Reflections in Hypertension

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Why Don't We Use Nitrates to Treat Older Hypertensive Patients?

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According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7),[1] isolated systolic hypertension is a fate that awaits nearly all of us if we live long enough. It quotes a study from the Framingham data[2] showing that this risk is about 90% in both men and women by the age of 85. We know from the same Framingham Heart Study and many others that systolic hypertension increases the risk of cardiovascular disease and that lowering the systolic pressure can dramatically reduce that risk. It is also well established, however, that controlling systolic pressure in the elderly is not always easy. An article using the National Health and Nutrition Examination Survey (NHANES) data reported that of all the identifiable factors leading to poor blood pressure (BP) control, old age was the most important.[3]

ARTERIAL CHANGES WITH AGING

The pathology underlying systolic hypertension in the elderly is different from the processes leading to hypertension in younger people, and it is generally agreed that the dominant factor is increased stiffness of the arteries. This has two important effects on BP. The first is that if the heart is pumping into a stiff vascular bed, the systolic pressure will increase more than if it is pumping into a compliant one. The second effect of increasing stiffness has to do with wave reflection. The idea is that the arterial pressure wave is actually made up of two waves. The first is the outgoing, or incident, wave and the second is the reflected wave, which interacts with the incident wave. The resultant wave is a combination of the two, and its shape varies according to the shapes of the two waves and when they coalesce. The timing of this will depend on the distance from the reflection point (which is thought to be in the pelvis) and the pulse wave velocity. If the artery is stiff and the distance is short, the reflected wave may coincide with the end of the systolic peak of the outgoing wave so that it will augment the systolic pressure in the central part of the circulation. In a young person with compliant vessels, the pulse wave velocity is slow, so the reflected wave arrives during the diastolic downslope of the incident wave and does not affect the systolic pressure. Other things being equal, the pressure wave becomes more spiky, i.e., a high systolic and lower diastolic pressure, as it travels toward the periphery, because the overall capacitance of the circulation decreases as the wave progresses further from the heart. There is peripheral vasoconstriction in older people (accounting for increased peripheral resistance) that enhances the wave reflection. One of the consequences of these changes is that in an older person with stiff arteries, there is a smaller difference between the central aortic pressure and the peripheral arterial pressure (measured in the brachial or radial artery) than in a young person with compliant arteries.

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THE EFFECTS OF ANTIHYPERTENSIVE DRUGS ON ARTERIAL STIFFNESS

Most of the antihypertensive drugs in current use act principally by reducing peripheral resistance, which is determined by the arterioles or resistance vessels. An increased peripheral resistance is the primary abnormality in younger patients with hypertension. The increased arterial stiffness that is characteristic of systolic hypertension affects mainly the larger arteries, however. A consequence of this is that a drug that reduces arterial stiffness will have a particularly favorable effect on the systolic pressure of older patients who have stiff arteries. By using techniques such as Doppler ultrasound measurements of brachial artery diameter and flow, it is possible to separate the effects of drugs on peripheral resistance and large artery stiffness.[4] It is now also possible to measure both the peripheral and central arterial pressure by applanation tonometry, which uses a noninvasive device to record the shape of the arterial wave at the radial artery or elsewhere.[5] This technique has not yet found its way into routine clinical practice, but the time is soon approaching when it will.

There is, at present, considerable debate as to how stiffness should be measured, which at times has an almost religious flavor. Two popular measures are the pulse wave velocity and the augmentation index, but many others have been described.[6] Measurement of pulse wave velocity is achieved by recording the pulse wave at different locations in the arterial tree. Measuring the augmentation index requires the ability to separate the incident and reflected waves from the recorded pulse, which can be done by Fourier analysis or other mathematical techniques. It is defined as the percentage of the central pulse pressure, which is attributed to the reflected pulse wave, and thus will be high in patients with systolic hypertension.[7] In patients with end-stage renal disease who have very stiff arteries, a high augmentation index has been shown to be an independent predictor of cardiovascular morbidity[8] and tends to be increased in patients with other cardiovascular risk factors.[9]

The next question is how different antihypertensive drugs affect peripheral resistance vs. arterial stiffness. Some drugs, such as calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors, affect both peripheral resistance and arterial stiffness, while hydralazine reduces peripheral resistance without affecting arterial stiffness and nitrates lower stiffness without changing peripheral resistance.[4] A study by Morgan et al.[10] using radial artery tonometry compared a β blocker (atenolol), ACE inhibitors, calcium channel blockers, and a thiazide diuretic with placebo in elderly patients with systolic hypertension. All the active drugs reduced the first peak of the systolic pressure waveform, but the second (reflected wave) peak and, hence the central pulse pressure, was reduced by all the drugs except the β blocker. Calcium channel blockers and diuretics reduced the augmentation index, while ACE inhibitors had no effect, and the β blocker tended to increase it. This finding is of interest because there is general agreement that diuretics and calcium channel blockers are better than β blockers for treating older patients.

