

## Center of Biomedical Research Excellence in Cardiovascular Health

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Cardiovascular diseases (CVD) such as heart disease, heart failure, and stroke remain the number one cause of death in the U.S. for both men and women.<sup>1</sup> CVD is largely preventable, and is related to modifiable risk factors prevalent in the state of Delaware and surrounding region such as poor diet, obesity, hypertension, physical inactivity, and tobacco use. The American Heart Association defines ideal cardiovascular health as the absence of clinically manifest CVD as described above, along with optimal levels of blood pressure, cholesterol, blood glucose (sugar), body weight, physical activity, a healthy diet, and not smoking.<sup>2</sup> These 7 metrics have been termed the Simple 7. Using these metrics it is clear that cardiovascular health in the United States is generally poor, with only <1 to 9% of adults meeting recommendations for 6-7 metrics.<sup>1</sup> When examining individual metrics of cardiovascular health, the prevalence of ideal cardiovascular health ranges from 0.8% for having a healthy diet to 77.1% for not smoking. Improving cardiovascular health is important as those with the greatest ideal cardiovascular health metrics have a lower risk of stroke, coronary disease, cardiovascular death, and death from all causes.<sup>1</sup> In addition to these measures of cardiovascular health, other chronic conditions increase the risk for cardiovascular events and death such as metabolic syndrome and chronic kidney disease, which also have a high prevalence.

With support from the National Institute of General Medical Sciences (NIGMS) at the National Institutes of Health (NIH), the Center of Biomedical Research Excellence (COBRE) in Cardiovascular Health was recently established at the University of Delaware.

This Center aims to catalyze cardiovascular health research by fostering the independent research careers of a team of new investigators – each focusing on aspects of cardiovascular health – and designed to transition these new investigators to independent funding from NIH. The COBRE in Cardiovascular Health is led by Dave Edwards, PhD, Professor in the Department of Kinesiology and Applied Physiology. There are 5 COBRE projects led by NIH defined new investigators who have faculty appointments in various departments at the University of Delaware.

These projects are investigating the mechanisms and consequences of declining cardiovascular health as well as interventions to improve cardiovascular health (each project is described below). The COBRE also aims to strengthen the research infrastructure and capacity to perform cardiovascular health research by establishing core facilities that will enhance cardiovascular research capabilities of the new investigators, as well other investigators in the center, university, and region. Support for new equipment in the Delaware Biotechnology Institute Bio-Imaging Core has also been provided, and pilot funding is available for small-scale cardiovascular related projects and new investigators will be recruited to the University.

The COBRE Cardiovascular Research Core (CVRC) Laboratory at the University of Delaware has been established for assessing cardiovascular function and health in research participants. While multiple measures of cardiovascular function are assessed, a main underlying theme of the core is to assess vascular function. Two common aspects of vascular function that are assessed for investigators are endothelial function and arterial stiffness. The endothelium lines our blood vessels and releases important vasoactive substances that are critical for maintaining vascular homeostasis. Importantly, measures of endothelial function are used as an indicator of

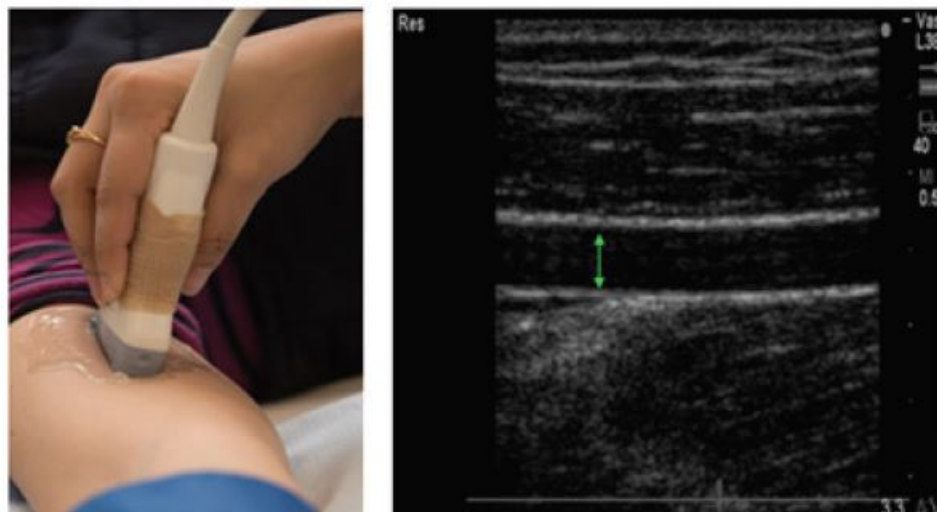
cardiovascular health<sup>3,4</sup> as impairments in endothelial function precede the development of atherosclerosis and CVD.<sup>5-7</sup> Endothelial function is assessed in the CVRC by measuring flow-mediated dilation in the brachial artery (Figure 1).

