At high cardiac output, diesel exhaust exposure increases pulmonary vascular resistance and decreases distensibility of pulmonary resistive vessels.

NEW & NOTEWORTHY

This study demonstrates, for the first time in human subjects exposed to diesel exhaust, a pulmonary vasomotor tone impairment. A 2-h exposure to diesel exhaust alters pulmonary vessel distensibility at high cardiac output and increases pulmonary vascular resistance.

AIR POLLUTION is a growing public health issue, especially in developing countries, and is responsible for up to 7 million deaths/year worldwide. Air pollution is considered as an important and potentially modifiable cardiovascular risk factor (26, 38, 55). Epidemiological studies have demonstrated a consistent link between elevated ambient particulate matter (PM) concentrations and new onset cardiac atherothrombotic events (43, 44). In addition to its vascular effects, air pollution also appears to be an important precipitating factor for heart failure. Results from a recent metaanalysis showed that increases in concentrations of PM <2.5 μm (PM2.5) are associated with heart failure hospitalizations and deaths (48).

There is now considerable evidence demonstrating the effects of polluted air on the cardiovascular system. Air pollution notably elicits peripheral vascular dysfunction through endothelial dysfunction and vasoconstriction (4, 33, 42, 52). It also induces a prothrombotic state, characterized by increased in vivo thrombus formation through platelet activation and decreased endogenous fibrinolytic capacity (28, 32, 53). A recent overview of the physiopathological mechanisms underlying the cardiovascular effect of air pollution considered pulmonary tissue to be an important determinant of a systemic oxidative, inflammatory, and neurohumoral reaction (38). Human data regarding the effects of dilute diesel exhaust (DE) on pulmonary hemodynamics are scarce. An echocardiographic study in which the maximal velocity of the tricuspid regurgitation jet was assessed in resting conditions in 81 children demonstrated elevated mean pulmonary artery pressure (mPpa) in polluted urban areas compared with rural areas (7). In 11 patients with heart failure, analysis of a continuous implantable heart monitoring system demonstrated that same-day mean PM2.5 concentration was associated with small but significant increases in estimated pulmonary artery and right ventricular (RV) diastolic pressure using a pacemaker algorithm-based calculation of vascular impedance (47).
epidemiological relationship between air pollution and heart failure (48). Intervventional studies performed in animal models have confirmed the ability of air pollution to elicit pulmonary vasoconstriction, which seemed to be related to an impaired nitric oxide (NO) pathway (11, 29). Models in which animals are chronically exposed to polluted urban air showed marked pulmonary arterial remodeling with a decrease in the lumen-to-wall ratio (5, 12). Moreover, chronic exposure induced pulmonary arterial vasoconstriction. This vascular effect is coupled to overexpression of the endothelin (ET) receptor and local, but not systemic, inflammation (12, 30). In contrast, increase in pulmonary tone may also reflect a response to increased vasoconstrictive factors. Indeed, several studies have reported that exposure to PM consistently increased the circulating levels of ET-1, a potent pulmonary vasoconstrictor, and others have demonstrated increased peripheral vascular sensitivity to ET-1 (7, 22, 42).

We designed the present study to test the hypothesis that standardized exposure of healthy subjects to dilute DE would acutely increase PVR and may potentiate acquired pulmonary hypertension. We used a standardized exposure protocol that has been widely used in previous experiments in human subjects (28, 32, 33). Consistent with previous echocardiographic research in the same field, we studied PVR at rest and the mPpa-cardiac output (Q) relationship during dobutamine or exercise stress (24, 35). To produce an external increase in pulmonary pressure, we used an experimental model of hypoxia-mediated pulmonary hypertension (13, 18, 35). Finally, we explored the effect of DE exposure on exhaled NO and circulating ET-1 concentrations. Using this approach to assess both resting and dynamic changes in pulmonary pressure after air pollution exposure, we believed that this study improves our understanding of the acute effects of air pollution on pulmonary vascular function.

