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BRIEF ARTICLE

Air pollution and heart failure: Relationship with the ejection fraction

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Abstract

AIM: To study whether the concentrations of particulate matter in ambient air are associated with hospital admission due to heart failure in patients with heart failure with preserved ejection fraction and reduced ejection fraction.

METHODS: We studied 353 consecutive patients admitted into a tertiary care hospital with a diagnosis of heart failure. Patients with ejection fraction of $\geqslant$ 45% were classified as having heart failure with preserved ejection fraction and those with an ejection fraction of < 45% were classified as having heart failure with reduced ejection fraction. We determined the average concentrations of different sizes of particulate matter (< 10, < 2.5, and < 1 μm) and the concentrations of gaseous pollutants (carbon monoxide, sulphur dioxide, nitrogen dioxide and ozone) from 1 d up to 7 d prior to admission.

RESULTS: The heart failure with preserved ejection fraction population was exposed to higher nitrogen dioxide concentrations compared to the heart failure with reduced ejection fraction population (12.95 ± 8.22 μg/m^3 *vs* 4.50 ± 2.34 μg/m^3, $P < 0.0001$). Multivariate analysis showed that nitrogen dioxide was a significant predictor of heart failure with preserved ejection fraction (odds ratio ranging from (1.403, 95%CI: 1.003-2.007, $P = 0.04$) to (1.669, 95%CI: 1.043-2.671, $P = 0.03$).

CONCLUSION: This study demonstrates that short-term nitrogen dioxide exposure is independently associated with admission in the heart failure with preserved ejection fraction population.

Key words: Air pollution; Heart failure; Preserved ejection fraction; Reduced ejection fraction; Nitrogen dioxide

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INTRODUCTION

Ambient air pollution is a recognized risk factor for cardiovascular morbidity and mortality[1-3]. Nitrogen dioxide (NO_2) is a strong respiratory irritant gas originating from high-temperature combustion. Main outdoor sources of NO_2 include vehicle exhausts (particularly those equipped with diesel engines) and fossil-fuel power plants, whereas the most important indoor sources are gas heaters, stoves, and environmental tobacco smoke[4].

Large meta-analyses of studies on the short-term health effects of NO_2 have been carried out in Europe[5,6], the United States[7,8], and Canada[9]. The results indicate a positive association between daily increases of NO_2, cardiovascular and respiratory mortality. Several studies using administrative databases have shown a positive association between short-term increases in respirable or fine particles and the risk of hospitalization for congestive heart failure (HF)[10-12].

The aim of this investigation was to study whether the concentrations of particulate matter in ambient air are associated with hospital admission due to HF in patients with HF with preserved ejection fraction (HF-PEF) and reduced ejection fraction (HF-REF).

MATERIALS AND METHODS

Study population

We prospectively enrolled 458 consecutive patients admitted into a tertiary care hospital with a diagnosis of HF. The diagnosis of HF had to be established according to the clinical Framingham criteria[13]. We did not include patients with severe primary valve heart disease (n = 13), chronic obstructive pulmonary disease (n = 30), airway hyperresponsiveness (n = 25), asthma (n = 16) and presence of respiratory infection 15 d before admission (n = 21). Hence, 353 patients were included in the study. Patients with ejection fraction of $\geqslant$ 45% were classified as having HF-PEF and those with an ejection fraction of < 45% were classified as having HF-REF[14].

The study was planned according to the Declaration of Helsinki and approved by the local ethics committee, and all patients provided signed informed consent. Clinical data, including age, sex, arterial hypertension (> 140/90 mmHg), hypercholesterolemia (> 5.17 mmol/L), smokers, diabetes and left ventricular ejection fraction, were analyzed as baseline variables on admission. The left ventricular ejection fraction was measured using the modified Simpson's rule[15].

Air pollution measurements

The atmospheric pollutants were measured in an urban background monitoring station using reference methods (Directive 2008/50/EC). Concentrations of particulate matter (PM) smaller than 10, 2.5 and 1 μm (PM10, PM2.5 and PM1 respectively) were measured with automatic analyzer and the gravimetric method[16].

The concentrations of gaseous pollutants were measured using different methods: (1) sulphur dioxide was measured using ultraviolet fluorescence (Thermo Electron Corporation™, model 43C); (2) NO_2 was measured using chemiluminescence (Thermo Electron Corporation™, model 42C); (3) ozone was measured using ultraviolet absorption (Thermo Electron Corporation™, model 49C); and (4) carbon monoxide was measured using the technique NDIR-Gas Correlation Filter Analyser (Thermo Electron Corporation™, model 48C). The analyzers were calibrated every 3 mo and they always had a high linearity (r^2 = 0.99)[17]. Meteorological variables (temperature, relative humidity and wind speed) were measured using standard techniques. These variables were measured with 1 min resolution. Then, 24 h averages from the previous day up to 7 d prior to admission were calculated.

