Brief Review

Introduction to the American Heart Association’s Hypertension Strategically Focused Research Network


In 2014, the American Heart Association (AHA) announced the funding of a Strategically Focused Research Network (SFRN) focused on hypertension. Hypertension was chosen for a SFRN because interdisciplinary hypertension research has great potential to impact the AHA’s mission and 2020 goals of improving the cardiovascular health of all Americans by 20% while reducing deaths from cardiovascular disease (CVD) and stroke by 20% by 2020. Four centers with highly integrated basic, clinical, and population science projects were selected for the AHA SFRN: Cincinnati Children’s Hospital, Medical College of Wisconsin (MCW), University of Alabama at Birmingham (UAB), and University of Iowa (UI). The Cincinnati center is studying ambulatory blood pressure (BP) and hypertensive target organ damage in adolescents. The MCW center is studying epigenetics of hypertension by conducting studies of genome-wide DNA methylation patterns. The UAB center is studying racial differences in the science being conducted at each center and describe the shared resources available through the science being conducted to build partnerships through the Hypertension SFRN. A goal of the Hypertension SFRN is to facilitate collaborative research. Therefore, we describe opportunities and resources available to researchers interested in collaborating with SFRN investigators. The AHA Hypertension SFRN has the potential to identify new approaches for the prevention and treatment of hypertension and, ultimately, improve the cardiovascular health of Americans.

The SFRN is a mechanism initiated by the AHA to address key strategic issues as determined by the AHA Board of Directors. In 2014, hypertension was selected for a SFRN because improvement in its prevention and treatment has the potential to impact the AHA’s mission and 2020 goals: to improve the cardiovascular health of all Americans by 20% while reducing deaths from CVD and stroke by 20% by the year 2020. The AHA announced that it would be supporting 4 centers focused on research in the field of hypertension for a period of 4 years. This award mechanism embraces a Network Center concept. Each Center was required to propose a designated Center Director, basic, clinical, and population science projects that are synergistic and related to the topic of hypertension, and a research postdoctoral fellowship training component.

After peer-review, 4 SFRN hypertension centers were awarded: Cincinnati Children’s Hospital, MCW, the UAB, and the UI. This brief review provides an introduction to the AHA Hypertension SFRN, which was launched in April of 2015. We review the science proposed by each of the funded centers (Figure). A major focus of the SFRN is building collaborations to advance the science of hypertension. Therefore, we describe opportunities for collaborative research and the shared resources available through the science being conducted to build partnerships through the Hypertension SFRN. Lastly, we provide an overview of the innovative training component for postdoctoral fellows in the Hypertension SFRN.

Hypertension SFRN Science

Cincinnati Children’s Hospital Center

The goals of the Study of High Blood Pressure In Pediatrics: Adult Hypertension Onset in Youth (SHIP AHoy) are to 1) redefine the thresholds for childhood hypertension, based on evidence; 2) better define the clinical phenotype of BP associated target organ damage (TOD); and 3) shift the paradigm from regarding high BP as a risk factor for subsequent CVD to...
Hypertension

an actual disease-causing condition in the young. Investigators will conduct an integrated series of population, clinical, and basic science research studies.

The population science project, Threshold for development of blood pressure-related target organ damage in youth, will attempt to advance our knowledge about the timing of hypertension-induced TOD development, with the hypothesis that hypertensive cardiovascular injury is not limited to long-standing hypertension in adults but emerges at an early phase of primary hypertension. The specific aims of this project are to 1) demonstrate an increase in measures of TOD from low-, to mid-, to high-risk BP levels; 2) determine the prevalence and BP threshold for hypertensive left ventricular hypertrophy in a cohort of adolescents with normal, mid-, and high-risk BP; and 3) determine the prevalence and BP threshold for secondary measures of TOD (ie, microalbuminuria, increased pulse wave velocity).

The clinical science project, Hemodynamic and metabolic predictors of target organ damage in youth with primary hypertension, will provide further evidence on the evolution of hypertensive CVD in youth by testing the hypothesis that a combination of BP (hemodynamic) phenotype and metabolic phenotype (ie, lipids and glycemic control) will be superior to clinic BP in predicting underlying TOD in adolescents with high-risk BP. The specific aims of this project are to 1) determine if BP phenotype, based on a combination of casual (clinic) and ambulatory BP readings, predicts underlying TOD in asymptomatic adolescents and 2) determine if there is a metabolic phenotype that is predictive of TOD.

