

Negative association between resting blood pressure and chest pain in people undergoing exercise stress testing for coronary artery disease

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ABSTRACT

Sustained and acute increases in blood pressure can dampen pain in experimental animals and humans. The most important clinical implication of this relationship may be the phenomenon of silent cardiac ischemia. High blood pressure is common in people at risk for cardiac ischemia and may reduce angina, the key symptom of life-threatening ischemia. The relationship between resting blood pressure and angina was examined in 904 people undergoing exercise stress testing for coronary artery disease. The presence or absence of ischemia was documented with single photon emission computed tomography (SPECT). Participants with ischemia had higher scores on the McGill Pain Questionnaire (MPQ) following exercise though this was moderated significantly by diastolic blood pressure (DBP), especially in women. People with higher pre-exercise resting DBP who displayed SPECT-diagnosed ischemia had MPQ scores comparable to people who did not display ischemia, independent of age, exercise duration, medication, and cardiac history. Awareness of the potential association between blood pressure and angina may provide patients with coronary artery disease and their physicians' important guidance.

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1. Introduction

A considerable literature indicates that both sustained and acute increases in blood pressure dampen pain in experimental animals and humans [4,19,23,41]. For example, McCubbin et al. [31] observed an inverse relationship between pre-experimental blood pressure and reports of pain during the cold pressor test in healthy young adults that was reversed by naltrexone. In addition to endogenous opioids, sinoaortic and cardiopulmonary baroreceptor stimulation are also probably involved in the relationship [10,13,32,34]. The impact of blood pressure on pain may have originated as part of the system that regulates pain during stressful, emergency situations [23,41].

The most important clinical implication of the negative association between blood pressure and pain may be the phenomenon of silent cardiac ischemia (SI). As unpleasant as angina may be, it often serves as a crucial warning. The absence or relative lack of pain

during cardiac ischemia may delay preventive or emergency health care. While changes in lifestyle are not unimportant, the main cause of reduced mortality due to heart attack in recent years has been increased emphasis on prompt treatment [8,35,40]. Unfortunately, the higher blood pressure common among many people at risk for a heart attack may dampen pain associated with cardiac ischemia.

Several studies have examined this idea in the controlled context of exercise stress testing [2,12,15,25,28]. In an early chart review study of individuals with positive tests, Krittayaphong and Sheps [28] found that resting blood pressure was significantly higher among those who did not experience pain (silent ischemia) compared to those who experienced pain. More recently, we found that peak exercise SBP was significantly lower in a group of patients who reported pain while experiencing ischemia [2]. Unfortunately, most of the research in this area has been retrospective in nature. That is, archival data were used to examine relationships among exercise, blood pressure, and chest pain. One of the main goals of the Mechanisms and Outcome of Silent Myocardial Ischemia (MOSMI) study was to examine these associations prospectively. Another limitation of previous research, related to the retrospective nature of the studies, has been a relative lack of psy-

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chological information about participants. The negative association between blood pressure and pain due to cardiac ischemia does not appear to be mediated by medical variables such as medication use or disease severity, but the involvement of several psychological confounds has not been ruled out. This is particularly important given the recent emphasis on depression in cardiac patients [22,29]. Participants in the present study completed a lengthy questionnaire assessing variables such as depression, anxiety, and hypochondriasis. Finally, the present study addressed several medical limitations of previous studies such as the inclusion of only people with serious heart disease (limiting the range of angina) and limited documentation of ischemia during exercise testing. With a few exceptions (discussed below), consecutive referrals for the assessment of cardiac ischemia using a single photon emission computed tomography (SPECT) exercise testing were recruited to study relationships among the presence or absence of cardiac ischemia, chest pain, and blood pressure.

2. Methods

2.1. Participants

Participants were individuals who had been referred to the exercise stress testing service of the Institut de Cardiologie de Montréal for assessment of possible coronary ischemia. Nine hundred and four volunteers (624 men, 280 women) who met inclusion criteria participated. Potential participants had to be adults over 18 years old, able to speak English or French, not suffering any form of chronic pain other than angina or having used analgesic medication in the last 7 days, and not suffering from any other serious illness such as cancer or COPD. Table 1 presents a number of characteristics of study participants. Background information was obtained from both a medical interview and patient charts.

