

# Ultrafiltration Versus Usual Care for Hospitalized Patients With Heart Failure

## The Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF) Trial

Bradley A. Bart, MD, FACC,\* Andrew Boyle, MD,\* Alan J. Bank, MD, FACC,\*  
Inder Anand, MD, FACC,\* Maria Teresa Olivari, MD, FACC,\* Mark Kraemer, MD,\*  
Shari Mackedanz, RN, BSN, CCRC,\* Paul A. Sobotka, MD, FACC,†  
Mike Schollmeyer, DVM,† Steven R. Goldsmith, MD, FACC\*

Minneapolis and Brooklyn Park, Minnesota

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<b>OBJECTIVES</b>	The purpose of this research was to assess the safety and efficacy of ultrafiltration (UF) in patients admitted with decompensated congestive heart failure (CHF).
<b>BACKGROUND</b>	Ultrafiltration for CHF is usually reserved for patients with renal failure or those unresponsive to pharmacologic management. We performed a randomized trial of UF versus usual medical care using a simple UF device that does not require special monitoring or central intravenous access.
<b>METHODS</b>	Patients admitted for CHF with evidence of volume overload were randomized to a single, 8 h UF session in addition to usual care or usual care alone. The primary end point was weight loss 24 h after the time of enrollment.
<b>RESULTS</b>	Forty patients were enrolled (20 UF, 20 usual care). Ultrafiltration was successful in 18 of the 20 patients in the UF group. Fluid removal after 24 h was 4,650 ml and 2,838 ml in the UF and usual care groups, respectively ( $p = 0.001$ ). Weight loss after 24 h, the primary end point, was 2.5 kg and 1.86 kg in the UF and usual care groups, respectively ( $p = 0.240$ ). Patients tolerated UF well.
<b>CONCLUSIONS</b>	The early application of UF for patients with CHF was feasible, well-tolerated, and resulted in significant weight loss and fluid removal. A larger trial is underway to determine the relative efficacy of UF versus standard care in acute decompensated heart failure. (J Am Coll Cardiol 2005;46:2043–6) © 2005 by the American College of Cardiology Foundation

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Loop diuretics are used in 88% of patients admitted for congestive heart failure (CHF) (1). However, concerns about the safety and therapeutic efficacy of diuretic-based treatment strategies have been raised (1–4). Ultrafiltration (UF) is an effective method of fluid removal with several advantages over diuretic-based approaches: adjustable fluid removal volumes and rates, no effect on serum electrolytes, and decreased neurohormonal activity (5–8).

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Recently, a less invasive UF device has been approved for fluid removal (System 100, CHF Solutions Inc., Brooklyn Park, Minnesota) (9). This device can be used outside the intensive care unit setting and does not require specialized nursing or central intravenous (IV) access. With the availability of this less invasive UF device, we performed a

randomized controlled trial to assess the feasibility, efficacy, and safety of performing UF in patients hospitalized for CHF.

### METHODS

This was an investigator-initiated multicenter randomized controlled trial involving six hospitals in the Minneapolis-St. Paul metropolitan area associated with the Minnesota Heart Failure Consortium. The protocol was approved at each participating site by the human subjects' research ethics committee.

Study patients were hospitalized with the primary diagnosis of CHF. They were required to have at least 2+ edema of the lower extremities *and* at least one of the following: elevated jugular venous pressure  $>10$  cm H<sub>2</sub>O, pulmonary edema or pleural effusion on chest X-ray, pulmonary rales, pulmonary wedge or left ventricular end-diastolic pressure  $>20$  mm Hg, ascites, or pre-sacral edema. Exclusion criteria were: severe stenotic valvular disease, acute coronary syndromes, systolic blood pressure  $<90$  mm Hg at time of consent, hematocrit  $>40\%$ , poor peripheral venous access, hemodynamic instability, use of iodinated radiocontrast within 72 h of consent or anticipated use of

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From the \*Minnesota Heart Failure Consortium, Minneapolis, Minnesota; and †CHF Solutions Inc., Brooklyn Park, Minnesota. Dr. Sobotka and Mr. Schollmeyer are employees of CHF Solutions Inc.; Dr. Goldsmith has received grant support as director of the Minnesota Heart Failure Consortium for administrative fees and overhead in connection with this trial. Funding for the project was provided by CHF Solutions Inc.

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**Abbreviations and Acronyms**

CHF = congestive heart failure  
IV = intravenous  
UF = ultrafiltration

radiocontrast during the index hospitalization, severe concomitant disease.

