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Decreased Pain Perception and Risk for Hypertension: Prospective Findings and Potential Mechanisms

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Abstract

A growing literature has reported a significant reduction in pain sensitivity among hypertensive animals and humans. One of the key questions about this finding is whether a reduced sensitivity to pain can be observed in normotensive individuals who go on to develop high blood pressure. Blood pressure was re-assessed in one hundred and fifteen 19 year-old boys initially tested at age 14, when they were also presented with a pain stimulus (mechanical finger pressure). Analyses indicated that information regarding pain sensitivity improved prediction of changes in blood pressure beyond that afforded by differences in blood pressure at age 14, parental history of hypertension, and body mass index. Similar results were found in comparable analyses predicting 24-hour blood pressure recorded in one hundred and seventeen of the young men at age 22. Significant associations were also observed between pain sensitivity in 14 year-olds and 24-hour heart rate variability in various frequency bands at age 22, suggesting increased sympathetic and reduced parasympathetic tone among individuals less sensitive to pain. In order to further assess the relationship between autonomic function and pain sensitivity, one hundred and sixteen adolescent boys were assessed for pain sensitivity and autonomic responses to orthostatic challenge. Analyses indicated that exaggerated autonomic responses to postural change were associated with reduced pain sensitivity. Finally, to examine the potential role of endogenous opioids in blood pressure-related hypoalgesia, a group of young normotensive men were administered low-frequency transcutaneous electrical nerve

stimulation (TENS), which has been demonstrated to elicit endogenous opioid release, prior to being presented with two painful stimuli (electric shock and arm ischemia). A negative association between pain and resting blood pressure was significantly strengthened by administration of low-frequency TENS. The results of these studies provide evidence that pain sensitivity may be associated with physiological processes involved in the development of hypertension, and that this relationship may involve opioid mechanisms and the autonomic nervous system.

Résumé

La littérature a rapporté une sensibilité à la douleur réduite chez les animaux et les humains hypertensifs. Cette constatation soulève un questionnement à savoir si une sensibilité à la douleur réduite peut être observée chez les individus normotensifs qui développeront une pression artérielle élevée. La pression artérielle de cent quinze jeunes hommes de 19 ans initialement testés à 14 ans et à qui un stimulus douloureux (pression mécanique du doigt) avait alors été présenté a été mesurée. Les analyses ont indiqué que la sensibilité à la douleur contribue à prédire les changements dans la pression artérielle au-delà des changements attribuables aux différences dans la pression artérielle à 14 ans, l'histoire familiale d'hypertension et l'indice de masse corporelle. Des résultats similaires ont été obtenus lors d'analyses prédisant la pression artérielle sur une période de 24 heures enregistrée à 22 ans chez cent dix-sept des jeunes hommes. Des associations significatives entre la sensibilité à la douleur à 14 ans et la variabilité du rythme cardiaque à diverses fréquences sur une période de 24 heures à 22 ans ont également été observées, ce qui suggère une activation sympathique accrue et parasympathique réduite chez les individus moins sensibles à la douleur. Afin d'investiguer davantage la relation entre la fonction autonome et la sensibilité à la douleur, la réponse autonome à un défi orthostatique et la sensibilité à la douleur de cent seize adolescents ont été évaluées. Les analyses ont indiqué que des réponses autonomes exagérées au changement de position sont associées à une sensibilité à la douleur réduite. Enfin, pour examiner le rôle potentiel des opioïdes endogènes dans l'hypoalgésie

reliée à la pression artérielle, une neurostimulation électrique transcutanée à basse fréquence (TENS) a été administrée à un groupe de jeunes hommes normotensifs avant que deux stimulus douloureux (choc électrique et ischémie du bras) leur soient présentés. Une association négative entre la douleur et la pression artérielle au repos a été significativement renforcée par l'administration de TENS à basse fréquence. Les résultats de ces études fournissent des preuves que la sensibilité à la douleur pourrait être associée aux processus physiologiques impliqués dans le développement de l'hypertension et que cette relation pourrait impliquer les mécanismes opioïdes et le système nerveux autonome.

Statement of Original Contributions

This research program has made important contributions to the study of the association between pain sensitivity and blood pressure, an area that is receiving increasing attention by researchers and clinicians. Part of this stems from the availability of a unique group of participants who are involved in a larger, ongoing research project conducted by the Groupe de Recherche sur l'Inadaptation Psychosociale Chez l'Enfant (GRIP) at the Université de Montréal. The GRIP organizes several longitudinal studies of human development in the Montreal area. Although they are primarily focused on the development of psychosocial adaptation in men, I was able to follow-up one of their samples, a group of young francophone men now in their early twenties, whose pain sensitivity and blood pressure were originally assessed when they were 14 years old. As a result, I could investigate one of the most important areas in the hypertension-related hypoalgesia literature, and in doing so provide perhaps the best evidence to date that the reduced pain sensitivity observed among individuals with hypertension precedes the onset of increases in blood pressure. In addition, this program of research made important strides in improving the understanding of potential mechanisms underlying the blood pressure-pain relationship, highlighting the role of the autonomic nervous system and endogenous opioids.

Study One of this thesis has been accepted for publication in the journal, *Health Psychology* (Campbell et al., in press), while Study four was published in

the journal, *Psychophysiology* (Campbell & Ditto, 2002). Studies Two and Three have been submitted to peer-reviewed scientific journals for their consideration.

Statement of Authorship

In all of the research presented in this thesis, Blaine Ditto served in a direct advisory capacity, helping me to formulate research ideas, methodology, and analytic strategy. He made significant contributions to the writing and revision of the manuscripts. He also obtained funding to support this research.

Jean Séguin acted as co-supervisor on Studies One, Two, and Three of this thesis. He arranged for access to archival data from the 14-year old boys followed-up in these studies and also had significant input in the revision of the manuscripts describing this research.

Enrico Mezzacappa provided assistance in analyzing and interpreting the heart rate variability data described in Study Three.

Jean-Marc Assaad and Daniel Nagin participated in data collection for Study One.

Sarah Sinray helped to collect data for Study Two as part of the requirements for an Honours undergraduate degree in psychology at McGill University.

Marios Roussos worked as a research assistant and helped in data preparation for study 4. He also contributed ideas relating to the design of these experiments.

Robert Pihl and Richard Tremblay authored grants to secure partial research funding for Studies One, Two, and Three.

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I wish first and foremost to acknowledge my research supervisor, Blaine Ditto, for his tremendous encouragement and support. It was a privilege to be mentored by a truly world-class psychophysiologist whose comprehensive knowledge of psychosomatic medicine and genuine enthusiasm for the field was nothing short of infectious. Dr. Ditto afforded me a great deal of autonomy while always making himself available for consultation and advice, a style of supervision that made for a rewarding learning experience. Jean Séguin of the Groupe de Recherche sur l'Inadaptation Psychosociale Chez l'Enfant also played an important role in my development as a researcher and provided excellent input and always prompt feedback with respect to this group of studies. He was my supervisor at the Université de Montréal and made me feel like a part of their team. I would also like to thank Enrico Mezzacappa of Harvard University, who was very helpful with respect to interpretation of physiological recordings.

Much of this research was conducted with the assistance of several dedicated and hard working honours students and research assistants, including Marios Roussos, Sarah Sinray, Deb Scharf, and Anita Crerar. I would like to express my gratitude for their enthusiasm and camaraderie.

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General Introduction

Hypertension is a disorder relating to the average level at which blood pressure is regulated and has traditionally been defined by values exceeding a threshold of 140 mm HG systolic and 90 mm HG diastolic. It is among the most common of the risk factors for cardiovascular disease. Specifically, hypertension is associated with an increased risk of developing coronary heart disease, stroke, congestive heart failure, renal insufficiency, and peripheral vascular disease (MacMahon et al., 1990; Stamler, Neaton, & Wentworth, 1989). Results of recent epidemiological surveys have highlighted the seriousness of the health problem posed by hypertension. With a prevalence of 20% of the world's adult population (WHO Expert Committee, 1996), hypertension increases the cardiovascular risk of vast numbers of people.

While controlled clinical trials have demonstrated that anti-hypertensive drugs reduce cardiovascular risk in persons with established hypertension (Collins et al., 1990), treatment remains problematic. Tremendous resources are required to identify and treat incident cases. In the United States alone approximately 2 million new hypertensive cases per year are added to the number of patients requiring treatment for high blood pressure (Joint National Committee, 1997). The situation is complicated by the fact that many hypertensives are unaware of their condition (Mancia, Sega, Milesi, Cesana, & Zanchetti, 1997). In particular, significant numbers of hypertensives sustain vascular damage to their heart, brain, eyes, or kidneys before their condition has been recognized and even then many are inadequately treated (Strasser, 1996).

Over the past 20 years, data from surveys of representative samples from the United States population such as the National Health and Nutrition Examination Surveys (NHANESs) indicates that the percentages of people in the U.S. who are aware of their hypertension, who are being treated, and who are controlled (defined as blood pressure lower than or equal to 140/90 mm Hg) has risen considerably from the late 1970s to the early 1990s (Joint National Committee, 1997). In addition, the prevalence of hypertension appears to have diminished, perhaps because more people have modified their lifestyles, resulting in lowered blood pressure. However, the lower prevalence figures are likely in part a reflection of improvements in the techniques of measuring blood pressure, rather than a substantial decrease. The most recent NHANES survey assessed blood pressure on two occasions (one taken in the home) where the effects of "white coat" hypertension were less likely than previous NHANES which measured blood pressure on one occasion in a physician's office (Burt, Cutler, & Higgins, 1995). Still, most hypertension remains uncontrolled, and NHANES data suggest a reduction in awareness and control over the past few years. Estimates suggest that approximately one-third of recent NHANES survey participants classified as having a blood pressure of 140/90 mmHg or greater reported that they were previously unaware of their hypertensive status (Burt et al., 1995). In addition, only 49 percent of those previously diagnosed with hypertension were receiving anti-hypertensive medications and only 21 percent of those being treated with anti-hypertensive medications had a blood pressure of les than 140/90 mmHg. Thus, hypertension remains a widespread and

serious problem, continuing to contribute in a major way to the most common causes of disability and death in developed societies (WHO Expert Committee, 1996). Even those who derive optimal benefit from their antihypertensive treatment are likely to have a higher risk of morbidity and mortality than untreated normotensives with similar levels of blood pressure (Abernethy, 1986). In addition, treatment of hypertension is an expensive undertaking for both the individual and society, particularly when newer and more expensive medications are prescribed (Stason, 1989). This is compounded by the fact that control of hypertension typically requires a lifelong commitment to therapy since this approach reduces risk but does not cure the condition (Medical Research Council, 1986).

The increased risk of morbidity and mortality affects not only those with established hypertension by conventional definitions, but also to those with blood pressures at the higher end of the "normal" range. In fact, the majority of problems associated with hypertension occur not in the relatively few with severe disease but in the masses of patients with blood pressures that are only minimally elevated (Stamler, Stamler, & Neaton, 1993). Using estimates of relative risk and data concerning prevalence, it is possible to calculate the risk of blood pressure-related cardiovascular disease. Results provide an indication of the cardiovascular disease that can be attributed to blood pressure at different levels, using the rate of cardiovascular disease at the lowest blood pressure as a baseline. Such an analysis was undertaken in the Multiple Risk Factor Intervention Trial (MRFIT) of 347, 987 men in which "excess deaths" from

coronary heart disease were estimated in relation to systolic blood pressure levels (Stamler, Stamler, & Neaton, 1993). The excess deaths were those that were attributable to blood pressure after taking into account other known cardiovascular risk factors. The findings showed that 31.9% of coronary heart disease deaths attributable to blood pressure occurred in men with a systolic pressure of less than 140 mm Hg, compared with 24.1% of excess coronary heart disease deaths attributable to systolic blood pressure in subjects with pressures greater than 160 mm Hg. Overall, the risks of cardiovascular disease increase progressively with incremental increases in blood pressure from the optimal level of < 120 mmHg systolic and < 80 mmHg diastolic to the highest levels of systolic and diastolic blood pressure (Joint National Committee, 1997). As pointed out in 1972 by Sir George Pickering, hypertension is arbitrarily defined at a point in a continuous blood pressure distribution (Pickering, 1972). These cut-off points are based largely on tradition rather than on any biological significance of the values, with little evidence for a significant threshold of risk (Kannel, Garrison, & Dannenberg, 1993).

For all of these reasons, identification and treatment of the hypertensive patient represents an important but insufficient response to the problem of blood pressure related cardiovascular disease. Primary prevention would appear to be an integral part of the long-term solution to hypertension. It represents a logical extension of efforts directed at the detection and treatment of patients with established hypertension. However, blood pressure regulation is a complex physiological function, relying on the integrated actions of cardiovascular, renal,

neural, and endocrine systems. Perhaps it should not be terribly surprising therefore that an estimated 85-95% of all cases of hypertension are classified as "Essential," referring to the fact that the etiology is unknown or at least poorly understood (Folkow, 1995). While there is strong evidence for a heritability component and lack of exercise and obesity are known contributing factors, all known biological risk factors together account for no more than 30% of the explained variance in blood pressure differences (Joint National Committee, 1997). In order for efforts aimed at early identification and prevention of hypertension to be successful, it would appear necessary to gain a far greater understanding of the natural history of the disorder.

Hypertension is clinically important because chronically elevated BP damages the heart, blood vessels, and kidneys (MacMahon et al., 1990). However, in its early stages hypertension does not cause obvious disturbances of cardiovascular function. Most of the functional cardiovascular perturbations of hypertension are the result of compensatory mechanisms elevated blood pressure causes, including atherosclerosis and nephrosclerosis (Folkow, 1978). Therefore, investigating the pathophysiology of hypertension requires understanding the mechanisms of normal blood pressure control and identification of phenomena that precede or coincide with the rise of blood pressure to hypertensive levels. The review will evaluate an area of research examining associations between pain and blood pressure regulatory systems, and the possibility this may aid in understanding some of the possible physiological causes, correlates, and consequences of hypertension. Finally,

general objectives for a program of research comprising laboratory-based, ambulatory, and longitudinal studies of pain sensitivity and risk for hypertension are described.

Blood Pressure and Sensitivity to Pain

As noted earlier, many individuals with hypertension are unaware of their elevated blood pressure. In fact, hypertension is often referred to as the "silent killer." This might be because hypertension in and of itself does not produce subjective symptoms but there also exists a compelling body of evidence linking reduced levels of pain sensitivity with increased levels of blood pressure. This area of research, which began more than 20 years ago with the demonstration of reduced levels of pain in hypertensive compared to normotensive animals (Dworkin, Filewich, Miller, Craigmyle, & Pickering, 1979; Maixner, Touw, Brody, Gebhart, & Long, 1982; Randich, & Hartunian, 1983; Saavedra, 1981; Sitsen & de Jong, 1984), has been extended not only to hypertensive humans (Ghione, Rosa, Mezzasalma, & Panattoni, 1988; Guasti et al., 1995; Guasti et al., 1999; Sheps et al., 1992; Rau et al., 1994; Rosa, Vignocchi, Pannatoni, Rossi, & Ghione, 1994), but also to normotensive animals and humans deemed to be at increased risk for the disorder (Al'Absi, Buchanan, & Lovallo, 1996; D'Antono, Ditto, Rios, & Moskowitz, 1999; Maixner et al., 1982; Saavedra, 1981; Wendel & Bennett, 1981). Unsurprisingly, there has been a great deal of speculation as to the relevance of this phenomenon in the pathophysiology of hypertension. While for many years it has been known that cardiovascular and pain regulatory systems are interrelated (Randich & Maixner, 1984; Randich & Maixner, 1986),

the possibility that there is some functional significance for these associations remains uncertain. In addition, considerable interest has begun to develop as to the possible clinical implications of hypertension-related hypoalgesia as a possible marker for sustained high blood pressure (France, 1999).

Hypertension-Related Hypoalgesia in Animal Models of Hypertension

Evidence of hypertension-related hypoalgesia was first presented in a classic 1979 article in the journal *Science* by Dwokin and colleagues (Dworkin, Filewich, Miller, Craigmyle, & Pickering, 1979), who found that administration of the blood pressure elevating drug phenylephrine to rats reduced a behavior (wheel running) required to terminate or avoid aversive trigeminal stimulation. Since this classic research was conducted, a number of studies have confirmed that experimental elevation of blood pressure in animals using different alpha-adrenergic drugs designed to provoke acute increases in arterial pressure results in antinociception (Randich, & Hartunian, 1983; Randich, & Maixner, 1984; Randich & Maixner, 1986). Reports of reduced sensitivity to pain following other experimental means of inducing hypertension in animals supported the notion that this effect was not simply the result of the pressor agents themselves (Randich, & Maixner, 1984; Randich & Maixner, 1986). For example, while reduced pain was observed in rats following a surgical procedure designed to increase blood pressure (occlusion of the abdominal aorta proximal to the renal arteries), a similar operation that did not increase blood pressure (occlusion of the aorta distal to the renal arteries) also did not result in altered nociception (Thurston & Randich, 1990). Studies using rats have also demonstrated that

several other experimental means of inducing increased arterial pressure, including deoxycorticosterone acetate salt-induced hypertension (Maixner, Touw, Brody, Gebhart, & Long, 1982) and social deprivation-induced hypertension (Randich & Maixner, 1986) are positively associated with antinociception. These reductions in pain sensitivity following experimental elevation of arterial pressure have been associated with the relative magnitude of blood pressure increase (Randich & Maixner, 1986). Moreover, studies of hypertensive animals have observed reduced sensitivity to a variety of acute experimental pain paradigms such as flinch jump (Sitsen & De Jong, 1983), paw-pinch (Zamir, Simatov, & Segal, 1980), and tail flick (Saavedra, 1981). Although there have been some negative findings with regards to a hypertension-hypoalgesia relationship (Sitsen & De Jong, 1983; Tsai & Lin, 1987), these have been largely attributed to varying methodologies and the use of different rat strains among studies (Ghione, 1996).

Hypertension-Related Hypoalgesia in Humans

A smaller but consistent body of research has accumulated evidence of reduced pain sensitivity among hypertensive humans. The first published report appeared in 1980, when Zamir and Shuber (1980) used an ascending series of electrical stimulation currents to the tooth pulp in order to determine the minimum amount of stimulation required to elicit painful sensations (pain threshold) among a group of hypertensives relative to normotensive controls. Since tooth pulp contains only A-delta and C-fibers, which are believed to transmit pain sensations exclusively, graded electrical tooth pulp stimulation is advantageous in determining pain thresholds because it is presumably unaffected by other non-

painful sensations such as pressure which may be elicited by alternate forms of noxious stimulation (Ahlquist, Edwall, Franzen, & Haegerstam, 1984). The results of this study indicated that the hypertensive group exhibited a higher average pain threshold and greater tolerance compared to normotensive participants. These initial findings of reduced pain thresholds using tooth pulp stimulation were later replicated in borderline hypertensives compared to normotensives (Ghione, Rosa, Mezzasalma, & Panattoni, 1988). Moreover, Guasti et al. (1995) reported a similar association for pulpar stimulation threshold in hypertensives relative to normotensives using ambulatory blood pressure monitoring, which allowed for multiple measures of 24-hour blood pressure and as a result a more accurate assessment of hypertensive status. It should be noted that the relationship between increased pain threshold and blood pressure in this study was stronger for mean 24-hour values than for blood pressure assessed in the laboratory, suggesting that pain sensitivity is more closely associated with true arterial pressure rather than transient emotional or situational influences on blood pressure.

Confidence in the existence of hypertension-related hypoalgesia in humans has been confirmed by studies reporting diminished pain sensitivity in hypertensives using a variety of other noxious stimuli including thermal (Sheps et al., 1992; Rau et al., 1994) and cutaneous electrical pain (Rosa, Vignocchi, Panattoni, Rossi, & Ghione, 1994)

Reduced Pain Sensitivity and Risk for Hypertension: An Overview

An important consideration regarding the phenomenon of hypertension-related hypoalgesia is whether the reduction in pain sensitivity displayed by hypertensive animals and humans precedes the actual development of clinically elevated blood pressure or if it is a correlate or result of hypertension. Many of the early studies examining this issue regarded hypoalgesia as a direct consequence of increased blood pressure. In support of this notion is evidence that both acute and chronic experimental elevation of blood pressure in animals and humans results in decreased pain sensitivity (Droste et al., 1994; Dworkin et al., 1994). However, the results of other studies indicate that the idea of increased blood pressure causing hypoalgesia cannot fully explain hypertension-related hypoalgesia. In particular, a reduction of blood pressure among hypertensive humans does not necessarily result in increased sensitivity to pain. Ghione, Rosa, Mezzasalma, & Panattoni (1988) found no changes in pain sensitivity among hypertensive patients treated with Beta-blockers, diuretics, or a low-salt diet, despite significant reductions in blood pressure, although Guasti et al. (1998) recently noted a significant increase in dental pain sensitivity in hypertensives treated with ACE inhibitors. Furthermore, there is a growing body of research examining pain sensitivity in groups of animals and humans deemed to be at increased risk of developing hypertension by virtue of the fact that they have a genetic predisposition, exaggerated cardiovascular responses to stress, or high normal blood pressure (France, 1999). The results of these studies (reviewed below) provide evidence that reduced pain sensitivity precedes

hypertension and may be in some way related to mechanisms involved in provoking increased blood pressure.

Genetics of Hypertension and Hypoalgesia

The spontaneously hypertensive rat (SHR) is a widely used model developed to study genetic predisposition in human essential hypertension. At four to five weeks of age, the SHR has similar blood pressure levels to normotensive Wistar Kyoto controls (Sitsen & de Jong, 1983). However, by twelve weeks of age (after a diet of normal feed), the SHR dependably exhibit average systolic blood pressures greater than 200 mmHg, accompanied by hypernordrenergic innervation of blood vessels and vascular hypertrophy (Wendel & Bennett, 1981). In support of the notion that hypoalgesia precedes the onset of hypertension, several investigators have cited evidence from experiments indicating that a reduction in pain sensitivity can be observed in the SHR as early as 4 weeks of age, well before the onset of sustained high blood pressure in the SHR (Maixner et al., 1982; Saavedra, 1981; Wendel & Bennett, 1981). For example, young spontaneously hypertensive rats were observed to have reduced tail-flick responses to extreme heat as early as three weeks old, a characteristic which they maintain into adulthood (Saavedra, 1981). The SHR model allows the study of the entire period of hypertension development, which is difficult in human studies. However, while comparable prospective research has not been conducted with humans, normotensive adolescents and adults with hypertensive parents have been assessed for sensitivity to pain (Al'Absi,

Buchanan, & Lovallo, 1996; D'Antono, Ditto, Rios, & Moskowitz, 1999; France, Adler, France, & Ditto, 1994; Stewart & France, 1996).

The impact of genetic factors on human blood pressure has been established by repeated demonstrations of a significant association between blood pressure levels of parents and their biological children (Munger, Prineas, & Gomez-Marin, 1988; Zinner, Levy, & Kass, 1971) in combination with a lack of association between blood pressure levels of parents and their adopted children (Mongeau, 1987). Blood pressure levels of siblings are also correlated (Zinner, Levy, & Kass, 1971), while in twin studies the association for blood pressure is stronger among monozygotic compared with dizygotic twin pairs (Rose, Miller, Grim, & Christian, 1979). Results from the Muscatine study, an adolescent blood pressure screening program, indicated that individuals with a systolic blood pressure over the age and gender specific 95th percentile had a higher prevalence of a positive family history of hypertension, ischaemic heart disease, and stroke (Schieken, Clarke, & Lauer, 1981). Prospective studies also highlight the role of genetic factors in hypertension. In a longitudinal study using a large population-based sample of high school students, family history of hypertension was shown to significantly predict future onset of hypertension in young adults after 13 years of follow-up (Hunt, Williams, & Barlow, 1986). The strength of the prediction depended on the definition of a positive family history. Having any first-degree relative with hypertension was only a weak predictor of future hypertension. Two or more relatives with hypertension at an early age (less than 55) identified individuals who were at much higher risk. Taken as a whole, the

evidence from research examining genetic influences on human blood pressure is that genetic factors play a strong role.

