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Particulate Matter 2.5 Level Modulates Brachial Artery Flow-Mediated Dilation Response to Aerobic Exercise in Healthy Young Men

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Abstract: Particulate matter 2.5 ($PM_{2.5}$) is an environmental pollutant linked with the risk of cardiovascular disease. Aerobic exercise performed in polluted environments may have fewer benefits because of increased $PM_{2.5}$ inhalation during exercise. However, the vascular responses to aerobic exercise in high $PM_{2.5}$ ($HPM_{2.5}$) conditions remain unknown. This study aimed to examine the acute flow-mediated dilation (FMD) response to moderate-intensity treadmill running in $HPM_{2.5}$ levels compared to low PM2.5 ($LPM_{2.5}$) levels in healthy young males. Treadmill running in both $HPM_{2.5}$ and $LPM_{2.5}$ levels was completed by nine subjects. Brachial artery FMD was measured before and after the exercise to assess vascular endothelial function. Indoor $PM_{2.5}$ concentration was significantly higher in $HPM_{2.5}$ than in $LPM_{2.5}$ conditions ($p < 0.001$). Scaled FMD significantly increased after the exercise in $LPM_{2.5}$ conditions but not in $HPM_{2.5}$ ($p = 0.03$), and baseline diameter increased only in $HPM_{2.5}$ conditions after the exercise ($p = 0.001$). Baseline diameter and peak diameter were smaller, and time to peak dilation was delayed in $HPM_{2.5}$ compared to $LPM_{2.5}$ in pre-exercise intervention measurements ($p < 0.05$). Therefore, acute $PM_{2.5}$ exposure can counteract the positive effect of aerobic exercise on vascular endothelial function in young males.

Keywords: particulate matter 2.5; vascular endothelial function; flow-mediated dilation; aerobic exercise

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Citation: Kim, J.-S.; Lee, D.G.; Hwang, M.-H. Particulate Matter 2.5 Level Modulates Brachial Artery Flow-Mediated Dilation Response to Aerobic Exercise in Healthy Young Men. *Appl. Sci.* **2023**, *13*, 4936. https://doi.org/10.3390/app13084936

Academic Editor: Mark King

Received: 13 March 2023
Revised: 13 April 2023
Accepted: 13 April 2023
Published: 14 April 2023

1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide. Exposure to particulate matter 2.5 ($PM_{2.5}$), which is an inhalable particle that is 2.5 µm or even smaller, independently increases CVD incidence and mortality [1–3]. Additionally, increased $PM_{2.5}$ concentrations even below the United States (US) standard for $PM_{2.5}$ increased the risk of CVD [2]. $PM_{2.5}$ causes systemic inflammation that occurs and transfers from the respiratory system and alters the autonomic nervous system by activating alveoli sensory receptors [4,5]. Moreover, $PM_{2.5}$ translocates to the bloodstream due to the size of fine particles, thereby directly damaging the cardiovascular system [4,5]. Thus, $PM_{2.5}$-induced pathophysiological changes in respiratory and cardiovascular systems can negatively influence vascular structure and endothelial function.

The endothelium is an important anatomical structure that maintains vascular tone by releasing various vasoactive substances. Endothelial dysfunction is an early marker of atherosclerosis and a predictor for future CVD events [6–8]. Brachial artery flow-mediated dilation (FMD) is a clinical and noninvasive measure for assessing vascular endothelial function through endothelium-dependent vasodilation in response to the physiological