Figure 1. Measuring flow-mediated dilation to assess endothelial function.



Using a high-resolution ultrasound, the change in diameter of the brachial artery is measured in response to increased blood flow and shear induced by a brief period of forearm ischemia. The ability of the vessel to dilate is calculated as a percent change, and is indicative of cardiovascular health (Figure 2).

Figure 2. An ultrasound is used to image the brachial artery (left) and the change in diameter (right) in response to an increase in blood flow after a brief ischemic period is used as a measure of endothelial function.



For example, impairments in flow-mediated dilation are evident with aging,<sup>8</sup> and in disease states such as coronary artery disease,<sup>5</sup> hypertension or chronic kidney disease.<sup>9</sup> In addition to endothelial function, the CVCR Laboratory also commonly measures arterial stiffness. Arterial stiffness is assessed by carotid to femoral pulse wave velocity (Figure 3), which is considered the gold standard assessment of arterial stiffness.<sup>10</sup>

Figure 3. Measure of Pulse Wave Velocity



This is done by placing a pressure probe over the carotid and femoral arteries to record pressure waves while simultaneously recording an ECG. By determining the time delay between the arrival of carotid and femoral pressure waves and the distance between recording sites, pulse wave velocity can be calculated. This is an important measure because arterial stiffness is a predictor of mortality.<sup>11-14</sup>

Cardiovascular disease is not only an important issue on a national level, but also important for Delawareans. The rates of CVD in Delaware are consistent with, or higher than those seen on a national level. Delaware has the 23rd highest death rate from heart disease in the country.<sup>15</sup> The COBRE in CV Health is therefore uniquely positioned to favorably impact CV health for Delawareans, and also for the country as a whole. For more information on the COBRE in CV Health, please visit <http://sites.udel.edu/cvhealth/>.

## Individual COBRE Projects:

### 1. Dietary Potassium and Vascular Function.

Limiting dietary sodium intake is part of a healthy diet, as excess dietary sodium intake is known to affect cardiovascular health. Shannon Lennon, RD, PhD, Associate Professor in the Department of Kinesiology and Applied Physiology is leading a project titled “Interactive Effects of Dietary Potassium and Sodium on Vascular Function.”

Dietary sodium restriction is a common lifestyle modification for CVD and a key recommendation from the 2015-2020 Dietary Guidelines for Americans (DGA).<sup>16</sup> While the DGA goal is to reduce sodium consumption to less than 100 mmol/day (2300 mg), the data continue to illustrate that the average U.S. intake is 1.5 times higher, and in the case of the elderly, African Americans, or those with chronic disease, it is 2.3 times higher than recommended.<sup>16</sup> In contrast, U.S. adults are under-consuming potassium, a key mineral in our diet. Current estimates show that the median consumption of potassium is 55% of the recommended intake of 120 mmol (4700 mg).<sup>17</sup>

Recent studies in humans indicate that a lower urinary sodium to potassium excretion ratio, reflective of greater potassium intake, is associated with significantly fewer cardiovascular events.<sup>18</sup> Excess sodium intake has been shown to increase BP and lead to hypertension<sup>19,20</sup> while consumption of a potassium rich diet has been shown to have BP lowering properties.<sup>21,22</sup> While the role of these two nutrients on BP is widely accepted, their impact on the vasculature has received less attention. This is an important area of inquiry as most young and middle-aged adults (~74%) are salt-resistant<sup>23</sup> (i.e. BP does not increase on a high salt diet) and yet many salt-resistant individuals go on to develop hypertension (1 in 3 adults)<sup>1,23</sup> which may be attributable to a detrimental impact of sodium on the vasculature and in particular endothelial function.

Recently, studies from our laboratory in salt-resistant humans have demonstrated that high salt intake impairs endothelial function providing evidence that this effect is independent of any BP effect.<sup>24,25</sup> In contrast, potassium has been shown to be protective against arterial damage in rodents.<sup>26</sup> Further, the beneficial effects of a high potassium intake appear to be more substantial in the presence of high sodium<sup>27,28</sup> suggesting that dietary potassium may counteract the damaging effect of sodium on the vasculature. The chronic role of potassium in protecting the endothelium from a high sodium diet has yet to be investigated in humans.

The objective of Dr. Lennon's study is to determine the interaction between dietary potassium and sodium on the vasculature independent of BP by studying salt-resistant adults. Participants will be enrolled in a 21-day controlled feeding study containing varying levels of sodium and potassium. Vascular function will be studied at two levels of the vasculature (conduit artery and microvascular) and oxidative stress and endothelial cell stiffness will be examined to gain insight into the mechanisms.