With respect to pain sensitivity, normotensives with a parental history of hypertension have been observed to display a reduced sensitivity to a variety of different painful stimuli including the cold pressor (Al'Absi, Buchanan, & Lovallo, 1996), thermal pain (Bragdon, Light, Girdler, & Maixner, 1997), arm ischemia (Campbell & Ditto, 2002), and venipuncture (France, Adler, France, & Ditto, 1994). For example, in an experiment employing constrictive thigh-cuff stimulation (France, Ditto, & Adler, 1991), normotensive men with a parental history of hypertension required higher levels of cuff pressure in order to elicit subjective reports of pain threshold relative to participants with no parental history. In addition, participants with a positive parental history reported lower pain ratings even at higher maximum cuff pressures. Outside of the laboratory, in the context of the arguably more naturalistic setting of a blood donation clinic, France, Adler, France, and Ditto (1994) found that among inexperienced donors the pain of blood donation was rated lower by women whose parents confirmed the presence of hypertension in both parents versus women with a no parental history.

In another study suggesting the generalizability of the relationship between family history of hypertension and reduced sensitivity to pain, D'Antono, Ditto, Rios, and Moscowitz (1999) exposed young women with and without a parental history of hypertension to finger pressure and cold pressor tests. Women with a parental history of hypertension reported significantly less pain.

Furthermore, pain ratings of the laboratory stimuli were significantly correlated with reports of naturally occurring daily pain over 32 days.

Finally, France et al. (1996) examined the issue of pain sensitivity and family history of hypertension using what some consider a more objective measure of pain, the exteroceptive suppression of masseter and temporalis muscle activity. This refers to an inhibition of jaw-closing muscle activity following trigeminal stimulation, and represents a defensive withdrawal reflex in response to noxious stimuli. The electrical stimulation delivered during this procedure elicits two successive suppression periods, the second of which has been demonstrated in previous research to be enhanced by analgesic medication (Gobel, Ernst, Jeschke, Keil, & Weigle, 1992). Furthermore, exteroceptive suppression has been identified as a possible noninvasive index of endogenous pain control (Schoenen, 1993). Following perioral electrical stimulation, offspring of hypertensives displayed a significant increase in exteroceptive suppression for both muscle sites. Based on their findings, the authors suggested that the decreased pain sensitivity observed in individuals with a parental history of hypertension might be related to enhanced central pain modulation. The results of this study are important in that they support the notion of a genuine hypoalgesia in human offspring of hypertensives as opposed to reduced reporting of physical symptoms or a personality style that tolerates pain longer. This finding, in combination with the results of other studies reporting no association between personality and the pain sensitivity/risk for hypertension relationship suggest that this is unlikely to be the case.

While there have been occasional exceptions to these findings of an association between parental history of hypertension and reduced sensitivity to pain (Ghione, Rosa, Mezzasalma, & Panattoni, 1988), the results of these studies may be complicated by the use of small sample sizes lacking the requisite power to find an effect, floor effects, as well as the failure to determine family history through either direct parental of physician contact. Overall, the findings suggest that a blunted sensitivity to pain is characteristic of groups with a parental history of hypertension relative to those without.

Normatively Elevated Blood Pressure, Risk for Hypertension and Hypoalgesia

Although a great deal of interest has focused on hypoalgesia among individuals with established hypertension, the relevance of high-normal blood pressure values is also very relevant when considering the development of the disorder. Numerous studies have provided longitudinal information on the association between normatively elevated blood pressure and increased risk for hypertension (Julius & Hansson, 1983). In most this research, change in blood pressure is related to an individual's starting level of blood pressure (Oberman, Lane, Harlan, Graybiel, & Mitchell, 1967; Svardsudd & Tibblin, 1980; Wu, Ware, & Feinleib, 1980). Thus, while it is certainly true that blood pressure levels tend to increase with age (Joint National Committee, 1997), there exists significant variability in this trend. Individuals with the lowest level of blood pressure at the beginning of prospective studies tracking blood pressure change over time tend to have a relatively weak age – blood pressure relationship. In contrast, those with mean initial blood pressure values in the upper range of the blood pressure

distribution display a much stronger relationship between age and blood pressure values and have an increased risk of developing hypertension. For example, borderline hypertension in young adults is a reasonably good predictor of future hypertension; these individuals have at least twice the frequency of developing established hypertension later in life than similarly aged groups of individuals with lower normal blood pressure values (Julius & Hannson, 1983). Thus it seems particularly relevant to consider normotensive blood pressure levels in research aimed at understanding the determinants of hypertension.

Interestingly, the relationship between pain sensitivity and hypertension extends into the normotensive blood pressure range, with results of studies indicating that normatively elevated blood pressure (Ditto, Séguin, Boulerice, Pihl, & Tremblay, 1998; Bruehl, Carlson, & McCubbin, 1992; Fillingim, & Maixner, 1996) is associated with reduced levels of pain. For example, Bruhel, Carlson, & McCubbin (1992) found a significant inverse relationship between blood pressure and pain ratings in a group of normotensive young adult men exposed to finger pressure pain. Similarly, other investigations have reported significant inverse relationships between blood pressure in the normotensive range and sensitivity to noxious stimuli including cold pressor (McCubbin & Bruehl, 1994), electric shock (Campbell & Ditto, 2002), and thermal pain (Bragdon, Light, Girdler, & Maixner, 1997).

Although the continuous nature of the relationship between pain sensitivity and normotensive blood pressure has been established in several studies, it should be noted that some of the participants used in this research were close to

hypertensive status. Studies examining associations between pain and blood pressure in the "normal" range have typically focused on participants in their second and third decade of life and have sometimes included borderline hypertensive individuals. For example, in the Bruehl et al (1992) study described above, the strongest relationship between blood pressure and pain was found for men whose blood pressures began to approach hypertensive levels. In a similar study using thermal pain, Fillingham and Maixner (1996) reported that although a significant relationship between blood pressure and pain sensitivity was observed for normotensive men, no such relationship was observed for normotensive women. However, the mean systolic blood pressure for the men in this study was at the higher end of the normotensive range (129 mmHg), while the values for the women were considerably lower. In addition, the pain ratings of the women were considerably higher than those reported by the male participants. When blood pressure was added as a covariate to this comparison, the gender differences in pain sensitivity became nonsignificant. The authors suggested that the gender differences in pain sensitivity might have been in part a result of higher blood pressure values of the male participants.

In a study designed to address the question of how early in the disease process a relationship between blood pressure and pain sensitivity can be observed, Ditto, Séguin, Boulerice, Pihl, and Tremblay (1998) administered a painful finger pressure stimulator to a group of 177 normotensive 14-year-old boys. The mean blood pressure for the sample was 107/61 mmHg, a level well below that reported in the all other research on pain and human blood pressure.

Boys with normatively elevated blood pressure tolerated painful finger pressure longer than boys with lower blood pressure, a result that provides strong support for the notion that the relationship between pain sensitivity and blood pressure can be observed well before the onset of hypertension.

Cardiovascular Responses to Stress, Hypertension, and Hypoalgesia

There exists tremendous variability among individuals in the magnitude of their cardiovascular responses to stress. Performing challenging or aversive tasks can result in increases in blood pressure of over 35 mmHg for some individuals, while others under the same demands may exhibit little or no change (Fredrickson & Matthews, 1990). In addition, individual differences have been shown to exist in the underlying hemodynamic adjustments that underlie increases in blood pressure levels. For example, an increase in blood pressure in response to a stressor may be due to an elevated cardiac output or to an elevated peripheral vascular resistance (Folkow, 1990). These individual differences in cardiovascular reactivity have been demonstrated as early as childhood and have modest reliability over time (Van Egeren & Sparrow, 1989).

For many years, researchers have hypothesized that exaggerated blood pressure and heart rate responses to physical and mental stress contribute to risk for hypertension and cardiovascular disease (Folkow, 1978). In fact, evidence has accumulated that risk for increased blood pressure may be elevated among those individuals who react to stress with relatively large increases in blood pressure and heart rate. Some longitudinal research evidence indicates that exaggerated hemodynamic responses to a cold pressor challenge

predict the appearance of hypertension thirty years later (Menkes et al., 1989). Other research suggests that cardiovascular reactivity may predict relative increases in blood pressure among normotensive individuals over shorter intervals (Light, Dolan, Davis, & Sherwood, 1992; Matthews, Woodall, & Allen, 1993).

The impact of exaggerated reactivity on the development of hypertension and cardiovascular disease is not entirely clear. However, potential pathophysiological mechanisms have been examined. Briefly, it has been suggested that stressors initially produce transient increases in blood pressure by neurohumoral mechanisms, and that these elevations may in turn induce structural changes in the arterial wall which eventually results in a sustained increase of vascular resistance and therefore of blood pressure (Folkow, 1990).

Recent studies suggest that enhanced cardiovascular reactivity is also associated with reduced pain sensitivity. For example, France and Stewart (1995) observed that individuals who displayed the largest increases in blood pressure during exposure to a cold pressor task reported the lowest pain ratings during a subsequent painful arm ischemia challenge. Similar results have been obtained using other stimuli including electric shock (Ditto France, & France, 1997), thermal pain (Bragdon, Light, Girdler, & Maixner, 1997), and cold pain (Caceres & Burns, 1997).

One potential difficulty in interpreting the findings relating hypoalgesia to exaggerated cardiovascular reactivity concerns the phenomenon of stress-induced analgesia. Stress-induced analgesia is a phenomenon in which

reductions in pain sensitivity arise during stressful (but not painful) circumstances (Randich, & Maixner, 1986). It is theorized to be an adaptive response to life-threatening situations during which the experience of pain would reduce the ability to engage in coping behaviors. It is possible that these studies simply identified individuals who are generally predisposed to strong reactions to stress and are not particularly relevant to the blood pressure – pain sensitivity issue. Although this might be a possibility, in one of these studies (Ditto, France, & France, 1991) normotensive participants were administered painful electric shock and a cold pressor test in two laboratory sessions. The sessions were identical except that participants were exposed to a stressful videogame before the pain stimuli on one occasion and a non-stressful control task with similar motor requirements on the other (doodling on a pad of paper). Women with high blood pressure reactivity to the videogame showed reduced sensitivity to pain on *both* the day in which the pain stimuli were preceded by the videogame and the day in which the pain stimuli were preceded by the non-stressful control task, suggesting that this was a fairly stable characteristic of these individuals that may be associated to their risk for hypertension. Of course, it is also possible that the high reactors to the videogame also displayed high but undetected physiological reactions to the stressful procedure of presenting pain stimuli, explaining their lower nociception. To some degree, it may not be necessary to distinguish these hypotheses and the phenomenon of blood pressure-related hypoalgesia may be a more characterological variant of stress-induced analgesia. Prehypertensive animals and humans have long been thought to be predisposed towards stronger

or more frequent stress or defensive reactions (Fredrickson & Matthews, 1990; Sallis, Dimsdale, & Caine, 1988), a trait that might explain their reduced sensitivity to pain. For example, Guasti et al. (1995) found that following mental arithmetic stress, participants with early hypertension displayed increased thresholds to electrical tooth pulp stimulation, while the increase among their normotensive counterparts did not reach statistical significance. These results were interpreted as reflecting the possibility of greater increases in the activation of humoral and cortical mechanisms during the stress test among participants with higher blood pressure. It is even possible that the research indicating reduced sensitivity to pain in spontaneously hypertensive rats is related to stress-induced analgesia. For example, it is possible that these rats, that have often been described as "hyper-emotional" (Frohlich, 1986), were more stressed by the pre-pain handling, removal from their cages, and placement in the experimental apparatus, which may have been associated with the prior experience of pain. On the other hand, this may not have been the case and Ditto, France, and France (1991) did not find that presenting a stressful videogame prior to pain stimuli accentuated group differences between offspring of hypertensives and normotensives or high and low blood pressure reactors in pain sensitivity. This points to the importance of considering possible mechanisms of the association between blood pressure and pain.

Potential Mechanisms Underlying Hypertension-Related Hypoalgesia

The studies described above indicate that the altered pain sensitivity in blood pressure-related hypoalgesia is not modality-specific, a finding that

suggests this phenomenon is related to central processing of pain information. Other kinds of evidence also lead to this conclusion, including data from the animal literature suggesting that blood pressure related hypoalgesia is the product of endogenous opioid activity. For example, the lower pain sensitivity exhibited by spontaneously hypertensive rats, even young rats that have yet to develop hypertension, can be reversed by the broad spectrum opioid receptor blocker naloxone (Delbarre, Casset-Senon, Delbarre, Sestillange & Christin, 1982; Saavedra, 1981; Sitsen & de Jong, 1984). Far less research of this nature has been done with human participants. However, two studies have examined the effects of naloxone on the relationship between human blood pressure and pain. In the first of these, McCubbin and Bruehl (1994) found that although opioid blockade with naloxone diminished the inverse relationship between systolic blood pressure and pain sensitivity in individuals with high normal blood pressure (from r = -.54 to -.11), this result did not achieve statistical significance in their sample of 16 participants. Schobel and colleagues (1998) reported that, overall, the inverse correlation between pain perception and resting blood pressure in their small sample (n=21) was not significantly affected by naloxone. Although naloxone increased pain ratings in the normotensive participants, it had no effect on the borderline hypertensive group.

A more extensive body of research concerns endogenous opioid levels in blood plasma and hypertensive status. For example, Sheps and colleagues (1992) found higher plasma beta-endorphin levels and lower pain sensitivity in hypertensives compared to normotensives. Moreover, Guasti, Cattaneo, Daneri,

Bianchi, Gaudio, Grandi, Bertolini, Restelli, and Venco (1996) found significant intercorrelations among pain sensitivity, circulating beta-endorphin and mean 24-hour diastolic blood pressure.

In a set of related studies, McCubbin and colleagues (McCubbin, Surwit & Williams, 1985; 1988; McCubbin, Surwit, Williams, Nemeroff & McNeilly, 1989) examined the effects of naloxone on blood pressure reactivity in normotensives. On initial testing, participants with higher than average casual blood pressures showed greater blood pressure responses to stress compared to those with below average blood pressure. However, administration of naloxone increased responses of those with lower blood pressure while having no effect on those with higher arterial pressure. The results were interpreted as reflecting a deficiency in CNS opioidergic inhibition of sympathetic nervous system activity among those at greater risk for hypertension.

This possibility corresponds with the findings from a large body of research indicating that many individuals who go on to develop hypertension display a neurologically elicited "hyperkinetic" circulation characterized by increased sympathetic and reduced parasympathetic nervous system activity (Folkow, 1987; Brook & Julius, 2000). For example, the increased cardiac output displayed by borderline hypertensives compared to normotensives is abolished following a combination of sympathetic and parasympathetic pharmacological blockade (Julius, Pascual, & London, 1971). Building on these ideas, France and Ditto (1996) have proposed that individuals at risk for hypertension may have decreased sensitivity to endogenous opioids among certain hypothalamic

neurons, resulting in increased sympathetic nervous system activity, a tendency towards increased peripheral and central release of opioid substances, and decreased sensitivity to pain.

Support for this theory comes from Fontana et al. (1994), who reported that normotensive individuals with a family history of hypertension displayed larger stress-induced increases in plasma levels of met-enkephalin relative to those with no family history of hypertension. The presentation of a non-painful stressor has also been found to accentuate the differences in pain sensitivity between hypertensives and normotensives (Guasti, Merlo, Verga, Cattaneo, Gaudio, Bianchi, Zanzi, Grandi, Bossi, & Venco,1995). However, a major difficulty in interpreting many of these findings is that they are based on measurement of peripheral, plasma levels of opiates, which may not be relevant to blood pressure related hypoalgesia. For example, opiate antagonists which do not cross the blood-brain barrier (e.g. N-methyl-naloxone bromide) do not appear to have any effect on pain sensitivity in the spontaneously hypertensive rat, a finding pointing to the importance of opioid substances within the central nervous system (Sitsen & de Jong, 1984).

France and Ditto (1996) have also suggested that increased autonomic arousal resulting from opioid insensitivity among individuals at risk for hypertension may activate other pain dampening mechanisms, in particular baroreflex stimulation. Baroreceptors are stretch sensitive receptors that regulate blood pressure by acting on cardiac output and peripheral resistance. Baroreceptors not only play an essential role in blood pressure regulation but in

addition their experimental activation to simulate increases in blood pressure produces a reduction in pain (Droste et al., 1994; Dworkin et al., 1994). However, experimental support for the notion that blood pressure-related hypoalgesia springs from greater baroreflex stimulation has been mixed. Support for this view comes from a study by Elbert et al., (1994), who found that individuals displaying the greatest reductions in pain sensitivity during stimulation of the carotid sinus baroreflex using the negative external cervical pressure technique ("neck suction") and reporting the most life stress were the most likely to have increases in resting blood pressure over a 20-month period. Similarly, Brody and Rau (1994) found a relationship between more baroreceptor stimulation-dependent pain inhibition and increases in diastolic blood pressure over 19 months. On the other hand, France, Ditto, and Adler (1991) reported that stimulation of the carotid baroreceptors had no effect on the differences in sensitivity to ischemic pain between offspring of hypertensives and normotensives. Similarly, Rau et al. (1994) found that neck suction had no impact on the difference between borderline hypertensive and normotensive individuals in thermal pain sensitivity.

In summary, although promising results have been obtained, it is clear that an understanding of the mechanisms underlying the relationship between pain perception and blood pressure requires considerable work.

Preface to Current Program of research

Consistent evidence from studies of hypertensive animals and humans indicates that high blood pressure is associated with significant reductions in

sensitivity to a variety of experimental pain stimuli (Dworkin, Filewich, Miller, Craigmyle, & Pickering, 1979; Maixner, Touw, Brody, Gebhart, & Long, 1982; Ghione, Rosa, Mezzasalma, & Panattoni, 1988; Guasti et al., 1995; Guasti et al., 1999; Sheps et al., 1992; Rau et al., 1994). Moreover, a number of investigators have observed reduced pain among groups judged to be at increase risk of developing hypertension, including normotensive men and women with parental histories of hypertension (Al'Absi, Buchanan, & Lovallo, 1996; D'Antono, Ditto, Rios, & Moskowitz, 1999; France, Adler, France, & Ditto, 1994; Stewart & France, 1996), normatively elevated blood pressure (Bruehl, Carlson, & McCubbin, 1992; Ditto, Séguin, Boulerice, Pihl, & Tremblay, 1998; Fillingim, & Maixner, 1996), or enhanced cardiovascular responses to stress (Ditto, France, & France, 1997; France & Stewart, 1995).

Unfortunately, it cannot be determined with certainty that these at-risk individuals with high-normal blood pressure, exaggerated cardiovascular reactivity or a family history of hypertension will subsequently develop hypertension. In fact, evidence exists suggesting the majority of individuals judged to be at-risk for hypertension using these variables will not go on to develop hypertension (Hunt, Williams, & Barlow, 1986; Jamerson & Julius, 1991). This should not be surprising because, as previously mentioned, 95% of hypertension is classified as essential (Folkow, 1995). Thus, these studies can only be considered as suggestive with regard to a relationship between risk for hypertension and hypoalgesia, a fact that underscores the need for prospective research. The present research was in part undertaken to evaluate whether

individual differences in pain sensitivity were related to actual increases in blood pressure during adolescence, a developmental period characterized by significant cardiovascular change (Task Force on Blood Pressure Control in Children, 1987). Confidence in this conclusion would suggest that hypoalgesia is associated with pathophysiological processes involved in the development of hypertension.

In contrast to adults, adolescent hypertension is defined as a blood pressure that exceeds the 95th percentile for age (Task Force on Blood Pressure Control in Children, 1987), an arbitrary division that results in changing thresholds for high blood pressure during development. This convention for identifying hypertension highlights the fact that there are highly clinically significant increases in blood pressure during adolescence. In fact, the relevance of the childhood antecedents of hypertension has been receiving increased attention (Heise, Moore, Reid, & Goodman, 1987; Sever & Poulter, 1989). Blood pressure levels show gradual increases throughout childhood and a dramatic rise during adolescence (Task Force on Blood Pressure Control in Children, 1987). Furthermore, it has long been recognized that adult blood pressures are related to adolescent levels (Sever & Poulter, 1989). As a result, adolescents with the highest blood pressure levels are at the highest risk for hypertension. Since this pattern of high blood pressure is evident early in life, relatively large increases in blood pressure during adolescence may reflect pathophysiological changes implicating endogenous pain control mechanisms that have a hypertension-promoting effect. Studies One and Two of the present

research program examined this issue by assessing blood pressure in a group of young men (first in the laboratory and then in the field) whose pain sensitivity and blood pressure had previously been measured at age 14. Since a better prediction of future high blood pressure is obtained when multiple risk factors are considered (Paffenbarger, Thorne, & Wing, 1968), several indicators of risk including parental history of hypertension and blood pressure at age 14 were included in analyses predicting future blood pressure values.

In addition to furthering the literature concerning hypoalgesia and future blood pressure, the present program of research also sought to explore some of the mechanisms that may be involved in the blood pressure-pain sensitivity relationship. As noted above, there exists some controversy as to whether the differences in pain sensitivity exhibited by groups differing in cardiovascular reactivity reflects a short-term stress induced analgesia or a relationship between a general predisposition to demonstrate exaggerated autonomic responses to stressors and reduced sensitivity to pain. Study Three addressed this issue by examining measures of pain sensitivity and cardiovascular responses to an orthostatic challenge.

Another potential mechanism associated with hypertension-related hypoalgesia involves endogenous opioids. Although several researchers have suggested that endogenous opioids mediate the relationships between blood pressure levels, risk for hypertension, and pain sensitivity, this possibility has received little attention in the human literature. Study Four sought to examine the effects of low-frequency transcutaneous electrical nerve stimulation (TENS),

a procedure that appears to stimulate endogenous opioid activity, on blood pressure-related hypoalgesia in a group of normotensives. If individuals deemed to be at greater risk for developing hypertension exhibit altered opioidergic inhibitory mechanisms, leading to a tendency towards increased opioid release, low frequency TENS may have particularly pronounced effects on pain sensitivity and blood pressure in this group.

A LONGITUDINAL STUDY OF PAIN SENSITIVITY AND BLOOD PRESSURE IN ADOLESCENT BOYS: RESULTS FROM A 5 YEAR FOLLOW-UP

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Abstract

A growing literature has observed a significant reduction in pain sensitivity among hypertensive animals and humans. One of the key questions about this finding is whether a reduced sensitivity to pain can be observed in normotensive individuals who go on to develop high blood pressure. Blood pressure was re-assessed in one hundred and fifteen 19 year-old boys initially tested at age 14, when they were also presented with a pain stimulus (mechanical finger pressure). Hierarchical regression analyses indicated that information regarding pain tolerance improved prediction of changes in SBP beyond that afforded by differences in SBP at age 14, parental history of hypertension (PH), and body mass index (BMI). Similar results were found in comparable analyses predicting diastolic blood pressure. These analyses suggest that pain sensitivity may be associated with physiological processes involved in the development of sustained high blood pressure.

Key words: hypertension, blood pressure, risk, longitudinal, pain sensitivity

A Longitudinal Study of Pain Sensitivity and Blood Pressure: Results From a 5 Year Follow-up

Several distinct lines of research suggest that a reduced sensitivity to pain accompanies increased blood pressure. This area of investigation began over 20 years ago with animal studies showing greater pain tolerance in various models of hypertension, including the spontaneously hypertensive rat (Dworkin, Filewich, Miller, Craigmyle, & Pickering,1979; Maixner, Touw, Brody, Gebhart, & Long, 1982; Randich, & Hartunian, 1983; Saavedra, 1981; Sitsen & de Jong, 1984). Since that time, it has become clear that this difference in pain sensitivity can also be observed in hypertensive humans. First reported by Zamir and Shuber (1980) using electrical tooth-pulp stimulation, the inverse relationship between hypertension and pain sensitivity has been confirmed using many different painful stimuli, large groups of individuals, and ambulatory confirmation of blood pressure status (Ghione, Rosa, Mezzasalma, & Panattoni, 1988; Guasti et al., 1995; Guasti et al., 1999; Sheps et al., 1992; Rau et al., 1994; Rosa, Vignocchi, Pannatoni, Rossi, & Ghione, 1994).