stimulus. Exercise training is a well-known behavioral intervention to improve FMD, and even acute aerobic exercise may increase FMD [9–11]. However, the benefits of exercise on vascular endothelial function may differ with $PM_{2.5}$ levels. Generally, increased minute ventilation during exercise increases $PM_{2.5}$ inhalation compared to resting, which is a non-active condition. A higher frequency of mouth breathing during exercise circumvents the filtration in the nasal cavity [12–14]. Additionally, an exercise-induced increase in airflow velocity facilitates the movement of inhaled $PM_{2.5}$ into the deeper region of the respiratory system [14]. Only a few studies have demonstrated the effect of exercise on endothelial function in high $PM_{2.5}$ ($HPM_{2.5}$) concentrations and reported inconsistent findings [15–18]. Moreover, previous studies were conducted using diesel exhaust in an indoor exposure chamber or an outdoor ambient environment. Understanding the influence of exercise in an indoor space with higher $PM_{2.5}$ levels compared with lower $PM_{2.5}$ conditions on vascular endothelial function is important because outdoor $PM_{2.5}$ rapidly infiltrates into indoor spaces and influences indoor air quality [19]. Therefore, our study controlled the indoor $PM_{2.5}$ concentrations with penetrated outdoor ambient $PM_{2.5}$ to emphasize the importance of managing $PM_{2.5}$ levels in indoor exercise spaces. This study aimed to examine and compare the influence of low and high $PM_{2.5}$ levels during acute moderate-intensity aerobic exercise on brachial artery FMD in healthy young males. We hypothesized that the effect of exercise on brachial artery FMD would be limited in $HPM_{2.5}$ levels compared to lower $PM_{2.5}$ ($LPM_{2.5}$) levels due to its negative influence on the cardiovascular system.

2. Materials and Methods

2.1. Subjects

This study included nine healthy young males (aged 23–27 years). They were all nonsmokers and free from cardiovascular, respiratory, and musculoskeletal diseases. The benefits, risks, and purpose of this study were fully explained to the participants, and they signed an informed consent form before participating in the study. All study procedures complied with the Declaration of Helsinki and were approved by the Incheon National University Institutional Review Board.

2.2. Study Design

Participants performed one bout of moderate-intensity aerobic exercise in both $HPM_{2.5}$ and $LPM_{2.5}$ conditions with a crossover study design. The exercise intervention consisted of indoor treadmill running at participants' 70% of peak heart rate (HR_{peak}) for 30 min. The Polar H7 HR sensor (Polar Electro Oy, Kempele, Finland) and Polar Team App (version 1.8.8, Polar Electro Oy, Kempele, Finland) were used to continuously monitor the heart rate (HR) during the treadmill running. Vascular endothelial function was assessed by brachial artery FMD before and after the exercise intervention in $HPM_{2.5}$ and $LPM_{2.5}$ conditions. Participants were initially allocated to either $HPM_{2.5}$ or $LPM_{2.5}$ conditions based on the indoor exercise facility and outdoor ambient $PM_{2.5}$ levels. A randomized crossover design could not be used because $HPM_{2.5}$ and $LPM_{2.5}$ condition visits had proceeded when participants' schedules and uncontrollable $PM_{2.5}$ levels were perfectly matched for each condition. Fortunately, the $HPM_{2.5}$ and $LPM_{2.5}$ condition visits were completed by five and four participants, respectively, as their first exercise visit. Participants were asked to fast (>6 h), avoid any intense exercise (>24 h), and refrain from caffeine and any other supplements (>12 h) that might affect the cardiovascular system before two different $PM_{2.5}$ condition visits [20]. At least 7 days of washout period was established between two $PM_{2.5}$ condition visits to eliminate acute confounding effects of aerobic exercise and $PM_{2.5}$ exposure from the previous $PM_{2.5}$ condition visit.

2.3. Body Composition

Height was measured by a conventional stadiometer, and body weight was measured with an InBody 720 Scale (Biospace, Republic of Korea). Body composition was assessed by dual-energy x-ray absorptiometry (Prodigy, GE HealthCare, Chicago, IL, USA). In $HPM_{2.5}$

and $LPM_{2.5}$ condition visits, the body weight and body composition were measured before the exercise intervention.

