Air Pollution, Physical Activity, and Cardiovascular Function of Patients With Implanted Cardioverter Defibrillators: A Randomized Controlled Trial of Indoor Versus Outdoor Activity

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Objective: To investigate whether implanted cardioverter defibrillator (ICD) patients exercising indoors on higher air pollution (AP) days had reduced adverse cardiovascular effects compared with those exercising outdoors. **Methods:** Eighteen participants were randomly divided into control or intervention groups. Blood pressure (BP), pulse rate (PR), and oxygen saturation (O_2SAT) were measured daily before and after participants walked outdoors for 30 minutes. On days with higher forecast AP the intervention group exercised indoors. **Results:** AP was significantly associated with increased BP and PR, and reduced O_2SAT. After adjustment for exercise levels, AP was associated with increased diastolic BP and PR in controls only. Significant improvements in cardiovascular measures over time were observed in both groups. **Conclusion:** In ICD patients, reducing AP exposure may reduce adverse cardiovascular effects, while daily mild exercise may benefit cardiovascular function.

Keywords: advice, air pollution, air quality health index, cardiac patients, cardiovascular function, implanted cardioverter defibrillator, intervention, physical activity, randomized controlled trial

The Air Quality Health Index (AQHI) is a risk communication tool intended to provide information to the public on current and forecast air quality conditions. It was developed by Health Canada and Environment and Climate Change Canada, based on a weighted sum of concentrations of nitrogen dioxide (NO_2), ozone (O_3), and particulate matter of median aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$), where weights are based on an analysis of the association between air pollution and mortality in Canada's 12 largest cities.[1] AQHI is designed to help Canadians make decisions to protect their health by limiting short-term exposure to air pollution and adjusting their activity levels during periods of increased levels of air pollution. This index pays particular attention to people who are sensitive to air pollution and provides them with advice on how to protect their health when air quality is classified as low, moderate, high, and very high health risk (https://www.canada.ca/en/environment-climate-change/services/air-quality-health-index/use.html. Last accessed on June 20, 2019). People with existing cardiovascular disease are one of the target groups for AQHI health messages. Although AQHI has been used for several years, little research has been done to qualitatively or quantitatively characterize the benefits that may be achieved by following AQHI advice to reduce exposure.

Learning Objectives

- Discuss the Canadian Air Quality Health Index (AQHI) and the rationale for the current study evaluating the benefits of AQHI advice to reduce exposure among people sensitive to air pollution.
- Summarize the new findings on cardiovascular effects of outdoor air pollution in people with implanted cardioverter-defibrillators (ICDs).
- Discuss the benefits of reducing exposure to air pollution based on AQHI in this population of patients.

Warburton et al[2] conducted a systematic review in which the effects of air pollution on persons living with coronary heart disease were examined, and the use of AQHI to communicate risk to patients exercising in cardiac rehabilitation settings was recommended. The influence of air pollution exposure on arrhythmias has been investigated in patients with an implantable cardioverter defibrillator (ICD) in a small number of studies, as reviewed by Link and Dockery,[3] Watkins et al,[4] and Yang et al.[5] Adverse outcomes examined include ICD discharges and arrhythmia events such as atrial or ventricular tachyarrhythmias. Long follow-up periods such as 3 to 4 years were required as ICD events can occur infrequently or not at all. Significant positive associations were reported in some of the studies for the three pollutants that form the AQHI ($PM_{2.5}$, O_3, and NO_2), as well as SO_2, CO, PM_{10}, black carbon, and sulphate.

Many ICD patients remain physically active outdoors and are therefore likely to be exposed to outdoor air pollution and to benefit from advice provided through the AQHI.[6] In the current study, we investigated whether ICD patients advised to exercise indoors on days with elevated AQHI might have reduced adverse impacts on cardiovascular measures compared with their counterparts exercising outdoors on those days.

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Clinical Significance:

Results demonstrate that outdoor air pollution was associated with adverse changes in cardiovascular measures in cardiac patients.

Advice to reduce exposure to air pollution based on Air Quality Health Index may help reduce adverse impacts on cardiovascular measures.

Daily mild exercise may benefit cardiovascular function in this population of patients.

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METHODS

Study Design and Participant Recruitment

This study used a non-blinded, randomized controlled trial design. Patients with structural heart disease with an ICD in situ, 19 years of age and older, living and working in Toronto (Canada) and surrounding area were recruited. Other inclusion criteria were: patients selected from the Peter Munk Cardiac Centre at Toronto General Hospital with Medtronic or St. Jude Medical ICDs that had follow-up visits; stable myopathic patients NYHA I or II (the New York Heart Association Functional Classification) who received ICDs for prophylactic reasons; non-smoker and not living in a smoking household. Participants also needed to be healthy enough for mild outdoor activity (a 30-minute walk) and thus likely to benefit from following exposure reduction advice provided through the AQHI. The participant follow-up periods were May 27 to November 15, 2016, and August 20 to December 8, 2017.

The following ICD patients were excluded: decompensated heart failure (CHF) patients, defined as a hospital admission for CHF or intravenous ionotropic administration within the preceding 6 months; patients being treated with class I and II antiarrhythmic medications; congenital heart disease patients; patients who had experienced frequent or recent shocks (within the last 3 months of the experiment); and patients who had underlying conditions that would interfere with mild daily exercise. During the study participating patients were not restricted in their use of cardiovascular medication or antioxidants.

Study volunteers went through an initial screening to ensure that their age, home location, and health conditions fit the inclusion/exclusion criteria. Following an informed consent, a baseline questionnaire was administered. Information collected on the baseline health questionnaire consisted of demographic information, smoking history, presence of respiratory or cardiovascular disease, medications, and housing characteristics. Daily questionnaires were also completed to document recent medication use, outdoor activity, symptoms, and indoor exposures (cooking, burning, hobby activities).