One of the most important questions in this research area is whether or not the reduction in pain sensitivity exhibited by hypertensive humans and animals precedes the actual development of clinically elevated blood pressure. If so, this would mean that the reduced sensitivity to pain may be associated with processes involved in the development of the disorder. Confidence in this conclusion has been bolstered by evidence from the animal literature that a reduction in pain sensitivity can be observed well before the onset of sustained

high blood pressure (Maixner et al., 1982; Saavedra, 1981; Wendel & Bennett, 1981). For example, young spontaneously hypertensive rats were observed to have reduced tail-flick responses to extreme heat as early as three weeks old, a characteristic which they maintain into adulthood (Saavedra, 1981). However, comparable prospective research in humans has not been conducted. Studies from our laboratory and others have demonstrated that reduced pain sensitivity is often evident in groups judged to be at increased risk for hypertension, including normotensive men and women with parental histories of hypertension (Al'Absi, Buchanan, & Lovallo, 1996; D'Antono, Ditto, Rios, & Moskowitz, 1999; France, Adler, France, & Ditto, 1994; Stewart & France, 1996), normatively elevated blood pressure (Ditto, Séguin, Boulerice, Pihl, & Tremblay, 1998; Bruehl, Carlson, & McCubbin, 1992; Fillingim, & Maixner, 1996), or enhanced cardiovascular responses to stress (Ditto, France, & France, 1997; France & Stewart, 1995). Furthermore, these differences in pain sensitivity have often been shown to be unrelated to personality style or emotional state (Al'Absi et al., 1996; Bruehl et al., 1992; Ditto et al., 1998). In an important study that addressed a related but slightly different issue, Elbert et al. (1994) found that the magnitude of pain suppression produced by acute activation of carotid baroreceptors was positively associated with the degree of blood pressure increase over a 20 month period. Similarly, Brody and Rau (1994) found a relationship between more baroreceptor stimulation-dependent pain inhibition and increases in diastolic blood pressure over 19 months.

The present study, however, was the first attempt to re-examine a group of normotensive individuals at a later age to determine if individual differences in basic pain sensitivity predict subsequent blood pressure. If pain sensitivity is able to provide predictive information regarding blood pressure status beyond the more obvious, traditional risk factors such as current level of blood pressure, body mass index (BMI), and parental history of hypertension, several exciting possibilities are implied. Clinically, this finding could encourage the potential use of pain assessment as a marker of risk for hypertension. Hypertension is among the most common of the risk factors for cardiovascular disease which, according to data from the National Heart, Lung, and Blood Institute (1998) affects 28 percent of adults in the United States, with substantially greater proportions among minorities and the poor.

The main objective of the present study was to test the predictive relationship between pain sensitivity and change in blood pressure following an important developmental period. In our initial study of 177 14 year-old boys (Ditto et al., 1998), we found that those with normatively elevated blood pressure tolerated mechanical finger pressure significantly longer than boys with lower blood pressure. Furthermore, boys with both normatively elevated blood pressure and a parental history of hypertension reported significantly less pain during finger pressure than lower risk participants. While five years is not, in terms of overall life-span, a particularly long period of time, it is quite informative in relation to risk for high blood pressure. Blood pressure levels tend to be fairly stable through childhood, gradually climbing to an average systolic value of 102

mmHg for ten-year old boys (Task Force on Blood Pressure Control in Children, 1987). The mean SBP in our original sample of 14-year olds was 107 mmHg. During adolescence, however, blood pressure levels climb rapidly to age 18, where the mean SBP is approximately 119 mmHg. Afterwards, blood pressure levels generally stabilize again, albeit with a gradual upward trend. In addition to these physiological changes, adolescence is also marked by a combination of complex behavioral and psychosocial developments, a result of which may be to obscure the effect of pain sensitivity on future blood pressure. Therefore, the fact that this study was completed following a period of significant cardiovascular and psychological development seemed a particularly appropriate and powerful challenge to our hypothesis.

Method

Participants

One hundred and fifteen 19-year-old, French speaking, Caucasian men were re-tested from our original sample of 177 14-year old boys. These young men were originally recruited from a larger group of 1,037 enrolled in a longitudinal study of aggression in men. Participants were initially obtained using a community sample of the 53 schools with the lowest socioeconomic index of the largest school board in Montreal at the time. The details of their selection are fully described elsewhere (Séguin, Harden, Pihl, Tremblay, & Boulerice, 1995). Baseline comparisons of the follow-up sample to those who were not followed up showed no differences in resting systolic or diastolic blood pressure at age 14, 106/60 versus 107/61 mmHg, respectively. Similarly, there were no differences

between the follow-up sample and the others on any measure of pain sensitivity or threshold, or body mass index (BMI). Furthermore, there were no differences between either the follow-up group and those not followed or between the follow-up group and those in the larger aggression study in BMI at ages 14 and 19, or in personality assessed at ages 6, 10, 11 and 12 years using measures of fighting, inattention, hyperactivity, anxiety, prosociality, and family adversity from the Social Behavior Questionnaire (Tremblay et al., 1991). The presence or absence of hypertension among parents in our original study was operationalized as being told by one's physician that they had high blood pressure and resulted in a sample of 20 offspring of hypertensives, 11 of whom were retested. At age 19, parental history was confirmed by the reported use of antihypertensive medications, which resulted in a total of 20 participants with at least one hypertensive parent. Participant characteristics are presented in Table 1.

Procedure

The same pain stimulus which was presented to participants at age 14, a version of Forgione and Barber's (1971) strain gage pressure pain stimulator, was re-administered. The middle phalange of the non-dominant middle finger was placed under a plastic wedge with a 400g weight on top for 4 minutes (3 minutes at age 14), or until the participant asked that it be removed. This is a widely-used, well-controlled pain stimulus which produces a growing, aching-pain not unlike many clinical pains. A 2 kg version of this pain pressure stimulator was judged to be non-harmful by a panel of orthopedic surgeons for a 60 sec application (Bruehl et al., 1992).

At age 14, participants were instructed to rate their experience of pain on a visual analog scale from 0 (no pain) to 100 (intolerable pain) on a sheet of paper with a pencil every 15 seconds as indicated by the experimenter for a maximum duration of 180 sec (3 min). The procedure was terminated for those who reached a rating of 100 before 3 minutes, and this time was recorded and used as one of the dependent measures, pain tolerance. All subsequent missing values were considered maximum pain ratings, and entered in calculations of average pain. Maximum pain was also used as a dependent measure.

At age 19, pain was assessed using two visual analogue scales presented on a computer screen. One scale was labelled intensity and the other pleasantness, and both were bordered by 0 and 100. Participants were prompted through headphones by an experimenter in an adjoining room to make verbal ratings into a microphone at 20 seconds intervals. It was felt that removing the experimenter (a potential source of social support) from the room and adding the pleasantness dimension would result in an atmosphere that was less distracting and lead to a more thorough assessment of acute pain. Maximum and average values for intensity and minimum and average values for pleasantness were calculated, and tolerance was determined by recording the time until a maximum intensity rating was reached, to a maximum of 4 minutes. Just prior to the pressure-pain task, participants completed the State-Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970).

The method of assessment of blood pressure at ages 14 and 19 was identical. Three seated measurements were obtained during the 3 min prior to

the pain stimulus (following a 15 minute rest period) and during the 3 minutes immediately following the pain stimulus using a portable Sunbeam digital monitor (Model 7621). The Sunbeam monitor uses the oscillometric principle for determining brachial pressure. According to the manufacturer, it is accurate to within $\pm$ 3 mmHg for blood pressure. This monitor received the highest rating for accuracy in a test of 15 commercially available models (Consumers Union, 1992).

Repeated pain ratings at age 14, and intensity and pleasantness ratings at age 19, obtained during finger pain were averaged to obtain means for the entire duration of the task. If a participant terminated before the end of the pain task, a maximum pain or intensity score (or a minimum pleasantness score) was inserted for the remaining time. Baseline SBP and DBP were determined by taking the mean of the three pre-pain recordings. These values were used in the analyses because they were significantly lower than post-pain measures and more reflective of actual resting levels. It should be noted, however, that analyses using post-pain BP values yielded similar results.

Results

To determine whether pain ratings were influenced by anxiety, correlations between these ratings and STAI scores were calculated. None were significant. Similarly, there were no significant correlations between negative affect, as rated on the Social Behavior Questionnaire, or anxiety, as rated on the STAI, and BP at 14 or 19 years of age. As a result, these variables were not used as

covariates in the pain and BP analyses. Pain data at initial assessment and follow-up are also presented in Table 1.

Hierarchical regression analyses were conducted to examine the relationship between pain sensitivity and blood pressure. In order to control for variables with well-established effects on BP in the cross sectional-analysis, BMI and parental history of hypertension were forced into the equations and considered as covariates. For the longitudinal analysis, a regression was used to test for significant changes in BP from age 14 to 19 as they relate to pain sensitivity. The same covariates that were controlled for in the cross-sectional analysis were again entered into the equations, with the addition of baseline BP at age 14. Initial correlational analyses used Pearson correlations except for parental history of hypertension, where Point-Biseral correlations were calculated. All reported significance levels are 2-tailed.

Cross-Sectional Results in Pain Sensitivity and Blood Pressure at Age 19

As indicated in Table 2, significant correlations were observed between SBP and average pain intensity rating (r = -.31, p < .001), maximum intensity rating (r = -.30, p < .001), and minimum pleasantness rating (r = .23, p < .05). SBP was also significantly correlated with BMI (r = .31, p < .001) and positive parental history of hypertension at age 19 (r = .22, p < .05). For DBP, similar significant correlations were observed. For parental history of hypertension, significant correlations were also found with maximum pain intensity rating (r = .29, p < .05), and average pain rating (r = .53, p < .01), indicating that individuals with a positive parental history reported less pain relative to those with no

parental history. It should also be noted that a series of independent sample t-tests comparing correlations between blood pressure and pain reports for the two parental history groups revealed no evidence of differences in the strength or direction of these relationships as a function of parental history status.

To determine the ability of pain sensitivity to predict current SBP and DBP above and beyond classic demographic predictors, regressions analyses were conducted using the various pain measures. Since all of the analyses yielded similar statistically significant results, only the findings for maximum pain intensity rating are presented, as this variable yielded the strongest results. BMI and parental history of hypertension, both well-known risk factors for high blood pressure, were entered on Step 1 of the analysis. As indicated in Table 3, this combination of variables accounted for 16% of the variance in SBP. Using a forward regression procedure, maximum intensity was then included in Step 2 as a possible predictor. Maximum intensity rating was a significant additional predictor, accounting for an additional 13% of the variance in SBP (β = -.37; ΔF = 16.54, $p < .001$). The results of a hierarchical regression equation predicting DBP yielded comparable results (Table 3).

Longitudinal Results

Results of repeated measures t-tests revealed significant increases in SBP, $t(114) = 9.62$, $p < .001$, and DBP, $t(114) = 9.49$, $p < .001$, between 14 and 19 years of age. With a mean blood pressure at age 19 of 118/70 mmHg, the follow-up participants are fairly representative of young, low SES adult male francophones in Montreal.

Pain sensitivity at ages 14 and 19. Since the present study involved a re-assessment of pain sensitivity as well as blood pressure, we examined participants' pressure pain ratings at ages 14 and 19 to determine whether pain sensitivity was stable over a five-year time span. Simple correlations were conducted among the various pain measures at 14 and 19 years of age. As indicated in Table 4, pain measures at age 14 correlate highly among themselves. Similar significant correlations were observed among the various pain measures at age 19. More importantly, however, the pain measures at age 14 showed significant correlations with the intensity and pleasantness ratings at age 19 (Table 4). Despite the fact that both the procedure and the adjectives used to assess pain sensitivity varied somewhat between these two occasions, the participants appear to be characterized by relatively enduring levels of pain sensitivity.

Pain sensitivity and baseline blood pressure. Results of initial correlational analyses yielded significant correlations between SBP at age 19 and pain tolerance and maximum pain measured at age 14 (Table 2). As illustrated in Figure 1, greater pain tolerance at age 14 was associated with greater SBP five years later. SBP at age 19 was also associated with SBP at age 14 ($r = .42$, $p < .05$), and BMI at age 14 ($r = .31$, $p < .01$). Similar results were found with DBP at age 19 (Table 2) and the following measures obtained at age 14: pain tolerance ($r = .20$, $p < .05$), and DBP ($r = .20$, $p < .05$). In addition, DBP at age 19 was significantly related to a positive parental history of hypertension measured at 14 years of age ($r = .31$, $p < .05$), but not to BMI ($r =$

.16, n. s.), maximum pain rating (r = -.07, n. s.), or average pain rating (r = -.01, n. s.) measured at age 14. There were no significant relationships between parental history at age 14 and any of the pain measures at age 19.

The combination of control variables, i.e., SBP, BMI, and parental history of hypertension at age 14, were entered on Step 1 of a regression analysis to predict increases in SBP from age 14 to age 19. As indicated in Table 5, these variables accounted for 42% of the variance in SBP changes, with blood pressure at age 14 being the main significant predictor. Using a forward regression procedure, pain tolerance at age 14 was then entered as a possible predictor variable to determine if the addition of information regarding pain tolerance improved prediction of change in SBP beyond that afforded by SBP, BMI, and parental history measured at age 14. This variable accounted for an additional 5% of the variance in SBP changes (β = .24; ΔF = 4.96, $p < .05$), indicating that greater pain tolerance at age 14 predicted larger increases in blood pressure over 5 years. The results of a hierarchical regression equation predicting change in DBP yielded comparable results (Table 5).

Discussion

As expected, blood pressure levels were negatively correlated with pain sensitivity at age 19. This finding adds to a growing body evidence for a relationship between blood pressure in the normotensive range and pain sensitivity. In our laboratory as well as in others, high normal blood pressure has often been demonstrated to be related to lower pain ratings in young men and women (Ditto et al., 1998; D'Antono et al., 1999; McCubbin & Bruehl, 1994) .

More important, however, is that these results provide evidence, for the first time, that pain sensitivity can be used to predict changes in blood pressure levels across several years. For many years, it has been known that individuals with sustained high blood pressure display a reduced sensitivity to pain (Ghione et al., 1988; Guasti et al., 1995; Zamir & Shuber, 1980). Furthermore, a number of studies have demonstrated hypoalgesia among groups of individuals known to be at increased risk of developing hypertension. Until now, however, it was impossible to state whether or not pain sensitivity was associated with within-subject change in blood pressure over time. The fact that pain tolerance remains a significant predictor even after initial blood pressure levels and BMI are accounted for indicates that this measure taps into variability unaccounted for by traditional risk factors. Although the elevations in blood pressure exhibited by the young men in the study did not result in classification as hypertensive, they nevertheless showed the substantial increases typical of this developmental period, which will likely reflect values over the next decade (Bao, Threefoot, Srinivasan, & Berenson, 1995).

An examination of the literature on blood pressure related hypoalgesia reveals several positions regarding the relationship between blood pressure and pain perception. It has often been argued that hypoalgesia is the result of increased blood pressure. This belief developed primarily from research indicating that experimental elevation of blood pressure results in decreased pain sensitivity (Droste et al., 1994; Dworkin et al., 1994). Although these findings may partially explain blood pressure related hypoalgesia, other results indicate

that a reduction of blood pressure among hypertensives does not necessarily result in increased sensitivity to pain. Ghione et al. (1988) found no changes in pain sensitivity among hypertensive patients treated with Beta-blockers, diuretics, or a low-salt diet, despite significant reductions in blood pressure, although Guasti et al. (1998) recently noted a significant increase in dental pain sensitivity in hypertensives treated with ACE inhibitors.

Another possibility is that hypoalgesia precedes hypertension and is in some way related to mechanisms involved in provoking increased blood pressure. As noted above, this position is supported by a great deal of evidence from both human and animal studies that hypertension related hypoalgesia occurs well before the onset of sustained hypertension. For example, some of the earliest studies of spontaneously hypertensive rats (SPR) revealed that although manipulations of resting blood pressure could produce changes in pain sensitivity, the SPR displays increased tolerance to pain at 4 weeks of age, well before they begin to exhibit elevated blood pressure (Maixner et al., 1982; Sitsen & de Jong, 1984). Similar research with human participants has also shown that individuals thought to be at increased risk of developing hypertension by virtue of either genetic history (Al'Absi et al., 1996; France et al., 1994), enhanced cardiovascular reactivity (Bragdon, Light, Girdler, & Maixner, 1997; France & Stewart, 1995), or high normal blood pressure (Guasti et al., 1995; Sheffield et al., 1997) also show a reduced sensitivity to various noxious stimuli. The major finding from the present study, that elevations in blood pressure during adolescence are predicted by pain sensitivity at an earlier age, provides some of

the best evidence to date that hypoalgesia is related to processes involved in the development of hypertension rather than the reverse.

The mechanisms of blood pressure-related hypoalgesia were not assessed in the present study. However, evidence that decreased pain perception precedes greater increases in blood pressure suggests that a common mechanism may be responsible for both phenomena. McCubbin's opioid theory of stress hyperreactivity and cardiovascular risk (1991) proposes that risk for hypertension may be due in part to a deficiency in CNS opioidergic inhibition of sympathetic nervous system activity. Specifically, it suggests that increased autonomic arousal resulting from opioid dysfunction among hypothalamic neurons in individuals at risk for hypertension may result in both an exaggerated blood pressure responses to stress and a decreased sensitivity to pain. In an extension of McCubbin's model, France and Ditto (1996) have suggested that attenuation of normal opioid inhibition may be responsible for greater central release of opioid substances in high risk individuals, in part as an attempt to restore homeostasis, and decreased pain perception. Support for this theory comes from a recent study in our laboratory using the pain relieving device, transcutaneous electrical nerve stimulation (TENS), which when delivered at low frequencies, is known to result in CNS opioid release. Endogenous opioid involvement in blood pressure related hypoalgesia was supported by the finding that the negative correlation between blood pressure level and pain sensitivity increased following pre-treatment with low frequency TENS (Campbell & Ditto, 2002).

France and Ditto (1996) have also suggested that increased autonomic arousal resulting from opioid insensitivity among individuals at risk for hypertension may activate other pain dampening mechanisms, in particular baroreflex stimulation. Experimental activation of the carotid baroreceptors to simulate their stimulation by elevations in blood pressure has been shown to increase pain thresholds for several painful stimuli (Droste et al.,1994; Dworkin et al., 1994). Support for this view comes from a study by Elbert et al., (1994), who found that individuals displaying the greatest reductions in pain sensitivity during stimulation of the carotid sinus baroreflex and reporting the most life stress were the most likely to have increases in resting blood pressure over a 20-month period.

In summary, although the mechanisms underlying the relationship between pain perception and blood pressure remain uncertain, the finding that pain sensitivity contributes significantly to the prediction of increases in blood pressure 5 years later indicates that it is likely associated with physiological processes involved in the development of sustained high blood pressure.

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TABLE 1

Means, Standard Deviations and Ranges for Demographic and Cardiovascular Variables as Well as Anxiety and Pain Ratings

	Age 14			Age 19		
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*
Systolic BP	107.43	10.62	31.67	117.59	10.47	30.50
Diastolic BP	60.22	7.10	20.33	69.63	9.33	32.67
BMI	21.32	3.91	24	23.21	4.10	26
Negative affect (SBQ)	2.48	1.76	3.10	-	-	-
STAI	-	-	-	38.13	7.20	12
Average Pain	40.88	21.62	86.62	-	-	-
Maximum Pain	71.75	31.5	89	-	-	-
Tolerance (min.)	2.52	.84	2.50	3.98	.53	2.32
Average Intensity	-	-	-	43.02	19.87	75.85
Maximum Intensity	-	-	-	73.15	30.25	89
Average Pleasantness	-	-	-	43.13	24.39	95.08
Minimum Pleasantness	-	-	-	25.25	31.24	90
Positive Parental History (%,*n*)	(9.56, 11)			(17.39, 20)		

TABLE 2

Correlations between Pain Measures and Baseline Blood Pressure at Ages 14 and 19

	Age 14		Age 19	
	SBP	DBP	SBP	DBP
Measures Obtained Age 14				
Maximum Pain	-.07	.05	-.24**	-.06
Average Pain	-.01	.12	-.16	-.01
Pain Tolerance	.13	.02	.32**	.19*
Measures Obtained Age 19				
Maximum Intensity	-.13	.13	-.30**	-.23*
Average Intensity	-.10	.05	-.31**	-.22*
Minimum Pleasantness	-.21*	.08	.23*	.22*
Average Pleasantness	-.00	.22*	-.02	-.12
Pain Tolerance	.08	.05	.18	.15

Note. SBP = systolic blood pressure; DBP = diastolic blood pressure.

*$p < .05$; **$p < .01$

TABLE 3

Cross-Sectional Prediction of Resting Systolic and Diastolic Blood Pressure at age 19 Using Hierarchical Multiple Regression

Predictor variable	Δ R^2	β	ΔF	Predictor t
Systolic blood pressure				
Step 1	.16		8.42**	
Parental History		.20		2.06*
BMI		.33		3.40**
Step 2				
Maximum Intensity	.13	-.37	16.54**	-4.07**
Diastolic blood pressure				
Step 1	.09		2.48	
Parental History		.31		2.21
BMI		-.00		-.01
Step 2	.15		9.18**	
Maximum Intensity		-.41		-3.03**

*$p < .05$; **$p < .01$

TABLE 4

Correlations between 14 and 19 year-old Pain Measures

	Measures Obtained Age 14		
	Maximum Pain	Average Pain	Pain Tolerance
Measures Obtained Age 14			
Maximum Pain	1.00	-	-
Average Pain	.86**	1.00	-
Pain Tolerance	-.50**	-.32**	1.00
Measures Obtained Age 19			
Maximum Intensity	.45**	.43**	-.37**
Average Intensity	.30**	.27**	-.23*
Minimum Pleasantness	.37**	.35**	-.34**
Average Pleasantness	.37**	.38**	-.24*

*$p < .05$; **$p < .01$

TABLE 5

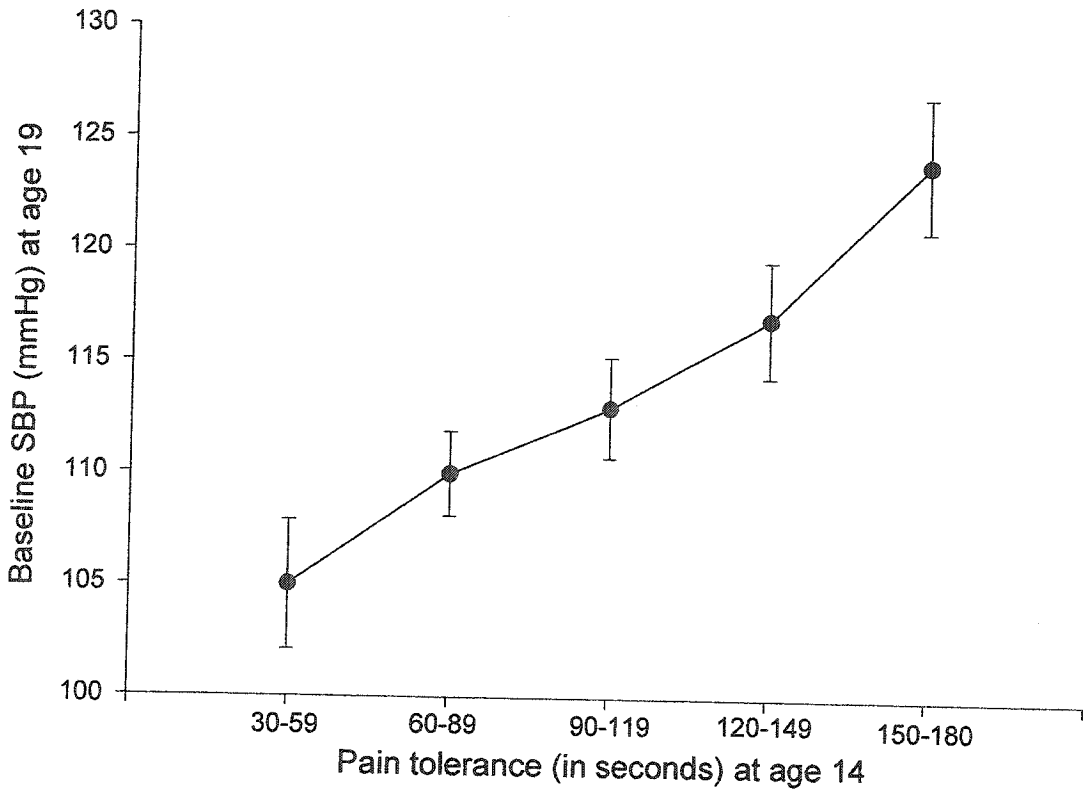
Hierarchical Multiple Regression Predicting Change in Resting Systolic (SBP) and Diastolic (DBP) Blood Pressure From Age 14 to Age 19.

