Original articles

A low pulse pressure is an independent predictor of mortality in heart failure: data from a large nationwide cardiology database (IN-CHF Registry)

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Blood pressure; Epidemiology; Heart failure; Prognosis.

Background. **A high pulse pressure (PP) predicts cardiovascular mortality in hypertension and in the elderly. We analyzed the data from the Italian Network of Congestive Heart Failure Registry to test the prognostic role of PP in patients with heart failure.**

Methods. **A total of 8660 patients with heart failure (mean age 64 ± 12 years, 73% male) were divided into four groups according to their PP (< 40, 40-49, 50-59, and ≥ 60 mmHg), and followed prospectively.**

Results. **After 1 year, 995 patients (11.5%) died. Both the mean arterial pressure and systolic blood pressure were found to be inversely associated with mortality at univariate and multivariate analyses. An inverse univariate relation was observed between PP and all-cause mortality. An excess mortality risk in the lowest PP group (odds ratio 1.40, 95% confidence interval 1.09-1.79 vs the highest PP group) was confirmed in a multivariate analysis which took into account the effect of several other variables, including mean arterial pressure. Similar findings were obtained for cardiovascular mortality. When we replaced systolic blood pressure with mean arterial pressure in the model, PP did not retain its independent prognostic role, possibly because of the high co-linearity between these two variables (r = 0.87).**

Conclusions. **For any given level of mean arterial pressure, a low PP is an independent predictor of all-cause and cardiovascular death in patients with heart failure. The association may be partly related to the strong influence of low systolic blood pressure on mortality. Different pathophysiological mechanisms may underlie the opposite prognostic significance of PP in hypertension and heart failure.**

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See Appendix for a complete list of participating Centers and Investigators.

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Introduction

Several studies have demonstrated that a high pulse pressure (PP) is an independent cardiovascular risk factor in the general population[1-3], in hypertensive patients[4-6], and in patients with previous myocardial infarction and an impaired left ventricular function[7,8]. This adverse association has been shown to be independent of mean arterial pressure and other covariates believed to influence the cardiovascular outcome. It has also been speculated that an increased PP may help to explain the higher incidence of stroke in patients with isolated systolic hypertension as opposed to those with diastolic or mixed systolic/diastolic hypertension[9].

PP is considered a crude index of aortic stiffness. An increased stiffness of the conduit vessels results in an increased characteristic impedance of the aorta and decreased arterial compliance, which in turn cause an increase in systolic blood pressure (BP) and PP, as well as a decrease in diastolic BP. In addition, arterial stiffness causes an increase in pulse-wave velocity. A greater pulse-wave velocity results in a premature rebound of the reflected pressure wave to the central aorta during systole rather than during diastole and this further increases PP. On the other hand, for any given level of aortic stiffness, a high PP is determined by stroke volume and the rate of left ventricular ejection[10,11].

Given the complex interplay between the multiple determinants of PP, the results obtained in the general or hypertensive populations may not be automatically extended to other settings. As a matter of fact, mean arterial pressure is directly associated with mortality in the general population[12], but inversely related in congestive heart failure[13]. We speculated that the prognostic value of PP in patients with clinically overt congestive heart failure might differ from that of subjects without heart failure, possibly because in these patients PP might be more critically dependent on left ventricular ejection. In the present study, we used the database of the Italian Network of Congestive Heart Failure (IN-CHF)[14,15], a nationwide, observational, multicenter investigation, to explore the association between PP as a measure of pulsatile BP load and all-cause and cardiovascular mortality in a large population of outpatients with heart failure, after considering the confounding effect of mean arterial pressure and several other covariates.

Methods

A total of 11 070 consecutive patients with congestive heart failure were enrolled in the IN-CHF Registry from March 1995 to December 1999[14,15]. The present analysis includes 8660 patients for whom complete 1-year follow-up data were available on January 1, 2002.

