

# Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure

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**Background** Treatment of decompensated heart failure often includes the use of intravenous vasoactive medications, but the effect on outcome has not been clearly defined.

**Methods** Data from 433 patients enrolled in the ESCAPE trial were analyzed to determine 6-month risks of all-cause mortality and all-cause mortality plus rehospitalization associated with the use of vasodilators, inotropes, and their combination. Patients had a mean left ventricular ejection fraction of 19%, 6-minute walk distance of 414 ft, and systolic blood pressure of 106 mm Hg. The main outcome measure was multivariable risk-adjusted 6-month hazard ratios (HRs).

**Results** Overall 6-month mortality was 19%. Risk-adjusted HRs were not statistically significant for vasodilators (1.39, 95% CI 0.64-3.00), but were significant for inotropes (2.14, 95% CI 1.10-4.15) and the combination (4.81, 95% CI 2.34-9.90). Risk-adjusted 6-month mortality plus rehospitalization HRs were not significant for vasodilators (1.20, 95% CI 0.81-1.78,  $P = .37$ ), but were significant for inotropes (1.96, 95% CI 1.37-2.82,  $P < .001$ ) and their combination (2.90, 95% CI 1.88-4.48,  $P = .001$ ). The decision to use vasodilators or inotropes was determined by hemodynamic parameters and renal function, but the main factor was treatment site.

**Conclusions** In ESCAPE, the choice of medications was mainly determined by the treatment site. Use of inotropic agents was associated with adverse outcomes, whereas the use of vasodilators was not. Inotropes in combination with vasodilators identified a group with the highest mortality. Prospective studies are needed to establish the appropriate use of vasoactive medications in this population. (*Am Heart J* 2007;153:98-104.)

The treatment of patients hospitalized for severe decompensated heart failure (HF) often includes the use of intravenous vasoactive medications such as inotropes and vasodilators. Reasons for the use of these drugs and their effect on outcomes have not been clearly defined, but some studies have suggested possible detrimental effects.<sup>1-7</sup> Further evaluations in larger, carefully characterized populations with severe, high-risk HF who may be candidates for vasoactive medications are needed to

establish their effect on long-term outcomes and provide guidelines for their use.

The ESCAPE was a randomized multicenter evaluation of the efficacy and safety of pulmonary artery catheter (PAC)-guided therapy versus clinical assessment alone in 433 patients hospitalized with severe decompensated HF.<sup>8,9</sup> The objective of this post hoc analysis was to evaluate the reasons for use of intravenous therapy with inotropes or vasodilators, and the effects of these drugs on clinical outcomes in patients with severe decompensated HF who are likely to receive vasoactive medications.

## Methods

The design of the ESCAPE trial has been previously described.<sup>8</sup> Briefly, ESCAPE was a multicenter randomized evaluation of 433 patients hospitalized with severe decompensated HF at 26 academic medical centers in the United States and Canada. Additional inclusion criteria were age >18 years; documented history of HF for  $\geq 3$  months; treatment with angiotensin-converting enzyme (ACE) inhibitors and diuretics for  $\geq 3$  months; documented left ventricular ejection fraction (LVEF) of  $< 30\%$  in the 12 months before randomization; systolic blood pressure  $\leq 125$  mm Hg; elevated left ventricular (LV) filling pressure as indicated by at least 1 physical

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sign and 1 symptom; and at least 1 prior admission for exacerbation of HF during the previous 12 months or aggressive outpatient therapy for at least the previous month. Aggressive outpatient therapy was defined as >160 mg/d of furosemide; >100 mg/d of torsemide; >4 mg/d of bumetanide; 2 intravenous doses of loop diuretics on separate days; or any unscheduled visit to the office or emergency department that included intravenous therapy for HF within the past 6 months. After providing informed consent, eligible patients were randomly assigned 1:1 to treatment guided by clinical assessment and the PAC or treatment guided by clinical assessment alone. With the exception of the PAC, patients were not randomized as to therapy and could receive any of the other standard therapies and medications for HF. However, inotrope use was actively discouraged in study guidelines and conference calls, and this was specifically addressed with all investigators. Patients were seen at 7 to 14 days, and at 1, 2, 3, and 6 months after discharge.

### End points

The primary end point of this analysis was the effect of intravenous vasoactive therapy on all-cause mortality. For this end point, intravenous vasoactive therapy was categorized as vasodilatory, inotropic, both, or neither.