Predictor variable	Δ R^2	β	ΔF	Predictor t
Systolic blood pressure				
Step 1	.42		11.97**	
14 year-old SBP		-.60		-4.92**
BMI		-.02		-.15
Parental History		.21		1.92
Step 2				
14 year-old Pain Tolerance	.05	.24	4.96*	2.23*
Diastolic blood pressure				
Step 1	.41		11.29**	
14-year-old DBP		-.54		-4.52**
BMI		-.06		-0.52
Parental History		.26		2.33*
Step 2				
14 year-old Pain Tolerance	.05	.24	4.74*	2.18*

*$p < .05$; **$p < .01$

Figure Caption

Figure 1. Systolic Blood Pressure (SBP) at age 19 as a function of pain tolerance among 14 year-olds.


130
125
120
115
110
105
100
Baseline SBP (mmHg) at age 19
30-59
60-89
90-119
120-149
150-180
Pain tolerance (in seconds) at age 14

Preface to Study Two

Although the results of Study One were important with respect to the demonstration that pain sensitivity at age 14 was able to predict increases in blood pressure over five years, they were also somewhat limited by the reliance on measures of resting blood pressure obtained on one occasion in the laboratory. As a result, Study Two involved the assessment of 24-hour ambulatory blood pressure in these individuals eight years following initial assessment. The observation of a predictive relationship between 14-year old pain sensitivity and blood pressure as determined by ambulatory monitoring, the "gold standard," would be an even more convincing demonstration of a prospective association. It is widely agreed that ambulatory blood pressure values are more valid indicators of a person's typical levels than those obtained in unfamiliar laboratory or clinic settings (Joint National Committee, 1997). Further, although various experimental tasks or stressors can be administered in a laboratory environment in order to estimate the reactivity or range of variability of physiological activity, this cannot match the variability displayed in real life. Individuals can be asleep or awake, sitting quietly or engaged in physical exercise, and exposed to a variety of psychological stimuli. In addition to the assessment of blood pressure, 24-hour ambulatory sequential cardiac interbeat interval values were measured and used to assess autonomic activity via spectral analysis of heart rate variability. The autonomic nervous system is known to be involved in the pathogenesis of hypertension (Brook & Julius, 2000), and individuals at risk for the disorder often display increased levels of

sympathetic and reduced levels of parasympathetic tone. Thus, the potential association between pain sensitivity at age 14 and autonomic function at age 22 was also evaluated.

ADOLESCENT PAIN SENSITIVITY PREDICTS CARDIOVASCULAR AUTONOMIC FUNCTION AND INCREASE IN BLOOD PRESSURE OVER 8 YEARS

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Running head: Pain Sensitivity Predicts Autonomic Function and Blood Pressure

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Abstract

Low pain sensitivity has been reported in hypertensives as well in groups deemed to be at increased risk of developing the disorder. However, it is uncertain whether individual differences in pain sensitivity are associated prospectively with increases in blood pressure. In the present study, 24-hour blood pressure and heart rate variability were recorded in 117 22 year-old men previously assessed at age 14 for casual blood pressure and pain sensitivity (mechanical finger pressure). Significant correlations were observed between pain tolerance in 14 year-olds and: current 24 hr. systolic blood pressure ($r = .35$, $p < .01$), and diastolic blood pressure ($r = .33$, $p < .01$). Hierarchical multiple regression analyses indicated that information regarding pain tolerance improved prediction of systolic blood pressure and diastolic blood pressure at age 22 beyond that afforded by differences in blood pressure, parental history of hypertension, and body mass index at age 14. Similar analyses revealed that average pain at age 14 was also predictive of 24-hour high frequency heart rate variability ($r = .46$, $p < .01$), and low frequency/high frequency heart rate variability at age 22, suggesting increased sympathetic and reduced parasympathetic tone among individuals less sensitive to pain. These results provide further evidence that blood pressure related hypoalgesia might be related to processes involved in blood pressure regulation as well as in the development of sustained high blood pressure.

Key words: pain sensitivity, blood pressure, autonomic tone, risk, longitudinal.

Adolescent Pain Sensitivity Predicts Cardiovascular Autonomic Function and Increase in Blood Pressure Over 8 Years

A growing literature concerns the negative association between pain sensitivity and hypertension, a phenomenon referred to as hypertension-related hypoalgesia. Since the first animal studies using the spontaneously hypertensive rat (SHR) reported a relationship between nociception and blood pressure more than 20 years ago (Dworkin, Filewich, Miller, Craigmyle, & Pickering, 1979; Maixner, Touw, Brody, Gebhart, & Long, 1982; Randich & Hartunian, 1983; Saavedra, 1981; Sitsen & de Jong, 1984), the relationship between pain sensitivity and arterial pressure has been observed in hypertensive humans (Guasti et al., 1999; Rosa, Vignocchi, Panattoni, Rossi, & Ghione, 1994; Zamir & Shuber, 1980), as well as both normotensive animals and humans deemed to be at increased risk for the development of sustained high blood pressure. For example, data has been reported showing an increased tolerance to pain among humans with a parental history of hypertension (Al'Absi, Buchanan, & Lovallo, 1996; France, Adler, France, & Ditto, 1994), exaggerated cardiovascular reactivity (Ditto, France, & France, 1997; France & Stewart, 1995), and elevated normal blood pressure (Bruehl, Carlson, & McCubbin, 1992; Ditto, Séguin, Boulerice, Pihl, & Tremblay, 1998; Fillingim & Maixner, 1996).

Although there are several different perspectives concerning the origins of blood pressure-related hypoalgesia (Ghione, 1996; France, 1999), one promising explanation involves the possible dual impact of altered endogenous opioid activity on autonomic activity and pain sensitivity. McCubbin and colleagues

(1991) have argued that opioid dysregulation may be involved in the increased sympathetic activity and blood pressure lability often displayed by young hypertensives, a process which might have an impact on the perception of pain (France & Ditto, 1996). The present study sought to determine 1) whether measures of pain tolerance obtained from a group of adolescent boys at age 14 were prospectively related to individual differences in ambulatory blood pressure at age 22, and 2) whether differences in pain sensitivity at age 14 were related to autonomic activity assessed via 24-hour heart rate variability (HRV). As noted above, many studies have observed a relation between blood pressure and pain sensitivity in humans in cross-sectional research (France, 1999). For example, Ditto et al. (1998) found that 14-year old boys with normatively elevated blood pressure tolerated painful mechanical finger pressure significantly longer than demographically similar boys with lower blood pressure. Lower sensitivity to pain has also been related to sympathetic activity. For example, it has been linked to increased blood pressure reactivity to the cold pressor test (Ditto, France, & France, 1997; France & Stewart, 1995).

However, while a prospective relation between lower sensitivity to pain and increased blood pressure has been demonstrated in experimental animals (Saavedra, 1981), little prospective research has been done in humans. Perhaps the best evidence to date comes from a 5-year follow-up study of the 14-year old boys involved in the study described above (Campbell, Ditto, Séguin, Assaad, Pihl, Nagin, & Tremblay, in press). The results of this study indicated, for the first time, that individual differences in pain sensitivity could be used to predict actual

increases in blood pressure across time, even after controlling for well established risk factors such as initial blood pressure, parental history of hypertension, and body mass index (BMI). However, a weakness of that study was a reliance on blood pressure assessment on one occasion in a laboratory setting. The present study sought to confirm and extend these findings by following up these boys, now young men, 8 years after initial pain and blood pressure assessment. We were interested in determining whether pain sensitivity in mid-adolescence was linked not only to blood pressure change from mid-adolescence to early adulthood, but also to mechanisms involved in blood pressure regulation.

Methods

Participants

One hundred and eighteen 22 year-old Canadian-born, Caucasian, French-speaking men were retested from the original sample of 177 14 year-old boys (Ditto, Séguin, Boulerice, Pihl, & Tremblay, 1998). The participants were part of a larger longitudinal study examining psychosocial adaptation in men. At age 6, participants were initially obtained using a community sample of the 53 schools with the lowest socioeconomic index of the largest school board in Montréal. Details of their selection are presented in detail elsewhere (Séguin, Harden, Pihl, Tremblay, & Boulerice, 1995). Comparisons of the follow-up sample to those who were not followed up for reasons independent from this study showed no differences in demographics or in 14 year-old pain sensitivity, systolic (SBP) or diastolic (DBP) blood pressure. Furthermore, there were no

differences between the follow-up group and those not followed in personality assessed at ages 6, 10, 11, and 12 years using the Social Behavior Questionnaire (Tremblay, Loeber, Gagnon, Charlebois, Larivée, & Leblanc, 1991). Results of repeated measures t-tests revealed significant increases in resting laboratory measures of SBP ($t = 9.62$, $p < .001$) and DBP ($t = 9.49$, $p < .001$) between 14 and 22 years of age. Participants gave informed consent and an institutional review board approved the methods. Participant characteristics are summarized in Table 1.

Pain Assessment

At age 14, all participants underwent pain assessment using a version of Forgione and Barber's (1971) strain gage pressure pain stimulator. The middle phalange of the non-dominant middle finger was placed under a plastic wedge with a 400g weight on top for 3 minutes, or until the participant asked that it be removed. This is a widely used, well-controlled pain stimulus that produces a growing, aching-pain not unlike many clinical pains. Participants were instructed to rate their experience of pain on a visual analog scale from 0 (no pain) to 100 (intolerable pain) on a sheet of paper every 15 seconds as for a maximum duration of 180 sec (3 min). The procedure was terminated for those who reached a rating of 100 before 3 minutes, and this time was recorded and used as one of the dependent measures, pain tolerance. All subsequent missing values were considered maximum pain ratings in calculations of average pain. Maximum pain was also used as a dependent measure.

Blood Pressure Measurement

At age 14 blood pressure was assessed by taking the mean of three seated measurements obtained during the 3 min prior to the pain stimulus (following a 15 minute rest period) using a portable Sunbeam digital monitor (Model 7621). The Sunbeam monitor uses the oscillometric principle for determining brachial pressure. According to the manufacturer, it is accurate to within $\pm$ 3 mmHg for blood pressure. This monitor received the highest rating for accuracy in a test of 15 commercially available models (Consumers Union, 1992).

At age 22 ambulatory blood pressure was assessed during a typical weekday. The participants wore an Accutracker DX ABP Monitor (Suntech Accutracker DX, Raleigh, NC) for 24 hrs, starting between 8 and 11 AM until the same time the following morning. The Accutracker DX measures blood pressure using the ausculatory technique. It was programmed to take 2 blood pressure measurements hourly at random intervals. Participants were instructed to follow their normal schedule and to complete a diary entry indicating posture, activity, and location at each blood pressure reading while awake. All blood pressure readings were reviewed and artifactual readings were deleted according to the manufacturer's recommendations.

Heart Rate Variability Measurement and Estimation of Autonomic Activity

Continuous ambulatory measures of cardiac interbeat intervals (IBI) were obtained using a Polar R-R monitor (Polar Electro, Finland). The monitor samples the EKG signal and measures the difference between successive R-

waves, storing 24 hours worth of data. Participants were instrumented with the Polar monitor during the blood pressure measurement period. Editing and analysis of the IBI data was done off-line using a Vagal Tone Monitor (Delta Biometrics, Bethesda, MD). Possible artifacts were screened using the editing program (VEDIT). HRV within several frequency bands was assessed. Low frequency HRV (LF; .02 to .15 Hz), believed to reflect a mixture of sympathetic and parasympathetic influences, and high frequency HRV (HF; .15 to .4 Hz), believed to reflect primarily vagal regulation of HR, were calculated. The ratio of low-frequency to high-frequency HRV (LF/HF) was used as a measure of sympathovagal balance. Estimates of activity within each frequency band were obtained for each 30-second window.

Results

Data Analysis

The following analyses were performed on the subsample of participants available at ages 14 and 22. Repeated pain ratings obtained during finger pain were averaged to obtain a mean for the entire duration of the task. If a participant terminated before the end of the pain task, the maximum pain score was inserted for the remaining time. Age 14 casual SBP and DBP were determined by taking the mean of the three pre-pain recordings. Twenty-four hour SBP and DBP at age 22 was computed based on all valid readings obtained during waking hours and sleep. Separate analyses conducted using waking and sleeping values had no significant effect on the outcomes reported. Twenty-four hour mean values of LF, HF, and LF/HF were also calculated.

To determine whether pain ratings were influenced by concurrent psychological variables, correlations between these ratings and negative affect, as rated on the Social Behavior Questionnaire, were calculated. None were significant in this subsample, which is consistent with the absence of a correlation in the complete age 14 sample (Séguin, Pihl, Boulerice, Tremblay, & Harden, 1996). As a result, this variable was not used as a covariate in the pain and blood pressure analyses. Pain data are presented in Table 1.

Hierarchical multiple regression analyses were conducted to examine the longitudinal relationship between pain sensitivity at age 14 and blood pressure at age 22. In order to control for variables with well-established effects on increases in BP over time, parental history of hypertension, BMI, and blood pressure at age 14 were forced into step one of the equations and considered as covariates.

For the evaluation of pain sensitivity as a possible determinant of the HRV measures, similar hierarchical multiple regression analyses were used after adjusting for BMI, PH, and SBP at age 14 by forcing them into step one of the equations.

Preliminary correlational analyses used Pearson correlations except for parental history of hypertension, where Point-Biseral correlations were calculated. All reported significance levels are 2-tailed.

Pain sensitivity and blood pressure:

Results of initial correlational analyses yielded significant correlations between 24 hr. SBP at age 22 and pain tolerance ($r = .35$, $p < .01$), average pain

(r = -.24, p < .01), and maximum pain (r = -.23 p < .05) measured at age 14 (Table 2). As illustrated in Figure 1, 14 year-old pain tolerance was positively associated with 24 hr. SBP measured 8 years later.

In addition, 24 hr. SBP at age 22 was positively associated with SBP at age 14 (r = .20, p < .05), but not BMI (r = .09, n. s.) or parental history of hypertension (r = .11, n. s.) at age 14. Similar results were found with 24 hr. DBP at age 22 (Table 2) and the following measures obtained at age 14: pain tolerance (r = .33, p < .01), maximum pain (r = -.28, p < .01), and average pain (r = -.22, p < .05). The relationship between DBP at age 14 and 24 hr. DBP at age 22 did not quite reach statistical significance (r = .16, p = .06). Twenty-four hr. DBP at age 22 was unrelated to a positive parental history (r = .10, n. s.) or to BMI (r = .07, n. s.) measured at 14 years of age.

The combination of control variables, i.e., 14 year-old SBP, BMI, and parental history of hypertension, were entered in Step 1 of a multiple regression analysis to predict 24 hr. SBP at age 22. As indicated in Table 3, these variables accounted for 8% of the variance in 24 hr. SBP values, with 14 year-old blood pressure being the main significant predictor. Using a forward multiple regression procedure, 14 year-old pain tolerance was then entered as a possible predictor variable to determine if the addition of information regarding pain tolerance improved prediction of 24 hr. SBP at age 22 beyond that afforded by 14 year-old SBP, BMI, and parental history. This variable accounted for an additional 11% of the variance in SBP increases (β = .34; ΔF = 15.21, p < .01), indicating that pain tolerance at age 14 positively predicted SBP assessed 8

years later. A similar analysis predicting 24 hr. SBP at age 22 but entering average pain at age 14 into step 2 found that average pain accounted for an extra 5.6% of the variance in SBP at age 22 (β = -.23; ΔF = 6.88, $p < .05$), while the results for maximum pain, which accounted for 4.5% of the variance in SBP at age 22, were also significant (β = -.21; ΔF = 5.46, $p < .05$).

An identical series of hierarchical multiple regression equations predicting 24 hr. DBP at age 22 yielded comparable results. Combined into step 1 of an equation predicting DBP at age 22, the control variables of BMI, and PH, and DBP measured at age 14 accounted for 4% of the variance in these values. The addition of pain tolerance in step 2 significantly improved prediction of DBP at age 22 (β = .35; ΔF = 15.62, $p < .01$), accounting for an additional 12% of the variance and indicating that tolerance for pain at age 14 also positively predicted 24 hr. DBP assessed 8 years later (Table 3). When maximum pain was entered into step 2 of the multiple regression equation predicting DBP at age 22, this measure accounted for an additional 10% of the variance (β = -.33; ΔF = 13.55, $p < .01$). The findings for average pain, which accounted for 7.8% of the variance in DBP at age 22, were also significant (β = -.28; ΔF = 9.38, $p < .01$)

Pain sensitivity and heart rate variability: Descriptive information about 24 hr heart rate, HF, LF, and LF/HF are presented in Table 1. Results of correlational analyses (Table 4) revealed a significant positive relationship between average pain at age 14 and HF at age 22 (r = .46, $p < .01$), indicating that lower levels of average pain were associated with lower levels of parasympathetic tone as assessed by spectral analysis of HRV. A similar result was obtained for

maximum pain and HF (r = .42, p < .01). While in the predicted direction, the correlation between pain tolerance and HF did not achieve statistical significance (r = -.15, n. s.). With respect to the other measures associated with risk for hypertension that were obtained at age 14, only BMI was significantly correlated with HF at age 22 (r = = -.18, p < .05), revealing a negative relationship between BMI values at age 14 and subsequent HF values. Conversely, SBP, DBP, and PH at age 14 were unrelated to HF 8 years later. However, HF was correlated with 24 hr SBP (r = -.30, p < .01) and DBP (r = -.25, p < .01) at age 22, indicating that level of parasympathetic tone was negatively associated with blood pressure. For the ratio of LF/HF, similar relationships were observed between this measure and the following variables measured at age 14; average pain (r = -.35, p < .01), maximum pain (r = -.38, p < .01), and BMI (r = .17, p < .05). The LF/HF ratio was also significantly related to 24 hr SBP (r = .23, p < .01) and DBP (r = .24, p < .01) measured at age 22, indicating that blood pressure levels were positively associated with LF/HF scores. However, none of the pain, blood pressure, or cardiovascular risk measures showed any significant correlations with LF (Table 4).

To determine whether average or maximum pain at age 14 could successfully predict HF at age 22, two hierarchical multiple regression equations were performed in which the impact of the same selected variables as in the analyses above (i.e. BMI, PH, and SBP measured at age 14) was controlled by forcing them into step 1 of the equations. The results are summarized in Table 5. In both cases, adolescent reports of pain sensitivity negatively predicted levels of

HF at age 22 (Figure 2). Similar analyses using average and maximum pain to predict LF/HF indicated that these measures positively predicted sympathovagal balance (Table 5).

Discussion

In finding a positive association between pain ratings at age 14 and blood pressure values assessed 8 years later, the present study provides evidence that individual differences in pain sensitivity may be used to predict blood pressure levels following the clinically significant increases observed during adolescence and may be associated with mechanisms involved in the development of sustained high blood pressure. Hypertension-related hypoalgesia has been variously described as a cause, consequence and correlate of blood pressure (Ghione, 1996), with some justification for each perspective. For example, Guasti et al. (1998) found that pharmacological treatment of hypertension increased sensitivity to dental pain, implying that hypoalgesia is a product of increased blood pressure. On the other hand, Ghione, Rosa, Mezzasalma, and Panattoni (1988) found no effect of successful anti-hypertensive treatment on pain sensitivity. Several studies have found that individuals deemed to be at increased risk of developing hypertension tend to show relatively less sensitivity to pain compared to those without identifiable risk factors. For example, in the original study of pain and blood pressure in our sample of boys at age 14, we found an association between increased tolerance to pain and normatively elevated blood pressure (Ditto, Séguin, Boulerice, Pihl, & Tremblay, 1998). Furthermore, such findings are typically unaffected by coping style or emotional

state (France, 1999). Unfortunately, these studies are limited by the fact that many of these "at risk" individuals will never go on to develop high blood pressure. Although there have been reports linking the magnitude of pain suppression produced by acute activation of carotid baroreceptors with the degree of blood pressure increase over several months (Brody & Rau; 1994; Elbert et al., 1994), there have not been published prospective studies relating simple pain sensitivity to hypertension in humans. Until now, the only evidence for a longitudinal relationship between pain sensitivity and blood pressure elevations came from studies using the SHR (Saavedra, 1981), and one study conducted in our laboratory using office blood pressure and a 5 year follow up (Campbell, Ditto, Séguin, Assaad, Pihl, Nagin, & Tremblay, in press). The addition of both a longer follow-up period as well as the utilization of ambulatory blood pressure to better characterize true arterial pressure provides additional support for our previous results. Clinically, this finding raises several exciting possibilities, including the possible use of pain assessment as a marker for future increases in blood pressure. Although blood pressure measured at age 14 was, unsurprisingly, a modest predictor of blood pressure at age 22 when placed into the first step of a multiple regression equation, pain sensitivity still accounted for variance above and beyond this important predictor variable.

The mechanisms linking reduced pain perception to altered autonomic nervous system activity remain to be elucidated. Nevertheless, linkages between pain perception and autonomic function are well-established in other contexts, such as the well-researched phenomenon of stress-induced analgesia

(Vaccarino & Kastin, 2000). It is possible that 14-year old pain perception was related to subsequent increases in blood pressure via a relationship with adolescent autonomic activity. As noted above, low sensitivity to pain has been associated with a tendency towards exaggerated cardiovascular reactivity in cross-sectional research (Ditto, France, & France, 1997; France & Stewart, 1995). A low sensitivity to pain may be a reflection of an early "hyperkinetic" circulation, or a product of a process that reflects both autonomic nervous system activity and pain perception. Building on McCubbin's (1991) opioid theory of stress hyperreactivity and cardiovascular risk, France and Ditto (1996) suggested that alterations in endogenous opioid activity might explain the link between ANS activity and pain.

Although this study is limited in its implications regarding hypertension by virtue of the fact that our population was normotensive, it is important to point out that the sample was drawn from a group with low socioeconomic status who, in spite of their young age, includes several participants already approaching hypertensive status. Future research will continue to track this sample's blood pressure and examine more closely potential mechanisms linking pain sensitivity and blood pressure, in particular autonomic tone.

