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Editorial

Dilemmas in Diagnosing and Managing Hypertension: Is White Coat Hypertension Benign?

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See article by Cloutier et al., pages 620-630 of this issue.

The diagnosis of hypertension, seemingly straightforward, needs to be obtained properly for this important condition to be managed and for individuals who are not hypertensive to be spared unnecessary medication. The review by Cloutier et al.[1] in this issue of the *Canadian Journal of Cardiology* adds important evidence that office blood pressure measurement should be performed with validated automated oscillometric devices, and emphasizes the importance of out-of-office blood pressure recording, including ambulatory blood pressure (ABP). However, there are additional issues that need to be considered.

Besides detection of white coat hypertension (WCH; the key issue identified by the authors), equally or more important reasons for performing ABP monitoring are the detection of masked hypertension (normal pressures in the office with high out-of-office pressures), and nondipping of nocturnal blood pressure. Both of these conditions are associated with increased risk of cardiovascular events.[2,3]

Another important issue in the diagnosis of hypertension is the problem of cuff artifact due to arterial thickening, which can lead to false increases of the blood pressure measured with a cuff. Approximately 4% of elderly patients will have a diastolic pressure that measures approximately 30 mm Hg higher using cuff pressure than intra-arterially.[4] This has been called "pseudohypertension,"[5] and should be suspected in elderly patients with vascular disease who complain of lightheadedness with pressures that do not seem to explain hypotensive symptoms. A clinical clue to this condition is the absence of hypertensive end-organ disease in a patient who is apparently hypertensive.[5] Diastolic pressure is affected more than systolic pressure, and mean arterial pressure tends to be more accurately measured using cuff methods.[6] False increase of the cuff diastolic pressure leading to overtreatment to very low intra-arterial diastolic pressure might explain part of the controversy about a U-shaped relationship between blood pressure and risk, because myocardial perfusion occurs mainly during diastole.

The other side of the coin is the rare patient with "pseudonormotension"—normal cuff blood pressures with high intra-arterial pressure because of subclavian artery occlusion. In a new patient with vascular disease, blood pressure should always be measured in both arms to exclude aortic dissection affecting one subclavian artery, or subclavian steal syndrome, with low pressure in one arm. However, bilateral subclavian occlusion might lead to "pseudonormotension" even if pressure is measured in both arms[6] (this is rare, but I have seen it at least twice). Similarly, the presence of hypertensive end-organ disease in the face of low/normal pressures should raise suspicion of this condition.

Cloutier et al.[1] emphasize the use of ambulatory or home blood pressure for exclusion of white coat syndrome so that treatment they presume is unnecessary might be avoided. However, the evidence reviewed does not satisfactorily justify their recommendation that WCH not be treated. They cite 3 meta-analyses favouring that conclusion, but then go on to say "One other meta-analysis of the **I**nternational **D**atabase of **Ho**me BP in Relation to **C**ardiovascular **O**utcome (IDHOCO) found an increased event rate among adults with WCH (adjusted hazard ratio 1.42; 95% confidence interval, 1.06-1.91). It has been suggested that WCH is associated with a greater risk of developing sustained hypertension in the next decade, as shown in the **P**ressione **A**rteriose **M**onitorate **E** **L**oro **A**ssociazioni (PAMELA) and Ohasama studies, and that subjects with WCH might have greater left ventricular mass index compared with normotensive subjects." WCH is hypertension.[7,8] There are important problems with meta-analyses, and a serious intellectual problem with stating that meta-analyses are 3 to 1 in favour of WCH being benign.

In meta-analyses, particularly meta-analyses of observational studies, the devil is in the details. Some of those problems might be overcome by large individual studies. One important example was the study of Verdecchia et al.,[9] which showed that for ABP to be benign, the pressures had to be very low: below 130/80 mm Hg. Even ABP between 130/80 mm Hg and 131/86 mm Hg (for women) or between 130/80

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and 136/87 mm Hg (for men) was as strongly associated with cardiovascular events as were higher pressures.

Another study that was important because it followed untreated patients prospectively for 5 years, and reported increased end-organ effects of hypertension in WCH, was the study of Puato et al.,[10] which showed a faster increase in intima-media thickness in WCH compared with in normotensive subjects; importantly, the increase in WCH was not different from that in sustained hypertension.

Patients with WCH react more to stressful stimuli such as mental arithmetic, mirror tracing, or a Stroop task.[11] Stress-induced hypertension is related to silent strokes[12] and to cognitive decline.[13] Blood pressure increases during mental stress induced by psychologically stressful tasks predicted an increase in left ventricular hypertrophy more than ABP or office pressure measurements,[14] and an increase in carotid plaque area, independent of resting blood pressure or other Framingham Risk factors.[15] Blood pressure reactivity also predicted increased coronary calcium scores[16] and aortic calcification,[17] and increased carotid intima-media thickness.[18] Increased blood pressure during mental stress was associated with increased levels of norepinephrine, and although amlodipine blunted blood pressure responses to stress, it increased plasma norepinephrine at baseline and during mental stress.[19] Pickering et al.[20] found that doxazosin, an α-adrenergic blocker, blunted the white coat effect. Thus, there are important problems with the consequences of stress responses that underlie the white coat effect. Waving in the air a handful of (partially contradictory) meta-analyses of observational studies does not adequately address those issues.

In observational studies, confounders, known and unknown, cannot be fully accounted for. They can only be addressed adequately in large randomized trials. Until such studies are done, the hypothesis that it is safe to withhold treatment in WCH remains untested. Therefore, the statements made by Cloutier et al.[1] regarding the advisability of not treating WCH must be taken with not a grain but a handful of salt.

There is a substantial risk that (abetted by the media) doctors and patients will take this recommendation as a reason to not treat hypertension when out-of-office blood pressures are < 140/90 mm Hg (well above the ABP levels shown to be innocent), with consequences of increased stroke, renal impairment, and congestive heart failure. This is likely to happen because patients who want an excuse not to be treated might take a single ABP measurement as a final answer, like a fire-and-forget surface-to-air missile. The cost of cardiovascular consequences of not treating hypertension need to be appropriately factored into the economic analyses.

Patients with WCH are at increased risk of cardiovascular events; based on the available evidence, most would need treatment to avoid the consequences of increased reactivity to stress, and most will develop sustained hypertension over time. Patients with high office pressures who are being considered for withholding of therapy on the basis of out-of-office pressures should be further evaluated and followed closely. Patients with WCH should at least be advised to implement nondrug therapies such as salt restriction, avoidance of licorice, decongestants, and nonsteroidal anti-inflammatory drugs, and moderation of ethanol intake. Further evaluation should include at least annual repeat ABP measurement, and perhaps periodic measurement of left ventricular mass and microalbuminuria.

Further research is needed in this area. A key study that should be performed would be to randomize patients with WCH to have their blood pressures treated on the basis of office pressure vs out-of-office pressure. Early end points could include change in creatinine clearance, microalbuminuria, and left ventricular mass at 1 or 2 years, but ideally the study should be carried on long enough, and in enough participants, to detect a difference in cardiovascular end points. My prediction would be that the study would need to be stopped early because of an excess of cardiovascular events among patients not treated for high office pressures. I also predict that the cost of adverse outcomes of hypertension would outweigh any savings achieved by not treating WCH.

Disclosures

The author has no conflicts of interest to disclose.

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