2.4. Maximal Cardiopulmonary Exercise Test

Participants completed the maximal cardiopulmonary exercise test (CPET) with a modified Bruce protocol to assess the maximal oxygen consumption (VO_{2max}) and HR (HR_{max}) before the first $PM_{2.5}$ condition visit ($HPM_{2.5}$ or $LPM_{2.5}$) [21]. The VO_{2max} and HR_{max} were obtained when the participant met at least three of the following criteria: (a) a plateau in oxygen consumption with increasing exercise intensity; (b) an HR within 10 beats/min of age-predicted HR_{max}; (c) at least 1.15 of maximal respiratory exchange ratio; (d) a score of $\geq$18 on the Borg rating of perceived exertion scale. However, VO_{2max} and HR_{max} are presented as peak oxygen consumption (VO_{2peak}) and HR_{peak} because more than one participant did not meet at least three criteria. Measured HR_{peak} was used for prescribing the accurate exercise intensity. At least 72 h of washout period was established before starting the first $PM_{2.5}$ condition visit to avoid the effect of maximal CPET on vascular endothelial function.

2.5. Blood Pressure and Brachial Artery Flow-Mediated Dilation

Blood pressure (BP) and brachial artery FMD were measured in a quiet and temperature-controlled laboratory with dimmed light. All measurements were performed after at least 10 min of rest in a supine position. An air purifier with a high-efficiency particulate absorbing filter in the laboratory was used to minimize the $PM_{2.5}$ exposure during baseline and post-exercise measures.

A SphygmoCor Xcel device (AtCor Medical, New South Wales. Australia) was used to measure the BP. The cuff was placed on the right upper arm, and the BP was measured at least three times. We averaged two systolic BP (SBP) and diastolic BP (DBP) values within 5 mmHg between measures.

Brachial artery FMD was assessed using a doppler ultrasound system (Aloka Prosound α7, Hitachi, Japan) with an 8–15 MHz linear array transducer (UST-5412, Hitachi, Japan). The participant's right arm was abducted in the supine position at the heart level. The pressure cuff was placed 1–2 cm distal to the antecubital fossa and connected to a rapid inflator/deflator system (E20 & AG101, D.E Hokanson, Washington, DC, USA). The brachial artery images were obtained approximately 5–10 cm proximal to the antecubital fossa. The transducer was clamped with the flexbar (Flexbar Machine Corporation, Islandia, NY, USA), after optimizing the image, to minimize the transducer's movement during the FMD procedure. Additionally, the distance between the transducer and the antecubital fossa was measured to capture the same portion of the brachial artery in the next visit. The blood velocity was assessed with $\leq 60°$ of the doppler's insonation angle. The baseline diameter and velocity were obtained for 1 min. Then, the pressure cuff was promptly inflated to 250 mmHg and maintained for 5 min. The diameter and velocity were recorded for 3 min after rapid cuff deflation to assess the vascular response to the reactive hyperemia. Acquired diameter and velocity were analyzed by commercially available automated wall detection software (Cardiovascular Suite, FMD Studio, Quipu, Italy). FMD was calculated as absolute (peak diameter–baseline diameter) and relative values ([peak diameter–baseline diameter]/baseline diameter). Additionally, FMD normalized by shear rate (SR) area under the curve up to the peak diameter (FMD/SR_{AUC}) was analyzed, and allometrically scaled FMD (scaled FMD) was assessed to eliminate any potential effects of changes in SR and baseline diameter on brachial artery FMD [20].

2.6. $PM_{2.5}$ Concentration

$PM_{2.5}$ levels were assessed by two SidePak AM520 personal aerosol monitors (TSI, Shoreview, MN, USA). Outdoor and indoor $PM_{2.5}$ concentrations were concurrently measured and recorded at each site during the exercise intervention. The recorded $PM_{2.5}$

concentrations were averaged each minute, and the personal aerosol monitors were located at the same spots throughout the study.

