Adolescent Pain Sensitivity Is Associated With Cardiac Autonomic Function and Blood Pressure Over 8 Years

Tavis S. Campbell, Blaine Ditto, Jean R. Séguin, Sarah Sinray, Richard E. Tremblay

Abstract—Low pain sensitivity has been reported in hypertensive subjects as well in groups deemed to be at increased risk of development of the disorder. However, it is uncertain whether individual differences in pain sensitivity are associated prospectively with increases in blood pressure. In the current study, 24-hour blood pressure and heart rate variability were recorded in 110, 22-year-old men previously assessed at age 14 years for casual blood pressure and pain sensitivity (mechanical finger pressure). Significant correlations were observed between pain tolerance in 14-year-olds and current 24-hour systolic blood pressure ($r = 0.37$, $P < 0.01$) and diastolic blood pressure ($r = 0.36$, $P < 0.01$). Hierarchical multiple regression analyses indicated that information regarding pain tolerance improved prediction of systolic and diastolic blood pressure at age 22 years beyond that afforded by differences in blood pressure, parental history of hypertension, and body mass index at age 14 years. Similar analyses revealed that average pain sensitivity at age 14 was also associated with 24-hour high-frequency heart rate variability ($r = 0.28$, $P < 0.01$) and low-frequency/high-frequency heart rate variability at age 22 ($r = -0.35$, $P < 0.01$), 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. (Hypertension. 2003;41:1228-1233.)

Key Words: adolescence ■ blood pressure ■ autonomic nervous system ■ risk factors ■ prospective studies

There is growing literature concerning 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 reported a relation between nociception and blood pressure more than 20 years ago,1-5 the relation between pain sensitivity and arterial pressure has been observed in hypertensive humans6-8 as well as in both normotensive animals and humans deemed to be at increased risk for the development of sustained high blood pressure. For example, data have been reported showing an increased tolerance to pain among humans with a parental history of hypertension,9,10 exaggerated cardiovascular reactivity,11,12 and elevated normal blood pressure.13-15

Although there are several different perspectives concerning the origins of blood pressure–related hypoalgesia, one promising explanation involves the possible dual impact of altered endogenous opioid activity on autonomic activity and pain sensitivity. McCubbin and colleagues have argued that opioid dysregulation may be involved in the increased sympathetic activity and blood pressure lability often displayed by young hypertensives, a process that might have an impact on the perception of pain.19 The current study sought to determine (1) whether measures of pain tolerance obtained from a group of adolescent boys at age 14 years were prospectively related to individual differences in ambulatory blood pressure at age 22 years and (2) whether differences in pain sensitivity at age 14 were related to autonomic activity assessed by 24-hour heart rate variability (HRV). 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 seventeen 22-year-old, Canadian-born, white, French-speaking men were retested from the original sample of 177, 14-year-old boys.13 The results of 7 participants were excluded from the analyses because of poor-quality cardiovascular recordings, resulting in a sample of 110 young men. Eleven participants had a confirmed history of hypertension in at least one parent. The participants were part of a larger longitudinal study examining psychosocial adaptation in men. At age 6 years, participants were initially enrolled by using a community sample of the 53 schools with the lowest socioeconomic index of the largest school board in Montréal.20 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-olds’ pain sensitivity and systolic (SBP) or diastolic (DBP) blood pressure. Furthermore, there

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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.21 Participants gave informed
consent, and an institutional review board approved the methods.

Pain Assessment
At age 14 years, all participants underwent pain assessment with
the use of a version of Forgione and Barber’s22 strain-gauge pressure
pain stimulator. The middle phalange of the nondominant middle
finger was placed under a plastic wedge with a 400-g weight on top
for 3 minutes or until the participant asked that it be removed. This
is a widely used 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 for a
maximum duration of 180 seconds (3 minutes). 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 years, blood pressure was assessed by taking the mean of
3 seated measurements obtained after a 15-minute rest period, using
a portable Sunbeam digital monitor (model 7621). The Sunbeam
monitor uses the oscillometric principle for determining brachial
pressure. To simplify procedures, we used a standard adult cuff for
all participants because (1) this was the appropriate size for all
participants in a pretest, (2) the Task Force on Blood Pressure
Control in Children recommended that errors in cuff selection
can be minimized by selecting the largest cuff that will fit a child’s arm,
and (3) in no case was the cuff found to be too large. This monitor
received the highest rating for accuracy in a test of 15 commercially
available models.24

At age 22 years, ambulatory blood pressure was assessed during a
typical weekday. The participants wore an Accutrack DX ABP
Monitor (Suntech Accutracker DX) for 24 hours, starting between 8
and 11 AM until the same time the following morning. The Accu-
tracker DX measures blood pressure with the auscultatory technique.
It was programmed to take 2 blood pressure measurements hourly
at random intervals: mean awake, asleep, and 24 hours. SBP and DBP
at age 22 were computed based on all valid readings obtained during
waking hours and sleep.

