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Respiratory Sinus Arrhythmia and Diseases of Aging: Obesity, Diabetes Mellitus, and Hypertension.

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Abstract

Associations between respiratory sinus arrhythmia (RSA) and several chronic diseases, including obesity, diabetes mellitus, and hypertension, have been documented in recent years. Although most evidence suggests reduced RSA is the result of chronic disease rather than the cause, some studies have documented reduced RSA among at-risk individuals prior to disease onset. These results raise the possibility that decreased vagal tone may play a role in the pathogenesis of certain chronic diseases. Presented here is a brief overview of studies which examine the relationship between vagal tone, as measured by RSA and baroreflex gain, and diseases of aging, including obesity, diabetes mellitus, and hypertension. Mechanisms by which vagal tone may be related to disease processes are discussed. In addition, we present results from a population-based study of RSA and hypertension in older adults. Consistent with previous studies, we found an inverse relationship between RSA and age, cigarette use, and diabetes. In logistic regression models which control for age, cigarette use, and diabetes, we found RSA was a significant negative predictor of hypertension. We conclude that the relationship between RSA and hypertension is somewhat independent of the age-related decline in parasympathetic activity.

Keywords

Cardiac vagal control; Cardiac vagal tone; Respiratory sinus arrhythmia; Aging; Obesity; Diabetes; Hypertension

1. Introduction

While the anatomic distribution of the vagus nerve has been known for decades (Gray, 1918), each year brings a better understanding of its relationship to organ function and health. For example, the dominant model of the autonomic nervous system has been one of reciprocity between the sympathetic and parasympathetic branches. Increased activity of one branch is expected to coincide with reduced activity of the other. In recent years, analysis of heart rate and its autonomic control has established that sympathetic stimulation of the heart is not

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necessarily accompanied by reduced parasympathetic tone (Berntson et al., 1991). Indeed, while sympathetic activation of the sinoatrial node and ventricular myocardium leads to increased chronotropy and inotropy, these effects may be accompanied by either an increase or decrease in parasympathetic modulation of heart rate via the vagus nerve (Berntson et al., 1993).

In recent years, associations have been found between cardiac vagal tone (as reflected by respiratory sinus arrhythmia (RSA) and other indices) and several physiologic processes, including congestive heart failure (Saul et al., 1988), diabetes (Lindmark et al., 2003), hypertension (Maver et al., 2004), and weight gain (Arrone et al., 1995). In addition, reliable individual differences in cardiac vagal tone have been established (Cacioppo et al., 1994) as have aging-associated reductions in vagal tone (Craft and Schwartz, 1995). It is unclear however, whether impaired vagal tone is a cause or consequence of chronic disease or whether a portion of the association between vagal activity and chronic disease simply reflects age-related declines in parasympathetic tone.

Over two decades of research have revealed much about the origins and nature of cardiac vagal tone. We now know that cardiac vagal tone is context-dependent and reflects input from vagal afferent nerve fibers as well as brain structures, including the cardiorespiratory center, amygdala, and hypothalamus (Berntson et al., 1993). Psychosocial characteristics are also associated with vagal tone. These characteristics include acute stress (Berntson et al., 1994), stress susceptibility (Porges, 1995), depression (O'Connor et al., 2005), hostility (Demaree and Everhart, 2004), defensiveness (Feldman et al., 2002), anxiety (Fuller, 1992; Watkins et al., 1998), and neuroticism (Haug et al., 1994). Many of these factors have also been implicated in the onset and development of chronic diseases. Hostility and depression, for example, have been shown to increase risk for morbidity and mortality, especially from cardiovascular diseases (Everson-Rose and Lewis, 2005) but the physiologic link between psychosocial factors and cardiovascular disease remains incompletely understood. Because efferent vagal signaling is influenced by higher brain centers and can have profound systemic effects, such signaling may play a mediating or moderating role in the relationship between psychosocial factors and a multitude of disease processes. In this paper, we briefly review the literature regarding the relationship between vagal tone, as reflected by respiratory sinus arrhythmia (RSA) and baroreflex gain, and several physiologic processes, including aging, diabetes, obesity, hypertension, and cardiovascular disease. We also report preliminary findings from an ongoing study examining the relationships between psychosocial characteristics and RSA and between RSA and traditional risk factors for cardiovascular disease. This study was designed to elucidate interactions among psychosocial characteristics, RSA, and cardiovascular outcomes in a population-based sample of older adults.

2. Neuroanatomy

The vagus nerve is a complex structure, having pre-ganglionic and post-ganglionic, as well as efferent and afferent components. Vagal efferents carry information from the central nervous system (CNS) to target tissues throughout the body. The two efferent components are 1) the branchial motor, supplying the voluntary muscles of the pharynx, most of the larynx, and one extrinsic muscle of the tongue and 2) the visceral motor, which provides parasympathetic innervation to the glands and smooth muscles of the pharynx, larynx, and thoracic and abdominal organs, including the heart, lungs, liver, pancreas, and gut. Vagal afferent nerves transmit information from target tissues to the CNS. The three afferent components are 1) the visceral sensory, which provides sensory information from the larynx, esophagus, trachea, and visceral organs, as well as chemoreceptors of the aortic bodies and stretch receptors of the aortic arch, 2) the general sensory, which transmits sensory information from the pharynx, portions of the tympanic membrane, and skin of the posterior ear and external auditory meatus,

and 3) the special sensory, which conducts taste sensation from the epiglottic region (Martin, 1996; Porges, 2003).