The IN-CHF Registry is a survey designed by an *ad hoc* Committee of the Italian Association of Hospital Cardiologists (ANMCO, Florence, Italy). Patients were recruited into the study and followed up for 1 year at 150 centers distributed across the whole country. Centers are more frequently located in Northern (46%) than in Central (24%) or Southern (30%) Italy, but well represent the Italian country. Short training sessions were organized to prepare clinicians to collect and enter data following standardized methods. Using an *ad hoc* designed software, the patients' data were recorded at each center by trained cardiologists and then pooled into a single database at the ANMCO Research Center. Entry into the database required that the patient had a diagnosis of congestive heart failure based on the guidelines of the European Society of Cardiology[16]. Demographic, clinical, instrumental and laboratory variables, and information on drug therapy were collected for each patient. A single BP measurement was obtained by sphygmomanometry at the time of enrollment. PP was calculated as the difference between systolic and diastolic BP. Mean arterial pressure was calculated as (2 × diastolic BP + systolic BP)/3. Subjects were divided into four groups according to their PP at enrollment: < 40, 40-49, 50-59, and ≥ 60 mmHg.

Patients were followed according to the routine clinical practice of the participating centers. In case of out-of-hospital death, the event was confirmed by telephone interview with the patient's relatives, using a standard questionnaire specifically aimed at determining the mode of death.

Statistical analysis. Data were prospectively collected by the participating centers using *ad hoc* local software and sent periodically to the ANMCO Research Center for statistical analysis. Data were analyzed using the SAS statistical package (SAS Institute Inc., Cary, NC, USA). The study groups were compared by means of analysis of variance for continuous variables, and using the χ^2 test for categorical variables. A logistic regression model was performed to test the effect of several potential predictors of mortality at 1 year. Fifty-nine patients were excluded from the logistic analysis because their heart rate data were missing.

The following variables were considered in the multivariate analysis: age, gender, heart rate, mean arterial pressure (or systolic BP), functional class (NYHA III-IV vs I-II), etiology (ischemic vs non-ischemic), left ventricular ejection fraction (< 30 vs ≥ 30%), atrial fibrillation, third heart sound, ventricular tachycardia, previous hospital admissions for heart failure, and the use of digoxin, diuretics, angiotensin-converting enzyme inhibitors and beta-blockers.

Systolic BP and mean arterial pressure were considered as continuous variables. With regard to PP, four groups (< 40, 40-49, 50-59, and ≥ 60 mmHg) were considered and three dummy variables were defined (< 40 vs ≥ 60 mmHg, 40-49 vs ≥ 60 mmHg, and 50-59 vs ≥ 60 mmHg). A p value of < 0.05 was considered as statistically significant.

Results

The main characteristics of the study population are reported in table I. The mean age was 64 ± 12 years. Twenty-seven percent of subjects were women, and 30% were classified as being in NYHA class III or IV. Patients in the lowest PP group (< 40 mmHg) appeared to be younger, more frequently male, and had more severe heart failure. As expected, patients with higher PP values also had higher systolic BP. More interestingly, even diastolic BP tended to increase across the PP groups, as a result of the strong direct association between PP and systolic BP ($r = 0.87$, $p < 0.0001$).

After 1 year of follow-up, 995 patients (11.5%) died, among whom 731 (73%) of cardiovascular causes. The causes of death are reported on table II. As depicted in figure 1, an inverse relation was found between PP and mortality. The all-cause death rate at 1 year was 18.4, 12.0, 10.2, and 9.0% in the first, second, third and fourth groups of the PP distribution, respectively. The corresponding cardiovascular death rates in the four groups were 13.9, 9.2, 7.8, and 6.0%. The Kaplan-Meier curves of survival by baseline PP are reported in figure 2. At multivariate analysis, both mean

Table I. Clinical characteristics of 8660 patients with congestive heart failure, divided by their baseline pulse pressure.

