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Acute Changes in Ambient Temperature Are Associated With Adverse Changes in Cardiac Rhythm

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Abstract

Background—Both increases and decreases in ambient temperature have been associated with increased cardiovascular mortality and morbidity. However, the mechanism(s) remain unclear.

Objectives—We examined associations between biomarkers of pathways thought to, in part, explain these associations and changes in ambient temperature in a panel of predominantly post-myocardial infarction or post-stent patients.

Methods—We studied 76 subjects who had a recent coronary event and were participating in a cardiac rehabilitation program. In these patients, we measured heart rate variability, repolarization, and baroreflex sensitivity parameters using Holter ECG recordings before and during supervised, graded, twice weekly, exercise sessions. Hourly temperature measurements were made at a monitoring site near the rehabilitation center.

Results—Using linear mixed models, we observed decreases in rMSSD (square root of the mean of the sum of the squared differences between adjacent NN intervals) and deceleration capacity, associated with increases in ambient temperature in the previous four days. Additionally,

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decreased rMSSD was associated with both increasing temperature (mean in previous 6 hours) in the summer and decreasing temperature (mean in the previous 3 weeks) in the winter.

Conclusions—In a panel of cardiac rehabilitation patients, changes in ambient temperature were associated with decreases in markers of heart rate variability and baroreflex sensitivity, which may lead to increased risk of arrhythmic events and sudden death in post-infarction patients.

Keywords

ambient temperature; cardiac rehabilitation; heart rate variability; repolarization

INTRODUCTION

Multiple studies have demonstrated acute increases in cardiovascular mortality and morbidity associated with both increasing and decreasing ambient temperature (Bhaskaran et al., 2009; Rocklov, Ebi, & Forsberg, 2011; Ye et al., 2011). Due to climate change, there is the potential for more extreme temperatures, both hot and cold, which may increase cardiovascular morbidity and mortality. (Huang et al., 2011; IPCC, 2007) However, the mechanisms through which these acute changes in temperature may act are unclear. Knowledge of these mechanisms may provide an avenue for prevention of cardiovascular morbidity associated, in part, with these more severe temperatures. Autonomic nervous system dysfunction is one proposed mechanism (Hampel et al., 2010; Ren et al., 2011). Changes in heart rate variability have been associated with both acute air temperature decreases and increases in experimental studies among healthy young adult subjects (Bruce-Low, Cotterrell, & Jones, 2006; Liu, Lian, & Liu, 2008; Yamamoto, Iwamoto, Inoue, & Harada, 2007; Yao et al., 2009), observational studies of healthy older males (Ren et al., 2011), and myocardial infarction survivors (Hampel et al., 2010). However, individuals with underlying cardiovascular disease, such as cardiac rehabilitation patients and older adults, may be more susceptible to changes in temperature due to existing underlying disease (Abrignani et al., 2009; Guo, Barnett, Pan, Yu, & Tong, 2011; Muggeo & Hajat, 2009; Ye et al., 2011).

Previously, we conducted a study of cardiovascular biomarker responses to increases in ambient particulate matter concentrations in a panel of cardiac rehabilitation patients with a recent coronary event (myocardial infarction [MI] or unstable angina). We reported decreased heart rate variability (HRV) and baroreflex sensitivity, and delayed repolarization associated with increased ultrafine particle (particles <100nm in diameter), accumulation mode particle (100–500nm) and fine particle (<2.5 μm) concentrations in the previous few hours and days (Rich et al., 2012). Using these same data, we now examine whether acute ambient temperature changes impact these same markers. Based upon these previously observed biomarker responses to pollutants and knowledge that these responses are markers of pathways thought to underlie previous reports of cardiorespiratory mortality and morbidity, we hypothesized that increases in ambient temperature would be associated with increased heart rate, decreased heart rate variability and baroreflex sensitivity, and delayed repolarization. Several studies have discerned a U- or J-shaped relationship where the lowest mortality is found at moderate temperatures, with higher mortality with warmer temperatures (response time within a few days) and colder temperatures (response time

within a few weeks) (Anderson & Bell, 2009; Baccini et al., 2008; Bhaskaran et al., 2009; Braga, Zanobetti, & Schwartz, 2002; Chang, Shipley, Marmot, & Poulter, 2004; Goodman, Dockery, & Clancy, 2004; Guo et al., 2011; Kovats, Hajat, & Wilkinson, 2004; Liang, Liu, Chou, & Kuo, 2008; Linares & Diaz, 2008; McMichael et al., 2008; Ye et al., 2011) Therefore, we also hypothesized that 1) in the winter months, decreases in ambient temperature would be associated with increased heart rate, decreased heart rate variability and baroreflex sensitivity, and delayed repolarization, especially over longer time periods (weeks versus days or hours), while 2) in the summer, increases in ambient temperature would be associated with these same changes, especially over shorter time periods (hours or days versus weeks).