Secondary end points included multivariable risk factors for all-cause mortality, effect of intravenous vasoactive therapy on the combined end point of all-cause mortality plus rehospitalization, multivariable risk factors for the combined end point of all-cause mortality plus rehospitalization, and multivariable analysis of the factors influencing the use of both vasodilators and inotropic agents by investigators.

### Statistical analysis

Statistical analyses were performed using SAS statistical software (version 8.2, SAS Institute Inc, Cary, NC). Predictors of inotrope and vasodilator use were assessed using univariable and multivariable logistic regression models with the treatment site effect determined using the reduction in sum of squares principle. Baseline characteristics and demographic variables (Table 1) were considered in the univariable prediction model. Risk factors for all-cause mortality and all-cause mortality plus rehospitalization were assessed using univariable and multivariable Cox proportional hazard models. Kaplan-Meier survival curves were used to depict the differential effects of the various vasoactive treatments. Variables in the univariable models that were significant ( $P < .05$ ) or promising ( $P < .1$ ) were considered in multivariable models. Right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP) were included only in the univariable analysis because they were available only in patients with PAC. Because this was a post hoc analysis of vasoactive therapy, one is unable to account for imbalances that a randomized trial would have accomplished. Thus, a propensity score analysis was undertaken to adjust for factors contributing to decisions to use vasoactive therapy. Variables such as serum urea nitrogen (SUN), sodium, blood pressure, cardiac index as well as sites were used in the analysis. A spline transformation of the propensity score was used in the multivariable outcome prediction models.

### Results

A total of 433 patients were enrolled in the ESCAPE trial. Of these, 215 were randomly assigned to the PAC

**Table 1.** Patient characteristics

Patients, no.	433
Age, mean (SD), y	56 (14)
Male, no. (%)	321 (74)
Race, no. (%)	
White	258 (60)
Black	117 (27)
Other	58 (13)
Ischemic etiology, no. (%)	215 (50)
Blood pressure, mean (SD), mm Hg	
Systolic	106 (16.3)
Diastolic	67 (11.5)
Heart rate, mean (SD), beat/min	82 (15.7)
Sodium, mean (SD), mmol/L	137 (4.4)
SUN, mean (SD), mg/dL	35 (22.7)
Creatinine, mean (SD), mg/dL	1.5 (0.6)
BNP, mean (SD), pg/mL	997 (131.3)
LVEF, mean (SD), %	19.3 (6.6)
Peak $\dot{V}O_2$ , mean (SD), mL $kg^{-1} min^{-1}$	10.0 (3.4)
6-minute walk distance, mean (SD), ft	414 (41.6)
Time to randomization, mean (SD), d	1.3 (2.2)

BNP, B-type natriuretic peptide.

group and 218 to the clinical assessment group. The mean time from hospital admission to randomization was 1.3 days. Table 1 summarizes the demographic and clinical characteristics of these patients. Patients had a mean age of 56 years, 74% were male, 60% were white, and 50% had an ischemic etiology for their HF. All patients had significant systolic dysfunction with a mean LVEF of 19.3%.

At baseline, 425 patients (98%) were taking a diuretic, 340 (79%) were taking an ACE inhibitor, and 268 (62%) were taking a  $\beta$ -blocker. Overall, 122 patients (28%, range 0%-50% at sites enrolling  $\geq 5$ ) received a vasodilator. Nesiritide was the most commonly prescribed vasodilator (66 patients [15%], median dose 0.01  $\mu g/kg/min$ ), followed by nitroprusside (50 patients [11%], median dose 5.58  $\mu g/min$ ) and nitroglycerin (10/122 patients, median dose 50  $\mu g/min$ ). Inotropic therapy was used in 180 patients (42%, range 6%-86% at sites enrolling  $\geq 5$ ), with dobutamine as the most commonly prescribed inotrope (155/180, median dose 4.0  $\mu g/kg$  per minute), followed by milrinone (72/180, median dose 0.38  $\mu g/kg$  per minute), dopamine (42/180, median dose 3.0  $\mu g/kg$  per minute), and amrinone (1/180, dose 0.3  $\mu g/kg$  per minute).