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TABLE 1

Means, Standard Deviations and Ranges for Demographic and Cardiovascular Variables, Anxiety and Pain Ratings

	Age 14			Age 22		
	Mean	*SD*	*Range*	*Mean*	*SD*	*Range*
Systolic BP	107.43	10.62	31.67	124.87	12.11	32.50
Diastolic BP	60.22	7.10	20.33	72.18	8.56	35.67
HFHRV (log ms^2)	-	-	-	5.02	1.38	7.37
LFHRV (log ms^2)	-	-	-	4.26	1.21	5.32
LF/HFHRV (log)	-	-	-	.70	.26	.94
BMI	21.32	3.91	24	23.21	4.10	26
Negative affect (SBQ)	2.44	1.72	3.03	-	-	-
Average Pain	40.43	21.05	75.00	-	-	-
Maximum Pain	73.30	30.37	89.00	-	-	-
Tolerance (min.)	2.32	.26	2.15	-	-	-
Positive Parental History (%,*n*)	9.56, 11			16.94, 20		

TABLE 2

Correlations between measures at age 14 and 24 hr. blood pressure at age 22

	Blood Pressure at age 22	
	SBP	DBP
Measures Obtained Age 14		
Maximum Pain	-.23*	-.28**
Average Pain	-.24**	-.22*
Pain Tolerance	.35**	.33**
Systolic Blood Pressure	.20*	.21*
Diastolic Blood Pressure	.05	.16
Parental History	.11	.10
BMI	.09	.03

*$p < .05$; **$p < .01$

TABLE 3

Hierarchical multiple regression predicting systolic (SBP) and diastolic (DBP) blood pressure at age 22

Predictor variable	ΔR^2	ß	ΔF	Predictor *t*
Systolic Blood Pressure				
Step 1	.08		2.98*	
SBP (age 14)		.24		2.41**
Parental History		.09		.99
BMI		.01		.10
Step 2				
Pain Tolerance	.11	.34	15.21**	3.90**
Diastolic Blood Pressure				
Step 1	.04		1.60	
DBP (age 14)		.18		1.79
Parental History		-.04		-.42
BMI		.04		.48
Step 2	.12		15.62**	
Pain Tolerance		.35		3.95**

*$p < .05$; **$p < .01$

TABLE 4

Correlations between measures at age 14 and heart rate variability at age 22

	Measures Obtained Age 22		
	HFHRV	LFHRV	LF/HFHRV
Measures Obtained Age 14			
Maximum Pain	.42**	-.08	-.37**
Average Pain	.46**	-.01	-.36**
Pain Tolerance	-.15	.09	.11
Systolic Blood Pressure	-.15	.07	.06
Diastolic Blood Pressure	-.13	-.04	.01
Body Mass Index	-.18*	.05	.17*
Parental History	.13	-.10	-.11

*$p < .05$; **$p < .01$

TABLE 5

Hierarchical Multiple Regression Predicting High Frequency Heart Rate Variability and Low Frequency/High Frequency Heart Rate Variability at age 22 using measures obtained at age 14

Predictor variable	ΔR^2	ß	ΔF	Predictor *t*
High Frequency				
Step 1	.07		2.47	
SBP		.00		.03
BMI		-.23		-1.91
Parental History		.17		.08
Step 2				
Average Pain	.20	.48	28.02*	5.29*
Step 2				
Maximum Pain	.23	.42	4.74*	4.61*
Low Frequency/High Frequency				
Step 1	.10		4.16*	
SBP		-.05		-.50
BMI		.33		3.14*
Parental History		-1.17		.24
Step 2				
Average Pain	.12	-.35	17.19**	-4.14**
Step 2				
Maximum Pain	.15	-.39	21.16**	-4.60

*$p < .01$; **$p < .001$

Figure Caption

Figure 1. Systolic Blood Pressure (SBP) at age 22 as a function of pain tolerance at age 14.

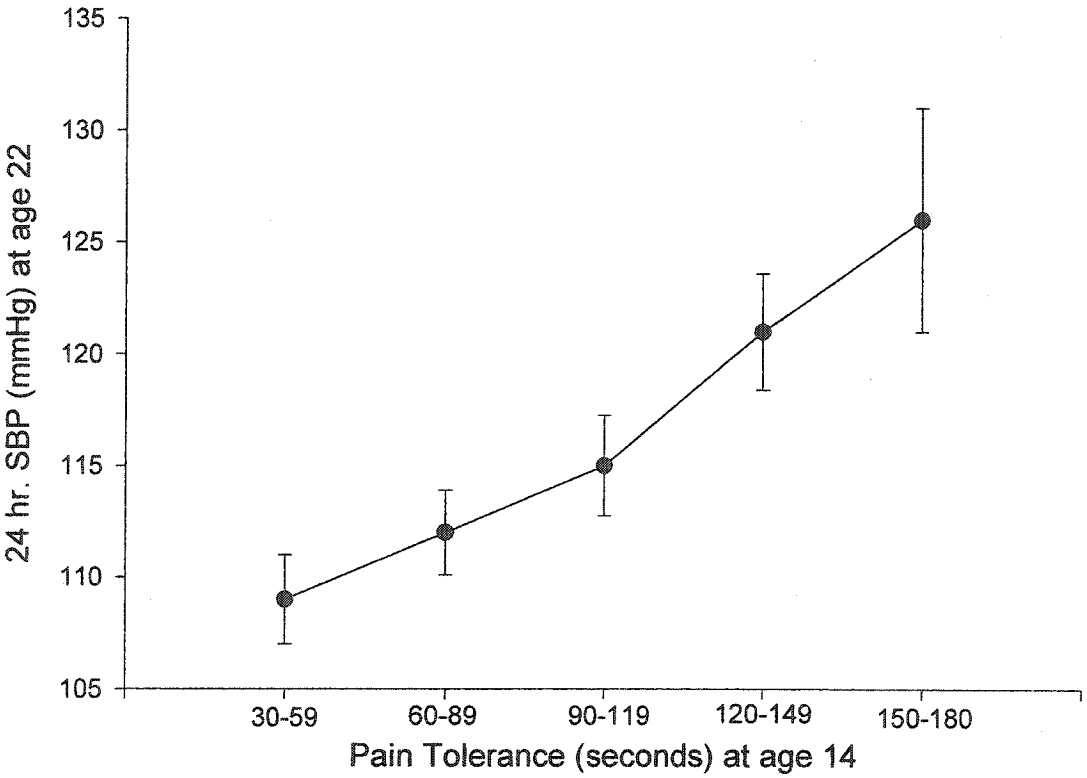
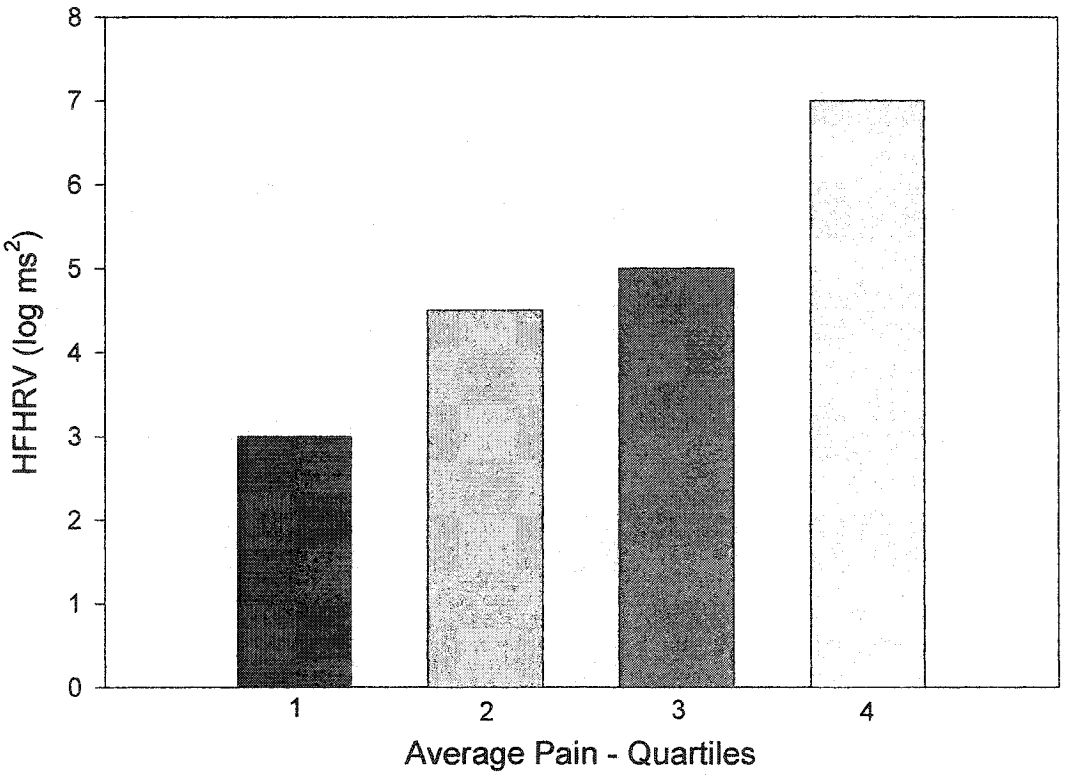

135
130
125
120
115
110
105
24 hr. SBP (mmHg) at age 22
30-59
60-89
90-119
120-149
150-180
Pain Tolerance (seconds) at age 14

Figure Caption

Figure 2. Twenty-two year-old High Frequency Heart Rate Variability (HFHRV) by Quartiles of average pain sensitivity at age 14.


8
7
6
5
4
3
2
1
0
HFHRV (log ms^2)
1
2
3
4
Average Pain - Quartiles

Preface to Study Three

The results of the ambulatory monitoring study revealed an association between pain sensitivity at age 14 and autonomic function as assessed by spectral analysis of heart rate variability at age 22. Interestingly, the increased sympathetic and reduced parasympathetic tone displayed by individuals with reduced sensitivity to pain is typical of the autonomic profile observed among a significant portion of individuals with a "hyperkinetic" hemodynamic pattern who are believed to go on to develop hypertension (Julius, 2000). In order to test the association between pain sensitivity and autonomic function more closely and to relate this to the literature indicating that reduced levels of pain are associated with increased cardiovascular responses to stress, 116 fourteen year-old boys assessed for pain sensitivity underwent an orthostatic challenge during which their autonomic responses were evaluated via spectral analysis of heart rate variability. In addition, presention of the painful stimulus prior to the orthostatic challenge was believed to be advantageous in order to address concerns that physical and psychological stressors delivered prior to painful stimulation might have an impact on subsequent reports of pain.

CARDIAC AUTONOMIC FUNCTION AND PAIN SENSITIVITY IN ADOLESCENT BOYS

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Running head: Autonomic Function and Pain

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Abstract

Cardiovascular responses to stress and pain sensitivity have been associated with each other and also with risk for hypertension. However, since most of these studies have assessed pain and cardiovascular reactivity in the same session, it remains unclear whether this association simply reflects a brief stress-induced analgesia among high reactors or a link between a general propensity to demonstrate exaggerated autonomic responses to stressors and reduced sensitivity to pain. One hundred and sixteen adolescent boys presented with a pain stimulus (mechanical finger pressure) also underwent an orthostatic challenge during which continuous measures of cardiac interbeat interval were recorded for four minutes while supine and for four minutes after standing. Cardiac autonomic tone was assessed using spectral analysis. Hierarchical regression analyses indicated that information regarding autonomic responses to postural change improved prediction of pain ratings beyond that afforded by differences in baseline autonomic tone, parental history of hypertension (PH), and body mass index (BMI). These analyses suggest associations among exaggerated cardiovascular reactivity, reduced pain sensitivity, and the pathogenesis of hypertension.

Key words: autonomic function, pain sensitivity, hypertension, risk

Cardiac Autonomic Function and Pain Sensitivity in Adolescent Boys

Several lines of research suggest that cardiovascular and pain regulatory systems overlap. For example, hypertensive animals and humans have been shown to have greater tolerance for a variety of different painful stimuli relative to their normotensive counterparts (Guasti et al., 1999; Maixner, Touw, Brody, Gebhart, & Long, 1982; Randich, & Hartunian, 1983; Sheps et al., 1992; Sitsen & de Jong, 1984). The spontaneously hypertensive rat (SHR), bred as an animal model of sustained high blood pressure, has been observed to display a reduced sensitivity to pain in research using the hot-plate (Maixner, Touw, Brody, Gebhart, & Long, 1982) and tail-flick (Saavedra, 1981) paradigms. Among hypertensive humans, hypoalgesia has been demonstrated using techniques including electrical tooth pulp stimulation (Rosa, Ghione, Panattoni, Mezzasalma, & Giuliano, 1986; Zamir & Shuber, 1980) and cutaneous thermal pain (Rau, et al., 1994; Sheps et al., 1992). Interestingly, this phenomenon, often referred to as hypertension-related hypoalgesia, also appears to extend to normotensive groups deemed to be at increased risk of developing sustained high blood pressure. Perhaps the best example of this comes from the animal literature, where reduced sensitivity to pain is evident in the SHR as early as 3 weeks of age, well before the onset of sustained high blood pressure (Saavedra, 1981). Although no directly comparable research with humans exists, hypoalgesia has been documented in a group of normotensive children who went on to develop relatively large increases in blood pressure during adolescence (Campbell, Ditto, Séguin, Assaad, Pihl, & Tremblay, in press). Furthermore, hypoalgesia has been

associated with several purported risk factors for hypertension including high normal blood pressure (Bruehl, Carlson, & McCubbin, 1992; Ditto, Séguin, Boulerice, Pihl, & Tremblay, 1998; Fillingim, & Maixner, 1996), family history of hypertension (Al'Absi, Buchanan, & Lovallo, 1996; D'Antono, Ditto, Rios, & Moskowitz, 1999; France, Adler, France, & Ditto, 1994; Stewart & France, 1996), and enhanced cardiovascular responses to stress (Ditto, France, & France, 1997; France & Stewart, 1995).

Although blood pressure related hypoalgesia and its involvement in risk for hypertension has been studied for over 20 years, the underlying mechanisms remain uncertain. While there is good evidence for the involvement of endogenous opiates from research conducted with animals (Delbarre, Casset-Senon, Delbarre, Sestillange & Christin, 1982; Saavedra, 1981; Sitsen & de Jong, 1984), results from studies examining endogenous opioids, blood pressure and pain sensitivity in humans are mixed (McCubbin and Bruehl, 1994; Schobel et al., 1998).

Several investigations have suggested that blood pressure related hypoalgesia might be a form of stress-induced analgesia (Ditto, France, & France, 1997; Dworkin, Filewich, Miller, Craigmyle, & Pickering, 1979; Guasti et al., 1995). Young individuals who go on to develop hypertension typically display a neurologically elicited "hyperkinetic" circulation associated with increased sympathetic and reduced parasympathetic nervous system activity (Folkow, 1987; Brook & Julius, 2000), which may be related to their diminished sensitivity to pain. In fact, several studies have observed relationships between

cardiovascular reactivity to stress and pain sensitivity. France and Stewart (1995) found that individuals who displayed large blood pressure responses to the cold pressor test reported less pain during a tourniquet test. Ditto, France, and France (1997) found that women with a parental history of hypertension who exhibited large blood pressure responses to a videogame reported less shock pain. However, in contrast, Caceres and Burns (1997) found that individuals who displayed large blood pressure responses to a mental arithmetic task showed a reduced pain threshold and tolerance to the cold pressor test.

With the exception of Ditto, France, and France (1997), a major problem in interpreting these results vis-à-vis the possible association between blood pressure-related autonomic nervous system reactivity and pain sensitivity is the fact that measurements of pain sensitivity and cardiovascular reactivity have been assessed during the same testing session, often during the same task. Further, although Ditto, France, and France (1997) had two days of testing, with only one involving the assessment of cardiovascular reactivity, pain stimuli were presented during both testing sessions. The designs of these studies make it difficult to tease apart the acute "state" effects of the various stimuli from the "traits" of autonomic nervous system reactivity and pain sensitivity. For example, measures of acute cardiovascular responses to stress, particularly during testing sessions involving pain, may reflect the participant's level of anxiety. While certain physiological aspects of anxiety may diminish sensitivity to pain, others (e.g. increased alertness and reporting) may increase pain or pain reports (Melzack & Wall, 1982).

The present study sought to determine whether or not a predisposition towards high autonomic nervous system responsivity was associated with a reduced sensitivity to pain by examining measures of pain sensitivity and cardiovascular responses to a classic, non-emotional stressor, i.e., postural change. Conventional measures of heart rate were supplemented with measures of heart rate variability, allowing for evaluation of the underlying autonomic mechanisms driving cardiac adjustments to postural change through spectral analysis of heart rate variability (HRV). The HRV response to orthostatic challenge is a simple noninvasive measure of cardiac autonomic modulation reflecting increases in sympathetic stimulation and decreases in parasympathetic tone in response to the demands of standing. We hypothesized that exaggerated autonomic responses to this challenge would predict reduced pain sensitivity to noxious stimulation.

Method

Participants

One hundred and sixteen 14-year-old, French speaking, Caucasian boys participated in the study. Informed consent was provided by both the boys and their parents. The participants were part of a larger study of 1, 037 participants examining pro-social behavior in men. All participants were from low-income families, lived in the inner city, attended public schools, and had parents with less than 15 years of education. Participants were selected using a community sample of the 53 schools with the lowest socioeconomic index of the largest school board in Montreal. All underwent personality assessment using the

teacher form of the Social Behavior Questionnaire (Tremblay et al., 1991). There were no significant differences between the boys who did and not participate in the present study in the prevalence of parental history of hypertension or the Social Behavior Questionnaire. None of the boys had previously been exposed to experimental pain stimuli. All were in good health, with no personal history of hypertension.

The presence or absence of hypertension among parents was operationalized as being told by one's physician that they had high blood pressure and resulted in a sample of 13 offspring of hypertensives.

Pain Assessment

Participants underwent pain assessment using a version of Forgione and Barber's (1971) strain gage pressure pain stimulator. Following a 15 minute rest period, the middle phalange of the non-dominant middle finger was placed under a plastic wedge with a 400g weight on top for 3 minutes, or until the participant requested that it be removed. A 2 kg version of this pain pressure stimulator was judged to be non-harmful by a panel of orthopedic surgeons for a 60 sec application (Bruehl et al., 1992). Participants were instructed to rate their experience of pain on a visual analog scale from 0 (no pain) to 100 (intolerable pain) on a sheet of paper with a pencil every 15 seconds as indicated by the experimenter for a maximum duration of 180 sec (3 min). The procedure was terminated for those who reached a rating of 100 before 3 minutes, and this time was recorded and used as a measure of pain tolerance. All subsequent missing

values were considered maximum pain ratings, and entered in calculations of average pain. Maximum pain was also used as a dependent measure.

Orthostatic Challenge and Spectral Analysis of Heart Rate Variability

Later the same day, participantsday underwent an orthostatic challenge. They were placed in a supine position and trained to breathe in synchrony with a metronome at a frequency of 15 breaths per minute to allow the heart rate variability associated with respiration, from which vagal tone is estimated, to be identified more precisely. During this task, continuous measures of cardiac interbeat interval were recorded using a surface EKG. After a 10-minute practice period, data was collected for four minutes in the supine position, following which the boys were asked to stand quietly for another four minutes while continuing to breath at the same frequency. Active standing usually took 3-4 seconds. The inter-beat intervals of the ECG (R wave to R wave) were digitized to within one millisecond. Editing and analysis of the interbeat interval data was done off-line using a Vagal Tone Monitor-II (Delta Biometrics). Possible artefacts were pre-screened using an editing program (VEDIT). HRV within several frequency bands was assessed. Low frequency spectral power (LF; .02 to .15 Hz), believed to reflect primarily sympathetic influences, and high frequency power (HF; .15 to .4 Hz), believed to reflect primarily respiratory vagal regulation of HR, were calculated. The ratio of low frequency to high frequency power (LF/HF) was used as an overall measure of sympatho-vagal balance.

Results

Data Analysis

In order to investigate the association of HRV during postural change and pain sensitivity, this study examined values of autonomic tone assessed by spectral analysis of HRV during each posture as well as changes in autonomic tone associated with postural change. Change scores for HRV values within the different frequency bands were calculated by subtracting mean supine from standing values. Hierarchical regression analyses were conducted to further assess the relationship between autonomic reactivity and pain sensitivity. In order to control for variables with possible associations with pain sensitivity, parental history of hypertension, body mass index (BMI), and the corresponding supine HRV mean were forced into equations predicting the various pain measures and considered as covariates.

Baseline Data

Initial correlational analyses revealed no relationships between any measure of heart rate (HR) or HRV within different frequency bands while supine and any measure of pain sensitivity. Similarly, no significant correlations were found between measures obtained while standing and pain sensitivity. Parental history of hypertension and BMI were also unrelated to pain sensitivity, HR and HRV measures. Means, standard deviations and ranges of HR and HRV indices while supine and standing are presented in Table 1.

Effects of Postural Change on Cardiac Indices

Results of matched pair t-tests comparing supine and standing values showed that for the total sample, mean HR increased upon standing from 75 to

103 beats per minute, $t(115) = 31.78$, $p < .001$. Similarly, mean LF and LF/HF variability increased upon assuming the upright posture, $t(115) = 5.16$, $p < .001$; $t(115) = 7.03$, $p < .001$, while HF variability decreased, $t(115) = 3.54$, $p < .01$. Table 1 summarizes the means and standard errors of the changes in the cardiac indices.

Autonomic Response to Postural Change and Pain Sensitivity

Significant correlations were observed between change in HF variability from supine to standing and maximum pain ($r = .31$, $p < .001$), average pain ($r = .26$, $p < .01$), and pain tolerance ($r = -.32$, $p < .001$). In addition, change in the LF/HF ratio in response to standing was correlated with maximum pain ($r = -.19$, $p < .05$) and average pain ($r = -.19$, $p < .05$), but not pain tolerance ($r = .13$, n.s.). Thus, on standing, HF decreased and LF:HF increased significantly for the sample as a whole, but these changes were significantly greater among boys who displayed less sensitivity to finger pressure pain. There was no relationship between the magnitude of change of HR or LF HRV and any of the measures of pain. Parental history of hypertension and BMI were also unrelated to changes in HRV within the various frequency bands.

The ability of the HRV responses to postural change to predict the various pain measures was analyzed using hierarchical multiple regression. The combination of control variables, i.e., parental history of hypertension, BMI and baseline HF was entered on Step 1 of a regression analysis to predict maximum pain ratings. As indicated in Table 2, these variables accounted for 4.5% of the variance in maximum pain. Change in HF was then entered into Step 2 of the

equation to determine if it improved prediction of maximum pain beyond that afforded by the variables already entered into the model. This resulted in a significant increase in R^2 (β = .29; ΔF = 9.48, p < .01), accounting for an additional 7% of the variance in maximum pain scores. As shown in Figure 1, larger decreases in the HF response to postural change were associated with lower maximum pain ratings to the finger pressure pain task. Similar results were obtained in hierarchical regression analyses using change in HF to predict average pain and pain tolerance (Table 2).

Analogous regression analyses predicting change in the various pain measures were conducted with change in LF/HF ratio as a potential predictor. The combination of control variables (BMI, PH, supine LF/HF) was entered into step 1 of an equation predicting maximum pain. As indicated in Table 3, this set of variables accounted for 3.2% of the variance in maximum pain scores. The addition of change in LF/HF ratio to step 2 of the equation predicting maximum pain explained another 3.8% of the variance (R^2 change = 3.8, p <.05), indicating that larger increases in sympathovagal balance to postural change were associated with lower maximum pain scores. The results of a hierarchical regression equation using change in LF/HF to predict average pain yielded comparable results (Table 3).

Conclusion

Hemodynamic responses to stressful laboratory stimuli may reflect an individual's emotional state, rather than a durable trait of persistent autonomic

alteration. In finding relationships between reports of pain and HRV responses to postural change, the results of the present study lend support to the notion that individuals with a general predisposition for exaggerated autonomic reactivity demonstrate a reduced sensitivity to pain. The use of orthostatic challenge to assess autonomic function in this study was deemed advantageous because it is unlikely to generate any acute anxiety among participants. While not precluding the possibility for a direct impact of stress induced analgesia on pain ratings under certain circumstances, the fact that assessment of autonomic functioning occurred following pain testing, such that the physiological effects of the orthostatic challenge had no impact on pain reports, suggests that reduced pain sensitivity displayed by individuals exhibiting exaggerated autonomic reactivity appears to be a distinct phenomenon.

The orthostatic challenge results in a shift of blood towards the lower body, and sets in motion a series of hemodynamic and autonomic adjustments. In particular, it is a task well-known to stimulate arterial baroreceptors. Baroreceptors are stretch sensitive receptors that regulate blood pressure by acting on cardiac output and peripheral resistance. Upon standing, afferent baroreceptor input to the CNS results in reflexive increases in heart rate and vascular resistance in order to compensate for the reduced blood flow towards the brain. The HRV response to postural change is a sensitive measure of alterations in cardiac autonomic balance underlying these hemodynamic adjustments, and reflects a switch from parasympathetic predominance to sympathetic control (Lombardi, Malliani, Pagani, & Cerutti, 1996). The findings of

the present study of an association between increased sympathovagal and parasympathetic reactivity to postural change and lower pain ratings coincide with the notion that pain reduced pain sensitivity is related to an increased risk for sustained high blood pressure. Specifically, several investigators have postulated that the autonomic nervous system is deeply involved in the pathogenesis of hypertension (Guzzetti et al., 1988; Guzetti et al., 1994; Liao et al., 1996) and that risk for the disorder is related to increased sympathetic activity and/or decreased parasympathetic tone (Julius, 1990; Mark, 1990). Autonomic function may influence the development and maintenance of elevated blood pressure through at least 3 mechanisms; a direct effect on the heart to increase heart rate and stroke volume, a direct effect on peripheral arterial resistance, and possibly by directly and indirectly increasing renin level and renin activity to increase blood pressure.

