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The Effect of Various LVEDPs on the Contractibility of Heart in Ischemia-Reperfusion Model in Rats Exposed to PM_{10}

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ABSTRACT

Cardiovascular disease (CVD) is the primary cause of death in the world**.** Ischemic heart disease (IHD) is one of the most common health threats to the population. Ischemic cardiac events account for the largest relative and absolute risk for mortality per 10- g/m3 elevation in particulate matters ($PM_{2.5}$). Particulate matters are the small particles, vapors, liquid droplets that have been associated with respiratory and cardiovascular morbidity and mortality in populations. The aim of this study was to determine the effect of PM_{10} in the dust of Ahvaz on hemodynamic parameters such as left ventricular developed pressure (LVDP) and +dp/dt (contractibility factors of heart) in various pressures of Left ventricular end-diastolic pressure (LVEDP) (10-90 mmHg) in ischemia reperfusion model of isolated hearts in rats. Adult male Wistar rats (250–300 g) were divided into four groups: control (0.1 ml normal saline, intratracheal instillation), PM1 (0.5 mg/kg PM_{10}, intratracheal instillation), PM2 (2.5 mg/kg PM_{10}, intratracheal instillation), PM3 (5 mg/kg PM10, intratracheal instillation). PM_{10} was instilled into trachea in two stages within 48 hours. The hearts were isolated and transferred to a Langendorff apparatus and subjected to 30 min of ischemia followed by 60 min of reperfusion. LVEDP increased (10-90 mmHg) then the LVDP and +dp/dt was measured in each stage. At LVEDP 10-30 mmHg, a significant increase in the LVDP and +dp/dt was observed. However, at the LVEDP 50-90 mmHg, a significant reduction in those options was seen. These effects on the reduction potential of contractibility in heart were worsened by PM.

Keywords: LVEDP, Particullate Matter, LVDP, +dp/dt, Ischemia–Reperfusion, Rat.

Abbreviations: I/R: ischemia-reperfusion**,** PM: particulate matter**,** MI: Myocardial infarction**,** PM_{10}: particles with aerodynamic diameter <10 μm**,** LVDP: left ventricular developed pressure**,** +dP/dt: rate of pressure development during myocardial contraction**,** LVDEP: Left ventricular end-diastolic pressure**,** IHD: Ischemic heart diseases

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INTRODUCTION

Cardiovascular disease (CVD) is the primary cause of death in the world having a death rate of 320.5 per 100,000 people and accounting for 38.0% of all deaths [1]. Ischemic heart disease (IHD) is one of the most common health threats to the population in which heart muscle is damaged or works inefficiently because of a deficiency or absence of its blood supply. This could cause atherosclerosis, chronic IHD acute myocardial infarction, and sudden death. Diabetes, gender, age, race, education, diet, serum cholesterol level, smoking, hypertension, and are important IHD risk factors [2].

Ischemic cardiac events account for the largest relative and absolute risk for mortality per 10- g/m3 elevation in particulate matters ($PM_{2.5}$) [3] also it has been found that exposure to air pollution is associated with a significantly increased risk of acute MI [4].

Reduction in PM levels could be a means for significantly reducing the CVD [5]. Studies have shown that the risk of an adverse post-MI outcome such as subsequent MI, death or first admission for heart failure is augmented with higher exposure to PM_{10} [6]. Particulate matters are the small particles, vapors, liquid droplets associated with respiratory and cardiovascular morbidity and mortality in populations [7].

