential cell counts. Serum C-reactive protein (CRP) was measured by using an immune-nephelometric assay (Dade-Behring Diagnostics, Deerfield, Illinois). BNP and troponin levels were assayed by using a direct chemiluminescence test (Siemens Healthcare Diagnostics, Tarrytown, New York), and catecholamine was measured by using high-performance liquid chromatography.

DATA ANALYSIS AND STATISTICS. We determined that a sample size of 30 subjects would be necessary to detect the superiority of filtered over unfiltered DE for RHi reduction, with a 2-sided significance level of 5% and a power of 80%. This approach agrees with data derived from other experimental studies (24,25), given an anticipated dropout rate of 15%.

Normality was assessed with the Kolmogorov-Smirnov test. Parametric data are presented as mean ± SD and were analyzed by using repeated measures analysis of variance. The Bonferroni test was used to detect differences between the values as well as to account for multiple comparisons between

TABLE 1 Baseline Subject Characteristics

	Patients With HF (n = 26)	Control Group (n = 15)
Age, yrs	51 ± 9	45 ± 10
Sex (male:female)	16:10	8:7
Race (white:other)	19:7	14:1
Body mass index, kg/m^2	28.1 ± 4.3	26.6 ± 4.0
Smoking history	17	7
Hypertension	15	5
Diabetes	6	1
Heart failure etiology		
Ischemic	9	
Nonischemic	14	
Chagasic	3	
NYHA functional class		
I–II	22	
III	4	
LVEF, %	30.3 ± 6.0	
Systolic blood pressure, mm Hg*	111.6 ± 22.9	127.1 ± 13.3
Diastolic blood pressure, mm Hg*	58.4 ± 16.0	69.5 ± 11.4
Creatinine, mg/dl	1.25 ± 0.3	1.08 ± 0.1
Drugs		
Beta-blocker*	26	2
ACE inhibitors/ARB*	26	1
Loop diuretic*	23	0
Aldosterone receptor antagonist*	12	0
Hydralazine (+ nitrate)	5	0

Values are mean ± SD or n unless otherwise noted. *p < 0.05 for patients with heart failure (HF) versus control subjects.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

TABLE 2 Filter Effects on Endothelial Function During Diesel Exhaust Exposure

	Clean Air	Air Pollution (~300 μg/m^3)	Filtered Pollution
Reactive hyperemia index			
Patients with HF	2.17 (1.8 to 2.5)*	1.72 (1.5 to 2.2)†	2.06 (1.5 to 2.6)
Control subjects	2.06 (2.0 to 2.5)	2.15 (1.7 to 2.3)	2.62 (1.9 to 2.9)
Augmentation index to assess arterial stiffness, %			
Patients with HF	14 (5 to 28)*	10 (-2 to 20)	8 (-2 to 19)‡
Control subjects	18 (2 to 34)	11 (-3 to 33)	5 (0 to 26)

Values are median (interquartile range), and Friedman's test was used to detect differences across multiple sessions. *p < 0.050 for clean air vs. air pollution. †p < 0.050 for air pollution vs. filtered pollution. ‡p < 0.050 for clean air vs. filtered pollution.

HF = heart failure.

groups and protocols. The nonparametric data are reported as medians with the interquartile range (IQR), and Friedman's test was used to detect differences across multiple sessions. The Mann-Whitney *U* test was used to evaluate whether nonparametric observations were drawn from the same distributions.

The statistical analyses were performed with SPSS software (IBM SPSS Statistics for Windows, Version 20.0, Armonk, New York) and StatCalc Version 8.0 (AcaStat Software, Poinciana, Florida). A probability value of p < 0.05 was considered statistically significant.