The findings of the present study are also consistent with current theoretical conceptualizations of hypertension related hypoalgesia highlighting the involvement of endogenous opioid activity. As noted above, there is good evidence for the involvement of endogenous opioids in animals, where hypertension related hypoalgesia has been largely eliminated following opiate blockade (Delbarre, Casset-Senon, Delbarre, Sestillange & Christin, 1982; Saavedra, 1981; Sitsen & de Jong, 1984). In humans, evidence for the involvement of endogenous opioids in the blood pressure-pain relationship is more limited. Although administration of the opioid blocker naloxone has been demonstrated to partially reduce the strength of the blood pressure-pain

relationship, these finding are mixed (McCubbin and Bruehl, 1994; Schobel et al., 1998). In a related series of studies, McCubbin and colleagues (McCubbin, Surwit, & Williams, 1985; 1988; McCubbin, Surwit, Williams, Nemeroff & McNeilly, 1989) examined the effects of naloxone on cardiovascular reactivity in normotensives. On initial testing, participants with higher than average casual blood pressures showed greater blood pressure responses to stress relative to those with below average blood pressure. However, administration of naloxone increased responses of those with lower blood pressure while having no effect on those with higher arterial pressure. The results were interpreted as reflecting a deficiency in CNS opioidergic inhibition of sympathetic nervous system activity among those at greater risk for hypertension. In an extension of McCubbin's model, France and Ditto (1996) have suggested that this attenuation of normal opioid inhibition among groups at increased risk for developing hypertension may result in increased sympathetic nervous system activity, a tendency towards increased peripheral and central release of opioid substances, and decreased sensitivity to pain. Although we did not attempt to assess opioid levels in the current study, our findings with respect to increased sympathovagal balance following postural change among individuals with reduced pain sensitivity are consistent with this model. Unlike previous research showing an association between parental history of hypertension and reduced pain sensitivity (Al'Absi, Buchanan, & Lovallo, 1996; D'Antono, Ditto, Rios, & Moskowitz, 1999; France, Adler, France, & Ditto, 1994; Stewart & France, 1996), the present study failed to find this relationship. However, this is likely related to both the small number of

offspring of hypertensives in the study as well as the young age of our participants. The prevalence of hypertension increases dramatically with age and it is probable that many of the boys' family history status will change as their parents' get older.

An obvious limitation of the present study is that it is limited to Caucasian male participants. Future research should examine whether these findings generalize to females and other ethnic groups.

In conclusion, adolescent boys who display enhanced HRV autonomic responses during postural adjustment perceive noxious stimuli as less painful than those with less reactivity. By presenting the orthostatic challenge at a non-stressful point in time, the reactivity elicited is thought to reflect an enduring characteristic rather than simply an acute reaction to the stress of the application of pain. Overall, the finding of a relationship between autonomic function and pain sensitivity could provide insight into understanding mechanisms involved in blood pressure regulation as well as the experience of pain.

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TABLE 1

Means and standard errors of supine, standing and Δ heart rate and heart rate variability indices

	Supine	Standing	Change
HR (bpm)	75.73(1.11)	103.67(1.34)	27.94(.87)
HF (log ms^2)	7.26(.10)	5.02(.13)	-2.24(.12)
LF (log ms^2)	4.47(.10)	4.98(.12)	.51(.13)
LF/HF (log)	.62(1.52E-02)	1.18(8.38E-02)	.56(7.98E-02)

TABLE 2

Hierarchical multiple regression predicting pain sensitivity measures using change in high frequency heart rate variability (HF) in response to postural change

Predictor variable	R^2 change	β	F change	Predictor t value
Maximum Pain				
Step 1	.04		1.65	
Supine HF		.13		1.37
Parental History		.07		.79
Body Mass Index		.13		1.37
Step 2	.07		9.48**	
ΔHF		.29		3.07**
Average Pain				
Step 1	.01		.38	
Supine HF		.06		.71
Parental History		.02		.28
Body Mass Index		.06		.66
Step 2	.07		8.99**	
ΔHF		.29		2.99**
Pain Tolerance				
Step 1	.03		1.17	
Supine HF		-0.01		-0.18
Parental History		-0.08		-0.86
Body Mass Index		-0.15		-1.58
Step 2	.11		13.62***	
ΔHF		-0.35		-3.69***

**$p < .01$; ***$p < .001$

TABLE 3

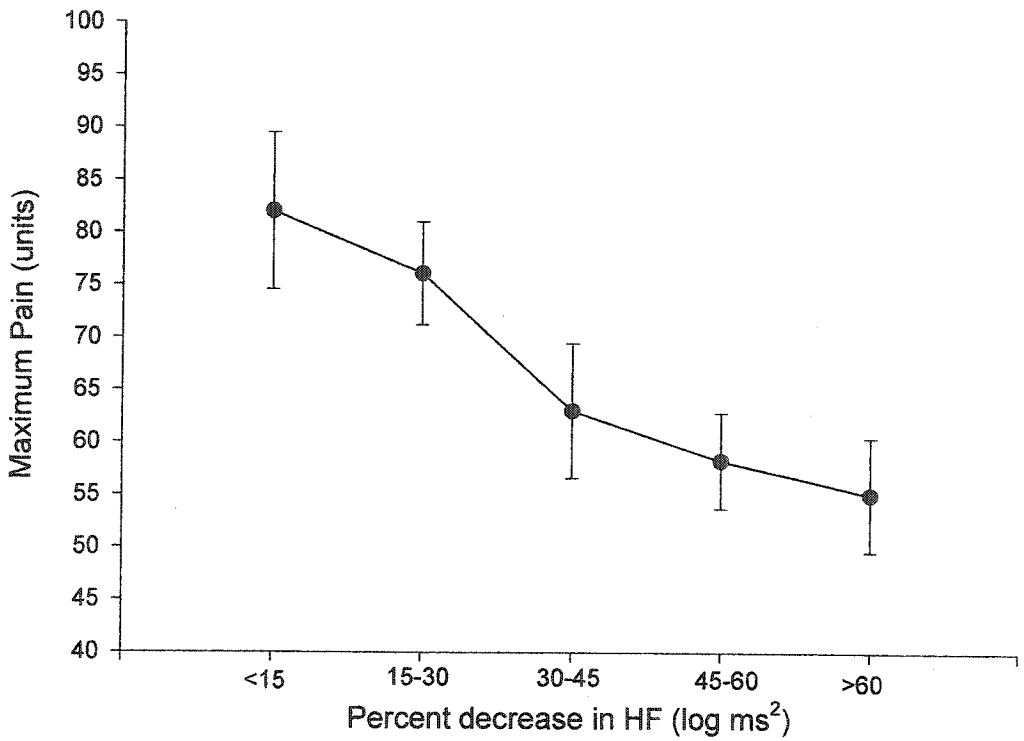
Hierarchical multiple regression predicting pain sensitivity measues using change in low frequency/high frequency heart rate variability (LF/HF) in response to postural change

Predictor variable	R^2 change	β	F change	Predictor t value
(Maximum Pain)				
Step 1	.03		1.15	
Supine HF		-0.06		-0.66
Parental History		.08		.90
Body Mass Index		.14		1.53
Step 2	.03		4.31*	
ΔHF		-0.20		-2.07*
(Average Pain)				
Step 1	.00		.32	
Supine HF		-0.05		-0.52
Parental History		.03		.36
Body Mass Index		.07		.81
Step 2	.04		4.58*	
ΔHF		-0.21		-2.14*

*$p < .05$

Figure Caption

Figure 1. Maximum pain ratings to mechanical finger pressure as a function of percent decrease in High Frequency Heart Rate Variability (HF) caused by upright posture.


100
95
90
85
80
75
70
65
60
55
50
45
40
Maximum Pain (units)
<15
15-30
30-45
45-60
>60
Percent decrease in HF (log ms^2)

Preface to Study Four

Studies One through Three demonstrated associations between reduced pain sensitivity and several factors related to the development of hypertension, including relatively large blood pressure increases over time and an autonomic profile characterized by increased sympathetic and decreased parasympathetic functioning. However, the mechanisms underlying the blood pressure-pain relationship were not directly assessed. A few investigators have suggested that blood pressure-related hypoalgesia is the product of endogenous opioid activity. Study Four investigated this possibility by applying low-frequency transcutaneous electrical nerve stimulation (TENS), a procedure believed to elicit the release of endogenous opioids, and evaluating its impact on pain-blood pressure associations.

Exaggeration of Blood Pressure-Related Hypoalgesia and Reduction of Blood Pressure with Low Frequency Transcutaneous Electrical Nerve Stimulation

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Abstract

Reduced pain perception has been observed in hypertensive individuals and normotensive individuals at risk for high blood pressure and may involve increased endogenous opioid release or receptor sensitivity. The present study examined the issue by administering two subjectively similar but physiologically different forms of the pain-reducing procedure transcutaneous electrical nerve stimulation (TENS). Men varying in resting blood pressure and parental history of hypertension participated in three testing sessions during which was presented 1) high frequency (100 HZ) TENS, 2) low frequency TENS (2 Hz) TENS, the type believed to elicit endogenous opioid activity, or 3) no TENS stimulation. Measurements of blood pressure (BP) and other physiological variables were obtained during this period. Afterwards, two pain stimuli were presented: a series of electric shocks and 5 minutes of arm ischemia . There was a significant negative association between pain and resting systolic blood pressure (SBP), and pain and parental history of hypertension in the no TENS and high frequency TENS conditions which was significantly strengthened by administration of low frequency TENS. As well, low frequency TENS produced a modest but significant acute reduction in SBP, especially among those with higher resting levels. These results provide further evidence that opioid mechanisms are involved in blood pressure-related hypoalgesia and blood pressure regulation.

Key words: hypertension, risk, transcutaneous electrical nerve stimulation (TENS), endogenous opioids, parental history, pain sensitivity.

Exaggeration of Blood Pressure-Related Hypoalgesia and Reduction of Blood Pressure with Transcutaneous Electrical Nerve Stimulation

A growing literature indicates that many hypertensive individuals experience a reduced sensitivity to pain (Ghione, Rosa, Mezzasalma, & Panattoni, 1988; Guasti, Zanotta, Petrozzino, Grimoldi, Diolisi, Garganico, Gaudio, Grandi, Bertolini, & Venco, 1999; Sheps, Bragdon, Gray, Ballenger, Usedom, & Maixner, 1992). This "blood pressure-related hypoalgesia" has a number of potentially important theoretical and clinical implications. For example, it may be involved in the phenomenon of silent cardiac ischemia (Krittayaphong & Sheps, 1996; Siegel, Cheitlin, Seeley, Black, & Hulley, 1992). It may also reflect processes involved in the development of sustained high blood pressure itself. A number of studies have found that individuals with a parental history of hypertension show a reduced sensitivity to pain (Bragdon, Light, Girdler, & Maixner, 1997; France & Stewart, 1995). Further, the inverse relationship between pain sensitivity and blood pressure appears to extend into the normotensive range, before the onset of sustained high blood pressure (Bruehl, Carlson, & McCubbin, 1992; Ditto, Seguin, Boulerice, Pihl, & Tremblay, 1998; Fillingim & Maixner, 1996).

The animal literature suggests that blood pressure related hypoalgesia is the product of endogenous opioid activity. For example, the lower sensitivity to pain of spontaneously hypertensive rats (SHR), even young still normotensive SHR rats, is often reduced by naloxone (Delbarre, Casset-Senon, Delbarre, Sestillange & Christin, 1982; Saavedra, 1981; Sitsen & de Jong, 1984).

However, little research of this nature has been done with human participants. Two studies have examined the effects of naloxone on the relationship between human blood pressure and pain, with somewhat inconclusive results. In the first of these, McCubbin and Bruehl (1994) found that although opioid blockade with naloxone diminished the inverse relationship between systolic blood pressure and pain sensitivity in individuals with high normal blood pressure (from r = -.54 to -.11), this result did not achieve statistical significance in their sample of 16 participants. Schobel and colleagues (1998) reported that, overall, the inverse correlation between pain perception and resting blood pressure in their small sample (n=21) was not significantly affected by naloxone. Although naloxone increased pain ratings in the normotensive participants, it had no effect on the borderline hypertensive group.

Several studies have examined endogenous opioid levels in blood plasma. For example, Sheps and colleagues (1992) found higher plasma beta-endorphin levels and lower pain sensitivity in hypertensives compared to normotensives. Furthermore, Guasti, Cattaneo, Daneri, Bianchi, Gaudio, Grandi, Bertolini, Restelli, & Venco (1996) found significant intercorrelations among pain sensitivity, circulating beta-endorphin and mean 24-hour diastolic blood pressure.

In a related series of studies, McCubbin and colleagues (McCubbin, Surwit & Williams, 1985; 1988; McCubbin, Surwit, Williams, Nemeroff & McNeilly, 1989) examined the effects of naloxone on blood pressure reactivity in normotensives. On initial testing, participants with higher than average casual blood pressures showed greater pressor responses to stress relative to those

with below average blood pressure. However, administration of naloxone increased responses of those with lower blood pressure while having no effect on those with higher arterial pressure. The results were interpreted as reflecting a deficiency in CNS opioidergic inhibition of sympathetic nervous system activity among those at greater risk for hypertension. France and Ditto (1996) have suggested this attenuation of normal opioid inhibition may be responsible for greater peripheral and central release of opioid substances in high risk individuals, in part as an attempt to restore homeostasis, and decreased pain perception.

Consistent with this theory are findings from Fontana et al. (1994) that normotensive individuals with a family history of hypertension displayed larger stress-induced increases in plasma levels of met-enkephalin relative to those with no family history of hypertension. The presentation of a non-painful stressor has also been found to accentuate the differences in pain sensitivity between hypertensives and normotensives (Guasti, Merlo, Verga, Cattaneo, Gaudio, Bianchi, Zanzi, Grandi, Bossi, & Venco, 1995). However, a major difficulty in interpreting many of these findings is that they are based on measurement of peripheral, plasma levels of opiates, which may not be relevant to blood pressure related hypoalgesia. For example, the lack of an effect on pain sensitivity in the SHR by opiate antagonists that do not cross the blood-brain barrier points to the importance of opioid substances within the central nervous system (Sitsen & de Jong, 1984).

In sum, while promising results have been obtained, it is clear that this is still a developing area that needs considerable work. An interesting methodological approach that has not yet been used in this area and might complement research with opiate blockers involves the pain-reducing technique of low frequency transcutaneous electrical nerve stimulation (TENS), which has a demonstrated effect on CNS opioids.

TENS involves the presentation of bursts of electrical stimulation that engage various endogenous pain control mechanisms. An extensive line of research has determined that the nature of the mechanisms which are engaged by TENS depend on certain stimulation parameters, most notably pulse frequency. Both animal and human evidence for endogenous opioid analgesia in TENS comes from studies showing naloxone antagonism of pain reduction produced by electrical stimulation at low frequencies (i.e., 1-3 HZ), which has often been compared to the effects of acupuncture or electroacupuncture (Chung, Lee, Hori, Endo, & Willis, 1983; Peets & Pomeranz, 1985; Pomeranz & Chiu, 1976; Pomeranz & Warma, 1988; Sjolund & Erikson, 1979; Willer, Roby, Boulu, & Boureau, 1982). Further, in animals, microinjection of naloxone blocks low frequency electro-acupuncture analgesia only at analgesic sites in the CNS (Bing et al., 1991; Xie, G. X., Han, J. S., & Hollt, V., 1983; Zhou, Du, Wu, Jiang, & Han, 1981). In fact, lesions of the arcuate nucleus of the hypothalmus and the periaquaductal gray (both sites of endorphins) abolish acupuncture analgesia (Takeshige & Tsuchiya, 1991; Takeshige, Zhao, Guo, 1991; Wang, Mao, & Han, 1990). Conversely, studies using high frequency (i.e., 60-100 HZ) TENS

typically do not find analgesic effects to be naloxone reversible (for a review, see Mayer & Price, 1995). The effectiveness of high-frequency TENS is generally explained using the gate control theory of pain. Specifically, high frequency TENS is thought to block impulses transmitted in small diameter fibers conveying nocioceptive information by stimulating larger diameter fibers.

Pomeranz (1998) has pointed to 17 distinct lines of experimentation which independently support the opioid hypothesis of low frequency electroacupuncture and TENS, including evidence from both the animal and human literature that endorphin levels rise in cerebral spinal fluid during low-frequency electrical stimulation (Hardebo, Ekman, & Erikson, 1989; He, Lu, Zhuang, Zhang, & Pan, 1985; Ho & Hen, 1989), that many different opioid antagonists block acupuncture analgesia (Chen, Geller, & Adler, 1996; Chen & Han, 1992), that there is cross-tolerance between acupuncture analgesia and morphine analgesia (Chen & Han, 1992; Han, Li, Tang, 1981), that a reduction in pituitary endorphins suppresses acupuncture analgesia (Takeshige, Nakamura, Asamoto, & Arai, 1992; Takeshige et al., 1993), and that acupuncture analgesia is enhanced by protecting endorphins from enzyme degredation (Cheng & Pomeranz, 1980; Chou, Tang, Yang, & Costa, 1984). To summarize, the vast majority of studies find that it is uniquely low frequency electroacupunture and TENS that produce CNS opioid release.

The present study sought to a) further the literature concerning blood pressure-related hypoalgesia, particularly in regards to the relationship between pain sensitivity and blood pressure in the normotensive range, and b) examine

the effects of this procedure that appears to stimulate endogenous opioid activity on blood pressure-related hypoalgesia. If individuals at greater risk for developing hypertension exhibit altered opioidergic inhibitory mechanisms, increasing CNS opioid release with low frequency TENS may compensate for this group's relative insensitivity and have possible implications for the prevention of sustained high blood pressure. It was predicted that normotensive individuals with a family history of hypertension and those with higher blood pressure levels would be particularly sensitive to the effects of low frequency TENS.

Methods

Participants

Forty-five healthy undergraduate men, 19 with a confirmed (via parental contact) history of hypertension in at least one parent and 26 without a parental history of hypertension, were recruited for the study. All subjects completed a health history questionnaire. Individuals who reported any serious health problems or current use of prescription medication or analgesics were excluded from consideration as participants in the study. The parental history groups did not differ significantly with regard to age (22$\pm$2.3 years) or weight (72.7 $\pm$2.8 kg). All but 4 of the subjects (2 with and 2 without a parental history of hypertension) were White.

Apparatus

A dual-channel commercially available stimulator (Tensplus Model #16-55012) with two 4.0 x 4.4 cm rubber electrodes was used to deliver low frequency (2 Hz, 250-microsecond pulse width) and high frequency (100 Hz,

110-microsecond pulse width) TENS. The electrodes were positioned on the dominant hand, with the negative one on the dorsal web between the first and second metacarpal bones and the positive one on the ulnar border of the same hand. The intensity was increased until local, rhythmic contractions of the fingers were obtained without producing pain, usually at 15-30 mA.

Mild to moderate electric shocks were delivered using a Farrell Instruments Model AV-2 Behavior Modification device. A concentric shock electrode was placed on the ventral surface of the wrist of the dominant arm just above the wristfold.

Systolic and diastolic blood pressure (SBP, DBP, in mmHg) were measured using a Critikon Dinamap 845XT automatic blood pressure monitor. The blood pressure cuff was placed on the subject's left thigh, and the resulting values corrected for distance from heart level following the manufacturer's recommendations. Casual SBP and DBP were determined by taking the mean of nine recordings, three following 20-minute rest periods on each of the three testing days. Blood pressure was also recorded at five minute intervals during the TENS periods and once each minute during the pain periods. Measurements of heart rate (HR, in bpm) were recorded continuously during the treatment and pain periods using a Grass Model 7P4 polygraph and a Delta Biometrics Vagal-Tone Monitor-II. The signal was obtained using disposable electrodes which were placed on either side of the lower rib cage and on the left hipbone. The VTM-II also yielded measurements of vagal tone (VT, in log units) derived from spectral analysis of heart rate variability. The VTM-II evaluates respiratory sinus

arrhythmia in adults by quantifying heart rate variability in the 0.12 to 0.40 Hz frequency band. Skin conductance readings (SC, in *u*S) were obtained using the polygraph and an IBM computer. Two Beckman electrodes attached to the first phalanges of the subject's non-dominant index and second fingers. The computer used Dataq CODAS software to sample skin conductance at 10 Hz.

Behavioral Measures

Repeated pain ratings were obtained using a pain "dial" attached to a potentiator and, in turn, to the polygraph and computer. Essentially an electronic version of a standard pencil-paper visual analogue scale, the meter had legends of no sensation (0), sensation (s), pain (1), moderate pain (10), and intense pain (20). Subjects were asked to rate their current level of pain throughout the pain periods by adjusting the dial. Pain was also assessed immediately following each pain period using the short-form of the McGill Pain Questionnaire (MPQ; Melzack, 1987).

Mood was measured at the end of baseline, TENS treatment, electric shock, and ischemic pain periods with seven visual analogue scales (VAS) assessing feelings of anger, anxiety, upset, irritation, happiness, depression, and guilt. Respondents made ratings by striking a 10-cm line between two labeled endpoints (e.g., very happy and not happy at all).

Several other questionnaires were administered to investigate whether pain ratings were associated with specific personality dimensions or coping styles. Anxiety and Anger were assessed using the Speilberger State-Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970) and State-Trait

Anger Inventory (Spielberger, Johnson, Russell, Crane, Jacobs, Worden, 1985), respectively. Measurements of the tendency to respond to questionnaires in a socially desirable manner were obtained with the Marlowe-Crowne Social Desirability Scale (Crowne & Marlowe, 1960).

Procedure

Participants attended three testing sessions of approximately two hours on three consecutive days. After obtaining informed consent, they were instrumented for physiological recording and sat quietly during a 20-minute resting baseline. Following the baseline period, they experienced one of three 30-minute treatment conditions: low-frequency TENS, high-frequency TENS, or no TENS. Order of presentation was counterbalanced across participants using a partial Latin-square design. During the TENS conditions, participants were requested to adjust the intensity of the TENS unit to an uncomfortable but tolerable level. In order to avoid any specific expectations concerning the two modes of stimulation, they were told only that TENS may be an effective method for treating pain. During the no TENS control condition, participants were asked to doodle casually on a pad of paper in order to approximate the level of motor movement induced by the TENS unit. Following the treatment conditions, they were presented with two painful stimuli presented in a fixed order, with a 5-minute rest period in between. First, participants received a total of 61 mild shocks (pulse width 5 msec) administered in ascending (.25-4 mA) and descending series at .25 mA increments. They rated the intensity of each shock by adjusting the dial on the pain meter. The MPQ and the VAS mood scales

were completed in the 5-minute post-pain period. The second pain stimulus was arm ischemia, based on the technique described by Maurset, Skoglund, Hustveit, Klepstad, & Oye (1991). Participants were asked to repeatedly squeeze and release a spring-loaded handgrip with their dominant hand at 30% maximum voluntary effort for 4 minutes. Immediately following the hand-grip, a blood pressure cuff placed on the dominant upper arm was inflated to 100 mm Hg above their resting systolic blood pressure for 5 minutes. Participants rated the intensity of the pain throughout the task by adjusting the dial on the pain meter and completed the MPQ and VAS mood scales immediately following cuff deflation.