METHODS

Study population

The study population has been described in detail elsewhere.(Rich et al., 2012) We recruited 76 subjects who had a recent coronary event (MI or unstable angina) and were referred to the University of Rochester Cardiac Rehabilitation Center (Center) by their cardiologist. We excluded subjects if they had cardiomyopathy in the absence of coronary disease, coronary bypass grafting within the last three months, type I diabetes, chronic atrial fibrillation, anemia, left bundle branch block, presence of a prosthetic heart valve or pacemaker, used amiodarone regularly, were active smokers or living with an active smoker, or resided greater than 10 miles (16.1 km) from the air pollution monitoring site at the Center. The study was approved by the Research Subjects Review Board of the University of Rochester, and informed written consent was obtained from all subjects.

Study protocol

Subjects participated in the standard cardiac rehabilitation program. For the study protocol, they participated in a maximum of 20 supervised exercise sessions during a 10-week program between June 2006 and November 2009. At these visits, study participants came to the Center 30–60 minutes prior to exercise. During this pre-exercise time, we recorded ECG and made blood pressure measurements before they began exercise. After these measurements, subjects exercised for 45–60 minutes on a bicycle, treadmill, or rowing machine, including warm-up (2–5 minutes of gentle stretching) and cool-down periods (10 minutes resting). We again recorded ECG measurements during and after the exercise session. We used these 1,359 subject-visits and their ECG recordings in the statistical analyses described below.

During the visits, we measured subjects' heart rate variability and baroreflex sensitivity using 3-lead (modified V2, V5, and AVF) Holter ECG recordings (Burdick Altair-Disc holter recorder; Cardiac Science, Bothell, WA), which were analyzed using the Vision Premier Burdick Holter System (Cardiac Science, Bothell, WA) and custom-made programs at the University of Rochester Medical Center (Bauer et al., 2008; Cygankiewicz et al., 2008). The Holters were first automatically annotated by the commercial Holter scanning algorithm (Vision Premier Burdick Holter System) and then annotated by a trained technician.

Our methods for measuring HRV parameters have been described previously (Rich et al., 2012). RR intervals were exported to a custom made HRV program that produced a set of HRV parameters. Short-term, 'pre-exercise,' resting recordings provided information regarding HRV parameters unaffected by sympathetic stimuli during exercise, whereas the 'whole session' recording (including the exercise session) reflected the overall behavior of heart rate and autonomic responses to daily conditions, including exercise. Based in part on Bigger et al (Bigger et al., 1992), filtering criteria eliminated two RR intervals after atrial beats or premature ventricular beats. We did not apply pre-processing filtering to eliminate extreme values. We examined 5-minute segments during the resting period to standardize conditions for all HRV and repolarization parameters, requiring at least 200 beats for HRV analyses. As a post-processing approach, we evaluated outliers and determined whether the values were valid or not based on intra-lab ranges developed during a prior study (Schneider et al., 2010).

We measured time domain HRV parameters, including the mean NN interval time between successive normal to normal beats (MeanNN) as a measure of heart rate, the standard deviation of all normal to normal beat intervals (SDNN; marker of overall variability in heart rate), and the square root of the mean of the sum of squared differences between adjacent NN intervals (rMSSD; marker of parasympathetic modulation of heart rate) during the entire recording ('whole session'). We also measured heart rate turbulence slope (HRT) and deceleration capacity (DC) across the 'whole session' using programs adopted from Bauer et al (Bauer et al., 2006) and from Schmidt et al. (Schmidt et al., 1999) HRT is a measure of baroreflex sensitivity (Bauer et al., 2008; Cygankiewicz, Wranicz, Bolinska, Zaslonka, & Zareba, 2004) and is characterized by a brief acceleration and subsequent deceleration of heart rate following a spontaneous premature ventricular contraction, with decreased HRT associated with increased risk of cardiac death (Bauer et al., 2008; Stein & Deedwania, 2009; Stein & Barzilay, 2011). DC is an additional measure of heart rate dynamics, reflecting the variability in heart rate during periods when the heart is slowing down, complementing information based on the other HRV and HRT parameters (Bauer et al., 2008). It describes the capacity of the sinus rhythm to slow down, without necessarily being linked to one particular physiological regulation process (e.g. respiratory, baroreflex mediated, or circadian). DC seems to correlate well with low frequency power, which is believed to reflect baroreflex responses (Goldstein, Bentho, Park, & Sharabi, 2011; Lewek et al., 2009).