Participants were randomly allocated to control and intervention groups. During the study, the control group walked outdoors daily for 30-minutes. On days when Environment and Climate Change Canada forecast AQHI level to be more than or equal to five, the intervention group was instructed to walk indoors for 30 minutes. On days when AQHI level was forecast less than five, the intervention group walked outdoors for 30 minutes. This AQHI level was chosen because it is defined as having moderate risk (https://www.canada.ca/en/environment-climate-change/services/air-quality-health-index/use.html). Both groups were contacted by phone to remind them of their daily health measures and exercise, and to ensure compliance at the same exercise level. Cardiovascular measurements were done both before and after the walk, as detailed in the following sections. These daily activities were carried out for a maximum of 10 weeks.

The Research Ethics Boards of Health Canada, the University of Toronto, and the University Health Network approved the study protocol.

Air Pollution Sampling and AQHI Calculation

Continuous hourly air pollution data for the years 2016 to 2017 were downloaded from Environment and Climate Change Canada's National Air Pollution Surveillance website, Ontario's Ministry of the Environment, Conservation and Parks Air Quality Ontario website, and the University of Toronto's air pollution monitoring station. Continuous hourly weather data were downloaded from the Government of Canada's Historical Climate Data website. Using ArcGIS 10.6 (ESRI, Redlands CA), the centroid of the participants' Forward Sortation Area (the first three digits of the Postal Code) was used to calculate the distance to air pollution and weather monitoring stations. Using SAS EG v5.1 (SAS Institute, Cary, NC), inverse distance weighting (IDW) was used to calculate 3-hour moving air pollution and weather exposure averages for each participant. IDW was calculated using the formula $(1/R^2)$ where R is distance. The closer the monitoring station is to the participant, the greater the weight.

AQHI values were calculated according to the formula:

$$\mathrm{AQHI} = \left(\frac{10}{10.4} \times 100\right) \times \left(e^{0.000537 \times \mathrm{O_3}} + e^{0.000487 \times \mathrm{PM_{2.5}}} + e^{0.000871 \times \mathrm{NO_2}} - 3\right)$$

where O_3, $PM_{2.5}$, and NO_2 are ambient concentrations of O_3 (ppb), $PM_{2.5}$ ($\mu g/m^3$), and NO_2 (ppb).

Health Outcome Measurements

At the time of enrollment, we measured the height and weight and calculated the body mass index (BMI) for each participant using standard procedures. Before and after the daily 30-minute exercise, participants measured their blood pressure, pulse rate, and oxygen saturation. Participants recorded the number of steps during exercise using a Timex pedometer.

Blood pressure (BP): Systolic and diastolic blood pressure was measured in the dominant arm with the subject seated, using an automated blood pressure monitor (model 3MS1–4K, BIOS Medical, Newmarket, Ontario, Canada), taking the average of the three readings 1 minute apart in keeping with clinical recommendations.[7] The resolution of blood pressure is 1 mmHg.

Oxygen saturation: Oxygen saturation was measured using a pulse oximeter with a finger sensor (Choice MMed, Beijing Choice Electronic, China). The oximeter was run continuously for approximately 1 minute, and the value recorded. This procedure was repeated for three times, and the average was used for statistical analysis. The resolution of oxygen saturation measurement is 1%.

Pulse rate: Pulse rate was measured using the pulse oximeter. The resolution of pulse rate measurement is one beat per minute.

Statistical Analysis

We calculated descriptive statistics for the two treatment groups and conducted Student t tests using SAS EG (64 bit) version 5.1 (Cary, NC).

We used mixed-effects linear regression models (with restricted maximum likelihood estimation) to analyze associations of exposure to air pollutants and AQHI with cardiovascular measures pre- and post-exercise. Mixed models accounted for the repeated measures, assuming random slopes for participants, and fixed effects for time-invariant individual covariates and time-variant environmental variables. Covariates in all models included age (continuous), sex (binary), BMI (continuous), smoking history (binary, never, or ever), use of antioxidants (binary, yes, or no), treatment group (binary), day-of-the-week and day-of-the-study for 2016 and 2017 separately (to account for time trend and temporal cycles). We included an interaction term between treatment group and pollution concentration to see the effect of group assignment. We considered daily use of vitamin C, vitamin E, fish oil, and acetylsalicylic acid as taking antioxidants. We did not include the use of cardiovascular medication in models, since all patients took more than one cardiac medication (including: angiotensin-converting-enzyme inhibitor, angiotensin II blocker, anti-arrhythmic, anti-coagulant, anti-platelet, beta-blocker, calcium channel blocker, diuretic, and dopamine antagonist medications). In the models we included air pollutant concentration variables individually with lags at 0 to 2 days, each with natural spline functions of temperature with three degrees of freedom at individual lags of 0 to 2 days. We used an autoregressive model of order-one to adjust for serial autocorrelation.

Percent change in health measures associated with air pollution was calculated as follows:

$$\Delta y(\%) = 100 \times \frac{\beta \times \Delta x}{\bar{y}}$$

where β is the regression coefficient, Δx is the increment in pollution concentration (in this study an increase in air pollutant levels from 25th percentile to 75th percentile [interquartile range, IQR]), and $\bar{y}$ is the mean value of the health measure pre- or post-exercise.

To adjust for potential day-to-day variations in participant factors such as diet, stress, exposure to environmental tobacco smoke, and other unknown factors that may have contributed to variations in health measures, we calculated percent change of cardiovascular measures post-exercise from pre-exercise using the following equation:

$$\begin{aligned}&\text{Percent change of health measure } (\%)\\&\quad = ([\text{post-exercise - pre-exercise}]/\text{pre-exercise}) \times 100.\end{aligned}$$

We then applied this variable as a dependent variable to mixed-effects linear regression models as described above to estimate the associations with air pollutant concentrations adjusting for exercise levels (the number of steps taken during exercise) as well as other covariates taken in the main models, and included an interaction term of the product of treatment group and the concentration of an air pollutant.

