Association between air pollution and ventricular arrhythmias in high-risk patients (ARIA study): a multicentre longitudinal study

Franco Folino, Gianfranco Buja, Gabriele Zanotto, Elena Marras, Giuseppe Allocca, Diego Vaccari, Gianni Gasparini, Emanuele Bertaglia, Franco Zoppo, Vittorio Calzolari, Rene Nangah Suh, Barbara Ignatiuk, Corrado Lanera, Alessandro Benassi, Dario Gregori, Sabino Iliceto

Summary

Background Although the effects of air pollution on mortality have been clearly shown in many epidemiological and observational studies, the pro-arrhythmic effects remain unknown. We aimed to assess the short-term effects of air pollution on ventricular arrhythmias in a population of high-risk patients with implantable cardioverter-defibrillators (ICDs) or cardiac resynchronisation therapy defibrillators (ICD-CRT).

Methods In this prospective multicentre study, we assessed 281 patients (median age 71 years) across nine centres in the Veneto region of Italy. Episodes of ventricular tachycardia and ventricular fibrillation that were recorded by the diagnostic device were considered in this analysis. Concentrations of particulate matter of less than 10 μm (PM_{10}) and less than 2·5 μm ($PM_{2·5}$) in aerodynamic diameter, carbon monoxide, nitrogen dioxide, sulphur dioxide, and ozone were obtained daily from monitoring stations, and the 24 h median value was considered. Each patient was associated with exposure data from the monitoring station that was closest to their residence. Patients were followed up for 1 year and then scheduled to have a closing visit, within 1 more year. This study is registered with ClinicalTrials.gov, number NCT01723761.

Findings Participants were enrolled from April 1, 2011, to Sept 30, 2012, and follow-ups (completed on April 5, 2014) ranged from 637 to 1177 days (median 652 days). The incidence of episodes of ventricular tachycardia and ventricular fibrillation correlated significantly with $PM_{2·5}$ ($p<0·0001$) but not PM_{10}. An analysis of ventricular fibrillation episodes alone showed a significant increase in risk of higher $PM_{2·5}$ ($p=0·002$) and PM_{10} values ($p=0·0057$). None of the gaseous pollutants were significantly linked to the occurrence of ventricular tachycardia or ventricular fibrillation. In a subgroup analysis of patients with or without a previous myocardial infarction, only the first showed a significant association between particulate matter and episodes of ventricular tachycardia or ventricular fibrillation.

Interpretation Particulate matter has acute pro-arrhythmic effects in a population of high-risk patients, which increase on exposure to fine particles and in patients who have experienced a previous myocardial infarction. The time sequence of the arrhythmic events suggests there is an underlying neurally mediated mechanism. From a clinical point of view, the results of our study should encourage physicians to also consider environmental risk when addressing the prevention of arrhythmic events, particularly in patients with coronary heart disease, advising them to avoid exposure to high levels of fine particulate matter.

Funding There was no funding source for this study.

Lancet Planet Health 2017; 1: e58–64

See **Comment** page e50

Department of Cardiac Thoracic and Vascular Sciences, University of Padua, Padua, Italy (F Folino MD, G Buj MD, E Bertaglia MD, C Lanera MS, Prof D Gregori MA, Prof S Iliceto MD); **Department of Cardiology, Mater Salutis Hospital, Legnago, Italy** (G Zanotto MD); **Department of Cardiology, S Maria dei Battuti Hospital, Conegliano, Italy** (E Marras MD, G Allocca MD); **Department of Cardiology, Civic Hospital, Montebelluna, Italy** (D Vaccari MD); **Department of Cardiology, Dell'Angelo Hospital, Mestre, Italy** (G Gasparini MD); **Department of Cardiology, Civic Hospital, Mirano, Italy** (F Zoppo MD); **Department of Cardiology, Ca' Foncello Hospital, Treviso, Italy** (V Calzolari MD); **Department of Cardiology, Civic Hospital, Portogruaro, Italy** (R Nangah Suh MD); **Department of Cardiology, Civic Hospital, Monselice, Italy** (B Ignatiuk MD); **and Regional Agency for Environmental Prevention and Protection of the Veneto Region, Padua, Italy** (A Benassi ChD)

Correspondence to:
Dr Franco Folino, Department of Cardiac Thoracic and Vascular Sciences, University of Padua, 35128 Padua, Italy
franco.folino@unipd.it

Introduction

In the past several decades, the empirical observations of an association between air pollution and an increased cardiovascular risk[1] have been validated in many epidemiological and observational studies, which have shown adverse effects of various components of air pollution on mortality and morbidity in select cohorts of patients[2,3] and in the general population.[4,5]

The specific effects of air pollution have received greater attention, particularly those that are related to the induction of arrhythmias. Controlled exposure studies in healthy volunteers have not shown any pro-arrhythmic effects of air pollution,[6] but several associations with the occurrence of out-of-hospital cardiac arrest have been reported.[7] Other studies showed that short-term exposure to fine particulate matter is associated with an increased risk of premature ventricular beats in healthy participants[8] and in patients with cardiovascular disease.[9]

The results in patients with implantable cardioverter-defibrillators (ICDs) have been conflicting, highlighting discrepancies in the analysis of the effects of specific components of air pollution.[10,11] However, a common finding in these studies is the increased sensitivity of patients with coronary artery disease to air pollution.[3,12]

These disparate findings can be explained by differences in air sampling methods, the qualitative composition of particulate matter, mutual interactions between the components of pollution, the clinical features of the populations, and differences in lag-time between clinical events and exposure.