Patient characteristics differed significantly among the various treatment groups (Table 2). Mean SUN levels, RAP, and PCWP were greater; mean cardiac indices lower; and mean 6-minute walk distances shorter in patients who received intravenous vasodilators, inotropes, or both compared with patients who did not receive these therapies. For the patients with PAC measurements, mean systemic vascular resistance was greater in those who only received an intravenous

**Table II.** Patient characteristics by in-hospital intravenous vasoactive therapy

	<b>Vasodilator (n = 75)</b>	<b>Inotrope (n = 133)</b>	<b>Both (n = 47)</b>	<b>Neither (n = 178)</b>	<b>P</b>
Age, mean (SD), y	54 (13)	56 (14)	57 (13)	57 (15)	.498
Male, no. (%)	53 (71)	98 (74)	37 (79)	133 (75)	.793
White, no. (%)	37 (49)	84 (63)	30 (64)	107 (60)	.226
Ischemic etiology, no. (%)	34 (46)	72 (55)	25 (53)	84 (47)	.507
Time to randomization (d)					
No. (%)	75 (100)	132 (99)	46 (98)	171 (96)	
Mean (SD)	1.2 (1.8)	1.1 (2.5)	1.0 (2.1)	1.7 (2.2)	<.001
Median (Q1, Q3)	0.8 (0.1, 1.3)	0.7 (0.1, 0.9)	0.6 (0.0, 0.9)	0.9 (0.1, 2.3)	
Blood pressure (mm Hg)					
No. (%)	71 (95)	132 (99)	47 (100)	177 (99)	
Systolic, mean (SD)	110 (17.8)	104 (16.5)	103 (16.0)	106 (15.4)	.057
Diastolic, mean (SD)	70 (12.6)	65 (10.6)	65 (11.8)	67 (11.5)	.025
Sodium (mmol/L)					
No. (%)	73 (97)	133 (100)	46 (98)	177 (99)	
Mean (SD)	137 (4.2)	136 (4.7)	136 (4.7)	137 (4.1)	.165
Median (Q1, Q3)	137 (135, 140)	137 (134, 139)	136 (135, 139)	137 (135, 140)	
SUN (mg/dL)					
No. (%)	73 (97)	133 (100)	46 (98)	176 (99)	
Mean (SD)	37 (25.5)	35 (22.2)	45 (29.5)	31 (18.6)	.016
Median (Q1, Q3)	28 (19, 45)	28 (19, 44)	36 (26, 56)	26 (19, 38)	
BNP (pg/mL)					
No. (%)	63 (84)	103 (77)	40 (85)	143 (80)	
Mean (SD)	954 (1134)	1154 (1620)	998 (961)	902 (1236)	.303
Median (Q1, Q3)	554 (220, 1278)	580 (252, 1146)	687 (419, 1411)	517 (187, 1061)	
LVEF (%)					
No. (%)	68 (91)	130 (98)	47 (100)	177 (99)	
Mean (SD)	18.6 (5.7)	18.3 (6.0)	20.4 (7.6)	20.1 (6.9)	.134
Median (Q1, Q3)	20 (15, 22)	20 (15, 21)	20 (15, 25)	20 (15, 25)	
6-min walk distance (ft)					
No. (%)	60 (80)	126 (95)	46 (98)	159 (89)	
Mean (SD)	358 (418)	323 (344)	288 (380)	544 (445)	<.001
Median (Q1, Q3)	162 (0, 668)	208 (0, 550)	108 (0, 459)	525 (96, 936)	
Peak $\dot{V}O_2$ (mL kg <sup>-1</sup> min <sup>-1</sup> )					
No. (%)	16 (21)	40 (30)	9 (19)	61 (34)	
Mean (SD)	10.0 (3.7)	9.8 (3.2)	8.2 (2.2)	10.5 (3.6)	.080
Median (Q1, Q3)	9.7 (7.2, 12.0)	9.4 (7.1, 11.1)	7.9 (7.7, 8.4)	10.0 (8.7, 11.7)	
RAP (mm Hg)					
No. (%)	47 (63)	61 (46)	33 (70)	59 (33)	
Mean (SD)	14.0 (7.2)	15.8 (13.7)	15.5 (8.6)	10.1 (4.6)	.002
Median (Q1, Q3)	14 (8, 19)	15 (7, 20)	15 (9, 20)	10 (7, 12)	
PCWP (mm Hg)					
No. (%)	46 (61)	58 (44)	32 (68)	56 (31)	
Mean (SD)	27.5 (7.9)	25.0 (8.4)	28.1 (10.2)	20.2 (8.5)	<.001
Median (Q1, Q3)	28 (20, 35)	25 (19, 31)	28 (22, 35)	20 (14, 25)	
Cardiac index (L min <sup>-1</sup> m <sup>-2</sup> )					
No. (%)	46 (61)	60 (45)	33 (70)	54 (30)	
Mean (SD)	1.9 (0.6)	1.9 (0.5)	2.0 (0.8)	2.2 (0.6)	.018
Median (Q1, Q3)	1.9 (1.4, 2.4)	1.9 (1.5, 2.2)	1.8 (1.5, 2.3)	2.1 (1.8, 2.5)	
SVR (dyne s <sup>-1</sup> cm <sup>-5</sup> )					
No. (%)	46 (61)	60 (45)	33 (70)	52 (29)	
Mean (SD)	1791 (1045)	1328 (831)	1300 (596)	1394 (583)	.019
Median (Q1, Q3)	1527 (1205, 2044)	1294 (829, 1595)	1226 (799, 1624)	1283 (1030, 1583)	
Duration of hospitalization (d)					
Mean (SD)	6.5 (3.8)	8.4 (6.3)	15.4 (22.5)	4.8 (3.3)	<.001
Median (Q1, Q3)	6 (4, 8)	7 (4, 10)	9 (6, 17)	4 (3, 6)	
Death, no. (%)	12 (16)	30 (23)	17 (36)	24 (13)	.003
Death or rehospitalization, no. (%)	48 (64)	89 (67)	41 (87)	104 (58)	.003