	All (n=8660)	Pulse pressure (mmHg)				p
		< 40 (n=1341)	40-49 (n=2128)	50-59 (n=2096)	≥ 60 (n=3095)	
Age (years)	64 ± 12	58 ± 13	61 ± 12	64 ± 12	68 ± 10	< 0.0001
Females	2334 (27%)	249 (19%)	475 (22%)	519 (25%)	1091 (35%)	< 0.0001
NYHA class III or IV	2625 (30%)	593 (44%)	681 (32%)	563 (27%)	788 (26%)	< 0.0001
Ejection fraction						< 0.0001
< 30%	1741 (20%)	449 (33%)	505 (24%)	424 (20%)	363 (12%)	
≥ 30%	3552 (41%)	412 (31%)	865 (41%)	898 (43%)	1377 (44%)	
Not available	3367 (39%)	480 (36%)	758 (35%)	774 (37%)	1355 (44%)	
Heart rate > 100 b/min	561 (7%)	115 (9%)	127 (6%)	121 (6%)	198 (6%)	0.006
Previous hospitalization	4890 (56%)	924 (69%)	1260 (59%)	1143 (54%)	1563 (50%)	< 0.0001
Ischemic etiology	3468 (40%)	590 (44%)	866 (41%)	849 (41%)	1163 (38%)	0.0007
Diabetes	963 (11%)	101 (8%)	191 (9%)	216 (10%)	455 (15%)	< 0.0001
Systolic BP (mmHg)	132 ± 22	105 ± 11	118 ± 10	130 ± 11	152 ± 16	< 0.0001
Diastolic BP (mmHg)	79 ± 11	75 ± 10	77 ± 10	79 ± 10	82 ± 11	< 0.0001
Systolic BP (mmHg)						< 0.0001
> 120	5135 (59%)	64 (5%)	498 (23%)	1535 (73%)	3038 (98%)	
100-120	3220 (37%)	987 (74%)	1615 (76%)	561 (27%)	57 (2%)	
< 100	305 (4%)	290 (22%)	15 (1%)	0	0	

BP = blood pressure.

Table II. Causes of death at 1 year for 8660 patients with congestive heart failure.

Worsening heart failure	272 (27%)
Sudden death	411 (41%)
Coronary artery disease	28 (3%)
Stroke	13 (1%)
Systemic embolism	7 (1%)
Pulmonary embolism	12 (1%)
Other	111 (11%)
Non-cardiac	57 (6%)
Unknown	84 (9%)
All causes	995 (100%)

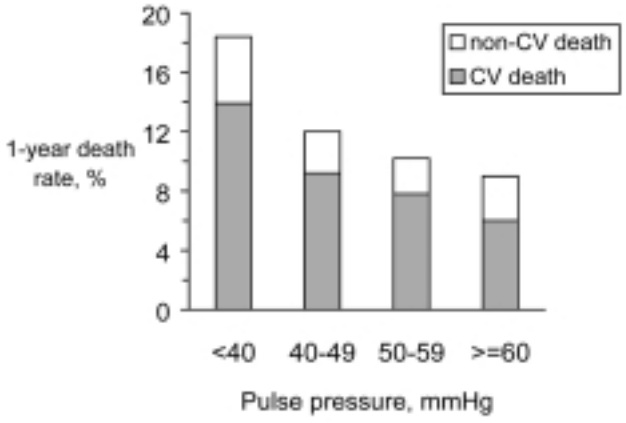

Figure 1. *One-year cardiovascular (CV) and non-CV death rates by baseline pulse pressure for 8660 patients with congestive heart failure.*

arterial pressure (odds ratio [OR] 0.98, 95% confidence interval [CI] 0.97-0.99) and systolic BP (OR 0.98, 95% CI 0.98-0.99) showed an independent inverse association with total mortality.

The excess risk for all-cause and cardiovascular mortality in the lowest PP group (Fig. 1) was confirmed in a multivariate analysis which took into account the effect of several other variables, including mean arterial pressure, age, sex, heart rate, NYHA class, atrial fibrillation, left ventricular ejection fraction, ventricular arrhythmias, renal dysfunction, and the use of digoxin, diuretics, angiotensin-converting enzyme inhibitors, and beta-blockers (Table III). In comparison to the group with the highest PP (≥ 60 mmHg), the group with the lowest PP (< 40 mmHg) showed a significant 40% excess risk for all-cause death (95% CI 9 to 79%) and a 47% excess risk for cardiovascular death (95% CI 10 to 95%).

When, in the model, we replaced mean arterial pressure with systolic BP, PP did not retain its independent prognostic role (all-cause death OR for the lowest vs highest PP group = 1.013, 95% CI 0.726-1.414, p = NS), possibly because of the strong direct correlation between systolic BP and PP (r = 0.87, p < 0.0001).