2.7. Statistical Analyses

Alterations in body weight, body composition, BP, and vascular endothelial function were assessed at baseline between $HPM_{2.5}$ and $LPM_{2.5}$ condition visits with the Wilcoxon signed rank test and paired *t*-test. The difference in outdoor and indoor $PM_{2.5}$ concentrations between $HPM_{2.5}$ and $LPM_{2.5}$ condition visits was confirmed with the Mann–Whitney U test. A 2 × 2 analysis of variance with repeated measures was performed to demonstrate the difference in the acute effect of moderate-intensity aerobic exercise on vascular endothelial function between $HPM_{2.5}$ and $LPM_{2.5}$ conditions. A generalized estimating equation (GEE) was used to control the influence of baseline diameter and SR on FMD data [20,22]. Using natural log-transforming baseline diameter (lnD_{base}), peak diameter (lnD_{peak}), and SR_{AUC} ($lnSR_{AUC}$), the GEE was employed with diameter difference (lnD_{peak}–lnD_{base}) as the dependent variable and lnD_{base} and $lnSR_{AUC}$ as covariates. Estimated means and estimated standard errors were back-transformed to scaled mean FMD and SE FMD with the following equations: scaled FMD mean = $(e^{EM} - 1) \times 100$; scaled FMD SE = $(e^{ESE} - 1) \times 100$. SR_{AUC}, FMD/SR_{AUC}, and scaled FMD were analyzed with data from eight participants excluding one outlier. Post hoc pairwise multiple comparisons were adjusted by Bonferroni correction. Data were presented as mean ± SE, and all statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics (version 27, USA). All statistical significance was set as $p < 0.05$.

3. Results

3.1. Subject Characteristics and $PM_{2.5}$ Concentrations

Body weight, body mass index, SBP, DBP, and HR were not different between $HPM_{2.5}$ and $LPM_{2.5}$ condition visits before the treadmill running (Tables 1 and 2). Both outdoor and indoor $PM_{2.5}$ concentrations in $HPM_{2.5}$ condition visits were 8.6- and 7.6-fold higher than the $LPM_{2.5}$ condition visits, respectively ($p < 0.001$; Table 1). Average indoor $PM_{2.5}$ concentration during the exercise in $HPM_{2.5}$ condition visits was higher than the 24 h $PM_{2.5}$ standard (35 μg/m^3) of the US Environmental Protection Agency (EPA) and categorized as "unhealthy for sensitive groups" or "unhealthy" by the US air quality index levels.

Table 1. Subject characteristics (n = 9) and $PM_{2.5}$ concentrations.

	$HPM_{2.5}$	$LPM_{2.5}$
Age, years	24.6 ± 0.4	
Height, cm	177.4 ± 1.5	
Body weight, kg	77.9 ± 1.6	77.5 ± 1.8
BMI, kg/m^2	24.8 ± 0.6	24.7 ± 0.7
Outdoor $PM_{2.5}$ concentration, μg/m^3	150.9 ± 27.1 *	17.6 ± 4.7
Indoor $PM_{2.5}$ concentration, μg/m^3	59.0 ± 2.1 *	7.8 ± 1.0

Values are mean ± SE. $HPM_{2.5}$, high particulate matter 2.5; $LPM_{2.5}$, low particulate matter 2.5; BMI, body mass index; PM, particulate matter. * $p < 0.001$ vs. $LPM_{2.5}$.

Table 2. Blood pressure and heart rate at pre- and post-exercise intervention.

	$HPM_{2.5}$		$LPM_{2.5}$		*p*-Value		
	pre	Post	pre	Post	C	T	C × T
SBP, mmHg	114.2 ± 2.0	120.3 ± 2.3	116.0 ± 2.3	119.7 ± 2.4	0.47	<0.001	0.22
DBP, mmHg	70.3 ± 2.6	73.6 ± 2.6	69.8 ± 3.0	73.0 ± 2.7	0.66	<0.001	>0.99
PP, mmHg	43.9 ± 1.5	46.8 ± 1.5	46.2 ± 1.3	46.7 ± 2.0	0.49	0.07	0.26
HR, bpm	59.3 ± 2.4	76.9 ± 1.9	60.3 ± 2.8	76.1 ± 2.8	0.94	<0.001	0.39

Values are mean ± SE. $HPM_{2.5}$, high particulate matter 2.5; $LPM_{2.5}$, low particulate matter 2.5; C, condition; T, time; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; HR, heart rate.