MATERIALS AND METHODS

Subjects. Thirty-three healthy male nonsmokers with normal physical examination were screened, and 18 subjects with an easily interpretable tricuspid regurgitation jet were selected for the study (mean age: 22.2 ± 0.5 yr and body mass index: 21.7 ± 0.5 kg/m²). The Ethical Committee of Erasme Hospital approved the study protocol (reference P2010/086), and informed written consent was obtained from all subjects.

Study design. Eighteen subjects were exposed to either nonfiltered ambient air (AA) or DE for 120 min using a randomized, crossover, double-blinded design (Fig. 1) with the different exposures occurring at least 1 wk apart. Pulmonary hemodynamic parameters were calculated using echocardiography, which was initiated 2 h after exposure.

Ten subjects performed the dobutamine stress protocol under AA and DE conditions. Eight subjects performed the exercise in acute hypoxia stress protocol, which consisted of the following three different exercise sessions: one exercise session in normoxia during AA exposure, one exercise session in hypoxia during AA exposure, and one exercise session in hypoxia during DE exposure.

DE exposure. Exposure sessions were performed in a dedicated room (2.65 × 2.65 × 2.65 m) (52). Semiautomated valves controlled gas arrival and extraction from the room to insure a stable concentration of pollutants throughout the experimental session. DE was generated by a PSA DW10 engine using a common ultralow sulfur diesel and diluted with AA in the conduction system. DE was delivered to achieve a PM2.5 concentration of 300 μg/m³ as previously described (23, 32, 52). The PM concentration was measured by photometry using a GRIMM Laser Aerosol Spectrometer 1109 (GRIMM Aerosol Technik, Airning, Germany). The subject’s blood pressure (BP), heart rate (HR), O₂ saturation (Compaq, Datex Ohmeda, Helsinki, Finland), and minute ventilation (Pneumotrace, Medical Electronic Construction, Brussels, Belgium) were recorded during each exposure. The Department for Protection and Prevention at Work of Université Libre de Bruxelles approved the experimental setting, the reliability of the technical equipment, and the accuracy of all safety procedures.

Echocardiographic measures. Based on our previous experiments that peripheral effects of DE on microvascular function were observed up to 2 h after exposure, we decided to start the echocardiographic measures 2 h after the exposure (52). These measurements were performed in the left lateral decubitus position in a quiet and temperature-controlled environment. As conventionally recommended, we followed a classic transthoracic echocardiographic protocol. We used a short-axis parasternal view for the acquisition of LV outflow tract diameter and a four- to five-chamber apical view for the acquisition of other parameters. Echocardiographic data were collected using CX 50 (Philips Healthcare, Best, The Netherlands) and Vivid 7 Dimension (GE Healthcare, Little Chalfont, UK) by experienced echocardiographers blinded to the randomization group. Postacquisition analysis was performed by the same investigator using a dedicated viewer (Xcelera, Philips Healthcare). Measurements were calculated from an average of three cardiac cycles. The reproducibility of these measurements has been assessed previously in our echolaboratory (14).

Echocardiographic data analysis. The primary end point of this study was the PVR at rest and the mPpa-Q relationship during cardiac stress tests. PVR was defined as the ratio of mPpa to Q. Q was calculated as the product of the velocity time integral of the pulsed Doppler tracing in the LV outflow tract, cross-sectional area of the LV outflow tract, and HR (Fig. 2A). Systolic pulmonary artery pressure was estimated from the transtricuspid pressure gradient calculated from the maximum velocity of continuous Doppler tricuspid regurgitation (Fig. 2A). Because the diameter of the inferior vena cava was <20 mm with a collapse into inspiration, right atrial pressure was considered as equal to 5 mmHg (56). We then calculated mPpa as
equation (27): pressed in %/mmHg) during stress tests according to the following
stress tests, the slope of the mPpa-Q relationship was determined by
the mitral (mitral inflow allowed us to calculate the maximal early (E) and late
(A) velocities in diastole. Left diastolic function was evaluated by
A (E-to-A) ratios. Using tissue Doppler analysis of the
velocity of the mitral annulus, left atrial pressure was estimated from the
mitral E-to-E’ (E/E’ ratio). This ratio provides a more reliable
evaluation of left atrial pressure than the E/A ratio, which is affected
by diastolic function (41). Tricuspid annular plane systolic excursion
(TAPSE) and the tissue Doppler tricuspid S wave, which evaluate RV
systolic function, were also measured.

