Continuous Aortic Flow Augmentation

A Pilot Study of Hemodynamic and Renal Responses to a Novel Percutaneous Intervention in Decompensated Heart Failure

Marvin A. Konstam, MD; Barbara Czerska, MD; Michael Böhm, MD, PhD; Ron M. Oren, MD; Jerzy Sadowski, MD, PhD; Sanjaya Khanal, MD; William T. Abraham, MD; Andrae Wasler, MD; Johannes B. Dahm, MD; Antonello Gavazzi, MD; Sinisa Gradinac, MD, PhD; Victor Legrand, MD; Paul Mohacsi, MD; Gerhard Poelzl, MD; Branislav Radovancevic, MD; Adrian B. Van Bakel, MD; Michael R. Zile, MD; Barry Cabuay, MD; Krzysztof Bartus, MD; Piet Jansen, MD

Background—Diminished aortic flow may induce adverse downstream vascular and renal signals. Investigations in a heart failure animal model have shown that continuous aortic flow augmentation (CAFA) achieves hemodynamic improvement and ventricular unloading, which suggests a novel therapeutic approach to patients with heart failure exacerbation that is inadequately responsive to medical therapy.

Methods and Results—We studied 24 patients (12 in Europe and 12 in the United States) with heart failure exacerbation and persistent hemodynamic derangement despite intravenous diuretic and inotropic and/or vasodilator treatment. CAFA (mean±SD 1.34±0.12 L/min) was achieved through percutaneous (n=19) or surgical (n=5) insertion of the Cancion system, which consists of inflow and outflow cannulas and a magnetically levitated and driven centrifugal pump. Hemodynamic improvement was observed within 1 hour. Systemic vascular resistance decreased from 1413±453 to 1136±381 dyne · s · cm^{-5} at 72 hours (P=0.0008). Pulmonary capillary wedge pressure decreased from 28.5±4.9 to 19.8±7.0 mm Hg (P<0.0001), and cardiac index (excluding augmented aortic flow) increased from 1.97±0.44 to 2.27±0.43 L · min^{-1} · m^{-2} (P=0.0013). Serum creatinine trended downward during treatment (overall P=0.095). There were 8 complications during treatment, 7 of which were self-limited. Hemodynamics remained improved 24 hours after CAFA discontinuation.

Conclusions—In patients with heart failure and persistent hemodynamic derangement despite intravenous inotropic and/or vasodilator therapy, CAFA improved hemodynamics, with a reduction in serum creatinine. CAFA represents a promising, novel mode of treatment for patients who are inadequately responsive to medical therapy. The clinical impact of the observed hemodynamic improvement is currently being explored in a prospective, randomized, controlled trial. **(*Circulation*. 2005;112:3107-3114.)**

Key Words: heart failure ■ hemodynamics ■ vasodilation ■ nitric oxide ■ heart-assist device

The prevalence of heart failure among Americans is nearly 5 million, with more than 500 000 newly diagnosed cases each year.[1] There are approximately 1 million annual US hospitalizations with the primary diagnosis of heart failure, with an estimated 44% of discharged patients readmitted within 6 months.[1,2] Although medical therapy for chronic heart failure has advanced substantially, improvements in the treatment of decompensated heart failure have lagged behind.[3]

Various types of mechanical circulatory support devices are approved for clinical practice, as a bridge to cardiac transplantation or as destination therapy.[4,5] Although selection of the type of device is based on type of heart failure, size of the patient, and experience of the institution, the main objective is to functionally supplement or replace flow from the failing ventricles in patients with decompensated heart failure. The placement of these devices, which pump blood from the left ventricle (LV) into the aorta, requires major

Received January 11, 2005; de novo received April 12, 2005; revision received August 10, 2005; accepted August 11, 2005.

