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Independent Prognostic Information Provided by Sphygmomanometrically Determined Pulse Pressure and Mean Arterial Pressure in Patients With Left Ventricular Dysfunction

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OBJECTIVES The purpose of this study was to evaluate the relationship of baseline pulse pressure and mean arterial pressure to mortality in patients with left ventricular dysfunction.

BACKGROUND Increased conduit vessel stiffness increases pulse pressure and pulsatile load, potentially contributing to adverse outcomes in patients with left ventricular dysfunction.

METHODS Pulse and mean arterial pressure were analyzed for their effect on mortality, adjusting for other modifiers of risk, using Cox proportional hazards regression analysis of data collected from 6,781 patients randomized into the Studies of Left Ventricular Dysfunction trials.

RESULTS Pulse and mean arterial pressure were related positively to each other, age, ejection fraction and prevalence of diabetes and hypertension and inversely to prior myocardial infarction and beta-adrenergic blocking agent use. Higher pulse pressure was associated with increased prevalence of female gender, greater calcium channel blocking agent, digoxin and diuretic use, lower heart rate and a higher rate of reported smoking history. Higher mean arterial pressure was associated with higher heart rate, lower calcium channel blocker and digoxin use and lower New York Heart Association functional class. Over a 61-month follow-up 1,582 deaths (1,397 cardiovascular) occurred. In a multivariate analysis adjusting for the above covariates and treatment assignment, higher pulse pressure remained an independent predictor of total and cardiovascular mortality (total mortality relative risk, 1.05 per 10 mm Hg increment; 95% confidence interval, 1.01 to 1.10; $p = 0.02$). Mean arterial pressure was inversely related to total and cardiovascular mortality (total mortality relative risk, 0.89; 95% confidence interval, 0.85 to 0.94; $p < 0.0001$).

CONCLUSIONS One noninvasive blood pressure measurement provides two independent prognostic factors for survival. Increased conduit vessel stiffness, as assessed by pulse pressure, may contribute to increased mortality in patients with left ventricular dysfunction, independent of mean arterial pressure. (J Am Coll Cardiol 1999;33:951–8) © 1999 by the American College of Cardiology

Common clinical wisdom suggests that reduced pulse pressure is associated with worse outcome in patients with left ventricular dysfunction and heart failure. However, the Survival and Ventricular Enlargement (SAVE) investigators have reported a seemingly paradoxical association between increased pulse pressure and adverse events after myocardial infarction in patients with left ventricular dysfunction (1). These investigators have suggested that increased conduit vessel stiffness, which may be due to elastin degeneration, collagen deposition or smooth muscle activation, increases pulse pressure and pulsatile load on the left ventricle and may contribute to an adverse outcome in patients with left ventricular dysfunction. A number of other prognostic markers have been identified in patients with heart failure, including New York Heart Association (NYHA) functional class, etiology, age, exercise performance, neurohumoral activation and alterations in both right and left ventricular function, size and shape. Neurohumoral activation is generally associated with advanced left ventricular dysfunction and reduced mean arterial pressure. This compensatory mechanism activates smooth muscle in both conduit and resistance vessels and serves to maintain mean arterial

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Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
CI	=	confidence interval
NYHA	=	New York Heart Association
SAVE	=	Survival and Ventricular Enlargement
SOLVD	=	Studies of Left Ventricular Dysfunction

pressure at the expense of increased peripheral vascular resistance and conduit vessel stiffness (2). Thus, pulse pressure and mean arterial pressure, calculated from sphygmomanometric blood pressure, may provide additional readily obtainable prognostic information in patients with heart failure.