HRV Measurement and Estimation of
Autonomic Activity
Continuous ambulatory measures of cardiac interbeat intervals were
obtained with the use of a Polar R-R monitor (Polar Electro). The
monitor samples the ECG signal and measures the difference
between successive R-waves, storing 24 hours of data. Participants
were instrumented with the Polar monitor during the blood pressure
measurement period. Editing and time series analyses of the interbeat
intervals data were done off-line with a Vagal Tone Monitor (Delta
Biometrics) and procedures described by Porges and Bohrer.25
Low-frequency HRV (LF; 0.02 to 0.15 Hz), believed to reflect a
mixture of sympathetic and parasympathetic influences,26 and high-
frequency HRV (HF; 0.15 to 0.4 Hz), believed to reflect primarily
vagal regulation of HR,27 were calculated. The ratio of low-
frequency to high-frequency HRV (LF/HF) was used as a measure of
sympathovagal balance.28 Estimates of activity within each fre-
quency band were obtained for each 30-second window and means
calculated for the 24-hour recording period.

Data Analysis
Hierarchical multiple regression analyses were conducted to examine
the longitudinal relation between pain sensitivity at age 14 years and
blood pressure and HRV at age 22 years. To control for variables
with well-established effects on increases in blood pressure over
time, parental history of hypertension, body mass index (BMI), and

<p>| Table 1. Mean and Standard Deviation for Cardiovascular Variables, BMI, and Pain Ratings |</p>
<table>
<thead>
<tr>
<th>Variables</th>
<th>Age 14</th>
<th>Age 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>107.4±10.6</td>
<td>128.2±11.1</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>60.2±7.1</td>
<td>75.5±8.1</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>—</td>
<td>90.1±11.1</td>
</tr>
<tr>
<td>HF, log ms²</td>
<td>—</td>
<td>3.6±1.9</td>
</tr>
<tr>
<td>LF, log ms²</td>
<td>—</td>
<td>4.6±1.4</td>
</tr>
<tr>
<td>LF/HF (log)</td>
<td>—</td>
<td>1.7±1.0</td>
</tr>
<tr>
<td>BMI</td>
<td>21.2±3.6</td>
<td>23.2±4.1</td>
</tr>
<tr>
<td>Average pain</td>
<td>40.4±21.0</td>
<td>—</td>
</tr>
<tr>
<td>Maximum pain</td>
<td>73.3±30.3</td>
<td>—</td>
</tr>
<tr>
<td>Tolerance, min</td>
<td>2.3±0.26</td>
<td>—</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, Heart Rate; HF, high frequency heart rate variability; LF, low frequency heart rate variability; LF/HF, ratio of low frequency to high frequency heart rate variability; BMI, body mass index.

blood pressure at age 14 were forced into step 1 of the equations and
considered as covariates.

Results
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.29 As a result, this variable was not used as a covariate in the pain and blood pressure analyses.

Pain Sensitivity and Blood Pressure
Results of repeated-measures t tests revealed significant
increases in resting laboratory measures of SBP (t=13.21,
P<0.001) and DBP (t=12.96, P<0.001) between 14 and 22
years of age. Participants’ BP values are presented in Table 1. Initial correlational analyses yielded significant correlations between 24-hours SBP at age 22 years and pain tolerance (r=0.37, P<0.01), average pain (r=-0.24, P<0.05), and maximum pain (r=-0.25 P<0.01) measured at age 14 (Table 2). As illustrated in the Figure, the results of independent measures t tests revealed that 24-hour SBP at age 22 was associated with lower pain tolerance (t(109)=4.17, P<0.01) higher maximum pain (t(109)=2.81, P<0.01), and higher average pain (t(109)=4.46, P<0.05) measured at age 14.

In addition, 24-hour SBP at age 22 was positively associated
with SBP at age 14 (r=0.28, P<0.01) but not BMI (r=0.09, NS) or parental history of hypertension (r=-0.08, NS) at age 14. Comparable results were found with 24-hour DBP at age 22 and the following measures obtained at age 14: pain tolerance (r=0.36, P<0.01), maximum pain (r=-0.33, P<0.01), average pain (r=-0.24, P<0.05), and DBP (r=0.19, P<0.05). Twenty-four hour DBP at age 22 was unrelated to a positive parental history of hypertension (r=-0.13, NS) or to BMI (r=0.08, NS) measured at 14 years.
of age. Similar results were obtained by using awake and asleep blood pressure values (Table 2).