Research in context

Evidence before this study

We searched MEDLINE with no language restrictions for articles published from Jan 1, 1990, to identify any published clinical trials assessing the correlations between ventricular arrhythmias and air pollution using the search terms "arrhythmias", "ventricular arrhythmias", "air pollution", "particulate matter", "cardiac arrest", "ICD", and "implantable defibrillators". Controlled exposure studies in healthy participants have not shown consistent pro-arrhythmic effects of air pollution, but several associations with the occurrence of out-of-hospital cardiac arrest have been reported. Conversely, different studies explored the effects of air pollution on ventricular arrhythmias in patients with implantable cardioverter-defibrillators (ICDs). Some of these studies have documented an increase of arrhythmias induced by fine particles, but also from carbon monoxide, nitrogen dioxide, and carbon black, suggesting a link with the pollutants induced by vehicular traffic and more generally with the fossil fuel combustion sources. By contrast, several other studies, despite analysing a wide range of solid and gaseous pollutants, showed no significant association of these components with the incidence of ventricular arrhythmias. Nevertheless, a common finding seems to emerge from all the experiments that have analysed the correlation between air pollution and arrhythmias: patients with coronary heart disease seem to be more sensitive to the effects of air pollutants.

Added value of this study

This multicentre prospective study is one of the largest studies to assess the occurrence of ventricular arrhythmias and changes in air pollution in patients who had been implanted with ICD or ICD-CRT. The occurrence of arrhythmias was recorded by a diagnostic system of the devices and communicated through a remote monitoring system. These data have been associated with the detection of a complete panel of pollutants, solid and gaseous, obtained from a broad network of permanent monitoring stations deployed near patients' residences. All patients were followed during a long-term follow-up.

Implications of all the available evidence

Particulate matter showed a positive association with the incidence of ventricular arrhythmia in patients with ICDs. By contrast, gaseous pollutants did not show any adverse effect. The pro-arrhythmic effect was more evident for fine particles and in patients with previous myocardial infarction. The time sequence of the arrhythmic events suggests there is an underlying neurally mediated mechanism. Based on our results, it is reasonable to advise high-risk patients to avoid exposure to high levels of fine particulate matter.

To determine the short-term effects of air pollution on arrhythmias, we examined the association between serious ventricular arrhythmias and exposure to various components of air pollution, solid and gaseous, as measured by nearby monitoring stations during long-term follow-up in a population of high-risk patients who had been implanted with ICDs or cardiac resynchronisation therapy defibrillators (ICD-CRT).

Methods

Study design and participants

ARIA was a multicentre prospective study that assessed the occurrence of atrial and ventricular arrhythmias and changes in air pollution during long-term follow-up in patients who had been implanted with a pacemaker, ICD, or ICD-CRT. Nine cardiological centres in the Veneto region of Italy were involved in the study. In this analysis, only ventricular arrhythmias in patients with an ICD or ICD-CRT were considered. The study included a first phase of recruitment lasting 1 year, followed by a minimum follow-up of 1 year. Upon completion of the follow-up, patients were scheduled to have a closing visit, within 1 more year.

The nine centres recruited consecutive patients, aged 18 years or older, who had been implanted with a Lumax, Lexos, Lumos, or Stratos (Biotronik, Berlin, Germany) ICD or ICD-CRT, compatible with remote monitoring systems with daily data transmission. The exclusion criteria were the presence of clinically manifest heart failure; concomitant illness or a severe disorder that severely limited life expectancy; any medical or surgical disorder that, at the discretion of the investigator, placed the patient at high risk for adverse clinical events for participation in the study; history of malignancy of any organ system in the last 2 years, regardless of whether it was treated, including leukaemia and lymphoma (with the exception of basal cell carcinoma of the skin) if there was evidence of local recurrence of metastasis; history of drug or alcohol use in the last 2 years; and residence in urban centres without environmental monitoring stations (20 km was the maximum distance allowed between a patient's residence and the monitoring station). The study was reviewed and approved by the appropriate local ethics committee, and written informed consent was obtained from all patients. This study is registered with ClinicalTrials.gov, number NCT01723761.

Procedures

The occurrence of arrhythmias was recorded by a diagnostic device and communicated through a remote monitoring system (Home Monitoring, Biotronik, Berlin, Germany). Diagnostic data from the device were transmitted at a programmed time every day (eg, 3 am) and on detection of a relevant arrhythmic or technical event.[13] A mobile transmitter, generally placed beside

the patient's bed, received these data and sent them through a Global System for Mobile Communications network to the Biotronik Home Monitoring Service Center. At this centre, data are posted on a secure internet site that is accessible to physicians.