The Studies of Left Ventricular Dysfunction (SOLVD) were designed to evaluate the effects of the angiotensin-converting enzyme (ACE) inhibitor enalapril in patients with left ventricular dysfunction (3,4). The patients in this study were sufficiently well characterized to permit a systematic examination of the effects of pulse pressure and mean arterial pressure after correcting for a number of well known covariates and comorbidities. Furthermore, the SOLVD trials included a broader spectrum of patients with more severe impairment of left ventricular function than the SAVE study, including a substantial number of patients with symptomatic heart failure. Thus, the specific aims of the present study were 1) to examine the independent prognostic information about all cause and cardiovascular mortality provided by sphygmomanometrically determined pulse pressure in patients with left ventricular dysfunction, and 2) to quantify the prognostic effect of mean arterial pressure in these patients.

METHODS

The SOLVD were a concurrent pair of randomized, double-blind, placebo-controlled trials designed to determine whether long-term therapy with the ACE inhibitor enalapril would improve survival in symptomatic (treatment trial) and asymptomatic (prevention trial) patients with left ventricular systolic dysfunction (3,4). Patients ≤80 years old who were not already on an ACE inhibitor and who had a left ventricular ejection fraction ≤0.35 were randomized to treatment with either enalapril or placebo. The patients clinically assessed as symptomatic (n = 2,569) were followed for a mean of 41.1 months, and the asymptomatic patients (n = 4,228) were followed for a mean of 37.4 months. For the current analysis, 16 patients did not have a valid baseline blood pressure at the time of randomization and were excluded (n = 6,781). The primary end point of the studies was total (all cause) mortality. The secondary end point of cardiovascular death was also evaluated in the present analysis. Before randomization, patient demographic information was obtained, and a history and physical examination were performed. This baseline information, including sphygmomanometrically determined arterial blood pressure just before randomization, is the primary focus of this study. Pulse pressure was determined by subtracting the diastolic from the systolic blood pressure, and mean arterial pressure was calculated by using the formula: [(systolic blood pressure) + (2 × diastolic blood pressure)]/3. The relationship between mean arterial pressure, pulse pressure and clinical outcomes was then assessed.

Statistical methods. Mean values for continuous variables and percentages for dichotomous variables known to affect pulse pressure or prognosis were displayed by quartiles of pulse pressure and also by quartiles of mean arterial pressure. Tests for linear trend across quartiles were performed using logistic regression for dichotomous variables and simple regression for continuous variables. Kaplan–Meier survival curve estimates corrected for age and ejection fraction were calculated for the four quartiles of pulse pressure and compared by the log-rank test. Cox proportional hazards regression analyses were performed to estimate the magnitude of changes in risk for both total and cardiovascular mortality conferred by unit changes in pulse pressure and mean arterial pressure, adjusted for ejection fraction, treatment and other patient characteristics by including these factors in the regression model. The effect size unit for pulse pressure and mean arterial pressure was taken as 10 mm Hg. Separate Cox regression analyses were also performed for the Treatment and Prevention trials.

RESULTS

Baseline characteristics of the study population. Evaluation by quartiles of pulse pressure, as anticipated, demonstrated an association between pulse pressure and mean arterial pressure (Table 1). However, the increase in mean pressure in higher pulse pressure quartiles was produced solely by an increase in systolic pressure, as diastolic pressure remained unchanged across the quartiles. A higher pulse pressure was associated with more advanced age, higher prevalences of hypertension and diabetes, female gender and a lower prevalence of prior myocardial infarction (Table 1). Although quantitatively small, lower heart rate and higher ejection fraction were observed in the higher pulse pressure quartiles. Higher pulse pressure was associated with more frequent use of calcium channel blocking agents, digoxin and diuretics and lower use of beta-adrenergic blocking agents.

Evaluation of quartiles of mean arterial pressure underscored the relatively normal blood pressure distribution curve in this population, with the median value of mean arterial pressure being 93 mm Hg (Table 2). As opposed to pulse pressure, the increase across quartiles of mean arterial pressure was associated with increases in both diastolic and systolic pressure. The lower quartiles of mean arterial pressure were associated with lower age and heart rate, lower prevalence of diabetes and hypertension and a higher prevalence of prior myocardial infarction. There was greater

