Air Pollution and Cardiac Arrhythmias: A Comprehensive Review

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Abstract: Air pollution is the mixture of some chemical and environmental agents including dust, fumes, gases, particulate matters, and biological materials which can be harmful for the environment and the human body. The increasing trend of the air pollution, especially in developing countries, may exert its detrimental effects on human health. The potentially harmful effects of air pollution on the human health have been recognized and many epidemiological studies have clearly suggested the strong association between air pollution exposure and increased morbidities and mortalities. Air pollutants are classified into gaseous pollutants including carbon mono oxide, nitrogen oxides, ozone and sulfur dioxide, and particulate matters (PMs). All air pollutants have destructive effects on the health systems including cardiovascular system. Many studies have demonstrated the effect of air pollutant on the occurrence of ST elevation myocardial infarction, sudden cardiac death, cardiac arrythmias, and peripheral arterial disease. Recently, some studies suggested that air pollution may be associated with cardiac arrhythmias. In this study, we aimed to comprehensively review the last evidences related to the association of air pollutant and cardiac arrythmias. We found that particulate matters (PM_{10}, $PM_{2.5}$, and

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UFP) and gaseous air pollutants can exert undesirable effects on cardiac rhythms. Short-term and long-term exposure to the air pollutants can interact with the cardiac rhythms through oxidative stress, autonomic dysfunction, coagulation dysfunction, and inflammation. It seems that particulate matters, especially $PM_{2.5}$ have stronger association with cardiac arrhythmias among all air pollutants. However, future studies are needed to confirm these results. (Curr Probl Cardiol 2021;46:100649.)

Introduction

Air pollution is the mixture of some chemical and environmental agents including dust, fumes, gases, particulate matters, and biological materials which can be harmful for the environment and the human body.[1,2] Air pollution is one of the challenging issues in the field of environmental health globally.[3] The increasing trend of the air pollution, especially in developing countries, may exert its detrimental effects on the human health.[4-6] The potentially harmful effects of air pollution on the human health has been recognized and many epidemiological studies have clearly suggested the strong association between air pollution exposure and increased morbidities and mortalities.[7-9]

Air pollutants are classified into gaseous pollutants, including carbon mono oxide (CO), nitrogen oxides, ozone (O_3), and sulfur dioxide (SO_2), and particulate matters (PMs).[10,11] All air pollutants have destructive effects on the health systems including respiratory function,[12,13] nervous system,[14] immune system,[15] intestinal function,[16,17] and cardiovascular system.[18] In fact, many studies have demonstrated the effect of air pollutant on the occurrence of ST elevation myocardial infarction,[19] sudden cardiac death,[20] cardiac arrythmias,[21] and peripheral arterial disease.[22]

Cardiac arrhythmias are a group of cardiac rhythm disorders associated with different cardiovascular disease, including sudden cardiac arrest and are related to low quality of life and high rate of mortality.[23] Recently, some studies suggested that air pollution may be associated with cardiac arrhythmias.[24] As there is no comprehensive review on this association, in this study, we aimed to explore the last evidences related to the

association of air pollutant and cardiac arrythmias regarding the type of air pollutants and the underlying pathophysiology.

Materials and Methods

Date resource and search strategy

For this narrative review, literature search was performed through PubMed, Embase, Scopus Cochrane, and Google Scholar databases. Our search involved all articles published from 1985 until 2020. The following titles were used as the research topics: (1) air pollution OR air pollutants OR particulate matters OR gaseous pollutants, (2) cardiovascular disease OR CVD OR cardiac arrhythmia OR cardiac dysrhythmia OR heart rate variability, (3) atrial arrythmia OR atrial dysrhythmia OR ventricular arrythmia OR ventricular dysrhythmia, (4) oxidative stress OR free radicals OR active oxygen OR biomarkers, 5) coagulation OR thrombosis disorders OR coagulation factors, (6) systemic inflammation OR inflammation cascade OR inflammatory factors.

Inclusion and exclusion criteria

After the initial search, 234 articles were entered into the review process. Some of the searched articles were not associated completely to our research concept and were excluded. Studies in languages rather than English were also excluded. Studies with the following criteria underwent final assessment: (1) Articles related to the properties of air pollutants, (2) Articles related the association of air pollution and cardiac arrhythmia, (3) Articles related to the pathophysiology of particulate matters in the development of arrhythmia, (4) Articles related to the pathogenesis factors of cardiac arrhythmia, (5) Articles aiming at all human populations (without any specific feature), (6) Articles with any study design of cross-sectional, cohort, observational, case-control, and cross-over designs.

Quality evaluation

After excluding unrelated papers, 181 articles were evaluated by 3 researchers. All articles were screened through the title and abstract. After excluding inappropriate data and unavailable studies, 121 studies were screened completely and included in the final review.

Results and Discussion

Air Pollutants and cardiac arrythmia

PM are mixtures of very small solid particles and liquid droplets, consisting of chemical agents, including acids, metals, soil, and dust.[25] PM are broadly categorized by aerodynamic diameter.[26] The particles with an aerodynamic diameter $\leq 10\ \mu$m are called coarse particles, particles with an aerodynamic diameter $\leq 2.5\ \mu$m are fine particles, and particles with a diameter below 0.1 μm are categorized as ultra-fine particles.[27] Furthermore, gaseous pollutants are other common types of air pollutants which can generally be generated from fossil fuel combustion and the transportation system.[28,29] CO, nitrogen oxides, SO_2, and O_3 are some of the major gaseous pollutants.[30,31]

Air pollutants, especially particulate matters (aerodynamic diameter less than 2.5 μm and $\leq 10\ \mu$m), are possible risk factors for cardiovascular events including cardiac arrhythmia.[32,33] Epidemiologic studies have assessed the association between the particulate matters and cardiac arrhythmia through implantable cardioverter-defibrillator (ICD) discharge episodes, electrocardiography study, hospital admission, and mortality data.[34] In the following article, the role of air pollutants in the development of cardiac arrhythmia will be evaluated separately.