Data Analysis

As noted above, casual SBP was defined as the subject's mean sitting SBP measured after the baseline resting periods, but before the TENS or no-TENS treatment periods, on three separate days with a well-validated device commonly used in clinical practice. Thus, these average values should be relatively good indices of subjects' typical daytime resting blood pressure. Similarly, baseline values for the other physiological measures were taken as the mean values of the final five minutes of the initial rest periods. The physiological measures obtained during the 30-minute pre-pain treatment periods were reduced by calculating mean values within 10-minute periods. Instead of dividing subjects into a number of semi-arbitrary groups based on casual systolic blood pressure, most analyses were conducted using SYSTAT's General Linear Modeling (GLM) program rather than conventional ANOVAs. This allowed casual

systolic blood pressure to be treated as a continuous variable. The between-subjects effects of parental history of hypertension and casual systolic blood pressure, and the within-subjects effects of treatment (no TENS, low frequency TENS, high frequency TENS) and time (10-minute period) on the pre-pain physiological measures were assessed using GLM. Preliminary analyses revealed no reliable effects of treatment order, consistent with the fact that order was counterbalanced across subjects. Thus, the analyses presented do not include order as a between subjects factor. However, its inclusion in supplementary analyses did not change the pattern of results. To assess the effects of the different types of TENS on physiological response to the pain stimuli, similar analyses were conducted except that the three levels of time were the final 10-minute treatment/rest value, the mean value during the shock period and the mean value during arm ischemia.

Finally, similar analyses were conducted on the behavioral measures obtained during (derived from the pain meter) and after (derived from the McGill Pain Questionnaire) presentation of the pain stimuli. These analyses included the between-subjects effects of parental history of hypertension and casual systolic blood pressure, and the within-subjects effects of treatment and pain stimulus (shock vs. arm ischemia).

The criterion for statistical significance used in the study was $p < .05$. To correct for possible violations of the assumption of the homogeneity of covariance, Greenhouse-Geisser corrected probability levels were used for analyses involving more than two levels of a repeated measure.

Results

Parental history groups had similar baseline DBP, HR, VT, SC, age, weight, and height, but men with a parental history of hypertension had significantly higher casual SBP. Means and standard errors of baseline measures are presented in Table 1.

Behavioral Pain Measures

To determine whether pain ratings were influenced by concerns about self-presentation, trait anxiety, or trait anger, correlations between these ratings and M-CSDS, STAI, and STAX scores were calculated. None were significant. As a result, these variables were not used as covariates in the pain analyses. There were also no significant correlations between mood VAS scores and pain reports.

Pain Dial

A pain stimulus (2) x PH (2) x SBP GLM analysis of mean pain intensity indicated with the pain meter produced a significant effect of pain stimulus, $F(1,42) = 15.053$, $p < .001$, due to the fact that ischemic pain was routinely rated as more painful than shock pain, a finding which was obtained in most ANOVAs and will not be mentioned again.

More importantly, the analysis also produced a significant main effect of parental history of hypertension, $F(1,42) = 14.643$, $p < .001$, due to lower reported pain among offspring of hypertensives, as well as a significant main effect of casual SBP, $F(1,42) = 13.008$, $p < .001$, and SBP x Pain Stimulus, $F(1,42) = 12.157$, $p = .001$, and SBP x Treatment, $F(2,84) = 3.566$, $p = .043$,

interactions. There were no significant interactions between PH and SBP. These findings can be understood using the correlations presented in Table 2. In general, baseline SBP was negatively correlated with pain. However, the SBP x Pain Stimulus interaction was due to the fact that the association between blood pressure and pain was stronger during arm ischemia than electric shock. Similarly, the SBP x Treatment interaction was due to the fact that the negative association between blood pressure and responses to both pain stimuli was stronger following treatment with low frequency TENS. As can be seen in Figure 1, which depicts the pain results when subjects were divided into groups on the basis of casual SBP, low frequency TENS significantly reduced pain compared to the control and high TENS conditions. Furthermore, this effect was more pronounced among those with higher baseline blood pressure.

Shock and arm pain thresholds were analyzed separately (i.e., not as a repeated measure) since shock pain threshold was expressed as the average value in mA where the person indicated "pain," and arm pain threshold was expressed in seconds. The PH (2) x SBP x treatment (3) analysis of shock pain thresholds revealed main effects of casual SBP, $F(1,42) = 6.183$, $p = .017$, and parental history of hypertension, $F(1,42) = 4.778$, $p = .034$, as well as SBP x treatment, $F(2,84) = 4.102$, $p = .027$, and parental history of hypertension x treatment, $F(2,84) = 4.265$, $p = .024$, interactions. Once again, there were no significant interactions between PH and SBP. Across treatment conditions, subjects with higher casual systolic blood pressure or a parental history of hypertension had higher pain thresholds. However, as can be seen in Figures 2,

these differences were more pronounced following treatment with low frequency TENS. Although analyses of pain thresholds for ischemic pain did not yield any significant results, this is likely due to the rapid onset of painful sensations during this task. All subjects reached their reported pain thresholds within 20 seconds following cuff inflation.

McGill Pain Questionnaire

The results generated by the total descriptors score of the McGill Pain Questionnaire administered after each pain stimulus were quite similar to those obtained during presentation of the pain stimuli. Most importantly, the Pain Stimulus (2) x treatment (3) x SBP x PH (2) GLM analysis yielded a significant Pain Stimulus x Treatment x Systolic Blood Pressure effect, $F(2,80) = 10.356$, $p = .001$. This interaction revealed a similar pattern to the pain dial results, indicating a particular reduction of arm pain among men with higher blood pressure following treatment with low frequency TENS. The analysis also produced a significant Pain Stimulus x Parental History interaction effect, $F(1,42) = 4.545$, $p = .039$, with no interactions between SBP and PH. Although subjects with a parental history of hypertension reported less pain on the MPQ for both pain tasks, this effect was more pronounced following ischemic arm pain.

Separate analyses of the sensory, affective, present pain inventory (PPI), and visual analogue scale (VAS) sections of the MPQ showed that only the sensory, affective, and VAS scores produced significant main effects of casual systolic blood pressure ($F(1,42) = 4.060$, $p = .05$; $F(1,42) = 5.541$, $p = .023$; and $F(1,42) = 7.022$, $p = .011$) and parental history of hypertension ($F(1,42) = 4.314$,

p = .044; F(1,42) = 11.925, p = .001; and F(1,42) = 4.774, p = .035), with no interactions between PH and SBP.

Effects of TENS on Resting Physiological Measures

The analysis of SBP during the treatment periods revealed a significant Treatment x Time x Casual SBP level interaction effect, F(4,168) = 4.664, p = .004. In the high frequency TENS condition, SBP remained stable during the 30-minute treatment period. There was a slight downward trend for participants in the no TENS condition. However, as shown in Figure 3, SBP decreased most dramatically during the periods in which low frequency TENS was administered, and this effect was most pronounced among those with somewhat elevated casual SBP. No significant effects involving treatment were observed in the analysis of DBP levels. Similarly, treatment with TENS had no effect on heart rate compared to the no TENS condition. A main effect of casual SBP on resting heart rate reflected higher heart rates among subjects with higher SBP, F(1,42) = 12.954, p = .001. No effects of treatment with TENS on vagal tone were observed. However, a main effect of condition on skin conductance was observed F(2,84) = 4.303, p = .027. As seen in figure 4, skin conductance was significantly lower in the low frequency TENS treatment condition compared to the high frequency TENS and no TENS conditions.

Effects of TENS on Physiological Reactivity

Most analyses examining of the effects of treatment with low frequency TENS on participants' physiological responses to electric shock and arm ischemia reiterated the findings on resting values. However, one interesting

effect which came out of the analysis of SC was a Condition x Time x SBP interaction, $F(4, 168) = 4.136$, $p = .017$. Separate Time x SBP analyses of each condition revealed higher SC levels during the pain stimuli among those with relatively higher SBP in both the No TENS, $F(2, 86) = 5.292$, $p = .018$, and High TENS $F(2, 86) = 7.183$, $p = .003$, treatments. As seen in Figure 5, however, pre-treatment with low frequency TENS eliminated these differences in SC levels.

Discussion

As expected, participants with relatively elevated blood pressure levels or a family history of hypertension displayed a reduced sensitivity to the painful stimuli. This finding reflects a phenomenon evident in a substantial body of research indicating that individuals with elevated blood pressure and normotensive humans at elevated risk for hypertension display lower pain sensitivity relative to controls (for reviews, see France, 1999; Ghione, 1996). More important, however, is suggestive evidence from this study that these relationships may be due to CNS endogenous opioids. Several studies have suggested that endogenous opioids mediate the relationships between blood pressure levels, risk for hypertension, and pain sensitivity, including those showing higher plasma beta-endorphin levels in hypertensives compared to normotensives (Guasti et al., 1996; Sheps et al., 1992) and correlations between circulating endogenous opioid levels and blood pressure levels (Guasti et al., 1996). Nevertheless, the strength of these relationships is often weak, and some studies have failed to obtain significant results. As mentioned above, it is possible that levels of plasma opioids play a smaller role in the blood pressure-

pain relationship than CNS opioids. Only two previous small-scale attempts have been made to manipulate central endogenous opioid mechanisms (McCubbin & Bruehl, 1994; Schobel et al., 1998), both through the use of pharmacological blockade and both with equivocal results. The present study was the first attempt to enhance levels of endogenous opioids in the CNS and record the effects on blood pressure related hypoalgesia. Endogenous opioid involvement in blood pressure related hypoalgesia is suggested by the finding that the effects of blood pressure level and parental history on pain sensitivity increased following pre-treatment with low frequency TENS.

France and Ditto (1996) have proposed that individuals at risk for hypertension may have decreased sensitivity to endogenous opioids among certain hypothalamic neurons, resulting in increased sympathetic nervous system activity, a tendency towards increased peripheral and central release of opioid substances, and decreased sensitivity to pain. Furthermore, a large body of research indicates that electrical stimulation at low frequencies results in a central release of endogenous opioids (Pomeranz & Chiu, 1976; Wang, Mao, Han, 1990; Zhou, Du, Wu, Jiang, Han, 1981). The selective effects of low frequency TENS on the relationship between pain and risk for hypertension may reflect a relatively greater release of endogenous opioid substances in the CNS among individuals at increased risk for hypertension, enhancing differences in pain sensitivity. Although some studies have observed increases in plasma beta-endorphin following low frequency TENS (Fabbri, & Fraioli,1979; Kiser, Khatami, Gatchel, Huang, Bhatia, Altshuller,1983; Malizia, Paolucci, Crescenzi), others

have not (Masala et al., 1983; Szczudlik, & Lypka, 1983), supporting the previously described notion that the analgesic effects of low frequency TENS depend on CNS opioids.

Results from the McGill Pain Questionnaire largely paralleled findings from the pain dial. Consistent with some previous research on hypertension related hypoalgesia (Fillingim, Maixner, Bunting & Silva, 1998), analyses of the various subscales revealed that while those measuring the sensory and affective components of pain produced significant effects, one of the two pain intensity measures, the PPI, failed to reach significance. Research on the different aspects of pain indicates that reduction of the emotional component of pain is most characteristic of endogenous opioid analgesia (Yang, Cai, & Wu, 1989).

It is interesting to note that the relationship between pain sensitivity and blood pressure, and pain sensitivity and family history of hypertension, was strongest for arm ischemia. This chronic pain stimulus was chosen because it has been shown to more closely model clinical pain than most other experimental stimuli (Chen & Treede, 1985; Smith, Chiang, Kitz, & Antoon, 1974). Further, some research implicates endogenous opioid substances in modulating pain during arm ischemia. For example, Schull, Kaplan, and O' Brien (1981) demonstrated that naloxone can increase pain ratings of this stimulus.

Although both sets of relationships were in the same direction and significant, the associations between pain ratings and SBP were stronger than those between pain and DBP. While research using hypertensive samples typically finds reliable associations between pain and DBP levels (e.g. Guasti et

al., 1996; Zamir & Shuber, 1980), previous research with young normotensives has sometimes failed to find this relationship. (Bruehl, Carlson, & McCubbin, 1992; McCubbin & Bruehl, 1994). It has been suggested that this may be due to a floor effect because of relatively low diastolic values typical of these normotensive groups (Bruehl, Carlson, & McCubbin, 1992).

The effects of low frequency TENS on resting autonomic functioning are also quite interesting. Perhaps most important, low frequency TENS produced a significant decrease in SC. Since the eccrine sweat glands are under sole neural control of the sympathetic nervous system, SC provides a good measure of sympathetic activity. Moreover, the transmitter used at the junction between SNS fibers and sweat glands is acetylcholine (rather that norepinephrine), resulting in measures uncontaminated by the influence of adrenal hormones. Thus, low frequency TENS appears to reduce sympathetic nervous system activity, perhaps by enhancement of CNS opioid release.

The observation of an effect of low-frequency TENS on SNS activity is not novel. Several investigators have noted greater increases in skin temperature following low frequency than high frequency TENS (Abram, Asiddao, & Reynolds, 1980; Kaada, 1982; Scudds, Helewa, & Scudds, 1995). The failure of some previous research to detect changes in autonomic function following low frequency stimulation is likely the result of variability in electrode location, intensity, and duration. In general, electrical stimulation applied to the peripheral nerves of the hand at intensities sufficient to elicit involuntary muscle contractions for a period of approximately 30 minutes seems to maximize the symatho-

inhibitory effects of low-frequency TENS (Pomeranz, 1998). These sympatho-inhibitory effects also appear to have had a beneficial effect on blood pressure. Participants receiving low frequency TENS had an average drop of 8.1 mm Hg in SBP, which is similar to changes seen in other studies (Kaada, Flatheim, & Woie, 1991; Kaada, Vik Mo, Rosland, Woie, & Opstad, 1990). It is noteworthy that the magnitude of these reductions in blood pressure was greater for those individuals with relatively higher SBP. The possibility that these participants had greater SNS activity to begin with is supported by their greater SC reactivity, which was eliminated following treatment with low frequency TENS. Surplus endogenous opioid release during low frequency stimulation may have overcome the relative opioid receptor insensitivity among those with increased risk of hypertension and reduced SNS activity to normal levels.

In the present study, high frequency TENS did not produce any significant pain reduction compared to the no TENS condition. As previously noted, high frequency TENS is thought to block transmission of impulses in afferent nerves (e.g., A-delta and C) conveying nocioceptive information, resulting in analgesia which ends shortly after the unit is disconnected (Garrison and Foreman, 1994; Hollman and Morgan, 1997). The fact that the TENS unit was not turned on during the pain stimuli may have reduced the chances of observing analgesic effects of high frequency TENS. The release of endogenous opioids as a result of low frequency TENS, however, has a prolonged analgesic effect (Sjound and Erikson, 1979).

One obvious limitation of the present study is that we did not attempt to directly assess endogenous opioid levels in our participants. Instead, we relied on a very extensive body of research indicating that low frequency electrical stimulation results in opioid release. On the other hand, as discussed above, the usual method of assessing opioid levels, through assay of plasma, may not be relevant for blood pressure related hypoalgesia. Nevertheless, our conclusions concerning opioids and blood pressure related hypoalgesia are limited by the extent to which the observed effects of low frequency TENS mimic naturally occurring opioid-blood pressure-pain relationships, making interpretation of the results tentative.

An additional limitation was the use of only male participants. We are currently planning to replicate the results using female participants, as in previous research (D'Antono, Ditto, Rios, & Moskowitz, 1999; Ditto, France, & France, 1997).

In conclusion, this study provides suggestive evidence for the involvement of CNS opioid mechanisms in the relationship between pain sensitivity and blood pressure, particularly among those at greater risk for the development of hypertension. The possible value of low frequency TENS in the treatment or prevention of hypertension also seems worth studying (Kaada, Flatheim, & Woie, 1991). Specifically, low frequency TENS or pharmacological methods for altering endogenous opioid release may have some potential influence in reducing risk for the development of sustained high blood pressure. This research area may

also have implications with regard to chronic pain disorders involving opioid dysfunction.

Future studies should further examine the relationships among blood pressure regulatory systems, endogenous opioids, and pain sensitivity. In light of the current findings, particular attention should be paid to CNS opioid activity.

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TABLE 1.

Means and Standard Errors of Characteristics of Men With (PH+, n= 19) and Without (PH-, n = 26) a Parental History of Hypertension

Variable	PH+	PH-
Age (years)	23.158 (.83)	22.923 (.94)
Weight (kg)	77 (2.1)	78 (2.3)
Height (cm)	178 (7)	177 (8)
SBP (mmHg)*	122.6 (1.1)	119.8 (1.2)
DBP (mmHg)	78.3 (1.2)	76.4 (1.4)
HR (Beats per min.)	72.6 (1.5)	68.7 (1.7)
VT (units)	6.5 (.3)	6.2 (.4)
SC (*u*S)	3.3 (.5)	3.3 (.4)

* $t = 2.313$, $p < .05$

TABLE 2

Correlations Between Casual Systolic Blood Pressure and Pain, by Treatment Condition and Pain Stimulus

	Systolic Blood Pressure (mm Hg) and Pain Reported During:
No TENS Electric Shock	-.424
Low TENS Electric Shock	-.569*
High TENS Electric Shock	-.376
No TENS Arm Ischemia	-.551*
Low TENS Arm Ischemia	-.701**
High TENS Arm Ischemia	-.543*

* $P < .01$

** $P < .001$

Figure Captions.

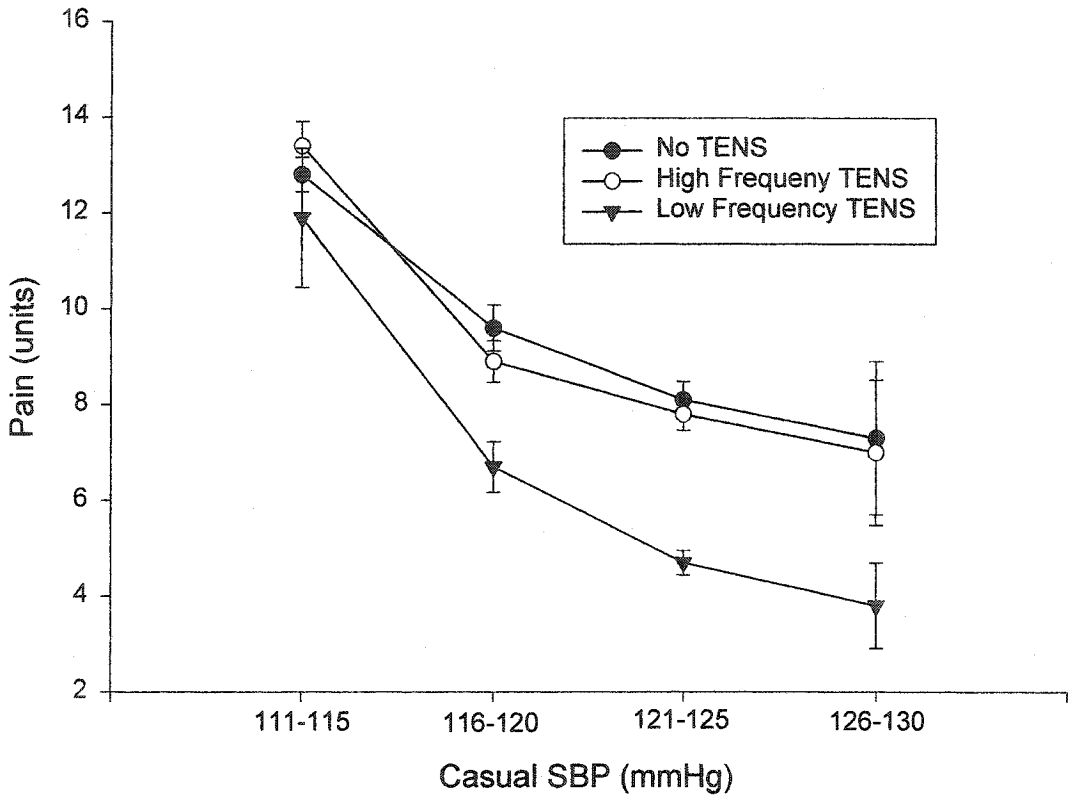
Figure 1. Mean (*SE*) pain dial ratings as a function of casual systolic blood pressure level.

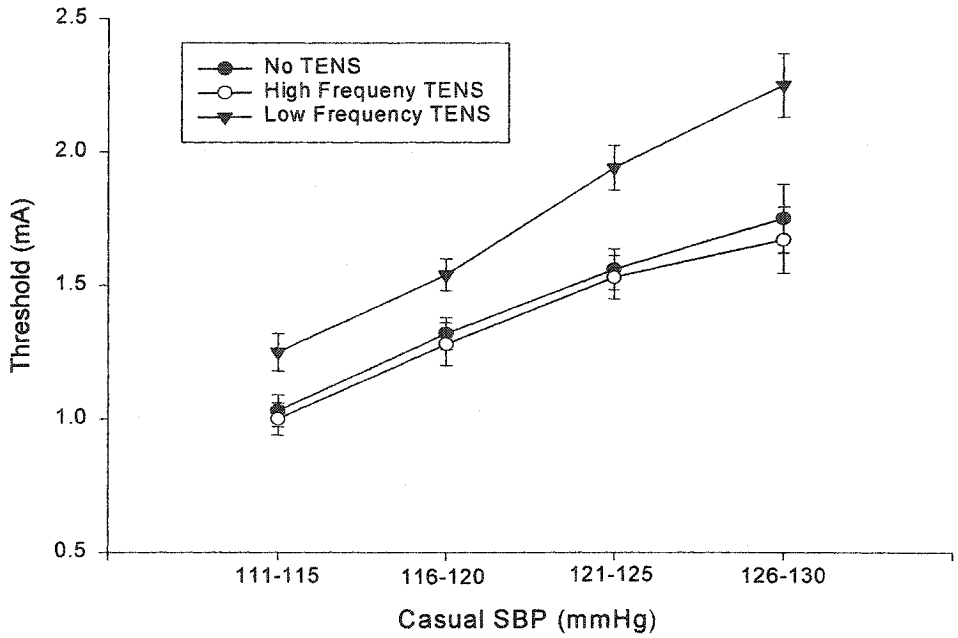
Figure 2. Mean (*SE*) intensity of electric shock required to elicit judgments of pain threshold as a function of casual systolic blood pressure level and of a positive/negative parental history of hypertension (PH+/PH-).

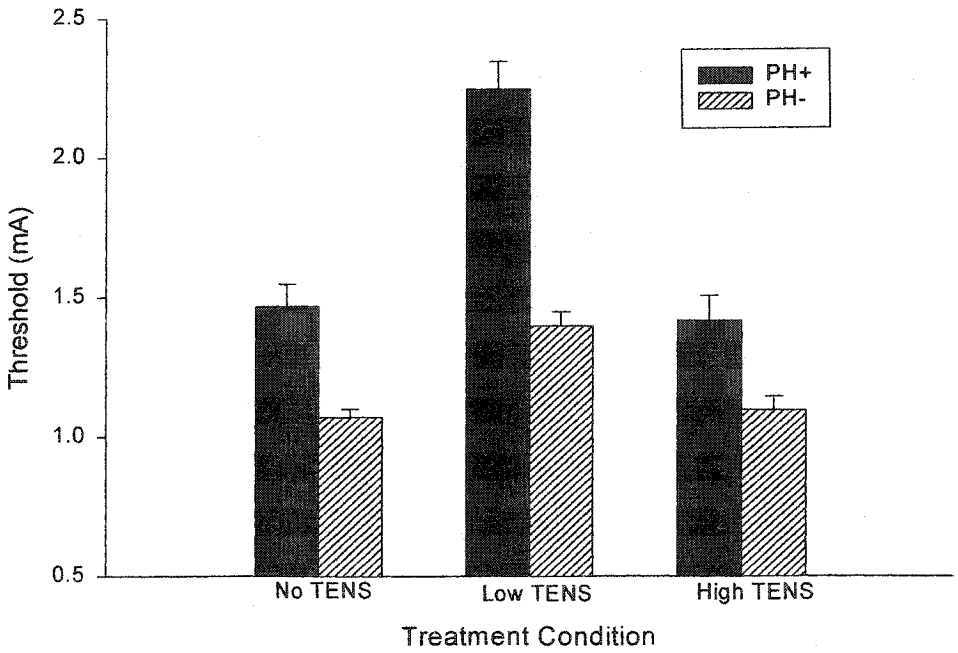
Figure 3. Mean (*SE*) systolic blood pressure levels during 30 minute treatment periods.