From Tufts-New England Medical Center and Tufts University (M.A.K.), Boston, Mass; Henry Ford Heart & Vascular Institute (B.C., S.K.), Detroit, Mich; University Hospital Saarland (M.B.), Homburg, Germany; University of Iowa (R.M.O., B.C.), Iowa City, Iowa; Jagiellonian University (J.S., K.B.), Krakow, Poland; The Ohio State University (W.T.A.), Columbus, Ohio; University Hospital Graz (A.W.), Graz, Austria; University Hospital (J.B.D.), Greifswald, Germany; Riuniti Hospital (A.G.), Bergamo, Italy; Dedinje Cardiovascular Institute (S.G.), Belgrade, Yugoslavia, Sart Tilman University Hospital (V.L.), Liege, Belgium; University Hospital Bern (P.M.), Bern, Switzerland, University Hospital Innsbruck (G.P.), Innsbruck, Austria; Texas Heart Institute at St. Luke's Episcopal Hospital (B.R.), Houston, Tex; Medical University of South Carolina (A.B.V.B., M.R.Z.), Charleston, SC; and Orqis Medical (P.J.), Lake Forest, Calif.

Correspondence to Marvin A. Konstam, MD, Tufts-New England Medical Center, 750 Washington St, Boston, MA 02111. E-mail MKonstam@tufts-nemc.org

Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/CIRCULATIONAHA.105.555367**

surgical expertise in specialized centers. A less invasive device, which can produce sustained hemodynamic and clinical improvement, would be desirable to fill this gap in treatment.

Investigations in a chronic, microembolic, ischemic heart failure canine model have demonstrated that institution of continuous aortic flow augmentation (CAFA), using the Cancion system (Orqis Medical Corporation), results in reduction in left heart filling pressure and volumes and augmented LV ejection fraction (EF).[6] On the basis of the hypothesis that reduced aortic flow results in adverse downstream vascular and renal signals, this novel system comprises a miniature extracorporeal pump that augments aortic flow continuously throughout the cardiac cycle. It does not require any mechanical connection to the heart. A previous report demonstrated hemodynamic and clinical improvement with this system in a single patient with severe, decompensated heart failure.[7] The observed salutary effects have been consistent with progressive vasodilation, ventricular unloading, and augmented renal perfusion.

We now report results from the first 24 patients undergoing CAFA with the Cancion system, who constitute the combined enrollment within feasibility trials performed in the United States and in Europe. Patients enrolled manifested acute exacerbation of chronic heart failure with hemodynamic derangement, which was uncorrected with intravenous diuretic and inotrope and/or vasodilator therapy. We report results of hemodynamics and renal function with up to 5 days of treatment.

Methods

Population

Patients were enrolled under 2 investigational protocols, one in Europe and one in the United States, with similar entry and exclusion criteria. Protocols were approved, respectively, by individual center ethics committees (Europe; 9 sites) and investigational review boards (United States; 4 sites). All patients gave written, informed consent. Entry criteria included the following: age 18 to 80 years; hospitalization owing to acute exacerbation of chronic heart failure manifesting increasing dyspnea and/or fatigue and/or exercise intolerance; need for hemodynamic monitoring, based on clinical judgment; treatment with intravenous diuretics and inotropic and/or vasodilator therapy, with either clinical response judged to be inadequate or recurrence of signs and symptoms on weaning attempt; elevated pulmonary capillary wedge pressure (PCWP; Europe: ≥20 mm Hg; United States: ≥18 mm Hg); stable drug doses (Europe: ≥2 hours; United States: ≥6 hours); reduced LVEF (Europe: ≤35%; United States: ≤25%); and abnormal renal function or high diuretic requirement (serum creatinine ≥1.5 mg%, estimated creatinine clearance ≤60 mL/min,[8,9] or intravenous furosemide dose ≥120 mg over 24 hours). Exclusion criteria included systolic blood pressure ≤80 mm Hg or clinical cardiogenic shock; recent Q-wave myocardial infarction (≤30 days) or cardiac surgery (Europe: ≤7 days; United States: ≤30 days); concomitant use of other forms of mechanical support; cerebral vascular accident or transient ischemic attack within the prior year; severe renal impairment (Europe: on dialysis; United States: on dialysis or serum creatinine >3.0 mg%); history of ventricular fibrillation or sustained ventricular tachycardia, in the absence of correctable cause, unless an implantable cardiac defibrillator was present; clinically significant peripheral vascular disease; coagulopathy or inability to receive heparin; evidence of systemic infection; and other life-threatening or debilitating disease.