Statistical analysis

Results for normally distributed continuous variables are expressed as mean ± SD. Continuous variables with non-normal distribution are presented as median values and interquartile intervals; categorical data are expressed as percentages. Analysis of normality of the continuous variables was performed with the Kolmogorov-Smirnov test. Differences between groups were assessed by unpaired 2-tailed t test and the Mann-Whitney U test for continuous variables, as appropriate. Categorical data and proportions were analyzed by use of χ^2 or Fisher's exact test when required. In our study, all of the pollutants were expressed as the 24 h average concentrations from the previous day up to 7 d prior to admission.

A multivariate analysis was carried out using a binary logistic regression model to estimate the risk of admission for HF-PEF compared to admission for HF-REF, according to sizes of particulate matter and concentrations of gaseous pollutants during 7 d prior to admission. All of the variables with a value of $P < 0.05$ in the univariate analysis were included in the model. Differences were considered statistically significant if the null hypothesis could be rejected with > 95% confidence. All probability values are 2 tailed. The SPSS 15 statistical software package (SPSS Inc, Chicago, IL, United States) was used for all calculations.

RESULTS

According to the pre-established criteria, 124 patients were classified as HF-PEF. The baseline characteristics of the patients with HF-PEF and HF-REF are listed in Table 1. The HF-PEF population was significantly older and included a larger proportion of women. There were no significant differences between groups regarding presence of conventional coronary risk factors for coronary

Table 1 Clinical variables of 353 consecutive patients with heart failure: Comparison between patients with heart failure and preserved ejection fraction and patients with heart failure and reduced ejection fraction *n* (%)

Variables	HF-PEF (*n* = 124)	HF-REF (*n* = 229)	*P* value
Age (yr)	69 ± 8	66 ± 12	0.01
Male gender	56 (45.2)	154 (67.2)	< 0.001
Hypertension	75 (60.5)	84 (36.7)	< 0.001
Hypercholesterolemia	35 (28.2)	52 (22.7)	0.25
Smokers	14 (11.3)	40 (17.5)	0.12
Diabetes	45 (36.3)	104 (45.4)	0.09
LVEF (%)	55 ± 9	33 ± 6	< 0.001

Data are expressed as mean ± SD, and *n* (%) for categorical variables. HF-PEF: Heart failure with preserved ejection fraction; HF-REF: Heart failure with reduced ejection fraction; LVEF: Left ventricular ejection fraction.

Table 2 Data on atmospheric pollution in ambient air and meteorological variables between the previous day and the 7 d prior to admission for both of the study group

	HF-PEF (*n* = 124)	HF-REF (*n* = 229)	*P* value
Meteorological variables			
Wind speedy (m/s)	2.72 ± 0.68	2.62 ± 0.78	0.21
Temperature (℃)	19.76 ± 2.52	20.08 ± 2.82	0.32
Relative humidity (%)	67.68 ± 6.10	66.85 ± 7.02	0.29
Gaseous pollutants (mg/m^3)			
CO	172.44 ± 23.89	177 ± 27.10	0.11
SO_2	8.1 ± 4.40	7.33 ± 3.46	0.06
NO_2	12.95 ± 8.22	4.50 ± 2.34	< 0.0001
O_3	59.80 ± 12.52	61.25 ± 11	0.26
Atmospheric particles (mg/m^3)			
PM10	21 (13-30)	25 (17.5-32)	0.02
PM2.5	13.5 (9-21)	16.5 (11-21)	0.12
PM1	8 (6-16)	9.5 (7-13)	0.42

All of the pollutants are expressed as the average concentration of the pollutant. Data are expressed as mean ± SD, and median values (interquartile intervals). HF-PEF: Heart failure with preserved ejection fraction; PM: Particulare material with an aerodynamic diameter; PM10: PM < 10 μm; PM2.5: PM < 2.5 μm; PM1: PM < 1 μm.

artery disease, with the exception of hypertension, which were higher in the patients with HF-PEF. Left ventricular ejection fraction was significantly reduced in the patients with HF-REF.

No statistically significant differences were found in the meteorological variables between both groups. Regarding gaseous pollutants, we found no statistically significant differences, except that there were higher concentrations of NO_2 exposure in patients with HF-PEF. When comparing, exposure to concentrations of sizes of particulate matter, between patients with HF-PEF and HF-REF, the first group tended to have lower values of PM10 (Table 2). We carried out partial multivariable binary logistic regression analyses, using a stepwise selection model. This analysis showed that exposure to NO_2 was a significant predictor of HF-PEF [odds ratio ranging from (1.403, 95%CI: 1.003-2.007, P = 0.04) to (1.669, 95%CI: 1.043-2.671, P =0.03); Table 3].

Table 3 Multivariate binary logistic regression analysis including nitrogen dioxide as the main independent variable

	OR	95%CI	*P* value
Model 1 (unadjusted)			
NO_2	1.428	1.001-2.055	0.04
Model 2			
NO_2	1.669	1.043-2.671	0.03
Age	1.278	0.912-1.618	0.33
Model 3			
NO_2	1.429	0.992-2.058	0.05
Gender	0.948	0.111-8.067	0.96
Model 4			
NO_2	1.403	1.003-2.007	0.04
Hypertension	0.36	0.037-3.482	0.37
Model 5			
NO_2	1.516	1.005-2.397	0.01
LVEF	1.024	0.791-1.324	0.85
Model 6			
NO_2	1.489	1.009-2.453	0.01
PM10	1.124	0.997-1.974	0.94

LVEF: Left ventricular ejection fraction; NO_2: Nitrogen dioxide; PM: Particulare material with an aerodynamic diameter; PM10: PM < 10 μm.

