

PROGNOSTIC IMPORTANCE OF ELEVATED JUGULAR VENOUS PRESSURE AND A THIRD HEART SOUND IN PATIENTS WITH HEART FAILURE

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ABSTRACT

Background The independent prognostic value of elevated jugular venous pressure or a third heart sound in patients with heart failure is not well established.

Methods We performed a retrospective analysis of the Studies of Left Ventricular Dysfunction treatment trial, in which 2569 patients with symptomatic heart failure or a history of it were randomly assigned to receive enalapril or placebo. The mean (\pm SD) follow-up was 32 ± 15 months. The presence of elevated jugular venous pressure or a third heart sound was ascertained by physical examination on entry into the trial. The risks of hospitalization for heart failure and progression of heart failure as defined by death from pump failure and the composite end point of death or hospitalization for heart failure were compared in patients with these findings on physical examination and patients without these findings.

Results In multivariate analyses that were adjusted for other markers of the severity of heart failure, elevated jugular venous pressure was associated with an increased risk of hospitalization for heart failure (relative risk, 1.32; 95 percent confidence interval, 1.08 to 1.62; $P < 0.01$), death or hospitalization for heart failure (relative risk, 1.30; 95 percent confidence interval, 1.11 to 1.53; $P < 0.005$), and death from pump failure (relative risk, 1.37; 95 percent confidence interval, 1.07 to 1.75; $P < 0.05$). The presence of a third heart sound was associated with similarly increased risks of these outcomes.

Conclusions In patients with heart failure, elevated jugular venous pressure and a third heart sound are each independently associated with adverse outcomes, including progression of heart failure. Assessment for these findings is clinically meaningful. (N Engl J Med 2001; 345:574-81.)

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THERE is concern that physicians are becoming less proficient at performing the physical examination.¹⁻⁴ For example, physicians in residency programs have been shown to have poor cardiac auscultatory skills.^{5,6} This decline in physical-examination skills may be due in part to an increasing availability and reliance on forms of technology such as echocardiography.¹⁻⁴ In an era of evidence-based medicine,⁷ the demonstration that physical findings provide useful information in patients with a

common illness such as chronic heart failure may motivate physicians and trainees to refine their diagnostic skills. Our study tested the hypothesis that the finding of elevated jugular venous pressure or a third heart sound (also called S_3 gallop) on physical examination would provide important and independent prognostic information in patients with heart failure.

METHODS

The Studies of Left Ventricular Dysfunction (SOLVD) treatment trial has been described in detail previously.^{8,9} A total of 2569 patients with symptomatic congestive heart failure or a history of it and a left ventricular ejection fraction of 0.35 or less were randomly assigned to receive enalapril or placebo. Patients were enrolled from June 1986 to March 1989. A prerandomization run-in phase consisted of a single-blind active-drug phase (2 to 7 days) followed by a placebo run-in phase (14 to 17 days). Patients with worsening heart failure during this phase were excluded from the trial. Treatment was initiated predominantly in the outpatient setting (in 99 percent of cases). The participants were followed for an average (\pm SD) of 32 ± 15 months. The study protocol was approved by the appropriate review boards of the participating centers, and written informed consent was obtained from the patients.

Data Collection and Definitions

Base-line demographic data including the New York Heart Association (NYHA) functional class and information on the medical history and current use of medications were obtained from all patients at the time of enrollment. Data on race and ethnic background were obtained from the SOLVD eligibility form, on which the ethnic and racial categories were American Indian, Asian, black, white, Hispanic, and other. At the time of enrollment, investigators evaluated patients for the presence or absence of elevated jugular venous pressure and a third heart sound on the basis of a routine physical examination. On separate lines of the SOLVD base-line visit form completed at the time of enrollment, the presence of elevated jugular venous pressure or a third heart sound was indicated in a "yes" or "no" format.

Definition of End Points

The primary end point of the SOLVD treatment trial was death from any cause. The cause of death was also classified on standard forms after a review by the principal investigator at each center of the circumstances surrounding each death. Deaths from cardiovascular causes could be classified as due to pump failure, probable arrhythmia with some antecedent worsening of heart failure, or probable arrhythmia with no antecedent worsening of heart failure. As previously described,^{10,11} in this study we classified all deaths attributed to pump failure and those attributed to probable arrhythmia

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mia with some antecedent worsening of heart failure as due to pump failure. Deaths due to probable arrhythmia with no antecedent worsening of heart failure were classified as deaths from arrhythmia. The primary SOLVD investigator at each center also classified the primary cause of hospitalization. As in a previous study,¹¹ we prespecified that both death from pump failure and the composite end point of death from all causes or hospitalization for heart failure would represent progression of heart failure.