**Dobutamine stress protocol.** Dobutamine was administered into
a brachial vein at an initial dose of 2 μg·kg⁻¹·min⁻¹ and progressively
increased by 2 μg·kg⁻¹·min⁻¹ every 5 min. Echocardiographic mea-
surements (CX 50, Philips Healthcare) were performed at rest to determine
the baseline parameters and during the infusion of 4, 6, and
8 μg·kg⁻¹·min⁻¹ dobutamine. We simultaneously recorded the sub-
ject’s BP, HR, and a three-lead electrocardiogram.

**Exercise in acute hypoxia stress protocol.** Before echocardi-
ographic measures, subjects were exposed to normoxic conditions or to
hypoxia with an inspired fraction of O₂ of 12% for 90 min using a
dedicated airtight mask (Rusch 4vent, Teleflex Medical, Athlone,
Ireland). This level of hypoxia has been previously demonstrated to be
optimal to produce a maximal hypoxic pulmonary pressure increase in
healthy humans with minimal changes in arterial PCO₂ (17). Hypoxia
was maintained during the echocardiographic measurements. Sym-
tomatic tolerance to hypoxia was assessed using the Lake Louise
score.

Echocardiographic measurements (Vivid 7 Dimension, GE Health-
care) were performed first at rest to determine the baseline parameters
and then during an incremental exercise schedule. Exercise echocar-
diography was performed in a semirecumbent position using a supine
ergometer (Ergoserve 1000, Ergoline, Bitz, Germany) with the table
tilted up to 30° in the left lateral decubitus position. The exercise test
was started at 10 W for 3 min followed by a 10-W increase every 3
min. Echocardiographic measurements were performed at each step
until the subject became uncomfortable or there was a loss of quality
in the echocardiographic images because of increased ventilation. We
standardized the within-subject workload in our exercise in hypoxia
protocol. The achieved workload was 57 ± 3 W. This schedule
enabled us to perform 4.5 ± 0.2 sets of measures for each of the three
tests.

Simultaneously with echocardiographic measurements, we re-
corded BP, HR, O₂ saturation (Nellcor Puritan Bennett), and three-
lead electrocardiogram of the subjects.

**ET-1 and fractional exhaled NO measures.** Blood samples
were collected immediately after each exposure (n = 10). Sera were
isolated after centrifugation at 2,000 g for 15 min at 20°C and stored
at −20°C until analysis. Serum concentrations of ET-1 were obtained
using commercially available ELISA kits (R&D Systems, Abingdon,
UK). Fractional exhaled NO (n = 10) values were obtained before and
immediately after exposure sessions using a NO monitor (Niox Mino,
Aerocrine, Solna, Sweden) according to 2005 American Thoracic
Society/European Respiratory Society guidelines (1).

**Statistical analysis.** Data are expressed as means ± SE. Statistical
analyses were performed using SPSS (SPSS 18.0, Chicago, IL).

Exposure pollution parameters were compared using a Student’s
r-test. Physiological parameters, echocardiographic measurements,
and α coefficients were compared using a Student’s t-test or one-way
ANOVA test. Two-way repeated-measures ANOVAs were used to
detect significant changes in PVR during the stress test. P values
for the intervention effect and the time to intervention interaction are
presented when the intervention effect P value alone was <0.05.
Bonferroni corrections were applied for between-group compar-
is. Based on previous data from our echolaboratory, our study
was designed to identify a 20% difference in the slope of the
mPpa-Q relationship with a statistical power of 80% with a
two-sided α error of 0.05 (13). Statistical significance was assumed
when P values were <0.05.