Regression analyses were conducted using R, version 3.3.2 (https://www.r-project.org/). A two tailed value of $P < 0.05$ was considered statistically significant.

RESULTS

We enrolled 10 ICD patients in 2016, and eight patients in 2017. One patient participated in both years. Table 1 presents characteristics of the participants by treatment group, and baseline health measures. The control group had 10 participants with 589 follow-up days in total, while the intervention group had eight participants with 391 follow-up days. Participants in the control group exercised outdoors on 99% of the study days, while those in

TABLE 1. Selected Characteristics of Study Participants

Characteristic	Control Group ($n = 10$)	Intervention Group ($n = 7$)
Age (yrs, mean [standard deviation])	55.9 (14)	61 (13)
Sex (count [%])		
Female	3 (30)	1 (14)
Male	7 (70)	6 (86)
Race (count [%])		
White	6 (60)	3 (43)
Other	2 (20)	4 (57)
Unknown	2 (20)	0
Education (count [%])		
≤High school	4 (40)	3 (43)
College and university	5 (50)	3 (43)
Other	1 (10)	1 (14)
BMI (count [%])		
<25	3 (30)	2 (28)
25–29	3 (30)	4 (57)
≥30	4 (40)	1 (14)
Ever smoked (count [%])	6 (60)	3 (43)
Alcohol drinking (count [%])	6 (60)	2 (29)
Tea drinking (count [%])	4 (40)	5 (71)
Coffee drinking (count [%])	7 [70]	4 (57)
Doctor-diagnosed allergies (count [%])	6 (60)	3 (43)
Doctor-diagnosed asthma (count [%])	1 (10)	0
Cardiac medication use (count [%])		
ACE inhibitor	5 (50)	2 (23)
Angiotensin II blocker	4 (40)	1 (17)
Anti-arrhythmic	5 (50)	2 (33)
Anti-coagulant	2 (20)	2 (33)
Anti-platelet	3 (30)	3 (43)
Beta-blocker	9 (90)	6 (86)
Calcium channel blocker	1 (10)	0
Diuretic	1 (10)	1 (17)
Dopamine antagonist	0	1 (17)
Statin	4 (40)	4 (57)
Oral hypoglycemic use (count [%])	0	2 (29)
Antioxidant use (count [%])*	5 (50)	3 (43)
Having air conditioner (count [%])	9 (90)	6 (86)
Having dehumidifier (all types) (count [%])	5 (50)	0
ICD type (count [%])		
Medtronic	5 (50)	4 (57)
St. Jude Medical	5 (50)	3 (43)
Pulse rate (beat/min, mean [standard deviation])	63 (6)	75 (12)
Systolic blood pressure (mmHg, mean [standard deviation])	116 (20)	125 (10)
Diastolic blood pressure (mmHg, mean [standard deviation])	73 (12)	74 (8)
Oxygen saturation (%, mean [standard deviation])	98 (1)	97 (1)

*Antioxidants: Daily use of vitamin C, vitamin E, fish oil, and acetylsalicylic acid.

TABLE 2. Summary Statistics of Environmental Characteristics (Daily Maximum of 3-hour Moving Average of Air Pollutant Concentrations)

Variable	Treatment Group	*N*	Mean	Standard Deviation	Minimum	25th Percentile	Median	75th Percentile	Maximum	IQR	*P**
AQHI	Control	589	3.2	0.9	1.6	2.5	3.1	3.7	6.2	1.2	0.014
	Intervention	391	3.3	0.8	1.4	2.7	3.2	3.9	6.0	1.2	
$PM_{2.5}$, μg/m^3	Control	589	11.7	5.6	2.7	7.5	10.9	14.8	37.7	7.3	0.391
	Intervention	391	11.4	5.4	2.3	7.3	10.4	14.0	37.0	6.7	
O_3, ppb	Control	589	40.2	14.4	10.9	29.4	38.4	49.1	88.6	19.7	0.609
	Intervention	391	39.7	12.8	9.7	29.8	38.7	48.3	76.0	18.5	
NO_2, ppb	Control	589	19.0	8.0	2.4	12.5	19.0	24.6	44.0	12.1	<0.0001
	Intervention	391	22.2	9.4	3.9	15.0	21.7	27.7	46.6	12.8	
SO_2, ppb	Control	589	1.2	1.0	0.0	0.7	1.0	1.3	6.4	0.7	0.155
	Intervention	387	1.1	1.2	0.0	0.3	1.0	1.3	7.7	1.0	
CO, ppm	Control	589	0.4	0.1	0.2	0.3	0.3	0.4	1.0	0.2	0.419
	Intervention	386	0.4	0.2	0.2	0.3	0.3	0.4	1.6	0.2	
Daily relative humidity (%)	Control	589	65.8	11.0	38.4	58.5	66.4	72.9	96.3	14.3	0.006
	Intervention	391	64.7	10.7	38.4	58.3	64.6	72.1	92.8	13.8	
Daily temperature, °C	Control	589	17.7	7.5	−7.6	14.0	20.2	23.4	28.8	9.3	0.129
	Intervention	391	18.9	6.2	0.0	15.9	20.8	23.5	28.6	7.7	

**P* value is for the difference between two treatment groups.

the intervention group exercised outdoors on 88% of the days and indoors on 12% of the days.