RESULTS

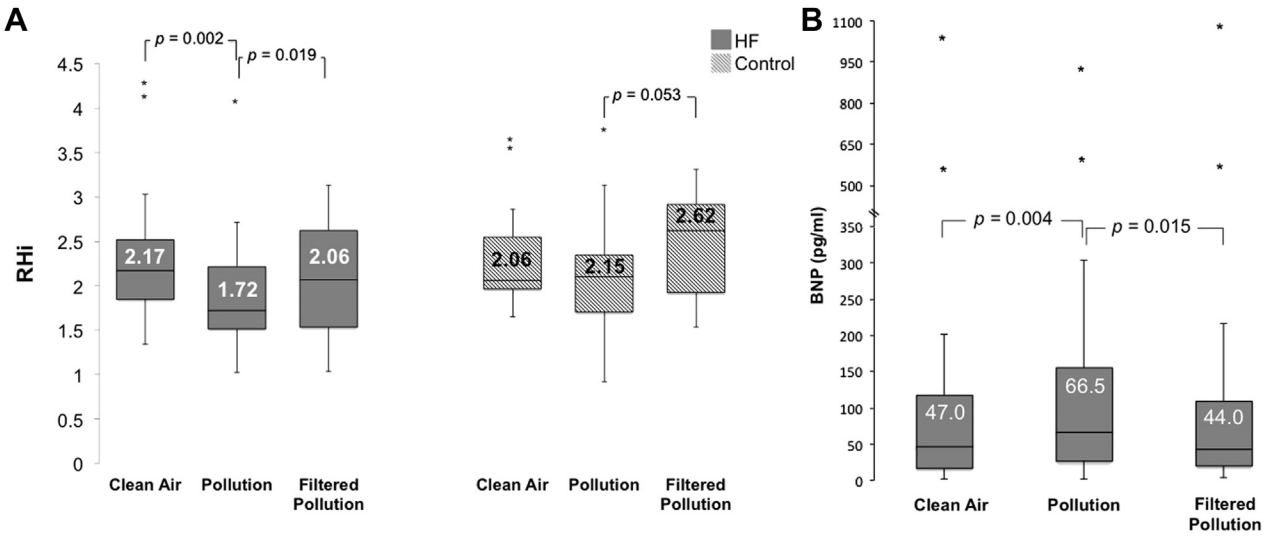
BASELINE CHARACTERISTICS OF STUDY SUBJECTS. Baseline characteristics and participant flow are depicted in Table 1 and Figure 1, respectively. As outlined, the majority of patients with HF were middle-aged white men, with nonischemic cardiomyopathy and a mean ejection fraction of 30.3% under optimal medical therapy. During the study period, 30 consecutive patients with HF were enrolled, with 4 participants lost to dropout. Fifteen control subjects were enrolled in the study. Although no significant differences were found in age, sex, or BMI between the 2 groups, patients with HF had higher baseline troponin, CRP, and BNP levels versus the control group (p = 0.009, p = 0.016, and p = 0.001, respectively). Each subject served as his or her own control. The primary endpoint (endothelial function) was assessed in all of the participants.

CONTROLLED POLLUTION EXPOSURE. The mean PM2.5 concentration was 325 ± 31 μg/m^3 and was associated with mean concentrations of 0.1 ppb (IQR: 0 to 0.3 ppb) for NO_2, 4.0 ppb (IQR: 1.1 to 15) for NO_x, and 15 ppm (IQR: 10 to 33 ppm) for CO. The filtration significantly reduced the PM2.5 concentration to 25 ± 6 μg/m^3 (p < 0.001), and levels of gaseous co-pollutants did not differ between filter and DE, with mean concentrations of 0.1 ppb (IQR: 0 to 0.2 ppb) for NO_2, 1.4 ppb (IQR: 0 to 12.8 ppb) for NO_x, and 10 ppm (IQR: 3 to 21 ppm) for CO. Overall, DE was well tolerated, and there were no severe adverse events during or after exposure sessions.

ENDOTHELIAL FUNCTION. In the HF group, RHi was significantly decreased by 21% during DE (p = 0.002 for clean air vs. DE) and improved by 20% during filtration (p = 0.019 for DE vs. filter) (Table 2, Figure 3A). In control subjects, there was no significant association between DE and RHi changes. Subjects with abnormally high RHi values were kept in the analysis but depicted as outliers. Compared with clean air, DE also decreased arterial stiffness (Aix) in the HF group (p = 0.007 for clean air vs. DE) and in the control group (p = 0.069 for clean air vs. DE). However, there were no differences between filtered and unfiltered DE.

