BIOGRAPHICAL SKETCH

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NAME: **Carll, Alex Perrow**

eRA COMMONS USER NAME (credential, e.g., agency login): ALEXCARLL

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Duke University	A.B.	05/2004	Envir. Science & Policy
University of North Carolina, Chapel Hill	M.S.P.H.	05/2008	Public Health
University of North Carolina, Chapel Hill	Ph.D.	12/2012	Environmental Health
Harvard T.H. Chan School of Public Health	Post-Doc	10/2015	Environmental Health

A. Personal Statement

I investigate the mechanisms underlying aerosol-induced cardiac dysfunction and ventricular remodeling. For over thirteen years I have studied how environmental aerosols affect cardiovascular physiology in rodents. I am proficient at assessing cardiac electrophysiology, arterial pressure, and cardiac mechanical performance in rodents during and after inhalation exposures to toxic aerosols. The central hypothesis of my research is that exposure to toxic aerosols impairs cardiac electrical stability and mechanical performance through altered autonomic nervous system regulation. Through assessment of electrocardiography, blood pressure and left ventricular pressure by radiotelemetry, as well as be echocardiography in conscious animals, I have demonstrated that exposure to manmade pollutant aerosols alters cardiac electrophysiology and left ventricular performance through the autonomic nervous system,[1-2] attaining two *Paper of the Year* awards for these findings. More recently, I expanded my research focus to the effects of tobacco products on cardiac electrophysiology both in animals and humans. As a new member of the American Heart Association Tobacco Regulation and Addiction Center (ATRAC), I conducted an epidemiologic study of the electrophysiologic and autonomic effects of smoking in the Louisville Health Heart Study cohort. Through a Fellowship in the ATRAC, I also recently investigated how exposure to electronic cigarette aerosols and their individual aldehyde constituents impairs cardiac electrophysiology and hemodynamic function in mice. Per my foundations in both inhalation toxicology and public health, I am dedicated to further delineating the cardiovascular harms of tobacco products and inhaled environmental pollutants.

B. Positions and Honors

Positions

2005-06 Student Contractor, Environmental Toxicology Division, U.S. Environmental Protection Agency, Research Triangle Park, NC
2006-12 Pre-doctoral Fellow, Environmental Public Health Division, U.S. EPA, Research Triangle Park, NC
2012-13 Post-Doctoral Representative, Cardiovascular Toxicology Specialty Section, Society of Toxicology
2013-15 National Institute of Environmental Health Sciences Post-Doctoral Fellow, T.H. Chan School of Public Health, Harvard University, Boston, MA
2013-15 Grants and Research Strategy Chair, Harvard School of Public Health Post-Doctoral Association
2015- Visiting Scientist, T.H. Chan Harvard School of Public Health, Harvard University, Boston, MA
2015- Assistant Professor, Department of Physiology, Institute of Molecular Cardiology, Diabetes & Obesity Center, School of Medicine, University of Louisville, Louisville, KY
2017-18 American Heart Association Tobacco Regulation and Addiction Center Research Fellow
2018- Councilor, Inhalation and Respiratory Specialty Section, Society of Toxicology

Honors

2011 Graduate Student Travel Award, Cardiovascular Toxicology Specialty Section, Society of Toxicology (SOT) Annual Meeting
2011 First Place Pre-Doctoral Trainee Poster Presentation, Research Triangle Visiting Pulmonary Scholar Series, Annual Meeting
2012 Student Travel Award, SOT Annual Meeting
2012 Mary O. Amdur Award for Inhalation Toxicology, SOT Annual Meeting
2013 Paper of the Year[1.] Inhalation & Respiratory Toxicology, SOT Annual Meeting
2014 Impact Paper of the Year[2.] Cardiovascular Toxicology, SOT Annual Meeting
2015 Harvard T.H. Chan School of Public Health Post-Doctoral Association Travel Award

Professional Memberships

2006- Society of Toxicology (SOT), member
2010- Sigma Xi, member
2013- Delta Omega, Public Health Honor Society
2015 American Thoracic Society, member
2017- American Heart Association, member

C. Contributions to Science

1. My early research focused primarily on developing a reproducible rat model of cardiomyopathy to incorporate into air pollution exposure studies. Rodent models of heart failure are commonly complicated by technically difficult surgeries that often cause premature mortality and a variable phenotype while also precluding additional surgeries such as telemetry implantation. Yet epidemiologic studies indicate a particularly strong link between air pollution exposure and cardiovascular morbidity and mortality among humans with preexisting heart failure. To facilitate toxicological investigations of the biological plausibility of these epidemiologic findings and their potential mechanisms, I developed rat models of noninvasively-induced cardiomyopathy using pharmacologic and dietary interventions. These models were particularly useful for air pollution investigations involving radiotelemetry, as demonstrated in my subsequent research.

a. **Carll AP**, Haykal-Coates N, Winsett DW, Rowan WH 3rd, Hazari MS, Ledbetter AD, Nyska A, Cascio WE, Watkinson WP, Costa DL, Farraj AK. 2010. Particulate matter inhalation exacerbates cardiopulmonary injury in a rat model of isoproterenol-induced cardiomyopathy. Inhal Toxicol 22(5):355-68. PMID: 20121584.
b. **Carll AP**, Haykal-Coates N, Winsett DW, Hazari MS, Nyska A, Richards JH, Willis MS, Costa DL, Farraj AK. 2011. Dietary salt exacerbates isoproterenol-induced cardiomyopathy in rats. Toxicol. Pathol. 39(6):925-37. PMID: 21878552.
c. **Carll AP**, Willis MS, Lust RM, Costa DL, Farraj AK. 2011. Merits of Non-Invasive Rat Models of Left Ventricular Heart Failure. Cardiovasc Toxicol. 11(2):91-112. PMID: 21279739.