Repolarization is a critical mechanism of the electrophysiology of cardiac cells, and plays an important role in arrhythmogenesis and the risk of sudden death. To measure repolarization duration, we used the 'pre-exercise' recordings only and manually measured the QT interval duration in lead II, correcting it for heart rate (QTc) using Bazett's formula (Bazett, 1920). We also measured the difference between the peak and end of the T-wave (TpTe) as a measure of late repolarization duration.

Ambient Temperature and Pollution Measurements

Hourly temperature, relative humidity, and barometric pressure measurements were taken at the New York State Department of Environmental Conservation (NYS DEC) site in

Rochester (~ 5.5 km from the Rehabilitation Center). We then used these hourly values to calculate the mean temperature, relative humidity (RH), and barometric pressure levels in the 24 hours before each clinic visit. In the same manner we calculated longer (e.g. mean temperature from lag hours 0–47, 0–71, 0–95, 0–119, 0–143, 0–167, and 0–304) and shorter mean weather values (lag hours 0 to 5). These mean temperatures, RH, and barometric pressure levels were then used in the statistical analyses described below.

Particle size distributions for ultrafine particles (UFP; 10–100 nm diameter) and for accumulation mode particles (AMP; 100–500 nm diameter) were measured using a wide range particle spectrometer (model 1000XP; MSP Corporation, Shoreview, MN) at the Cardiac Rehabilitation Center. Concentrations of $PM_{2.5}$ were measured using a tapered element oscillating microbalance (ThermoFisher, Franklin, MA) at the New York State Department of Environmental Conservation site in Rochester (~ 5.5 km from the Cardiac Rehabilitation Center).

Statistical Analysis

We used linear mixed models, with a compound symmetry covariance structure, to estimate the change in outcome (QTc, TpTe, MeanNN, SDNN, rMSSD, HRT, and DC) associated with each interquartile range increase in the mean temperature in the previous 24 hours, controlling for each subject's visit number, days since study inception, calendar month, weekday, and time of day. Barometric pressure, relative humidity, and ozone concentrations were not consistently associated with outcomes, and therefore not included in analyses. We also estimated changes in each outcome associated with interquartile range (IQR) increases in the mean temperature for shorter (mean of lag hours 0 to 5) and longer lag times (mean temperature from lag hours 0–47, 0–71, 0–95, 0–119, 0–143, 0–167 [1 week], and 0–304 [3 weeks]). From these models, we present the change in each outcome (and its 95% confidence interval) associated with each interquartile range increase in temperature in the specified time period.

Next, to examine whether there were different outcome responses to temperature changes in the winter (e.g. increased heart rate, decreased heart rate variability, decreased baroreflex sensitivity, and delayed repolarization associated with *decreased* temperature) versus the summer (increased heart rate, decreased heart rate variability, decreased baroreflex sensitivity, and delayed repolarization associated with *increased* temperature), we conducted separate analyses restricted to only winter months (December–February), and then to only summer months (June–August). To determine whether the effect of temperature within the summer was dependent upon the actual level of temperature, we re-ran the summer analysis replacing the continuous temperature variable with indicator variables for temperature quartile. We did the same analysis within the winter.

To evaluate whether any changes in these HRV, repolarization, and heart rate turbulence parameters associated with temperature changes were independent of increases in ambient pollutant concentrations in the previous few hours/days, we re-ran the models described above controlling for any pollutant previously found to be associated with each specific outcome.(Rich et al., 2012) Second, we evaluated whether our estimated changes in each marker associated with increased temperature were independent of heart rate, by including

MeanNN in the same models described above. All data management and statistical analyses were done using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Study subject characteristics are shown in Table 1. Of the 76 subjects, 63 (83%) completed all 20 rehabilitation visits, with six subjects (8%) completing less than 10 visits. Most subjects were older, white males, with a majority having a history of myocardial infarction, stent, or hypertension. Nearly all subjects were taking statins, with most also taking beta-blockers and angiotensin-converting enzyme inhibitors. Descriptive statistics of the HRV, repolarization, and heart rate turbulence parameters are shown in Table 2. The distribution of temperature, relative humidity, barometric pressure, and several air pollutants are shown in Table 3. The mean temperature throughout the study period was 11.8°C, with a mean in the winter and summer of −1.1°C and 22.2°C, respectively (Table 3).