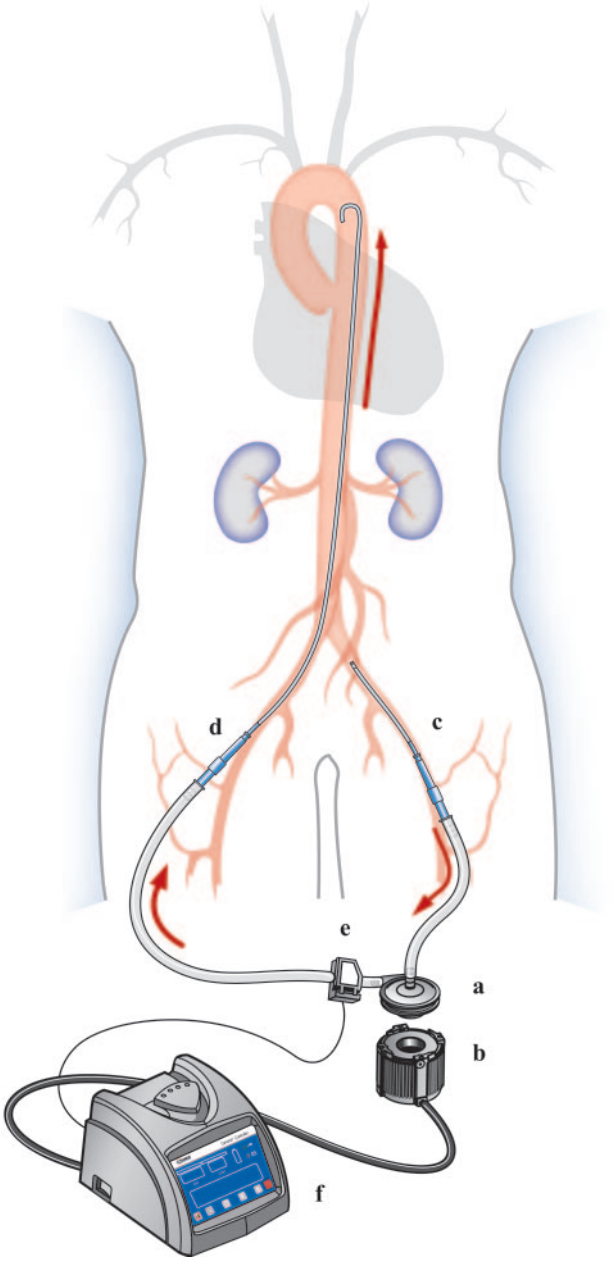

Figure 1. Cancion system for CAFA. The centrifugal flow pump (a), driven by a magnetic motor (b), draws blood from the percutaneously placed inflow cannula (c), positioned in the left iliac artery, and returns to the descending thoracic aorta via the pigtail outflow cannula (d), percutaneously placed via the right femoral artery. Flow is monitored by a flow sensor (e), positioned on the outflow tubing, and is regulated by the controller (f).

Description of the Device

In animal models of heart failure, we have found that superimposing additional continuous flow onto pulsatile aortic flow within the descending aorta results in ventricular unloading and improved hemodynamics. The Cancion system consists of a pump, tubing, and arterial access cannulas and is designed to recirculate blood from the iliac artery to the descending thoracic aorta in a continuous, nonpulsatile manner (Figure 1). Inflow to the pump is achieved with a 15-cm-long, 12F cannula percutaneously inserted via the left femoral artery. In the first 5 patients, outflow from the pump was via a 27-cm-long PVC/expanded PTFE graft cannula (6-mm expanded PTFE graft section) anastomosed to the left axillary artery (axillary-

femoral configuration). In the remaining 19 patients, pump outflow was via a 60-cm-long, 12F cannula inserted through a percutaneously inserted right femoral arterial sheath (femoral-femoral configuration). The terminal end-hole pigtail of the cannula was positioned under fluoroscopy in the thoracic aorta just above the level of the tracheal carina. The inflow and outflow cannulas were connected via PVC tubing to a bearingless, magnetically levitated centrifugal pump (32 mL priming volume) designed to minimize hemolysis and thrombosis. The blood capacity of the entire system (including the pump and the intracorporeal portions of the cannulas) is ≈108 mL. The pump is activated by a bearingless magnetoelectric motor connected to a controller. Pump speeds of 2000 to 5400 rpm were used to achieve flow rates of 1.1 to 1.5 L/min. When the pump is activated, the flow loop results in superimposition of additional nonpulsatile flow on pulsatile cardiac output within the descending aorta between the outflow and inflow cannulas.

