Ambulatory Pulse Pressure
Does It Improve Cardiovascular Risk Stratification?

Giuseppe Schillaci, Giacomo Pucci, Benjamin Gavish

See related article, p 229–237

Blood pressure (BP) traditionally has been measured in terms of peak (systolic) and trough (diastolic) values, with systolic BP being preferred compared with diastolic BP because of its stronger prognostic value for cardiovascular morbidity and mortality.[1] However, a more physiologically appropriate view considers the BP waveform as being composed of a steady component (mean arterial pressure) on which cyclic oscillations, with amplitude represented by pulse pressure (PP), are superimposed. PP reflects large artery stiffness as well as several other cardiovascular parameters, including timing and magnitude of reflected waves, stroke volume, and rapidity of ventricular ejection. PP is a better predictor of cardiovascular complications compared with mean arterial pressure in elderly individuals.[2] In the 2013 European Society of Hypertension/European Society of Cardiology guidelines, an office PP ≥60 mm Hg was included among the markers of asymptomatic organ damage to be used for cardiovascular risk stratification,[3] although the above cutoff value does not seem to be supported by any specific reference.

Despite a large body of literature, there is still controversy regarding the incremental value of PP as an independent cardiovascular risk factor. Also, PP measurement in the physician's office may overestimate usual PP levels in the single individual, because office BP measurement is usually accompanied by a greater rise in systolic than in diastolic BP.[4] Twenty-four-hour PP is considered a more accurate measure of an individual's usual PP and a stronger predictor of cardiovascular risk,[5] although its prognostic value has been examined in a relatively few studies with a limited number of events.[5–9]

In the current issue of *Hypertension*, Gu et al[10] shed new light on the role of PP in cardiovascular risk stratification. A total of 9938 individuals aged between 18 and 93 years drawn from 11 randomly recruited population cohorts from 3 continents were followed up for an average of 11.5 years. The primary outcome was a composite cardiovascular end point that included stroke, myocardial infarction, heart failure and cardiovascular death, although other relevant events were also taken into account (all-cause and cardiovascular mortality, as well as stroke and cardiac events taken separately). The long follow-up, the large number of events, the inclusion of several population-based cohorts from different countries, and the use of 24-hour ambulatory BP monitoring are among the strong points of the article.

Given that previous evidence suggested that the relative prognostic importance of the different BP components may differ by age,[2] the authors chose to analyze separately the 6028 individuals below and the 3910 individuals above the age of 60 years. Not unexpectedly, the relatively low number of events in the younger cohort limited the precision of the estimates in this age group. Also, the authors compared the risk of each tenth of the PP distribution with the average risk, instead of comparing it with a given healthy or reference group. Although this rather conservative approach may reduce the chances to demonstrate a difference, it also provides less arbitrary findings, avoids an artifactual inflation of the hazard ratio estimate, and accounts appropriately for the observed nonlinearity of the relation between 24-hour PP and end points.

A comprehensive set of analyses can be summarized along the following lines:

1. Both among younger and older participants, individuals in the highest tenth of the 24-hour PP distribution had a significantly higher-than-average cardiovascular risk in multivariable-adjusted models, which also took into account the effects of 24-hour mean arterial pressure. The prognostically adverse thresholds of the top tenth of 24-hour PP distribution were >56 mm Hg in the younger and >69 mm Hg in the older group. A high 24-hour PP also predicted cardiac events in the younger group, as well as all-cause and cardiovascular mortality, stroke, and cardiac events in the older group. Of note, in the latter group, 24-hour mean arterial pressure independently predicted cardiovascular events and stroke, but not cardiac events or mortality.
2. The additional prognostic contribution of 24-hour PP over and above that provided by traditional risk factors was relatively weak, although significant. The increase in the coefficient of determination, representing the proportion of total variation of outcomes explained by the model, never exceeded 0.3% in the different models.
3. When 24-hour PP and systolic BP were included in the same model (see Table S5 in the online-only Data Supplement of that article), both predicted a higher cardiovascular morbidity in the participants aged >60 years.

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

From Dipartimento di Medicina, Università di Perugia, Perugia, Italy (G.S., G.P.); Struttura Complessa di Medicina Interna, Azienda Ospedaliero-Universitaria di Terni, Terni, Italy (G.S., G.P.); and Yazmonit Ltd, Eshtaol, Israel (B.G.).