An intracardiac electrogram (IEGM) was transmitted automatically to the service centre after the detection of an episode that was classified as ventricular or supraventricular tachyarrhythmia, consisting of marker channels, episode details, and electrogram recordings from the left ventricular lead (CRT-D), right atrial lead (dual-chamber ICD and CRT-D), and right ventricular lead (all device types). For each recorded episode, the IEGM was reviewed and classified by three electrophysiologists who were blinded to air pollution levels. The onset interval, rate, QRS morphology during and before the episode, and response to treatment were used to categorise the rhythm as a ventricular arrhythmia (ie, ventricular tachycardia, polymorphic ventricular tachycardia, or ventricular fibrillation), supraventricular arrhythmia (eg, atrial flutter, atrial fibrillation, atrial tachycardia), sinus tachycardia, noise, or unknown. Only ventricular arrhythmias (ventricular tachycardia and fibrillation) were included in this analysis.

Concentrations of particulate matter of less than 10 μm in aerodynamic diameter (PM_{10}) and less than 2·5 μm ($PM_{2·5}$), carbon monoxide, nitrogen dioxide, sulphur dioxide, and ozone were obtained from permanent monitoring stations of the Regional Agency for Environmental Prevention and Protection of the Veneto Region (ARPAV), deployed throughout the Veneto region of Italy. Data at each monitoring site were collected hourly, and the 24-hour median value was considered. Each patient was associated with exposure data from the monitoring station that was nearest to their residence. Pollutant concentrations on the day of the arrhythmic events were analysed in this investigation. Data for temperature, humidity, and pressure were obtained from the meteorological centre of the same agency and were deemed to be confounding variables.

Statistical analyses

Continuous variables were expressed as median, with the interquartile range as a measure of variability. We assessed the effect of pollutants on the probability of arrhythmic events as a continuous covariate in a multivariable logistic model, always adjusting for sotalol, antiarrhythmic drugs, and β-blocker therapy; age; gender; median day pressure; humidity; and temperature, regardless of their significance. We modelled non-linear effects of pollutants with a restrictive cubic spline function. A non-linear effect introduces a non-proportionality in the increase of risk between two exposures levels, thus modelling higher risks for higher levels of exposure. Longitudinal and spatial correlation was modelled using a sandwich estimator with an unstructured working correlation matrix.[14] We assessed the significance of pollutants with Akaike Information Criterion (AIC),[15] and interaction between adjustment variables and pollutants was also assessed with AIC.

Cyclicity in the distribution of pollutants over time was tested with a continuous version of the Nam test.[16] Statistical significance was set to p less than 0·05. R-System and the MuMin and Harrell rms libraries were used for the analysis.

	Patients (n=281)
Men	233 (83%)
Age (years)	71 (63–77)
Body-mass index	26·50 (23·40–29·85)
Smokers	28 (10%)
Hypertensive cardiomyopathy	20 (7%)
Dilated cardiomyopathy	129 (46%)
Hypertrophic cardiomyopathy	11 (4%)
Arrhythmogenic right ventricular cardiomyopathy	2 (1%)
Coronary artery disease	153 (54%)
Myocardial infarction	127 (45%)
Valvular heart disease	19 (7%)
Brugada syndrome	5 (2%)
NYHA class	
I	44 (20%)
II	83 (38%)
III	11 (5%)
IV	0
Echocardiographic ejection fraction	35 (30–45)
Comorbidities	
Hypertension	143 (51%)
Diabetes	61 (22%)
Kidney failure	22 (8%)
Chronic broncopneumopathy	23 (8%)
Previous transient ischaemic attack	15 (5%)
Treatments	
ACE inhibitors	152 (54%)
Angiotensin receptor blockers	23 (8%)
β-blockers	206 (73%)
Diuretics	192 (68%)
Spironolactone	16 (6%)
Calcium-antagonists	24 (9%)
α-blockers	7 (3%)
Nitrates	24 (9%)
Digitalis	33 (12%)
Ivabradine	2 (1%)
Antiplatelet	122 (43%)
Oral anticoagulant	103 (37%)
Antiarrhythmic drugs	57 (20%)

Data are n (%) or median (IQR). NYHA=New York Heart Association. ACE=angiotensin-converting enzyme.

Table 1: **Baseline characteristics**

	Carbon monoxide	Nitrogen oxides	PM_{10}	$PM_{2·5}$	Sulphur dioxide
Energy production and fuels processing	0	7%	0	0	31%
Non-industrial combustion	63%	10%	68%	73%	8%
Industrial combustion	2%	14%	1%	1%	39%
Production processes	3%	3%	2%	1%	15%
Solvents use	0	0	3%	3%	0
Road transportation	27%	47%	13%	12%	0
Other mobile sources and machinery	5%	18%	5%	5%	5%
Agriculture	0	1%	4%	2%	0
Other sources and absorptions	0	0	4%	3%	2%

PM_{10}=particulate matter of less than 10 μm in aerodynamic diameter. $PM_{2·5}$= particulate matter of less than 2·5 μm in aerodynamic diameter.