Statistical Analysis

Patients with incomplete data were excluded from analysis, leaving 2479 participants. The following variables were treated as continuous: age, left ventricular ejection fraction, systolic blood pressure, heart rate, serum creatinine level, and serum sodium level. Dichotomous variables included elevated jugular venous pressure (yes or no) or audible third heart sound (yes or no); black race (yes or no); cause of left ventricular systolic dysfunction (ischemic or nonischemic); NYHA functional class (I or II vs. III or IV); electrocardiographic evidence of atrial fibrillation at base line (yes or no); history of medical conditions (yes or no for each), including diabetes, hypertension, myocardial infarction, and stroke; base-line use of medications at the time of randomization (yes or no for each), including diuretics, beta-blockers, digoxin, and antiarrhythmic agents; and random assignment to the enalapril group or the placebo group. We used Student's t-test to compare continuous data, assuming where appropriate that the variance was unequal, and the chi-square statistic to compare binary data. We used Cox proportional-hazard models to assess the univariate and multivariate association of independent variables with the outcome.

The risk of an outcome associated with the presence of physical-examination findings was assessed in three separate models, one for elevated jugular venous pressure, one for a third heart sound, and one for elevated jugular venous pressure or a third heart sound alone or in combination. We constructed two sets of Kaplan–Meier curves for the composite end point of death or hospitalization for heart failure, one according to the presence or absence of elevated jugular venous pressure and one according to the presence or absence of a third heart sound. We used the log-rank test to determine event-free survival according to the presence or absence of these findings. A two-sided P value of less than 0.05 was considered to indicate statistical significance in all analyses. The SOLVD data base, which is held by the National Heart, Lung, and Blood Institute, was acquired by the study investigators and independently analyzed at the Donald W. Reynolds Cardiovascular Clinical Research Center in Dallas.

RESULTS

Base-Line Characteristics of the Patients

The base-line characteristics of the patients with either elevated jugular venous pressure or a third heart sound are shown in Table 1. Patients with elevated jugular venous pressure and those with a third heart sound had more advanced heart failure than those without these physical findings, as assessed on the basis of other measures of the severity of heart failure, including NYHA functional class, left ven-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS, ACCORDING TO THE PRESENCE OR ABSENCE OF ELEVATED JUGULAR VENOUS PRESSURE AND A THIRD HEART SOUND.*

CHARACTERISTIC	ELEVATED JUGULAR VENOUS PRESSURE			THIRD HEART SOUND		
	PRESENT (N=280)	ABSENT (N=2199)	P VALUE	PRESENT (N=597)	ABSENT (N=1882)	P VALUE
Age (yr)	63±10	61±10	0.001	60±11	61±10	0.13
Male sex (%)	72	82	<0.001	76	82	0.002
Left ventricular ejection fraction	0.23±0.07	0.25±0.07	<0.001	0.23±0.07	0.25±0.07	<0.001
Black race (%)	19	15	0.09	18	14	0.02
Ischemic cardiomyopathy (%)	64	72	0.002	61	75	<0.001
NYHA functional class (%)			<0.001			<0.001
I or II	37	71		54	72	
III or IV	63	29		46	28	
Systolic blood pressure (mm Hg)	123±19	125±18	0.07	123±18	125±17	0.003
Heart rate (beats/min)	84±15	79±13	<0.001	85±14	78±13	<0.001
Serum creatinine (mg/dl)†	1.3±0.3	1.2±0.3	0.001	1.3±0.3	1.2±0.3	0.32
Serum sodium (mmol/liter)	139±4	140±3	0.003	139±3	140±3	0.007
Atrial fibrillation (%)	13	9	0.04	11	9	0.29
Medical history (%)						
Diabetes	34	25	0.001	26	26	0.95
Hypertension	49	41	0.01	44	41	0.16
Myocardial infarction	63	66	0.19	58	69	<0.001
Stroke	7	8	0.54	8	8	1.0
Use of medications (%)						
Diuretic	90	85	0.03	87	85	0.24
Beta-blocker	6	8	0.32	4	9	<0.001
Digoxin	64	68	0.21	66	68	0.46
Antiarrhythmic agent	23	22	0.78	21	22	0.69
Assigned to receive enalapril (%)	51	50	0.78	51	50	0.58

*Plus–minus values are means ±SD. NYHA denotes New York Heart Association.

