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The Relationship Between BP and Pain: The Nord-Trøndelag Health Survey

Chronic pain conditions, including headache, constitute large public health problems in most societies, but relatively little is known about their origins. During the last three decades, scientific evidence has accumulated about a relationship between pain and blood pressure (BP), showing that increased BP is related to lower pain sensitivity (so-called hypertension-associated hypalgesia). Most of this evidence stems from experimental studies on animals, in which the effect of BP manipulations on pain behaviour has been investigated, but there are also studies on humans where pain sensitivity has been related to BP levels.

HUNT studies

Relatively little has been known about the relevance of this phenomenon for the most prevalent pain conditions, but in the Nord-Trøndelag Health Survey (the Norwegian acronym is HUNT), where the whole population above 20 years of age in the Nord-Trøndelag county in Middle Norway was invited to participate (approximately 92,000), it has been possible to study the relation between BP and pain on a population level. Three HUNT surveys have been performed till now, in 1984-86, 1995-97, and 2006-08 (HUNT 1, 2 and 3), and the two last surveys in particular included a wide range of health-related questions, in addition to measurements (BP, weight, height and others) and blood and urine samples. In the last two surveys,

there was also a study among adolescents (HUNT Youth), covering the age group 13-19 years. The analysis of HUNT 3, when the data were released in 2009, has recently begun, whereas the HUNT 2 data have been thoroughly analysed.

Headache and BP

One of our early publications from the HUNT 2 was performed to test (or rather to disprove) the commonly held notion that headache was related to increased BP. In this paper, we looked prospectively at BP in HUNT 1 as a risk factor for developing headache 11 years later (HUNT 2).¹ In HUNT 1, there was no data on headache, but more than 59,000 respondents had answered questions about painkillers, and we assumed that 41,000 subjects never using such medication had a negligible amount of headache. Of the 41,000, almost 23,000 participated in HUNT 2 eleven years later. As expected, there was no positive association between BP and prevalence of headache. This was, however, not very surprising, since there had already been a consensus agreement expressed by the diagnostic classification of the International Headache Society that moderate to mild hypertension did not induce headache.²

It was surprising, however, that the prevalence of headache in general was 30% lower in the group with systolic BP > 150 mmHg compared to those with BP ≤ 140. Similar, but less clear findings were made in the cross-sectional analysis where

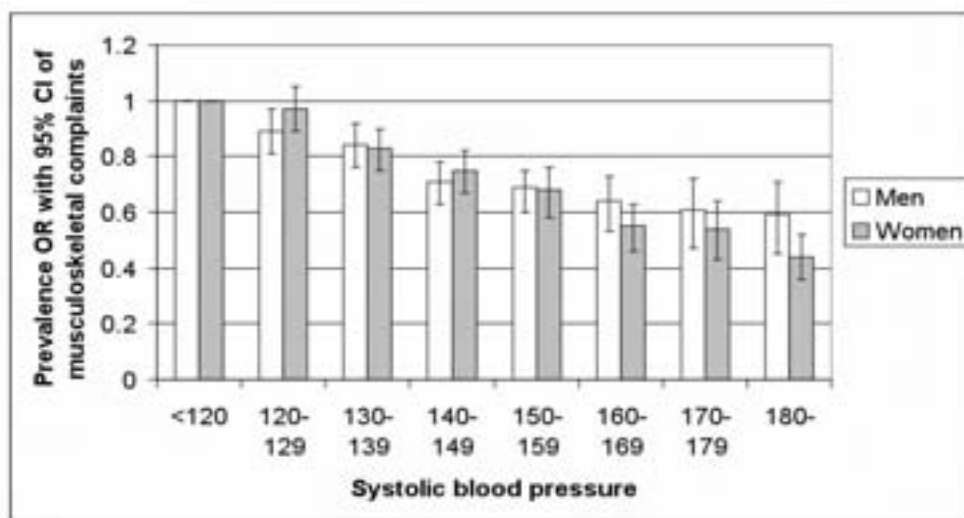


Figure: One-year prevalence of chronic musculoskeletal pain related to systolic BP level among 66140 men and women (From the HUNT study, published with permission from Blackwell Publishing Ltd).