Table 2 shows summary statistics of environmental variables by treatment group. Since AQHI is forecast at the maximum level, here we present the daily maximum of the 3-hour moving average levels. AQHI and NO_2 concentrations were slightly higher in the intervention group than in the control group, while exposure levels of other pollutants were similar between the two groups.

Table 3 shows percent change from mean value in health measures (95% confidence interval [CI]) for an increase in air pollutant levels from 25th percentile to 75th percentile (IQR) by treatment group, pre- and post-exercise, adjusted for the same-day temperature. Here we present the results for the air pollution lag day for which the strongest effect (largest *t*-ratio regardless of direction) was observed in the control or intervention group, together with results for the same lag for the other group. Full results for all lag days are presented in the Supplemental Digital Content file, http://links.lww.com/JOM/A684. Results show that: (1) before exercise in the intervention group, $PM_{2.5}$, NO_2, and CO were significantly associated with elevated systolic blood pressure. AQHI, $PM_{2.5}$, and NO_2 were significantly associated with elevated diastolic blood pressure. AQHI, $PM_{2.5}$, SO_2, and CO were significantly associated with reduced oxygen saturation. Pulse rate was also elevated in association with NO_2 in the intervention group. In the control group, these effects were not seen. (2) After exercise, in the intervention group, increased levels of AQHI, $PM_{2.5}$, NO_2, and CO were significantly associated with elevated systolic blood pressure. NO_2 was also associated with increased diastolic blood pressure, while SO_2 was associated with increased pulse rate. O_3 and CO were significantly associated with increased oxygen saturation. These effects were not seen in the control group. (3) Treatment group had significant influence on the associations between some of the air pollutants and health measures, illustrated by the significant *P* values for interaction terms. For example, the interaction terms for the treatment group and AQHI, NO_2, and CO were significant for pre-exercise blood pressure. The interaction term between SO_2 and post-exercise pulse rate was significant. (4) The results suggest that compared with the control group, the intervention group had stronger associations between increased air pollutant levels and adverse health measures, especially before exercise.

We also used percent change of blood pressure and pulse rate between post- and pre-exercise as a dependant variable in mixed-effects regression models adjusted for exercise levels. Since the change of oxygen saturation was smaller than the resolution of the pulse oximeter, this analysis was not done on oxygen saturation. Figure 1 illustrates the associations between exposure to air pollutants per IQR and percent change between post- and pre-exercise (95% CI) in health measures by treatment group. The control group had an increase in post-exercise diastolic blood pressure in response to an IQR increase in AQHI, $PM_{2.5}$, NO_2, and CO levels (1.13% [95% CI 0.10%, 2.16%], 0.79% [−0.16%, 1.74%], 1.01% [−0.23%, 2.26%], and 1.28% [95% CI 0.19%, 2.37%], respectively), and an increase in post-exercise pulse rate for an IQR increase in $PM_{2.5}$ (1.05% [95% CI 0.15%, 1.94%]), while the intervention group did not have any change. Increased SO_2 level in the control group was significantly associated with a decrease in post-exercise pulse rate (−1.03% [95% CI −1.55%, −0.52%]). Treatment group had significant influence on the associations between some pollutants and health measures (diastolic blood pressure with CO, and pulse rate with SO_2, illustrated by the significant *P* values [<0.05] for interaction terms).

Temperature lag days had minimal influence on the associations of air pollutants with pre- and post-exercise percent change of health measures from mean values. Figure 2 illustrates the associations between NO_2 concentrations and percent change of systolic blood pressure from the mean value for control (Fig. 2A) and intervention (Fig. 2B) groups, at daily temperature lag 0 to 2 days. Full results on temperature lag days can be found in the Supplemental Digital Content file, http://links.lww.com/JOM/A684.

Figure 3 shows the associations between study duration and the percent change of health measures from the mean value for all ICD patients. Mild exercise over 70 study days was significantly associated with cardiovascular measures in this cohort of participants, with reduced pulse rate and blood pressure, and elevated oxygen saturation before and after the exercise.

DISCUSSION

In this study, our aim was to investigate whether ICD patients who followed advice to exercise indoors on days when the AQHI was higher might have reduced adverse impacts on cardiovascular

TABLE 3. Percent Change from Mean Value in Health Measures (95% Confidence Interval) Per Interquartile Range Increase in Air Pollutant Levels by Treatment Group, Pre- and Post-Exercise