Changes in each outcome associated with each IQR increase in the mean temperature in the previous 6, 24, 48, 72 and 96 hours, as well as the previous 1 week (168 hours) and 3 weeks (304 hours) are presented in Table 4. Consistent with our *a priori* hypotheses, IQR increases in temperature were associated with increased QTc, increased TpTe, and decreased MeanNN at all moving average times. IQR increases in temperature were also associated with increased SDNN at all moving average times (inconsistent with our *a priori* hypothesis). However, all of these estimates were not statistically significant, with 95% confidence intervals including both negative and positive values. Although increases in temperature at all lags were associated with decreased rMSSD, the largest rMSSD change was associated with each IQR increase in temperature in the previous 24 hours (12.81 ms; 95% confidence interval = −18.76, −6.86). Consistently, decreases in DC were associated with increasing temperatures as well, with the largest DC decrease observed at 72 hours (0.35 ms; 95% CI = −0.57, −0.13). IQR increases in temperature were also associated with decreased HRT at all lags. The largest HRT decrease was associated with each IQR increase in temperature in the previous 96 hours (1.60 ms/RR; 95% CI = −3.16, −0.05; Table 4).

In the winter months (December–February), we observed the largest increase in rMSSD associated with each IQR increase in temperature in the previous 3 weeks (6.93 ms; 95% CI = 0.17, 13.69; Table 5; Figure 1), but little change associated with increased temperature in previous 48 hours. There was an increasing effect size as the moving average of time increased from 72 hours to 3 weeks. Whereas in the summer, we observed the largest change in rMSSD associated with each IQR increase in temperature in the previous 6 hours (−9.66ms; 95% CI = −15.60, −3.72; Table 5; Figure 1). In the winter, each IQR increase in the average temperature over the previous 96 hours was associated with a significant decrease in HRT (−1.21 ms/RR; −2.41, −0.01; Table 5), while in the summer, IQR temperature increases were associated with consistent, but smaller and not statistically significant decreases in HRT. In the winter and summer with fewer subjects per group, IQR increases in temperature at all lags were associated with small non-significant decreases in DC (Table 5).

Next, we evaluated whether the effect of temperature within the summer or within the winter was dependent upon the actual level of temperature. Within the summer, with each increasing quartile of temperature, we saw increasingly greater decreases in rMSSD (test for trend p=0.0002) (Table 6). In the winter, with each increasing quartile of mean temperature, we observed larger increases in rMSSD, as hypothesized, though the test for trend p-value was not significant (p=0.14) (Table 6). This suggests that our reported temperature effects on rMSSD were not limited to just the extreme temperatures.

Last, when we included air pollutant concentrations for these same lag times in our models, or when we included heart rate in our models, our effect estimates were not substantially different from our main analysis (Online Resources 1 and 2).

DISCUSSION

In a panel of post-infarction cardiac rehabilitation patients, increased temperature was associated with decreases in rMSSD, DC, and HRT in the next few days, suggesting parasympathetic modulation of heart rate and baroreflex sensitivity are impacted by acute temperature changes. In the summer, decreases in rMSSD were associated with *increased* temperature in the previous 6 hours, while in the winter, decreases in rMSSD were associated with *decreased* temperature in the previous 3 weeks. We saw no such season-specific associations between increased temperature and changes in HRT or DC. These relationships were independent of long term time trends, day of the week, hour of the day, particulate and gaseous pollutant concentrations, duration of participation in the rehabilitation program, and heart rate. These associations also were not limited to just the extreme temperatures in the summer or winter. These small changes in parasympathetic modulation of heart rate and baroreflex sensitivity may make patients with decreased cardiovascular health more susceptible to future cardiac events.