The cell bodies of the branchial motor neurons are located in the nucleus ambiguus while the cell bodies of the visceral motor neurons are located in the dorsal motor nucleus of the vagus. Both the nucleus ambiguus and the dorsal motor nucleus are medullary structures. Axons from these preganglionic neurons synapse with postganglionic neurons in peripheral autonomic or terminal ganglia, which are located on or near the target organs (Martin, 1996). The cell bodies of afferent neurons are located just outside the CNS, in the superior and inferior vagal ganglia. These cells transmit information from receptors in target tissues to the nucleus of the solitary tract, which is also located in the medulla (Cheng et al., 2004). Once in the nucleus of the solitary tract, vagal afferent information (i.e. blood pressure, gut distention) is relayed to other structures, including the hypothalamus and nucleus ambiguus. Lateral hypothalamic neurons project to the vagal nuclei in the medulla and therefore influence vagal efferent activity. Hypothalamic projections also influence sympathetic efferent activity via synapses in the lateral medulla. In the baroreceptor reflex, afferent information from the nucleus of the solitary tract is transmitted to the nucleus ambiguus where vagal efferent neurons are excited (Pilowsky and Goodchild, 2002). The same afferent information also leads to inhibition of descending sympathetic neurons. With neural connections to the hypothalamus and sympathetic nervous system, as well as target tissues throughout the body, the vagus nerve plays a central role in the regulation of organ function and diverse physiological processes.

3. RSA and Age

In the absence of disease, sympathetic control of the heart declines with age (Stratton et al., 1992). Numerous studies have also demonstrated an age-related decline in indices of cardiac parasympathetic control (Craft and Schwartz, 1995; Fluckinger et al., 1999; Fukusaki C et al., 2000). The age-related decrease in chronotropic effects associated with vagal withdrawal (Brodde et al., 1998; Craft and Schwartz, 1995) suggests resting heart rate becomes less dependent upon parasympathetic control over time. In a study of the cardiovascular effects of parasympathetic blockade, smaller increases in heart rate, cardiac index, systolic blood pressure, and early diastolic filling rate were found among older compared to younger participants (Stratton et al., 2003). No age-related difference in contractile response was found and the difference in cardiac index was attributed to smaller increases in heart rate among older participants.

Aging is associated with an increase in the incidence and prevalence of several metabolic and cardiovascular diseases. Given the age-related decreases in vagal activity and age-related increases in metabolic and cardiovascular dysfunctions, one should be vigilant to the possibility that bivariate associations between vagal activity and disease reflect the effects of age on both variables. We return to this issue in the final section of this report.

4. RSA and Glucose Metabolism

Many studies have examined the link between vagal activity, as reflected by various indices (including RSA), and glucose control. Most have found that impaired glucose regulation is associated with lower RSA but it is not clear whether reduced RSA is a cause or result of impaired glucose metabolism or whether both reflect the influence of a third variable (e.g. age). In addition, while vagal input to the pancreas and liver is an important component of glucose metabolism, the relationship between vagal stimulation of these abdominal organs and cardiac vagal tone is not well understood.

Under normal conditions, plasma glucose is tightly regulated by complex feedback systems involving the pancreas, liver, and peripheral tissues (Cryer, 2003). When glucose levels rise,

pancreatic β-cells release insulin into the hepatic portal circulation where it inhibits glycogenolysis and gluconeogenesis and promotes formation of fuel storage products (glycogen and triglycerides). Peripherally, insulin suppresses renal glucose production and promotes glucose utilization and storage by muscle and fat. When plasma glucose is low, insulin production decreases and pancreatic α-cells secrete glucagon into the hepatic portal circulation. In contrast to insulin, glucagon stimulates glucose production via glycogenolysis and gluconeogenesis in the liver.

The sympathetic nervous system is activated in response to falling plasma glucose. This leads to release of epinephrine from the adrenal medulla, which stimulates hepatic and renal glucose production and the mobilization of gluconeogenic precursors, including lactate, alanine, and glycerol. Epinephrine also increases plasma glucose by reducing skeletal muscle glucose utilization (Cryer, 2003). Activation of the sympathetic nervous system is thought to occur via glucose-sensing neurons in the ventromedial nucleus of the hypothalamus (Borg et al., 1995) as well as through chemoreceptors in peripheral locations, including the portal vein (Heavener et al., 2000).

With efferent projections to the pancreas and liver, the vagus nerve is also important to glucose regulation. Stimulation of vagal efferent nerve fibers results in insulin release by pancreatic β-cells (Roy et al., 1984) while stimulation of vagal efferents to the liver reduces hepatic glucose release and increases glycogen formation (Boyle et al., 1988). Thus, while hypoglycemia results in sympathetic activation and increased glucose production and mobilization, hyperglycemia leads to parasympathetic activation, decreased glucose production, and increased glucose storage. Impaired parasympathetic regulation of glucose is therefore a risk factor for chronic hyperglycemia and hyperinsulinemia. Also known as insulin resistance, chronic hyperinsulinemia is characterized by impaired suppression of hepatic glucose output, decreased glucose metabolism by skeletal muscle and fat cells, and persistently elevated circulating insulin (Buse et al., 2003). It is a predisease marker and hallmark of Type 2 diabetes and has been associated with parasympathetic dysfunction in humans (Takayama et al., 2001) and rats (Lautt, 1999).