SVR, Systemic vascular resistance.

**Table III.** Multivariable predictors of vasodilator and inotrope use

	OR (95% CI)	P
<b>Vasodilator use</b>		
Site	NA	<.001
SUN (10 U)	1.19 (1.07-1.33)	.001
PCWP*	1.08 (1.03-1.13)	.003
Pulmonary artery systolic pressure*	1.00 (0.97-1.03)	.856
<b>Inotrope use</b>		
Site	NA	<.001
RAP*	1.06 (1.01-1.12)	.024
SUN (10 U)	1.13 (1.01-1.26)	.042
Systolic blood pressure <100 (dichotomous)	1.54 (0.92-2.57)	.097
Sodium	0.96 (0.91-1.02)	.143
PCWP*	1.00 (0.96-1.05)	.920
Pulmonary artery systolic pressure*	1.01 (0.98-1.03)	.729

OR, Odds ratio.

\*In patients with a pulmonary artery catheter.

**Table IV.** Propensity score-adjusted multivariable risk factors for mortality

	HR (95% CI)	P
<b>IV vasoactive therapy</b>		
Vasodilator	1.39 (0.64-3.00)	.403
Inotrope	2.14 (1.10-4.15)	.024
Both	4.81 (2.34-9.90)	<.001
Sodium	0.92 (0.87-0.98)	.006
RAP*	1.03 (1.01-1.05)	.008
BNP (100 U)	1.02 (1.01-1.04)	.006
SUN (10 U)	1.13 (1.02-1.26)	.018
Age (10 y)	1.21 (0.97-1.51)	.087
Ischemic etiology	1.58 (0.91-1.73)	.104
Systolic blood pressure <100 (dichotomous)	1.60 (0.99-2.58)	.055

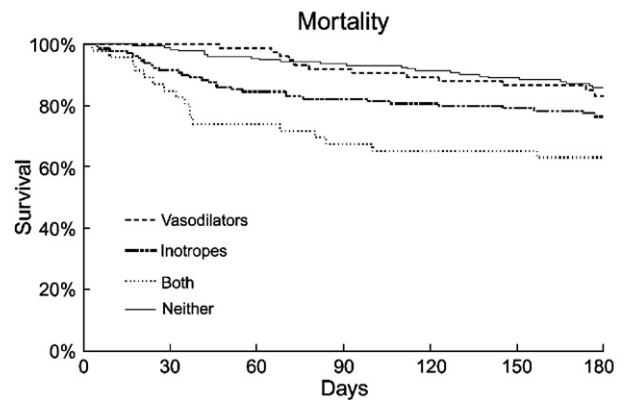
IV, Intravenous.

\*In patients with a pulmonary artery catheter.

vasodilator compared with those who received either an inotrope or neither.