†To convert values for serum creatinine to micromoles per liter, multiply by 88.4.

tricular ejection fraction, and heart rate. Patients with elevated jugular venous pressure and those with a third heart sound were also more likely to be women and to have a nonischemic cause of left ventricular dysfunction. Patients with elevated jugular venous pressure were more likely than those without elevated jugular venous pressure to have atrial fibrillation and a history of diabetes and to be treated with diuretics. Patients with a third heart sound were less likely than those without a third heart sound to have a history of myocardial infarction and to be treated with beta-blockers. Patients with elevated jugular venous pressure or a third heart sound and patients without these physical findings were equally likely to be assigned to receive enalapril.

Incidence of End Points

The incidence of death from all causes, hospitalization for heart failure, or a composite end point of death or hospitalization for heart failure is shown in Table 2 according to the presence or absence of elevated jugular venous pressure and a third heart sound. In both cases, patients with these physical findings had significantly increased rates of death, hospitalization for heart failure, the composite end point of death or hospitalization for heart failure, and death from pump failure, but not of death from arrhythmia. The event-free survival curves are shown in Figure 1 according to the presence or absence of elevated jugular venous pressure and a third heart sound.

Univariate Analysis

Univariate analysis showed that patients with elevated jugular venous pressure were at significantly higher risk than patients without elevated jugular venous pressure for death from all causes (relative

risk, 1.52; 95 percent confidence interval, 1.27 to 1.82; $P < 0.001$), hospitalization for heart failure (relative risk, 1.78; 95 percent confidence interval, 1.47 to 2.17; $P < 0.001$), the composite end point of death or hospitalization for heart failure (relative risk, 1.69; 95 percent confidence interval, 1.45 to 1.97; $P < 0.001$), and death from pump failure (relative risk, 1.99; 95 percent confidence interval, 1.57 to 2.52; $P < 0.001$), but not death from arrhythmia (relative risk, 1.10; 95 percent confidence interval, 0.72 to 1.68; $P = 0.66$).

The findings in patients with a third heart sound were similar to those in patients with elevated jugular venous pressure. On univariate analysis, patients with a third heart sound were at significantly higher risk than those without a third heart sound for death from all causes (relative risk, 1.35; 95 percent confidence interval, 1.17 to 1.55; $P < 0.001$), hospitalization for heart failure (relative risk, 1.70; 95 percent confidence interval, 1.46 to 1.97; $P < 0.001$), the composite end point of death or hospitalization for heart failure (relative risk, 1.42; 95 percent confidence interval, 1.26 to 1.60; $P < 0.001$), and death from pump failure (relative risk, 1.77; 95 percent confidence interval, 1.46 to 2.15; $P < 0.001$), but not death from arrhythmia (relative risk, 1.22; 95 percent confidence interval, 0.90 to 1.65; $P = 0.20$).

Multivariate Analysis

Multivariate analysis showed that patients with elevated jugular venous pressure and those with a third heart sound were at significantly increased risk for hospitalization for heart failure, the composite end point of death or hospitalization for heart failure, and death from pump failure, but not death from arrhythmia (Table 3).

TABLE 2. INCIDENCE OF END POINTS ACCORDING TO THE PRESENCE OR ABSENCE OF ELEVATED JUGULAR VENOUS PRESSURE AND A THIRD HEART SOUND.*

END POINT	ELEVATED JUGULAR VENOUS PRESSURE				THIRD HEART SOUND			
	PRESENT (N=280)		ABSENT (N=2199)		PRESENT (N=597)		ABSENT (N=1882)	
	no. of events (%)	incidence/100 person-yr	no. of events (%)	incidence/100 person-yr	no. of events (%)	incidence/100 person-yr	no. of events (%)	incidence/100 person-yr
Death from all causes	137 (49)	20.3	796 (36)	13.3†	265 (44)	17.5	668 (35)	13.0‡
Hospitalization for heart failure	120 (43)	23.8	658 (30)	13.0†	247 (41)	20.9	531 (28)	12.1‡
Death or hospitalization for heart failure	192 (69)	38.1	1118 (51)	22.0†	366 (61)	30.9	944 (50)	21.4‡
Death from pump failure	84 (30)	12.4	374 (17)	6.3†	157 (26)	10.4	301 (16)	5.9‡
Death from arrhythmia	24 (9)	3.6	190 (9)	3.2	57 (10)	3.8	157 (8)	3.1

*The unadjusted incidence is expressed as the rate per 100 person-years of follow-up.