In the population-based Atherosclerosis Risk in Communities (ARIC) study, an association was found between RSA (as measured by high frequency power (HF)) and glucose metabolism. After adjusting for age, ethnicity, and gender, the mean HF was 0.78 $(\text{beat/min})^2$ for diabetics and 1.27 $(\text{beat/min})^2$ for non-diabetics. In addition, there was a graded, inverse relationship between HF and fasting serum insulin among non-diabetics. HF was 1.14 $(\text{beat/min})^2$ among participants in the highest quartile of serum insulin and 1.34 $(\text{beat/min})^2$ among those in the lowest quartile after adjusting for age, ethnicity, and gender. A similar relationship was found between HF and fasting glucose in a univariate model, but not in the adjusted model. One interpretation of these results is that elevations in insulin and/or glucose adversely affect vagal tone to the heart prior to the onset of clinical diabetes (Vanninen et al., 1993). An alternative interpretation is that impaired cardiac vagal tone reflects global impairment of vagal function and this impairment may contribute to the development of insulin resistance and diabetes.

In a study comparing HF of first-degree relatives of patients with Type 2 diabetes with control participants, fasting blood glucose and glycosylated hemoglobin were similar in both groups. However, total spectral power and high-frequency power were lower in the relatives of diabetics compared to controls (Lindmark et al., 2003). In addition, insulin sensitivity was negatively associated with the ratio of low-frequency/high frequency spectral power. These results suggest that insulin resistance is associated with reduced parasympathetic activity or an imbalance between sympathetic and parasympathetic nervous activity. In a larger study of healthy young adults aged 24 to 39 years, high frequency spectral power was inversely associated with fasting glucose, insulin, and insulin resistance after controlling for age, gender,

waist circumference, smoking, and leisure-time physical activity (Koskinen et al., 2004). This study provides further evidence of a positive association between vagal cardiac tone and glucose homeostasis. However, none of these studies answers the question of whether reduced cardiac vagal tone precedes or follows impaired glucose metabolism.

There are several pathways by which low vagal tone or an imbalance between the sympathetic and parasympathetic nervous systems could increase risk for Type 2 diabetes mellitus. As alluded to above, decreased vagal tone reduces pancreatic insulin secretion and increases hepatic glycogenolysis and glucose production. In addition, activation of the sympathetic efferents increases circulating glucose via the effects of epinephrine on the liver, kidney, and peripheral tissues. Insulin resistance ensues when peripheral tissues are repeatedly exposed to elevated levels of glucose, insulin, cortisol, and free fatty acids (Buse et al., 2003). While the body's response to insulin resistance is to increase insulin production, frank diabetes occurs when this production is no longer sufficient to maintain plasma glucose in the normal range. Whether reduced vagal tone contributes to the development of diabetes via these pathways remains an open question.

5. RSA and Body Habitus

An association between autonomic activity and obesity in both adults and adolescents has also been identified. Measures of increased sympathetic activity in obese participants have included blood pressure response to handgrip exercise (Zahorskamarkiewicz et al., 1993), 24-hour urinary norepinephrine excretion (Karason et al., 1999), muscle sympathetic nerve activity (Alvarez et al., 2002), and low frequency power (Rabbia et al., 2003). Lower parasympathetic tone among obese patients has also been noted based upon tests of high frequency power (Karason et al., 1999; Rabbia et al., 2003; Zahorskamarkiewicz et al., 1993), and vagal baroreflex gain (Alvarez et al., 2002; Beske et al., 2002). Most studies suggest autonomic changes are the result, rather than the precursor, of weight change. Under experimental conditions, non-obese adults who increased their body weight by 10% demonstrated a decrease in parasympathetic control, as measured by the difference in mean RR-interval before and after administration of atropine. An increase in sympathetic control, as measured by mean RR after esmolol plus atropine minus mean RR after atropine alone, was also noted in this group. A comparison group of non-obese individuals who lost 10% of their body weight demonstrated an increase in parasympathetic control and a decrease in sympathetic control (Arrone et al., 1995). The authors concluded that the autonomic nervous system may regulate the metabolism and storage of energy via sympathetic and parasympathetic effects on heart rate variability. Other studies have confirmed the relationship between body weight changes and changes in autonomic activity. Karason et al. (1999) found obese patients who underwent bariatric gastroplasty and lost a mean of 32 kilograms had reduced urinary epinephrine excretion and increased high frequency heart rate variability. In another study, a three-week weight loss program resulted in reduced resting heart rate and increased parasympathetic activity, as measured by high frequency oscillation, among study participants (Facchini et al., 2003).

Autonomic activity appears to reflect not just body mass index but also distribution of body fat. Beske et al. (2002) compared non-obese men with and without high visceral to cutaneous fat ratios and found those with high ratios had lower baroreflex gain compared to those with low ratios. Excess visceral fat is a hallmark of the metabolic syndrome, which is also characterized by insulin resistance, elevated triglyceride levels, low HDL cholesterol levels, and hypertension. This syndrome has been associated with increased risk of coronary heart disease (Klein and Romijn, 2003). Beske et al. (2002) speculated that reduced arterial distensibility, a finding associated with abdominal fat collection, may impair transduction of arterial blood pressure via carotid stretch receptors and therefore attenuate efferent vagal tone. In addition, abdominal visceral fat expresses more angiotensinogen compared to subcutaneous

fat. Angiotensin, a metabolite of angiotensinogen, inhibits vagal tone and may contribute to the inverse relationship between excess visceral fat and cardiac vagal tone (Vaile et al., 1998).

An alternative explanation involves the effect that central obesity has on respiratory mechanics and lung volumes. The volume of air that can be taken in during inspiration is a function of many factors, including the presence or absence of central obesity. When significant central obesity is present, reductions in lung volumes, particularly forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC), can occur (Baydur et al., 2004; Ladosky et al., 2001) resulting in rapid, shallow breathing. RSA is substantially reduced during rapid compared to slow breathing (Brown et al., 1993; Grossman et al., 1991). This effect may also be present during pregnancy as high frequency heart rate variability (HRV) is reduced in the second (Ekholm et al., 1993) and third trimester of pregnancy (Eneroth-Grimfors et al., 1994). There is debate, however, as to whether reduced HRV in pregnancy is due to changes in lung volumes or other physiologic changes associated with pregnancy (Ekholm and Erkkola, 1996).