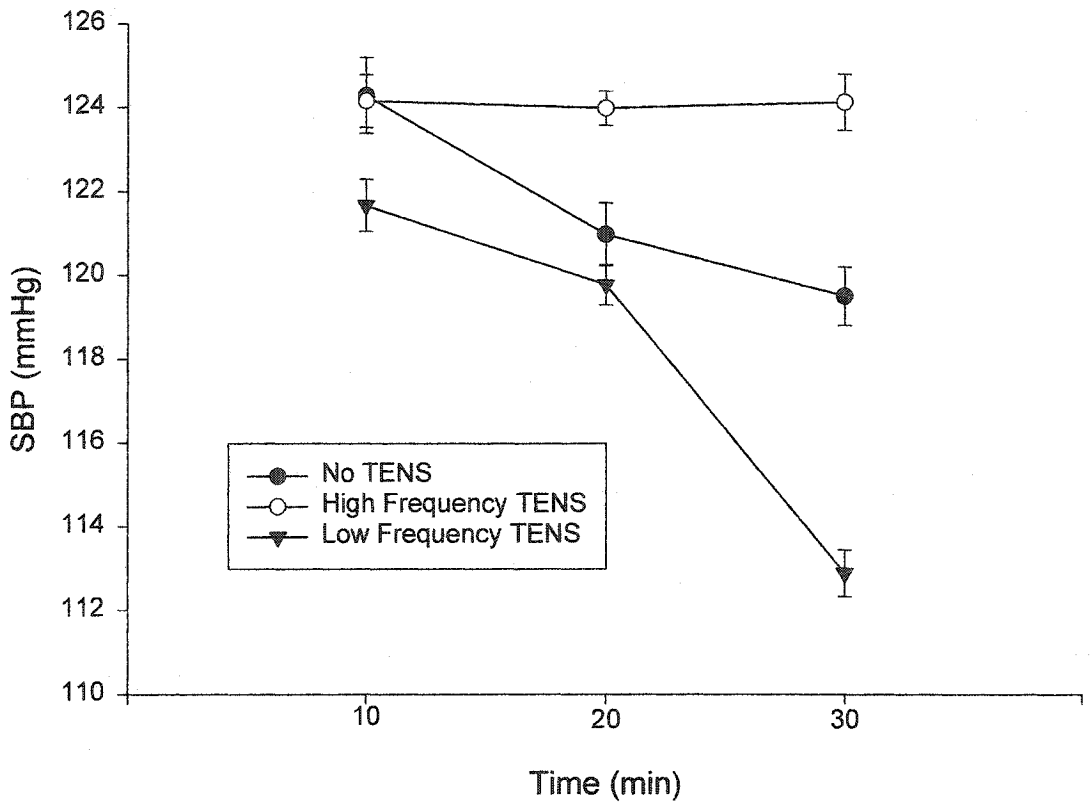
Figure 4. Mean (*SE*) skin conductance levels during treatment periods.

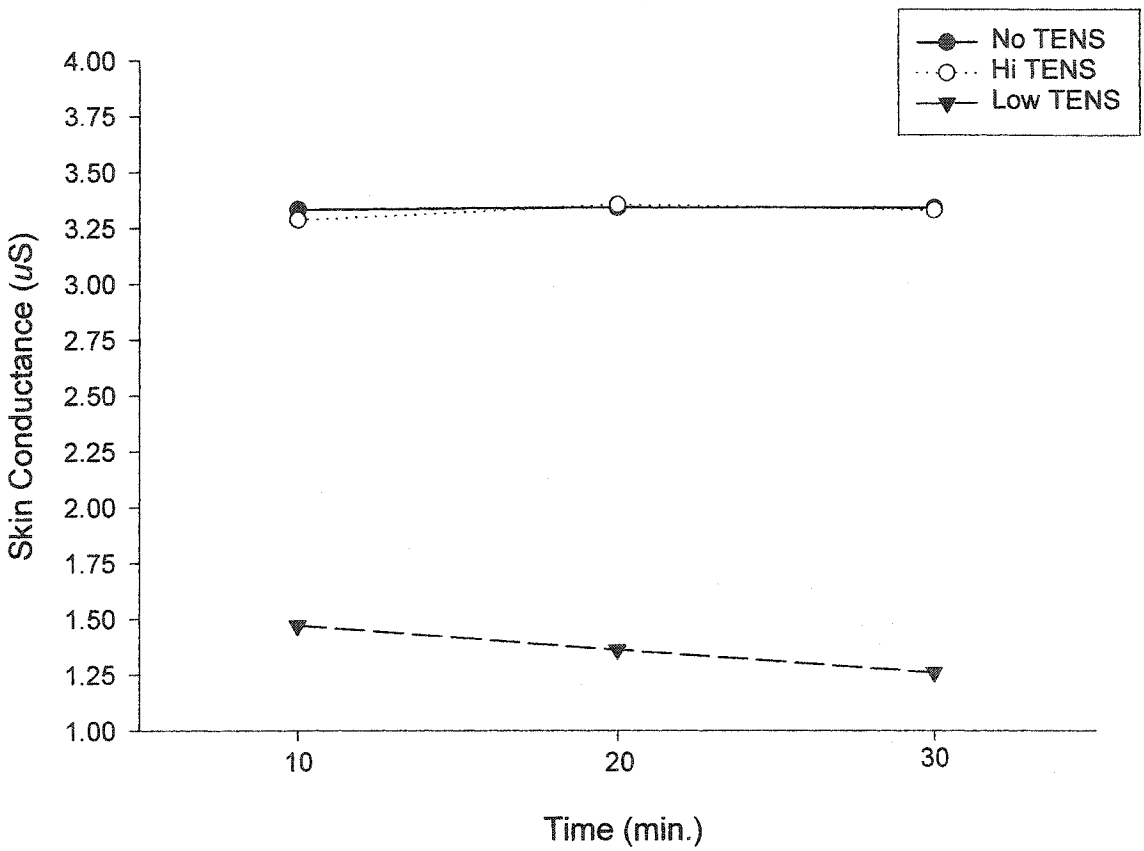
Figure 5. Mean (*SE*) skin conductance levels during presentation of painful stimuli as a function of treatment condition and a median split of casual systolic blood pressure.

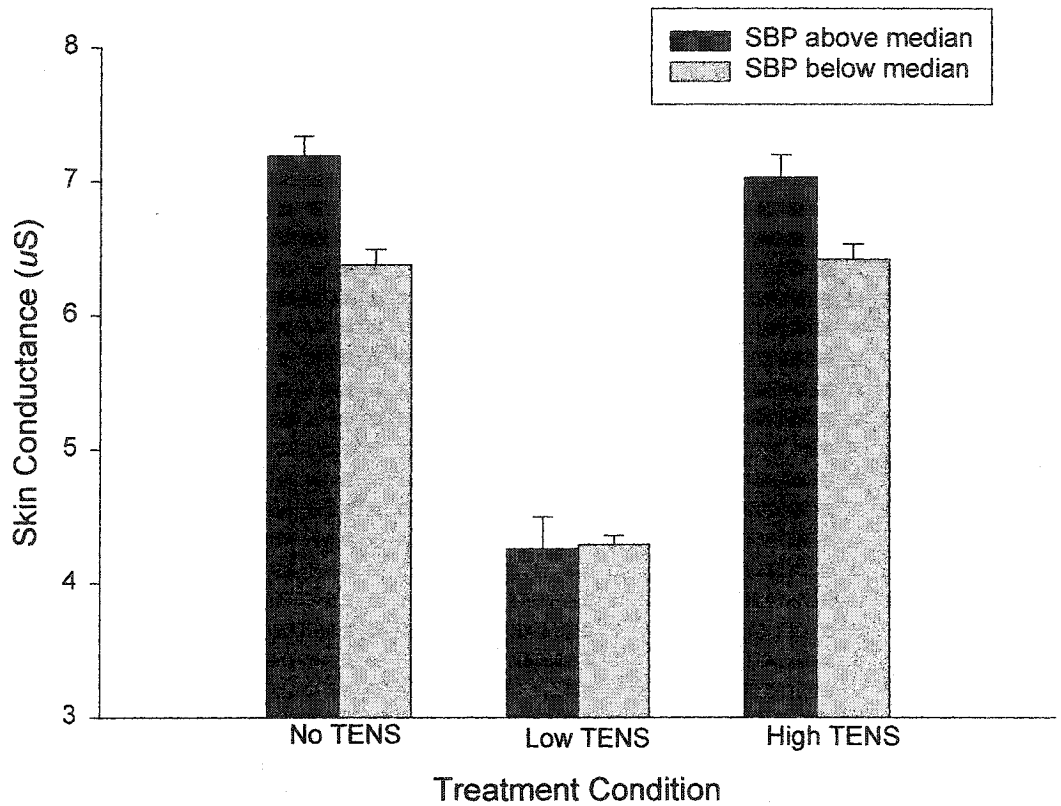

16
14
12
10
8
6
4
2
Pain (units)
No TENS
High Frequeny TENS
Low Frequency TENS
111-115
116-120
121-125
126-130
Casual SBP (mmHg)


2.5
2.0
1.5
1.0
0.5
Threshold (mA)
No TENS
High Frequeny TENS
Low Frequency TENS
111-115
116-120
121-125
126-130
Casual SBP (mmHg)


2.5
2.0
1.5
1.0
0.5
Threshold (mA)
PH+
PH-
No TENS
Low TENS
High TENS
Treatment Condition


126
124
122
120
118
116
114
112
110
SBP (mmHg)
No TENS
High Frequency TENS
Low Frequency TENS
10
20
30
Time (min)


No TENS
Hi TENS
Low TENS
4.00
3.75
3.50
3.25
3.00
2.75
2.50
2.25
2.00
1.75
1.50
1.25
1.00
Skin Conductance (uS)
10
20
30
Time (min.)


SBP above median
SBP below median
Skin Conductance (uS)
8
7
6
5
4
3
No TENS
Low TENS
High TENS
Treatment Condition

General Discussion and Conclusions

In demonstrating consistent inverse cross-sectional relationships between blood pressure and pain sensitivity in adolescents and young men, the current program of research confirms previous findings from a growing body of research linking reduced reports of pain with increased, but still normotensive, blood pressure levels. In a recent review, France (1999) cited 20 studies detecting a continuous relationship between normotensive blood pressure levels and pain sensitivity. In fact, evidence of associations between pain sensitivity and blood pressure has appeared in the scientific literature for more than 20 years (Zamir & Shuber, 1980). However, as with many facets of essential hypertension, we still lack a clear understanding as to the implications of this apparent connection between pain and cardiovascular regulatory systems for the pathophysiology, detection, and treatment of sustained high blood pressure. The current research program has extended scientific inquiry into blood pressure-pain associations by addressing several key unanswered questions relating to the temporal sequence of events in blood pressure related hypoalgesia and investigating potential mechanisms that may underlie this relationship and promote the development of hypertension.

Reports of reduced pain sensitivity among individuals deemed to be at increased risk of developing hypertension by virtue of having either a parental history of hypertension (Al'Absi, Buchanan, & Lovallo, 1996; D'Antono, Ditto, Rios, & Moskowitz, 1999; France, Adler, France, & Ditto, 1994; Stewart & France, 1996), exaggerated cardiovascular reactivity (Ditto, France, & France,

1997; France & Stewart, 1995), or high normal blood pressure (Ditto, Séguin, Boulerice, Pihl, & Tremblay, 1998; Bruehl, Carlson, & McCubbin, 1992; Fillingim, & Maixner, 1996) suggest that hypoalgesia is related to risk for hypertension rather than hypertension per se. However, unlike research with animal models of hypertension, where hypoalgesia has been observed well before the onset of sustained high blood pressure (Maixner et al., 1982; Saavedra, 1981; Wendel & Bennett, 1981), prospective research linking individual differences in pain sensitivity with future hypertension has never been reported. Studies One and Two extend the results of previous research on risk for hypertension and pain by demonstrating for the first time that in addition to the existence of cross-sectional relationships between pain sensitivity and blood pressure, individual differences in pain sensitivity are associated with blood pressure and blood pressure change over time. The results of Study Two in particular, with an eight-year follow-up conducted following a developmental period involving significant cardiovascular change and using ambulatory monitoring, the gold standard in blood pressure measurement, provide the best evidence to date that reduced pain sensitivity may precede human hypertension.

In demonstrating that hypoalgesia precedes clinically significant increases blood pressure, several exciting possibilities are suggested, including the potential for using hypoalgesia as a marker for early detection of hypertension (France, 1999). In the past, efforts aimed at reducing cardiovascular morbidity and mortality associated with high blood pressure have focused on the detection and treatment of established hypertension Joint National Committee, 1997).

Nevertheless, the prevalence of hypertension remains high, with over 20% of the world's population affected (WHO Expert Committee, 1996). Furthermore, the treatment of hypertension and its associated complications result in tremendous expenditures that comprise a significant portion of total health care resources (Joint National Committee, 1997). For these reasons, although there has been notable success in the treatment of established hypertension, emphasis must be placed on preventing its occurrence in the first place. While the etiology of essential hypertension is multi-factorial (Folkow, 1995), and there appear to be several different causes of high blood pressure among different groups in the population (Swales, 1994), the use of pain assessment as part of a comprehensive evaluation of risk for hypertension in primary prevention interventions aimed at blood pressure reduction may help to better identify individuals who are predisposed to develop clinically significant increases in blood pressure.

The use of multiple indices of risk for hypertension in the present group of studies provided a powerful and important challenge to our hypotheses. As mentioned previously, using several risk factors to predict future hypertension is far more effective in identifying actual cases than using single indicators of risk, where the number of false positives can be significant (Hunt & Williams, 1994). For example, having one first degree relative with hypertension, a commonly used measure of risk, is only a weak predictor of future hypertension, and most individuals classified as such will not go on to develop high blood pressure (Hunt, Williams, & Barlow, 1986), a finding that highlights the multi-faceted etiology of

essential hypertension. However, if family history is combined with other risk factors such as overweight status, prospective research reveals evidence of much higher relative risk (Delgado & Weder, 2000). Indeed, the findings from Studies One and Two that pain sensitivity could predict future variance in blood pressure even after the risk factors of parental history of hypertension, BMI, and current blood pressure were accounted for provides very good evidence for an association between pain and blood pressure regulatory systems as well as for the notion that reduced pain sensitivity precedes increased blood pressure.

In addition to finding links between pain sensitivity and increases in blood pressure over time, this program of research also found associations between reduced pain and a pattern of autonomic functioning that may indicate pre-hypertensive status. In particular, the results of Study 2 of reduced pain being associated with greater sympathetic and reduced parasympathetic tone coincides with the notion of a "hyperkinetic" circulatory state that characterizes individuals early on in the hypertensive process (Folklow, 1987; Brook & Julius, 2000). In many young mildly hypertensive individuals, hemodynamic functioning is very different from that found in older individuals with long-standing hypertension. Established hypertensives typically display high vascular resistance, whereas high cardiac output and heart rate is the hallmark of early hypertension (Julius, 1990; Mark, 1990). Among the mildly hypertensive, a combined blockade of sympathetic and parasympathetic cardiac receptors abolishes these elevations in cardiac output and heart rate (Julius, Pascual, & London, 1971). As a result, the hyperkinetic state is believed to be mediated by

increased sympathetic and decreased parasympathetic activity, implicating the autonomic nervous system as a key player in the etiology of hypertension. Support for the existence of a hyperkinetic state among individuals with hypoalgesia comes also from Study 3, in which exaggerated autonomic responses to postural change were found among individuals with lower pain sensitivity. Specifically, the larger increases in sympathetic tone and greater decreases in parasympathetic function among participants with reduced pain sensitivity reveal a pattern of reactivity to a classic, non-emotional challenge would be expected in a hyperkinetic profile.

The precise mechanisms underlying blood pressure related hypoalgesia remain uncertain. However, building on previous investigations using pharmacological blockade (McCubbin & Bruehl, 1994; Schobel et al., 1998), the results of study 4 suggest that endogenous opioid activity may be involved. While experimental evidence using animal models of hypertension indicates that hypertension related hypoalgesia is mainly the result of endogenous opiate activity (i.e. naloxone blocks hypoalgesia found in the spontaneously hypertensive rat: Delbarre, Casset-Senon, Delbarre, Sestillange & Christin, 1982; Saavedra, 1981; Sitsen & de Jong, 1984), research assessing this possibility with humans is still in its infancy. To this point, only two studies have attempted pharmacological blockade of opioid activity in humans and assess its impact on blood pressure related hypoalgesia, both using small samples and both with ambiguous results (McCubbin & Bruehl, 1994; Schobel et al., 1998). Study 4 provided a novel approach to this question by attempting to do the opposite of

pharmacological blocking studies, namely attempting to increase central nervous system (CNS) levels of endogenous opioids and record the impact on blood pressure – pain relationships. Although for practical reasons Study 4 did not involve direct assessment of CNS endogenous opioid levels, there exists an extensive literature on the ability of low-frequency electroacupuncture and transcutaneous electrical nerve stimulation (TENS) to elicit CNS opioid release. The main finding of this study, that administration of low frequency TENS resulted in a strengthened association between pain sensitivity and blood pressure, suggests the possibility that individuals at increased risk for hypertension exhibited a greater release of endogenous opioid substances in the CNS which enhanced differences in pain sensitivity.

The possibility that central opioid mechanisms are involved in blood pressure-related hypoalgesia is consistent with research examining altered endogenous opioid regulation of blood pressure responses to stress among individuals at increased risk for hypertension. In particular, McNeilly and Zeichner (1989) reported that participants with low-normal resting blood pressure displayed modest cardiovascular responses to stress that were considerably increased following pretreatment with naloxone, while individuals with high-normal blood pressure showed relatively large cardiovascular reactivity that was unaffected by naloxone. The results were interpreted by the authors as reflecting a diminished opioidergic inhibition of blood pressure during stress among individuals at greater risk for hypertension. Hypothesizing that the findings of this study were related to a relative insensitivity to endogenous opioids in the

hypothalmus and/or anterior pituitary in the higher risk group, McCubbin, Surwit, Williams, Nemeroff, and McNeilly (1989) examined the effects of stress and naloxone on plasma levels of the sympathoadrenomedullary catecholamines, as well as ACTH, beta-endorphin and cortisol among individuals classified as having either low-normal or high-normal blood pressure. As expected, individuals with low-normal blood pressure displayed naloxone-induced elevations in blood pressure reactivity accompanied by increased plasma epinephrine, ACTH, beta-endorphin, and cortisol. Also consistent with the McNeilly and Zechner (1989) study were findings that the high-normal blood pressure group displayed relative naloxone insensitivity with respect to blood pressure, sympathoadrenomedullary, and hypothalamic-pituitary adrenocortical reactivity. The authors proposed that opioidergic mechanisms mediating the group differences in blood pressure reactivity operate on paraventricular hypothalamic corticotropin releasing factor neurons that are thought to be important in the regulation of anterior pituitary function as well as central sympathetic outflow. Extending these hypotheses to blood pressure-related hypoalgesia, France and Ditto (1996) have suggested that individuals at increased risk for hypertension have a diminished sensitivity to endogenous opioids in certain hypothalamic regions resulting in increased sympathetic nervous system activity, increased opioid release, and a reduced sensitivity to pain.

Although not the main focus of Study 4, the finding that low frequency TENS resulted in modest reductions in casual blood pressure deserves special

attention. The reductions in blood pressure were larger among participants with higher baseline levels, suggesting the possibility that exaggerated sympathetic tone driving increased blood pressure levels among these individuals may have been reduced by the enhanced opioid release resulting from treatment with low frequency TENS. The possibility that manipulation of opioid levels may help to compensate for the autonomic dysfunction underlying the so-called "hyperkinetic" circulation among individuals with higher blood pressure levels is an exciting prospect. Overall, Study 4 provides suggestive evidence for a plausible mechanism through which opioids may be involved in blood pressure related hypoalgesia as well as blood pressure regulation.

Several possible limitations are apparent when considering the program of research. Perhaps the most obvious is that in the longitudinal studies, all of the boys, now young men, were still normotensive. However, as previously mentioned, hypertension is an arbitrary classification that has little objective use when considering cardiovascular risk associated with blood pressure levels (Pickering, 1972). The relationship between blood pressure levels and cardiovascular events is linear, and levels above the optimal 120/80 mmHg are associated with increased levels of risk. Furthermore, several of these young men are already approaching hypertensive status. This should not be too surprising considering that the sample was originally obtained using a community sample of the 53 schools with the lowest socioeconomic index of the largest school board in Montreal. It is well established that the prevalence of hypertension increases significantly among the poor (Joint National Committee,

1997). In consideration of this epidemiological evidence, it seems likely that many of these young men will display blood pressure levels classified as hypertensive within the next few years.

Overall, this program of research has helped to improve understanding of possible mechanisms involved in the development of high blood pressure and well as to provide the best evidence to date that hypoalgesia precedes hypertension in humans. Nevertheless, if a more thorough understanding of this phenomenon is to be achieved, more research effort needs to be directed at understanding the neural mechanisms involved in blood pressure and pain regulatory systems. In particular, new advances in brain imaging techniques such as functional magnetic resonance imaging and positron emission tomography may provide powerful tools to further unravel our understanding of basis of hypoalgesia and its possible impact on the pathophysiology, detection, and treatment of high blood pressure. In the meantime, the etiology of most hypertension remains essential, of unknown origin (Folkow, 1995). Considering the importance of elevated blood pressure in cardiovascular-renal disease, an understanding of its pathophysiology has become a major priority for behavioral and medical science (WHO Expert Committee, 1996). The possibility that the study of blood pressure related hypoalgesia might contribute to this endeavor remains an intriguing possibility.

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List of Appendices

McGill

	√ one
Faculty/Graduate/Honors/450 Students, New Submission	
Faculty/Graduate Renewal Request (old copy attached)	✓
Honors/450 Students Previously Approved, Current	

Department of Psychology
Stewart Biological Sciences Building

Département de psychologie
Pavillon Stewart des Sciences Biologiques

CERTIFICATION OF ETHICAL ACCEPTABILITY

FOR RESEARCH INVOLVING HUMAN SUBJECTS

A review committee consisting of:

NAME	FIELD OF RESEARCH
J. Ramsay, Chair	Quantitative-Modeling
M. Diksic	Neurochemistry (M.N.I.)
J. Gropen	Cognitive & Dev. Psychology
R. Koestner	Clinical Psychology
R. Melzack	Pain Mechanisms

have examined the application for funds in support of a project entitled:

Hypoalgesia and Risk for Hypertension

As proposed by B. Ditto (Applicant(s)) to Heart and Stroke Found. of Quebec (Granting agency)

and considers the experimental procedures, as outlined by the applicant(s), to be acceptable on ethical grounds for research involving human subjects.

Head of Department — March 17, 1998 (Date) — Dean of Faculty

Ethical review committees are to be convened by the Head of the Department in which the proposed research is to be done and is to consist of a representative appointed by the Dean, two individuals knowledgeable in the field of the proposed research but not associated with the proposed project and preferably not from the department in which the project is to be carried out, and one or more individuals who would represent a general point of view. The applicant should not serve on the Committee nor should he/she sign on behalf of the department of faculty. If the committee finds the proposed project unacceptable, the application for funds should of course be rejected.

Form 97/98-9

McGill University
Research Ethics Board II

Certificate of Ethical Acceptability of Research Involving Humans

Title of Project: High Blood Pressure and Decreased Pain Perception

Applicant's Name: Blaine Ditto

Department: Psychology

Undergraduate Student? (Y or N): N If Yes, Course #: _____

Graduate Student? (Y or N): N

Supervisor's Name (if applicable): _____

This project was approved on Sept. 12, 2000 by:

Departmental review _____ Expedited review ✓ Full review _____

The signatures below indicate that the project as described in this application is acceptable on ethical grounds.

1. Dr. Blaine Ditto, Psychology
2. Dr. Linda Davies, Social Work
3. Dr. Eleanor Stubley, Music Theory
4. Dr. Lydia White, Linguistics
5. Dr. Mark Baldwin, Psychology
6. Dr. Ann Gamsa, External
7. Departmental representative (for undergraduate projects suitable for departmental review):

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