***Table 2*: Percentage distribution of pollutant sources, Veneto region, Italy, 2013**

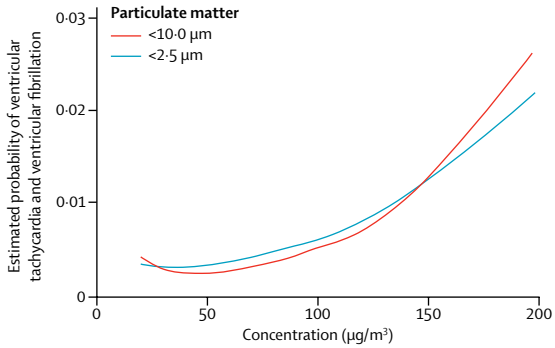

***Figure 1*: Estimated probability plot for ventricular tachycardia and ventricular fibrillation episodes at different concentrations of particulate matter of less than 10 μm (PM_{10}) and less than 2·5 μm ($PM_{2·5}$) in aerodynamic diameter**

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The enrolment period lasted from April 1, 2011, to Sept 30, 2012. The study cohort included 281 patients who lived in 137 municipalities of the Veneto region, Italy. The patients' clinical features are detailed in table 1. The follow-up period was concluded on April 5, 2014, and the overall follow-ups ranged between 637 and 1177 days (median 652 days). The ranges of the programmed intervals for ventricular tachycardia and ventricular fibrillation detection were ventricular tachycardia 1 (VT1): 330–400 ms, ventricular tachycardia 2 (VT2): 310–370 ms, and ventricular fibrillation, 270–320 ms. 48 patients died during follow-up.

Data were obtained from 19 monitoring stations, based on the location that was nearest the patient's city of residence. Particulate matter concentrations exceeded the limit of 50 μg/m³ for PM_{10} for 1335 days and the limit of 25 μg/m³ for $PM_{2·5}$ for 828 days during the follow-up (annual limits for human health protection established by Italian law). Particulate matter showed a clear seasonal distribution, with higher peak concentrations in winter, whereas nitrogen dioxide and ozone were the only gaseous pollutants that did so, peaking in winter and summer, respectively.

The main sources of air pollutants in the Veneto region were analysed by ARPAV. The last report from the agency (2013) suggests that with regard to particulate matter, and particularly for PM_{10}, the main sources are non-industrial combustion (68%) and road transportation (13%). For $PM_{2·5}$, sources have a similar distribution: non-industrial combustion (73%) and road transportation (12%).

By analysing in detail the emissions of PM_{10} from non-industrial combustion, we estimated that about 99% of this macro-sector results from the combustion of wood in the residential sector, particularly in open or closed fireplaces and traditional stoves. Compared with road transportation, about 80% of PM_{10} emissions are attributable to equipment powered by diesel, whereas the remaining 20% are attributable to gasoline (19%) and liquefied petroleum gas or methane (1%). With regard to gaseous pollutants, carbon monoxide sources are similar to those of particulate (non-industrial combustion, 63% and road transportation, 27%), whereas for nitrogen oxides, the main sources are road transportation (47%) and other mobile sources and machinery (18%). Finally, the sulphur dioxide sources are industrial combustion (39%) and energy production and fuels transformation (31%; table 2).[17]

During the follow-up, we recorded 426 episodes of VT1 or VT2 and 183 episodes of ventricular fibrillation. 41 (15%) of 281 patients received at least one ICD shock, and 14 (5%) of 281 patients received more than three ICD shocks.

The incidence of episodes of ventricular tachycardia and fibrillation correlated significantly with $PM_{2·5}$ but not PM_{10} (figure 1, table 3). For $PM_{2·5}$, the risk of episodes increased non-linearly (p value for non-linearity 0·0002) for concentrations above approximately 25 μg/m³ (for 75 μg/m³ *vs* 25 μg/m³: odds ratio [OR] 1·59, 95% CI 1·12–2·25). None of the gaseous pollutants were significantly associated with the occurrence of arrhythmias (table 3).

We confirmed a significant increase in risk of ventricular fibrillation episodes that was linear for higher concentrations of $PM_{2·5}$ (p value for non-linearity 0·0635), wherein the risk for 75 μg/m³ versus 25 μg/m³ had an OR of 1·80, 95% CI 1·04–3·09 (p value 0·0002). For PM_{10}, the risk increased non-linearly (p value for non-linearity 0·006) for 100 μg/m³ versus 50 μg/m³, with OR 1·45, 95% CI 0·78–2·72 (p value 0·0057; figure 2). Gaseous pollutants had no significant effects on the occurrence of ventricular fibrillation (table 3).