Dusts are defined as natural events with considerable PM concentrations occurring in arid, semi-arid, or desert areas [8]. Ahvaz, the capital of Khuzestan province in Iran, is located in an arid area in the south-western part of Iran near Kuwait, Iraq and Saudi Arabia that are the major sources of dust events in the Middle East. Low vegetation cover, high temperatures, strong surface winds and humidity are known as the major causes of dust storms [9]. Ahvaz in recent years, and particularly since 2004, has been experiencing desert dust events originating from the sources such as Kuwait, Iraq and Saudi Arabia [10]. The aim of this study was to determine the effect of PM_{10}in the dust of Ahvaz on hemodynamic parameters such as LVDP and +dp/dt (contractibility factors of heart) in various pressures of LVEDP (10 mmHg to 90 mmHg) in ischemia reperfusion model in isolated hearts of rats.

MATERIALS AND METHODS

Chemicals

Heparin sodium was purchased from Sigma-Aldrich Co. (USA), ketamine HCl (10 %) and xylazine (2 %) were obtained from Alfasan Co. (Netherlands). Krebs salts were purchased from Merck Co. (Germany).

Animal treatments

Adult male Wistar rats (weighing 250–300 g) were divided into four experimental groups (n=10): control (0.1 ml normal saline, intratracheal instillation), PM1 (0.5 mg/kg PM_{10}, intratracheal instillation), PM2 (2.5 mg/kg PM_{10}, intratracheal instillation), PM3 (5 mg/kg PM_{10}, intratracheal instillation) [11]. The rats were maintained at dark- light cycle of 12 h a temperature of 22±2 °C and had free access to tap water and standard rat chow diet (Pars Co., Iran). The groups of animals were maintained in the animal house of the Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. They were treated in accordance with the guidelines of the Animal Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (no. ajums APRC-9316).

The studied area and the origin of dust storm

Ahvaz, the capital of Khuzestan province in Iran, having the geographical location of 31° 20 N, 40° 48 E and 18 meters above sea level [9], is located in an arid area in southwestern part of Iran in the vicinity of Saudi Arabia, Iraq and Kuwait [10]. Ahvaz appears to be influenced by the dust carried by the hot northwesterly wind that carries large quantities of dust from southern areas of Iraq [12].

In this study, the trajectory model was used to identify the origin of incoming dust storms that is a common way to study interprets how aerosols vary over space and time and the transport of aerosol from source regions to receptor sites. The main idea behind the back trajectories is that there exists a relation between the aerosol observations at the receptor site and air mass path [13].

PM intratracheal instillation

The PM was pulled out up from the membrane by a surgical blade [14] and suspended in sterile saline at a specific concentration and mixed constantly for 20 min before use [15]. The rats were anesthetized with intraperitoneal injection of ketamine–xylazine and then intubated and ventilated. 0.1 ml of saline and specific concentration of PM was instilled into the trachea through a fine intubation tube and connected to the ventilator for an additional 5 min. Two days later, after anesthesia with intraperitoneal injection of ketamine–xylazine, and intraperitoneal injection of Heparin sodium, 1000 IU/kg, 0.1 ml of saline and PM was instilled into the trachea by a fine intubation tube and were connected to the ventilator for an additional 5 min. Thirty minutes later, the hearts were isolated.

Preparation of the isolated heart

The trachea of the rats was cannulated and ventilated by a ventilator (UGO BASILE Co., model 7025). After anesthesia, the thoracic cage was opened and a steel cannula was put into the aorta and fixed with a suture. The hearts were rapidly mounted to a Langendorff perfusion apparatus and perfused at a constant flow of 10 ml/min and a temperature of 37± 0.1 °C. The perfusion Krebs–Henseleit buffer consisted of $MgSO_4$ (1.2 mM), NaCl (118 mM), $CaCl_2$ (1.75 mM), KH_2PO_4 (1.18 mM), KCl (4.75 mM), $NaHCO_3$ (25 mM) and glucose (11.1 mM), in double distilled water, at pH 7.4 was equilibrated by 95 % O_2 and 5 % CO_2. Fresh perfusion buffer was filtered by a 1.2-µm microfiber filter (GF/C glass filters; Whatman) for each experiment. Before the induction of ischemia, the hearts were perfused for 30 min to allow stabilization of coronary perfusion pressure and then subjected to 30 min of no-flow global ischemia followed by 60 min of reperfusion [16]. The LVEDP was measured with an inflated latex balloon connected to a transducer. LVEDPs were monitored continuously by a PowerLab system (ADInstruments) [17]. The successful and effective induction of ischemia was resolved by S–T segment elevation on the ECG (electrocardiogram) [16]. LVEDP increased (10 mmHg to 90 mmHg) and then LVDP and +dp/dt was measured in each stage.