**RESULTS**

**Parameters before the cardiac stress test.** The concentration
of PM2.5 increased from 21 ± 1 μg/m³ in AA to 304 ± 1
μg/m³ in DE (P < 0.001; Table 1). BP, HR, O₂ saturation, and
minute ventilation were similar in DE and AA. Serum ET-1
Compared with resting conditions, dobutamine induced maximal increases in Q of 4.05 ± 0.47 l/min in DE (Table 2). BP and HR, and hypoxic responses to the exercise stress test in hypoxia were similar with exposure to AA and DE.

**DISCUSSION**

The main findings of our study can be summarized as follows. Recordings made 2 h after a 120-min exposure to DE revealed that DE 1) did not modify PVR in resting conditions; 2) increased the slope of the mPpa-Q relationship measured during cardiac stress, which was associated with decreased vessel distensibility at high Q; 3) did not enhance hypoxia-mediated pulmonary vasoconstriction. The Q and pulmonary pressure measures we used during transthoracic echocardiography are now part of daily clinical practice and are recommended in cardiology but also in critically ill patients (8, 31). Finally, DE did not modify fractional exhaled NO or serum ET-1 levels immediately after exposure.

We used a highly standardized method of DE exposure, which enabled us to generate a level of exposure of 300 μg/m³ for 2 h (52, 53). This level has been used by other authors to study the biological and physiological effects of DE exposure in humans (23, 32). Although rare, our exposure level has been encountered during recent pollution peaks in industrialized countries (51). Although the PM concentration was high, this occurred for a short period of time. If we extrapolate our

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**Table 1. Exposure session parameters**

<table>
<thead>
<tr>
<th>Exposure Data</th>
<th>AA</th>
<th>DE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollution parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM10, μg/m³</td>
<td>26 ± 1</td>
<td>311 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PM2.5, μg/m³</td>
<td>21 ± 1</td>
<td>304 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PM1, μg/m³</td>
<td>19 ± 1</td>
<td>300 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>21.0 ± 0.1</td>
<td>21.3 ± 0.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>NO, ppb</td>
<td>51 ± 4</td>
<td>835 ± 46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NO₂, ppb</td>
<td>31 ± 2</td>
<td>2,043 ± 106</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NOₓ, ppb</td>
<td>82 ± 5</td>
<td>2,878 ± 150</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CO, ppm</td>
<td>0 ± 0</td>
<td>21 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CO₂, ppm</td>
<td>0 ± 0</td>
<td>21 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CO₂, %</td>
<td>0 ± 0</td>
<td>21 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physiological parameters</td>
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</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>119 ± 1</td>
<td>118 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>72 ± 1</td>
<td>72 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>66 ± 1</td>
<td>66 ± 1</td>
<td>NS</td>
</tr>
<tr>
<td>O₂ saturation, %</td>
<td>97.7 ± 0.1</td>
<td>97.8 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Minute ventilation, l/min</td>
<td>8.5 ± 0.3</td>
<td>9.0 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Fractional exhaled NO, ppb</td>
<td>26.6 ± 3</td>
<td>25.6 ± 5.1</td>
<td>NS</td>
</tr>
<tr>
<td>Endothelin-1, pg/ml</td>
<td>11.7 ± 0.8</td>
<td>12.6 ± 0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE. AA, ambient air; DE, diesel exhaust; PM10, particulate matter (PM) of <10 μm; PM2.5, PM of <2.5 μm; PM1, PM of <1 μm; NO, nitric oxide; NOₓ, NO₂ and NO₃; CO, carbon monoxide; NS, not significant.

concentrations and fractional exhaled NO were also similar in the two exposure groups.