Particulate matters less than 10 μm. The role of PM_{10} in the development of cardiac arrhythmia has been discussed in several studies. Link *et al*. suggested that PM_{10} μm were associated with increased risk of atrial fibrillation onset after a few hours following exposure in patients with ICDs.[35] Rich et al. observed that the risk of ventricular arrhythmia is associated with the concentration of particulate matters in patients with ICD.[36] In the study of Ljungman et al., it was observed that the elevation of PM_{10} can be related to rapid onset of ventricular arrythmia.[37] In addition, in the study of Hoek et al., the risk of mortality associated with life-threatening arrhythmias was associated with black smoke and PM_{10}.[38] In the study of Liu et al., a 10 $\mu g/m^3$ increase in the concentration of PM_{10} was associated with 2.7% increase in the risk of atrial fibrillation.[39] Also, in the study of Santos et al., a 22.2 $\mu g/m^3$ increase in PM_{10} was associated with 6.7% increase in the emergency visit for cardiac arrythmia.[40] Tsai et al. observed an association between the high levels of particulate matters (2.5 and 10) and number of emergency room visit for cardiac arrythmia in cool days ($<23^{\circ}$).[41] Moreover, In the context of hospital admission and mortality report, Wichmann et al. nearly observed 50%

increase in hospital admission for cardiac arrhythmia in a 5 day exposure to air pollutants, especially particulate matters resulting from the smog.[42]

Particulate matters less than 2.5 μm. Several studies indicated the positive role of $PM_{2.5}$ in the cardiac arrhythmia. Feng et al. suggested that the risk of different arrhythmias, including supraventricular premature beat, atrial tachycardia, ventricular tachycardia and premature ventricular contraction, is associated with the concentration of $PM_{2.5}$.[43] In the study of Pope et al., it was concluded that long-term exposures to $PM_{2.5}$ was strongly associated with cardiovascular mortality related to the ischemic heart disease, cardiac arrhythmia and cardiac arrest due to inflammation and autonomic dysfunction.[44] Halonen et al. and Chen et al. observed high level of $PM_{2.5}$ was associated with arrythmia admission at the same day.[45,46] In the study of Ueda et al., high concentration of $PM_{2.5}$ was associated with cardiac mortality resulting from acute myocardial infarction, and cardiac arrhythmia in young aged patients.[47] Berger et al. also demonstrated that the $PM_{2.5}$ could increase the risk of supraventricular and ventricular arrhythmia in all age groups.[48] Furthermore, Ebelt et al. suggested that the risk of supraventricular arrhythmia is related to the ambient and non-ambient $PM_{2.5}$.[49]

Riediker et al. concluded that $PM_{2.5}$ may lead to some pathophysiologic changes involving inflammation, coagulation, and cardiac rhythm.[50] In the study of Chiu et al., the risk of cardiac arrhythmia emergency visit increased after short term exposure to $PM_{2.5}$ in both warm and cool days.[51] In the study of Liu et al., a 10 $\mu g/m^3$ increase in the concentration of $PM_{2.5}$ was associated with 3.8% increase in the risk of atrial fibrillation.[39] In addition, in the study of Zanobetti et al., the risk of ventricular ectopy increased after exposure to $PM_{2.5}$ and black carbon in elderly patients.[52] In an electrocardiographic evaluation, He et al. concluded that approximately 60-minute exposure to $PM_{2.5}$ was associated with increased premature ventricular contraction in healthy individuals.[53] It seems that, there are more evidences regarding the role of $PM_{2.5}$ in the development of cardiac arrhythmia rather than other pollutants.

Ultra-fine Particles. There are a few studies in the context of ultrafine particles effects on the cardiac arrhythmia. Berger et al. found that 2-5 days exposure to the UFP might be associated with the episodes of both ventricular and supraventricular arrhythmia.[48] Folino et al. suggested that exposure to ultrafine particles was associated with cardiac arrhythmia resulting from autonomic dysfunction in patients with the history of myocardial infarction; also, they found that the risk of arrhythmia was related

to the concentration of the particulate matters.[54] In the study of Xu et al., significant increases in Q-T interval was observed after 1-5 days exposure to ultrafine particles which was more significant in obese males and those who had high levels of C-reactive protein (CRP).[55] It is better to conform future original studies with resolutions on the ultrafine particle effect in cardiac arrhythmia.

Gaseous Pollutants. Evidences regarding the positive roles of gaseous pollutants on the development of cardiac arrhythmia are limited and contradictory. Rich et al. observed an increased risk of rapid ventricular response due to paroxysmal atrial fibrillation within hours after exposure to ambient ozone.[56] Moreover, Tsai et al. demonstrated a strong association between the concentration of SO_2 in warm days ($>23^{\circ}$) and NO_2 and O_3 in both warm and cool days with the emergency visit for cardiac arrythmia in a case-crossover study in Taiwan.[41] In the study of Santos et al., 1.5 ppm increase in CO and 49,5 $\mu g/m^3$ increase in NO_2 was associated with 12.3% and 10.4% increase in arrhythmia emergency visit.[40] Hoek et al., concluded that the risk of life-threatening arrhythmias increased after exposure to SO_2, CO, and NO_2.[38] Raza et al. found that short-term exposure to moderate levels of O_3 may be associated with the risk of cardiac arrest.[57] In addition, in the study of Nadzieko et al., no association was found between the frequency of spontaneous arrhythmia after the exposure to SO_2 and ultrafine carbon particle.[58] Moreover, in the study of Peters et al., the incidence of life threatening arrhythmia was associated with NO_2, CO, black carbon, and fine particle mass.[59] However, Liu et al. demonstrated no relation between NO_2, SO_2, CO, and O_3 exposure with the incidence of atrial fibrillation.[39] Considering the conflicting results, further studies are needed to confirm the role of gaseous pollutants in cardiac arrhythmia.

Pathophysiology

Following subtitles, are some of the possible mechanism related to the pathophysiology of arrhythmia development with exposure to air pollution (illustrated in Fig 1).