2. I applied rodent models of cardiomyopathy to reveal that underlying cardiac disease confers susceptibility to acute inhalation exposure to air pollutants. By applying a novel model of isoproterenol-induced cardiomyopathy in rats genetically predisposed to heart failure, I demonstrated that particulate matter (PM) inhalation transiently increases atrioventricular block arrhythmia and parasympathetic regulation of cardiovascular physiology solely in cardiomyopathic rats and not in their healthy counterparts. Similarly, I found that acutely inhaled diesel exhaust (DE) transiently increases parasympathetic influence, arrhythmia, left ventricular diastolic volume, and heterogeneity of ventricular repolarization in heart failure-prone rats, with age imparting greater sensitivity. Additionally, I determined that DE filtered free of PM also similarly causes arrhythmia, parasympathetic dominance, and repolarization defects.

a. **Carll AP**, Haykal-Coates N, Winsett DW, Hazari MS, Ledbetter AD, Richards JH, Cascio WE, Costa DL, Farraj AK. 2015. Cardiomyopathy confers susceptibility to particulate matter-induced oxidative stress, vagal dominance, arrhythmia, and pulmonary inflammation in heart failure-prone rats. Inhal Toxicol 27(2):100-12. PMID: 25600220.
b. **Carll AP**, Hazari MS, Perez CM, Krantz QT, King C, Winsett DW, Costa DL, Farraj AK. 2012. Whole and Particle-Free Diesel Exhausts Differentially Affect Cardiac Electrophysiology, Blood pressure, and Autonomic Balance in Heart Failure-Prone Rats. Toxicol. Sci. 128(2):490-9. PMID: 22543275. PMCID: PMC3937603.
c. [1]**Carll AP**, Lust RM, Hazari MS, Perez CM, Krantz QT, King C, Winsett DW, Cascio WE, Costa DL, Farraj AK. 2013. Diesel Exhaust Inhalation Increases Cardiac Output, Bradyarrhythmias, and

Parasympathetic Tone in Aged Heart Failure-Prone Rats. Toxicol. Sci. 131(2):583-95. PMID: 23047911. PMCID: PMC3937610.

3. At the outset of my subsequent research, it remained unclear how air pollution exposure might exacerbate heart failure. I thus tested the hypothesis that air pollution exposure impairs cardiac performance through ANS dysfunction. I applied treadmill exercise stress tests, antagonists of both autonomic branches, and surgical vagotomy in heart failure-prone rats exposed acutely to DE. Treadmill exercise indicated DE exposure caused time-dependent changes in autonomic imbalance and depression in contractility, with likely mediation by the sympathetic branch of the autonomic nervous system. Measures of LV pressure and vagotomy suggested DE impaired cardiac performance and autonomic balance via sympathetic dominance, likely originating from impaired vagal function. This information elucidated a mechanism underlying air pollutant-induced acute exacerbation of heart failure and offers biological plausibility to epidemiological observations, thereby guiding health assessments and air pollution regulations. I followed these studies by continuously measuring LV pressure via telemetry in normal rats exposed subchronically to vehicular-derived PM. These findings indicated repeat PM exposure diminished LV performance and impaired baroreflexes while also enhancing sympathetic and arrhythmic responses to a psychosocial stress test, and are in preparation.

a. [2]**Carll AP**, Hazari MS, Perez CM, Krantz QT, King C, Haykal-Coates N, Cascio WE, Costa DL, Farraj AK 2013. An Autonomic Link between Inhaled Diesel Exhaust and Impaired Cardiac Performance: Insight from Treadmill and Dobutamine Challenges in Heart Failure-Prone Rats. Toxicol. Sci. 135(2):425-36. PMID: 23872579. PMCID: PMC3937599.

4. More recently I examined effects of repeated exposure to traffic-derived PM at ambient levels in a rat model of metabolic syndrome induced by dietary fructose. Exposure to traffic PM at low, environmentally relevant levels diminished baroreflex sensitivity and caused sympathetic dominance and arrhythmia in metabolic syndrome rats, whereas normal healthy rats showed no such responses. These findings validate limited epidemiologic evidence that metabolic syndrome increases susceptibility to the adverse cardiovascular effects of PM, potentially through ANS imbalance.

a. ***Carll AP**, Crespo SM, Zati DH, Filho MS, Zati DH, Coull BA, Diaz EA, Raimundo RD, Jaeger TNG, Ricci-Vitor AL, Papapostolou V, Lawrence JE, Garner DM, Perry BS, Harkema JR, Godleski JJ 2017. Inhaled ambient-level traffic-derived particulates decrease cardiac vagal influence and baroreflexes and increase arrhythmia in a rat model of metabolic syndrome. Particle & Fibre Toxicology. 14(1):16. PMID: 28545487. PMCID: PMC5445437.