		AQHI			$PM_{2.5}$			O_3			NO_2			SO_2			CO		
Health Measure	Group	Lag Day	Mean (95% CI)	Inter. P^*	Lag Day	Mean (95% CI)	Inter. P^*	Lag Day	Mean (95% CI)	Inter. P^*	Lag Day	Mean (95% CI)	Inter. P^*	Lag Day	Mean (95% CI)	Inter. P^*	Lag Day	Mean (95% CI)	Inter. P^*
Pre-exercise																			
Pulse rate	Control	1	−0.08 (−1.02, 0.86)	0.097	0	−0.38 (−1.19, 0.42)	0.447	1	−0.01 (−1.07, 1.04)	0.091	1	0.31 (−0.68, 1.30)	0.176	0	0.37 (−0.04, 0.78)	0.9344	2	−0.41 (−1.12, 0.29)	0.942
	Intervention		0.85 (−0.05, 1.75)			0.09 (−0.76, 0.93)			1.02 (−0.02, 2.06)			**1.09 (0.15, 2.03)**			0.38 (−0.09, 0.86)			−0.46 (−1.23, 0.32)	
Systolic BP	Control	0	−0.44 (−1.46, 0.58)	**0.035**	0	0.67 (−0.21, 1.54)	0.103	0	−0.67 (−1.81, 0.47)	0.784	0	−0.16 (−1.23, 0.91)	**0.039**	2	0.33 (−0.11, 0.77)	0.2641	0	−0.27 (−1.00, 0.47)	**0.046**
	Intervention		1.01 (−0.07, 2.09)			**1.62 (0.62, 2.62)**			−0.39 (−1.66, 0.88)			**1.37 (0.27, 2.46)**			−0.06 (−0.67, 0.55)			**0.91 (0.04, 1.79)**	
Diastolic BP	Control	0	−0.26 (−1.16, 0.65)	**0.040**	0	0.51 (−0.26, 1.28)	0.209	2	0.07 (−0.84, 0.98)	0.446	0	−0.49 (−1.44, 0.45)	**0.015**	2	0.23 (−0.16, 0.62)	0.1256	0	−0.19 (−0.84, 0.46)	0.078
	Intervention		**1.04 (0.03, 2.05)**			**1.23 (0.29, 2.16)**			−0.46 (−1.55, 0.64)			**1.18 (0.16, 2.21)**			−0.30 (−0.87, 0.28)			0.78 (−0.04, 1.61)	
Oxygen saturation	Control	2	−0.05 (−0.12, 0.02)	0.315	2	−0.05 (−0.11, 0.01)	0.053	2	−0.02 (−0.09, 0.06)	0.557	2	−0.06 (−0.14, 0.02)	0.680	0	−0.02 (−0.06, 0.01)	0.3441	2	−0.01 (−0.06, 0.05)	0.067
	Intervention		**−0.10 (−0.18, −0.02)**			**−0.14 (−0.22, −0.06)**			−0.05 (−0.14, 0.04)			−0.09 (−0.18, 0.00)			**−0.06 (−0.11, −0.02)**			**−0.10 (−0.17, −0.03)**	
Post-exercise																			
Pulse rate	Control	1	0.24 (−0.84, 1.33)	0.554	2	0.46 (−0.44, 1.36)	0.311	2	0.52 (−0.59, 1.64)	0.293	1	0.05 (−1.16, 1.25)	0.339	0	−0.22 (−0.68, 0.25)	**0.029**	0	0.40 (−0.37, 1.17)	0.746
	Intervention		0.57 (−0.46, 1.60)			−0.23 (−1.15, 0.70)			−0.33 (−1.45, 0.80)			0.71 (−0.37, 1.78)			**0.59 (0.05, 1.13)**			0.59 (−0.26, 1.45)	
Systolic BP	Control	0	0.15 (−0.83, 1.12)	0.087	0	0.15 (−0.69, 0.99)	0.113	2	0.59 (−0.40, 1.58)	0.421	0	−0.15 (−1.24, 0.94)	**0.026**	1	**−0.49 (−0.92, −0.07)**	0.119	0	0.04 (−0.66, 0.74)	0.146
	Intervention		**1.20 (0.18, 2.23)**			**1.07 (0.12, 2.02)**			−0.03 (−1.14, 1.07)			**1.42 (0.38, 2.47)**			0.00 (−0.56, 0.56)			**0.88 (0.04, 1.72)**	
Diastolic BP	Control	0	0.26 (−0.67, 1.19)	0.229	0	0.51 (−0.29, 1.31)	0.749	1	−0.89 (−1.93, 0.15)	0.729	0	0.17 (−0.87, 1.21)	0.112	0	0.01 (−0.40, 0.41)	0.382	0	0.41 (−0.25, 1.08)	0.950
	Intervention		1.01 (−0.03, 2.05)			0.67 (−0.29, 1.63)			−0.59 (−1.80, 0.61)			**1.28 (0.22, 2.34)**			0.35 (−0.20, 0.90)			0.45 (−0.40, 1.30)	
Oxygen saturation	Control	2	0.01 (−0.07, 0.09)	0.418	2	−0.02 (−0.09, 0.05)	0.063	2	0.00 (−0.09, 0.09)	**0.033**	0	−0.04 (−0.13, 0.06)	0.247	2	**−0.04 (−0.08, 0.00)**	0.892	0	−0.05 (−0.11, 0.01)	**0.010**
	Intervention		0.06 (−0.04, 0.15)			0.09 (0.00, 0.17)			**0.14 (0.03, 0.25)**			0.04 (−0.06, 0.14)			−0.05 (−0.11, 0.00)			**0.08 (0.00, 0.17)**	

Models were adjusted for the same-day temperature.

*Inter. P: P value for the interaction term between treatment group and an air pollutant. Bold-faced values are statistically significant ($P < 0.05$).

measures compared with those who exercised outdoors on those days. In this randomized controlled study, the intervention group completed indoor mild exercise on 12% of the study days (when AQHI level was forecast more than five). The results show that in the ICD patients in both treatment groups, increased levels of AQHI and individual air pollutants were significantly associated with some cardiovascular measures. For example, in the control group before exercise, an IQR increase in AQHI was significantly associated with reduced blood oxygen saturation (–0.18% [95% CI –0.16%, –0.01%]). In the intervention group an IQR increase in AQHI was significantly associated with reduced pre-exercise oxygen saturation (–0.10% [–0.18%, –0.02%]) and increased diastolic blood pressure (1.04% [95% CI 0.03%, 2.05%]), and increased post-exercise systolic blood pressure (1.20% [95% CI 0.18%, 2.23%]). Several recent analyses have reported AQHI as a predictor for emergency visits for various diseases including ischemic stroke,[8,9] asthma,[10,11] otitis media,[12] and for adverse changes in heart rate variability[13,14] in Canada. Cities in China such as Shanghai[15] and Hong Kong[16] have adapted the Canadian AQHI approach and reported significant positive associations between AQHI and total mortality, hospital admissions, outpatient visits and emergency room visits,[15] and hospital admissions for cardiovascular and respiratory diseases.[16] Findings from our current study add supporting evidence demonstrating that ICD patients may experience adverse changes in cardiovascular measures on high AQHI days.