† $P < 0.001$ by the log-rank test for the comparison with patients with elevated jugular venous pressure.

‡ $P < 0.001$ by the log-rank test for the comparison with patients with a third heart sound.

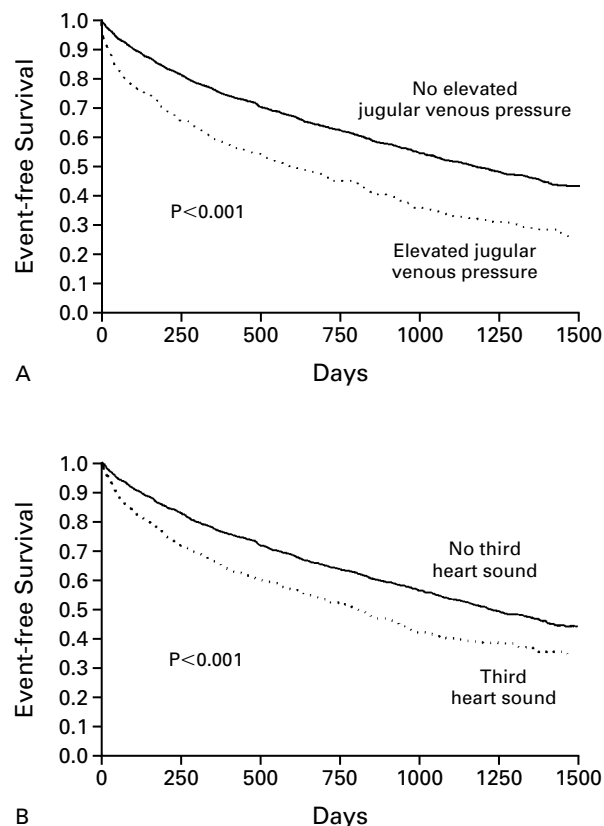


Figure 1. Kaplan–Meier Analysis of Event-free Survival According to the Presence or Absence of Elevated Jugular Venous Pressure (Panel A) and a Third Heart Sound (Panel B).

The end point was a composite of death or hospitalization for heart failure. In Panel A, the 280 patients with elevated jugular venous pressure were significantly more likely than the 2199 patients without elevated jugular venous pressure to reach the composite end point ($P < 0.001$ by the log-rank test). In Panel B, the 597 patients with a third heart sound were significantly more likely than the 1882 patients without a third heart sound to reach the composite end point ($P < 0.001$ by the log-rank test).

Of the 2479 patients, a total of 706 had elevated jugular venous pressure, a third heart sound, or both: 109 had elevated jugular venous pressure in the absence of a third heart sound, 426 had a third heart sound in the absence of elevated jugular venous pressure, and 171 had both elevated jugular venous pressure and a third heart sound. Multivariate analysis with the use of the same covariates as described above showed that, as compared with the 1773 patients with neither finding, patients with elevated jugular venous pressure, a third heart sound, or both were at significantly increased risk for death from all causes, hospitalization for heart failure, the composite end point of death or hospitalization for heart failure, and death from pump failure, but not death from ar-

rhythmia (Table 3). In addition, a multivariate analysis in which the 171 patients who had both elevated jugular venous pressure and a third heart sound were compared with the 535 patients who had only one of these physical findings showed that the risk of all outcomes, including hospitalization for heart failure (relative risk, 1.13; 95 percent confidence interval, 0.86 to 1.48; $P = 0.38$) and the composite end point of death or hospitalization for heart failure (relative risk, 1.05; 95 percent confidence interval, 0.84 to 1.30; $P = 0.69$), was similar.