DE exposure did not modify mPpa or PVR at rest compared with AA. Mitral E/A ratios, mitral E/E' ratios, TAPSE, and the tricuspid S wave were also not altered.

**Pulmonary hemodynamics during the dobutamine stress protocol.** Compared with resting conditions, dobutamine induced maximal increases in Q of 4.05 ± 0.47 l/min in AA and 3.98 ± 0.63 l/min in DE (P = not significant). The slope of the mPpa-Q relationship was higher with DE than with AA (3.9 ± 0.5 vs. 2.8 ± 0.5 mmHg·min⁻¹) during the dobutamine stress test (P < 0.05; Fig. 3A), and the α coefficient was lower (0.64 ± 0.12 vs. 0.96 ± 0.15%/mmHg, P < 0.01).

DE exposure did not modify mitral E/A ratio, mitral E/E' ratio, TAPSE, or the tricuspid S wave (Table 2). BP and HR responses to the dobutamine stress test were similar under AA and DE conditions.

**Pulmonary hemodynamics during exercise in the acute hypoxia stress protocol.** There were no differences in the decrease in O₂ saturation with hypoxia between AA and DE conditions. O₂ saturation at peak exercise in hypoxia was 66 ± 2.8% in AA conditions compared with 68.6 ± 2.8% in DE conditions (P = not significant). At the end of hypoxia, subjects had a Lake Louise score of 1.0 ± 0.5 with no difference between the exposure conditions. At rest, mPpa increased from 18.8 ± 0.8 mmHg in normoxia to 25.9 ± 1.1 mmHg in hypoxia (P < 0.001) and Q increased from 4.9 ± 0.3 to 5.8 ± 0.4 l/min (P < 0.05). PVR increased from 3.9 ± 0.2 mmHg·min⁻¹ in normoxia to 4.6 ± 0.2 mmHg·min⁻¹ in hypoxia (P < 0.05).

Compared with resting conditions, exercise induced comparable maximal increases in Q of 7.6 ± 0.3 l/min in normoxia, 7.7 ± 0.5 l/min in hypoxia under AA, and 6.4 ± 0.7 l/min in hypoxia under DE (P = not significant). During exercise stress, hypoxia induced an upper shift of the mPpa-Q relationship to a higher pressure regimen (hypoxia effect, P < 0.05; Fig. 3B). Hypoxia under AA or DE exposure did not alter the slope of the mPpa-Q relationship compared with AA in normoxia (2.1 ± 0.3 and 1.9 ± 0.5 vs. 2.5 ± 0.3 mmHg·min⁻¹, respectively, P = not significant by ANOVA).

Mitral E/A ratio, mitral E/E' ratio, α coefficients, TAPSE, and the tricuspid S wave were not affected by exposure to DE (Table 2). BP, HR, and hypoxic responses to the exercise stress test in hypoxia were similar with exposure to AA and DE.
Table 2. Cardiac stress tests measurements