Similar to previous studies, we found a decrease in heart rate variability (here rMSSD) associated with increases in temperature (Bruce-Low et al., 2006; Ren et al., 2011; Yamamoto et al., 2007). We found similarly sized decreases in rMSSD associated with each lagged temperature increase, with the largest in the previous 6 hours and 24 hours. This rapid rMSSD HRV response is similar to what we and others have observed with pollution (Brook et al., 2010; Rich et al., 2012; U.S. EPA, 2009). We also found that cold winter-time temperature and warmer summer temperatures both resulted in decreased rMSSD. However, this parasympathetic response to temperature was much more rapid in the summer (within 6 hours) than in the winter (within 3 weeks). Ren et al (Ren et al., 2011) reported only decreased HRV associated with increasing temperature in the warm season, but no effect of decreased temperature in the winter. However, other studies have reported adverse changes in CV biomarkers associated with decreased temperature (Okamoto-Mizuno, Tsuzuki, Mizuno, & Ohshiro, 2009; Schneider et al., 2008). Although these winter effects (i.e. decreased rMSSD associated with a decrease in the 3 week mean temperature) need to be replicated in further studies, this seasonal difference in temperature response is similar to the U-shaped relationship between temperature and mortality observed previously (Baccini et al., 2008; Braga et al., 2002; Kovats et al., 2004; Liang et al., 2008; Lin et al., 2009; Linares & Diaz, 2008; McMichael et al., 2008). To our knowledge, this is the first study to examine

the relationship between heart rate turbulence or deceleration capacity and ambient temperature.

The HRV, repolarization, and HRT variables included in our analysis were intended to allow us to assess whether acute temperature changes impacted the autonomic regulation of the heart and baroreflex sensitivity of the cardiovascular system. Our findings suggest that temperature increases, especially in the warm season, decrease parasympathetic modulation of heart rate and modify baroreflex sensitivity in as little time as 6 hours. The short timing of these HRT and rMSSD responses to temperature increases (HRT: 96 hours; rMSSD 6 and 24 hours) is consistent with the HRT and rMSSD responses to ambient air pollution we observed in this panel previously (HRT: 96 hours; rMSSD: 6 and 24 hours) (Rich et al., 2012). However, previously we reported prolongation of late repolarization duration (reduced TpTe) associated with increased AMP in the previous 24–47 hours (Rich et al., 2012), but we found no such repolarization parameter response to temperature increases. Further work is needed to replicate our season specific findings of decreased rMSSD HRV associated with increased temperature in the summer and decreased temperature in the winter.

Although this study had several strengths, including a large sample size, multiple observations per participant, and a wide range of temperatures throughout the study period, it had a few limitations. First, the temperature measure used was an outdoor temperature, but given the recent health event(s) of these subjects, they may have spent the majority of their time indoors. Therefore, they may not have been exposed to the outdoor temperature but for short periods of time each day (e.g. when traveling to the rehabilitation center), depending on the season. However, this error is likely non-differential with respect to rMSSD level (e.g. high versus low), resulting in a bias toward the null and underestimates of effect. Second, the secondary analyses examining temperature/outcome responses within the winter and summer seasons separately had limited sample sizes, decreasing the precision of our estimates. However, these were exploratory analyses examining the possible U-shaped response between temperature and outcomes. Future studies should be adequately powered to estimate and replicate these season specific effects. Third, we estimated a large number of temperature-outcome associations, increasing the potential for type one error. Our primary focus, however, was toward overall patterns of biomarker changes associated with multiple moving average temperature changes, not whether each individual effect was statistically significant. These patterns were consistent across moving averages of temperature and also consistent with our a priori hypotheses.

Last, most of the subjects included in the analysis for the winter season are different from those included in the analysis for the summer season. Four of the subjects had visits in both the winter and summer seasons (e.g. 14–19 visits in 1 season and 1–6 visits in the other season), with 26 subjects only in the winter analyses and 37 different subjects only in the summer analyses. Therefore, any seasonal difference in biomarker response to increased temperature by season could also be due to differences between the people studied each season. However, “winter” and “summer” subjects had similar study characteristics (data not shown), suggesting this was not the case.

In this panel of patients participating in a cardiovascular rehabilitation program, increases in outdoor temperature were associated with decreases in rMSSD, HRT, and DC. However, changes in rMSSD were in opposite directions in winter (decreased rMSSD associated with decreased temperature in the previous 3 weeks) and summer (decreased rMSSD associated with increased temperature in the previous 6 hours), providing some mechanistic explanation for previous reports of a U-shape relationship between ambient temperature and cardiovascular mortality. These sub-clinical changes in cardiac physiology (i.e. parasympathetic modulation of heart rate and baroreflex sensitivity) may be risk factors for future cardiovascular events. However, further work is needed to confirm these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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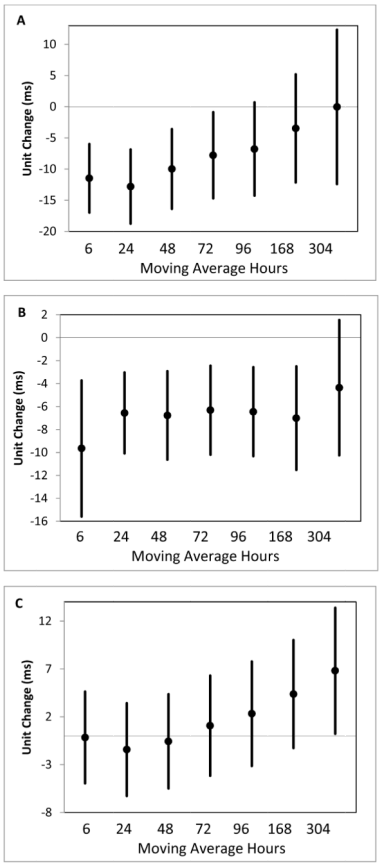