6-MIN WALK TEST. Compared with clean air, DE was associated with a significantly shorter 6-min walking

FIGURE 3 Filter Effects on Endothelial Function and BNP During Diesel Exhaust Exposure



(A) Endothelial function assessed by using the reactive hyperemia index (RHi) in patients with heart failure and control volunteers after exposure to clean air, diesel exhaust pollution, or filtered pollution. **(B)** B-type natriuretic peptide (BNP) levels in heart failure patients after exposure to clean air, diesel exhaust pollution, or filtered pollution. Both panels depict medians (bars) and interquartile ranges (whiskers). *Indicates outliers. HF = heart failure.

TABLE 3 Filter Effects on Exercise Performance During Diesel Exhaust Exposure

	Clean Air	Air Pollution (~300 μg/m³)	Filtered Pollution
6-min walk test, m*			
Patients with HF	243.3 ± 13.0†	220.8 ± 13.7	209.2 ± 15.1‡
Control subjects	292.3 ± 18.8†	252.7 ± 19.8	261.5 ± 21.9
Heart rate, beats/min			
Patients with HF			
At rest	65.2 ± 12.5	69.9 ± 18.2	68.4 ± 17.4
6-min walk	96.9 ± 18.1	95.0 ± 20.9	94.5 ± 22.2
Control subjects			
At rest	63.8 ± 6.1	66.1 ± 7.0	65.5 ± 6.8
6-min walk	111.3 ± 13.8	107.0 ± 9.82	102.9 ± 10.2
SBP, mm Hg			
Patients with HF			
At rest	108.7 ± 18.4	108.4 ± 18.6	106.9 ± 14.6
6-min walk	122.0 ± 21.8	121.9 ± 26.7	124.9 ± 19.8
Control subjects			
At rest	125.5 ± 13.8	124.7 ± 16.2	119.6 ± 7.5
6-min walk	141.8 ± 20.8	142.2 ± 21.2	146.7 ± 24.1
DBP, mm Hg			
Patients with HF			
At rest	57.1 ± 14.9	58.3 ± 14.1	57.4 ± 10.4
6-min walk	64.4 ± 15.5	64.1 ± 18.6	65.2 ± 18.3
Control subjects			
At rest	69.6 ± 12.1	68.5 ± 12.5	69.0 ± 9.6
6-min walk	76.0 ± 12.0	76.5 ± 13.0	74.4 ± 9.6

Values are mean ± SD and were analyzed by using analysis of variance with repeated measures. *Differences between control and subjects with heart failure (HF) are statistically significant ($p < 0.05$). †$p < 0.050$ for clean air vs. air pollution. ‡$p < 0.050$ for clean air vs. filtered pollution.

DBP = diastolic blood pressure; SBP = systolic blood pressure.

distance in both groups (Figure 3A) but with no improvement during filtration. Resting HR and blood pressure increased significantly with exercise in both groups, but in patients with HF, the HR response was slightly attenuated such that the increase was inferior to that in the control group ($p = 0.054$ for HR increase in HF vs. control group) (Table 3). There were no effects of filtered or unfiltered DE on HR or blood pressure.

SERUM BIOMARKERS. In the HF group, the level of BNP in the blood increased by 41.5% after diesel particulate inhalation ($p = 0.004$ for clean air vs. DE) and decreased by 33.8% during filtration ($p = 0.015$ for DE vs. filter) (Figure 3B). There were no systemic effects on hematologic indices or platelet counts in peripheral blood (Table 4).

HEART RATE VARIABILITY. No significant arrhythmias occurred during or after exposure sessions. Inhalation of DE for 15 min did not affect time or frequency domain measures of HRV in either control volunteers or patients with HF, and there were no differences compared with filter or clean air sessions (Table 5).

DISCUSSION

There are consistent temporal associations between exposure to air pollutants and HF hospitalizations and mortality (10,11). To our knowledge, this trial is

the first randomized study to show that a simple filter intervention could reduce endothelial dysfunction and BNP increases associated with short-term exposure to DE in patients with HF. Our findings suggest that PM2.5 is the most important cause of endothelial dysfunction associated with air pollution exposure. Surprisingly, we also found a reduction in arterial stiffness during DE, which was unaffected by the filter.