Statistical analysis

Results were analyzed using GraphPad Prism6 and expressed as mean±SEM. Comparisons between groups were performed by repeated measurements of ANOVA followed by LSD for multiple comparison tests. $p<0.05$ was considered statistically significant.

RESULTS

Trajectory analysis

According to Hoffmann classification, the type of dust storm with visibility< 1000 m, wind speed>17/ms, PM10 500–2000 µg/m−3/h−1, is categorized as DS2 [18].

The dust originated from erosion of crustal sources of earth around Ahvaz and countries adjacent to Iran. In the present study by means of HYSPLIT model, it was indicated that the dust had come to Iran from Iraq.

Hemodynamic parameters

In this study, LVEDP increased from 10 mmHg to 90 mmHg. At LVEDP 10-30 mmHg a significant increase in the LVDP and +dp/dt was observed. However, at the LVEDP 50-90 mmHg, a significant reduction in those options was seen. These changes in PM groups were more severe. In LVEDP 40 mmHg no significant change was seen (Fig 1 and 2).

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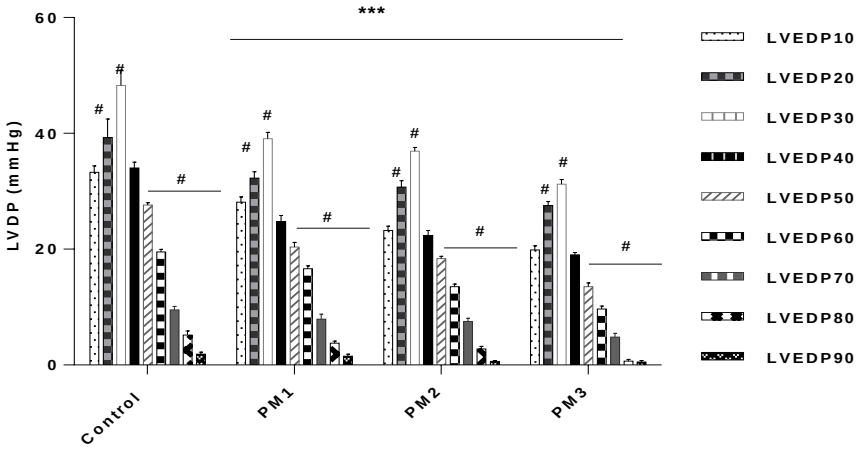

Figure 1: The Effect of PM on changes of LVDP imposed by LVEDP10-90 mmHg.

Results are expressed as mean ± SEM of 10 hearts per group. Control (0.1 ml normal saline, intratracheal Instillation), PM1 (0.5 mg/kg PM), PM2 (2.5 mg/kg PM), PM3 group (5 mg/kg PM). Repeated measurement ANOVA was used followed by the LSD test. ***p<0.001 vs. Control group. # p<0.001 vs. LVEDP 10 mmHg.