In the interaction analysis, with regard to the risk estimates for subgroups of patients with or without a previous myocardial infarction, we noted a non-significant association of $PM_{2·5}$ and PM_{10} with episodes

of ventricular tachycardia or ventricular fibrillation in the non-myocardial infarction group, whereas in the myocardial infarction group, the risk increased significantly for ventricular tachycardia and ventricular fibrillation. Gaseous pollutants maintained a non-significant association in both subgroups (table 4).

Discussion

Our study aimed to determine the harmful effects of air pollution on myocardial electrical stability in high-risk patients. We observed a significant correlation between increases in $PM_{2.5}$ and PM_{10} and the occurrence of severe ventricular arrhythmia. The subgroup of patients with a previous myocardial infarction developed a greater susceptibility to air particle pollution-induced arrhythmias.

None of the gaseous pollutants affected myocardial electrical stability. Despite the general consensus about the deleterious influence of particulate matter on cardiovascular mortality and morbidity, conflicting results have emerged on the correlation between air particle pollution and the occurrence of ventricular arrhythmias.[18] Various studies have shown a positive correlation with cardiac arrest,[7] but the results have been inconsistent with regard to arrhythmias and high-risk patients who have been implanted with ICDs.[10,11,19]

These heterogeneous results might be attributed to several factors. To overcome most of these limitations, our study was designed for a large, homogeneous cohort of high-risk patients, with continuous and reliable monitoring of arrhythmias, a critical validation process for recorded events, and a long-term follow-up, in which a complete panel of pollutants was monitored through a rigorous and continuous sampling system, located in the vicinity of the patients' towns of residence.

Our findings are consistent with previous studies that have shown an increase in arrhythmias[10,20] and out-of-hospital cardiac arrest[7] in relation to a rise in particulate matter concentrations. In these reports, arrhythmic events, recorded by ICDs or electrocardiogram monitoring, were associated with a large panel of pollutants that included ozone, $PM_{2.5}$, nitrogen dioxide, sulphur dioxide, carbon monoxide, elemental carbon, and organic carbon. Among them, fine particulate matter and black carbon induced up to a 19% increase in risks of ventricular arrhythmias, with a time lag ranging from 24 h to 4 days.

In our study, $PM_{2.5}$ and PM_{10} showed a non-linear increase with risk, considering all ventricular arrhythmias and only ventricular fibrillation episodes, an association that was evident at concentrations above 25 μg/m³ for fine particles and above 50 μg/m³ for PM_{10}. Bearing in mind that the WHO thresholds for 24 h means are 25 μg/m³ for $PM_{2.5}$ and 50 μg/m³ for PM_{10}, our results confirm the dangers of particulate matter above these concentrations.

The increased risk of ventricular arrhythmias due to fine particles seems to reflect a more pronounced effect of this fraction of particulate on electrical stability. We speculate that finer particles reach the smaller airways, inducing more diffuse inflammatory processes.

However, we must also consider that the triggering effect of particulate matter on the airways is likely to be related to the size of its contact surface; thus, at the same concentration, smaller particles will have greater contact surface than larger particles, as has been proposed for the effects of pollution by nanoparticles.[21] Toxicologically, particle size and surface area are important material characteristics: if the particle decreases, its surface area increases, and a greater proportion of its atoms or molecules are exposed on the surface, as are potentially reactive groups. As a result, the number of atoms or molecules on the surface of a particle might determine the reactivity of a material.

	Effect	Odds ratio	95% CI	p value (effect)	p value (non-linearity)
Ventricular tachycardia and ventricular fibrillation					
Carbon monoxide	0·4 *vs* 0·2	1·22	0·72–2·07	0·7195	0·4173
Nitrogen dioxide	40 *vs* 20	0·83	0·44–1·54	0·5107	0·8705
Sulphur dioxide	40 *vs* 20	0·93	0·79–1·11	0·1271	0·4228
Ozone	100 *vs* 50	0·87	0·34–2·20	0·6933	0·4195
$PM_{2.5}$	75 *vs* 25	1·59	1·12–2·25	0·0000	0·0002
PM_{10}	100 *vs* 50	1·43	0·63–3·26	0·1037	0·0355
Ventricular fibrillation only					
Carbon monoxide	0·4 *vs* 0·2	0·96	0·69–1·32	0·8895	0·9080
Nitrogen dioxide	40 *vs* 20	0·90	0·49–1·65	0·6694	0·4376
Sulphur dioxide	40 *vs* 20	1·00	0·64–1·56	0·5427	0·4339
Ozone	100 *vs* 50	1·70	0·41–7·10	0·5797	0·5073
$PM_{2.5}$	75 *vs* 25	1·80	1·04–3·09	0·0002	0·0635
PM_{10}	100 *vs* 50	1·45	0·78–2·72	0·0057	0·0060

Effects are estimated via robust SE and adjusted for sotalol, antiarrhythmic and β-blocker therapy, age, gender, median day pressure, humidity, and temperature. p values are presented both for overall effect and for non-linearity of the association, which was modelled using restricted cubic splines (3 knots). PM_{10}=particulate matter of less than 10 μm in aerodynamic diameter. $PM_{2.5}$= particulate matter of less than 2·5 μm in aerodynamic diameter.