To explore the hypothesis that a low PP in this population might be a hallmark of poor ventricular systolic function, we separately examined those patients for whom left ventricular ejection fraction was available (n = 5293). In the subgroup with an ejection fraction < 40% (n = 3578, with a total of 476 all-cause deaths), a multivariate analysis was run which incorporated all the above variables, including mean arterial pressure and PP, plus ejection fraction as a continuous variable. In this model, both mean arterial pressure (OR 0.985, 95% CI 0.976-0.994, p < 0.001) and ejection fraction

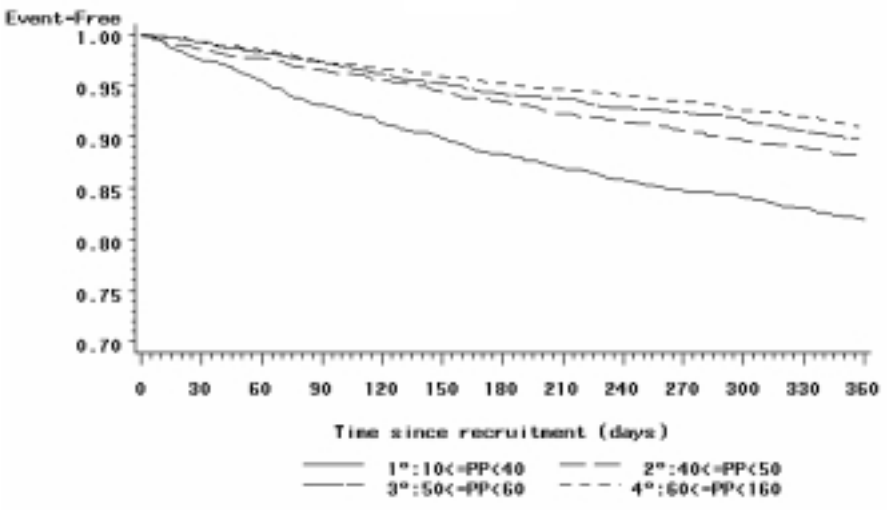

Figure 2. *Kaplan-Meier survival curves by baseline pulse pressure (PP) for 8660 patients with congestive heart failure.*

Table III. Independent predictors of the 1-year all-cause and cardiovascular mortalities for 8601 patients with congestive heart failure.

	Odds ratio (95% confidence limits)	
	All-cause mortality	Cardiovascular mortality
Age (years)	1.028 (1.021-1.035)	1.029 (1.020-1.037)
Mean arterial pressure (mmHg)	0.980 (0.974-0.987)	0.979 (0.971-0.987)
Heart rate (b/min)	1.007 (1.003-1.012)	1.008 (1.002-1.013)
NYHA class III-IV	1.795 (1.549-2.080)	1.710 (1.445-2.023)
Ischemic etiology	1.187 (1.025-1.376)	1.241 (1.050-1.468)
Previous hospitalization	1.582 (1.351-1.853)	1.532 (1.277-1.839)
Third heart sound	1.447 (1.239-1.689)	1.541 (1.295-1.835)
Serum creatinine > 2.5 mg/dl	2.201 (1.419-3.414)	1.751 (1.061-2.892)
Ventricular tachycardia	1.519 (1.118-2.066)	1.861 (1.319-2.624)
Ejection fraction < 30%	–	1.327 (1.073-1.641)
Pulse pressure < 40 vs ≥ 60 mmHg	1.396 (1.089-1.789)	1.465 (1.102-1.948)
Cardiothoracic ratio	–	1.634 (1.003-2.663)
Use of digoxin	0.736 (0.620-0.874)	0.764 (0.628-0.930)
Use of diuretics	0.572 (0.430-0.762)	0.634 (0.460-0.875)
Use of ACE-inhibitors	1.236 (1.038-1.473)	1.292 (1.061-1.573)
Use of beta-blockers	1.291 (1.039-1.604)	1.304 (1.014-1.677)

ACE = angiotensin-converting enzyme.

(OR 0.975, 95% CI 0.961-0.989, $p < 0.001$) showed an independent inverse association with total mortality, while PP had no independent prognostic significance.