3.2. Responses to Treadmill Running in $HPM_{2.5}$ and $LPM_{2.5}$ Conditions

3.2.1. Blood Pressure

Responses of BP and HR to the acute moderate-intensity treadmill running were not different between $HPM_{2.5}$ and $LPM_{2.5}$ conditions. SBP, DBP, and HR immediately increased after the exercise intervention regardless of $PM_{2.5}$ levels as a normal physiological response of the human body to exercise ($p < 0.001$ for time effect; Table 2).

3.2.2. Brachial Artery Flow-Mediated Dilation

The absolute and relative FMD responses to aerobic exercise were not influenced by $PM_{2.5}$ levels (Table 3; Figure 1). However, the scaled FMD was significantly increased after the exercise in the $LPM_{2.5}$ condition ($p = 0.03$; Figure 1). Additionally, the post-exercise scaled FMD in the $LPM_{2.5}$ condition was significantly higher than post-exercise scaled FMD in the $HPM_{2.5}$ condition ($p = 0.009$; Figure 1). Baseline and peak diameters were smaller in the $HPM_{2.5}$ condition than in the $LPM_{2.5}$ condition before the exercise ($p < 0.05$; Table 3). The baseline diameter significantly increased after the aerobic exercise in the $HPM_{2.5}$ condition ($p = 0.001$; Table 3). However, the baseline diameter was the same after the exercise intervention in the $LPM_{2.5}$ condition. The time to peak dilation (TTP) was longer in $HPM_{2.5}$ than $LPM_{2.5}$ condition before exercise ($p < 0.05$).

Table 3. Brachial artery diameter and flow-mediated dilation at pre- and post-exercise intervention.

	$HPM_{2.5}$		$LPM_{2.5}$		*p*-Value		
	pre	Post	pre	Post	C	T	C × T
Baseline diameter, mm	3.68 ± 0.11 #,†	3.78 ± 0.10 *	3.76 ± 0.11	3.74 ± 0.11	0.51	<0.01	<0.01
Peak diameter, mm	3.97 ± 0.11 †	4.07 ± 0.10	4.04 ± 0.10	4.06 ± 0.12	0.42	0.03	0.15
Absolute FMD, mm	0.29 ± 0.04	0.29 ±0.04	0.28 ± 0.03	0.32 ± 0.03	0.86	0.40	0.16
FMD/SR_{AUC}, 10^{-3} % s	0.14 ± 0.02	0.11 ± 0.01	0.12 ± 0.01	0.15 ± 0.02	0.37	0.23	0.35
SR_{AUC}, 10^3 s^{-1}	54.13 ± 5.14	63.88 ± 3.83	64.75 ± 7.11	65.74 ± 7.95	0.33	0.26	0.22
TTP, s	58.8 ± 1.0 †	57.4 ± 3.2	52.1 ± 2.8	55.3 ± 3.5	0.18	0.76	0.31

Values are means ± SE. $HPM_{2.5}$, high particulate matter 2.5; $LPM_{2.5}$, low particulate matter 2.5; C, condition; T, time; FMD, flow-mediated dilation; SR_{AUC}, shear rate area under the curve; TTP, time to peak diameter. * $p = 0.001$ vs. $HPM_{2.5}$ pre is from pairwise multiple comparisons adjusted by Bonferroni correction; # $p = 0.03$ vs. $LPM_{2.5}$ pre is from pairwise multiple comparisons adjusted by Bonferroni correction; † $p < 0.05$ vs. $LPM_{2.5}$ pre is from paired *t*-test.