6. RSA and Hypertension

The two main categories of hypertension are primary hypertension, which accounts for approximately 90% of cases, and secondary hypertension, which accounts for approximately 10% of cases. Primary hypertension reflects a constellation of adrenergic, renal, hormonal, and/or vascular abnormalities while secondary hypertension is the result of specific structural organ or gene defects. Risk factors for primary hypertension include excessive alcohol intake, high salt diet, obesity, glucose intolerance, genetic predisposition, and increasing age (Williams, 1998). Since hypertension is itself a risk factor for coronary artery disease and stroke, several studies have examined the relationship between autonomic activity and elevated blood pressure. Cross-sectional analysis of participants in the Framingham Heart Study revealed individuals with hypertension had both increased low frequency power and decreased high frequency power compared to normotensive individuals (Singh et al., 1998). Among normotensives followed over four years, elevations in low frequency power at baseline predicted the development of hypertension among men but not women. Because autonomic changes can result from cardiovascular disease, Maver et al. (2004) examined heart rate variability and microvascular alterations in normotensive participants with and without a family history of hypertension (FHH). Normotensives with a FHH had a higher mean systolic blood pressure and lower high-frequency power compared to controls. No difference in microvascular dilating capacity was noted between the two groups. In the absence of structural microvascular changes, the higher blood pressure in the FHH group was considered due to an increase in microvascular reactivity of local origin and/or a reduction in cardiac vagal activity. As with studies of diabetes and RSA, studies of hypertension and RSA suggest impaired cardiac vagal tone exists prior to the onset of overt disease. While impaired cardiac vagal tone may contribute to hypertension, it is equally likely that vascular or hemodynamic changes prior to the onset of clinical hypertension lead to impaired vagal tone, which is manifested as reduced RSA.

7. RSA and Other Cardiovascular Diseases

Cardiovascular disease is a non-specific term which encompasses several conditions, including hypertension, atherosclerosis of the coronary arteries, systolic and diastolic ventricular dysfunction, myocardial infarction, and congestive heart failure. Atherosclerosis refers to the accumulation of lipoprotein particles and thickening of the arterial intima (Libby, 1998). The primary modifiable risk factors for atherosclerosis are hypertension, hypercholesterolemia, smoking, and hyperglycemia associated with diabetes mellitus (Hackam and Anand, 2003).

Characterized by reduced cardiac output, congestive heart failure often follows long-standing, uncontrolled hypertension and/or myocardial infarction. A close association exists between cardiac output and autonomic tone. For example, sympathetic delivery of norepinephrine to the heart increases cardiac output via increased inotropy and chronotropy. Reduced vagal tone to the heart also enhances chronotropy and is associated with an increased risk of cardiac events, including fatal arrhythmia. In a population-based sample, Tsuji et al. (1994) found an inverse relationship between RSA and both cardiac events and mortality. Similar relationships have been found among patients with congestive heart failure (Nolan et al., 1998) and those with recent myocardial infarction (LaRovere et al., 1998).

The relationship between reduced vagal tone and fatal cardiac events can be explained in several ways. First, in addition to suppressing heart rate, cardiac vagal tone appears to reduce the risk of ventricular arrhythmia in ischemic myocardium, especially when background sympathetic tone is high (De Ferrari et al., 1992). In a study of dogs with myocardial infarction, 91% of those with low vagal tone (as measured by baroreflex sensitivity) versus 20% of those with high vagal tone experienced ventricular fibrillation (VF) during exercise-induced ischemia. In these dogs, pharmacological or electrical stimulation of the vagus nerve almost completely prevented exercise-induced VF (Vanoli et al., 1991). Epidemiological studies indicate fatal arrhythmias are a primary cause of death in patients with congestive heart failure and coronary artery disease. In a 38 year follow-up of participants in the Framingham Heart Study, the presence of heart failure or coronary artery disease increased the risk of sudden death five-fold (Kannel et al., 1998).

Through peripheral pre- and post-synaptic interactions, vagal tone may protect the heart via reduced catecholamine release from sympathetic nerve endings (Casado et al., 1994; Wantanabe et al., 1978). Exposure of myocardium to high levels of norepinephrine has been associated with both hypertrophic and cytotoxic effects (Communal et al., 1999; Mann et al., 1992). Reduction of this exposure may therefore reduce ischemia and ischemia-related cardiac events. A reduction in cardiac work and oxygen demand via chronotropic suppression is another mechanism of vagal cardioprotection. In addition, although vagal innervation of the ventricular myocardium is sparse, in vivo stimulation of the human vagus nerve has a significant negative inotropic effect (Lewis et al., 2001).

