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

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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 of <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).

In view of the small numbers of subjects involved in these retrospective studies and potential bias from postcapillary increases in pulmonary pressure, these data are not sufficient to draw definitive conclusions on a possible pulmonary vasoconstrictor effect of air pollution. Because pulmonary vascular resistance (PVR) is the main determinant of RV afterload, an acute pulmonary vasoconstrictor response to PM exposure may favor acute decompensated heart failure through increased RV afterload and limited left ventricular (LV) filling. If DE toxicity primarily affects pulmonary tissue, an air pollution-related pulmonary vasoconstrictive effect could thus be considered as an explanation for the
epidemiological relationship between air pollution and heart failure (48). Interventional 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, 35). 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 exercise stress (24, 35). To produce an external increase in pulmonary pressure, we used an experimental model of hypoxic-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 rest 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, Airring, 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

![Fig. 1. Study design.](http://ajpheart.physiology.org/10.1152/ajpheart.00149.2015)
equation (27): pressed in %/mmHg) during stress tests according to the following linear regression for each subject (Fig. 2 stress tests, the slope of the mPpa-Q relationship was determined by the mitral velocity of the mitral annulus, left atrial pressure was estimated from velocities in diastole. Left diastolic function was evaluated by (0.61/H11003 line) and polluted air (DE; dashed line).

We also measured the coefficient of vessel distensibility (A/E ratios. Using tissue Doppler analysis of the A/ max ratio, which is affected by diastolic function (41). Tricuspid annular plane systolic excursion ratio, which is affected

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0.61 × systolic pulmonary artery pressure + 2 mmHg (9). During stress tests, the slope of the mPpa-Q relationship was determined by linear regression for each subject (Fig. 2B). We also measured the coefficient of vessel distensibility (α; expressed in %/mmHg) during stress tests according to the following equation (27):

\[
m_{\text{Ppa}} = \left\{ \frac{(1 + \alpha P_{\text{La}})^5 + 5\alpha P_{\text{VR}} Q}{\alpha} \right\} \]

where \( P_{\text{La}} \) is left atrial pressure, estimated at 8 mmHg using the Nagueh formula (37), and \( P_{\text{VR}} \) is PVR at rest. Pulsed Doppler of the mitral inflow allowed us to calculate the maximal early (E) and late (A) velocities in diastole. Left diastolic function was evaluated by mitral E-to-A (E/A) ratios. Using tissue Doppler analysis of the velocity of the mitral annulus, left atrial pressure was estimated from the mitral E-to\(^{-}E^\prime\) (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 \( \mu \)g·kg\(^{-1}\)·min\(^{-1}\) and progressively increased by 2 \( \mu \)g·kg\(^{-1}\)·min\(^{-1}\) every 5 min. Echocardiographic measurements (CX 50, Philips Healthcare) were performed at rest to determine the baseline parameters and during the infusion of 4, 6, and 8 \( \mu \)g·kg\(^{-1}\)·min\(^{-1}\) dobutamine. We simultaneously recorded the subject’s BP, HR, and a three-lead electrocardiogram.

**Exercise in acute hypoxia stress protocol.** Before echocardiographic measures, subjects were exposed to normoxic conditions or to hypoxia with an inspired fraction of \( O_2 \) of 12% for 90 min using a dedicated airtight mask (Rüsch 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 PCO\(_2\) (17). Hypoxia was maintained during the echocardiographic measurements. Symptomatic tolerance to hypoxia was assessed using the Lake Louise score.

Echocardiographic measurements (Vivid 7 Dimension, GE Healthcare) were performed first at rest to determine the baseline parameters and then during an incremental exercise schedule. Exercise echocardiography was performed in a semirecumbent position using a supine ergometer (Ergoselect 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 echographic 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 recorded BP, HR, \( O_2 \) 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 \( t \)-test. Physiological parameters, echocardiographic measurements, and \( \alpha \) 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 comparisons. 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 \( \alpha \) 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 \( \mu \)g/m\(^3\) in AA to 304 ± 1 \( \mu \)g/m\(^3\) in DE (\( P < 0.001 \); Table 1). BP, HR, \( O_2 \) saturation, and minute ventilation were similar in DE and AA. Serum ET-1
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 l⁻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, HR, and hypoxemic 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 l⁻¹ in normoxia to 4.6 ± 0.2 mmHg·min⁻¹ l⁻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 l⁻¹, respectively, P = not significant by ANOVA).

Mitrail 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 hypoxemic responses to the exercise stress test in hypoxia were similar with exposure to AA and DE.

**DISCUSSION**

The main new 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
Table 2. Cardiac stress tests measurements

<table>
<thead>
<tr>
<th>Echocardiographic data</th>
<th>Dobutamine Stress Test</th>
<th>Hypoxia Exercise Stress Test</th>
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<tr>
<td></td>
<td>AA</td>
<td>DE</td>
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<td></td>
<td>Baseline</td>
<td>Maximum</td>
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<td></td>
<td>8 µg·kg⁻¹·min⁻¹</td>
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<tr>
<td></td>
<td>dobutamine</td>
<td>Maximum</td>
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<tr>
<td>Mean pulmonary artery pressure, mmHg</td>
<td>13.7 ± 0.4</td>
<td>13.6 ± 0.6</td>
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<tr>
<td>Cardiac output, l/min</td>
<td>4.9 ± 0.3</td>
<td>5 ± 0.3</td>
</tr>
<tr>
<td>α, %/mmHg</td>
<td>0.96 ± 0.15</td>
<td>0.64 ± 0.12</td>
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<tr>
<td>Mitral E/A</td>
<td>1.8 ± 0.1</td>
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<tr>
<td>Lateral mitral E/A</td>
<td>4.3 ± 0.3</td>
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<tr>
<td>Tricuspid S wave, cm/s</td>
<td>14.3 ± 0.8</td>
<td>13.3 ± 0.6</td>
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<tr>
<td>Tricuspid annulus plane systolic excursion, mm</td>
<td>25.7 ± 0.8</td>
<td>25.4 ± 1.1</td>
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<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>118 ± 2</td>
<td>119 ± 3</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>63 ± 1</td>
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<td>O₂ saturation, %</td>
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Physiological parameters

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<tr>
<th></th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Maximum</td>
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<td>8 µg·kg⁻¹·min⁻¹</td>
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Values are means ± SE; n = 10 subjects for the dobutamine stress test and 8 subjects for the hypoxic exercise stress test. α, coefficient of distensibility of pulmonary vessels. *P < 0.01.
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 sympat hetic 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


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