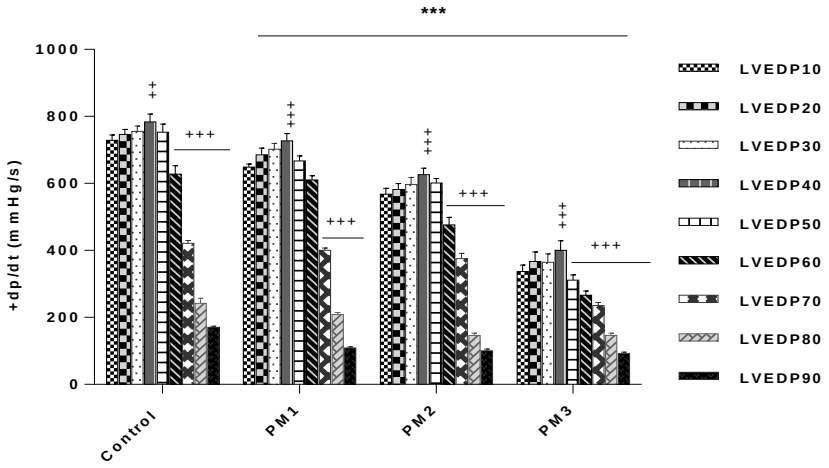

Figure 2: The Effect of PM on changes of +dp/dt imposed by LVEDP10-90 mmHg.

Results are expressed as mean ± SEM of 10 hearts per group. Control (0.1 ml normal saline, intratracheal Instillation), PM1 (0.5 mg/kg PM), PM2 (2.5 mg/kg PM), PM3 group (5 mg/kg PM). Repeated measurement ANOVA was used followed by the LSD test. ***p<0.001 vs. Control group. +++ p<0.001, ++ p<0.01 vs. LVEDP10 mmHg.

DISCUSSION

Exposures to particulate matter (PM) correlate most consistently with pulmonary and cardiovascular morbidity and mortality [19]. PM has been associated with increased risks of myocardial infarction (MI), arrhythmia, heart failure and stroke within hours to days of exposure in susceptible individuals [20].

Studies have indicated that PM can cause a direct increased risk for myocardial insult within 2h after exposure [21]. Studies have reported increased IHD hospital admissions related to short-term elevated concentrations of inhalable and/or fine PM air pollution [22].

In this study, an increase in LVEDP (10 mmHg to 90 mmHg) was shown to bring about a significant decrease in LVDP and +dp/dt in all groups, and this decrease was more pronounced in PM groups. Thus, increase in LVEDP reduced the potential of contractibility in heart.

Acute increases in risk for ischemic heart disease have been observed even as rapidly as 1-2 hours after exposure PM. The mechanism of induced IHD such as myocardial infarctions, from particulate matter pollution is not yet clear. It has been suggested that elevated PM2.5 may trigger myocardial infarction probably because of the association between homeostatic alterations and hemodynamic with particulate matter air pollution [23].

PM can increase Potential myocardial ischemia, infarct size and arrhythmias in experimental MI models. High concentrations of intratracheal PM instillation induced pulmonary inflammation and doubled the MI size in mice [24]. PM exposure causes a significant decrease in total myocardial flow (especially in the ischemic zone) and augments coronary vascular resistance with no alteration in rate-pressure product [25].

Ischemia -reperfusion in isolated rat hearts was associated with the suppression of contractile function by a decreased LVDP, impairment of the inotropic force of myocardial contraction and relaxation, and an increased LVEDP [26].

In Bagate et al.'s study in 2006 on spontaneously hypertensive (SH) rats that exposed intratracheal instillation to standard urban PM, a significant decrease was observed in LVDP before and after I/R in isolated rat hearts at 4h post exposure [27].

In our previous study it was shown that exposure to PM caused an increase in LVEDP and decreased LVDP in I/R model of rats [16].

CONCLUSION

In this study an increase in LVEDP (from 10 mmHg to 90 mmHg) reduced the potential of contractibility in heart. These effects on reduction potential of contractibility in heart were worsened by exposure to PM.