The basic science project, Influence of regulatory genome on target organ damage in hypertensive youth, will allow a better understanding of the transition points from risk factors for disease to measureable TOD to true clinical disease in patients with systemic hypertension. It will test the hypothesis that the presence of systemic hypertension, on a genetic background and in the presence of common intermediate-phenotypes, including obesity and metabolic abnormalities, leads to TOD in primary hypertension in youth. The specific aims of this project are to 1) demonstrate that epigenetic modifications of candidate genes associated with hypertension and left ventricular hypertrophy are linked to the presence or absence of disease-modifying conditions or intermediate phenotypes and 2) demonstrate that there is altered expression of potentially disease-modifying miRNAs, specifically those miRNAs associated with left ventricular hypertrophy, among youth with hypertension.

Medical College of Wisconsin Center

The MCW center focuses on investigating the epigenomics of hypertension. Hypertension, the leading identifiable cause of death worldwide, in most cases, is the result of interactions between genetic background and environmental factors, including diet and other lifestyle choices. BP is one of the most notable examples in which DNA polymorphisms, identified by Genome Wide Association Studies, account for only a small fraction of the variation of the trait. The missing heritability of BP variation may be because of several reasons, including epigenetics.
Epigenetic studies examine molecular changes, called epigenetic marks or mediators, and associated phenotypes that are mitotically inheritable but do not involve changes in the DNA sequence, whereas epigenomics is defined as the study of epigenetic marks or mechanisms at a genome or near-genome scale. Major types of epigenetic mediators include DNA methylation, histone modification, noncoding RNA, and chromatin structure. A significant role of epigenetic modifications in the development of hypertension is supported by numerous studies. 

For example, studies have shown that parental exposure to a specific environment, fetal exposure to a specific in utero environment, as well as early life environment can affect the development of hypertension in adulthood. Epigenetic changes in several genes, such as 11β-hydroxysteroid dehydrogenase type 2 and angiotensin-converting enzyme, are associated with the development of hypertension; however, studies of epigenetic modifications in hypertension at the genome or near-genome scale are just beginning to emerge. The epigenomics of hypertension remains a large, open field, and with recent technological advances, this field of study seems ripe for paradigm-shifting discoveries in hypertension research.

The main objective of the MCW center program is to carry out a systematic investigation of the relevance of genome-wide DNA methylation patterns to hypertension. The overall hypothesis is that dietary salt intake and other lifestyle factors, maternal dietary exposures, and gene–environment interactions cause genome-wide changes in DNA methylation, which contribute to the development of hypertension and can be used as predictive or diagnostic markers of hypertension and related diseases. The basic science project will test the general hypothesis that the maternal dietary environment alters the epigenomic program in immune cells in salt-sensitive rats and their de novo methylation response to an increased salt intake later in adult life, which in turn affects immune cell infiltration and activation in the kidney and modifies salt-sensitive hypertension and renal disease. The clinical project will examine the effects of lifestyle factors, including dietary salt intake on epigenomic changes in human subjects, and whether such effects can reveal potential mechanisms of hypertension. The population project will investigate whether DNA methylation patterns are associated with levels of BP and predict the development of hypertension and related cardiovascular events in an black cohort. All 3 projects will analyze DNA methylation at near–genome-wide scale using the technology of reduced representation bisulfite sequencing as described previously.

**University of Alabama at Birmingham Center**

Ambulatory BP monitoring allows for the determination of several BP measures that cannot be ascertained in the clinic or through home monitoring. Ambulatory BP monitoring can assess diurnal BP patterns including nocturnal hypertension and nondipping BP (ie, when BP does not decline by the usual 10–20% at night). Studies from Europe and Asia have reported strong associations between nocturnal hypertension and a nondipping BP pattern with an increased risk for CVD and all-cause mortality. Preliminary data suggest that blacks may have higher nocturnal BP and may be more likely to be nondippers compared with whites. The UAB SFRN investigators are conducting an integrated series of research studies on diurnal BP patterns.

The population science project, Racial differences and US population estimates of nocturnal hypertension and nondipping, involves the examination of racial differences in the prevalence of nocturnal hypertension and nondipping BP. This project will determine if the association of risk factors, including psychosocial factors and sleep disordered breathing, with these phenotypes differ by race as well as determining the association of nocturnal hypertension and nondipping BP on TOD. For this study, ambulatory BP monitoring will be conducted in 700 black and white participants at the Year 30 Coronary Artery Risk Development in Young Adults (CARDIA) study visit. Additionally, questionnaires on sleep, anxiety, and stress will be completed by the participants. The US population burden of nocturnal hypertension and nondipping BP will also be estimated using simulation methods.