Discussion

The present analysis investigates the impact of PP on the risk of death in a cohort of patients with chronic heart failure. It demonstrates that a low PP is associated with an increased risk of all-cause and cardiovascular death independent of the confounding effects of mean arterial pressure and several other variables.

BP has been traditionally measured in terms of peak (systolic) and trough (diastolic) values, but a more physiological interpretation considers BP waveform as being composed of a steady component (mean arterial pressure), upon which cyclic oscillations, represented by PP, are superimposed. PP, the difference between systolic and diastolic BP, is an easily measurable correlate of the pulsatile hemodynamic load during the cardiac cycle. It is a complex parameter which is modified not only by large-artery stiffness and the timing of the reflected waves from the peripheral circulation, but also by heart rate and the pattern of left ventricular ejection[10]. At any given value of left ventricular ejection and heart rate, large-artery stiffness and wave reflection represent the major determinants of PP. In contrast, the steady component of arterial pressure, estimated by mean arterial pressure, is entirely determined by cardiac output and peripheral resistance governed by the arteriolar system[11].

A link has been observed between the stiffness of the conduit vessels and cardiovascular morbidity and mortality. Measures of aortic stiffness have been demonstrated to be associated with left ventricular hypertrophy[17], myocardial infarction[1,3], stroke[18] and congestive heart failure[19] both in normotensive and hypertensive populations. Stiffening of the conduit vessels increases the pulse-wave velocity, which results in a premature return of the reflected pressure wave to the heart during systole. The reflected pressure wave adds to the forward wave and increases left ventricular afterload, whereas the reflected flow wave diminishes the forward flow and stroke volume[20]. An earlier return of the reflected wave from diastole into systole diminishes coronary diastolic perfusion pressure and has been shown to produce ischemia in animal models both with[21] and without[22] epicardial coronary stenoses.

This study demonstrates that, in patients with heart failure, a low PP is an independent risk factor for cardiovascular and total mortality for every given level of mean arterial pressure. Thus, the pulsatile component of BP in patients with congestive heart failure is related to mortality in a manner which appears to be quite different from that observed in the general[1-3] or hypertensive[4-6] populations. A potential explanation for this finding is that in patients with heart failure, low PP values may preferentially reflect a more advanced degree of cardiac dysfunction, which in turn confers an increased risk of death. In these patients, the reduction in ventricular function might obscure any direct relation between PP, as a measure of conduit vessel stiffness, and adverse events. In heart failure, a low PP may be the hallmark of an impaired left ventricular function, with a consequent low forward flow and stroke volume, more than an index of arterial stiffness. We suggest that a decreased PP in heart failure may be a sign of a decrease in systolic BP consequent to a reduced left ventricular performance more than to an increase in diastolic BP. This hypothesis is supported by the fact that when systolic BP is considered in the multivariate analysis, PP does not retain its prognostic significance to confirm a close correlation between these two variables. On the other hand, an increased PP might preferentially reflect an increased conduit artery stiffness and its detrimental prognostic effect in populations free from congestive heart failure, especially the elderly. Quite interestingly, the existence of a monotonically linear relationship between PP and mortality has been questioned by a recent analysis of a representative sample of the non-institutionalized United States population aged ≥ 65 years[23], in which a J-shaped association between PP and mortality was found, with a change point estimate set at 41.8 mmHg for all-cause mortality and 35.5 mmHg for cardiovascular mortality. As stated by the authors, the clinical implications of this observation remain uncertain because of the limited number of observations below the change point. Our findings extend those observations to a large, nationwide representative sample of outpatients with congestive heart failure.