Table 1. Patient Characteristics by Quartiles of Pulse Pressure

Quartile of Pulse Pressure	First	Second	Third	Fourth	p Value
Number	1,752	1,706	1,655	1,668	—
Mean arterial pulse pressure range (mm Hg)	6 to 38	39 to 46	47 to 56	57 to 110	—
Mean pulse pressure (SD) (mm Hg)	32 (5)	42 (2)	51 (2)	67 (9)	—
Mean systolic blood pressure (SD) (mm Hg)	109 (10)	119 (10)	129 (10)	144 (13)	< 0.0001
Mean diastolic blood pressure (SD) (mm Hg)	77 (9)	77 (9)	78 (10)	77 (11)	NS
Average mean arterial pressure (SD) (mm Hg)	88 (9)	91 (9)	95 (10)	100 (11)	< 0.0001
Age (SD) (years)	55 (10)	59 (10)	61 (9)	64 (8)	< 0.0001
Heart rate (SD)	78 (13)	76 (13)	76 (13)	76 (12)	< 0.0001
Mean NYHA functional class (1–4)	1.7	1.7	1.7	1.7	NS
Ejection fraction (SD)	26 (7)	27 (6)	27 (6)	28 (6)	< 0.0001
History of smoking (%)	25	24	22	21	0.0015
Gender (% female)	13	12	15	18	< 0.0001
Diabetes (%)	13	17	19	28	< 0.0001
Hypertension (%)	30	34	40	52	< 0.0001
Previous MI (%)	76	79	74	69	< 0.0001
Beta-blocker use (%)	21	18	17	16	<0.0001
Calcium channel blocker use (%)	31	32	34	37	<0.0001
Aspirin use (%)	43	50	47	46	NS
Digitalis use (%)	33	29	33	38	<0.0001
Diuretic use (%)	44	39	40	48	0.007
Percent of patients in treatment arm	39	34	37	41	NS

*p value for test for trend.
MI = myocardial infarction; NYHA = New York Heart Association.

use of beta-blockers, calcium channel blockers and digitalis in the lower quartiles. The NYHA functional class was higher in the low mean arterial pressure group as is also indicated by a greater proportion of patients in the Treatment compared to the Prevention arm in the lowest mean arterial pressure group (Table 2).

The effects of pulse pressure were first assessed in a Cox model that adjusted for mean arterial pressure to evaluate

Table 2. Patient Characteristics by Quartiles of Mean Arterial Pressure

Quartile of Mean Arterial Pressure	First	Second	Third	Fourth	p Value
Number	1,745	1,470	1,889	1,677	—
Mean arterial pressure range	59 to 86	87 to 93	94 to 100	101 to 149	—
Mean arterial pressure (SD) (mm Hg)	80 (5)	90 (2)	96 (2)	107 (6)	—
Systolic blood pressure (SD) (mm Hg)	107 (9)	120 (9)	129 (9)	144 (13)	—
Diastolic blood pressure (SD) (mm Hg)	66 (6)	74 (5)	80 (4)	89 (6)	—
Pulse pressure (SD) (mm Hg)	41 (11)	45 (13)	49 (13)	56 (14)	< 0.0001
Age (SD) (yr)	59 (11)	60 (10)	60 (10)	61 (9)	< 0.0001
Heart rate (SD)	75 (13)	76 (13)	77 (13)	79 (12)	< 0.0001
NYHA functional class (1–4)	1.72	1.66	1.67	1.62	0.0001
Ejection fraction (SD)	26 (6)	27 (6)	27 (6)	27 (6)	< 0.0001
History of smoking (%)	23	23	23	23	NS
Gender (% female)	14	15	14	14	NS
Diabetes (%)	18	19	19	21	0.008
Hypertension (%)	26	33	37	60	< 0.0001
Previous MI (%)	79	76	75	69	< 0.0001
Beta-blocker use (%)	21	18	17	16	< 0.0001
Calcium channel blocker use (%)	35	36	32	30	0.0002
Aspirin use (%)	47	46	48	44	NS
Digitalis use (%)	37	34	32	30	< 0.0001
Diuretic use (%)	45	41	40	45	NS
Percent of patients in treatment arm	41	38	36	36	< 0.0001

*p value for test for trend. Abbreviations as in Table 1.