Oxidative stress. Several studies observed an increment in oxidative stress after exposure to elevated level of particulate matters.[60-62] Oxidative stress is a stimulator factor for calcium calmodulin kinase II activation.[63] The calcium calmodulin kinase II is a serine/threonine kinase with critical roles in human body.[64] The level of calcium calmodulin kinase II

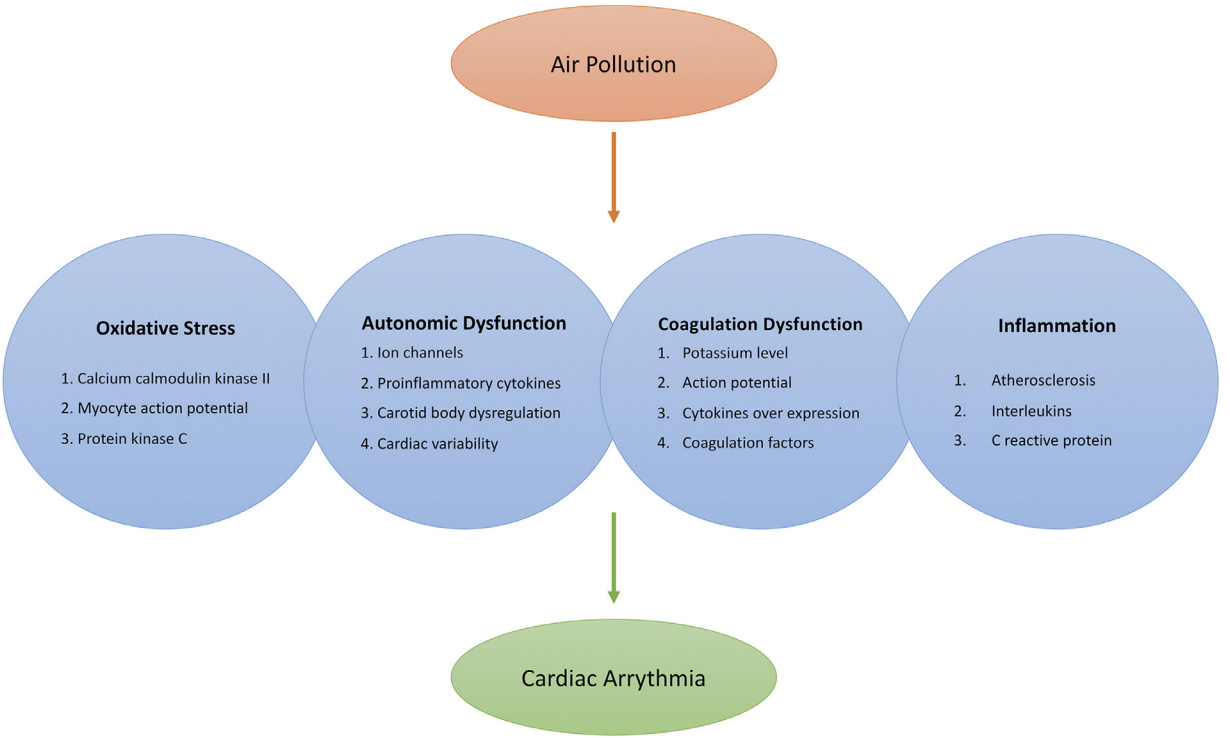

FIG 1. Possible mechanisms related to the pathophysiology of arrhythmia development with exposure to air pollution.

tends to be high in heart disease and higher level of calcium calmodulin kinase II is associated with heart failure and arrhythmia.[65-67] In the study of Wu et al., high level of calcium calmodulin kinase II was associated with inducing the arrythmia in cardiac hypertrophy in vivo.[68] Van Oort et al. found that calcium calmodulin kinase II could induce ryanodine receptors phosphorylation which can be associated with abnormal calcium release from sarcoplasmic reticulum and lethal ventricular arrythmia.[69] In addition, in another study by Greer-Short et al., calcium calmodulin kinase II was related to the atrial myocyte late sodium current and atrial fibrillation.[70]

Oxidative stress may induce arrythmia by influencing on the myocyte action potential.[71] Xie et al. observed that oxidative stress could induce early after depolarization and impair sodium current inactivation, that are responsible for ventricular arrythmia.[72] In the study of Karagueuzian et al., it was observed that oxidative stress could reduce repolarization reserve by effecting the L-type calcium current, the late sodium, and the sodium-calcium exchanger, and cause sudden cardiac death through ventricular arrythmia.[73] In addition, in the study of Pezhouman et al., oxidative-stress-related after depolarization was associated with atrial fibrillation through sodium current blockage.[74] Furthermore, in the study of Kim et al., it was found that the exposure to diethyl phthalate, one of the particulate matters, could be associated with oxidative stress and prolong action potential through calcium current and calcium calmodulin kinase II activation, which could be prevented by antioxidants.[75] It seems that protein kinase C activation may be responsible for oxidative-stress-related afterdepolarization.[76]

Autonomic dysfunction. Autonomic nervous system has a critical role in the cardiac rhythm regulation and arrhythmia triggering.[77-79] In fact, it seems that autonomic nervous system can interact with the cardiac rhythm through cardiac ion channels or proinflammatory cytokines.[80-82] Air pollutants can influence the cardiac rhythm by affecting the heart rate variability or carotid body tone.[83-85]

Changes in the heart rate variability due to PMs exposure is associated with cardiac arrythmia.[86] There are several studies that assessed the associations between daily changes in particulate matters change and the cardiac variability, as an indicating variable for autonomic function of the heart.[87-90] It is suggested that exposure to the particulate matters is related to the reductions in the majority indices of heart rate variability.[91,92]

Carotid body dysregulation is another mechanism of PMs related cardiac arrythmia through autonomic dysfunction.[93,94] In the study of Wang

et al., it was found that the exposure to PMs could reduce the heart rate variability and increase the risk of ventricular arrythmia through carotid body afferent nerve responses in mice with congestive heart failure.[95] However, it is better to evaluate the effect of PMs on the human carotid body responses in the future studies.