The combination of control variables, that is, 14-year-old SBP, BMI, and parental history of hypertension, were entered into step 1 of a multiple regression analysis to predict 24-hours SBP at age 22. As indicated in Table 3, these variables accounted for 8.1% of the variance in 24-hours 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-hours SBP at age 22 beyond that afforded by 14-year-old SBP, BMI, and parental history of hypertension. This variable accounted for an additional 14% of the variance in 24-hour SBP ($β=0.38; ΔF=17.78, P<0.01$), indicating that pain tolerance at age 14 years positively predicted SBP assessed 8 years later. A similar analysis predicting 24-hour SBP at age 22 but entering average pain at age 14 into step 2 found that average pain accounted for an extra 4.9% of the variance in 24-hour SBP at age 22 ($β=−0.22; ΔF=5.56, P<0.05$), whereas the results for maximum pain, which accounted for 5.1% of the variance in 24-hour SBP at age 22, were also significant ($β=−0.22; ΔF=5.82, P<0.05$).

An identical series of hierarchical multiple regression equations predicting 24-hour DBP at age 22 yielded comparable results. Step 1 of an equation predicting 24-hour DBP at age 22, which included the control variables of BMI, parental history of hypertension, and DBP measured at age 14, accounted for 5.3% of the variance in these values. The addition of pain tolerance in step 2 significantly improved prediction of 24-hour DBP at age 22 ($β=0.37; ΔF=16.72, P<0.01$), accounting for an additional 13% of the variance and indicating that tolerance for pain at age 14 also positively predicted 24-hour DBP assessed 8 years later (Table 3). When maximum pain was entered into step 2 of the multiple regression equation predicting 24-hour DBP at age 22, this measure accounted for an additional 10% of the variance ($β=−0.33; ΔF=12.69, P<0.01$). The findings for average pain, which accounted for 6.1% of the variance in 24-hour DBP at age 22, were also significant ($β=−0.25; ΔF=6.75, P<0.05$).

### Pain Sensitivity and Heart Rate Variability

Descriptive information about 24-hour HF, LF, and LF/HF are presented in Table 1. Results of correlational analyses

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>$ΔR^2$</th>
<th>$β$</th>
<th>$ΔF$</th>
<th>Predictor t</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SBP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 1</td>
<td>0.08</td>
<td>0.23</td>
<td>2.93*</td>
<td></td>
</tr>
<tr>
<td>SSB (age 14)</td>
<td></td>
<td></td>
<td>2.13*</td>
<td></td>
</tr>
<tr>
<td>Parental history</td>
<td>−0.08</td>
<td></td>
<td>−0.84</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.05</td>
<td></td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td>0.14</td>
<td>0.38</td>
<td>17.78**</td>
<td>4.21**</td>
</tr>
<tr>
<td>Pain tolerance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DBP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 1</td>
<td>0.05</td>
<td>0.13</td>
<td>1.86</td>
<td></td>
</tr>
<tr>
<td>DBP (age 14)</td>
<td></td>
<td></td>
<td>1.26</td>
<td></td>
</tr>
<tr>
<td>Parental history</td>
<td>−0.12</td>
<td></td>
<td>−1.21</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.08</td>
<td></td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td>0.13</td>
<td>0.37</td>
<td>16.70**</td>
<td>4.08**</td>
</tr>
<tr>
<td>Pain tolerance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$*P<0.05; **P<0.01.$
TABLE 4. Hierarchical Multiple Regression Predicting 24-Hour Heart Rate Variability at Age 22 Using Measures Obtained at Age 14

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>ΔR²</th>
<th>β</th>
<th>ΔF</th>
<th>Predictor t</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 1</td>
<td>0.06</td>
<td>2.37</td>
<td>1.13</td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average pain</td>
<td>0.08</td>
<td>0.28</td>
<td>9.52*</td>
<td>3.08*</td>
</tr>
<tr>
<td>Maximum pain</td>
<td>0.08</td>
<td>0.29</td>
<td>9.69*</td>
<td>3.11*</td>
</tr>
<tr>
<td>LF/HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 1</td>
<td>0.10</td>
<td>3.06*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average pain</td>
<td>0.12</td>
<td>−0.35</td>
<td>15.00**</td>
<td>−3.87**</td>
</tr>
<tr>
<td>Maximum pain</td>
<td>0.14</td>
<td>−0.37</td>
<td>17.70**</td>
<td>−4.20**</td>
</tr>
</tbody>
</table>

HF indicates mean 24-hour high frequency heart rate variability; LF/HF, mean 24-hour ratio of low frequency to high frequency heart rate variability. *P<0.01; **P<0.001.

