**Mind the Gap: Pulse Pressure, Cardiovascular Risk, and Isolated Systolic Hypertension**

Ian B. Wilkinson and John R. Cockcroft

Hypertension is an age-old problem, and the importance of arterial blood pressure as a determinant of cardiovascular risk has been clearly demonstrated by a number of major studies since the introduction of the mercury sphygmomanometer nearly 100 years ago. Similarly, the benefits of treating hypertension have been equally well established by randomized, controlled trials. However, many of these studies focused almost exclusively on diastolic pressure, as convention dictated that this was the best predictor of risk. Moreover, despite repeated protests,1 data from the Framingham study2 in particular, demonstrating that systolic blood pressure is probably more important than diastolic pressure in defining cardiovascular risk, were largely ignored in favor of the “conventional view.” However, much recent evidence has challenged the preeminence of diastolic pressure, emphasizing the importance of systolic and, latterly, pulse pressure as more accurate predictors of cardiovascular risk.

Essential hypertension is characterized by increased peripheral vascular resistance and, therefore, an increased mean arterial pressure, which is more closely related to diastolic pressure. However, pulse pressure—the “gap” between systolic and diastolic pressure—is defined mainly by the compliance of the large arteries and the cardiac output as, indeed, noted by Bramwell and Hill in 19223: “Hence the difference between systolic and diastolic pressure, that is the pulse pressure, other things being equal will vary directly as the rigidity of the arterial walls.”

Aging is associated with stiffening of the large arteries4,5 and a widening of the pulse pressure in almost all populations6: a consequence of arteriosclerosis. The most recent data from the Framingham study have not only confirmed the increase in systolic and decrease in diastolic pressure associated with the normal aging process, but indicate that this increase in pulse pressure, at least in the persons aged more than 50 years, is a better predictor of a cardiovascular event than systolic or diastolic pressure in isolation.7 Similar findings have been reported from epidemiologic studies in normotensive8 and hypertensive individuals,9,10 and in those surviving a myocardial infarction.11 Together, these data suggest that arterial stiffness is a better predictor of cardiovascular risk than peripheral vascular resistance, at least in the middle-aged and older subjects. This view is supported by more direct assessment of arterial stiffness, using aortic pulse wave velocity measurement, in patients with renal failure12 and hypertension.13

Isolated systolic hypertension, defined as an increased systolic (>160 mm Hg) but normal diastolic pressure (<90 mm Hg) affects almost half of those aged more than 60 years14; a burden that is likely to grow with increasing life expectancy. It is a consequence of the age-related stiffening of the large arteries and, therefore, isolated systolic hypertension may be considered as an exaggeration of the natural aging process—something that we might all develop should we live long enough. Moreover, in contrast to essential hypertension, it is not associated with any appreciable change in peripheral vascular resistance. Therefore, isolated systolic hypertension and essential hypertension can no longer be viewed as the same condition.

Historically, isolated systolic hypertension was viewed
as part of the natural aging process and considered to be essentially a benign condition. However, the emerging importance of pulse pressure, together with data from both observational and interventional studies, indicate that individuals with isolated systolic hypertension have a substantially increased risk of cardiovascular disease and death. The benefits of treating isolated systolic hypertension have been clearly demonstrated by three large, multicenter intervention trials in which antihypertensive therapy significantly reduced cardiovascular morbidity and mortality. Moreover, data from the latest Cochrane review indicate that treating isolated systolic hypertension in the elderly confers a similar relative risk reduction in cardiovascular morbidity and mortality to that obtained from antihypertensive therapy in younger individuals with essential hypertension. However, because the elderly are at a substantially higher absolute risk of events, they stand to benefit significantly more from treatment. Indeed, the number of elderly patients with isolated systolic hypertension that need to be treated for 5 years to prevent one stroke, is around half that of the number of younger subjects with “mild” hypertension. As such, treating isolated systolic hypertension could be considered more cost effective. Moreover, concerns regarding the tolerability of drug therapy in older individuals seem largely unjustified. Indeed, in the Systolic Hypertension in the Elderly Program pilot study and Swedish Trial in Old Patients with Hypertension (STOP) study, discontinuation rates were similar in the active treatment and placebo groups. However, a number of questions regarding therapy for isolated systolic hypertension remain, such as what target pressure to aim for and whether conventional antihypertensive drugs, developed mainly for treating essential hypertension, will enable these targets to be achieved. Such issues need to be addressed by large randomized, controlled trials.

Despite the evidence regarding the risks associated with isolated systolic hypertension, and the benefits of treatment, it is frequently ignored and undertreated. Recent data from the National Health and Nutrition Examination Survey (NHANES) III demonstrate that despite isolated systolic hypertension being the predominant form of hypertension in both treated and untreated hypertensives over the age of 50 years, there is still a selection bias in favor of treating diastolic rather than systolic blood pressure, and in targeting younger subjects. Similar results were obtained by recent polls of British General Practitioners and Hospital Consultants. The roots of this insensitivity originate from a century of overreliance on diastolic pressure, and have been perpetuated by unjustified concerns about potential adverse consequences of treatment and ageism within the medical profession itself.

Almost 100 years since the introduction of the mercury sphygmomanometer we have finally come to recognize the ascendancy of systolic over diastolic pressure for accurate assessment of cardiovascular risk. Nevertheless, although suggested by some researchers, diastole cannot be abandoned, as the gap between systolic and diastolic pressure—the pulse pressure—is probably the best predictor of cardiovascular risk for most individuals. The latest World Health Organization–International Society of Hypertension guidelines for the management of hypertension emphasize the importance of pulse pressure and arterial stiffness as predictors of cardiovascular risk and call for further investigation of the prognostic relevance of other indices of arterial distensibility and stiffness. However, the importance of arterial stiffness as a measure of health was recognized by nineteenth century physicians, who developed devices to assess stiffness in a qualitative manner. Moreover, Bramwell and Hill not only understood the physiological basis and clinical relevance of a raised pulse pressure in 1922, but also the need for more accurate methods of assessing arterial stiffness. Perhaps the current problem is as noted by Andre Gide in 1891, that: “Everything has been said before, but since nobody listens we have to keep going back and beginning all over again.”

The major challenge, at present, is in persuading the medical profession to accept the evidence, change practice, and to treat the elderly with isolated systolic hypertension. Perhaps, then we can address the important issues such as defining target pressure, and developing new therapies to specifically reduce large artery stiffness.

REFERENCES