Coagulation dysfunction. Changes in the blood flow to the myocytes can lead to an ischemic reaction by interacting with the level of potassium, the action potential, and over expression of cytokines.[96-98]

Myocardial ischemia has some characteristics including ionic and biochemical dysfunction that can lead to an unstable electrical activity and promote the cardiac arrhythmia.[99] Recent studies suggested that air pollution may stimulate the coagulation and thrombosis process.[100,101] In addition, some studies found that air pollutants can be effective in the coagulation cascade through shortening the prothrombin time, decreasing factor VII, changing the tissue plasminogen activator and platelet count and altering platelet activity.[102,103]

Chuang et al. demonstrated that high-sensitivity C-reactive protein (hs-CRP), 8-hydroxy-2′-deoxyguanosine (8-OHdG), plasminogen activator fibrinogen inhibitor-1, and tissue-type plasminogen activator (which are related to the coagulation process) are associated with increased level of particulate matters.[104] Wu et al. suggested that $PM_{2.5}$ are associated with hs-CRP, tumor necrosis factor alpha, fibrinogen, plasminogen activator fibrinogen inhibitor-1, tissue-type plasminogen activator, von Willebrand factor, soluble platelet selectin (sP-selectin), and total homocysteine.[105] In the study of Rückerl et al., increased levels of PM_{10} and ultrafine particles were associated with high levels of CRP, which imposed an effect on the coagulation and coronary events through a 2 day interval.[106] In addition, Panasevich et al. found that short-term exposure to O_3 was associated with increased fibrinogen level.[107] Furthermore, Croft et al. suggested that high concentrations of $PM_{2.5}$ and ultrafine particles were associated with increased CRP and fibrinogen levels, although the levels of D-dimer, von Willebrand factor, or P-selectin were not significantly associated with air pollutants.[108]

Inflammation. Recent studies suggested that systemic inflammation plays a critical role in the development of cardiovascular diseases.[109] In fact, systemic inflammation can trigger cardiac arrhythmia directly or in the context of atherosclerosis and ischemic heart disease.[110,111] Interleukin (IL) 1, IL-6, IL-8, and IL-18 are some of the inflammatory factors which play a role in the pathogenesis of cardiovascular diseases.[112-115]

Furthermore, previous studies have shown the role of IL-1 and IL-6 in the development of cardiac arrhythmia.[116,117] Thus, air pollutants can interact with the cardiac rhythm by affecting the inflammatory markers including interleukins and other inflammatory factors.

There are many studies indicating the role of air pollutants in systemic inflammation. Dabass et al. found that short-term exposure to high levels of $PM_{2.5}$ was related with the increment of CRP level as a pro inflammatory marker in the metabolic syndrome patients.[118] In another study, there was an increase in the levels of IL-1β, IL-6, and GM-CSF after exposure to PM_{10} during an episode of acute air pollution.[119] Ljungman et al. observed that air pollution might be associated with inflammatory responses and the polymorphism of IL-6.[120] In addition, in the study of Barraza-Villarreal et al., the level of IL-8 was associated with high levels of $PM_{2.5}$.[121]

Conclusion

Air pollution is a global health issue that is associated with different health problems including cardiovascular disease. Particulate matters (PM_{10}, $PM_{2.5}$, and UFP) and gaseous air pollutants can exert undesirable effects on cardiac rhythms. Short-term and long-term exposure to the air pollutants can interact with the cardiac rhythms through oxidative stress, autonomic dysfunction, coagulation dysfunction, and inflammation. It seems that particulate matters, especially $PM_{2.5}$ have stronger association with cardiac arrhythmias among all air pollutants. However, future studies are needed to confirm these results.

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REFERENCES

1. Paul LA, Burnett RT, Kwong JC, Hystad P, van Donkelaar A, Bai L, et al. The impact of air pollution on the incidence of diabetes and survival among prevalent diabetes cases. *Environ Int* 2020;134:105333.
2. Akbarzadeh MA, Khaheshi I, Sharifi A, Yousefi N, Naderian M, Namazi MH, et al. The association between exposure to air pollutants including PM10, PM2. 5, ozone, carbon monoxide, sulfur dioxide, and nitrogen dioxide concentration and the relative risk of developing STEMI: a case-crossover design. *Environ Res* 2018;161:299–303.

3. Ravindra K, Kaur-Sidhu M, Mor S. Air pollution in rural households due to solid biomass fuel use and its health impacts. Indoor Environmental Quality. Springer; 2020. p. 27–33.
4. Urhie E, Afolabi A, Afolabi A, Matthew O, Osabohien R, Ewetan O. Economic growth, air pollution and health outcomes in Nigeria: a moderated mediation model. *Cogent Social Sci* 2020;6:1719570.
5. Khaniabadi YO, Sicard P, Takdastan A, Hopke PK, Taiwo AM, Khaniabadi FO, et al. Mortality and morbidity due to ambient air pollution in Iran. *Clin Epidemiol Global Health* 2019;7:222–7.
6. Adeuti BR. Analysis of environmental pollution in developing countries. *Am Scient Res J Eng Technol Sci (ASRJETS)* 2020;65:39–48.
7. Le Thi H. Health impacts of traffic-related air pollution: cause-effect relationships and mitigating measures. CIGOS 2019, Innovation for Sustainable Infrastructure. Springer; 2020. p. 1031–6.
8. Norbäck D. Future directions of research on indoor environment, indoor air quality (IAQ), and health. Indoor environmental quality and health risk toward healthier environment for all. Springer; 2020. p. 321–33.
9. Weisenberg H, Zhao T, Heinrich J. Combinations of epidemiological and experimental studies in air pollution research: a narrative review. *Int J Environ Res Public Health* 2020;17:385.
10. Martinelli N, Olivieri O, Girelli D. Air particulate matter and cardiovascular disease: a narrative review. *Eur J Int Med* 2013;24:295–302.
11. Garelnabi M. Emerging evidences from the contribution of the traditional and new risk factors to the atherosclerosis pathogenesis. *J Med Sci* 2010;10:153–61.
12. Urman R, Garcia E, Berhane K, McConnell R, Gauderman WJ, Gilliland F. The potential effects of policy-driven air pollution interventions on childhood lung development. *Am J Respir Crit Care Med* 2020;201:438–44.
13. Havet A, Hulo S, Cuny D, Riant M, Occelli F, Cherot-Kornobis N, et al. Residential exposure to outdoor air pollution and adult lung function, with focus on small airway obstruction. *Environ Res* 2020;183:109161.
14. Costa LG, Cole TB, Dao K, Chang Y-C, Coburn J, Garrick JM. Effects of air pollution on the nervous system and its possible role in neurodevelopmental and neurodegenerative disorders. *Pharmacol Ther* 2020:107523.
15. Glencross DA, Ho T-R, Camiña N, Hawrylowicz CM, Pfeffer PE. Air pollution and its effects on the immune system. *Free Radic Biol Med* 2020.
16. Feng J, Cavallero S, Hsiai T, Li R. Impact of air pollution on intestinal redox lipidome and microbiome. *Free Radic Biol Med* 2020.
17. Fitch MN, Phillippi D, Zhang Y, Lucero J, Pandey RS, Liu J, et al. Effects of inhaled air pollution on markers of integrity, inflammation, and microbiota profiles of the intestines in Apolipoprotein E knockout mice. *Environ Res* 2020;181:108913.
18. Miller MR, Newby DE. Air pollution and cardiovascular disease: car sick. *Cardiovasc Res* 2020;116:279–94.
19. Pan H-Y, Cheung S-M, Chen F-C, Wu K-H, Cheng S-Y, Chuang P-C, et al. Short-term effects of ambient air pollution on ST-elevation myocardial infarction events:

are there potentially susceptible groups? *Int J Environ Res Public Health* 2019;16:3760.
20. Ho AFW, Wah W, Earnest A, Ng YY, Xie Z, Shahidah N, et al. Health impacts of the Southeast Asian haze problem—a time-stratified case crossover study of the relationship between ambient air pollution and sudden cardiac deaths in Singapore. *Int J Cardiol* 2018;271:352–8.
21. Liu S, Yu JZ, Wang T, Huang W. High level of source-specific particulate matter air pollution associated with cardiac arrhythmias. 2018.
22. Ngu NL, McEvoy M. Environmental tobacco smoke and peripheral arterial disease: a review. *Atherosclerosis* 2017;266:113–20.
23. Murakoshi N, Aonuma K. Epidemiology of arrhythmias and sudden cardiac death in Asia. *Circ J* 2013;77:2419–31.
24. Kim JB, Prunicki M, Haddad F, Dant C, Sampath V, Patel R, et al. Cumulative lifetime burden of cardiovascular disease from early exposure to air pollution. *J Am Heart Assoc* 2020;9:e014944.
25. Lee BJ, Fettweis M, Toorman E, Molz FJ. Multimodality of a particle size distribution of cohesive suspended particulate matters in a coastal zone. *J Geophys Res* 2012;117(C3).
26. Embiale A, Zewge F, Chandravanshi B, Sahle-Demessie E. Commuter exposure to particulate matters and total volatile organic compounds at roadsides in Addis Ababa, Ethiopia. *Int J Environ Sci Technol* 2019;16:4761–74.
27. Yang D, Zhang H, Li J. Changes in concentrations of fine and coarse particles under the CO2-induced global warming. *Atmos Res* 2019;230:104637.
28. Nowak DJ. The atmospheric system: Air quality and greenhouse gases. Understanding Urban Ecology. Springer; 2019. p. 175–99.
29. Chong HS, Kwon S, Lim Y, Lee J. Real-world fuel consumption, gaseous pollutants, and CO_2 emission of light-duty diesel vehicles. *Sustain Cities Society* 2020;53:101925.
30. Song X, Liu Y, Hu Y, Zhao X, Tian J, Ding G, et al. Short-term exposure to air pollution and cardiac arrhythmia: a meta-analysis and systematic review. *Int J Environ Res Public Health* 2016;13:642.
31. Shahrbaf MA, Mahjoob MP, Khaheshi I, Akbarzadeh MA, Barkhordari E, Naderian M, et al. The role of air pollution on ST-elevation myocardial infarction: a narrative mini review. *Future Cardiol* 2018;14:301–6.
32. Chen R, Yin P, Meng X, Liu C, Wang L, Xu X, et al. Fine particulate air pollution and daily mortality. A nationwide analysis in 272 Chinese cities. *Am J Respir Crit Care Med* 2017;196:73–81.
33. Xie X, Wang Y, Yang Y, Xu J, Zhang Y, Tang W, et al. Long-term exposure to fine particulate matter and tachycardia and heart rate: results from 10 million reproductive-age adults in China. *Environ Pollut* 2018;242:1371–8.
34. Watkins A, Danilewitz M, Kusha M, Massé S, Urch B, Quadros K, et al. Air pollution and arrhythmic risk: the smog is yet to clear. *Can J Cardiol* 2013;29:734–41.