Despite these mean differences, whether patients received a vasodilator or an inotrope appeared to be only partially influenced by their clinical parameters. In multivariable analyses, the greatest determinant of both intravenous vasodilator and inotrope use was the study site (hospital) to which the patient was admitted (Table III). The only other significant multivariable predictors of the use of a vasoactive agent were SUN level and PCWP for vasodilators, and SUN level and RAP for inotropes (Table III). The use and choice of vasoactive therapy were not significantly influenced by blood pressure or cardiac index.

**Figure 1**



Kaplan-Meier survival curve for all-cause mortality by intravenous vasoactive medication use.

**Table V.** Propensity score-adjusted multivariable risk factors for mortality or rehospitalization

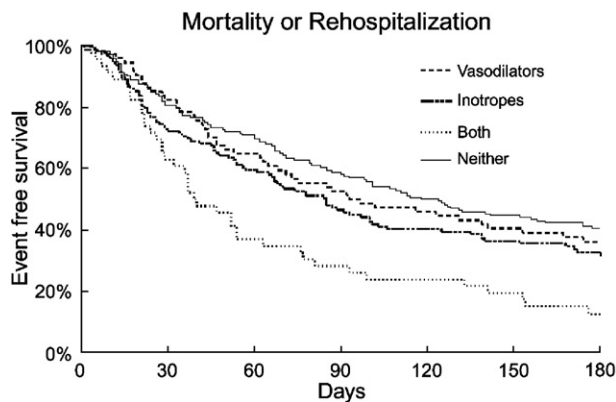
	HR (95% CI)	P
<b>IV vasoactive therapy</b>		
Vasodilator	1.20 (0.81-1.78)	.370
Inotrope	1.96 (1.37-2.82)	<.001
Both	2.90 (1.88-4.48)	<.001
SUN (10 U)	1.12 (1.05-1.20)	.001
Site	NA	.064
Systolic blood pressure <100 (dichotomous)	1.48 (1.13-1.92)	.004
PCWP*	1.02 (0.99-1.04)	.079
Ischemic etiology	1.14 (0.88-1.49)	.318
Sodium	0.98 (0.95-1.01)	.227

\*In patients with a pulmonary artery catheter.

After adjusting for factors known to affect mortality in this population, therapy with intravenous vasodilators had no significant association with mortality risk (hazard ratio [HR] 1.39, 95% CI 0.64-3.00,  $P = .403$ ). In contrast, significant association was found between the use of intravenous inotropic therapy (HR 2.14, 95% CI 1.10-4.15,  $P = .024$ ) and both therapies in combination (HR 4.81, 95% CI 2.34-9.90,  $P < .001$ ) and increased mortality risk (Table IV, Figure 1).

After adjusting for factors known to affect the composite end point of mortality plus rehospitalization, therapy with intravenous vasodilators was also not associated with a significant affect on this combined end point (HR 1.20, 95% CI 0.81-1.78,  $P = .37$ ). The HR was the same for nesiritide as for the other vasodilators. In contrast, therapy with an intravenous inotrope, either alone (HR 1.96, 95% CI 1.37-2.82,  $P < .001$ ) or in

Figure 2



Kaplan-Meier survival curve for freedom from death or rehospitalization by intravenous vasoactive medication use.

combination with a vasodilator (HR 2.90, 95% CI 1.88-4.48,  $P < .001$ ), was associated with a significant increase in the 6-month risk of the combined end point (Table V, Figure 2). Overall, the median unadjusted freedom from death plus rehospitalization was 93 days in patients who received vasodilators without inotropes, 85 days in patients who received inotropes without vasodilators, 39 days in patients who received both inotropes and vasodilators, and 118 days in patients who received neither.

## Discussion

This analysis provided information on the relative use of vasoactive medications and the factors determining their selection by clinicians for the treatment of patients with severe decompensated HF. Renal function and right atrial pressure were significant predictors for use of inotropes, whereas renal function and PCWP predicted the use of vasodilators. These data suggest that impairments of renal function and more severe hemodynamic abnormalities seem to influence the use of vasoactive medications. At the same time, however, the most powerful determinant of the use of both inotropes and vasodilators was the study site and the physicians managing the patients. These findings demonstrate a lack of consensus among clinicians about the management of patients with severe decompensated HF, and emphasize the need for well-designed prospective studies to further establish the appropriate use of intravenous vasoactive therapy in this population.