DISCUSSION

Short-term exposure to air pollution is associated with acute cardiovascular events[18-20]. Our results show that HF-PEF is common and accounts for a significant proportion of admissions in patients with HF, 35% of our patients. This rate of patients is similar to that reported in previous studies[14,21]. This group of patients had different characteristics from those of patients with HF-REF, including older population, higher proportion of women, and more frequent history of hypertension. In the present study, we demonstrated that short-term exposure to raised NO_2 levels are an independent risk factor for admission to hospital for HF-PEF population, even superior to classical described predictors, such as age, sex, hypertension and left ventricular ejection fraction[21,22].

Despite the large body of evidence linking NO_2 with daily mortality, few studies have addressed the issue of susceptibility to NO_2 by performing analyses by age, sex, and chronic morbidity[6]. Recents epidemiology studies have focused on cardiopulmonary dysregulation, including the role of air pollutant exposure in provoking decompensated congestive HF[3,10,23]. A number of mechanisms have been proposed to explain the cardiovascular effects of air pollutant. At the cellular level, these various mechanisms involve free radical production, oxidative stress, cytokine release, inflammation, endotoxin-mediated damage, stimulation of capsaicin receptors, autonomic nervous system activity and covalent modification of key cellular molecules[24-27].

Ongoing investigation suggests that, although diastolic abnormalities may be present in many patients with HF-PEF, other aspects of pathophysiology likely also contribute to symptoms. Previous studies have concluded that inflammation contributes to diastolic abnormalities in HF-PEF[28]. In our study, we discovered that NO_2 may

be a precipitating factor for admission for HF-PEF rather than the cause of this condition. The short-term elevations of NO_2 could play an important pathophysiologic role in HF-PEF population, perhaps through of the activation of molecular inflammatory pathways that could be transduced systemically even in the absence of obvious alveolitis or interstitial pneumonitis[29]. In this way, Briet et al demonstrated that exposure to urban gaseous pollutant (including NO_2) affect artery endothelial function in patients as well as healthy control subjects[30].

Our study has some limitations. We did not use time series analysis in our study to examine the short-term relationship between the variations in atmospheric pollution and HF. This was because daily variations in the pollutants during the 7 d prior to admission were small enough to allow us to exclude the time series analysis[29]. Moreover, the sample size could be small, but the association between NO_2 and HF-PEF was highly significant.

This is the first study that demonstrates that short-term exposure to NO_2 is independently associated with the HF-PEF population, when compared to the HF-REF population.

COMMENTS

Background

Several studies using administrative databases have shown a positive association between short-term increases in respirable or fine particles and the risk of hospitalization for congestive heart failure.

Research frontiers

Heart failure is of growing incidence and prevalence and is now the main cause for hospital admission among the elderly and increasing expenditure in medicine. Ambient air pollution is a recognized risk factor for cardiovascular morbidity and mortality. Despite the large body of evidence linking nitrogen dioxide with daily mortality, few studies have addressed the issue of susceptibility to nitrogen dioxide by performing analyses by age, sex, and risk of admission for heart failure with preserved ejection fraction and reduced ejection fraction.

Innovations and breakthroughs

Nitrogen dioxide is a strong respiratory irritant gas originating from high-temperature combustion. Main outdoor sources of nitrogen dioxide include motor vehicles (particularly those equipped with diesel engines) and fossil-fuel power plants, whereas the most important indoor sources are gas heaters, stoves, and environmental tobacco smoke. In this study, authors found statistically significant association between nitrogen dioxide and admission in the heart failure with preserved ejection fraction population.

Applications

Several precautionary recommendations can be made for healthcare providers who interact with individuals who are at risk for cardiovascular diseases. Although they have not been clinically tested or proven to reduce mortality, they are practical and feasible measures that may help to reduce exposures to air pollution and therefore potentially lower the associated cardiovascular risk. These recommendations can be: (1) all patients with cardiovascular disease should be educated about the cardiovascular risks posed by air pollution; (2) part of patient education should include the provision of information regarding the available sources (local and national newspapers) that provide a daily air quality index; and (3) on the basis of the forecast air quality index, prudent recommendations for reducing exposure and limiting activity should be provided based on the patient's level of risk.

Terminology

Heart failure is a condition that is usually caused by a reduction of the contractile function of the ventricular chambers or an impairment of the relaxation properties of the cardiac chambers. Air pollution is the introduction into the atmosphere of chemicals, particulate matter, or biological materials that cause discomfort, disease, or death to humans.

Peer review

This is a good descriptive study in which the authors analyze effect of short-term exposure of nitrogen dioxide in patients with the clinical syndrome of heart failure with preserved and depressed left ventricular ejection fraction. The results are interesting and suggest that other aspects, as the exposure of nitrogen dioxide can contribute to pathophysiology of the heart failure with preserved ejection fraction. These data are of public health importance.

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