***Table 3*: Estimated effects of pollutants on ventricular arrhythmias**

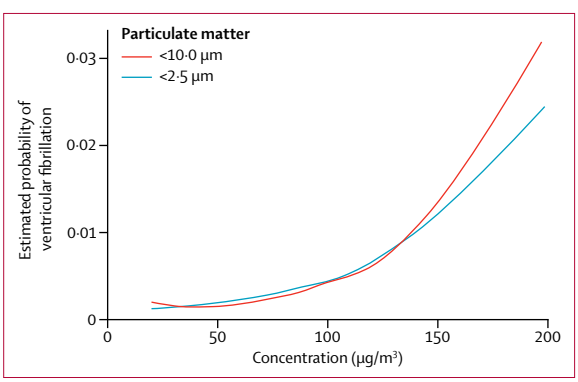

***Figure 2*: Estimated probability plot for ventricular fibrillation episodes at different concentrations of particulate matter of less than 10 μm (PM_{10}) and less than 2·5 μm ($PM_{2.5}$) in aerodynamic diameter**

	Effect	No myocardial infarction group		Myocardial infarction group		p value (interaction)	p value (effect)
		Odds ratio	95% CI	Odds ratio	95% CI		
Ventricular tachycardia and ventricular fibrillation							
Carbon monoxide	0·4 *vs* 0·2	2·61	0·65–10·45	0·82	0·37–1·80	0·2764	0·2356
Nitrogen dioxide	40 *vs* 20	0·42	0·10–1·66	1·08	0·64–1·82	0·4292	0·6286
Sulphur dioxide	1·5 *vs* 1	1·25	0·94–1·67	1·22	0·84–1·76	0·1195	0·3724
Ozone	100 *vs* 50	0·67	0·17–2·61	0·85	0·28–2·53	0·0923	0·2929
$PM_{2·5}$	75 *vs* 25	0·74	0·06–9·24	4·77	1·72–13·21	0·0390	0·0000
PM_{10}	100 *vs* 50	0·61	0·10–3·75	2·04	1·11–1·44	0·0018	0·0006
Ventricular fibrillation							
Carbon monoxide	0·4 *vs* 0·2	1·45	0·56–3·75	0·85	0·38–1·89	0·3507	0·2256
Nitrogen dioxide	40 *vs* 20	0·62	0·20– 1·96	1·09	0·66–1·82	0·5218	0·6913
Sulphur dioxide	40 *vs* 20	0·90	0·52–1·53	1·14	0·70–1·86	0·4325	0·2373
Ozone	100 *vs* 50	1·96	0·31–12·33	1·37	0·26–7·08	0·1752	0·1316
$PM_{2·5}$	75 *vs* 25	1·04	0·06–17·84	5·55	2·55–2·08	0·0162	0·0000
PM_{10}	100 *vs* 50	1·09	0·31–3·83	2·48	1·26–4·87	0·0109	0·0231

Effects are estimated using an interaction term with absence or presence of a previous myocardial infarction, via robust SE and adjusted for sotalol, antiarrhythmic and β-blocker therapy, age, gender, median day pressure, humidity, and temperature. p values are presented both for overall effect and for the interaction term. PM_{10}=particulate matter of less than 10 μm in aerodynamic diameter. $PM_{2·5}$=particulate matter of less than 2·5 μm in aerodynamic diameter.

Table 4: **Estimated effects of pollutants on ventricular arrhythmias in patients with or without a previous myocardial infarction**

Although the pro-arrhythmic effects of particulate matter are well defined, the effects of gaseous pollutants had non-significant correlations. The scientific literature suggests that few cases show a positive correlation between carbon monoxide and arrhythmias.[22] Also, data for ozone (one of the most extensively studied gaseous pollutants) are conflicting, reporting positive[7,10,23] and negative[22,24,25] correlations, rendering it one of the most controversial aspects of the cardiovascular effects of air pollution.

It is also noteworthy that in patients at high risk of ventricular arrhythmias who were implanted with ICD, ozone did not show negative effects on electrical instability.[22,25] Conversely, the same pollutant was associated with an increased risk of death due to respiratory causes.[24] Our results also suggest that patients with a previous myocardial infarction have a greater susceptibility to ventricular arrhythmias due to air pollution. This observation might generally be related to more severe underlying heart disease, but could be, more specifically, due to the presence, in most cases, of a myocardial scar, which represents an efficient arrhythmic substrate.