Figure 1.

Unit change and 95% confidence interval in rMSSD measured across the whole rehabilitation session associated with an IQR in ambient temperature for the whole year (A), summer months (B), and winter months (C).

Table 1

Characteristics of study population at baseline (N=76).

Characteristic	N	%
Age		
<50 years	13	17%
50–54 years	11	14%
55–59 years	10	13%
60–64 years	14	18%
65–69 years	12	16%
70–74 years	9	12%
75–79 years	5	7%
≥ 75 years	2	3%
Male	51	67%
White	68	88%
Body mass index category		
Normal Weight (18.5 kg/m^2 to <25 kg/m^2)	10	13%
Overweight (25 kg/m^2 to <30 kg/m^2)	31	41%
Obese (≥30 kg/m^2)	35	46%
History of:		
Myocardial infarction	45	59%
Coronary bypass surgery	4	5%
Stent	65	86%
Chronic obstructive pulmonary disease	13	17%
Type 2 diabetes mellitus	17	22%
Hypertension	45	59%
Smoking		
Never	40	53%
Former	36	47%
Daily Medication use at 1st Visit:		
Angiotensin Receptor Blocker	10	13%
Beta-blocker	66	87%
Angiotensin Converting Enzyme Inhibitor	50	66%
Calcium channel blocker	7	9%
Digitalis	1	1%
Diuretic	20	26%
Statin	73	96%

Table 2

Mean and standard deviation of each outcome, at the first cardiac rehabilitation visit.

Biomarker levels at baseline	Mean	Standard Deviation	Minimum	25th %tile	Median	75th %tile	Maximum
Pre-exercise resting period							
QTC (ms)	419.91	32.67	354.57	399.12	412.66	432.67	593.50
TpTe (ms)	89.06	12.05	55.89	81.64	87.04	93.51	149.25
Whole Session							
MeanNN (ms)	733.32	110.4	475.88	653.96	728.02	817.29	1102.68
SDNN (ms)	132.07	43.32	27.76	101.10	126.38	157.04	296.99
rMSSD (ms)	77.70	38.15	11.47	50.97	72.56	96.82	274.62
Heart Rate Turbulence Slope (ms/RR)	6.08	4.31	0	2.89	4.83	8.06	19.50
Deceleration Capacity (ms)	3.84	1.40	0.0005	2.93	3.84	4.72	9.79

Table 3

Descriptive statistics of daily air pollution concentrations and weather characteristics during the study period (June 26, 2006 to November 25, 2009. N=1249 possible days of measurement)

Weather Characteristic	Mean	Standard Deviation	Minimum	25th %tile	Median	75th %tile	Maximum
Whole Year							
Temperature (°C)	11.8	10.1	−13.8	3.6	13.0	20.1	31.3
Relative Humidity (%)	64.7	12.7	12.5	56.6	65.6	73.6	93.2
Barometric Pressure (inches Hg)	29.4	0.27	27.4	29.2	29.4	29.6	30.1
Winter (December–February)							
Temperature (°C)	−1.1	5.8	−13.8	−5.1	−1.2	2.1	16.4
Relative Humidity (%)	68.9	10.8	41.0	61.3	70.0	77.5	92.3
Barometric Pressure (inches Hg)	29.3	0.22	27.4	29.2	29.3	29.5	29.7
Summer (June–August)							
Temperature (°C)	22.2	3.5	10.7	19.8	22.1	24.3	31.3
Relative Humidity (%)	63.4	9.7	42.8	56.3	62.8	70.6	86.5
Barometric Pressure (inches Hg)	29.4	0.27	28.5	29.2	29.4	29.6	30.0

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Table 4

Change in each outcome associated with each IQR increase in ambient temperature, by moving average of time before outcome measurement was made.