Aside from its chronotropic and inotropic effects, the vagus nerve may provide cardiovascular protection via its effect on the inflammatory response. It is now well-established that atheroma formation within coronary arteries is an inflammatory process (Ross, 1999). Endothelial cell damage results in a complex inflammatory response which involves expression of inflammatory cytokines, such as tumor necrosis factor (TNF)-α, adhesion of leukocytes and platelets to the endothelial surface, migration and proliferation of smooth muscle cells, increased binding of LDL cholesterol to arterial endothelial and smooth muscle cells, and eventual development of intra-arterial plaques comprised of lipids and necrotic tissue. Macrophages release TNF-α when exposed to bacterial lipopolysaccharides and other noxious stimuli. This release can be inhibited by acetylcholine, the principle parasympathetic neurotransmitter (Tracey, 2002). Experiments in the setting of endotoxemia indicate direct electrical stimulation of the efferent vagus nerve inhibits TNF-α synthesis in the visceral organs and reduces serum TNF-α concentrations (Borovikova et al., 2000). Exaggerated TNF-α release is thought to be a factor in many chronic inflammatory diseases, including rheumatoid arthritis and Crohn's disease. Indeed, anti-TNF-α agents have led to marked clinical improvement of these conditions (Hanauer, 2004; Lipsky et al., 2000). Thus, in addition to increased risk of fatal arrhythmia, reduced cardiac vagal tone may predispose to coronary artery disease via decreased control of TNF-α-mediated inflammation.

8. The CHASRS Study

Three limitations characterize most of the research examining the associations between vagal tone and both metabolic and cardiovascular dysfunction. First, many of the studies have been conducted with either patient populations or samples of convenience. Although such studies are important, population-based studies of older adults are needed to determine the actual associations between vagal activity and health outcomes. Second, many studies have not controlled statistically for multiple known risk factors such as age, body mass index, cigarette use, and total cholesterol. Without controls for these factors, any measured association between vagal activity and health disorders could be attributable to the operation of one of these known third factors. Third, prior studies have tended to focus on vagal activity and single health disorders (e.g., hypertension, diabetes, or cardiovascular disease), and it is unclear whether the associations between reduced vagal activity and these disorders are related or not.

To address these limitations in the prior literature, we conclude our discussion with a review of findings from the population-based Chicago Health, Aging, and Social Relations Study (CHASRS). In this study, we sought first to determine the relationship between psychosocial factors and RSA and then to determine whether RSA was associated with traditional risk factors for hypertension and cardiovascular disease.

Given results from previous studies, we hypothesized that certain psychosocial variables (depressive symptoms, hostility, and perceived stress) would be inversely associated with RSA and that social support would be positively associated with RSA. We also hypothesized that RSA would be inversely associated with age, BMI, cigarette use, diabetes, hypertension, and other cardiovascular disease as demonstrated in previous studies. Finally, we evaluated the relationship between RSA and both hypertension and other cardiovascular disease while controlling for traditional risk factors for hypertension and cardiovascular disease. We hypothesized that lower RSA would remain a significant predictor of hypertension and other cardiovascular disease after controlling for age, BMI, cigarette use, total cholesterol, and diabetes.

Method

Data for this study were collected in the first and second years of the five-year Chicago Health, Aging, and Social Relations Study (CHASRS), a longitudinal, population-based study of persons aged 50 to 67 years. This age range was chosen because it represents the period at which the prevalence of hypertension increases from approximately 30% at 40–59 years to approximately 65% at 60 years and older (Hajjar and Kotchen, 2003). CHASRS was designed to examine the social, psychological, and biological aspects of social isolation and health. The target population included White, Black, and Hispanic persons living in Cook County, Illinois, who were English-speaking and sufficiently ambulatory to come to the University of Chicago for a daylong visit to the laboratory. The sample was selected using a multistage probability design in which Blacks and Hispanics were oversampled. A sample of households was selected then screened by telephone for the presence of an age-eligible person, who was asked to participate in the study. If a household contained more than one age-eligible person, the person with the most recent birthday was selected. A quota sampling strategy was used to achieve an approximately equal distribution of respondents across racial/ethnic groups. The response rate among eligible persons was 45%, comparable with those for other well-conducted telephone surveys. The final sample size of 229 older adults consisted of 81 Blacks/African Americans (37 males), 66 non-Black Hispanics (33 males), and 82 non-Hispanic Caucasians (39 males).

After arriving at the laboratory between 8:00 and 9:00 a.m. and providing informed consent, participants began a day of assessments that included an interview and a cardiovascular protocol. Participants were queried regarding depressive symptoms, hostility, perceived stress,

and social support using the Center for Epidemiologic Studies Depression Scale (CES-D) (Redloff, 1977), the Cook-Medley Hostility Scale (CMHO) (Cook and Medley, 1954), the Perceived Stress Scale (PSS)(Cohen et al., 1983), and the Interpersonal Support Evaluation List (ISEL)(Cohen and Hoberman, 1983), respectively. Participants were also asked whether they had a history of hypertension, coronary artery disease, acute myocardial infarction, congestive heart failure, stroke, or diabetes. In addition, participants listed their medications and number of packs of cigarettes smoked per day. The cardiovascular protocol included an assessment of blood pressure, height, weight, and electrocardiography. Body mass index (BMI) was calculated as weight in kg/(height in m)^2. In year 2, a finger stick blood sample (Cholestech LDX System; Hayward, California) was obtained to measure total cholesterol. Blood samples were not collected in year 1 in an attempt to minimize participant stress during their first year in this longitudinal study.

Participants were seated in a comfortable padded chair (a “recliner” in the full upright position) and provided with a footrest if their legs were too short to rest their feet on the floor. While in a seated position, a Colin Vital Statistics Monitor (Model BP-508; Vital Signs, Minster, OH) was used to obtain systolic, diastolic, and mean arterial blood pressure readings. The Colin monitor records a pulse wave tonometrically by partial occlusion of the radial artery against the radius of the wrist, allowing for beat-to-beat measurement of blood pressure. The tonometer was calibrated against an initial blood pressure reading obtained using an oscillometric cuff and was periodically recalibrated either automatically or on experimental initiation. Continuous tonometric blood pressure readings were edited for quality and minute-by-minute mean blood pressure levels were averaged across four minutes in a seated position to produce blood pressure values used to help ascertain hypertensive status.

