Pain and Blood Pressure

Thomas G. Pickering, MD, DPhil

We are living in the Decade of Pain Control and Research, as officially designated by Congress in January 2001. There was no new legislation or funding attached to this designation, unfortunately, but it may, at least, raise awareness of the issue. Pain is a phenomenon that we all experience to a greater or lesser extent, and the associations between pain and blood pressure are potentially of great interest but poorly understood. There are a number of issues here, some practical and others of more theoretical interest. It is well recognized that pain can raise blood pressure acutely, but it is not so well known that hypertension is associated with a diminished sensitivity to pain (hypalgesia). We know relatively little about the relationships between blood pressure and chronic pain like that in arthritis, and there is also the issue of whether high blood pressure can cause pain like headache. Headache has been discussed previously in this column,[1] but there are surprising new data on the subject.

ACUTE PAIN AND BLOOD PRESSURE

Acute pain leads to generalized arousal and increased sympathetic nerve activity. This has been shown in studies where sympathetic nerve activity is measured directly from electrodes inserted into the peroneal nerve, a technique that detects two types of sympathetic nerves: those going to skin, which are involved in thermoregulation, and others going to muscle, which are under the control of the baroreceptors. The most commonly used stimulus for inducing pain is the cold pressor test, where one hand is immersed in ice water. This produces a dramatic increase in muscle sympathetic nerve activity (MSNA), which is paralleled by a marked increase of blood pressure.[2] Other types of painful stimuli do the same thing—thus both MSNA and blood pressure increase during the application of physical pressure to the nail beds or the skin of the cheek, or during electrical stimulation of a digital nerve.[3] Another widely used stimulus has been forearm ischemia produced by a cuff inflated to cut off the blood supply—here the degree of pain correlates with the increase of blood pressure and vascular resistance.[4]

ALTERED PAIN PERCEPTION IN HYPERTENSIVE SUBJECTS—FINDINGS THAT MAY HAVE PRACTICAL IMPLICATIONS

A very consistent finding in studies of pain perception in hypertensive subjects has been that they do not feel pain as intensely as normotensives.[5–7] This has also been demonstrated in a variety of animal models of experimental hypertension. In the Goldblatt hypertension model, clipping a renal artery of a rat induced hypalgesia as well as hypertension.[8] The same phenomenon has been reported in other models like DOCA-salt hypertension Dahl salt-sensitive rats on a high-salt diet, and spontaneously hypertensive rats.[7] These suggest hypalgesia is merely a consequence of the hypertension, but this is not necessarily the case. It is possible to breed strains of rats where the diminished pain sensitivity does not cosegregate with the hypertension, and lowering the blood pressure with antihypertensive drugs does not necessarily reverse the hypalgesia.[7] Although clipping the renal artery raises the blood pressure in all strains of rats, the hypalgesia does not occur in all strains.[8] There is also a chicken-and-egg question because in spontaneously hypertensive rats the hypalgesia is present at a young age, even before the hypertension develops.[9]

Human studies have used a number of different painful stimuli, such as tooth pulp, electrical stimulation, and thermal stimulation.[6] One of the interesting findings is that the association between pain sensitivity and blood pressure holds even within the normal

From the Behavioral, Cardiovascular Health, and Hypertension Program, Columbia University College of Physicians and Surgeons, New York, NY.
Address for correspondence:
Thomas G. Pickering, MD, DPhil, Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York, NY 10032

www.lejacq.com **ID: 2830**

range of blood pressure.[7] There is also evidence that hypalgesia may precede hypertension because there is a series of observations that normotensive persons with a family history of hypertension show hypalgesia,[10] and more convincingly by a recent finding that pain tolerance measured at age 14 years predicts ambulatory blood pressure at age 22 years.[11]

It is clear that there is a close but not invariable relationship between pain sensitivity and blood pressure, which raises the next question: What is the mechanism? It has been known for many years that stimulation of baroreceptors lowers cerebral arousal. Some years ago I was involved in a study designed to test the hypothesis that raising the blood pressure in rats would reduce the effects of a painful stimulus as a result of this baroreflex effect.[12] Rats were put on a treadmill and exposed to a painful electrical stimulus (stimulation of the trigeminal nucleus). They were trained so that if they started to run they could avoid the stimulus. When blood pressure was raised by infusing phenylephrine, this response was attenuated, as shown by less running on the treadmill. To show that this was mediated by the baroreceptors, another group of rats that had their baroreceptors denervated was put through the same procedure, but in this instance raising the pressure with phenylephrine did not affect their running. This experiment had two important implications: first, stimulation of the baroreceptors might be one explanation for the hypalgesia of hypertension, and second, even more interestingly, hypertension could be a learned behavior pattern that would reduce the effects of stress.