Our findings on endothelial dysfunction during DE are consistent with experimental HF mouse models (26) and similar to reports in healthy volunteers (27,28) and patients with diabetes (29). Two pathways have been proposed to explain these effects: first, a pulmonary acute phase response could release inflammatory mediators into the circulation and be a causal link between particle inhalation and cardiovascular disease (30); second, inhaled particles could translocate into the circulation, with potential direct cardiovascular effects (31). Previous observational and experimental studies have explored the association between PM inhalation and pulmonary inflammation "spillover." The evidence is not entirely consistent, but it suggests mild systemic inflammatory responses to PM exposure (4,24,32-34). In contrast, our short-term model outcomes are in line with previous studies that observed no systemic inflammation (14,35,36), sympathetic involvement (13), or effects on activated partial thromboplastin time or prothrombin time (37) during the early stages of brief DE inhalation. These disparities could be explained by methodological differences, such as distinctive PM2.5 concentrations and experimental settings. It should be noted that our blood samples were taken immediately after 21 min of DE exposure, which could be too short to observe an increase in inflammatory biomarkers, as systemic inflammation would need more time to develop. Collectively, our findings suggest that the endothelial dysfunction associated with brief exposure to air pollutants is not related to an acute systemic inflammatory response.

Mechanisms by which PM exposure could cause direct cardiovascular dysfunction are still inconclusive. The claims that fine particles may translocate from deposition sites in the lungs to the systemic circulation and also if the translocated amount would be sufficient to cause systemic adverse effects are controversial (38-40). Although some experimental animal models of inhaled artificial particles reported no translocation to remote organs (40), other studies have shown very different amounts of translocation to the systemic circulation (41). In a rat model, clearance of artificial radiolabeled ultrafine particles was found to be primarily via the airways into the gastrointestinal tract, and only a small fraction (<1%) translocated into secondary organs (41,42). However, some models with artificial radiolabeled ultrafine particles have been criticized because most of the observed data on translocation could be explained by the distribution of free radioactivity unbound to nanoparticles (43). In humans, the literature on extrapulmonary translocation of particles remains

TABLE 4 Filter Effects on Biomarkers During Diesel Exhaust Exposure

	Clean Air	Air Pollution (~300 μg/m³)	Filtered Pollution
Hemoglobin, g/dl			
Patients with HF	13.9 ± 0.4	13.8 ± 0.4	13.7 ± 0.4
Control subjects	14.3 ± 0.4	14.2 ± 0.4	13.1 ± 1.3
Leukocytes, x10^9 cells/l			
Patients with HF	7.8 ± 0.5	7.8 ± 0.5	6.9 ± 0.3
Control subjects	6.2 ± 0.4	6.1 ± 0.4	6.2 ± 0.3
Neutrophils, x10^9 cells/l			
Patients with HF	5.1 ± 0.4	5.3 ± 0.5	4.6 ± 0.3
Control subjects	3.9 ± 0.3	3.8 ± 0.2	3.8 ± 0.2
Lymphocytes, x10^9 cells/l			
Patients with HF	1.8 ± 0.1	1.8 ± 0.1	1.7 ± 0.1
Control subjects	1.7 ± 0.1	1.9 ± 0.1	1.8 ± 0.1
Monocytes, x10^9 cells/l			
Patients with HF	0.4 ± 0.03	0.4 ± 0.05	0.3 ± 0.02
Control subjects	0.3 ± 0.03	0.3 ± 0.04	0.3 ± 0.04
Platelets, x10^9 cells/l			
Patients with HF	228.1 ± 17.2	246.7 ± 10.6	240.5 ± 14.1
Control subjects	240.8 ± 9.5	243.1 ± 12.0	239.5 ± 9.1
Troponin I, ng/ml*			
Patients with HF	0.011 [0 to 0.023]	0.009 [0 to 0.027]	0.001 [0 to 0.020]
Control subjects	0	0	0
C-reactive protein, mg/l*			
Patients with HF	1.55 [0.8 to 3.3]	1.95 [0.9 to 4.0]	1.99 [1.0 to 4.0]
Control subjects	0.76 [0.4 to 1.0]	1.10 [0.5 to 1.5]	0.68 [0.5 to 1.5]
BNP, pg/ml*			
Patients with HF	47.0 [17.3 to 118.0]	66.5 [26.5 to 155.5]	44.0 [20.0 to 110.0]
Control subjects	10.5 [9.3 to 12.8]	11.5 [6.3 to 15.0]	9.5 [6.3 to 10.0]
Norepinephrine, pg/ml			
Patients with HF	720 ± 89	647 ± 131	703 ± 128
Control subjects	274 ± 47	611 ± 47	403 ± 45
Prothrombin time, s			
Patients with HF	17.2 ± 1.7	16.9 ± 1.7	17.3 ± 1.6
Control subjects	14.7 ± 0.5	14.4 ± 0.4	14.8 ± 0.4
International normalized ratio			
Patients with HF	1.0 [1.0 to 1.2]	1.0 [1.0 to 1.0]	1.1 [1.0 to 1.2]
Control subjects	1.0 [0.9 to 1.1]	1.0 [1.0 to 1.1]	1.0 [1.0 to 1.1]
Partial thromboplastin time, s			
Patients with HF	28 ± 2.1	27 ± 2.5	30 ± 1.3
Control subjects	29 ± 1.0	29 ± 0.7	30 ± 1.1