An electrocardiogram was obtained using the standard lead II configuration. A Biopac MP100 System (Goleta, CA) was used to measure the electrocardiogram (ECG) signals, which were digitized at 1000 Hz. Custom software (Mindware, Lafayette Instruments) was used to verify, edit, and analyze the ECG signals. RSA is a measure of changes in heart period associated with respiration, which increases in magnitude with increased parasympathetic activation of the heart (Berntson et al., 1993; Cacioppo et al., 1994). RSA was derived by spectral analysis (fast-Fourier transform) of an interbeat interval time series calculated from ECG following procedures specified by Berntson et al. (1997). As a reflection of vagal-cardiac nerve traffic, IBI oscillations at the respiratory frequency (0.15 Hz to 0.4 Hz)(Berntson et al., 1997) were used to compute minute-by-minute mean RSA values during four minutes in a seated posture, and the mean RSA across these four minutes was used for RSA analysis.

Hypertension was defined as either 1) reporting being diagnosed as hypertensive or having “high blood pressure” by a physician, 2) taking anti-hypertensive medications, or 3) having a systolic blood pressure over 140 mm Hg when in the laboratory. Cardiovascular disease was defined as having a history of myocardial infarction, congestive heart failure, coronary artery disease, or stroke.

Pearson correlations statistics were used to explore the bivariate relationships between RSA and traditional risk factors for cardiovascular disease (age, BMI, smoking, cholesterol, diabetes, hypertension) as well as between RSA and cardiovascular disease. Four linear regression models were used to predict RSA and test whether social support was a significant predictor of RSA either alone or in models which sequentially added demographic characteristics as covariates. We used a set of three multiple logistic regression models to predict hypertension and four models to predict cardiovascular disease. The sequence of models enabled us to test whether relationships between vagal activity (as reflected by RSA) and health (hypertension, cardiovascular disease) were independent of any observed relationships between other risk factors and health. For hypertension, Model 1 predictors

included age, BMI, number of packs of cigarettes smoked per day, total cholesterol, and the presence or absence of diabetes. In Model 2, RSA was substituted for diabetes as a predictor of hypertension. Model 3 included both diabetes and RSA as covariates.

For cardiovascular disease, Model 1 predictors were the same risk factors used to predict hypertension. As with the hypertension models, RSA was substituted for diabetes in Model 2 while Model 3 included both diabetes and RSA as covariates. Model 4 built upon Model 3 with the addition of hypertension as a covariate. All models were estimated using SPSS software. Given the directional nature of the hypotheses, one-tailed t-tests were used to assess for significance.

Results

Of the 229 participants in the study, 184 had no missing data for variables included in models predicting hypertension and cardiovascular disease. These 184 cases constituted the data set for all subsequent analyses. In this group, 103 met the study criteria for hypertension while 20 participants had both hypertension and cardiovascular disease. Four participants had cardiovascular disease but did not meet the study criteria for hypertension. We found no differences in either systolic blood pressure or rates of cardiovascular disease by race/ethnicity.

As shown in Table 1, correlational analyses did not reveal any significant associations between the psychosocial variables and RSA, $|r|$'s < .1, p's > .2. Likewise, in a series of regression models which cumulatively held constant (a) demographic variables (i.e., age, gender, ethnicity, education, income), (b) marital status, and (c) BMI, social support was not a significant predictor of RSA. See Table 2. Comparable models did not reveal any significant associations between RSA and either depressive symptoms, hostility, or perceived stress.

In contrast, RSA was negatively associated with age, cigarette use, diabetes, hypertension, and cardiovascular disease. See Table 3. RSA was not associated with BMI or total cholesterol. In the first regression model of hypertension (Table 4), age, BMI, and diabetes were all significant predictors while cigarette use and total cholesterol were not significantly associated with hypertension. In Model 2, RSA showed a negative association with hypertension independent of the effects of the traditional hypertension risk factors. When both RSA and diabetes were included as covariates in Model 3, they each continued to be significant predictors of hypertension.

For the first cardiovascular disease model (Table 5), only age was a significant predictor of this outcome. Unlike Model 1 for hypertension, BMI and diabetes were not significantly associated with cardiovascular disease. Substituting RSA for diabetes in Model 2 did not yield a significant association between RSA and cardiovascular disease. Likewise, when both diabetes and RSA were included in Model 3, neither was significantly associated with the likelihood of cardiovascular disease. In model 4, a significant positive association was found between hypertension and cardiovascular disease while none of the other covariates was significantly associated with cardiovascular disease.

We conducted a preliminary formal test of the hypothesis that the RSA-cardiovascular disease relationship is mediated by hypertension. Due to limited power in the full models depicted in Table 5, the mediational analyses were constrained to the three variables of interest (RSA, hypertension, cardiovascular disease) to maximize the ability to detect relationships ($N = 220$). As per the mediation test procedure described by Baron and Kenny (Baron and Kenny, 1986), a series of three regression analyses was conducted and revealed that (1) RSA was a significant predictor of hypertension, $b = -0.25$, $SE = 0.11$, $p < .05$; (2) RSA was a significant predictor of cardiovascular disease, $b = -0.31$, $SE = 0.16$, $p = .05$; and (3) hypertension retained a significant association with cardiovascular disease when RSA was held constant, $b = 1.43$,

SE = 0.52, $p < .01$. A Sobel test (Baron and Kenny, 1986;Preacher and Leonardelli, 2001) showed that hypertension approached significance as a mediator of the RSA-cardiovascular disease relationship, test statistic = 1.74, $p = .08$. The alternative hypothesis, that the hypertension-cardiovascular disease relationship is mediated by RSA, was not supported by the data: RSA was not associated with cardiovascular disease when hypertension was held constant, $b = -0.21$, *SE* = 0.15, $p = .17$, Sobel test statistic = 1.19, $p > .2$.