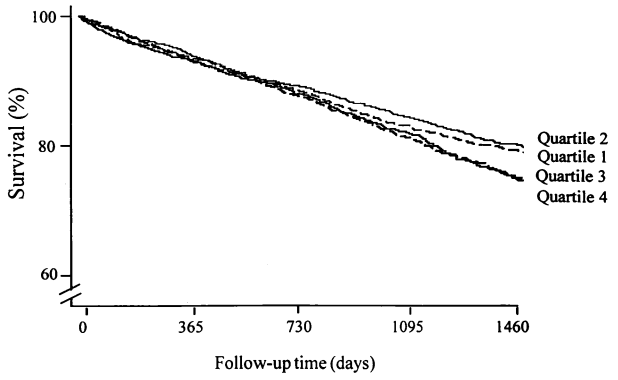

Figure 1. Survival by quartiles of pulse pressure adjusted for age and ejection fraction.

the relative effects on total mortality of the pulsatile and steady-flow components of hemodynamic load. Each 10 mm Hg rise in pulse pressure was associated with an 11% increase in the risk of total mortality (relative risk 1.11, 95% confidence interval [CI] 1.07 to 1.15, $p < 0.0001$) and a 10% increase in the risk of cardiovascular mortality (relative risk 1.10, 95% CI 1.06 to 1.15, $p < 0.0001$). Furthermore, each 10 mm Hg decrease in baseline mean arterial pressure was associated with a 14% increase in the risk of total mortality (relative risk 0.86, 95% CI 0.82 to 0.91, $p < 0.0001$), with identical risk ratio for cardiovascular mortality. Higher pulse pressure was associated with a higher event rate after adjusting for age and ejection fraction (Fig. 1).

To determine whether pulse pressure and mean arterial pressure provide independent prognostic information, Cox proportional hazard models were constructed that included these variables as well as age, heart rate, ejection fraction, history of smoking, gender, diabetes, hypertension, previous myocardial infarction, medication use and functional status. In this more inclusive proportional hazards analysis, pulse pressure remained independently predictive of total mortality (Table 3). For each 10 mm Hg increase in pulse pressure there was a 5% increase in the risk of death. A lower mean arterial pressure was predictive of increased mortality with an 11% increase for each 10 mm Hg decrement in baseline mean arterial pressure. An analysis for cardiovascular mortality provided results essentially identical to those for total mortality (Table 4). These data demonstrate that the independent contribution of pulse pressure and mean arterial pressure to the risk of death is a consequence of their influence on cardiovascular deaths.

Subanalysis of the Treatment and Prevention trials separately yielded similar results with respect to the prognostic importance of mean arterial pressure and pulse pressure.

DISCUSSION

Present findings. This analysis demonstrates that a single determination of blood pressure by sphygmomanometry provides two powerful, independent predictors of adverse cardiovascular events in a large population of patients with left ventricular dysfunction—pulse pressure and mean arterial pressure. Furthermore, the analysis underscores a more physiologic approach to interpreting blood pressure data in terms of mean and pulsatile components rather than peak

Table 3. Cox Proportional Hazards Analysis for All Cause Mortality

Factor	Risk Ratio	p Value	95% Limits on Risk Ratio
Pulse pressure (10 mm Hg)	1.05	0.019	1.01 to 1.10
Mean arterial pressure (10 mm Hg)	0.89	< 0.0001	0.85 to 0.94
Age	1.02	< 0.0001	1.01 to 1.03
Heart rate	1.00	NS	0.99 to 1.01
Ejection fraction	0.96	< 0.0001	0.96 to 0.97
NYHA functional class (per unit increase)	1.36	<0.0001	1.26 to 1.47
History of smoking	1.08	NS	0.95 to 1.22
Female gender	0.86	0.032	0.74 to 0.99
Diabetes	1.28	< 0.0001	1.14 to 1.44
Hypertension	1.09	NS	0.98 to 1.21
Previous MI	0.98	NS	0.87 to 1.10
Beta-blocker use	0.85	0.058	0.72 to 1.00
Calcium channel blocker use	1.16	0.008	1.04 to 1.29
Aspirin use	0.84	0.002	0.75 to 0.94
Digitalis use	1.38	< 0.0001	1.23 to 1.54
Diuretic use	1.39	< 0.0001	1.23 to 1.57
ACE inhibitor use	0.88	0.009	0.79 to 0.97