However, when percent change of a health measure from its mean value was used to estimate associations with air pollutant concentrations, compared with the control group, the intervention group experienced stronger associations between increased AQHI and individual air pollutant levels and adverse cardiovascular measures. These results are counterintuitive, as we expected the intervention group to be less affected by air pollution. Additionally, in both treatment groups pre-exercise associations between air pollutant concentrations and cardiovascular measures were stronger than post-exercise associations, although exercise is expected to increase the ventilation rate leading to elevated exposures. Daily cardiovascular measures can be affected by day-to-day changes in factors such as daily diet, sleep quality, stress, exposure to environmental tobacco smoke, indoor air pollutant levels and other unknown factors that could not be controlled by randomization of the treatment groups. In an attempt to adjust for the influence of these factors as well as the exercise level, we calculated the daily percent change between post- and pre-exercise and used this variable to run the regression models with an adjustment for exercise level. After these adjustments, indeed we found that the control group had an increase in post-exercise diastolic blood pressure in response to elevated AQHI, $PM_{2.5}$, NO_2, and CO levels, and an increase in post-exercise pulse rate in response to elevated $PM_{2.5}$, while the intervention group had no change in post-exercise blood pressure or pulse rate. This suggests that advice to reduce exposure to air pollution based on AQHI forecast may help reduce adverse effects on cardiovascular measures.

Few studies have evaluated the benefits that may be achieved from exposure avoidance in quantitative or semi-quantitative manner. Licskai et al[17] conducted a nonrandomized pilot intervention study in Windsor (Ontario, Canada) for the development of a mobile health system to support asthma self-management. In this study, daily AQHI forecast for the next day was sent to 22 adult patients with asthma with corresponding risk reduction message, and e-mail alerts were sent for moderate and high-risk days; and asthma control assessment displayed as green, yellow, or red zone with the corresponding asthma management advice. Their results show that 50% of participants changed their behavior at least once in response to a moderate risk AQHI health message that read "consider reducing or rescheduling strenuous activities outdoors if you are experiencing

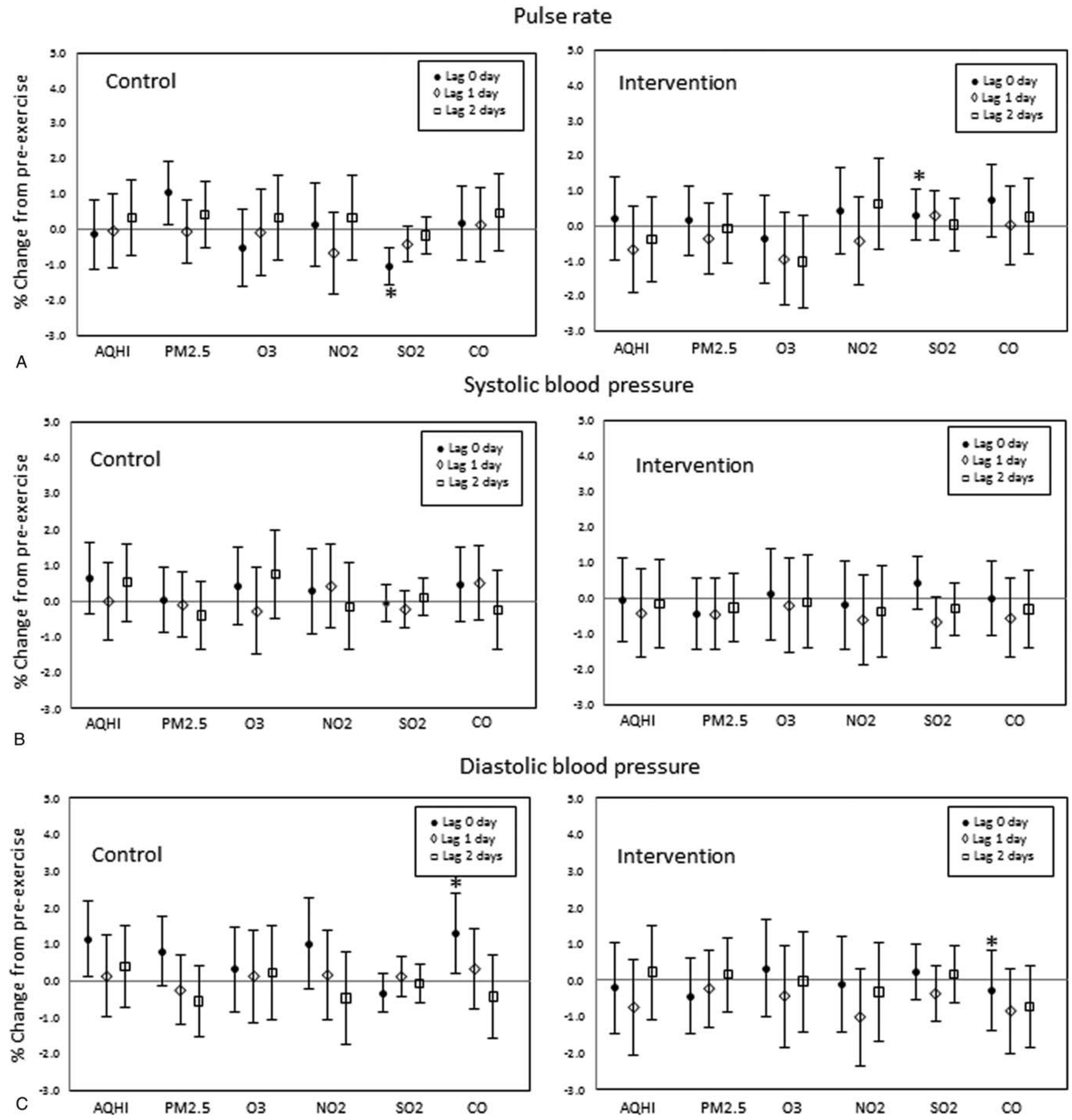

FIGURE 1. Percent change of health measures (95% confidence interval) between post- and pre-exercise for an IQR increase in air pollutants, at daily temperature lag 1 day. Exercise levels were adjusted in the models. *, statistically significant ($P < 0.05$) in the interaction term between treatment group and air pollutant concentrations.