35. Link MS, Luttmann-Gibson H, Schwartz J, Mittleman MA, Wessler B, Gold DR, et al. Acute exposure to air pollution triggers atrial fibrillation. *J Am Coll Cardiol* 2013;62:816–25.
36. Rich DQ, Kim MH, Turner JR, Mittleman MA, Schwartz J, Catalano PJ, 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;63:591–6.
37. Ljungman PL, Berglind N, Holmgren C, Gadler F, Edvardsson N, Pershagen G, et al. Rapid effects of air pollution on ventricular arrhythmias. *Eur Heart J* 2008;29:2894–901.
38. Hoek G, Brunekreef B, Fischer P, van Wijnen J. The association between air pollution and heart failure, arrhythmia, embolism, thrombosis, and other cardiovascular causes of death in a time series study. *Epidemiology* 2001;12:355–7.
39. Liu X, Kong D, Liu Y, Fu J, Gao P, Chen T, et al. Effects of the short−term exposure to ambient air pollution on atrial fibrillation. *Pacing Clin Electrophysiol* 2018;41:1441–6.
40. Santos U, Terra-Filho M, Lin C, Pereira L, Vieira T, Saldiva P, et al. Cardiac arrhythmia emergency room visits and environmental air pollution in Sao Paulo, Brazil. *J Epidemiol Commun Health* 2008;62:267–72.
41. Tsai S-S, Chiu H-F, Wu T-N, Yang C-Y. Air pollution and emergency room visits for cardiac arrhythmia in a subtropical city: Taipei, Taiwan. *Inhal Toxicol* 2009;21:1113–8.
42. Wichmann H, Mueller W, Allhoff P, Beckmann M, Bocter N, Csicsaky M, et al. Health effects during a smog episode in West Germany in 1985. *Environ Health Perspect* 1989;79:89–99.
43. Feng B, Song X, Dan M, Yu J, Wang Q, Shu M, et al. High level of source-specific particulate matter air pollution associated with cardiac arrhythmias. *Sci Total Environ* 2019;657:1285–93.
44. Pope CA, III, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004;109:71–7.
45. Halonen JI, Lanki T, Yli-Tuomi T, Tiittanen P, Kulmala M, Pekkanen J. Particulate air pollution and acute cardiorespiratory hospital admissions and mortality among the elderly. *Epidemiology* 2009:143–53.
46. Chen Y-C, Weng Y-H, Chiu Y-W, Yang C-Y. Short-term effects of coarse particulate matter on hospital admissions for cardiovascular diseases: a case-crossover study in a tropical city. *J Toxicol Environ Health, Part A* 2015;78:1241–53.
47. Ueda K, Nitta H, Ono M. Effects of fine particulate matter on daily mortality for specific heart diseases in Japan. *Circ J* 2009;73:1248–54.
48. Berger A, Zareba W, Schneider A, Rückerl R, Ibald-Mulli A, Cyrys J, 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.

49. Ebelt ST, Wilson WE, Brauer M. Exposure to ambient and nonambient components of particulate matter: a comparison of health effects. *Epidemiology* 2005:396–405.
50. Riediker M, Cascio WE, Griggs TR, Herbst MC, Bromberg PA, Neas L, et al. Particulate matter exposure in cars is associated with cardiovascular effects in healthy young men. *Am J Respir Crit Care Med* 2004;169:934–40.
51. Chiu H-F, Tsai S-S, Weng H-H, Yang C-Y. Short-term effects of fine particulate air pollution on emergency room visits for cardiac arrhythmias: a case-crossover study in Taipei. *J Toxicol Environ Health, Part A* 2013;76:614–23.
52. Zanobetti A, Coull BA, Gryparis A, Kloog I, Sparrow D, Vokonas PS, et al. Associations between arrhythmia episodes and temporally and spatially resolved black carbon and particulate matter in elderly patients. *Occup Environ Med* 2014;71:201–7.
53. He F, Shaffer ML, Rodriguez-Colon S, Yanosky JD, Bixler E, Cascio WE, et al. Acute effects of fine particulate air pollution on cardiac arrhythmia: the APACR study. *Environ Health Perspect* 2011;119:927–32.
54. Folino AF, Scapellato ML, Canova C, Maestrelli P, Bertorelli G, Simonato L, 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.
55. Xu H, Chen J, Zhao Q, Zhang Y, Wang T, Feng B, et al. Ambient air pollution is associated with cardiac repolarization abnormalities in healthy adults. *Environ Res* 2019;171:239–46.
56. Rich DQ, Mittleman MA, Link MS, Schwartz J, Luttmann-Gibson H, Catalano PJ, et al. Increased risk of paroxysmal atrial fibrillation episodes associated with acute increases in ambient air pollution. *Environ Health Perspect* 2006;114:120–3.
57. Raza A, Bellander T, Bero-Bedada G, Dahlquist M, Hollenberg J, Jonsson M, et al. Short-term effects of air pollution on out-of-hospital cardiac arrest in Stockholm. *Eur Heart J* 2014;35:861–8.
58. Nadziejko C, Fang K, Narciso S, Zhong M, Su WC, Gordon T, et al. Effect of particulate and gaseous pollutants on spontaneous arrhythmias in aged rats. *Inhal Toxicol* 2004;16:373–80.
59. Peters A, Liu E, Verrier RL, Schwartz J, Gold DR, Mittleman M, et al. Air pollution and incidence of cardiac arrhythmia. *Epidemiology* 2000;11:11–7.
60. Valavanidis A. Oxidative stress and pulmonary carcinogenesis through mechanisms of reactive oxygen species. How respirable particulate matter, fibrous dusts, and ozone cause pulmonary inflammation and initiate lung carcinogenesis. Oxidative Stress in Lung Diseases. Springer; 2019. p. 247–65.
61. Rao X, Zhong J, Brook RD, Rajagopalan S. Effect of particulate matter air pollution on cardiovascular oxidative stress pathways. *Antioxid Redox Signaling* 2018;28:797–818.
62. Riggs DW, Zafar N, Krishnasamy S, Yeager R, Rai SN, Bhatnagar A, et al. Exposure to airborne fine particulate matter is associated with impaired endothelial function and biomarkers of oxidative stress and inflammation. *Environ Res* 2020;180:108890.