Several prior evaluations have suggested that intravenous inotropes may increase mortality risk compared with placebo or other therapy.<sup>1,4,5,10-12</sup> The OPTIME-CHF study evaluated<sup>4</sup> 951 patients hospitalized for

decompensated HF, but excluded patients who were felt to require inotropic therapy by their physicians. In-hospital and 60-day mortalities were greater in those randomly assigned to receive milrinone compared with placebo (in-hospital: 3.8% milrinone vs 2.3% placebo; 60-day: 10.3% milrinone vs 8.9% placebo). However, this trial did not have adequate power to detect a difference in mortality, which was not statistically significant. Nonetheless, a significant increase in in-hospital mortality risk with milrinone was detected in the subset of OPTIME-CHF patients with ischemic HF (milrinone 5.0%, placebo 1.6%,  $P = .04$ ).<sup>5</sup>

The mortality risks of inotropes versus vasodilators have been compared in 2 large multicenter registry or cohort analyses. In a retrospective nonrandomized analysis of data from >33 000 HF hospitalizations in the ADHERE, the covariate and propensity-adjusted in-hospital mortality risk was significantly greater in patients receiving the inotropes dobutamine or milrinone compared with those receiving the vasodilators nesiritide or nitroglycerin.<sup>11</sup> Similarly, in a retrospective cohort analysis of 2130 patients from 32 academic centers, in-hospital mortality was significantly higher in patients receiving dobutamine (10.2%) and milrinone (7.9%) compared with nesiritide (2.9%).<sup>12</sup> Compared with nesiritide, the adjusted mortality odds ratios for dobutamine and milrinone were 3.5 and 4.1 ( $P < .0001$ ).

Our evaluation also demonstrates that therapy with an intravenous inotrope was associated with a significant increase in the risk of mortality alone and the combined end point of all-cause mortality plus rehospitalization. In addition, both risk associations were highly increased when this therapy was combined with that of an intravenous vasodilator. Furthermore, these increases in risk association could not be attributed to an increased use of inotropes in higher risk patients with poor hemodynamics. Use of an inotrope was a significant independent risk factor, even after controlling for other potential risk factors to the extent possible using a propensity score-adjusted multivariable analysis.

Although this study seems to confirm the results of previous reports, it also provides an independent contribution. In contrast to other studies the ESCAPE trial enrolled a highly selected group of high-risk patients with severe decompensated HF reflected by low blood pressure,<sup>13</sup> markedly depressed LV systolic function, poor exercise tolerance, decreased peak  $\dot{V}O_2$ , impaired renal function, and a high incidence (8%) of cardiac transplantation or LV assist device placement during the duration of the study. Such patients are often considered by clinicians as candidates for treatment with intravenous vasoactive medications and are likely to be treated with inotropic support. This assumption is supported by the frequent use of vasoactive medications in this study. Although <25% of patients hospitalized for decompensated HF and included in the ADHERE registry were

reported to receive vasoactive medications,<sup>11</sup> 70% of patients enrolled in the ESCAPE trial received such therapy and almost half of all patients received inotropic drugs. This high use of inotropes is especially striking because the use of these agents for routine management was consistently and explicitly discouraged.<sup>9</sup> The uniqueness of the ESCAPE population is also reflected by the frequent use of standard recommended HF therapy on discharge, including ACE inhibitors/angiotensin receptor blockers in 90% of the patients and  $\beta$ -blockers in 62% of the patients. Therefore, the results of the present study extend previous observations and demonstrate an association between the use of inotropic drugs and unfavorable long-term effect even in hospitalized patients with severe, symptomatic, and hemodynamic impairments treated after discharge with standard chronic HF therapy.

The group in which both vasodilators and inotropes were used demonstrated a significantly worse prognosis compared with all other groups. However, these patients represented the most severe profile or baseline decompensation, with lower blood pressure, shorter 6-minute walk distance, higher SUN level, and higher PCWP. Length of hospital stay was over twice as long in this group compared with patients receiving vasodilators alone. In view of the marked differences of this group at baseline, worse outcome would be predicted regardless of therapy received.