Forty patients were enrolled and randomized to usual care (n = 20) or UF plus usual care (n = 20). Patients assigned to usual care were treated by their attending physicians with encouragement to use standard CHF therapies conforming to best medical/community standards. A 35-cm, 16-g catheter was placed in the antecubital fossa of patients randomized to UF. These patients received a single, 8-h course of UF with fluid removal rates determined by the attending physician (to a maximum of 500 cc/h). Diuretics were held during the 8 h of UF; thereafter, they were administered at the discretion of the attending physician. Additional courses of UF were allowed at the discretion of the treating physician, but only after the 24-h end points were assessed.

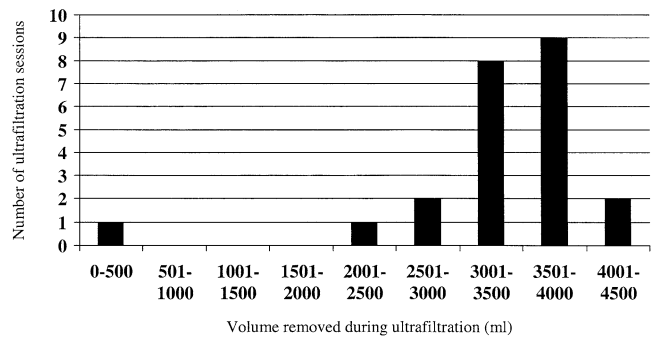
The primary end point was weight loss 24 h after obtaining consent. Weights were obtained by research personnel at baseline and 24 h using the same scale with the patient shoeless in a hospital gown. Other end points included: total volume removal at 24 and 48 h, global CHF and dyspnea assessments, serum electrolytes, and length of hospital stay.

**Statistical analysis.** All group comparisons were performed on an intention-to-treat basis. The significance of differences between groups was tested using a two-sided Fisher exact test for 2 × 2 contingency tables and a two-sided Wilcoxon rank sum test for continuous variables except weight loss. Because the study hypothesis predicted greater weight loss among UF patients compared to usual care patients, a one-sided Wilcoxon rank sum test was used rather than the two-sided test. The study provided 99% power with 20 patients per group to detect a difference in

**Table 1.** Baseline Characteristics

Variables	Ultrafiltration (n = 20)	Usual Care (n = 20)
Median age (yrs)	67.5	69.5
Male gender (%)	70	70
Diabetes (%)	35	53
Hypertension (%)	60	65
Prior MI (%)	30	30
Prior revascularization	45	40
EF <40% (%)	69	78
NYHA functional class III/IV (%)	16/84	35/65
Systolic BP (mm Hg)	119.5	117
Heart rate	79	84.5
JVD >10 cm H <sub>2</sub> O (%)	95	80
Rales (%)	47	50
3+ to 4+ pretibial edema (%)	65	47

BP = blood pressure; EF = ejection fraction; JVD = jugular venous distension; MI = myocardial infarction; NYHA = New York Heart Association.



**Figure 1.** Frequency distribution of ultrafiltrate removed during each individual ultrafiltration session. Twenty-three separate ultrafiltration sessions were attempted on 19 patients with intravenous access.

weight loss of 1 kg assuming a variance of 0.4 kg for the UF group, 0.7 kg for the standard therapy group, and alpha of 0.05.

**RESULTS**

Forty patients were enrolled and randomized at the six participating hospitals between July 2003 and May 2004. Characteristics at the time of enrollment are shown in Table 1. Intravenous access was unsuccessful in one patient, and one patient could not be treated due to inability to withdraw blood from the catheter. The median time from consent to initiation of UF was 3.9 h; the median duration of UF was 8 h per session, and the frequency distribution of ultrafiltrate removed for all UF sessions is shown in Figure 1. The median volume of ultrafiltrate removed during UF was 3,213 ml. Four patients (20%) had an additional UF treatment session 24 to 48 h from the time of consent resulting in an additional 3,650 to 4,175 ml of ultrafiltrate removal.

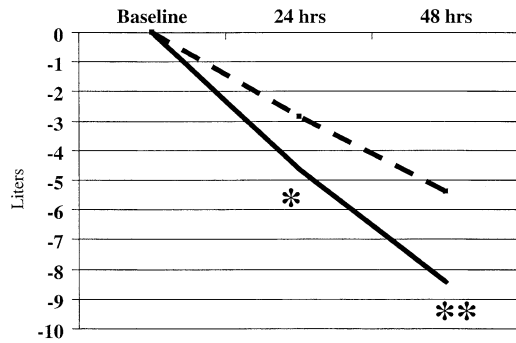
Medications received by patients in the first 24 h are shown in Table 2. The median cumulative dose of furosemide (or equivalent doses of other IV diuretics) received during the first 24 h was 160 mg and 80 mg for the usual care and UF groups, respectively (p = 0.238).