Discussion

Consistent with our hypotheses and with previous studies, we found negative associations between RSA and age, diabetes, hypertension, and cardiovascular disease. While several studies have documented differences in heart rate variability *between* younger and older adults, we found an inverse association between age and RSA *within* a cohort of older adults. Our finding of a negative association between RSA and cigarette use is consistent with previous research which has shown that smoking is associated with decreased heart rate variability (Hayano et al., 1990; Nabors-Oberg et al., 2002) while smoking cessation is associated with increased heart rate variability (Minami et al., 1999; Yotsukura et al., 1998). We did not assess the causal nature of the relationship between diabetes and lower RSA but our results are consistent with previous studies which have shown that elevated glucose and insulin can be toxic to peripheral nerves and lead to autonomic neuropathy (Greene et al., 1999; Zochadne, 1999).

Previous studies have demonstrated sympathetic overactivity (Julius, 1991) as well as an increased ratio of sympathetic to parasympathetic activity (Mark and Kerber, 1982; Rea and Hamdan, 1990) in the setting of hypertension. Sympathetic activation and parasympathetic withdrawal are inappropriate responses to hypertension as they both lead to blood pressure elevation. As a result, it has been proposed that autonomic dysregulation underlies some forms of primary hypertension (Kaplan, 1990). In contrast, sympathetic activation and parasympathetic withdrawal are appropriate responses to the decreased cardiac output associated with congestive heart failure (Saul et al., 1988) and myocardial dysfunction (LaRovere et al., 1998). Our finding of an inverse relationship between RSA and cardiovascular disease is consistent with compensatory vagal withdrawal in the setting of CHF and/or previous myocardial infarction.

We did not find significant correlations between RSA and BMI or between RSA and the psychosocial characteristics tested. In addition, hostility was the only psychosocial factor we found to be significantly related to hypertension. Given the lack of association between social support and RSA in the correlational analysis, it was not surprising that social support was not a significant predictor of RSA in linear regression models which sequentially added demographic characteristics as covariates. In those models, age and Hispanic ethnicity were the most robust predictors of RSA. The lack of association between psychosocial variables and RSA was contrary to our hypothesis and somewhat surprising given previous studies which have shown an inverse relationship between RSA and other psychosocial characteristics, including acute stress (Berntson GG et al., 1994), depression (O'Connor et al., 2005), hostility (Demaree and Everhart, 2004), and anxiety (Fuller, 1992; Watkins et al., 1998).

In the first multivariate regression model of hypertension, age, BMI and the presence of diabetes were significant predictors while cigarette use and total cholesterol were not. These results are consistent with previous studies of hypertension, which demonstrate cigarette use and hypercholesterolemia are less significant predictors compared to other risk factors (Krousel-Wood et al., 2004). In regression Models 2 and 3, lower RSA was a significant predictor with and without inclusion of diabetes as a covariate. Although RSA is associated with diabetes and diabetic vascular changes are associated with hypertension, the relationship between RSA and hypertension does not appear to be completely mediated by diabetes. Rather,

RSA appears to be independently associated with hypertension, either as a causal factor or as part of a physiologic (albeit inappropriate) response to elevated blood pressure. Since 20 of the 103 participants with hypertension in this study also had cardiovascular disease, the inverse association between RSA and hypertension may partially reflect the compensatory changes expected with congestive heart failure and/or previous myocardial infarction.

It is noteworthy that RSA was significantly associated with hypertension after controlling for age and other known risk factors in the multivariate models. Previous studies have demonstrated a decline in RSA associated with age as well as a positive association between age and hypertension, raising the possibility that the association between RSA and hypertension simply reflects the age-related decline in RSA. Our results suggest the RSA-hypertension relationship is not explained by age but reflects an independent association. Nevertheless, investigators might be well advised in future studies to ensure any reported associations between RSA and health disorders are not dependent on age or other known risk factors (e.g., BMI, cigarette use, total cholesterol).

In the multivariate models of cardiovascular disease, only hypertension was a significant predictor of this outcome. We did not find age, BMI, cigarette use, total cholesterol, diabetes, or RSA to be significant predictors of cardiovascular disease. That RSA is associated with cardiovascular disease in bivariate analysis but not in multivariate analysis suggests the relationship between RSA and cardiovascular disease may be mediated by hypertension. We formally tested this hypothesis using mediational analysis (Baron and Kenny, 1986; Preacher and Leonardelli, 2001) and found that hypertension approached significance ($p = .08$) as a mediator of the relationship between RSA and cardiovascular disease. Similar analysis revealed RSA did not mediate the relationship between hypertension and cardiovascular disease ($p = .17$).

Several factors should be considered prior to generalizing the results presented. First, it is important to note that all of the data included in this study were obtained at the same time except for total cholesterol, which was obtained in year 2. It is possible that changes in total cholesterol over the course of one year obscured the relationship between this predictor and other covariates as well as hypertension and cardiovascular disease. The cross-sectional nature of the study design also precludes causal inferences regarding the relationships between RSA and the outcomes studied. A final consideration is the use of medications among study participants. Many of the study participants took angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB's), or nonsteroidal anti-inflammatory drugs (NSAID's) such as aspirin or ibuprofen as part of their medication regimen. Angiotensin II has been shown to inhibit vagal activity (Vaile JC et al., 1998) and ACE inhibitors have been shown to increase both RSA (Adigun AQ, Asiyanbola B, & Ajayi AAL, 2001) and baroreflex activation (Osterziel KJ & Dietz R, 1996). In addition, vagus nerve activity is enhanced in the presence of NSAID's (Arai I, Hirose H, Muramatsu M, Okuyama S, & Ahira H, 1985). Therefore, both the recorded blood pressure and RSA may reflect the effects of one or more of these medications.