It is important to consider the limitations of the current evaluation. Patients in this trial had severe advanced decompensated HF with an ejection fraction and systolic blood pressure lower than the average patient hospitalized with decompensated HF. The ESCAPE trial was conducted by HF specialists in academic medical centers, potentially limiting the generalization of the findings. The relatively small number of patients may have limited the ability to evaluate mortality, and patients were not randomized with respect to intravenous vasoactive therapy, a fact that may have lead to a potential selection bias. Although reasons for selection of various therapeutic options were limited to poor renal function, hemodynamic abnormalities, and treatment site, there were other factors that could not be detected by the statistical methods used. Because it is not possible to identify and adjust for all possible factors, the differences between patients treated in different sites and the influences of other nonmeasured factors cannot be completely excluded. In addition, treatment was started at various times during hospitalization, leading to potential inception time bias. Because of the small number of patients and deaths in each of the treatment groups, the 95% CIs on the mortality HRs are broad and encompass a >2-fold difference in risk. As a result, these analyses cannot detect small differences in mortality risk nor can they evaluate potential differences in this risk within the

various therapeutic classes. Therefore, these data will have to be confirmed by properly designed prospective, randomized trials.

## Conclusions

In this multivariable analysis of patients hospitalized for severe decompensated HF, the decision to use vasodilators or inotropes was determined by hemodynamic parameters and renal function, but the main factor was the treatment site. The use of intravenous inotropes was associated with a significantly increased risk of all-cause mortality and all-cause mortality plus rehospitalizations. No rational pattern of inotrope administration was detected within this population. The use of intravenous vasodilators was not associated with a significant increase in the adjusted risk of all-cause mortality or all-cause mortality plus rehospitalization. Inotropes in combination with vasodilators identified a group of patients with the highest mortality. These findings reinforce the critical need for additional well-designed adequately powered evaluations to establish the efficacy and safety of various therapies and provide guidance for the selection of vasoactive drugs for the management of hospitalized patients with severe decompensated HF.

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## Effects of acute changes in pulmonary wedge pressure on periodic breathing at rest in heart failure patients

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**Background** Patients with heart failure (HF) display a number of breathing abnormalities including periodic breathing (PB) at rest. Although the mechanism(s) contributing to PB remain unclear, we examined whether changes in pulmonary wedge pressure (PWP) and pulmonary vascular resistance (PVR) alter PB in patients with established HF.

**Methods** We studied 12 male patients with HF (age,  $50 \pm 11$  years; ejection fraction,  $18.3 \pm 3.8\%$ ; New York Heart Association class,  $3.2 \pm 0.4$ ), with PB at rest, who are undergoing right heart catheterization with infusion of nitroprusside.

**Results** At baseline, patients with HF displayed minute ventilation ( $V_E$ ) oscillations with amplitude of  $5.5 \pm 2.7$  L/min ( $57 \pm 34\%$  of the average  $V_E$ ) and cycle length of  $61 \pm 18$  seconds. Cardiac index (CI), PVR, and mean PWP averaged  $2.0 \pm 0.4$  L min<sup>-1</sup> m<sup>-2</sup>,  $281.9 \pm 214.9$  dyne/s per cm<sup>-5</sup>, and  $28.3 \pm 5.4$  mm Hg, respectively. During

nitroprusside infusion, CI increased to  $3.1 \pm 0.6$  L min<sup>-1</sup> m<sup>-2</sup>, PVR decreased to  $163.9 \pm 85.2$  dyne/s per cm<sup>-5</sup>, and PWP fell to  $10.0 \pm 4.2$  mm Hg. Nitroprusside reduced the amplitude ( $2.6 \pm 2.4$  L/min,  $23 \pm 21\%$  of average  $V_E$ ;  $P < .01$ ) and cycle length ( $41.4 \pm 28.8$  seconds;  $P < .01$ ) of  $V_E$  oscillations while abolishing oscillations in 3 patients. Although average  $V_E$  and PaCO<sub>2</sub> remained unchanged, there was a significant increase in the ratio of tidal volume to inspiratory time ( $V_T/T_I$ ;  $P < .01$ ), suggesting an increase in ventilatory drive. The change in the amplitude of  $V_E$  oscillations was positively correlated with the change in PWP ( $r = 0.75$ ;  $P < .01$ ), negatively correlated with the change in PVR ( $r = 0.63$ ;  $P < .05$ ), and not correlated with the change in CI.

**Conclusions** These data suggest that PWP (left atrial pressure) may play a direct role in the PB observed in HF at rest. (*Am Heart J* 2007;153:104.e1-104.e7.)