Correspondence to Giuseppe Schillaci, Dipartimento di Medicina, Università degli Studi di Perugia, Struttura Complessa di Medicina Interna, Azienda Ospedaliero-Universitaria di Terni, Piazzale Tristano di Joannuccio, 1, IT-05100 Terni, Italy. E-mail giuseppe.schillaci@unipg.it

(*Hypertension*. 2014;63:217-219.)

***Hypertension* is available at http://hyper.ahajournals.org**
DOI: 10.1161/HYPERTENSIONAHA.113.02436

Despite the obvious multicollinearity problems resulting from such analyses, the data suggest that both systolic BP and PP over 24 hours may be prognostically relevant in the elderly participants. Unfortunately, excess risk was expressed differently for PP (risk in the top tenth relative to the average risk in the whole population) and for other BP components (risk associated with 1 SD increase of the variable). This makes it difficult to directly compare the prognostic strength of the different BP measures.

4. The consistency of the above results was confirmed in several sensitivity analyses, which took into account ethnicity, sex, presence or absence of hypertension, and use or nonuse of antihypertensive drugs, as well as daytime and nighttime PP.

The study also provides an answer to the question of whether the various 24-hour BP components have a different impacts on cardiac versus cerebrovascular morbid events. In a previous cohort of 2311 hypertensive subjects,[7] 24-hour PP was the dominant predictor of cardiac events, whereas mean arterial pressure was the strongest predictor of cerebrovascular events. Similarly, in the Ohasama study, 24-hour mean arterial pressure was better than 24-hour PP in predicting stroke.[9] The study extends the above findings to a larger general population. Above the age of 60 years, stroke (n=402 events) was predicted by 24-hour mean arterial pressure (hazard ratio, 1.39 for each SD; 95% confidence interval [CI], 1.23–1.58; $P<0.0001$) at least as well as by PP (hazard ratio, 1.40 for the top tenth relative to the average risk; 95% CI, 1.04–1.89; $P\leq0.05$). However, cardiac events (n=505) were independently predicted by a high 24-hour PP (hazard ratio, 1.69 for the top tenth relative to the average risk; 95% CI, 1.33–2.15; $P<0.0001$), not by mean arterial pressure. Also, total and cardiovascular mortality were predicted by pulse, not mean, pressure. Similarly, when 24-hour systolic BP and PP were both included as explanatory variables in the same model in the older group, systolic BP predicted stroke, whereas PP predicted cardiac events (see Table S5 in that article). By and large, these results are in line with those of observational studies based on office BP, in which PP was less useful in predicting long-term stroke risk compared with either mean or systolic BP.[11,12] This may not be an unexpected finding if one considers that a wide PP might reflect diffuse atherosclerotic processes potentially involving the large coronary arteries as well, whereas the small penetrating end-arteries that supply the medial and basal portions of brain and brain stem may be particularly vulnerable to the adverse effects of steady BP components (mean and systolic BP) because they arise directly from the main arterial trunks.

Besides the limitations inherent in nonexperimental observational studies,[13] probably the main shortcoming of the article is that it does not provide an answer to the controversial issue of whether PP has a different prognostic impact in the young adult versus the elderly group. The number of events in the young group was relatively low, especially when considering specific outcomes—67 cardiovascular deaths, 63 strokes, 153 cardiac events. More importantly, the average age of individuals in the young group who will have an event was relatively high. Only 4 cardiovascular deaths and 11 cardiovascular events were observed in the subjects aged <50 years at enrollment; corresponding figures for those <55 years were 11 and 36, respectively. Because most of the events in the young cohort were reported in subjects who entered the study at >55 years and were followed for >10 years, we cannot derive from this study reliable information on whether PP in the young (ie, below the age of 50 as suggested in the Framingham study)[2] is less harmful than in older subjects.