These data are at variance with those reported in two previously published studies which had enrolled patients with left ventricular dysfunction and previous myocardial infarction[7,8]. In the Survival and Ventricular Enlargement study[7], 2231 patients with a left ventricular ejection fraction ≤ 40% and no overt congestive heart failure were enrolled early (3-16 days) after myocardial infarction. In such patients, a direct linear relationship between PP and total mortality, as well as recurrent myocardial infarction, was observed. This study included a highly selected population of patients with a recent myocardial infarction, an impaired left ventricular function and no clinically overt heart failure; therefore, these results are not easily comparable with ours. PP was an independent predictor of death also in the Studies of Left Ventricular Dysfunction, in which 6781 patients with asymptomatic (62%) or symptomatic (38%) heart failure were followed for 3.2 years[8]. However, several differences between this study and the IN-CHF database deserve to be mentioned. The all-cause death rate at 1 year was 7% in the Studies of Left Ventricular Dysfunction, while it was 11.5% in our study. In the former study, only patients who were eligible for treatment with angiotensin-converting enzyme inhibitors were enrolled, while the IN-CHF database included an unselected population with heart failure enrolled during routine clinical practice. For this reason, 19% of the enrolled patients were not receiving angiotensin-converting enzyme inhibitors. Thus, the population of the present registry appears to be at considerably higher risk than those of the two previous studies[7,8]. Our large, nationwide database of unselected outpatients with congestive heart failure of different etiologies may be considered as being more representative of the real-world population of patients with heart failure. We might speculate that in patients with more advanced degrees of heart failure, PP may more critically depend on left ventricular systolic performance than on large-artery stiffness. Interestingly, preliminary data from the Studies of Left Ventricular Dysfunction show that a low PP predicts a worse outcome in patients with severe heart failure, but not in those with milder degrees of disease[24]. Indeed, in our study, when the ejection fraction was included among the covariates as a continuous variable, PP no longer remained an independent predictor of mortality in the higher risk subgroup of patients with low systolic function.

A limitation of the present study is that the results were based on a single measurement of BP, and thus are probably underestimates of true associations due to regression dilution bias. Nevertheless, as shown in many prospective studies, a single BP reading is strongly predictive of future cardiovascular mortality.

In conclusion, a low PP is independently related to a worse outcome for every given level of mean arterial pressure in a large, unselected, nationwide outpatient

population of individuals with heart failure. The adverse prognostic significance of a high PP, which had been documented in other clinical settings[1-6], was not confirmed in this population. Overall, these data suggest that high PP values may preferentially reflect low arterial compliance in hypertension and in the general population, while they may be more closely related to the maintenance of an adequate stroke volume in chronic heart failure.

Appendix

Participating Centers and Investigators

Piemonte Borgomanero (A. Mezzani, M. Bielli); Cuneo (U. Milanese, G. Ugliengo); Orbassano (R. Pozzi, F. Rabajoli); Veruno (E. Bosimini); *Valle d'Aosta* Aosta (G. Begliuomini); *Lombardia* Belgioioso (A. Ferrari, F. Barzizza); Bergamo (M.G. Valsecchi, F. Dadda); Brescia (P. Faggiano); Cassano d'Adda (G. Castiglioni, G. Gibelli); Chiari (A.L. Turelli); Como (R. Belluschi); Cremona (C. Bianchi, C. Emanuelli); Desio (S. Gramenzi, G. Foti); Erba Medicina (D. Agnelli); Esine (G. Mascioli); Garbagnate Milanese (E. Cazzani); Gussago (E. Zanelli, D. Domenighini); Legnano (C. Castelli); Mariano Comense (E. Moroni); Milano Fondazione Don Gnocchi (E. Gara); Milano Ospedale Sacco Medicina (S. Guzzetti, S. Muzzupappa, M. Turiel, E. Cappiello, G. Sandrone); Milano Ospedale Niguarda II Cardiologia (F. Recalcati); Milano Pio Albergo Trivulzio (D. Valenti); Monza (F. Achilli, A. Vincenzi); Passirana (F. Rusconi, M. Palvarini); Pavia Policlinico San Matteo (S. Ghio, A. Fontana, A. Giusti, L. Scelsi, R. 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References