symptoms'' and 32% changed their behavior at least six times. Stieb et al[18] evaluated the impact on personal exposure to air pollutants of following advice which typically accompanies air quality advisories and indices. This study was conducted in Toronto (Ontario, Canada), and demonstrates that following smog advisory advice results in reduced personal exposures to some pollutants, while at the same time increasing personal exposure to others, since some air pollutants have indoor sources. The authors suggest that advice need to be refined giving consideration to overall personal exposure. Our analysis on cardiovascular measures suggests that following the advice to exercise indoors on days when AQHI is forecast more than or equal to five may help reduce adverse impacts on cardiovascular measures in the ICD patients.

Consistent with our previous reports,[13,14] over the period of exercising days we observed a significant improvement in cardiovascular measures in this cohort of participants, demonstrated by significant reduction in pulse rate (–2.7% pre-exercise; –6.1% post-exercise) and systolic (–3.5% both pre- and post-

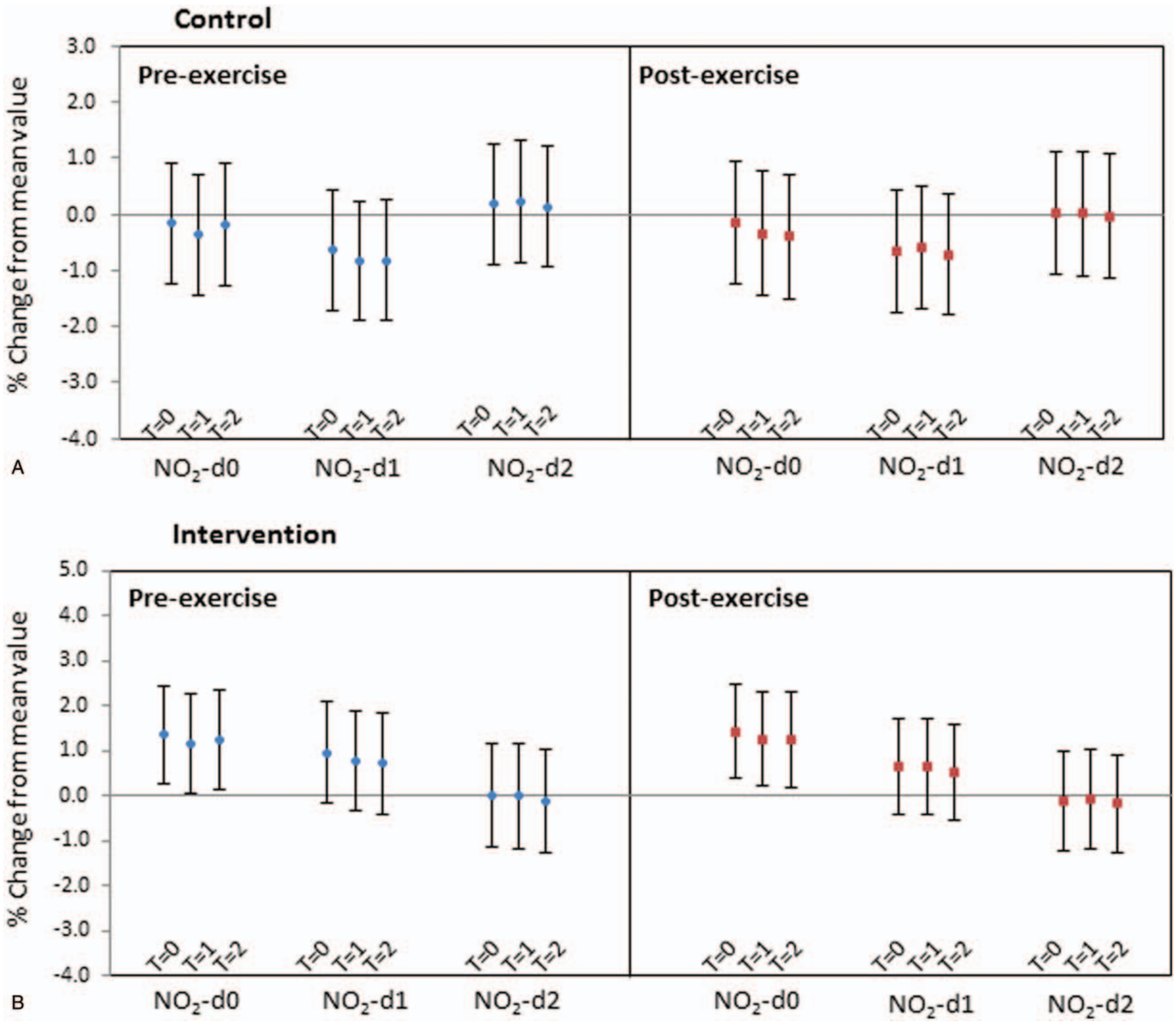

FIGURE 2. Percent change (95% confidence interval) from mean value in systolic blood pressure (A—Control and B—Intervention) for an IQR increase in NO_2, at daily temperature lag 0 to 2 days ($T = 0$ to $T = 2$). NO_2-d0, NO_2-d1, NO_2-d2: NO_2 concentrations lag 0 to 2 days.