Volume removal and weight loss are shown in Figures 2 and 3. Volume removal 24 h after the time of consent was 4,650 ml and 2,838 ml in the UF and usual care groups, respectively (p = 0.001). After 48 h, fluid removal was 8,415

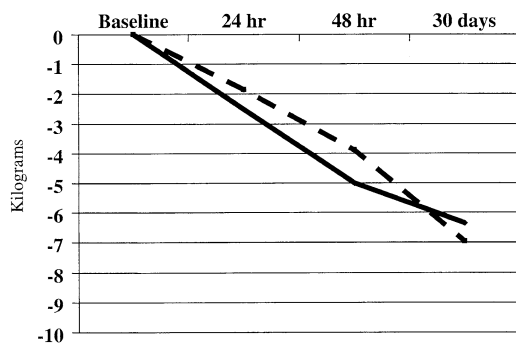
**Table 2.** Medical Management During First 24 h After Enrollment

Variables	Ultrafiltration (n = 20)	Usual Care (n = 20)
IV diuretics (%)	65*	95
ACE inhibitors/ARBs (%)	70	70
Beta-blockers (%)	75	65
Digoxin (%)	0	0
Nesiritide (%)	20	50
IV inotropes (%)	0	10

\*p = 0.044 (two-sided Wilcoxon rank sum test) compared to usual care group.  
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; IV = intravenous.



**Figure 2.** Median cumulative fluid removal at 24 and 48 h in patients assigned to ultrafiltration (solid line) and usual care (dashed line). \* $p = 0.001$ ; \*\* $p = 0.012$ .



**Figure 3.** Median weight loss at 24 and 48 h in patients assigned to ultrafiltration (solid line) and usual care (dashed line).

ml and 5,375 ml in the UF and usual care groups, respectively ( $p = 0.012$ ). Weight loss at 24 h, the primary end point of the study, was greater in the UF group, but failed to reach statistical significance ( $p = 0.240$ ). Other treatments, specifically the use of nesiritide in the usual care group, did not contribute to the weight loss observed (1.27 kg with and 1.95 kg without nesiritide,  $p = NS$ ).

Changes in hemodynamics and blood tests are shown in Table 3. Compared to usual care, UF was not associated with significant changes in heart rate, blood pressure, or electrolytes. Patients receiving UF had a slight decrease in hemoglobin compared to the usual care group ( $p = 0.004$ ).

**Table 3.** Hemodynamics and Laboratory Assessment

	Ultrafiltration (n = 20)					Usual Care (n = 20)				
	BL	24 h	$\Delta 24$	48 h	$\Delta 48$	BL	24 h	$\Delta 24$	48 h	$\Delta 48$
Heart rate (beats/min)	79	81	+0.5	80	+0.5	85	79	+0.5	76	-3.5
Systolic BP (mm/Hg)	120	104	-7.5	113	+1	117	115	-10	113	-10
Sodium (mEq/l)	137	136	0	136	-0.5	139	139	0	138	0
Potassium (mEq/l)	3.9	4.0	+0.1	4.0	+0.1	4.0	3.9	-0.05	3.9	0
Chloride (mEq/l)	100	100.5	0*	100	0	104	100	-1	101	-3
Bicarbonate (mEq/l)	27	27	-0.5	28	+0.5	26	29	+1	29	+2
BUN (mg/dl)	36	38	+1	44	+8	36	31	-2	37	+2
Creatinine (mg/dl)	1.6	1.8	+0.1	1.9	+0.1	1.8	1.8	0	1.9	+0.1
Hemoglobin (g/dl)	11.3	10.7	+0.1	10.1	-0.4†	10.7	11	+0.05	11.3	+0.55

\* $p = 0.041$  (two-sided Wilcoxon rank sum test) for difference in change in chloride from baseline to 24 h compared to usual care group; † $p = 0.004$  (two-sided Wilcoxon rank sum test) for difference in change in hemoglobin from baseline to 48 h compared to usual care group.

BL = baseline; BP = blood pressure; BUN = bilirubin urea nitrogen.

At 30-day follow-up, there were no significant differences in hemoglobin between the two treatment groups.

All patients experienced improvement in symptoms during the treatment period. Global dyspnea and CHF assessments are shown in Tables 4 and 5. Dyspnea and CHF symptoms were significantly improved in the UF group compared to usual care at 48 h ( $p = 0.039$  and  $p = 0.023$  for dyspnea and CHF symptoms, respectively).