Table: Chronic musculoskeletal pain reported in HUNT 2 specified at different locations related to high BP in HUNT-1 and HUNT 2* (Reproduced with permission from the Archives of Internal Medicine 6)

Location of musculoskeletal symptoms	HUNT-1				HUNT-2			
	SBP ≥ 160 mm Hg		DBP ≥ 100 mm Hg		SBP ≥ 160 mm Hg		DBP ≥ 100 mm Hg	
	OR#	(95% CI)	OR#	(95% CI)	OR#	(95% CI)	OR#	(95% CI)
Neck (n=9,010)	0.7	(0.6-0.7)	0.7	(0.6-0.8)	0.7	(0.6-0.7)	0.7	(0.7-0.8)
Shoulder (n=10,139)	0.6	(0.6-0.7)	0.7	(0.6-0.8)	0.7	(0.7-0.8)	0.7	(0.7-0.8)
Elbows (n=4,284)	0.6	(0.5-0.6)	0.6	(0.5-0.7)	0.6	(0.5-0.7)	0.7	(0.6-0.8)
Wrist/hands (n=6,357)	0.6	(0.6-0.7)	0.6	(0.5-0.7)	0.6	(0.6-0.7)	0.7	(0.6-0.8)
Chest/abdomen (n=2,477)	0.5	(0.5-0.6)	0.6	(0.5-0.7)	0.6	(0.5-0.7)	0.6	(0.5-0.8)
Upper back (n=4,365)	0.5	(0.5-0.6)	0.6	(0.5-0.7)	0.6	(0.5-0.6)	0.6	(0.6-0.7)
Low back (n=8,182)	0.6	(0.6-0.7)	0.6	(0.5-0.7)	0.6	(0.6-0.7)	0.6	(0.6-0.7)
Hip (n=7,257)	0.6	(0.6-0.7)	0.7	(0.6-0.8)	0.7	(0.6-0.7)	0.7	(0.6-0.7)
Knees (n=7,263)	0.7	(0.6-0.7)	0.8	(0.7-0.9)	0.7	(0.6-0.8)	0.7	(0.6-0.8)
Ankles/feet (n=5,932)	0.7	(0.6-0.7)	0.8	(0.7-0.9)	0.6	(0.6-0.7)	0.7	(0.6-0.8)

§ High BP defined as Systolic BP (SBP) ≥ 160 mm Hg and diastolic BP (DBP) ≥ 100 mm Hg.
Odds ratio (OR) with 95% CI. The reference group (OR=1.0) are individuals with normal BP (SBP < 140 mm Hg, and DBP < 90 mm Hg, respectively). Adjusted for age, gender, education, and use of antihypertensive drug therapy.

data on both headache and BP came from the HUNT 2 study. A later, more thorough analysis of the HUNT data confirmed these results.³ The most clear cut relation was found for the variable pulse pressure (ie the difference between systolic and diastolic pressure) showing that a large pulse pressure was related to a low prevalence of headache. This was true for both sexes, for both migraine and non-migraineous headache, and in both the prospective and the cross-sectional analyses. It could not be due to some effect of BP medication since the pain-BP-relationship was most marked for those not using antihypertensives in all the analyses.

A similar inverse association between headache and BP on a population level has also been demonstrated by other groups, in Brazil, France and Iceland (for references, see 3). We have also recently confirmed the findings in another HUNT 2 cohort among adolescents (HUNT Youth),⁴ although this cohort was smaller (<6000), and the relation more complex to analyse because the headache prevalence increases markedly with age in this age group.

Chronic musculoskeletal complaints and BP

The HUNT 2 also contained data on chronic musculoskeletal complaints (cMSCs) (ie pain in one part of the body lasting more than three months during the last year). CMSCs were found to be comorbid with headache in the sense that such pains occurred almost twice as often among those with either migraine or non-migraineous headache compared to the general population.⁵

For cMSC, the relation to BP was similar to the one found for headache.⁶ The Figure shows how the prevalence decreases gradu-

ally with increasing systolic BP in this population of more than 66,000 individuals. It could also be demonstrated that those with low BP (systolic < 140 mmHg and diastolic < 90 mmHg) had much higher prevalence rates than those with high BP (systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg), in all parts of the body (Table). The effects were large, with ORs from 0.4-0.8, i.e. from 20% to 60% lower prevalence rates among those with the highest BP values. As was the case with headache, the effects were more marked in the prospective than in the cross-sectional analyses.