To obtain well defined results, we only analysed exposure samples on the same day on which arrhythmias were detected. The positive correlations confirm the acute arrhythmogenic effects that are induced by pollutants, which must be linked to a mechanism that is activated with an extremely short latency. Of the various mechanisms that have been proposed to explain the effects of pollution on the cardiovascular system, only those that are mediated by the autonomic nervous system are the most likely to be activated in such short intervals.[26] Based on previous studies, we postulate that local inflammatory processes, or other non-inflammatory irritant reactions that are induced by pollutants in the upper and lower airways,[27] activate the pathophysiological cascade, consequently triggering afferent signals through autonomic nervous system fibres, ultimately increasing sympathetic drive and myocardial electrical instability.[28,29]

This reflex has been emphasised in many studies that have analysed the changes in autonomic activity induced by air pollution.[30,31] Particularly, we assessed in a previous study[32] the short-term effects of air pollution, measured by personal samplers in patients with myocardial infarction, on cardiac autonomic activity and on the occurrence of ventricular arrhythmias. We found a negative correlation between indexes of heart variability and exposure to fine particles ($PM_{0·25}$), in a group of patients not taking β-blockers. Moreover, we reported severe ventricular arrhythmias at the highest concentrations of PM_{10} and $PM_{2·5}$.

High $PM_{2·5}$ values have been associated with morbidity and mortality in short-term and long-term studies. However, epidemiological data have shown generally greater increases in all-cause mortality for long-term versus short-term exposure.[33]

Based on these data, we assume that the effects of short-term pollution are based primarily on the mechanisms that are mediated by the autonomic nervous system and that long-term exposure activates other pathophysiological processes, such as systemic inflammation, prothrombotic factors, and alterations in endothelial structure and function.

In conclusion, our study has reported the acute pro-arrhythmic effects of particulate matter in a panel of high-risk patients, wherein stronger effects are associated with exposure to fine particles. Patients with a previous myocardial infarction are more susceptible to ventricular arrhythmias when exposed to higher concentrations of particulate. The dynamics of these events suggests an underlying neurally mediated mechanism exists.

Contributors

FF and GB conceived and designed the study, DG and CL contributed to the protocol and design of the study. FF, GB, and SI provided management and oversight of the trial as members of the study steering group. FF and DG coordinated the study design process and implementation of the trial on behalf of the study steering group. GZ, EM, GA, DV, GG, EB, FZ, VC, RNS, BI, and AB contributed to the field implementation of the trial. DG and CL did the statistical analyses. FF, GB, and SI contributed to data interpretation. DG wrote the scripts for the statistical tests. FF, GB, SI, and DG contributed to the preparation of the report. All authors critically reviewed and approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

We thank the Regional Agency for Environmental Prevention and Protection of the Veneto Region (ARPAV) for providing meteorological and exposure data, Marcello Lotti and Piero Maestrelli for their critical review of the manuscript, and Biotronik Italy for technical support for the data management. The study took place in the following

participating centres: Department of Cardiac Thoracic and Vascular Sciences, University of Padua, Padua, Italy; Department of Cardiology, Mater Salutis Hospital, Legnago, Italy; Department of Cardiology, S Maria dei Battuti Hospital, Conegliano, Italy; Department of Cardiology, Civic Hospital, Montebelluna, Italy; Department of Cardiology, Dell'Angelo Hospital, Mestre, Italy; Department of Cardiology, Civic Hospital, Mirano, Italy; Department of Cardiology, Ca' Foncello Hospital, Treviso, Italy; Department of Cardiology, Civic Hospital, Portogruaro, Italy; and Department of Cardiology, Civic Hospital, Monselice, Italy. The Clinical Event Committee comprised Gianfranco Buja, Barbara Ignatiuk, and Michela Maddalosso.

References

1 Bell ML, Davis DL. Reassessment of the lethal London fog of 1952: novel indicators of acute and chronic consequences of acute exposure to air pollution. *Environ Health Perspect* 2001; **109** (suppl 3): 389–94.

2 Miller KA, Siscovick DS, Sheppard L, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med* 2007; **356:** 447–58.

3 Bartell SM, Longhurst J, Tjoa T, Sioutas C, Delfino RJ. Particulate air pollution, ambulatory heart rate variability, and cardiac arrhythmia in retirement community residents with coronary artery disease. *Environ Health Perspect* 2013; **121:** 1135–41.

4 Dockery DW, Pope CA 3rd, Xu X, et al. An association between air pollution and mortality in six US cities. *N Engl J Med* 1993; **329:** 1753–59.

5 Shah AS, Langrish JP, Nair H, et al. Global association of air pollution and heart failure: a systematic review and meta-analysis. *Lancet* 2013; **382:** 1039–48.

6 Watkins A, Danilewitz M, Kusha M, et al. Air pollution and arrhythmic risk: the smog is yet to clear. *Can J Cardiol* 2013; **29:** 734–41.

7 Ensor KB, Raun LH, Persse D. A case-crossover analysis of out-of-hospital cardiac arrest and air pollution. *Circulation* 2013; **127:** 1192–99.

8 He F, Shaffer ML, Rodriguez-Colon S, et al. Acute effects of fine particulate air pollution on cardiac arrhythmia: the APACR study. *Environ Health Perspect* 2011; **119:** 927–32.

9 O'Neal WT, Soliman EZ, Efird JT, Howard VJ, Howard GH, McClure LA. Fine particulate air pollution and premature ventricular contractions: the reasons for geographic and racial differences in stroke (REGARDS) Study. *Environ Res* 2017; **154:** 115–19.