ACE = angiotensin-converting enzyme; other abbreviations as in Table 1.

Table 4. Cox Proportional Hazards Analysis for Cardiovascular Mortality

Factor	Risk Ratio	p Value	95% Limits on Risk Ratio
Pulse pressure (10 mm Hg)	1.05	0.019	1.01 to 1.10
Mean arterial pressure (10 mm Hg)	0.89	< 0.0001	0.84 to 0.94
Age	1.02	< 0.0001	1.01 to 1.02
Heart rate	1.00	0.075	1.00 to 1.01
Ejection fraction	0.96	< 0.0001	0.95 to 0.97
NYHA functional class (per unit increase)	1.39	< 0.0001	1.29 to 1.51
History of smoking	1.04	NS	0.91 to 1.18
Female gender	0.86	0.049	0.74 to 1.00
Diabetes	1.29	< 0.0001	1.14 to 1.46
Hypertension	1.08	NS	0.97 to 1.22
Previous MI	1.02	NS	0.90 to 1.15
Beta-blocker use	0.87	NS	0.73 to 1.04
Calcium channel blocker use	1.17	0.007	1.04 to 1.31
Aspirin use	0.85	0.006	0.76 to 0.95
Digitalis use	1.38	< 0.0001	1.22 to 1.56
Diuretic use	1.40	< 0.0001	1.23 to 1.60
ACE inhibitor use	0.84	0.002	0.76 to 0.94

Abbreviations as in Table 3.

(systolic) and trough (diastolic) values. The large, well characterized population studied permitted a quantitative estimate of the effects of mean arterial and pulse pressure on outcome after extensive correction for age, gender, smoking, comorbid disease, medication use and functional class at randomization. Each 10 mm Hg increase in baseline pulse pressure was associated with a 5% increase in mortality, whereas a 10 mm Hg decrease in mean arterial pressure was associated with an 11% increase in risk. The effects of both mean arterial and pulse pressure were adjusted for covariates of pulse pressure and other predictors of outcome in patients with ventricular dysfunction.

Physiologic considerations. Additional physiologic correlates of increased pulse pressure in these patients may help to explain the adverse prognostic implications of this simple measurement. Pulse pressure may increase with increased stroke volume or rate of ejection. However, although a range of stroke volume and ejection fraction was likely present, it seems unlikely that the higher stroke volume or ejection fraction would have been the explanation for an association of increased pulse pressure and risk of death. In this population, the increase in pulse pressure was probably most often related to increased aortic stiffness. Repetitive cyclical stress leads to breakdown of elastin with aging and reduces the compliance of the conduit vessels (5). Other disease processes including diabetes, hypertension, atherosclerosis and heart failure (5–10) contribute to conduit vessel stiffening as a result of accelerated elastin breakdown, increased collagen deposition or increased mass or tone of the smooth muscle component of the conduit vessel wall. Excess vessel wall stiffness increases aortic impedance to pulsatile flow, resulting in an increase in the amplitude of the forward pressure wave for a given flow wave (11). Since peripheral resistance is increased in heart failure, a greater percentage of this already enhanced forward pressure wave is reflected back toward the heart. This increased reflection coefficient is a consequence of the worsened impedance mismatch between the low impedance conduit vessels and the high impedance resistance vessels. In addition, stiffening of the arterial wall increases pulse wave velocity, which leads to premature return of the reflected pressure wave from the periphery (11). The reflected wave therefore returns to the proximal aorta in mid-to-late systole, rather than in diastole and augments pulse pressure and left ventricular load while simultaneously diminishing diastolic pressure. Such a shifting of the reflected wave from diastole to systole would have no effect on mean arterial pressure, while producing the highly unfavorable combination of an increase in myocardial oxygen demand and a decrease in coronary perfusion pressure. The presence of a late systolic pressure peak is also associated with impaired ventricular relaxation (12,13) and left ventricular hypertrophy (14).