2.2. Apparatus and procedure

Participants were recruited as they awaited their exercise stress tests. The study was integrated in the typical diagnostic procedure. Participants were asked to provide separate 0 (no)–100 (maximum) ratings of chest pain intensity and pain unpleasantness immediately following exercise. The short form of the McGill Pain Questionnaire [33] was administered as well as the Beck Depression Inventory [3], Spielberger State and Trait Anxiety Scales [38], the Whiteley Hypochondriasis Scale [36].

To assess coronary ischemia, the radioactive tracer Tc-99 m-technetium is injected at peak exercise during the standard Bruce

treadmill protocol. Afterwards, 360° images revealing coronary blood flow are obtained with SPECT. Details of SPECT equipment and exercise procedures can be found in Bacon et al. [2]. Images of blood flow in the coronary arteries following exercise are compared to images obtained on a non-exercise day and scored for the presence of significant reversible ischemia in at least one major coronary artery using standard nuclear cardiology procedures, i.e., the stress–rest differential score [39].

Systolic and diastolic blood pressure (SBP, DBP) were assessed using a manual sphygmomanometer (Welch Allyn Tycos-767 series, Skaneateles Falls, NY, USA) before, during, and after exercise. Given the fast moving nature of the Bruce protocol it is standard clinical procedure to measure blood pressure only once at each point in time. Unfortunately, this limits the reliability of the values somewhat though this may have been offset by the fact that blood pressure was measured by an experienced hospital technician using the gold standard auscultatory technique. For safety and diagnostic purposes, 12-lead electrocardiograms were also obtained allowing measures of exercise-related heart rate and rate pressure product to be calculated. The present report will focus on the relationships between pre-exercise resting blood pressure and exercise-induced chest pain. A subsequent paper will discuss the interactions between exercise-related cardiovascular adjustments and pain.

2.3. Data analysis

The primary analyses were 2 sex (male/female) \times 2 SPECT-diagnosed ischemia (present/absent) \times resting blood pressure (treated as a continuous variable) general linear models (GLMs). Sex was included as a factor given possible sex differences in angina and the moderation of the effects of blood pressure by sex [11]. Two sets of five GLMs were conducted, one using systolic blood pressure as the independent variable and the other using diastolic blood pressure. The five primary dependent variables were the post-exercise ratings of chest pain intensity and unpleasantness, the total MPQ score and MPQ sensory and affective subscales. Patient age, exercise duration, use of antihypertensive or other cardiovascular medications, prior cardiac history (e.g., previous myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention), and the presence or absence of diabetes were included as covariates in all analyses.

3. Results

As can be seen from Table 1, while testing was not conducted in an emergency setting, the sample included a large number of people with significant coronary histories. Thirty-five percent displayed clear evidence of coronary ischemia during exercise (SPECT diagnosed ischemia).

3.1. Systolic blood pressure

There were no significant effects in the analyses involving SBP.

3.2. Diastolic blood pressure

In contrast to SBP, analyses using DBP revealed several significant associations with chest pain. The ischemia \times DBP interaction was significant in the analysis of total MPQ score, $F(1775) = 5.01$, $p = .025$. As can be seen in Fig. 1 which for purposes of illustration divides participants on the basis of the median, while people with exercise-related coronary ischemia reported significantly more chest pain than people without ischemia, those with higher DBP were less affected. Among people with ischemia, the partial correlation (adjusting for covariates) between DBP and total MPQ score

Table 1
Demographic and medical characteristics of the 904 participants (% or mean \pm SD).