10 Rich DQ, Schwartz J, Mittleman MA, et al. Association of short-term ambient air pollution concentrations and ventricular arrhythmias. *Am J Epidemiol* 2005; **161:** 1123–32.

11 Anderson HR, Armstrong B, Hajat S, et al. Air pollution and activation of implantable cardioverter defibrillators in London. *Epidemiology* 2010; **21:** 405–13.

12 Berger A, Zareba W, Schneider A, et al. Runs of ventricular and supraventricular tachycardia triggered by air pollution in patients with coronary heart disease. *J Occup Environ Med* 2006; **48:** 1149–58.

13 Nägele H, Lipoldová J, Oswald H, et al. Home monitoring of implantable cardioverter-defibrillators: interpretation reliability of the second-generation "IEGM Online" system. *Europace* 2015; **17:** 584–90.

14 White HA. Heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. *Econometrica* 1980; **48:** 817–38.

15 Burnham KP, Anderson DR. Model selection and multimodel inference: a practical information-theoretic approach. New York: Springer Science & Business Media, 2003.

16 Nam JM. Interval estimation and significance testing for cyclic trends in seasonality studies. *Biometrics* 1995; **51:** 1411–17.

17 Regional Agency for Environmental Prevention and Protection of the Veneto Region (ARPAV). Inventory INEMAR Veneto Region 2013. http://89.96.234.242/inemar/webdata/main.seam (accessed Feb 15, 2017).

18 Newby DE, Mannucci PE, Tell GS, et al, on behalf of ESC Working Group on Thrombosis, European Association for Cardiovascular Prevention and Rehabilitation and ESC Heart Failure Association. Expert position paper on air pollution and cardiovascular disease. *Eur Heart J* 2015; **36:** 83–93.

19 Metzger KB, Klein M, Flanders WD, et al. Ambient air pollution and cardiac arrhythmias in patients with implantable defibrillators. *Epidemiology* 2007; **18:** 585–92.

20 Zanobetti A, Coull BA, Gryparis A, et al. Associations between arrhythmia episodes and temporally and spatially resolved black carbon and particulate matter in elderly patients. *Occup Environ Med* 2014; **71:** 201–07.

21 Nel A, Xia T, Mädler L, Li N. Toxic potential of materials at the nanolevel. *Science* 2006; **311:** 622–27.

22 Dockery DW, Luttmann-Gibson H, Rich DQ, et al. Association of air pollution with increased incidence of ventricular tachyarrhythmias recorded by implanted cardioverter defibrillators. *Environ Health Perspect* 2005; **113:** 670–74.

23 Arjomandi M, Wong H, Donde A, et al. Exposure to medium and high ambient levels of ozone causes adverse systemic inflammatory and cardiac autonomic effects. *Am J Physiol Heart Circ Physiol* 2015; **308:** H1499–509.

24 Jerrett M, Burnett RT, Pope CA 3rd, et al. Long-term ozone exposure and mortality. *N Engl J Med* 2009; **360:** 1085–95.

25 Rich DQ, Kim MH, Turner JR, et al. Association of ventricular arrhythmias detected by implantable cardioverter defibrillator and ambient air pollutants in the St Louis, Missouri metropolitan area. *Occup Environ Med* 2006; **63:** 591–96.

26 Middlekauff HR, Park J, Moheimani RS. Adverse effects of cigarette and noncigarette smoke exposure on the autonomic nervous system mechanisms and implications for cardiovascular risk. *J Am Coll Cardiol* 2014; **64:** 1740–50.

27 Mills NL, Donaldson K, Hadoke PW, et al. Adverse cardiovascular effects of air pollution. *Nat Clin Pract Cardiovasc Med* 2009; **6:** 36–44.

28 Tracey KJ. The inflammatory reflex. *Nature* 2002; **420:** 853–59.

29 Perez CM, Hazari MS, Farraj AK. Role of autonomic reflex arcs in cardiovascular responses to air pollution exposure. *Cardiovasc Toxicol* 2015; **15:** 69–78.

30 Liao D, Shaffer ML, He F, et al. Fine particulate air pollution is associated with higher vulnerability to atrial fibrillation—the APACR study. *J Toxicol Environ Health A* 2011; **74:** 693–705.

31 He F, Shaffer ML, Li X, et al. Individual-level $PM_{2.5}$ exposure and the time course of impaired heart rate variability: the APACR Study. *J Expo Sci Environ Epidemiol* 2011; **21:** 65–73.

32 Folino AF, Scapellato ML, Canova C, et al. Individual exposure to particulate matter and the short-term arrhythmic and autonomic profiles in patients with myocardial infarction. *Eur Heart J* 2009; **30:** 1614–20.

33 Brook RD, Rajagopalan S, Pope CA 3rd, et al. Particulate matter air pollution and cardiovascular disease. An update to the scientific statement from the American Heart Association. *Circulation* 2010; **121:** 2331–78.