In summary, the study by Gu et al[10] convincingly demonstrates that an elevated PP over 24 hours, namely >56 mm Hg and >69 mm Hg in individuals below and above the age of 60 years respectively, is an independent predictor of cardiovascular risk in the general population. Do these data support the use of 24-hour PP as an additional tool for cardiovascular risk stratification? Although compelling, the study results are also somewhat contrasting. The "glass half full" side is that 24-hour PP provides independent prognostic information, at least in the elderly group. This is particularly true for cardiac events, whereas its predictive value for stroke is not superior or even lower than that of other BP components. The "glass half empty" side is that the incremental prognostic information provided by PP is small, with a contribution <0.3% to the coefficient of determination. Although clinical trials and observational studies remain the mainstay for establishing the clinical role of PP, future research should also focus on the pathophysiological determinants of PP in different age groups. Since arterial properties change continuously during the cardiac cycle, PP can be considered as the expression of the progressive increase in stiffness which is observed from diastolic to systolic pressure values.[14] It is hoped that appropriate modeling may add further insight into the relation of arterial properties with PP and its clinical consequences.

Disclosures

None.

References

1. Schillaci G, Pirro M, Mannarino E. Assessing cardiovascular risk: should we discard diastolic blood pressure? *Circulation*. 2009;119:210–212.
2. Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, Levy D. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. *Circulation*. 2001;103:1245–1249.
3. Mancia G, Fagard R, Narkiewicz K, et al; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31:1281–1357.
4. Mancia G, Bertinieri G, Grassi G, Parati G, Pomidossi G, Ferrari A, Gregorini L, Zanchetti A. Effects of blood-pressure measurement by the doctor on patient's blood pressure and heart rate. *Lancet*. 1983;2:695–698.
5. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Pede S, Porcellati C. Ambulatory pulse pressure: a potent predictor of total cardiovascular risk in hypertension. *Hypertension*. 1998;32:983–988.
6. Khattar RS, Swales JD, Dore C, Senior R, Lahiri A. Effect of aging on the prognostic significance of ambulatory systolic, diastolic, and pulse pressure in essential hypertension. *Circulation*. 2001;104:783–789.
7. Verdecchia P, Schillaci G, Reboldi G, Franklin SS, Porcellati C. Different prognostic impact of 24-hour mean blood pressure and pulse pressure on stroke and coronary artery disease in essential hypertension. *Circulation*. 2001;103:2579–2584.
8. Staessen JA, Thijs L, O'Brien ET, Bulpitt CJ, de Leeuw PW, Fagard RH, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J, Safar ME; Syst-Eur Trial Investigators. Ambulatory pulse pressure as predictor of outcome in older patients with systolic hypertension. *Am J Hypertens*. 2002;15(10 Pt 1):835–843.

9. Inoue R, Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hoshi H, Hashimoto J, Totsune K, Satoh H, Kondo Y, Imai Y. Predicting stroke using 4 ambulatory blood pressure monitoring-derived blood pressure indices: the Ohasama Study. *Hypertension*. 2006;48:877–882.
10. Gu Y-M, Thijs L, Li Y, et al, on behalf of the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) Investigators. Outcome-driven thresholds for ambulatory pulse pressure in 9938 participants recruited from 11 populations. *Hypertension*. 2014;63:229–237.
11. Miura K, Soyama Y, Morikawa Y, Nishijo M, Nakanishi Y, Naruse Y, Yoshita K, Kagamimori S, Nakagawa H. Comparison of four blood pressure indexes for the prediction of 10-year stroke risk in middle-aged and older Asians. *Hypertension*. 2004;44:715–720.
12. Vishram JK, Borglykke A, Andreasen AH, et al; MORGAM Project. Impact of age on the importance of systolic and diastolic blood pressures for stroke risk: the MOnica, Risk, Genetics, Archiving, and Monograph (MORGAM) Project. *Hypertension*. 2012;60:1117–1123.
13. Schillaci G, Battista F, Pucci G. Are observational studies more informative than randomized controlled trials in hypertension? Con side of the argument. *Hypertension*. 2013;62:470–476.
14. Gavish B. The relationship between systolic and diastolic pressures: a possible link between risk-related clinical measures and arterial properties. *Hypertens Res*. 2010;33:657–658.

Hypertension
Journal of the American Heart Association

Ambulatory Pulse Pressure: Does It Improve Cardiovascular Risk Stratification?

Giuseppe Schillaci, Giacomo Pucci and Benjamin Gavish

Hypertension. 2014;63:217-219; originally published online December 9, 2013;
doi: 10.1161/HYPERTENSIONAHA.113.02436
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563