Multivariate Analysis Stratified According to NYHA Functional Class and Treatment Assignment

In the light of the disparities at base line in the NYHA functional class between patients with and those without the physical findings, we performed a multivariate analysis that was stratified according to the NYHA class (1671 patients were in NYHA class I or II and 808 were in NYHA class III or IV). With the exception of the NYHA functional class, the same covariates included in the primary analysis were entered into these models. As shown in Table 4, the results of this subgroup analysis were consistent with those of the primary analysis. In both NYHA class strata the presence of elevated jugular venous pressure alone; a third heart sound alone; or elevated jugular venous pressure, a third heart sound, or both was associated with a relative risk of more than 1.00 in the case of hospitalization for heart failure, the composite end point of death or hospitalization for heart failure, and death from pump failure, though not all values reached statistical significance.

To determine whether treatment with angiotensin-converting-enzyme inhibitors altered the prognostic value of the physical-examination findings, we also performed a multivariate analysis that was stratified according to treatment assignment. With the exception of treatment assignment, the same covariates included in the primary analysis were entered into these models. As shown in Table 4, the presence of elevated jugular venous pressure alone; a third heart sound alone; or elevated jugular venous pressure, a third heart sound, or both was associated with similar risks for most outcomes in the two treatment groups. In addition, there was no evidence of a statistically significant interaction between treatment assignment and elevated jugular venous pressure or between treatment assignment and a third heart sound with respect to the risk of death, hospitalization for heart failure, the composite end point of death or hospitalization for heart failure, and death from pump failure when these interaction terms were included in multivariate models ($P > 0.1$ for all comparisons).

DISCUSSION

These data suggest that the finding of elevated jugular venous pressure or a third heart sound on phys-

TABLE 3. RESULTS OF THE MULTIVARIATE ANALYSIS.*

END POINT	ELEVATED JUGULAR VENOUS PRESSURE (N=280)	THIRD HEART SOUND (N=597)	ELEVATED JUGULAR VENOUS PRESSURE, THIRD HEART SOUND, OR BOTH (N=706)
	relative risk (95% confidence interval)		
Death from all causes	1.15 (0.95–1.38)	1.15 (0.99–1.33)	1.17 (1.02–1.35)†
Hospitalization for heart failure	1.32 (1.08–1.62)‡	1.42 (1.21–1.66)§	1.43 (1.23–1.66)¶
Death or hospitalization for heart failure	1.30 (1.11–1.53)	1.22 (1.08–1.38)**	1.28 (1.14–1.45)¶
Death from pump failure	1.37 (1.07–1.75)††	1.40 (1.14–1.71)**	1.47 (1.21–1.79)¶
Death from arrhythmia	0.96 (0.62–1.49)	1.13 (0.82–1.54)	1.08 (0.80–1.46)

*Each model also included age, left ventricular ejection fraction, New York Heart Association class, treatment assignment (enalapril or placebo), sex, cause of left ventricular systolic dysfunction (ischemic or nonischemic), black race (yes or no), electrocardiographic evidence of atrial fibrillation at base line (yes or no), serum sodium level, serum creatinine level, presence or absence of a history of diabetes mellitus or hypertension, and presence or absence of base-line use of a beta-blocker, digoxin, or a diuretic.

†P<0.05 for the comparison with patients with neither elevated jugular venous pressure nor a third heart sound.

‡P<0.01 for the comparison with patients without elevated jugular venous pressure.

§P<0.001 for the comparison with patients without a third heart sound.

¶P<0.001 for the comparison with patients with neither elevated jugular venous pressure nor a third heart sound.

||P<0.005 for the comparison with patients without elevated jugular venous pressure.

**P<0.005 for the comparison with patients without a third heart sound.

††P<0.05 for the comparison with patients without elevated jugular venous pressure.

ical examination conveys important prognostic information in patients with symptomatic heart failure. The presence of these signs was associated with subsequent hospitalization for heart failure and an increased risk of progression of heart failure, as assessed by the incidence of death from pump failure and the composite end point of death or hospitalization for heart failure. The subgroup of patients with elevated jugular venous pressure, a third heart sound, or both was also at increased risk for death from all causes. These associations persisted even after adjustment for many other markers of the severity of heart failure, including the left ventricular ejection fraction, the NYHA functional class, and the serum sodium level.