63. Park H, Park H, Kim H, Mun D, Cui S, Pak H, et al. P4492Real urban air pollutants induces arrhythmia via oxidative stress and calcium calmodulin kinase II activatioin. *Eur Heart J* 2017;38(suppl_1).
64. Hund TJ, Mohler PJ. Role of CaMKII in cardiac arrhythmias. *Trends Cardiovasc Med* 2015;25:392–7.
65. Sufu-Shimizu Y, Okuda S, Kato T, Nishimura S, Uchinoumi H, Oda T, et al. Stabilizing cardiac ryanodine receptor prevents the development of cardiac dysfunction and lethal arrhythmia in Ca2+/calmodulin-dependent protein kinase IIδc transgenic mice. *Biochem Biophys Res Commun* 2020.
66. Trum M, Wagner S, Maier L, Mustroph J. CaMKII and GLUT1 in heart failure and the role of gliflozins. *Biochimica et Biophysica Acta (BBA)-Mol Basis Dis* 2020:165729.
67. Lebek S, Pichler K, Reuthner K, Trum M, Tafelmeier M, Mustroph J, et al. Enhanced CaMKII-dependent late INa induces atrial pro-arrhythmic activity in patients with sleep-disordered breathing. *Circ Res* 2020.
68. Wu Y, Temple J, Zhang R, Dzhura I, Zhang W, Trimble R, et al. Calmodulin kinase II and arrhythmias in a mouse model of cardiac hypertrophy. *Circulation* 2002;106:1288–93.
69. Van Oort RJ, McCauley MD, Dixit SS, Pereira L, Yang Y, Respress JL, et al. Ryanodine receptor phosphorylation by calcium/calmodulin-dependent protein kinase II promotes life-threatening ventricular arrhythmias in mice with heart failure. *Circulation* 2010;122:2669–79.
70. Greer-Short A, Musa H, Alsina KM, Ni L, Word TA, Reynolds JO, et al. Calmodulin kinase II regulates atrial myocyte late sodium current, calcium handling, and atrial arrhythmia. *Heart Rhythm* 2020;17:503–11.
71. Pereira C, Ximenes C, Merlo E, Sciortino A, Monteiro J, Moreira A, et al. Cardiotoxicity of environmental contaminant tributyltin involves myocyte oxidative stress and abnormal Ca2+ handling. *Environ Pollut* 2019;247:371–82.
72. Xie L-H, Chen F, Karagueuzian HS, Weiss JN. Oxidative stress−induced afterdepolarizations and calmodulin kinase II signaling. *Circ Res* 2009;104:79–86.
73. Karagueuzian H, Nguyen TP, Qu Z, Weiss JN. Oxidative stress, fibrosis, and early afterdepolarization-mediated cardiac arrhythmias. *Front Physiol* 2013;4:19.
74. Pezhouman A, Cao H, Fishbein MC, Belardinelli L, Weiss JN, Karagueuzian HS. Atrial fibrillation initiated by early afterdepolarization-mediated triggered activity during acute oxidative stress: efficacy of late sodium current blockade. *J Heart Health* 2018;4.
75. Kim J-B, Kim C, Choi E, Park S, Park H, Pak H-N, et al. Particulate air pollution induces arrhythmia via oxidative stress and calcium calmodulin kinase II activation. *Toxicol Appl Pharmacol* 2012;259:66–73.
76. Fei Y-D, Li W, Hou J-W, Guo K, Chen X-M, Chen Y-H, et al. Oxidative stress-induced after depolarizations and protein kinase C signaling. *Int J Mol Sci* 2017;18:688.
77. Shen MJ, Zipes DP. Role of the autonomic nervous system in modulating cardiac arrhythmias. *Circ Res* 2014;114:1004–21.

78. Dusi V, De Ferrari GM, Schwartz PJ. There are 100 ways by which the sympathetic nervous system can trigger life-threatening arrhythmias. *Eur Heart J* 2020.
79. Herring N, Kalla M, Paterson DJ. The autonomic nervous system and cardiac arrhythmias: current concepts and emerging therapies. Nat Rev Cardiol; 20191–20.
80. Tan AY, Verrier RL. The role of the autonomic nervous system in cardiac arrhythmias. *Handbook of clinical neurology* 2013:135–45.
81. Gordan R, Gwathmey JK, Xie L-H. Autonomic and endocrine control of cardiovascular function. *World J Cardiol* 2015;7:204.
82. Marionneau C, Abriel H. Cardiac sodium current under sympathetic control: protein phosphatase 2A regulates cardiac Na+ channels. *Am Heart Assoc* 2019.
83. Trivedi T, Androulakis M, Redd KT, Alonso A, Soliman E, Magnani J, et al. Is low heart rate variability, a marker of autonomic dysfunction, the missing link between migraine with visual aura and cardioembolic stroke? *Stroke* 2019;50(Suppl_1). A14-A.
84. Shah AS, Vajravelu ME, Bacha F, Farrell RM, Gidding SS, Katz LEL, et al. Heart rate variability and cardiac autonomic dysfunction: prevalence, risk factors, and relationship to arterial stiffness in the treatment options for type 2 diabetes in adolescents and youth (TODAY) study. *Diabetes Care* 2019;42:2143–50.
85. Iturriaga R, Del Rio R, Idiaquez J, Somers VK. Carotid body chemoreceptors, sympathetic neural activation, and cardiometabolic disease. *Biol Res* 2016;49:13.
86. Watanabe E, Kiyono K, Yamamoto Y, Hayano J. Heart rate variability and cardiac diseases. Clinical assessment of the autonomic nervous system. Springer; 2017. p. 163–78.
87. Pope CA, III, Dockery DW. Health effects of fine particulate air pollution: lines that connect. *J Air Waste Manage Assoc* 2006;56:709–42.
88. 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.
89. Huang F, Wang P, Pan X, Wang Y, Ren S. Effects of short-term exposure to particulate matters on heart rate variability: a systematic review and meta-analysis based on controlled animal studies. *Environ Pollut* 2020;256:113306.
90. Tang C-S, Wu T-Y, Chuang K-J, Chang T-Y, Chuang H-C, Lung S-CC, et al. Impacts of in-cabin exposure to size-fractionated particulate matters and carbon monoxide on changes in heart rate variability for healthy public transit commuters. *Atmosphere* 2019;10:409.
91. An Z, Jin Y, Li J, Li W, Wu W. Impact of particulate air pollution on cardiovascular health. *Curr Allergy Asthma Rep* 2018;18:15.
92. Link MS, Dockery DW. Air pollution and the triggering of cardiac arrhythmias. *Curr Opin Cardiol* 2010;25:16.
93. Fujii K, Saku K, Kishi T, Oga Y, Tohyama T, Nishikawa T, et al. Carotid body denervation markedly improves survival in rats with hypertensive heart failure. *Am J Hypertens* 2017;30:791–8.
94. Iturriaga R. Carotid body ablation: a new target to address central autonomic dysfunction. *Curr Hypertens Rep* 2018;20:53.