The clinical science project, Mechanisms of nocturnal hypertension and non-dipping blood pressure, will identify the effect of dietary sodium restriction on nocturnal BP and nondipping and assess whether the effects are because of improvements in obstructive sleep apnea. Whether aldosterone levels potentiate the response of nocturnal BP, nondipping BP, and severity of sleep apnea to dietary sodium will also be determined. This project involves a randomized crossover feeding trial enrolling 60 participants (30 blacks and 30 whites) with nocturnal hypertension identified from the population project. Participants will be fed 10 days of a low- or high-sodium diet followed by a washout period and then 10 days of the opposite diet. During the last 2 days of each feeding period, participants will collect buccal cells every 4 hours for use in the basic science project.

The basic science project, Novel mechanisms of salt-sensitivity and diurnal blood pressure rhythm, will address 3 aims: (1) elucidate whether high-salt diet induces renal microvascular dysfunction through the activity of histone deacetylase 1 leading to reduced nitric oxide or increased reactive oxygen species; (2) determine the impact of dietary salt intake on BP rhythms in a rat model of nocturnal hypertension, the Dahl salt–sensitive rat, and whether the nondipping is related to renal vascular reactive oxygen species production; and (3) analyze changes in the expression of clock genes (CLOCK, Bmal1, per1, per2, cry1, and cry2) in the buccal cells during consumption of low- versus high-sodium diets from human participants in the clinical science project.

**University of Iowa Center**

Preeclampsia, a rapidly progressive condition characterized by high BP and proteinuria, affects 8% of all pregnancies. Often not diagnosed until late pregnancy, it is the cause of 76 000 maternal and 500 000 infant deaths per year. Absence of a robust, early biomarker of preeclampsia that directs mechanistic research and treatment for the disorder represents a fundamental gap in knowledge and clinical practice.

The UI center proposal was based on 3 seminal observations. First, high circulating copeptin, a stable, easily detectable biomarker for arginine vasopressin (AVP), robustly predicts development of preeclampsia early in pregnancy. Second, women who have elevated copeptin in the first
trimester of pregnancy demonstrate reduced endothelial function and increased arterial stiffness in the second trimester compared with women with low copeptin. Third, UI investigators have developed a new mouse model in which chronic low-dose AVP infusion during pregnancy phenocopies preeclampsia. Collectively, these findings lead to the hypotheses that copeptin represents a novel and powerful predictive diagnostic test for preeclampsia, and that AVP may play a causal role in the early pathogenesis of the disorder. The goal of the UI SFRN is to translate these findings and develop preventative, therapeutic, and curative modalities against preeclampsia.

The Population Project, Predicting preeclampsia via copeptin: underrepresented minorities & synergy with other biomarkers, will assess the predictive power of copeptin in diverse populations and compare it with current biomarkers of preeclampsia. The central hypotheses are 1) copeptin will be predictive of preeclampsia in the first trimester of pregnancy regardless of comorbidities or demographics and 2) copeptin will serve as an earlier and better predictor of preeclampsia than other biomarkers.

The Clinical Project, Early vascular dysfunction and elevated copeptin in human preeclampsia, will assess temporal changes in vascular endothelial function and arterial stiffness throughout pregnancy in women stratified to either high or low copeptin measured in the first trimester of pregnancy. This project addresses 2 main hypotheses: compared with women with low copeptin 1) early- and mid-gestation women with elevated copeptin will demonstrate reduced vascular endothelial function and elevated arterial stiffness before traditional signs of preeclampsia and 2) women with high copeptin and reduced vascular function will have a higher incidence of preeclampsia.

The Basic Project, Molecular mechanisms of vasopressin-induced preeclampsia, uses a novel mouse model of preeclampsia to examine the mechanisms of vascular dysfunction in preeclamptic mothers and adult offspring. This model will be used to 1) examine the importance of vascular dysfunction in the mother and adult offspring from preeclamptic
The AHA SFRN program is characterized by its emphasis on collaborative and team science, which will serve as a paradigm for interaction within each center, across the 4 centers and with the hypertension research community more broadly. An oversight Advisory Committee, assembled by the AHA, is available to guide interactions between the centers and facilitate collaborations between SFRN centers and other hypertension researchers.