There are limited data regarding the prognostic value of the detection of elevated jugular venous pressure on physical examination in patients with heart failure.¹² An increased right atrial pressure is associated with a poor prognosis in patients with heart failure.^{13,14} Such data may not be applicable to estimates of jugular venous pressure obtained by physical examination, since the latter correlate poorly with findings derived from invasive measurements of right atrial pressure.^{15–20} Recent suggestions may improve

the accuracy of the clinical assessment of venous pressure.²¹ There is an association between a finding of elevated jugular venous pressure on physical examination and a finding of elevated left-sided filling pressures on right heart catheterization in patients with heart failure.^{22–25} A recent study of patients with a history of NYHA class IV symptoms showed that a low congestion score, as assessed by a five-point clinical scoring system that included one point for elevated jugular venous pressure, was associated with a favorable outcome.²⁶

Although the finding of a third heart sound is reported to be an unfavorable prognostic sign in patients with heart failure,²⁷ this association is based on relatively small observational studies.^{12,13,28–31} In addition, the majority of these studies did not adjust for other markers of the severity of heart failure such as the left ventricular ejection fraction. In a study of 50 patients with advanced heart failure, nearly all (96 percent) had a third heart sound,²² suggesting that this sign would have limited use as a discriminatory factor. Several studies have shown that the agreement between observers with respect to the presence of a third heart sound is moderate or low^{32–35} even among experienced physicians, raising serious ques-

TABLE 4. RESULTS OF THE MULTIVARIATE ANALYSIS STRATIFIED ACCORDING TO THE NEW YORK HEART ASSOCIATION (NYHA) CLASS AND TREATMENT ASSIGNMENT.*

END POINT AND RISK FACTOR	NYHA CLASS		TREATMENT ASSIGNMENT	
	I OR II (N=1671)	III OR IV (N=808)	PLACEBO (N=1241)	ENALAPRIL (N=1238)
	relative risk (95% confidence interval)			
Death from all causes				
Elevated jugular venous pressure	1.13 (0.81–1.57)	1.16 (0.92–1.46)	1.26 (0.98–1.63)†	1.04 (0.79–1.38)
Third heart sound	1.29 (1.05–1.59)‡	1.01 (0.82–1.25)	1.10 (0.89–1.34)	1.23 (1.00–1.53)†
Elevated jugular venous pressure, third heart sound, or both	1.23 (1.01–1.51)‡	1.12 (0.91–1.36)	1.13 (0.93–1.37)	1.26 (1.02–1.55)‡
Hospitalization for heart failure				
Elevated jugular venous pressure	1.30 (0.92–1.84)	1.35 (1.05–1.73)‡	1.33 (1.01–1.74)‡	1.23 (0.90–1.68)
Third heart sound	1.36 (1.09–1.71)§	1.44 (1.16–1.80)¶	1.57 (1.28–1.93)	1.21 (0.95–1.55)
Elevated jugular venous pressure, third heart sound, or both	1.37 (1.10–1.70)¶	1.46 (1.18–1.82)	1.50 (1.22–1.83)	1.29 (1.02–1.64)‡
Death or hospitalization for heart failure				
Elevated jugular venous pressure	1.22 (0.92–1.61)	1.36 (1.11–1.65)¶	1.33 (1.07–1.65)‡	1.22 (0.96–1.55)†
Third heart sound	1.28 (1.07–1.52)§	1.15 (0.96–1.37)	1.26 (1.06–1.49)§	1.17 (0.97–1.42)†
Elevated jugular venous pressure, third heart sound, or both	1.25 (1.05–1.48)‡	1.30 (1.10–1.54)¶	1.28 (1.09–1.51)¶	1.27 (1.06–1.52)§
Death from pump failure				
Elevated jugular venous pressure	1.50 (0.96–2.32)†	1.31 (0.98–1.77)†	1.49 (1.06–2.08)‡	1.26 (0.87–1.82)
Third heart sound	1.59 (1.18–2.14)¶	1.23 (0.94–1.61)	1.42 (1.08–1.87)‡	1.37 (1.02–1.85)‡
Elevated jugular venous pressure, third heart sound, or both	1.61 (1.21–2.15)¶	1.34 (1.03–1.74)‡	1.45 (1.11–1.89)§	1.53 (1.14–2.04)§

*Each model also included age, left ventricular ejection fraction, sex, cause of left ventricular systolic dysfunction (ischemic or nonischemic), black race (yes or no), electrocardiographic evidence of atrial fibrillation at base line (yes or no), serum sodium level, serum creatinine level, presence or absence of a history of diabetes mellitus or hypertension, and presence or absence of base-line use of a beta-blocker, digoxin, or a diuretic. In the case of the models that were stratified according to NYHA class, treatment assignment (enalapril or placebo) was entered as a covariate. In the case of the models that were stratified according to treatment assignment, NYHA class was entered as a covariate.