<table>
<thead>
<tr>
<th>Hypoxia DE</th>
<th>Hypoxia AA</th>
<th>Normoxia AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Maximum</td>
<td>Baseline</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>Dobutamine</td>
<td>Dobutamine</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Maximum</th>
<th>Baseline</th>
<th>Maximum</th>
<th>Baseline</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>27 ± 3</td>
<td>27 ± 3</td>
<td>26 ± 3</td>
<td>26 ± 3</td>
<td>26 ± 3</td>
<td>26 ± 3</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>63 ± 8</td>
<td>63 ± 8</td>
<td>63 ± 8</td>
<td>63 ± 8</td>
<td>63 ± 8</td>
<td>63 ± 8</td>
</tr>
<tr>
<td>Tricuspid annular plane systolic excursion, mm</td>
<td>25.7 ± 4</td>
<td>25.7 ± 4</td>
<td>25.7 ± 4</td>
<td>25.7 ± 4</td>
<td>25.7 ± 4</td>
<td>25.7 ± 4</td>
</tr>
<tr>
<td>Tricuspid S wave, cm/s</td>
<td>14.3 ± 3</td>
<td>14.3 ± 3</td>
<td>14.3 ± 3</td>
<td>14.3 ± 3</td>
<td>14.3 ± 3</td>
<td>14.3 ± 3</td>
</tr>
<tr>
<td>Lateral mitral E/A</td>
<td>1.8 ± 0.3</td>
<td>1.8 ± 0.3</td>
<td>1.8 ± 0.3</td>
<td>1.8 ± 0.3</td>
<td>1.8 ± 0.3</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>Pulmonary arterial systolic pressure, mmHg</td>
<td>35.8 ± 1</td>
<td>35.8 ± 1</td>
<td>35.8 ± 1</td>
<td>35.8 ± 1</td>
<td>35.8 ± 1</td>
<td>35.8 ± 1</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>4.9 ± 0.3</td>
<td>4.9 ± 0.3</td>
<td>4.9 ± 0.3</td>
<td>4.9 ± 0.3</td>
<td>4.9 ± 0.3</td>
<td>4.9 ± 0.3</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mmHg</td>
<td>24 ± 3</td>
<td>24 ± 3</td>
<td>24 ± 3</td>
<td>24 ± 3</td>
<td>24 ± 3</td>
<td>24 ± 3</td>
</tr>
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</table>

Values are means ± SE, n = 10 subjects for the dobutamine stress tests and n = 8 subjects for the hypoxic exercise stress tests. The slopes of the mPpa-Q relationship and pulmonary vascular effects of air pollution (40). The slope of the mPpa-Q relationship and α coefficient values observed in our control conditions are concordant with a previous study and within normal ranges (35). We demonstrated that for each 1 l/min increase in Q, pulmonary pressure increased by 1 mHg under DE exposure than under AA. This represents a relative PVR increase of 35% after DE exposure. Multipoint mPpa/Q plot analysis also showed a slightly curvilinear relationship generated by vascular distensibility at high Q, which can be addressed using an α coefficient calculation (27). We observed a reduction in the distensibility of pulmonary resistive vessels at high Q after DE exposure. Loss of pulmonary vessel distensibility at high Q appears to be a new pathophysiological pathway that may explain the effect of DE exposure on pulmonary hemodynamics (46). Hence, using standardized exposure and a state-of-the-art measure of PVR, we have demonstrated, for the first time in humans, a change in pulmonary vascular tone after DE exposure, characterized by increased PVR and decreased vessel distensibility at high Q.

In accordance with previous studies, acute hypoxia increased mPpa but had no effect on the slope of the mPpa-Q relationship (14, 15). Moreover, we found that DE exposure did not enhance the hypoxic modification of the mPpa-Q relationship. However, this result may not be sufficient to rule out a potential change in pulmonary hemodynamics secondary to DE in the preexisting situation of pulmonary hypertension. Indeed, both DE and hypoxemia-related pulmonary vasoconstriction share some common mechanisms and sites of actions on small resistive arteries (6, 49). Thus, similar end pathways of DE and hypoxia may explain why our hypoxic pulmonary vasoconstrictive stimulus masked the effects of DE. Nevertheless, the mPpa-Q relationship and vessel distensibility changes we observed in our healthy subjects did also not affect RV exposure to a daily basis, as suggested by air pollution guidelines, it would represent an additive exposure of 12.5 μg·m⁻³·h⁻¹ for 24 h. This is a common daily variation of PM2.5 observed in Western countries. The increase in Q we observed with dobutamine or exercise corresponds to moderate physical activity (14). We have previously shown that exercise in a polluted environment enhances the thrombogenic effect of air pollution (53). Our study illustrates, for the first time, a change in pulmonary hemodynamics after DE exposure at high Q, which may, therefore, occur in real-life scenarios.