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REFERENCES

[1] American Heart Association. 2005 http://www.americanheart.org/downloadable/heart/1105390918119HDSStats2005Update.pdf
[2] Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Arch Intern Med 2002; 162:1867-72.
[3] Pope CA 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. Circulation 2004; 109:71–77.
[4] Tonne C, Melly S, Mittleman M, Coull B, Goldberg R, Schwartz J. Environ Health Perspect 2007;115:53–57
[5] Patrick Mastin J. Sustain 2006; 13.
[6] Zanobetti A, Schwartz J. Environ Health Perspect 2007; 115:769–775.
[7] Dockery DW. Ann Epidemiol 2009; 19: 257–263.
[8] Wang S, Wang J, Zhou Z, Shang K. Atmospheric Environment 2005; 39: 509e520.
[9] Heidari-Farsani M, Shirmardi M, Goudarzi G, Alavi-Bakhtiarivand N, Ahmadi-Ankali K, Zallaghi E. J Adv Environ Health Res 2014; 1(2): 120-8.
[10] Shahsavani A, Naddafi K, Jaafarzadeh HN, Mesdaghinia A, Yunesian M, Nabizadeh R, et al. 2012; 184 (11): 6683-92.
[11] Golomb E , Matza D, Cummings CA, Schwalb H, Kodavanti UP, Schneider A, et al. Toxicol Patho 2012; 40: 779-88.
[12] Goudie AS, Middleton NJ. Springer,Germany. 2006.

[13] Soleimani Z, Parhizgari N, Dehdari Rad H, Akhoond MR, Kermani M, Bagherian M, et al. Aerobiologia 2015; 31(2): 127-41.
[14] Manzano-Leon N, Quintana R, Sanchez B, Serrano J, Vega E, Vazquez-Lopez I, et al. J Biochem Mol Toxicol , 2013; 27(1): 87–97.
[15] Kodavanti U P, Schladweiler MC, Gilmour PS, Wallenborn J G, Mandavilli B S, Ledbetter A D et al. Environ Health 2008; 116(1): 13-20.
[16] Dianat M, Radmanesh E , Badavi M , Mard SA , Goudarzi G. Environ Sci Pollut Res 2015.(in press) doi 10.1007/s11356-015-5759-x.
[17] Garcia-Villalon AL, Monge L, Fernandez N, Salcedo A. Cardiovasc Res 2009; 81: 336–43.
[18] Hoffmann C, Funk R, Wieland R, Li Y, Sommer M. Journal of Arid Environments 2008; 72(5): 792-807.
[19] Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, McConnell R, Kuenzli N, Lurmann F, Rappaport E, Margolis H, Bates D, Peters J. N Eng J Med 2004; 351 : 1057–1067.
[20] Brook RD, Rajagopalan S, Pope C A 3rd, Brook J R, Bhatnagar A, Diez-Roux AV, Holguin F et al. Circulation 2010; 121:2331-78.
[21] Peters A, von Klot S, Heier M, Trentinaglia I, HoHE, Lo¨rmann A, Wichmann¨wel H. N Engl J Med 2004; 351: 1721–1730.
[22] Dominici F, Peng RD, Bell ML, Pham L, McDermott A, Zeger SL, Samet JM. JAMA 2006; 295: 1127–1134.
[23] Peters A, Dockery DW, Muller JE, Mittleman MA. Circulation 2001; 103: 2810-5.
[24] Cozzi E, Hazarika S, Stallings HW 3rd, Cascio WE, Devlin RB, Lust RM, Wingard CJ, Van Scott MR. Am J Physiol Heart Circ Physiol 2006; 291:H894–H903.
[25] Bartoli CR, Wellenius GA, Coull BA, Akiyama I, Diaz EA, Lawrence J, Okabe K, Verrier RL, Godleski JJ. Environ Health Perspec. 2009; 117:333–337.
[26] Osada M, Netticadan T, Tamura K, Dhalla NS. Am J Physiol 1998; 274: 2025–34.
[27] Bagate K, Meiring J J, Gerlofs-Nijland M E, Cassee F R, Wiegand H, Osornio-Vargas A, Borm PJA. Inhalation Toxicol 2006; 18(9): 633-43.