9. Conclusion

In summary, our results confirm previous findings of correlations between vagal tone as reflected by RSA and several phenomena, including aging, cigarette use, diabetes, and hypertension. In addition, RSA was a significant negative predictor of hypertension after accounting for other traditional risk factors, including age, BMI, and diabetes. The association between RSA and non-hypertensive cardiovascular disease in the bivariate analysis did not persist in the multivariate analysis, suggesting the RSA-cardiovascular disease relationship may be mediated by hypertension. Mediational analysis provided some evidence supporting

this hypothesis. Given the study design, we could not determine whether reduced RSA was part of a primary hypertensive process or a compensatory response to hypertension, congestive heart failure, or previous myocardial infarction. Nevertheless, the consistent associations found between autonomic dysregulation, as measured by reduced RSA, and a variety of cardiovascular risk factors and disease processes make RSA an important target for further investigation.

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Table 1

Pearson correlations (*n*) among psychosocial and outcome variables

	CES-D	ISEL	PSS	CMHO
RSA	−0.01 (214)	−0.08 (209)	−0.04 (214)	−0.10 (203)
Hypertension (yes/no)	0.06 (223)	−0.03 (218)	0.09 (223)	0.15 (212)*
CV disease (yes/no)	0.03 (223)	0.03 (218)	0.11 (223)	−0.02 (212)

RSA=respiratory sinus arrhythmia, CV=cardiovascular, CES-D=Center for Epidemiologic Studies Depression Scale, ISEL=Interpersonal Support Evaluation List, PSS=Perceived Stress Scale, CMHA=Cook-Medley Hostility Scale

* $p < .05$

Table 2

Linear regression models predicting RSA (*b*, *SE)*

	Model 1	Model 2	Model 3	Model 4
Intercept	5.213 (0.590)	10.449 (1.660)	10.564 (1.665)	10.935 (1.823)
Social Support	−0.023 (0.045)	−.058 (0.045)	−0.057 (0.045)	−0.059 (0.045)
Age		−0.102 (0.023)**	−0.102 (0.023)**	−0.104 (0.024)**
Female (vs. male)		0.194 (0.192)	0.154 (0.197)	0.163 (0.198)
African American (vs. White)		0.226 (0.138)	0.218 (0.139)	0.230 (0.141)
Hispanic (vs. White)		−0.340 (0.148)*	−0.355 (0.149)*	−0.359 (0.149)*
Years education		0.048 (0.033)	0.041 (0.034)	0.040 (0.034)
Household income		0.021 (0.253)	0.116 (0.272)	0.117 (0.272)
Married (vs. not married)			−0.212 (0.220)	−0.210 (0.221)
BMI				−0.007 (0.015)

** $p < .01$,

* $p < .05$

Table 3

Correlation matrix of risk factors and cardiovascular outcomes

	Age	Body Mass Index	Cigarette Use	Total Cholesterol	Diabetes	RSA	Hypertension	Cardio-vascular Disease
Age	1							
Body Mass Index	−.096	1						
Cigarette Use	−.077	−.035	1					
Total Cholesterol	−.003	−.010	0.012	1				
Diabetes	.150*	.182*	−.082	0.059	1			
RSA	−.283**	0.047	−.143*	−.068	−.247**	1		
Hypertension	0.136*	.246**	0.045	−.017	0.284**	−.205**	1	
Cardiovascular Disease	0.142*	−.001	0.058	−.071	0.061	−.127*	.213**	1

* Correlation is significant to the 0.05 level (1 tailed)

** Correlation is significant to the 0.005 level (1 tailed)

Table 4

Multiple logistic regression models predicting hypertension (b, SE)

	Model 1	Model 2	Model 3
Intercept	−5.88(2.579)**	−4.024(2.831)	−3.425(2.977)
Age	.066(.039)*	.056(.039)	.045(.041)
Body Mass Index	.077(.027)**	.095(.027)**	.080(.027)**
Cigarette Use	.648(.581)	.303(.597)	.473(.598)
Total Cholesterol	−.001(.004)	−.001(.003)	−.002(.004)
Diabetes	1.858(.645)**		1.670(.655)*
RSA		−.328(.140)*	−.244(.147)*

* $p < 0.05$ (1 tailed),

** $p < 0.005$ (1 tailed)

Table 5

Multiple logistic regression models predicting cardiovascular disease (b, SE)

	Model 1	Model 2	Model 3	Model 4
Intercept	−6.563(3.601)*	−4.945(4.007)	−4.834(3.987)	−4.719(3.952)
Age	.097(.052)*	.084(.054)	.083(.054)	.069(.054)
Body Mass Index	.002(.037)	.008(.037)	.005(.038)	−.012(.039)
Cigarette Use	.732(.670)	.548(.679)	.584(.685)	.432(.687)
Total Cholesterol	−.006(.005)	−.006(.005)	−.006(.005)	−.006(.006)
Diabetes	.369(.585)		.253(.593)	−.038(.602)
RSA		−.199(.180)	−.154(.183)	−.114(.175)
Hypertension				1.426(.600)*

* $p < 0.05$ (1 tailed)