Investigators at each center are enthusiastic to collaborate with researchers within and beyond the Hypertension SFRN to fully use the vast amount of resources being assembled and data being collected in the research studies (Table 1). The concept of Interest Groups has been proposed to encourage collaboration and the design of new collaborative studies. Although these Interest Groups are still in a nascent phase, they may involve conference calls, a SharePoint site and in-person meetings at national conferences (eg, AHA Council on Hypertension meeting). As Interest Groups are initiated, involvement by investigators from outside of the SFRN will be encouraged to participate. Resources beyond those directly being used in the scientific projects are available at each of the 4 centers to conduct collaborative research and advance the science of hypertension (Table 2).

The Hypertension SFRN has been invited to provide an overview of the network activities, science, and opportunities for collaboration at the 2016 American Society of Hypertension Scientific Meeting (May 14–17, 2016). Investigators interested in learning more about shared resources and opportunities for collaboration with the SFRN are encouraged to attend this meeting. Also, in September 2015, investigators from each center presented research at the 26th annual UAB Vascular Biology and Hypertension Symposium in Birmingham, AL. This gathering resulted in scientific exchange and the opportunity to begin the development of collaborations. The 27th annual symposium is being planned for Fall 2016 and is open to all hypertension researchers and trainees. Through collaborations, the Hypertension SFRN will provide networking opportunities for trainees, share knowledge and methods, and provide a stimulating atmosphere to develop and conduct novel research.

### Hypertension SFRN Training Program

The goal of the Hypertension SFRN Training Program is to train the next generation of hypertension researchers and
Table 3. Contact Information for the Center Directors, Training Directors, and Scientific Project Principal Investigators

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SFRN indicates Strategically Focused Research Network.

provide postdoctoral fellows with knowledge and hands-on experience to lead focused investigations in basic, clinical, and population science as well as cross-disciplinary research studies. The 4 centers in the Hypertension SFRN will collectively train 12 fellows during the 4-year project period, building the capacity for future research to advance the science of hypertension. In addition to the fellow’s primary mentor, a team of senior investigators with training expertise will help the fellow to maximize the training opportunity and overcome unanticipated barriers. There are 2 aspects to these centers’ training programs that distinguish them from more customary programs: interdisciplinary training and opportunities for cross-center collaborations.

The integrated nature of the basic, clinical, and population science projects within each center will serve as the training ground for the centers’ fellows, and fellows will have some experience in each of these projects, regardless of their primary research discipline. The more usual approach to training would encourage the fellow to develop expertise in only one area of science, whether basic, clinical, or population. We are taking a different approach in recognition of the growing need for scientists who can thrive in large teams across multiple disciplines. Each fellow will have their own project and focus area within one of the center’s 3 research projects but will also have a meaningful training experience within the other 2 projects. These latter experiences may include spending physical time becoming integrated into the project teams by taking on a specific role (eg, performing a research test such as ambulatory BP monitoring or flow-mediated dilation on the study participants for the clinical or population project or learning to perform a specific assay for the basic science project). These experiences will be substantial enough to assure that the fellow has become conversant in the language and traditions of scientific domains outside of their own area of focus, assuring readiness to participate and excel in team science in the future.

A second unique feature of the Hypertension SFRN training programs is the opportunity for cross-center collaborations and training experiences. The fellows will learn of each center’s projects and expertise available at the centers through monthly conference calls and annual in-person Hypertension SFRN meetings. Fellows will present their own work and the work they are doing within their own centers population, clinical, and basic science projects. Through these interactions, fellows will be given opportunities to broaden their own professional networks by getting to know each other as well as scientists at the other centers. They will be encouraged to develop cross-center projects, possibly even spending time at the other centers to learn specific skills. In this way, the hypertension SFRN center fellows will develop broad skills not only through interactions within their own centers but across centers, building a solid foundation for successful careers in hypertension research. Further information on training opportunities at the 4 Hypertension SFRN centers can be obtained by contacting the center or training directors (Table 3).

**Perspectives**

The AHA initiated the SFRN program with the explicit goal of addressing key strategic issues and improving the cardiovascular health of all Americans. Given its high prevalence and the excess coronary heart disease and stroke risk it confers, hypertension was a natural choice for a SFRN. The 4 funded centers incorporate research studies that cover hypertension throughout the life course from fetal exposures, through childhood, in pregnancy, and adulthood. Investigators within the SFRN are beginning to develop collaborations and welcome opportunities to develop new partnerships with investigators outside of the SFRN to leverage the infrastructure being developed and data being generated. The Hypertension SFRN has a dedicated program to train the next generation of hypertension researchers. In conclusion, the AHA Hypertension SFRN provides the
opportunity to greatly increase our knowledge of hypertension and identify new approaches for its prevention, treatment, and, ultimately, improve the cardiovascular health of Americans.

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References


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