## **2. Cognitive Function and Cardiovascular Disease.**

Among the consequences associated with poor cardiovascular health and CVD are deficits in cognitive function. Cognitive function is an important quality of life indicator for older adults, and deficits in cognitive function can inhibit everyday activities, planning, decision-making, and independent living.<sup>29,30</sup> Regina Wright, PhD, Associate Professor in the School of Nursing, is leading a project titled "Subclinical cardiovascular disease, brain, and cognition."

Subclinical cardiovascular diseases, (i.e., prior to overt signs and symptoms of disease) including atherosclerosis, arterial stiffness, and reduced endothelial function are pre-cursors to clinical manifestations of CVD. Yet, they can confer as much, if not more, risk for cardiac events than traditional CVD risk factors.<sup>31</sup> Prior to the emergence of life altering outcomes such as stroke and dementia, subclinical CVD is associated with subtle cognitive decrements and decline that reduce quality of life and may precede more severe clinical events.<sup>32-35</sup> A role for vascular changes in cognitive function is beginning to be appreciated; however, little is known about the

unique contribution of reduced endothelial function to cognitive outcomes. As described above, the endothelium is critical for maintaining vascular health. Reduced endothelial function is a key early step in the development of hypertension,<sup>36</sup> atherosclerosis,<sup>37</sup> and arterial stiffening,<sup>38</sup> thus reduced endothelial function may represent an early marker of subclinical CVD related cognitive decrements and a critical target for intervention. Further, despite the known tendency for subclinical CVDs (including reduced endothelial function) to occur together,<sup>39</sup> there is also a limited understanding of the cumulative impact of subclinical CVDs on cognitive function, or the combination of subclinical CVDs that is most strongly associated with cognitive decrements.

Subclinical alterations in the brain may be a key link underlying relations of reduced endothelial function and other subclinical CVDs to cognitive function. Magnetic resonance imaging (MRI)-assessed brain abnormalities have been reliably associated with cognitive decrements as well as a spectrum of traditional CVD risk factors<sup>40,41</sup>; however, there has been little investigation of the mediating role of specific changes in brain pathology in the linkages between subclinical CVD and cognitive function.

The objective of Dr. Wright's project is to determine whether reduced endothelial function is associated with poorer cognitive function and greater presence of MRI-assessed brain abnormalities, and whether MRI- assessed brain abnormalities mediate these associations in older adults. Given the high health and financial burdens conferred by stroke and dementia, and given that vascular risk factors are potentially modifiable, identifying the earliest signs of vascular deterioration and their impact on cognition is important for the lives of older adults.

### **3. Hypertension in Postmenopausal Women.**

Hypertension is a major risk factor for cardiovascular disease (CVD).<sup>1</sup> Approximately 1 in 3 adults in the US have hypertension. Consistent with the national average, ~35% of adults in Delaware are hypertensive. Megan M. Wenner, PhD, Assistant Professor in the Department of Kinesiology and Applied Physiology is leading a project titled "Mechanisms contributing to hypertension in postmenopausal women."

Prior to menopause, men have higher blood pressure and greater prevalence of hypertension and CVD-related mortality compared to age-matched women. However, after menopause, this sex difference is reversed, and postmenopausal women have a higher prevalence of hypertension and mortality from CVD.<sup>42,43</sup> Despite these sex differences in hypertension, women are treated therapeutically the same as men. Furthermore, postmenopausal women are more likely to have uncontrolled or resistant hyper tension despite medication.<sup>44</sup> The mechanisms contributing to hypertension in postmenopausal women are complex and not well understood.

Evidence in experimental female animals suggest that a vasoconstricting substance called endothelin-1 plays a major role in contributing to hypertension after menopause.<sup>45,46</sup> However, the degree to which endothelin-1 contributes to hypertension in humans, particularly postmenopausal women, is not known. Furthermore, the constrictive actions of this pathway also interact with other pathways commonly involved with hypertension, such as angiotensin II.

The objective of Dr. Wenner's project is to investigate the role of endothelin-1 in mediating vasoconstrictor tone in hypertensive postmenopausal women alone and in combination with a commonly prescribed angiotensin II receptor antagonist. Her laboratory will assess vascular function using a variety of techniques to determine if blocking both constricting pathways improves vascular function more than single therapy. Reaching optimal blood pressure control is

of vital importance in achieving optimal cardiovascular health, particularly in postmenopausal women.