1. Darne B, Girerd X, Safar M, Cambien F, Guize L. Pulsatile versus steady component of blood pressure: a cross-sectional analysis and a prospective analysis on cardiovascular mortality. Hypertension 1989; 13: 392-400.
2. Benetos A, Safar M, Rudnichi A, et al. Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. Hypertension 1997; 30: 1410-5.
3. Madhavan S, Ooi WL, Cohen H, Alderman MH. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. Hypertension 1994; 23: 395-401.
4. Fang J, Madhavan S, Cohen H, Alderman MH. Measures of blood pressure and myocardial infarction in treated hypertensive patients. J Hypertens 1995; 13: 413-9.
5. Abernethy J, Borhani NO, Hawkins CM, et al. Systolic blood pressure as an independent predictor of mortality in

the Hypertension Detection and Follow-Up Program. Am J Prev Med 1986; 2: 123-32.
6. 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: 983-8.
7. Mitchell G, Moye L, Braunwald E, et al, for the SAVE Investigators. Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. Circulation 1997; 96: 4254-60.
8. Domanski MJ, Mitchell GF, Norman J, Pitt B, Exener D, Pfeffer MA. Independent prognostic information provided by sphygmomanometrically determined pulse pressure and mean arterial pressure in patients with left ventricular dysfunction. J Am Coll Cardiol 1999; 33: 951-8.
9. Nielsen WB, Lindenstrom E, Vestbo J, Jensen GB. Is diastolic hypertension an independent risk factor for stroke in the presence of normal systolic blood pressure in the middle-aged and elderly? Am J Hypertens 1997; 10: 634-9.
10. Safar ME. Pulse pressure in essential hypertension: clinical and therapeutical implications. J Hypertens 1989; 7: 769-76.
11. Benetos A, Laurent S, Asmar RG, Lacolley P. Large artery stiffness in hypertension. J Hypertens 1997; 15 (Suppl): S89-S97.
12. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-13.
13. Cleland JG, Dargie HJ, Ford I. Mortality in heart failure: clinical variables of prognostic value. Br Heart J 1987; 58: 572-82.
14. Pulignano G, Del Sindaco D, Tavazzi L, et al, on behalf of IN-CHF Investigators. Clinical features and outcomes of elderly outpatients with heart failure followed up in hospital cardiology units: data from a large nationwide cardiology database (IN-CHF Registry). Am Heart J 2002; 143: 45-55.
15. Baldasseroni S, De Biase L, Fresco C, et al, on behalf of the Italian Network on Congestive Heart Failure (IN-CHF) Investigators. Cumulative effect of complete left bundle-branch block and chronic atrial fibrillation on 1-year mortality and hospitalization in patients with congestive heart failure. Eur Heart J 2002; 23: 1692-8.
16. Remme WJ, Swedberg K, on behalf of the Task Force for the Diagnosis and Treatment of Chronic Heart Failure, European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001; 22: 1527-60.
17. Girerd X, Laurent S, Pannier B, Asmar R, Safar M. Arterial distensibility and left ventricular hypertrophy in patients with sustained essential hypertension. Am Heart J 1991; 122: 1210-4.
18. Kannel WB, Wolf PA, McGee DL, Dawber TR, McNamara P, Castelli WP. Systolic blood pressure, arterial rigidity, and risk of stroke: the Framingham study. JAMA 1981; 245: 1225-9.
19. Chae C, Pfeffer M, Glynn RJ, Mitchell GF, Taylor JO, Hennekens C. Increased pulse pressure and risk of heart failure in the elderly. JAMA 1999; 281: 634-9.
20. Nichols WW, O'Rourke MF. McDonald's blood flow in arteries. 3rd edition. Philadelphia, PA: Lea & Febiger, 1990: 216-50.
21. Watanabe H, Ohtsuka S, Kakihana M, Sugishita Y. Coronary circulation in dogs with an experimental decrease in aortic compliance. J Am Coll Cardiol 1993; 21: 1497-506.
22. Buckberg GD, Fixler DE, Archie JP, Hoffman JI. Experimental subendocardial ischemia in dogs with normal coronary arteries. Circ Res 1972; 30: 67-81.
23. Pastor-Barriuso R, Banegas JR, Damian J, Appel LJ, Guallar E. Systolic blood pressure, diastolic blood pressure, and pulse pressure: an evaluation of their joint effect on mortality. Ann Intern Med 2003; 139: 731-9.
24. Kostis JB, Ranjan R, Wilson AC, Nelson LJ, Subraya RG, Lacy CR. High pulse pressure predicts better outcomes in patients with severe heart failure in SOLVD. (abstr) J Hypertens 2002; 20 (Suppl 4): S82.