(Table 2) revealed a significant positive relation between average pain at age 14 and HF at age 22 (r=.28, P<0.01), 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=.28, P<0.01). While in the predicted direction, the correlation between pain tolerance and HF did not achieve statistical significance (r=.09, NS). SBP, DBP, BMI, and parental history of hypertension at age 14 were unrelated to HF 8 years later. However, 24-hour HF was correlated with 24-hour SBP (r=−0.31, P<0.01) and DBP (r=−0.28, P<0.01) at age 22, indicating that level of parasympathetic tone was negatively associated with blood pressure. For the ratio of LF/HF, similar relations were observed between this measure and the following variables measured at age 14: average pain (r=−0.35, P<0.01), maximum pain (r=−0.39, P<0.01), and BMI (r=−0.23, P<0.05). However, none of the pain, blood pressure, or cardiovascular risk measures showed any significant correlations with LF (Table 2).

To determine whether average or maximum pain at age 14 could successfully predict 24-hour 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 (ie, BMI, parental history of hypertension, and SBP measured at age 14) were controlled by forcing them into step 1 of the equations. The results are summarized in Table 4. In both cases, adolescent reports of pain sensitivity negatively predicted levels of HF at age 22. Similar analyses using average and maximum pain to predict LF/HF indicated that these measures positively predicted sympathovagal balance (Table 4).

**Discussion**

In finding a positive association between pain ratings at age 14 and blood pressure values assessed 8 years later, the present study provides suggestive evidence that individual differences in pain sensitivity may be prospectively associated with blood pressure levels after adolescence and may also be associated with mechanisms involved in the development of increases in blood pressure. Hypertension-related hypoalgesia has been variously described as a cause, consequence, and correlate of blood pressure, with some justification for each perspective. For example, Guasti et al 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 et al found no effect of successful antihypertensive treatment on pain sensitivity. Several studies have found that individuals deemed to be at increased risk of development of hypertension tend to show relatively less sensitivity to pain compared with 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 higher blood pressure values. Furthermore, such findings are typically unaffected by coping style or emotional state. Unfortunately, these studies are limited by the fact that many of these “at risk” individuals will never go on to have 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, there have not been published prospective studies relating simple pain sensitivity to hypertension in humans. Until now, the only evidence for a longitudinal relation between pain sensitivity and blood pressure elevations came from studies using the spontaneously hypertensive rat and one study conducted in our laboratory using office blood pressure and a 5-year follow-up. In the current study, the addition of both a longer follow-up period as well as the use of ambulatory blood pressure to better characterize true arterial pressure provides additional support for our previous results. Although blood pressure measured at age 14 had, unsurprisingly, a modest association with 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 variable.

Also of potential importance is the finding that reduced pain sensitivity at age 14 was associated with decreased HF and increased LF/HF ratio at age 22. Several studies have found that cardiac autonomic function as assessed by spectral analysis of HRV is associated with hypertension and that reduced vagal tone along with an imbalance of sympathovagal function are associated prospectively with the risk of development of hypertension. Although the mechanisms linking reduced pain perception to altered autonomic nervous system activity remain to be elucidated, it is possible that 14-year-old pain perception was related to subsequent in-
creases in blood pressure through a relation with adolescent autonomic activity. Linkages between pain perception and autonomic function are well established in other contexts, such as the well-researched phenomenon of stress-induced analgesia. In addition, as noted above, low sensitivity to pain has been associated with a tendency toward exaggerated cardiovascular reactivity in cross-sectional research. 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 opioid theory of stress hyperreactivity and cardiovascular risk, France and Ditto 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, despite 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.

Perspectives

Given the evidence for a significant longitudinal association between pain sensitivity and blood pressure, it seems particularly important to understand the mechanisms underlying this relation. The finding of an association between pain sensitivity at age 14 and HRV 8 years later provides some suggestive evidence for the way in which decreased pain sensitivity confers an increased likelihood of larger elevations in blood pressure during adolescence. Although the current study did not attempt to specify with certainty the mechanisms through which increased tolerance to pain is related to increases in blood pressure, our findings with respect to high-frequency HRV fit within the framework of our current understanding of the phenomenon. It has been suggested that attenuation of inhibitory opioid input to the hypothalamus may have important implications for both pain perception and autonomic tone. Individuals at risk for hypertension may show exaggerated blood pressure reactivity as the result of increased autonomic arousal that may, in turn, elicit enhanced activation of baroreflex pain–dampening mechanisms. Activation of baroreflex arcs has been demonstrated to increase pain thresholds to various painful stimuli. Overall, the finding of associations among blood pressure, autonomic function, and pain sensitivity could provide insight into understanding mechanisms involved in blood pressure regulation.

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References


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