Pulse Pressure

Is This a Clinically Useful Risk Factor?

Michael O’Rourke, Edward D. Frohlich

A

gain, the Framingham group has provided another surprise to the medical community with publication of its longitudinal follow-up study of persons over 50 years of age that has linked cardiovascular (and in particular coronary) mortality with pulse pressure. In this study, mortality was related independently with initial systolic, diastolic, and pulse pressure, but the strongest association was with pulse pressure, and when systolic pressure was initially considered, there was a negative association with diastolic pressure. In other words, for a given systolic pressure, lower diastolic pressure was associated with greater mortality. A series of questions arise from this study. What corroboration does it have from other studies on similar cohorts? How does one reconcile the findings with the well-established association of coronary and stroke mortality with diastolic pressure? What possible mechanism can explain a greater association between coronary mortality and greater pulse pressure (or lower diastolic pressure)? And above all, what implications does this study have to patient management?

Corroboration

For some 30 years, the Framingham group has pointed to a more robust association between systolic, rather than diastolic, pressure and cardiovascular events and has used systolic, not diastolic, pressure in their predictive tables. Fifteen years ago, Fisher challenged the preoccupation with diastolic rather than systolic pressure, and soon after, Dustan referred to a change in hypertensive disease, with problems shifting from the young and middle-aged subjects with diastolic hypertension to older subjects with systolic hypertension. In 1989, Darme noted that pulse pressure added further risk to patients with elevated diastolic or mean pressure, at least with respect to cerebral events. A series of prospective and cross-sectional studies has followed that has associated pulse pressure with cardiovascular events.

The most recent, the follow-up of nearly 20,000 initially healthy Parisians, followed up for 19 years, showed that the relationship between pulse pressure and death rates existed for persons with normal, as well as raised, systolic pressure, which was also seen in the Framingham cohort.

Reconciliation

The second question is how to reconcile these recent findings with the hallowed concepts of diastolic pressure elevation, and especially with the seemingly irrefutable meta-analyses published by MacMahon et al in 1990 and 1999. The original idea that elevated diastolic pressure is bad and that elevated systolic pressure is good is attributed to Sir James MacKenzie, whose books on the heart, arteries, and veins established cardiology as a discipline in the early part of the twentieth century. A study of these books reveals that MacKenzie had a much more sophisticated view of sphygmonomeric measurements and that the simplistic notion that related elevated diastolic pressure to increased arteriolar tone as bad, and elevated systolic pressure to cardiac strength as good, was inserted by another person in the last edition of MacKenzie’s textbook, which was published posthumously. Other criticisms of this simplistic notion were voiced by Fisher in his appropriately titled review “The Ascendancy of Diastolic Blood Pressure Over Systolic Blood Pressure”.

But what of the meta-analyses? MacMahon’s 1990 review published results of studies reported between 1963 and 1989, in which subjects were recruited between 1938 and 1983. These subjects were quite different from those reported by Franklin et al, in that they were generally younger, their diastolic pressure covered a much wider range (from <69 to >110 mm Hg), and they were recruited at a time when a diastolic pressure of up to 105 mm Hg was considered only moderately elevated (and elevated systolic pressure was considered irrelevant), when therapy was not as effective or as well tolerated as it is today, when most subjects were not treated with any therapy at all, and when introduction of therapy was based on the level of diastolic pressure alone. In the most recent review, subjects studied in China and Japan were analyzed, and many of these same comments can be made even though recruitment occurred at a later time.

The MacMahon meta-analyses referred to persons who represent the old problem of diastolic hypertension as described by Dustan, not the new problem she described, which is better represented by the Framingham cohort of patients over 50 years old than most of the others referred to above. Although these criticisms are in accord with our argument, it should be said that the most recent follow-up by MacMahon and colleagues, not yet published, still shows an association between mortality and diastolic pressure and no definite relationship with pulse pressure. It is possible that the phenomenon of pulse-wave amplification in young subjects

Received June 18, 1999; accepted July 15, 1999.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the University of New South Wales, St Vincent’s Hospital, Sydney, Australia (M.O.), and the Alton Ochsner Medical Foundation, New Orleans, La (E.D.F.).

Correspondence to Michael O’Rourke, MD, DSc, Professor of Medicine, St Vincent’s Clinic, University of New South Wales, Suite 810, Level 8, 438 Victoria Street, Darlinghurst, Sydney 2010, Australia.

(Hypertension. 1999;34:372-374.)

© 1999 American Heart Association, Inc.

Hypertension is available at http://www.hypertensionaha.org
may have skewed the data for those in their twenties and thirties\textsuperscript{16} (see below).

**Mechanism**

With respect to mechanisms, we are on stronger ground. Elevated pulse pressure causes greater stretch of arteries, induces fatigue and fracture of elastic elements more quickly,\textsuperscript{16} is more likely to hasten development and ultimate rupture of aneurysms, and is more likely to hasten development of the intimal damage that leads to atherosclerosis and thrombotic events.\textsuperscript{16} Elevated pressure during systole favors left ventricular hypertrophy, predisposes to left ventricular failure, and increases myocardial oxygen demands, whereas absolute or relative lower values of pressure throughout diastole are a potential limiting factor to coronary perfusion and so predispose to ischemia, especially when, as in left ventricular hypertrophy, diastolic perfusion time is shortened.\textsuperscript{16} From a mechanistic viewpoint, elevation of pulse pressure or systolic pressure or both is potentially deleterious, and so is reduction of pressure during diastole.\textsuperscript{16}