Sex (% female)	31
Age (years)	60.3 (9.9)
Education (years)	13.6 (4.4)
Smoker (% current or previous)	68
Body mass index (kg/m ²)	27.6 (4.4)
Diabetes (%)	15
Hypertensive (%)	61
Antihypertensive medication (%)	52
Previous MI (%)	22
Previous CABG (%)	14
Previous PCI (%)	25
Exercise duration (s)	461.8 (106.2)
Resting SBP (mmHg)	133.3 (17.7)
Resting DBP (mmHg)	81.1 (10.7)
Resting HR (bpm)	71.7 (13.4)
Peak exercise SBP (mmHg)	165.9 (26.1)
Peak exercise DBP (mmHg)	83.9 (10.9)
Peak exercise HR (bpm)	133.1 (22.8)

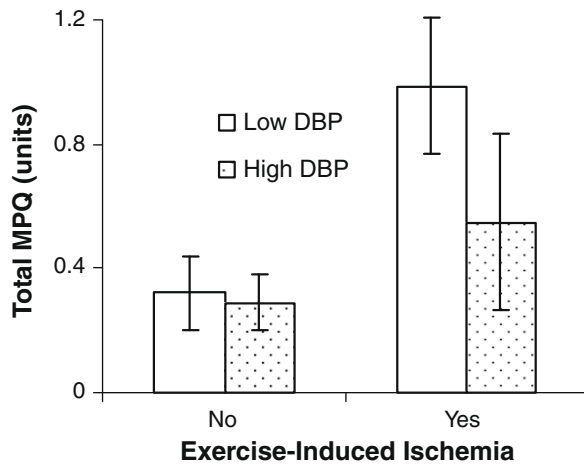


Fig. 1. McGill Pain Questionnaire scores in relation to exercise-induced ischemia and pre-exercise blood pressure (mean \pm SE).

was, $r = -.10$, $p = .049$. Though the three-way DBP \times ischemia \times sex interaction was not significant, this association was much stronger in women with ischemia, $r = -.42$, $p = .023$. This was mainly due to an impact on the affective dimension of pain. There were no significant effects involving blood pressure in the analysis of the sensory subscale, but the sex \times ischemia \times DBP interaction was significant in the analysis of the affective subscale, $F(1775) = 12.16$, $p = .001$ (Fig. 2). Among women with ischemia, the correlation between DBP and affective score was, $r = -.50$, $p = .008$. A similar interaction was obtained in the GLM of the rating of chest pain unpleasantness, $F(1775) = 9.56$, $p = .002$. Among women with ischemia, the correlation with DBP was, $r = -.46$, $p = .014$.

Comparable analyses of Beck Depression Inventory, state and trait anxiety, and hypochondriasis scores revealed no significant effects involving blood pressure. Thus, the previous effects remained significant when these variables were included as covariates.

3.3. Clinical diagnosis and family history of high blood pressure

Although Falcone et al. [15] found that people with diagnosed hypertension were significantly less likely to report exercise-related chest pain, supplementary analyses examining relationships between having a clinical diagnosis of hypertension and pain revealed no significant associations. However, the results of 2 sex

(male/female) \times 2 SPECT-diagnosed ischemia (present/absent) \times 2 family history of high blood pressure (the presence or absence of a first or second degree relative with diagnosed hypertension) analyses of covariance yielded interesting findings consistent with previous research. Both the main effects of ischemia, $F(1777) = 11.36$, $p = .001$, and family history, $F(1777) = 3.96$, $p = .047$, were significant in the ANOVA of MPQ affective score. People with a family history of hypertension had lower scores than people without ($M = 0.11$ vs. 0.24). As well, the ANOVA of post-exercise rating of pain unpleasantness produced a significant sex \times ischemia \times family history interaction, $F(1777) = 8.99$, $p = .003$. As can be seen in Fig. 3, women with ischemia and no family history of hypertension reported considerably more pain than all other groups, particularly women with ischemia and a positive family history. This was not simply a reflection of current blood pressure levels. The addition of current resting SBP, DBP, and hypertensive status as covariates did not eliminate the effect, $F(1772) = 9.28$, $p = .002$.