exercise) and diastolic blood pressure (−2.7% pre-exercise; −2.3% post-exercise), and elevation of oxygen saturation (0.2% pre-exercise; no change post-exercise). The results suggest that daily mild exercise over 70 days may benefit cardiovascular function in this population of ICD patients. This finding is in line with physical activity recommendations for persons living with coronary artery disease summarized by Warburton et al.[2]

This study has obvious limitations. Recruiting a sufficient number of ICD patients was a challenge for reasons such as harsh weather in Toronto, exposure to environmental tobacco smoke, reduced mobility, disinterest, or health concerns. In Toronto, air pollutant levels were relatively low and days with AQHI levels more than or equal to five were infrequent, and thus we had only 12% days when participants in the intervention group exercised indoors. These factors limit statistical power to detect significant changes in health measures following the advice to avoid exposure to increased outdoor air pollution. Nevertheless, we observed significant associations between exposure to outdoor air pollutants and adverse cardiovascular measures, suggesting that indeed this panel of patients was sensitive to the exposure. When feasible, a larger number of participants and more sensitive cardiac measures such as heart rate variability may lead to more definitive conclusions. We did not measure indoor air pollutant levels which also might influence cardiovascular measures. The application of daily percent change between post- and pre-exercise of cardiovascular measures for the mixed-effect regressions may, to some extent, have adjusted for daily variations of indoor exposures.

In conclusion, findings from the present study suggest that outdoor air pollution in Toronto is associated with adverse changes in cardiovascular measures in patients with ICD. While differences in response to air pollution did not consistently favor the intervention group, advice to reduce exposure to air pollution based on AQHI forecast may help reduce adverse impacts on cardiovascular measures. Daily mild exercise over 70 days may benefit cardiovascular function in this population of ICD patients.

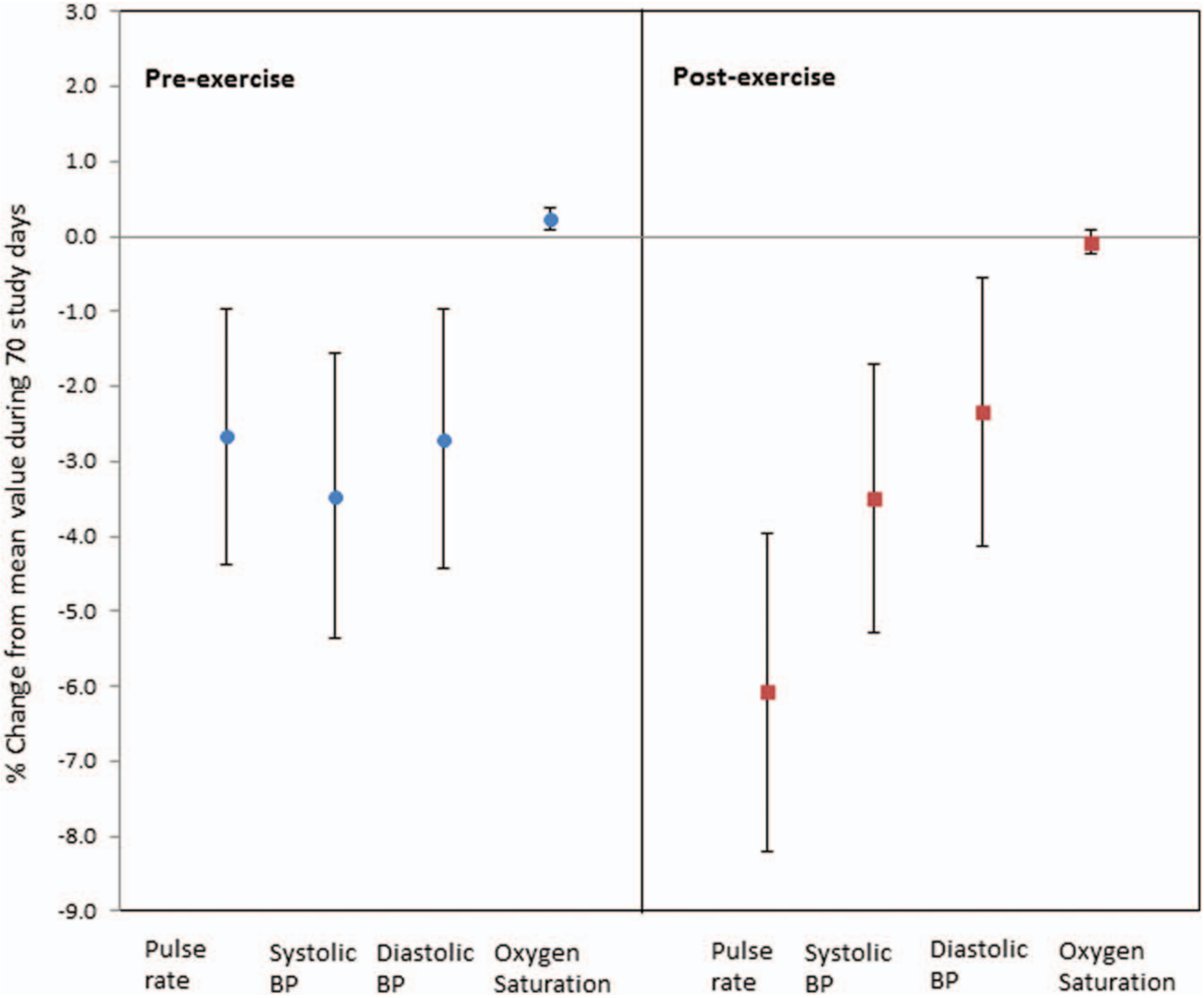

FIGURE 3. Percent change (95% confidence interval) from mean value in health measures during 70 study days for all ICD patients, in models adjusted for AQHI (lag 2 days) and same-day temperature.

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