Elevated pulse pressure is usually regarded as a manifestation of increased arterial stiffness. But there are other diseases in which pulse pressure is elevated and in which increased pulse pressure may contribute to vascular and cardiac events. The most obvious is aortic coarctation, in which pulse pressure is markedly increased in upper-body arteries, and in which arterial complications such as aortic medionecrosis and dissection and cerebral aneurysms and hemorrhage are much more frequent than in persons with essential hypertension and a similar level of mean arterial pressure.\textsuperscript{17} Aortic valve incompetence, patent ductus arteriosus, and Paget’s disease are other examples in which high pulse pressure is due to high stroke volume, not aortic stiffness or aortic coarctation. In these conditions, the pathophysiological principles referred to above no doubt apply, but progress of the disease is usually attributed to other problems (eg, left ventricular enlargement and failure, pulmonary hypertension, fractures, and sarcoma).

There is another mechanistic factor, whose relevance has yet to be assessed, and this is the difference in pulse pressure and systolic pressure between the aorta and upper limb arteries where pressure is measured clinically. Diastolic and mean arterial pressure show little difference between central and peripheral arteries,\textsuperscript{18} but in young adults, brachial pulse pressure may be 50\% greater than in the aorta and systolic pressure may be 10 to 20 mm Hg higher than in the aorta.\textsuperscript{16,18,19} In older and hypertensive subjects, these differences are small\textsuperscript{16} and probably irrelevant in the Framingham Heart Study. However, this point is a potential source of variability for measured systolic pressure in younger subjects, such as those entering the work force or applying for insurance policies, and may have clouded assessment of the importance of systolic and pulse pressure in actuarial and other studies.

The NHANES study\textsuperscript{20} showed a progressive decrease in pulse pressure between adolescence and middle age despite an acknowledged increase in aortic stiffness over this age range.\textsuperscript{16} Such a phenomenon can only be explained on the basis of changing amplification of the pulse wave between the central aorta and brachial artery.\textsuperscript{16} This, too, clouds interpretation of pulse pressure as a risk factor in persons under age 40.

**Implications**

Finally, what are the clinical implications of the recent Framingham and other studies? Framingham refers only to persons over 50 years of age. In such middle-aged and older subjects, systolic pressure values are all-important, and decisions on treatment should be based on such values, as demonstrated clearly by SHEP,\textsuperscript{21} Syst-Eur,\textsuperscript{22} and other studies.\textsuperscript{4,5,8–11} What extra value could be provided by the diastolic pressure? The published data at present indicate a greater risk for a person with a persistent blood pressure of 160/70 mm Hg than 160/90 mm Hg. Clearly, both should be treated. But with treatment, who might be expected to do better, and what should be the goals for diastolic pressure? We simply do not know at present, and there is a very real need to conduct trials on therapy for patients with elevated pressure at different levels of diastolic pressure, as well as to further confirm the fascinating data emanating from Framingham. The common clinical problem of elevated blood pressure continues to provide unexpected surprises and new issues to be explored and untangled.

Let us explore two other examples concerning patients with more severe degrees of hypertensive disease. The first might be a young, high-risk patient with severe diastolic hypertension (eg, 188/124 mm Hg; pulse pressure 64 mm Hg). This is the classic patient with diastolic hypertension included in the earlier multicenter trials who benefited from antihypertensive therapy. The patient’s blood pressure might have been reduced to 142/64 mm Hg (pulse pressure 78 mm Hg). This patient’s risk would have been increased further if we refer to the recent studies.\textsuperscript{9–13} Alternatively, the second example relates to a very different patient population emphasized by Dustan,\textsuperscript{7} with risk associated with systolic hypertension (190/88 mm Hg) with pulse pressure of 102 mm Hg that is greater than that of the previous patient with severe diastolic hypertension. That risk is also markedly diminished by antihypertensive therapy to 142/78 mm Hg (pulse pressure 64 mm Hg); but this patient’s improved risk (by pulse pressure) is precisely the same as that of the untreated patient with severe diastolic hypertension. We must conclude, for the time being, that antihypertensive therapy must have markedly benefited both patients. The question remains, however: are their risks comparable?

Clearly, prospective studies comparing these two groups are necessary. Perhaps the answer can be provided by plumbing the data of past multicenter studies (eg, Veterans Administration Cooperative Study, Hypertension Detection Follow Up Program, the Systolic Hypertension in the Elderly, and Stop-Hypertension Trials). These data may be in their respective repositories and may be readily available to their respective investigators’ review. If retrieval of these data is possible, we may soon have some very important answers in a shorter time than it would take to initiate lengthy and expensive prospective trials. We may then have answers relative to (1) the validity of comparing risk data before and during therapy; (2) whether equivalent pulse pressure data
before and during therapy are comparable; and (3) whether the pulse pressure data generated prior to treatment are of value in evaluating efficacy of therapy. One such report, reanalyzing the SHEP data, appears in this issue of Hypertension.\(^{23}\) Another report, reanalyzing the British MRC trial data, has just been published in the Journal of Hypertension.\(^{24}\) Yet another, reanalyzing the SYSTEUR data, was presented orally at the most recent European Society of Hypertension meeting in June 1999. All three support views presented here and provide new quantitative information on elevation of mean pressure and of pulse pressure in older persons.

References

Key Words: pulse pressure · risk factors · editorials
Pulse Pressure: Is This a Clinically Useful Risk Factor?
Michael O'Rourke and Edward D. Frohlich

Hypertension. 1999;34:372-374
doi: 10.1161/01.HYP.34.3.372

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/34/3/372