The median length of stay for the index hospitalization was six days in the UF group and five days in the usual care group ( $p = NS$ ). There was one death in the UF group during the 30-day follow-up period (unrelated to UF) and one catheter site infection that required a 4-week course of IV antibiotics.

## DISCUSSION

Early UF in patients hospitalized with CHF resulted in a trend toward greater weight loss at 24 h and greater fluid removal compared to usual care; UF was well-tolerated, and there were no serious complications other than one line infection and a modest drop in hemoglobin in the first 48 h. The latter finding is unexplained, but may relate to modest blood loss due to concomitant use of heparin and the retention of blood in the UF circuit. There were no clinical consequences associated with the change in hemoglobin, and at 30 days there was no longer a difference between the two treatment groups. There were no significant problems with electrolyte depletion or acute renal failure.

Our experience with this form of UF is similar to that reported by Jaski et al. (9). In that study, 21 patients were treated with a single 8-h course of UF using the same device. The average amount of ultrafiltrate removed was 2,611 ml, which is less than what we observed in the current study (3,213 ml).

There are numerous case series reports of UF for acute CHF. In this setting, UF is well-tolerated and associated with effective volume removal, relief of symptoms, improved hemodynamics, increased responsiveness to subsequent diuretic therapy, and increased sodium excretion despite decreasing doses of diuretics (9-12). Ultrafiltration has also

**Table 4.** Changes in Global Heart Failure Symptoms

Heart Failure Symptoms	24 h		48 h	
	Ultrafiltration	Usual Care	Ultrafiltration	Usual Care
Worse	—	1 (5.3%)	—	—
No change	2 (10.5%)	4 (21.1%)	1 (6.3%)	3 (18.8%)
Mild improvement	4 (21.1%)	3 (15.8%)	2 (12.5%)	6 (37.5%)
Moderate improvement	9 (47.4%)	6 (31.6%)	4 (25%)	4 (25%)
Marked improvement	4 (21.1%)	5 (26.3%)	9 (56.3%)	3 (18.8%)

p = 0.644 (two-sided Wilcoxon rank sum test) at 24 h; p = 0.023 (two-sided Wilcoxon rank sum test) at 48 h.

**Table 5.** Changes in Global Dyspnea Symptoms

Dyspnea Symptoms	24 h		48 h	
	Ultrafiltration	Usual Care	Ultrafiltration	Usual Care
Worse	1 (5.3%)	1 (5.3%)	—	—
No change	3 (15.8%)	3 (15.8%)	1 (6.3%)	6 (37.5%)
Mild improvement	1 (5.3%)	6 (31.6%)	5 (31.3%)	5 (31.3%)
Moderate improvement	12 (63.2%)	8 (42.1%)	5 (31.3%)	3 (18.8%)
Marked improvement	2 (10.5%)	1 (5.3%)	5 (31.3%)	2 (12.5%)

p = 0.258 (two-sided Wilcoxon rank sum test) at 24 h; p = 0.039 (two-sided Wilcoxon rank sum test) at 48 h.

been studied in patients with chronic, stable CHF and is associated with improvements in sympathetic tone, hemodynamics, exercise capacity, and increased responsiveness to diuretics (6-8,13).

The primary end point of this trial, weight loss at 24 h, trended in favor of patients randomized to UF. In addition to small sample sizes, one of the reasons the primary end point did not reach statistical significance is the effective and aggressive use of diuretics in the usual care group. These patients produced nearly 3 l of urine in the first 24 h and lost 1.86 kg at 24 h and 3.9 kg at 48 h. This degree of diuresis and weight loss substantially exceeds usual practices as described in Acute Decompensated Heart Failure National Registry (ADHERE) (1) and a recent acute CHF clinical trial with similar end points (14).

**Study limitations.** The small size of this study limits the ability to draw definitive conclusions about the clinical impact of UF versus usual care. Assessing outcomes at a later time point (beyond 24 h) and allowing treating physicians to continue UF until a state of a euvolemia was achieved may have demonstrated more dramatic advantages to UF. The safety of UF with respect to renal function and anemia should be addressed in a larger clinical trial.

**Conclusions.** Early use of UF for patients hospitalized with CHF is feasible, well-tolerated, and resulted in significant weight loss and fluid removal. A larger trial is underway to determine the relative efficacy of UF versus standard care in acute decompensated heart failure.

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**Reprint requests and correspondence:** Dr. Bradley A. Bart, O5 HCMC, 701 Park Avenue South, Minneapolis, Minnesota 55415. E-mail: bartx006@umn.edu.