Support for the involvement of the baroreceptors comes from human studies where baroreceptor stimulation using neck chamber suction and pressure has been found to modulate pain sensitivity.[13] Whereas this might explain some of the acute effects, it is less easy to explain the chronic relationship between hypalgesia and hypertension because the baroreceptors would be expected to reset to the higher level of pressure. It must be admitted that the baroreceptor analgesic effects do not necessarily reset in parallel with the blood pressure effects, and in fact denervation of the baroreceptors reverses the hypalgesia in rats with chronic experimental hypertension.[14]

The proposed baroreceptor mechanism has basically a peripheral origin because it depends on the inhibitory effects of baroreceptor stimulation by increased blood pressure. Another possibility is that the hypalgesia-hypertension relationship depends on a central link between the regulation of pain and of blood pressure. The central nervous system pathways for pain are complex and diffuse, but some areas, such as the nucleus tractus solitarius (the first relay point of the baroreceptor afferents in the brain), the periaqueductal gray matter, and the locus ceruleus appear to be involved in the regulation of both pain and blood pressure.[7] A promising area of research is the role of endorphins, which are thought to be the most important neurotransmitters for pain perception. In rats, hypertension-associated hypalgesia can be suppressed by the opiate antagonist naloxone.[9] Furthermore, elevated levels of endogenous opioids have been found in the brains of rats in several models of experimental hypertension, including spontaneously hypertensive rats and Goldblatt hypertensive rats.[15] In a human study comparing normotensive individuals with borderline hypertensives, Schobel et al.[15] found that administering a painful stimulus (pinching the skin) resulted in an increase of MSNA, plasma norepinephrine, and blood pressure. Opioid blockade with naloxone increased the subjective pain rating and the MSNA response in the normotensives but did not affect either in the hypertensives. The authors concluded that these results did not support the idea that the reduced pain sensitivity in the hypertensives (which they did observe in this sample) could be explained by increased activity of the endogenous opioid system.

PRACTICAL IMPLICATIONS OF HYPERTENSION-ASSOCIATED HYPALGESIA

This discussion may seem esoteric, but there are some interesting practical implications. The first is the phenomenon of silent myocardial ischemia and silent infarcts. In general, patients who exhibit silent ischemia have a higher pain threshold, for example, to tooth pulp testing.[16] In addition, silent ischemia may be more common in hypertensives than in normotensives, and in the Framingham study, unrecognized or silent myocardial infarcts were nearly twice as common in hypertensives as in normotensives.[17]

Another possible implication is headache. Although both physicians and patients tend to equate headache with hypertension, we have previously discussed how doubtful this relationship is,[1] and the official viewpoint of the International Headache Society is that mild-to-moderate hypertension does not cause headache.[18] A recently published Norwegian population survey measured the blood pressure in more than 22,000 adults in 1984–1986 and gave them a headache questionnaire 11 years later.[19] (This was not part of the first survey but in the subsequent analysis people who reported using analgesics at the time of the first survey were excluded.) The surprising finding was that those individuals who initially had a systolic pressure 150 mm Hg or higher had a 30% lower risk of reporting headaches than those with a systolic pressure below 140 mm Hg. The authors suggest that hypertension-associated hypalgesia might explain this otherwise paradoxical phenomenon.

CHRONIC PAIN AND BLOOD PRESSURE

The relationship between chronic pain and blood pressure is much less well understood. It has been reported

in a number of studies that there may be a deficiency of endogenous opioids in chronic pain patients.[20] The blood pressure-pain relationship was studied by Bruehl et al.[21] in 118 patients with chronic lower back pain. The main finding was that in patients in whom the duration of the pain was relatively short (less than a year) there was a weak inverse correlation between the symptoms of pain and blood pressure, but in those who had been suffering from pain for more than 2 years the correlation was positive—those who reported more frequent or intense pain had higher blood pressures. Maixner et al.[22] found no relationship between blood pressure and sensitivity to acute pain in patients with temporomandibular joint disorders. Thus, the normal pain-blood pressure relationship is absent or reversed in these patients, which raises questions about which comes first: Are people who do not show the usual pain-blood pressure relationship more likely to develop chronic pain, or does chronic pain impair the relationship? The effects of the duration of exposure to pain reported by Bruehl et al.[21] favor the latter explanation, leading those authors to propose the following sequence of events: persistent pain leads to generalized arousal and elevation of blood pressure. This in turn leads to baroreceptor stimulation, which acutely lowers pain sensitivity, partly through release of endogenous opioids. However, over the long term progressive opioid dysfunction occurs, resulting in a decrease of endogenous opioids and their painkilling effects, and hence a vicious cycle whereby further pain leads to further arousal and decreased pain tolerance. Additional support for this view comes from a study showing that in women with acute pelvic pain of 2–3 days' duration, endorphin levels are increased.[23]

CONCLUSIONS

Although this area of research has so far made no impact on the everyday practice of medicine, it has some very interesting implications regarding lifestyle behavior patterns. It seems clear that a transient increase of blood pressure can have a pain-relieving and possibly stress-relieving effect due to increased endorphin release. It has even been suggested that one way smoking may relieve stress is through stimulation of the baroreceptors resulting from the nicotine-induced blood pressure surge.[24] Chronic stress and chronic pain lead to reduced endorphin levels and a paradoxical increase of pain sensitivity.[25] One stimulus that leads to increased endorphin release is exercise,[26] and it may be that this is yet another reason why we should encourage arthritic patients not to give up on regular exercise.

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