THE FORGOTTEN NITRATES

Nitrates have been around for a long time and may claim to be the first BP-lowering agents to be discovered. T. Lauder Brunton first described the beneficial effects of amyl nitrite on angina in his collected papers published in 1871 and concluded that its effects were due to a direct vasodilator effect on the arteries.[11] The discovery of NO more than 20 years ago led to the concept of nitrates being "nitric oxide donors," which thus cause vasodilation differently from other antihypertensive drugs.[12] Nitrates are rarely used for the treatment of hypertension, however, and in JNC 7 they are not mentioned at all. But a series of publications over the past 20 years have suggested that nitrates may have a powerful antihypertensive action in patients with isolated systolic hypertension that cannot be controlled with other drugs.

The possibility of using nitrates was first put forward by Dr. Michel Safar,[13] who was evaluating measures of arterial compliance and was one of the first investigators to show that the main hemodynamic change in systolic hypertension was not just an increase of peripheral resistance, but a decrease of compliance in the large arteries. In a letter to *The New England Journal of Medicine* in 1980, he distinguished vasodilators such as hydralazine that affect the resistance vessels and lower BP by reducing peripheral resistance from those such as nitroglycerine that selectively affect large arteries. He wrote "On the basis of this evidence, it seems that only nitroglycerine-like drugs (and not hydralazine) can be expected to be efficient in the management of systolic hypertension of the elderly." The first major study was published in 1987 by Safar's group[14] and included 40 elderly hypertensive patients who were hospitalized for 16–18 weeks. After 12 weeks of therapy with either isosorbide dinitrate given twice daily (20–40 mg b.i.d.) or

placebo, it was found that systolic BP decreased by 14 mm Hg more in the nitrate group than in the placebo group. In some patients, an additional 2 weeks was added at the end of the trial to investigate withdrawal effects, and the pressure in the actively treated group increased to baseline. Side effects were rare and heart rate did not change.

Most of the clinical studies have been performed by Dr. Gordon Stokes in Australia, who not long ago summarized his work in *The Journal of Clinical Hypertension*.[15] A study by Stokes's group randomized 10 elderly hypertensives with refractory systolic hypertension, all of whom were still hypertensive despite taking one to three antihypertensive drugs.[16] They were treated either with placebo or isosorbide mononitrate for 2 weeks and then switched to the other agent. The BP effect was evaluated by ambulatory monitoring. Daytime systolic pressure was about 10 mm Hg lower with the nitrate than with the placebo, but nighttime pressure was unaffected. In a later study,[17] the effects of single doses of isosorbide mononitrate, captopril, and eprosartan were compared in patients with hypertension resistant to other drugs. The nitrate lowered systolic pressure more than the others, but also produced a dramatic fall in the augmentation index. This was also seen in patients already taking ACE inhibitors.

IS NITRATE TOLERANCE A PROBLEM?

One of the most critical issues with the long-term use of nitrates has been the development of tolerance. It is well established in the cardiology literature that if blood levels of nitrates are maintained at high levels throughout a 24-hour period, their effectiveness decreases. It has been shown, for example, that when isosorbide mononitrate is given in once-daily dosing, it is an effective antianginal therapy. But when given twice daily, it loses its effect.[18] The study by Safar's group used twice-daily dosing and showed no loss of effect over the 12 weeks, but Stokes' studies used once-daily dosing. One way of looking at tolerance is to examine the effects of sudden withdrawal of a drug in patients who have been taking it for a long period of time. This was done in a study by Stokes et al.,[19] who substituted placebo for a single dose in patients who had been taking isosorbide mononitrate for between 16 and 109 months and who were wearing ambulatory monitors at the time of the switch. Taking a placebo instead of an active drug resulted in a marked difference of systolic pressure that reached 16 mm Hg higher than while taking the nitrate 3 hours after the dosing time; the effect lasted about 8 hours. Changes in the augmentation index were also seen. This study strongly suggests that tolerance was not a problem.

CONCLUSIONS

It is perhaps ironic that nitrates, the first group of antihypertensive agents to be discovered, have been neglected for so many years and are only now finding a niche in the treatment of hypertension. Two technologic advances have spurred this evolution. The first is the use of applanation tonometry to estimate BP in the central circulation, and the second is the discovery of the central role of NO in the regulation of vascular tone. While nitrates are certainly not the ideal antihypertensive agents, they have a unique mode of action affecting arterial stiffness that should be helpful in patients with hard-to-control systolic hypertension in whom increased stiffness may play a major factor. When given in conjunction with other antihypertensives in once-daily dosing, they may help to control the daytime systolic pressure. Unfortunately we do not have any large-scale studies describing the effectiveness and safety of their use, because they have been around too long and are too inexpensive to be of interest to their manufacturers. Given the large number of patients with systolic hypertension who remain uncontrolled on more conventional drugs, however, it would seem worthwhile to give them a wider evaluation. A promising screening technique that deserves further evaluation is the measurement of the augmentation index using applanation tonometry, since patients in whom it is high might show the most favorable response.

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