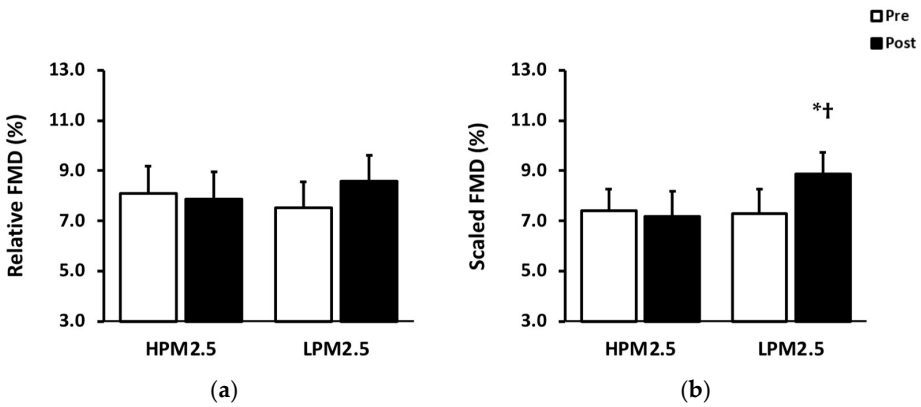

Figure 1. (**a**) Relative flow-mediated dilation and (**b**) scaled flow-mediated dilation at pre- and post-exercise intervention. $HPM_{2.5}$, high particulate matter 2.5; $LPM_{2.5}$, low particulate matter 2.5; FMD, flow-mediated dilation. Scaled FMD showed a significant interaction (condition × time) effect ($p < 0.001$). * $p = 0.03$ vs. $LPM_{2.5}$ pre is from pairwise multiple comparisons adjusted by Bonferroni correction; † $p < 0.01$ vs. $HPM_{2.5}$ pre and $HPM_{2.5}$ post are from pairwise multiple comparisons adjusted by Bonferroni correction.

4. Discussion

The current study investigated the difference in the response of vascular endothelial function to aerobic treadmill exercise between $HPM_{2.5}$ and $LPM_{2.5}$ levels. Consistent with our study hypothesis, the acute improvement of vascular endothelial function by aerobic exercise was demonstrated to be nullified in $HPM_{2.5}$ conditions. Additionally, the baseline diameter of the brachial artery was increased only after exercising in $HPM_{2.5}$ conditions. Baseline and peak diameters were smaller, and TTP was delayed in $HPM_{2.5}$ conditions compared to $LPM_{2.5}$ conditions before exercise.

To our knowledge, this is the first study that examined the influence of inhaled fine particulate matter on vascular endothelial function while exercising under indoor $HPM_{2.5}$ and $LPM_{2.5}$ conditions, naturally created by outdoor ambient $PM_{2.5}$. Previous studies explored the effect of aerobic exercise in $HPM_{2.5}$ concentrations on vascular function, but findings were inconsistent, and exercise interventions were conducted with different $PM_{2.5}$ sources [15–18,23,24]. Studies involving outdoor cycling in a high-traffic route did not reveal any relationship between vascular function and $PM_{2.5}$ concentrations [15,17]. The high-traffic route $PM_{2.5}$ concentrations were lower than the US EPA 24 h $PM_{2.5}$ standard, which might not negatively affect the cardiovascular system in healthy adults, although these studies were conducted with similar $PM_{2.5}$ sources to our study using ambient $PM_{2.5}$. Additionally, stationary cycle exercise in an exposure chamber with 300 $\mu g/m^3$ of $PM_{2.5}$ created by diesel exhaust did not influence brachial artery FMD in healthy young males [16]. However, our study used ambient $PM_{2.5}$ to form the $HPM_{2.5}$ condition, which can explain the discrepancy of findings with studies that only used diesel exhaust.

Previous studies reported FMD improvement in response to exercise [25,26]. These findings support our result in $LPM_{2.5}$ conditions and suggest exercise as beneficial to enhance vascular endothelial function. However, high ambient PM environment exposure can negate the positive effect of exercise on FMD. We found that the increased scaled FMD in $LPM_{2.5}$ conditions disappeared when the same exercise was performed in $HPM_{2.5}$ conditions. Similarly, FMD was significantly decreased after 30 min of running in a high ambient PM_1 condition in young adults [27]. PM exposure generally increases reactive oxygen species (ROS) production [28,29]. Oxidative stress induces the reduction in nitric oxide (NO) production and availability, which are key factors for vasodilation in response to reactive hyperemia [30]. Additionally, PM inhalation may facilitate leukotriene synthesis by ROS, which engenders endothelial dysfunction [31]. Furthermore, sympathetic nervous system activation by PM exposure might be associated with decreased FMD [32,33]. Collectively, increased PM inhalation during exercise may cause vascular endothelial dysfunction by oxidative stress, inflammation, and sympathetic nervous system activation.