5. I also recently published critical reviews of how the autonomic nervous system acts both as a mediator and marker of toxin- and disease-induced cardiovascular dysfunction. These involved an exhaustive review on the ANS's role in toxicology in a book chapter, as well as a critical review of existing literature on the effects of tobacco product use on autonomic balance and cardiac function.

a. ***Carll AP,** Farraj AK, and Roberts AM 2018. The Role of the Autonomic Nervous System in Cardiovascular Toxicity. In: McQueen, C.A. (ed.), *Comprehensive Toxicology, 3e, Vol. 13*, Oxford: Elsevier Ltd. Pp. 61-114. ISBN 9780081006016. DOI: 10.1016/B978-0-12-801238-3.64259-9.
b. Conklin DJ, Schick SF, Blaha MJ, **Carll AP**, DeFilippis A, Ganz P, Hall ME, Hamburg NM, O'Toole TE, Reynolds LM, Srivastava S, Bhatnagar A 2019. Cardiovascular injury induced by tobacco products: Assessment of risk factors and biomarkers of harm: A Tobacco Center of Regulatory Science (TCORS) Compilation. *Am J Physiol Heart Circ Physiol.* 2019 Feb 1. doi: 10.1152/ajpheart.00591.2018. [Epub ahead of print] PMID: 30707616.

*: corresponding author.

Complete list of references:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40314864/?sort=date&direction=descending

D. Research Support

Ongoing

2U54HL120163, Bhatnagar/Robertson (Co-PIs) 9/1/18 – 6/30/23 $1,825,179 1.8 Calendar

NIH
American Heart Association Tobacco Center for Regulatory Science (A-TRAC) 2.0
Center investigators will study the cardiovascular toxicity of tobacco products and the relationship between tobacco product use and subclinical progression of cardiovascular disease to identify sensitive and robust biomarkers of cardiovascular injury related to tobacco product exposure.
There is no overlap.
Role: Project 1 **Co-Investigator**

NIOSH PO-212-2012-M-5117 (PI: Demokritou) 05/01/12-08/10/19
Physico-Chemical, Pharmacokinetic and Toxicological Studies of Engineered Nanoparticles Emitted from Photocopiers and Printing Equipment. The main objective of this proposed multidisciplinary research project is to characterize the physicochemical, morphological and toxicological properties of emitted particles from photocopiers and office printers, including effects on electrocardiography and left ventricular performance.
There is no overlap.
Role: **Paid Consultant**

Completed
AHA FX-ATRAC-UL1-05 (PI: Carll)
American Heart Association-Tobacco Regulation and Addiction Center Fellowship 7/2017-7/2018
Project: Acute Electrophysiologic and Hemodynamic Effects of ENDS Aerosols and Their Constituents.
The main purpose of this fellowship project was to determine the acute effects of e-cigarette aerosols and their constituents on cardiac electrophysiology and to train in tobacco regulatory science.
Role: PI. $49,760

University of Louisville School of Medicine Basic Grant (PI: Carll) 9/2016-9/2018
Project: Air Pollution and Heart Failure – Role of Autonomic Nervous System in Cardiac Dysfunction and Decreased Regenerative Capacity
This project examines whether β-adrenergic receptor inhibition prevents ambient PM exposure-induced exacerbation of cardiac hypertrophy in a mouse model of transverse aortic constriction.
Role: **Principal Investigator**

EPA RD 83479801 (PI: Koutrakis) 12/01/10 - 11/30/15
EPA Clean Air Research Center (CLARC): Air Pollution Mixtures: Health Effects Across Life Stages
The fundamental objectives of the Center are to investigate the effects of individual pollutants, pollution source types and multi-pollutant mixtures on cognitive and neuropsychological function, cardiovascular and endothelial function, inflammation, birth weigh and growth, CVD hospitalization and mortality across life stages; and, to identify susceptibility and vulnerability factors that can modify these effects.
Role: Participating Investigator

Harvard NIEHS Center Pilot (P30ES000002) (MPI: **Carll**, Godleski) 4/2014-4/2015
Project: Does Inhalation of Traffic-Related Particulates Impair Cardiac Performance?
The goal of this project was to apply chronic LV pressure telemetry and stress tests in rats to determine if repeated exposure to traffic-derived PM impairs cardiac performance via autonomic imbalance.
Role: PI

SOUTH AMERICAN CONSORTIUM. (PI: Koutrakis) 1/2012 - 12/2014
Health and Environmental Impacts of Exhaust from Biofuels
Role: Participating Investigator

NIH Individual T32 (HL007118). (PI: Fredberg) 2/2013-10/2015
Training in Interdisciplinary Pulmonary Sciences.
Role: Research Fellow