#### **4. Smoking Cessation and Sleep.**

Despite declines in adult smoking rates during the past 50 years, cigarette smoking remains the number one cause of cardiovascular diseases both nationally and in Delaware.<sup>47,48</sup> Nationally, current smoking prevalence is 15.1%,<sup>49</sup> while in Delaware rates are 19.9% and climb to as high as 45% among low-socioeconomic groups, making Delaware 28th in the country for tobacco use.<sup>50-52</sup> Limiting progress to meeting the Healthy People 2020 guidelines of a 12% smoking prevalence is the fact that current FDA treatments for nicotine dependence (e.g., nicotine replacement therapy, bupropion, varenicline) are effective for only 1 in 3 smokers.<sup>53</sup> The identification of adjunctive therapies to optimize the efficacy of current treatments for nicotine dependence are needed.<sup>54</sup>

Freda Patterson, PhD, Assistant Professor in the Department of Behavioral Health and Nutrition is leading a project titled “Sleep as a Target for Optimizing Responses to Nicotine Dependence Treatment.” As a common biologic function, sleep plays a central role in metabolic regulation, emotion regulation, performance, memory consolidation, brain recuperation processes, and learning.<sup>55,56</sup> Inadequate sleep duration is a determinant of poor cardiovascular health outcomes including hypertension,<sup>57</sup> myocardial infarction and stroke.<sup>58-60</sup> Importantly, short sleep duration (<7 hours/night), insomnia symptoms (difficulty falling and/or staying asleep, more time in lighter sleep stages), and evening sleep timing (later to bed and to rise), are poor sleep patterns that are more prevalent in smokers than non-smokers,<sup>61-66</sup> and have been associated with increased craving to smoke, higher smoking rate, and relapse to former smoking practices in smokers trying to quit.<sup>67-76</sup> Moreover, although insomnia is a clinically-recognized nicotine withdrawal symptom,<sup>77</sup> to date, there are no clinical guidelines for ameliorating insomnia symptoms in treatment seeking smokers.<sup>78</sup>

The objective of Dr. Patterson’s project is to determine if addressing poor sleep characteristics in treatment- seeking smokers could promote cessation and produce additive improvements in cardiovascular health. Her research group is conducting a randomized-controlled- trial to test the efficacy of a sleep advancement counseling intervention on smoking cessation and measures of cardiovascular health. All participants receive a standard 12-week course of pharmacotherapy (Chantix, provided by Pfizer) for smoking cessation.

The novel sleep intervention utilizes cognitive- behavioral techniques to address sleep duration and insomnia symptoms. Findings from this study have the potential to transform clinical guidelines for smoking cessation and the cardiovascular health of smokers.

#### **5. Vascular Function in Children with Muscular Dystrophy.**

Muscular dystrophy includes a heterogeneous group of neuromuscular disorders that are associated with progressive skeletal, respiratory, and cardiac muscle weakening. Duchenne muscular dystrophy is the most common form of muscular dystrophy, occurring in approximately 1 in every 5,000 boys born in the United States.<sup>79</sup> Historically, respiratory failure was the major cause of morbidity and mortality in patients with Duchenne muscular dystrophy but with changing treatments, cardiac disease has recently been recognized as the leading cause of death.

Unfortunately, symptoms of cardiac disease often go unrecognized in patients with Duchenne muscular dystrophy as limited physical activity and respiratory complications often obscure the diagnosis.<sup>80</sup> Thus, the contributing mechanisms, clinical markers, and methods of early detection for Duchenne muscular dystrophy cardiomyopathy are largely unexplored. Melissa Witman, PhD, Assistant Professor in the Department of Kinesiology and Applied Physiology is leading a project titled “Vascular Consequences of Duchenne Muscular Dystrophy.”

Vascular dysfunction is a systemic pathology that impairs the health and vasomotor control of both conduit and resistance vessels and is a non-traditional risk factor that often precedes the development of various cardiovascular diseases.<sup>7,8,81</sup>

Dysfunction of the vasculature is also an independent predictor of cardiac morbidity and mortality.<sup>82</sup> Specifically, much of the vascular dysfunction observed in the different cardiovascular diseases is often due to a decrease in nitric oxide synthesis and bioavailability.<sup>83</sup> Vascular dysfunction has been observed in animal models of Duchenne muscular dystrophy through a dysfunction of nitric oxide production and release by the endothelium,<sup>84,85</sup> but this has yet to be investigated in patients.

The objective of Dr. Witman’s project is to investigate the peripheral vascular consequences of Duchenne muscular dystrophy, associate them with clinical cardiac measures, and determine if current pharmaceutical therapies are having an effect on the health of the vasculature. Dr. Witman’s laboratory is working with the A.I. duPont Nemours Hospital for Children in Wilmington, DE. Having a greater understanding of the disease mechanisms and effects of the pharmaceutical therapies will inform future clinical trials and interventions. The ultimate goal of this research is to improve the lives of young patients struggling with Duchenne muscular dystrophy.

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