	Biomarkers and moving averages evaluated	N Subjects (Subject-Visits)	IQR (°C)	Change in Biomarker	95% CI
PRE-EXERCISE RESTING PERIOD	**QTc (ms)**				
	0–5	76 (1263)	17.4	2.10	−1.69, 5.89
	0–23		17.4	2.23	−1.86, 6.32
	0–47		17.3	1.62	−2.76, 6.00
	0–71		17.4	2.36	−2.38, 7.10
	0–95		17.6	3.06	−2.03, 8.15
	0–167 (1 week)		17.6	3.40	−2.48, 9.29
	0–503 (3 weeks)		17.6	6.80	−1.6, 15.21
	TpTe (ms)				
	0–5	76 (1253)	17.4	0.89	−0.74, 2.52
	0–23		17.4	1.12	−0.65, 2.88
	0–47		17.3	0.95	−0.94, 2.84
	0–71		17.4	0.48	−1.56, 2.53
	0–95		17.6	0.43	−1.77, 2.63
	0–167 (1 week)		17.6	1.70	−0.83, 4.23
	0–503 (3 weeks)		17.6	1.79	−1.82, 5.41
WOHLE SESSION	**MeanNN(ms)**				
	0–5	76 (1359)	17.4	−6.83	−17.74, 4.08
	0–23		17.4	−8.56	−20.37, 3.24
	0–47		17.3	−4.53	−17.18, 8.13
	0–71		17.4	−4.54	−18.21, 9.14
	0–95		17.6	−4.01	−18.77, 10.74
	0–167 (1 week)		17.6	−4.26	−21.39, 12.86
	0–503 (3 weeks)		17.6	−4.43	−28.86, 20.00
	SDNN(ms)				
	0–5	76 (1357)	17.4	0.28	−4.62, 5.18
	0–23		17.4	0.79	−4.52, 6.09

Biomarkers and moving averages evaluated	N Subjects (Subject-Visits)	IQR (°C)	Change in Biomarker	95% CI
0–47		17.3	2.58	−3.10, 8.26
0–71		17.4	2.65	−3.49, 8.78
0–95		17.6	3.15	−3.47, 9.77
0–167 (1 week)		17.6	6.06	−1.61, 13.74
0–503 (3 weeks)		17.6	7.50	−3.46, 18.45
HRT(ms/RR)[a]				
0–5	76 (504)	17.4	−0.41	−1.59, 0.77
0–23		17.4	−0.63	−1.90, 0.64
0–47		17.3	−0.60	−1.94, 0.74
0–71		17.4	−1.23†	−2.68, 0.23
0–95		17.6	−1.60*	−3.16, −0.05
0–167 (1 week)		17.6	−1.45	−3.29, 0.39
0–503 (3 weeks)		17.6	−0.73	−3.39, 1.94
DC(ms)				
0–5		17.4	−0.29**	−0.46, −0.11
0–23		17.4	−0.32**	−0.51, −0.13
0–47		17.3	−0.34**	−0.54, −0.14
0–71	76 (1314)	17.4	−0.35**	−0.57, −0.13
0–95		17.6	−0.32**	−0.56, −0.08
0–167 (1 week)		17.6	−0.25†	−0.52, 0.03
0–503 (3 weeks)		17.6	−0.40*	−0.79, −0.01
rMSSD (ms)				
0–5		17.4	−11.48**	−16.98, −5.98
0–23		17.4	−12.81**	−18.76, −6.86
0–47	76 (1353)	17.3	−9.99**	−16.39, −3.59
0–71		17.4	−7.78*	−14.7, −0.86
0–95		17.6	−6.78†	−14.25, 0.69

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Biomarkers and moving averages evaluated	N Subjects (Subject-Visits)	IQR (°C)	Change in Biomarker	95% CI
0–167 (1 week)		17.6	−3.48	−12.15, 5.19
0–503 (3 weeks)		17.6	−0.03	−12.41, 12.35

[a]Note: Since HRT is measured only when premature ventricular contractions (PVC) occur, these analyses include only those subject-visits with 1 or more PVCs.

[†]p<0.10

[*]p<0.05

[**]p<0.01

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Table 5

Change in each outcome associated with each IQR increase or decrease in ambient temperature, by moving average of time before outcome measurement was made, by season.