Values are mean ± SD and were analyzed by analysis of variance with repeated measures. Nonnormal data values are reported as the median (interquartile range), and Friedman's test was used to detect differences across multiple sessions. $p > 0.050$ for all comparisons. *Differences between the control group and the heart failure (HF) group are statistically significant ($p < 0.05$).

BNP = B-type natriuretic peptide.

TABLE 5 Filter Effects on Heart Rate Variability During Diesel Exhaust Exposure

	Clean Air	Air Pollution (~300 μg/m³)	Filtered Pollution
RMSSD, ms			
Patients with HF	47.4 ± 5.8	43.2 ± 6.1	46.0 ± 6.0
Control subjects	30.0 ± 4.1	28.5 ± 3.2	28.6 ± 3.9
PNN50, ms			
Patients with HF	7.5 (1.9 to 15.2)	3.3 (0.2 to 15.5)	3.55 (1.1 to 17.7)
Control subjects	2.5 (0.3 to 3.8)	1.6 (0.4 to 5.4)	2.2 (0.7 to 4.4)
SDNN, ms			
Patients with HF	58.5 ± 7.6	44.7 ± 5.4	46.8 ± 4.6
Control subjects	55.0 ± 5.7	47.0 ± 4.2	46.4 ± 3.5
LF power, ms²			
Patients with HF	1,044 ± 247	898 ± 209	878 ± 175
Control subjects	624 ± 207	502 ± 118	542 ± 125
HF power, ms²			
Patients with HF	861 ± 236	810 ± 203	750 ± 203
Control subjects	368 ± 98	364 ± 86	383 ± 100
LF/HF ratio			
Patients with HF	177 ± 22	202 ± 40	163 ± 29
Control subjects	224 ± 62	193 ± 41	216 ± 73
Mean heart rate, beats/min			
Patients with HF	65 ± 2	70 ± 3	68 ± 3
Control subjects	64 ± 2	66 ± 2	64 ± 2

Values are mean ± SD and were analyzed by using an analysis of variance with repeated measures. Nonnormal data values are reported as the median (interquartile range), and Friedman's test was used to detect differences across multiple sessions. $p > 0.050$ for all comparisons.

HF = high-frequency component; LF = low-frequency component; PNN50 = percentage of adjacent intervals that varied by greater than 50 ms; RMSSD = rroot mean square successive difference between adjacent normal interbeat intervals; SDNN = standard deviation of the normal interbeat intervals.

conflicting (38,44). Passage of inhaled particles into the bloodstream was demonstrated in 1 human study (44), but other similar studies have failed to show such effect (40).

Our results are consistent with previous reports of inhaled particles in remote organ and vessels (44,45). Nevertheless, we did not investigate if our findings were caused by a direct contact between the endothelium and the particles or by a biological response triggered from small amounts of particle translocation. It is plausible that the adjacent apposition of alveoli and capillary network makes translocation likely either as "naked" particles, assuming that even very small amounts could activate a systemic response, or through the pulmonary tissue after ingestion by alveolar macrophages (38,46). The percentage of particles able to translocate depends on the experimental design, even if high percentages are very unlikely (47,48). The ability to cross the lung-blood barrier is likely to be influenced by a number of factors, including particle size and charge, chemical composition, exposure route, and animal species (38,40).