95. Wang T, Lang GD, Moreno-Vinasco L, Huang Y, Goonewardena SN, Peng YJ, et al. Particulate matter induces cardiac arrhythmias via dysregulation of carotid body sensitivity and cardiac sodium channels. *Am J Respir Cell Mol Biol* 2012;46:524–31.
96. Morand J, Arnaud C, Pepin J-L, Godin-Ribuot D. Chronic intermittent hypoxia promotes myocardial ischemia-related ventricular arrhythmias and sudden cardiac death. *Sci Rep* 2018;8:1–8.
97. De Jong JS, Dekker LR. Platelets and cardiac arrhythmia. *Front Physiol* 2010;1:166.
98. Chen R, Li H, Cai J, Wang C, Lin Z, Liu C, et al. Fine particulate air pollution and the expression of microRNAs and circulating cytokines relevant to inflammation, coagulation, and vasoconstriction. *Environ Health Perspect* 2018;126:017007.
99. Ghuran A, Camm A. Ischaemic heart disease presenting as arrhythmias. *Br Med Bull* 2001;59:193–210.
100. Brook RD, Rajagopalan S, Pope CA, III, Brook JR, Bhatnagar A, Diez-Roux AV, 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.
101. Robertson S, Miller MR. Ambient air pollution and thrombosis. *Part Fibre Toxicol* 2018;15:1.
102. Baccarelli A, Martinelli I, Zanobetti A, Grillo P, Hou L-F, Bertazzi PA, et al. Exposure to particulate air pollution and risk of deep vein thrombosis. *Arch Intern Med* 2008;168:920–7.
103. Baccarelli A, Zanobetti A, Martinelli I, Grillo P, Hou L, Giacomini S, et al. Effects of exposure to air pollution on blood coagulation. *J Thromb Haemost* 2007;5:252–60.
104. Chuang K-J, Chan C-C, Su T-C, Lee C-T, Tang C-S. The effect of urban air pollution on inflammation, oxidative stress, coagulation, and autonomic dysfunction in young adults. *Am J Respir Crit Care Med* 2007;176:370–6.
105. Wu S, Deng F, Wei H, Huang J, Wang H, Shima M, et al. Chemical constituents of ambient particulate air pollution and biomarkers of inflammation, coagulation and homocysteine in healthy adults: a prospective panel study. *Part Fibre Toxicol* 2012;9:49.
106. Ruckerl R, Ibald-Mulli A, Koenig W, Schneider A, Woelke G, Cyrys J, et al. Air pollution and markers of inflammation and coagulation in patients with coronary heart disease. *Am J Respir Crit Care Med* 2006;173:432–41.
107. Panasevich S, Leander K, Rosenlund M, Ljungman P, Bellander T, de Faire U, et al. Associations of long-and short-term air pollution exposure with markers of inflammation and coagulation in a population sample. *Occup Environ Med* 2009;66:747–53.
108. Croft DP, Cameron SJ, Morrell CN, Lowenstein CJ, Ling F, Zareba W, et al. Associations between ambient wood smoke and other particulate pollutants and biomarkers of systemic inflammation, coagulation and thrombosis in cardiac patients. *Environ Res* 2017;154:352–61.

109. McNicholas WT. Chronic obstructive pulmonary disease and obstructive sleep apnea: overlaps in pathophysiology, systemic inflammation, and cardiovascular disease. *Am J Respir Crit Care Med* 2009;180:692–700.
110. Lazzerini PE, Capecchi PL, Laghi-Pasini F. Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis. *Eur Heart J* 2017;38:1717–27.
111. Vonderlin N, Siebermair J, Kaya E, Köhler M, Rassaf T, Wakili R. Critical inflammatory mechanisms underlying arrhythmias. *Herz* 2019;44:121–9.
112. Fearon WF, Fearon DT. Inflammation and cardiovascular disease: role of the interleukin-1 receptor antagonist. *Am Heart Assoc* 2008.
113. Kanda T, Takahashi T. Interleukin-6 and cardiovascular diseases. *Jpn Heart J* 2004;45:183–93.
114. Apostolakis S, Vogiatzi K, Amanatidou V, Spandidos DA. Interleukin 8 and cardiovascular disease. *Cardiovasc Res* 2009;84:353–60.
115. Everett BM, Bansal S, Rifai N, Buring JE, Ridker PM. Interleukin-18 and the risk of future cardiovascular disease among initially healthy women. *Atherosclerosis* 2009;202:282–8.
116. Ali A, Boutjdir M, Aromolaran AS. Cardiolipotoxicity, inflammation, and arrhythmias: Role for Interleukin-6 molecular mechanisms. *Front Physiol* 2019;9:1866.
117. De Jesus NM, Wang L, Lai J, Rigor RR, Stuart SDF, Bers DM, et al. Antiarrhythmic effects of interleukin 1 inhibition after myocardial infarction. *Heart Rhythm* 2017;14:727–36.
118. Dabass A, Talbott EO, Rager JR, Marsh GM, Venkat A, Holguin F, et al. Systemic inflammatory markers associated with cardiovascular disease and acute and chronic exposure to fine particulate matter air pollution (PM2. 5) among US NHANES adults with metabolic syndrome. *Environ Res* 2018;161:485–91.
119. van EEDEN SF, Tan WC, Suwa T, Mukae H, Terashima T, Fujii T, et al. Cytokines involved in the systemic inflammatory response induced by exposure to particulate matter air pollutants (PM10). *Am J Respir Crit Care Med* 2001;164:826–30.
120. Ljungman P, Bellander T, Schneider A, Breitner S, Forastiere F, Hampel R, et al. Modification of the interleukin-6 response to air pollution by interleukin-6 and fibrinogen polymorphisms. *Environ Health Perspect* 2009;117:1373–9.
121. Barraza-Villarreal A, Sunyer J, Hernandez-Cadena L, Escamilla-Nuñez MC, Sienra-Monge JJ, Ramírez-Aguilar M, et al. Air pollution, airway inflammation, and lung function in a cohort study of Mexico City schoolchildren. *Environ Health Perspect* 2008;116:832–8.