PVR was measured noninvasively using a previously described methodology (24, 36). To uncover early stages of vascular dysfunction, we applied a multipoint pulmonary coordinate pulmonary artery pressure/Q analysis during a cardiac stress test (13–15, 35). Indeed, as shown in our study, a single point measurement in resting conditions is not sufficient to identify subtle hemodynamic changes in the low-pressure, high-flow pulmonary circuit. Our results confirm accumulating evidence suggesting that the assessment of the pulmonary circulation under dynamic stress provides important clinical information in addition to resting measurements, as in "early" pulmonary arterial hypertension (10, 21, 24, 45).
systolic function. However, patients with heart failure, an acute vasoconstrictive pulmonary response to DE exposure might lead to a worsen RV function and alter LV filling. Large epidemiological studies are needed to further confirm if DE-related changes in pulmonary hemodynamics can exacerbate heart failure.

The vasomotor tone of pulmonary vessels is under complex regulatory control. The pulmonary endothelium releases vasoactive agents, such as ET-1, NO, and prostacyclin (16). However, the hemodynamic effects of DE observed in our study seem to be independent of the ET-1 pathway. Compared with another study (7) that demonstrated an increase in ET-1 in a chronic DE exposure model, the fact that our blood samples were collected immediately after acute exposure may explain the lack of effect observed. Decreased NO bioavailability is a major player in the toxicity of DE and is responsible for part of the pollution-induced systemic vascular dysfunction (20, 39, 52). Contrary to animal studies, DE did not alter fractional exhaled NO in our subjects. This suggests that the pulmonary endothelial production of NO did not change (11, 29). However, fractional exhaled NO is not specific, and, despite the very short timeline between exposure and measurements, NO produced in the DE or an acute lung inflammatory reaction might have confounded fractional exhaled NO measurements (34). Finally, DE particles, similar to other airborne pollutants, stimulate afferent sensitive C-fibers, which modulate sympathetic drive toward the pulmonary circulation (2, 25, 54). Further studies are required to confirm the involvement of an adrenergic vasoconstrictive reflex mechanism in the pulmonary hemodynamic effects of DE exposure.

Study limitations. The diesel fuel and engine setting used in our protocol are similar to those previously reported and correspond to a classic motor vehicle. Inference to other types of fuel, such as biodiesel, could not be made because the type of fuel may influence the health effects associated with exposure (19). We used two modalities for the cardiac stress test in our study: first, dobutamine in normoxia to guarantee the best image acquisition and the best measurement accuracy and, second, exercise in hypoxia, which is the best validated and most widely described modality in the literature (13, 15, 35). Reproducibility between these two techniques of cardiac stress testing in the pulmonary circulation evaluation has been previously demonstrated (24). Although not significant, we observed a difference in baseline PVR in our two populations, which may be related to differences in the experimental setting. Experimental conditions were standardized inside each protocol. However, the presence of an airtight respiratory mask and a supine ergometer in the exercise protocol explain why these results were not compared with the dobutamine protocol.

Our study was designed to test the effects of DE exposure on PVR. However, the power of the study may not be sufficient to provide definitive conclusions regarding the effects of DE on physiological (HR and BP), biological, or other echocardiographic parameters. As recently reported, some genetic patterns may influence vascular reactions to DE and explain the variability in the BP response to DE observed among studies (50). Further research is needed to specifically address the mechanistic hypotheses behind the lack of changes in ET-1 and fractional exhaled NO reported in our study.

Conclusions. We observed, for the first time, an acute increase in pulmonary vasomotor tone after a 2-h exposure to dilute DE in healthy young male subjects. Impairment in pulmonary vessel distensibility at high Q appears to be the main mechanism involved. Further studies are needed to establish the role of vascular oxidative stress, inflammation, and sympathetic system in DE-related pulmonary vascular dysfunction.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


H2144

AIR POLLUTION AND PULMONARY VASCULAR RESISTANCE