Increases in conduit vessel stiffness are not purely structural. The aorta and other large conduit vessels contain a significant muscular component in the media, which is capable of modifying the functional characteristics of the vessels. Increases in the activity of the sympathetic nervous system and in levels of intrinsic vasoconstrictors lead to increased smooth muscle tone in both resistance and conduit vessels, resulting in elevated peripheral resistance and increased large vessel stiffness (2,9,10). Neurohumoral activation has been shown to portend an unfavorable outcome in patients with congestive heart failure (15,16). One component of this adverse association may relate to increases in pulsatile load due to dynamic and potentially reversible increases in conduit vessel stiffness.

In addition to increasing load on the ventricle, the increased stiffness indicated by the elevated pulse pressure might be a nonspecific marker for the presence and/or severity of atherosclerosis, which may reduce aortic compliance (6). Furthermore, independent of the presence of aortic atherosclerosis, increased vascular stiffness is associated with risk factors for coronary artery disease, including diabetes (8), age (17–19), hypertension (5) and a family history of coronary disease (20). In the present analysis, a significant positive relationship was found between pulse pressure and age, diabetes and hypertension. However, even after adjusting for these associated factors, we still found an independent relationship between pulse pressure and adverse cardiovascular events.

In patients with congestive heart failure, the reduction in resting cardiac output is associated with a lower mean arterial pressure. Indeed, lower mean arterial pressure has been associated with poorer prognosis in patients with congestive heart failure (21,22), although a quantitative relationship has not been established previously. We have shown that lower mean arterial pressure predicted a worsened prognosis in the SOLVD population. This relationship was observed despite the fact that younger age, lower heart rate, a lower incidence of diabetes and more frequent use of beta-blockers, as seen in the lower mean arterial pressure quartiles, each would have predicted a better prognosis. The reduction in cardiac output causes neurohumoral activation as a compensatory mechanism that increases systemic vascular resistance. As noted above, neurohumoral activation may have also increased stiffness of the conduit vessels in these patients. For example, a patient with a "normal" blood pressure of 120/80 mm Hg has a mean arterial pressure of 93 mm Hg and a pulse pressure of 40 mm Hg. In contrast, SOLVD patients in the third quartile for mean arterial pressure had a near normal mean arterial pressure (96 mm Hg), yet they had an elevated pulse pressure (49 mm Hg). Thus, the adverse prognosis imparted by directionally opposite changes in pulse pressure and mean arterial pressure may in part represent a common mechanism.

Previous studies of pulsatile load and adverse events. Few studies have directly evaluated the relationship between pulse pressure and cardiac events. However, a number of studies have related left ventricular mass to various measures

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of pulsatile load, including proximal aortic elastance (23), pulse wave velocity (24), characteristic impedance of the aorta (25–27), pulse pressure (28), brachial artery compliance (29) and premature arrival of the reflected wave (30). Because left ventricular mass has been related to adverse events, it is reasonable to hypothesize that elevated pulse pressure, an indicator of pulsatile load, might constitute a cardiovascular risk factor. Indeed, it has recently been shown that pulse pressure is an independent predictor of total mortality and recurrent myocardial infarction in patients with impaired ventricular function after a myocardial infarction (1). No other studies have specifically addressed the relationship between pulse pressure and cardiac events in patients with left ventricular dysfunction. Furthermore, this is the first prospective analysis that has evaluated the effects of pulse pressure in a population of patients with left ventricular dysfunction that includes a significant number of patients with overt heart failure.