The present study revealed lower pre-exercise baseline and peak diameters of the brachial artery in $HPM_{2.5}$ conditions than in $LPM_{2.5}$ conditions. We assume that vasoconstriction occurred due to $PM_{2.5}$ inhalation on the way from the participants' residence to the laboratory. Unfortunately, we were unable to accurately track the $PM_{2.5}$ exposure of study participants before starting pre-exercise measures. Participants spent 30 min to 2 h on the road or on public transportation to visit our laboratory. The brachial artery could have been constricted in response to the increased $PM_{2.5}$ inhalation before the pre-exercise procedures because participants were likely to be exposed to a high outdoor $PM_{2.5}$ environment in the $HPM_{2.5}$ visit. Interestingly, constricted pre-exercise brachial artery baseline diameter under $HPM_{2.5}$ conditions in this study revealed a similar magnitude of vasoconstriction to the previous studies with a high concentration of $PM_{2.5}$ exposure (150–200 $\mu g/m^3$) [18,34]. We speculate that increased sympathetic nerve activity and endothelin-1 (ET-1) secretion, which is an intrinsic vasoconstrictor, constricted the brachial artery in $HPM_{2.5}$ conditions. $PM_{2.5}$ inhalation was found to rapidly upset the autonomic nervous system balance by activating the sympathetic nervous system [32]. Moreover, elevated systemic and local oxidative stress and inflammation by $PM_{2.5}$ inhalation may increase ET-1 production [18,35].

Delayed pre-exercise TTP was found in $HPM_{2.5}$ conditions compared to $LPM_{2.5}$ conditions. Delayed peak dilation has been associated with the risks of CVD [36–39]. Increased

arterial stiffness caused by $PM_{2.5}$ exposure possibly induced the slower pre-exercise TTP in the $HPM_{2.5}$ visit, although mechanisms of delayed TTP are unclear. In two previous studies, shortened TTP was found to be associated with a decrease in arterial stiffness, which makes it possible to infer the relationship between TTP and arterial stiffness that may increase with exposure to air pollution [40,41]. Additionally, $PM_{2.5}$-induced oxidative stress and inflammation might impair the mechanosensor of endothelium and alter enzyme rates related to vasodilation signaling pathways. Moreover, the pre-exercise SR_{AUC} in $HPM_{2.5}$ showed a lower tendency compared to $LPM_{2.5}$ conditions ($p = 0.08$). This might occur due to the impaired vascular shear stress sensors and cause delayed TTP. Furthermore, the diameter change rate in response to reactive hyperemia can be slowed down by increased sympathetic nervous system activation due to $PM_{2.5}$ exposure [32]. Therefore, delayed vascular smooth muscle changes in response to hyperemia may occur in $HPM_{2.5}$ conditions before the exercise intervention. However, future studies are necessary to explore the potential mechanisms of delayed TTP by $PM_{2.5}$.

Our study demonstrated the significantly increased brachial artery baseline diameter after exercising in only the $HPM_{2.5}$ condition. The different response of baseline diameter to an acute aerobic exercise between $HPM_{2.5}$ and $LPM_{2.5}$ conditions might be related to a smaller baseline diameter before the exercise intervention in the $HPM_{2.5}$ condition than the $LPM_{2.5}$ condition. Increased SR during the aerobic exercise may have redeemed the baseline diameter of the brachial artery, although the pre-exercise baseline diameter of the brachial artery can be constricted in the $HPM_{2.5}$ visit, as we discussed above. Additionally, aerobic exercise can decrease plasma ET-1 concentration, which attenuates ET-1-induced brachial artery constriction [42]. The increased blood flow in the respiratory system during exercise is also likely to help reduce the circulating ET-1 by binding to ET_B receptors in the lungs [43]. Thus, we assume that treadmill running helps to recover the constricted baseline diameter of the brachial artery in the $HPM_{2.5}$ condition.