In the literature, there is less epidemiological evidence about a BP-pain relationship for pains other than headache, but it has been found that hypertensive patients experience less intense pain during angina and myocardial infarction than the normotensive patients (for discussion, see 7)

Hypertension-associated hypalgesia

This phenomenon is the most likely explanation for the inverse relation between BP levels and prevalence of the pain conditions demonstrated in the HUNT survey. The phenomenon is well known as a part of the "fight or flight reaction", in which BP increases as pain sensitivity decreases, in addition to many other changes (For review, see 7-9). Several studies have shown a diminished perception of painful stimuli in hypertensive animals, independent of the method used to increase BP (by pharmacological means, increasing salt intake, or with surgery to renal arteries) or to deliver nociceptive stimuli. This effect can be abolished by cutting the nerves from the baroreceptors. It is also present in rats with spontaneous hypertension compared to normotensive rats, and in humans, patients with hypertension have

been shown to have decreased pain sensitivity to dental pulp stimulation. This phenomenon is also present within the normotensive range, and it seems to be mediated by endogenous opioids as the hypalgesia can be blocked by naloxone.⁷

There is probably a genetic influence on this pain-BP relation, as it is possible to breed rat strains in which the relation is not present. Also, the relation may not be one of simple cause and effect, as it has been shown that in spontaneously hypertensive rat strains, there is hypalgesia at a young age, before the hypertension develops. Similarly, among humans it has been found that pain sensitivity among 14 year olds can be used to predict BP at the age of 22.¹⁰ Importantly, it seems that the pain-BP association can be reduced or abolished by chronic pain.¹¹ This may explain why the relation was more evident in the prospective HUNT analyses, where BP was measured in pain-free individuals and related to pain conditions 11 years later, than in the cross-sectional analyses where BP was measured among subjects both with and without pain.

As to the mechanisms for hypertension-associated hypalgesia, there is evidence that stimulation of the baroreflex arch due to increased BP may inhibit pain transmission at both spinal and supraspinal levels, possibly due to interactions with brain areas that modulate nociception and cardiovascular reflexes in the brainstem, e.g. the nucleus tractus solitarius, the locus coeruleus and the periaqueductal grey substance, areas known to be involved in the regulation of both pain and BP.

In some analyses we found that the pulse pressure had an even clearer relationship to pain than systolic BP. It has previously been shown that increased pulse pressure in

healthy middle-aged subjects is associated with reduced baroreflex sensitivity, which has been shown to correlate with reduced sensitivity to pain. This accords with a case-control study by our group, demonstrating increased baroreceptor sensitivity among female migraineurs,¹² but another study has shown decreased baroreflex sensitivity in migraine.¹³

Undoubtedly, chronic pain conditions in different body parts may also have "local" causes in various peripheral tissues (muscles, joints, intestines, vessels, meninges etc), and the relative contribution of nociceptive impulses from the periphery and of centrally determined sensitivity to pain may vary. However, according to the HUNT studies, the effect of hypertension-associated hypalgesia on pain in the population is large, the difference between groups with high and low BP being from 20 to 60% in our analyses, both for headache and cMSCs.

Conclusion

The HUNT studies have, with epidemiological methods, convincingly shown that the mechanisms involved in hypertension-associated hypalgesia are operative in the common pain conditions in the population. These mechanisms are not of minor importance but can explain a substantial part of the variation in pain between individuals. We are eager to explore these mechanisms further in the HUNT 3 study, where we have even better prospective data, high quality brain MRI images of a sample of the population, and possibility to do genetical analyses. More knowledge about the precise mechanisms mediating the relation between BP and pain conditions could lead to better prevention and treatment of these prevalent, costly and disabling disorders. ♦

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