		Winter (December–February)				Summer (June–August)			
	Biomarkers and moving averages evaluated	**N Subjects (N Subject-Visits)**	**IQR (°C)**	**Change in Biomarker per IQR increase**	**95% CI**	**N Subjects (N Subject-Visits)**	**IQR (°C)**	**Change in Biomarker per IQR increase**	**95% CI**
WHOLE SESSION	**HRT(ms/RR)**[a]								
	0–5	30 (118)	7.9	−0.47	−1.71, 0.77	41 (121)	7.2	−0.10	−1.83, 1.63
	0–23		7.3	−0.86	−2.08, 0.35		4.3	−0.32	−1.29, 0.65
	0–47		6.9	−0.53	−1.74, 0.69		4.2	−0.66	−1.74, 0.42
	0–71		6.5	−0.82	−2.06, 0.41		3.8	−0.61	−1.71, 0.50
	0–95		6.1	−1.21*	−2.41, −0.01		3.5	−0.60	−1.75, 0.55
	0–167 (1 week)		5.5	−1.02	−2.27, 0.24		3.1	−0.86	−2.30, 0.58
	0–503 (3 weeks)		4.6	−0.34	−1.94, 1.25		2.5	−0.07	−1.76, 1.62
	DC(ms)								
	0–5	30 (276)	7.9	−0.14	−0.32, 0.04	41 (379)	7.2	−0.10	−0.29, 0.09
	0–23		7.3	−0.11	−0.30, 0.07		4.3	−0.06	−0.18, 0.05
	0–47		6.9	−0.12	−0.30, 0.07		4.2	−0.09	−0.21, 0.04
	0–71		6.5	−0.12	−0.32, 0.08		3.8	−0.08	−0.20, 0.05
	0–95		6.1	−0.12	−0.33, 0.09		3.5	−0.06	−0.19, 0.06
	0–167 (1 week)		5.5	−0.09	−0.31, 0.12		3.1	−0.05	−0.20, 0.09
	0–503 (3 weeks)		4.6	−0.09	−0.34, 0.16		2.5	−0.01	−0.20, 0.18
	rMSSD (ms)								
	0–5	30 (283)	7.9	−0.17	−4.95, 4.62	41 (390)	7.2	−9.66**	−15.60, −3.72
	0–23		7.3	−1.43	−6.28, 3.42		4.3	−6.56**	−10.09, −3.03
	0–47		6.9	−0.57	−5.49, 4.35		4.2	−6.77**	−10.63, −2.91
	0–71		6.5	1.07	−4.17, 6.30		3.8	−6.32**	−10.19, −2.44
	0–95		6.1	2.32	−3.14, 7.77		3.5	−6.45**	−10.33, −2.56

	Winter (December–February)				Summer (June–August)			
Biomarkers and moving averages evaluated	**N Subjects (N Subject-Visits)**	**IQR (°C)**	**Change in Biomarker per IQR increase**	**95% CI**	**N Subjects (N Subject-Visits)**	**IQR (°C)**	**Change in Biomarker per IQR increase**	**95% CI**
0–167 (1 week)		5.5	4.37	−1.28, 10.01		3.1	−7.01 **	−11.52, −2.49
0–503 (3 weeks)		4.6	6.80 *	0.22, 13.39		2.5	−4.36	−10.26, 1.53

[a] Note: Since HRT is measured only when premature ventricular contractions (PVC) occur, these analyses include only those subject-visits with 1 or more PVCs.

† p<0.10

* p<0.05

** p<0.01

Table 6

Change in rMSSD associated with each quartile of mean temperature in the previous 6 hours (summer) or previous 3 weeks (winter).

	Quartile	Minimum (°C)	Median (°C)	Maximum (°C)	Change in rMSSD (ms)	95% CI	Test for trend p-value
SUMMER (6 hours)	1st Quartile	8.00	17.04	18.42	0.00	--	0.0002
	2nd Quartile	18.43	20.20	21.88	−5.10	−12.91, 2.70	
	3rd Quartile	21.96	23.45	25.26	−13.70	−22.22, −5.17	
	4th Quartile	25.34	27.54	34.75	−17.52	−27.81, −7.23	
WINTER (3 weeks)	1st Quartile	−7.52	−6.09	−2.43	0.00	--	0.14
	2nd Quartile	−2.39	−1.50	−0.63	3.51	−6.91, 13.93	
	3rd Quartile	−0.62	0.17	1.97	8.32	−3.99, 20.64	
	4th Quartile	1.98	4.81	7.41	9.46	−4.94, 23.86	