†P<0.10 for the comparison with the patients without the respective physical examination finding or findings.

‡P<0.05 for the comparison with the patients without the respective physical examination finding or findings.

§P<0.01 for the comparison with the patients without the respective physical examination finding or findings.

¶P<0.005 for the comparison with the patients without the respective physical examination finding or findings.

||P<0.001 for the comparison with the patients without the respective physical examination finding or findings.

tions about the usefulness of this sign.³⁶ Such findings are probably representative of an overall decline in cardiac auscultatory skills in physicians, as documented by assessments of recent medical school graduates.^{5,6} Our findings nevertheless suggest that the detection of a third heart sound on physical examination is an important independent prognostic factor in patients with heart failure.

Why elevated jugular venous pressure or a third heart sound was associated with an increased risk of progressive heart failure is uncertain. Elevated jugular venous pressure reflects increased right atrial pressure, which itself correlates with elevated left-sided filling pressures in patients with chronic heart failure.³⁷ Elevated left-sided filling pressures have been associated with adverse outcomes in patients with heart failure^{12,14,30,38,39} possibly as a result of apoptosis⁴⁰ due to myocardial stretch or enhanced activation of the sympathetic nervous system.^{41,42} Patients with heart failure may have a third heart sound as a result of low ventricular compliance, increased filling pressures,

or increased early diastolic filling rates.⁴³⁻⁴⁶ A similar combination of pathophysiological events in diastole in patients with left ventricular systolic dysfunction as assessed by echocardiography^{47,48} has been associated with an unfavorable prognosis.⁴⁹⁻⁵¹

Our retrospective analysis has several important limitations. There may have been residual confounding by unmeasured and measured variables despite our efforts to adjust for known risk factors with the use of multivariate modeling. The manner in which the physical examination was performed to detect elevated jugular venous pressure or a third heart sound was not standardized in the SOLVD trials, although the approach was probably representative of clinical practice. Physical examination has inherent inaccuracies, and no confirmatory test was performed (e.g., phonocardiography for a third heart sound), although any random misclassification resulting from physicians' errors would bias the results toward the null hypothesis. A physician's estimate of the overall severity of the patient's condition may have affected his

or her assessment of whether elevated jugular venous pressure or a third heart sound was present. However, such estimates of disease severity would probably also affect the NYHA classification, and our conclusions were based on multivariate models that adjusted for the NYHA class. Furthermore, the findings of a subgroup analysis stratified according to the NYHA class were consistent with those of the primary analysis.

The decision to hospitalize a patient with heart failure may have been affected by the presence of either elevated jugular venous pressure or a third heart sound. Such bias is unlikely to explain the results of our study, since the findings of the physical examination were noted at the time of enrollment and hospitalization for heart failure often occurred many months later, since the presence of a third heart sound by itself would probably not be an indication for hospitalization, and since the presence of at least one of the physical-examination findings was associated with an increased risk of death from all causes in addition to end points incorporating hospitalization. The classification of the cause of death as pump failure may also have been affected by the finding of elevated jugular venous pressure or a third heart sound near the time of death, although these findings would often have been noted well after the base-line physical examination had been performed.

Because of the infrequent use of beta-blockers in the SOLVD trials, we could not determine whether beta-blockers affect the prognostic value of the finding of elevated jugular venous pressure or a third heart sound. However, the multivariate models in this study did adjust for the use of beta-blockers. We also did not address the usefulness of the finding of elevated jugular venous pressure or a third heart sound as an indicator of left ventricular systolic dysfunction^{25,52} since the entry criteria for the SOLVD treatment trial included an ejection fraction of 0.35 or less.

In conclusion, the detection of elevated jugular venous pressure or a third heart sound in patients with heart failure was associated with adverse outcomes, including progression of heart failure, even after adjustment for other markers of the severity of disease. These findings may increase confidence in the belief that focused bedside assessment is clinically meaningful and may give physicians in training further impetus to refine their skills in physical examination.

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