4. Discussion

People with higher resting diastolic blood pressure reported less chest pain during exercise-related coronary ischemia relative to those with lower DBP, independent of other aspects of their medical condition. This could not be explained by psychological characteristics such as the level of depression or propensity to report symptoms. The fact that associations were observed between exercise-related chest pain and resting DBP further supports the idea of a specific effect of blood pressure on chest pain. That is, while magnitude of exercise-related change in blood pressure may have an important influence on pain (e.g., mediated by baroreceptor stimulation), blood pressure response to exercise is a much more complex variable. With the exception of Krittayaphong and Shep's [25] retrospective study, it is interesting that other previous studies of relationships between blood pressure and exercise-related chest pain have found associations between exercise-related but not resting blood pressure and pain [2,9,22]. Although these may be legitimate, it is more difficult to rule out alternative explanations in these cases. For example, while they controlled for exercise duration, it is possible that other variables related to participant fitness might have led to relations between vigorous behavioral and cardiovascular responses to exercise and low pain. In the present case, there are no clear alternative psychological or medical explanations for the associations between pre-exercise resting DBP and exercise-related chest pain in this group at risk for heart disease.

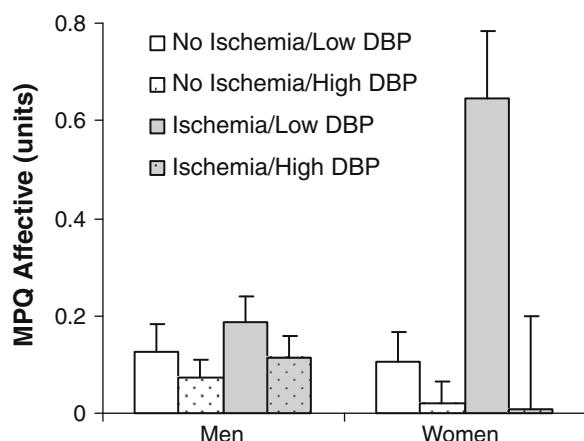


Fig. 2. McGill Pain Questionnaire affective subscale scores in relation to ischemia, sex, and pre-exercise blood pressure (mean \pm SE).

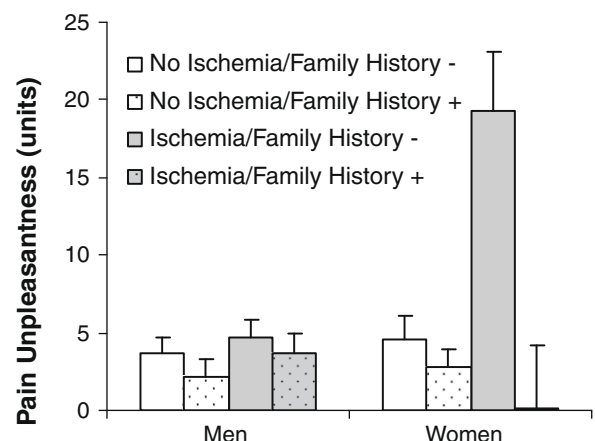


Fig. 3. Chest pain unpleasantness ratings in relation to ischemia, sex, and family history of high blood pressure (mean \pm SE).

As far as the mechanisms of the apparent effect of DBP on chest pain, the present results provide few clues. It is interesting to note that several studies have found that people with silent ischemia are often less sensitive to *non-cardiac* pain such as electrical stimulation of dental pulp [14,16,24]. It is also interesting that the present findings are similar to others in that blood pressure seems to have a greater impact on affective than sensory measures of pain [10,17]. Further, in our previous study of the effects of naltrexone on blood pressure-related analgesia [30], opioid blockade had a greater impact on analgesia related to diastolic than systolic blood pressure. DBP is arterial pressure during the resting phase of the heart and therefore more closely related to vascular constriction than SBP which, in turn, is more closely related to cardiac and sino-aortic baroreceptor activity than DBP. Thus, there is a mild suggestion of a possible association between chronic vasoconstriction, opioid activity, and reduced pain.