The strength of our study was that exercise intervention was performed in naturally formed high and low indoor $PM_{2.5}$ conditions with ambient air. Additionally, it provides insight into the response of vascular endothelial function to acute aerobic exercise in $HPM_{2.5}$ conditions that we often encounter in real life. Moreover, our results might convey the importance of managing $PM_{2.5}$ concentration in indoor exercise facilities. However, several limitations should be mentioned. First, our sample size was small, and we did not analyze physiological mechanisms to explain our new findings. Therefore, future research with large sample sizes is required in various populations, and this research must assess possible mechanisms to explain the response of vascular endothelial function to exercising in a polluted environment. Second, we only measured brachial artery FMD to evaluate endothelium-dependent vasodilation before and approximately 30 min after the exercise in healthy young males. However, the timing of post-exercise FMD measurement is known to influence results. Additionally, the influence of inhaled $PM_{2.5}$ on the cardiovascular system might be different with time. Thus, brachial artery FMD needs to be measured at multiple time points after exercise intervention to precisely analyze the effects of $PM_{2.5}$ during exercise. Herein, we could not measure vascular smooth muscle responsiveness to NO donors to assess intact endothelium-independent vasodilation in our study participants. Previous studies reported inconsistent findings about the effect of $PM_{2.5}$ on endothelium-independent vasodilation, and studies evaluating the effects of $PM_{2.5}$ on endothelium-independent vasodilation are scarce [23,29]; thus, future studies should examine both endothelium-dependent and endothelium-independent vasodilation after exercise in $HPM_{2.5}$ conditions. Third, we could not control the participants' $PM_{2.5}$ exposure before the scheduled experimental visits. The amount of inhaled $PM_{2.5}$ before the pre-exercise measurements may have varied among participants and affected the vascular response to the exercise intervention. Lastly, we could not separately measure and analyze all the pollutants during exercise. Different pollutants (e.g., carbon monoxide, sulfur dioxide, ozone, nitrogen oxide, and ultrafine particles) may additionally impair

the cardiovascular system [44]; thus, all pollutants have to be measured and analyzed to elucidate the influence of each pollutant on the response of vascular function to exercise.

5. Conclusions

Acute moderate-intensity treadmill running in $HPM_{2.5}$ levels, which is greater than the 24 h $PM_{2.5}$ standard (35 μg/m^3) of the US EPA, can nullify the benefits of exercise on brachial artery FMD in healthy young males. However, aerobic exercise may help restore constricted conduit arteries that are likely induced by $PM_{2.5}$ inhalation. To our best knowledge, the current study has the closest study design to a real-world situation that people can experience in daily life, but the conclusions must be interpreted carefully by considering the limitations.

Author Contributions: Conceptualization, J.-S.K. and M.-H.H.; methodology, J.-S.K., D.G.L. and M.-H.H.; software, J.-S.K., D.G.L. and M.-H.H.; formal analysis, J.-S.K. and M.-H.H.; investigation, J.-S.K. and M.-H.H.; resources, D.G.L. and M.-H.H.; data curation, J.-S.K.; writing—original draft preparation, J.-S.K. and M.-H.H.; writing—review and editing, D.G.L. and M.-H.H.; visualization, J.-S.K.; supervision, M.-H.H.; project administration, M.-H.H.; funding acquisition, M.-H.H. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by the Incheon National University Research Grant in 2018.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Incheon National University (7007971-201907-004-01-02 and 09/05/2019).

Informed Consent Statement: Written informed consent was obtained from all participants involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: The authors are grateful to the study participants for their time and effort.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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