Although the BNP values in our population of compensated HF patients seem low, we are unaware of any other prospective study reporting BNP increases during DE exposure. Our findings are in contrast with a retrospective analysis of a clinical trial (49), which observed no associations between short-term fluctuations in ambient pollution and circulating BNP levels. However, epidemiological studies reported a positive association between short-term increases in ambient particles and hospitalization for HF, which is a clinical condition related to increased BNP (50–53). We believe that DE may, directly or indirectly, cause transient systolic and/or diastolic ventricular dysfunction through several mechanisms acting alone or together, such as endothelial dysfunction, pulmonary vascular resistance (54), increased ventricular afterload, and myocardial toxicity (55).

The Aix reduction during DE exposure in both patients with HF and in control subjects is inconsistent with previously reported arterial stiffness increases during acute DE in healthy volunteers (56). Experimental settings may explain the contradictory findings, as previous controlled exposure studies have used considerably less CO (13,14,57). It is possible that higher CO levels could be involved in modulating vascular elasticity. Unfiltered co-pollutants, such as NO_x, sulfur oxides, and organic compounds (including aromatic and alkane substances), as well as elemental carbon particles, could explain the neutral effects of filter on Aix response.

Our results of decreased exercise performance during short-term DE inhalation are consistent with results of previous studies (58,59); however, the present report is the first in patients with HF. Multiple factors could be involved, such as impaired diffusion capacity, pulmonary arterial hypertension, tissue hypoxia through CO-induced reductions in the oxygen-carrying capacity of blood, systemic and pulmonary vasoconstriction, decreased oxygenation of muscle microcirculation or endothelial dysfunction, and a potential impairment in cardiac function, supported by our findings of BNP increases. In addition, the filter did not prevent the exercise intolerance, suggesting a mechanism unrelated to PM that could involve other co-pollutants.

Our neutral findings on HRV are consistent with previous controlled exposure studies of DE effects on autonomic function, which also did not identify any reproducible effects on HRV in healthy volunteers (60) or patients with coronary heart disease (61). It is therefore unlikely that autonomic dysfunction explains our findings.

STUDY LIMITATIONS. The study's sample size limits the possibility of detecting small effects of DE on

secondary endpoints. All subjects were asked to report their perception of DE, and there were no reports of noticeable smell; however, more sensitive patients may not have been truly blinded. There are no data regarding the tolerability of wearing face masks for prolonged periods in patients with HF. A respiratory filter has the potential to exacerbate respiratory resistance, hypercapnia and hypoxemia, heat, and lack of clear communication. In our short-term model, all participants were blinded to the filtration, and there were no reports of respiratory discomfort during the filter protocol. We chose RHi as the primary outcome to avoid the user dependence of flow-mediated dilation, as RHi is obtained through a semi-automated method. The existence of a pollution "dose-response" for endothelial dysfunction was not investigated; however, we believe that our model reflects real-life experiences, such as during rush hour. Finally, interpreting numerous p values is difficult. Multiple endpoints within 3 exposure conditions require multiple comparisons and increase the possibility of type I and II errors.

CONCLUSIONS

To our knowledge, this trial is the first to show that a simple respiratory filter can reduce the adverse effects of pollution on endothelial function and BNP in patients with HF. Given the worldwide prevalence of exposure to traffic-related air pollution, these findings could be relevant for public health, especially in this highly susceptible population.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: We have provided a plausible and simple intervention to potentially reduce the HF decompensation associated with air pollution exposure. Given these potential benefits, the widespread use of filters in patients with HF exposed to traffic-derived air pollution may have a beneficial public health impact and reduce the burden of HF. Our results may also be important for other populations, given that endothelial dysfunction has emerged as a potentially valuable prognostic tool for predicting the development of atherosclerosis and coronary heart disease.

TRANSLATIONAL OUTLOOK: The pioneering demonstration that a filter intervention is effective in improving endothelial dysfunction and preventing the elevated BNP levels associated with diesel pollution exposure could provide a new strategy for treating and preventing pollution-related HF morbidities. Mask filters should be tested in a larger sample of subjects during controlled exposure to DE.

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