The notion of lower pain being a relatively stable characteristic of these individuals is consistent with the findings of the present and other studies indicating reduced pain among people with a family history of high blood pressure, especially the affective dimension of pain [1,7,18,19,21]. For example, similar to Fig. 3, France et al. [18] found that female blood donors with a parental history of hypertension reported significantly less venipuncture pain than women without a parental history. Also similar to the present study, male donors generally reported much less pain, making it difficult to discern the effects of blood pressure. These trends may be manifest early in life. In a longitudinal study of teenage boys, Campbell et al. [6] found that pain reported during mechanical finger pressure at age 19 was strongly correlated with response to the same task at age 14 and that there was a continuing negative association between blood pressure and pain across this age span. An intriguing recent study observed an even earlier association between pain and blood pressure regulation. Neonates whose mothers had a family history of hypertension had shorter crying times following an injection than infants whose mothers had no history of hypertension [21]. Though perhaps surprising, this is consistent with findings from young spontaneously hypertensive rats who display a reduced sensitivity to nociceptive stimuli at a very early age [37].

Regardless of the mechanisms, a number of studies have observed negative relationships between blood pressure and different forms of clinical pain. As noted before, several studies have noted a possible link between blood pressure and exercise-induced silent cardiac ischemia [2,12,15,25,28]. There is also preliminary evidence suggesting that this relationship generalizes to daily life, that is, a negative association between blood pressure and self-reported daily angina [12,15]. In a diary study, D'Antono et al. [9] found that women at risk for hypertension due to a family history of the disorder and normotensives reported fewer daily aches and pains, but not other symptoms, across a month that included one menstrual cycle. In a much larger population study, Hagen et al. found inverse relationships between blood pressure and risk of headache [26] and musculoskeletal pain [27]. Several studies have observed relationships between risk for hypertension or blood pressure and pain induced by medical procedures. France et al. [18] noted a negative relationship between blood donation-related pain and risk for hypertension in women. France and Katz [20] found lower post-surgical pain in men with higher pre-surgical blood pressure. Thus, people with higher blood pressure tend to experience less pain in variety of situations and it is reasonable to predict this may dampen angina.

That said, there are several important limitations of the study. While blood pressure was measured carefully, it was done only once. Perhaps more important, the pain produced by exercise was generally modest, even in people with diagnosed ischemia. This is understandable in that exercise was intended to elicit only

brief, safe ischemia for diagnostic purposes, and ischemia may have been quite regionalized. As a result, many people with SPECT-diagnosed ischemia did not report pain. The impact on the generalizability and clinical significance of the findings is unclear. On the one hand, it may be impressive that an effect of blood pressure was observed even in the context of mild angina. On the other hand, it is important to note that the absence of pain should not be overinterpreted as suggesting silent ischemia. The potential importance of the results is probably limited to people who have clear coronary artery disease and are at risk for a major event such as a heart attack. For these people, it may be useful to be aware of the possible pain dampening effects of high blood pressure, which is common in this population, and that even minor angina may be associated with clinically significant ischemia.

Other questions include the fact that while a family history of clinical hypertension was associated with chest pain, a personal diagnosis of hypertension was not. This may be due to the imperfect association between actual blood pressure and being diagnosed with hypertension, which is related to differential physician practices. Perhaps more important, virtually all (84%) of participants with a clinical diagnosis of hypertension had been prescribed some antihypertensive medication, possibly obscuring relationships between personal diagnostic category and pain. Further research to clarify these issues is required. Another slightly puzzling feature is the stronger association between DBP and pain than SBP and pain. In general, the reverse is the case in the experimental pain literature [4,10,31] though not always [30]. It is possible that there is something about the coronary artery disease process (e.g., arterial changes, medication use) that influences relations between blood pressure and pain. There is precedent for this idea in that the development of a chronic pain disorder has been found to affect the relationship between blood pressure and pain [5].

In sum, while further research is required, awareness of the potential association between blood pressure and angina may provide patients with coronary artery disease and their physicians' important guidance.

5. Summary

Higher resting diastolic blood pressure may impair the detection of angina in people with clinically significant coronary ischemia, as determined by exercise stress testing.

6. Conflict of interest

The authors have no financial or other relationships to report involving potential conflict of interest.

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