Other major studies have addressed the relationship between pulse pressure and cardiac events in normal or hypertensive patient populations. In a prospective study of healthy adults, the pulsatile component index, a strong correlate of pulse pressure, was associated with an increased risk of death from coronary artery disease in women (31). In a recently published update to this study, with 19.5 years of follow up in 19,083 men, pulse pressure again proved to be associated with cardiovascular events after adjusting for age, cholesterol and tobacco use (32). The relative effects of diastolic, systolic and pulse pressure on five-year mortality were evaluated in hypertensive adults in the Hypertension Detection and Follow-up Program (33). Pulse pressure was shown to be a significant predictor of total mortality in a logistic regression model that included age, race, gender, randomized antihypertensive therapy, diabetes, hypertensive end-organ damage and smoking. In another prospective evaluation of hypertensive patients, those in the highest tertile of pulse pressure before the initiation of therapy ($\geq$63 mm Hg) had an increased risk of myocardial infarction and stroke during an average follow up of five years (34). Multivariate analysis revealed that pretreatment pulse pressure was an independent predictor of myocardial infarction. A follow-up analysis in an expanded patient population of treated and untreated hypertensive patients confirmed that pulse pressure was the only measure of blood pressure independently associated with myocardial infarction after adjustment for other risk factors (35).

Previous studies of mean arterial pressure and outcome. Many studies have alluded to an association between mean arterial pressure and an adverse outcome in patients with varying degrees of heart failure. However, few have controlled for other factors that contribute to an adverse outcome. In a prospective study of 182 patients with advanced heart failure, patients who died had a lower baseline mean arterial pressure, which was associated with reduced cardiac output and elevated systemic vascular resistance (36). The patients in this study were well characterized with respect to other predictors of outcome. However, a multivariate analysis was not performed. Another prospective study of 152 patients with NYHA functional class II–IV heart failure demonstrated a significant relationship between mean arterial pressure and outcome. Lower mean arterial pressure was associated with a lower serum sodium concentration, higher functional class score and larger diastolic left ventricular size. Lower mean arterial pressure remained an independent predictor of outcome in a stepwise multivariate analysis, although no estimate of effect size was given (37).

Clinical implications. Prospective studies that evaluate the clinical implications of interventions that improve conduit vessel compliance have not been done. However, agents such as ACE inhibitors, which have been shown to have a salutary effect on conduit vessel function, are highly effective in improving outcome in patients with asymptomatic left ventricular dysfunction (38) and all stages of congestive heart failure (3,4,39,40). Clinical studies have confirmed that abnormalities in conduit vessel function are modifiable (25,41–46). Thus, abnormal conduit vessel function, whether due to increased smooth muscle mass or tone, increased collagen or diminished elastin appears to be at least partially responsive to various therapeutic interventions. This provides a rationale for testing therapeutic agents with a preferential effect on conduit vessel function and pulse pressure.

Limitations. Our analysis was based on a single blood pressure measurement and could, therefore, suffer from regression to the mean. However, this would tend to obscure, rather than enhance, an important association between hemodynamic parameters and outcome. Pulse pressure is an imperfect indicator of conduit vessel stiffness, and more direct measures are needed for future studies. Nonetheless, it is difficult to envision how increases in other potential determinants of pulse pressure, such as peak ejection rate or stroke volume, would be associated with an adverse prognosis in patients with left ventricular dysfunction. It is important to note that this analysis was exploratory in nature and was not a prespecified end point of the SOLVD studies. These findings apply only to patients with left ventricular dysfunction. As with any risk factor, it is difficult to apply it to a particular individual rather than to the entire population. However, our model indicates that pulse pressure provides independent prognostic information.

Conclusions. These data provide strong evidence for associations between conduit vessel stiffness, which contributes to increased pulse pressure, resistance vessel activation, which accompanies a fall in mean arterial pressure and adverse cardiovascular events in patients with left ventricular dysfunction. We speculate that therapies directed at reduc-

ing pulse pressure may offer potential advantages in the treatment of congestive heart failure.

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