In vitro and in vivo safety studies have demonstrated that the Cancion system produces a minimal or an acceptable degree of hemolysis (predefined as absence of an increase in plasma free hemoglobin to >40 mg/dL on 2 consecutive measurements) when used for up to 5 days. For the duration of circulatory support, anticoagulation with continuous infusion of unfractionated heparin was used to maintain activated partial thromboplastin time between 65 and 85 seconds. The system was inserted and removed in a cardiac catheterization laboratory (femoral-femoral) or an operating room (axillary-femoral). After insertion, the patient was transferred to an intensive care unit for the duration of device treatment, for up to 5 days. After the device was removed, the patient remained in the intensive care unit for an additional 24 hours of hemodynamic monitoring.

Measurements

Baseline hemodynamic measurements were performed in duplicate and were averaged. In the United States, PCWP was recorded at 6-hour intervals beginning 24 hours before device implantation. Cardiac output was determined by the thermodilution technique. After device implantation, hemodynamic and laboratory data were acquired at predefined time intervals during the study and were continued after device explantation for an additional 24 hours.

Statistical Analysis

Results are expressed as mean±SD, unless otherwise specified. Overall significance for each parameter was tested with linear regression, testing for a trend over time. The regression considered patients as random effects; repeated-measures analysis was used because of potential within-patient correlations. Measurements at each time point were compared with baseline values with 2-tailed paired *t* tests; no adjustment for multiple comparisons has been performed when reporting these probability values. Two-sided probability values are reported. Statistical computations were performed with SAS version 8.2.

Approximately 8% (27/327) of the PCWP values were missing. For pointwise comparisons against baseline and for the summary statistics, missing values were imputed with the last observation carried forward (LOCF) technique; missing values at the 1-hour time point were imputed to be the mean of the baseline and 2-hour values. This LOCF method is slightly biased against detecting a trend over time. The regressions used actual observed data only, although the same significance is obtained with the LOCF data. A similar situation prevailed with the other response variables.

Results

Between December 2001 and March 2004, 24 patients (12 in the United States and 12 in Europe) underwent treatment with the Cancion system (3 females, 21 males). Baseline characteristics are listed in Table 1. The average age was 54 years, with a range from 26 to 75 years. Eight patients had ischemic cardiomyopathy, 14 had idiopathic dilated cardiomyopathy, 1 had valvular heart disease, and 1 had graft arteriosclerosis 39 months after cardiac transplantation.

The Cancion system was implanted for a duration of 2 to 119 hours, with an average of 77±33 hours. Pump flows ranged between 1.07 and 1.56 L/min, with an average of 1.34±0.12 L/min. One patient (with graft arteriosclerosis) was in cardiogenic shock with hyperkalemia at the time of implantation and died 2 hours after the implantation, with continued cardiogenic shock and progressive hyperkalemia. Efficacy analysis was performed in the remaining 23 patients. Medication doses remained stable throughout the treatment period. The most commonly prescribed intravenous inotropic/vasodilator agents were dobutamine (n=17) and milrinone (n=14). Among patients completing 3 days of treatment, mean doses of dobutamine and milrinone were 6.3±3.8 and 5.6±2.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 0.48±0.21 and 0.44±0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at baseline and day 3, respectively. Daily furosemide doses averaged 134±183 and 135±128 mg at baseline and day 3, respectively.

At baseline, PCWP averaged 28.4±4.9 mm Hg, cardiac index (CI) averaged 1.94±0.42 $L \cdot min^{-1} \cdot m^{-2}$, and mean arterial pressure averaged 76.9±9.3 mm Hg. Table 2 lists mean hemodynamic values at baseline and throughout the first 24 hours after device implantation. Table 3 lists hemodynamic values at baseline and at 8-hour intervals up to 72 hours after device implantation, and then 12 and 24 hours after device removal, for the 20 patients who received treatment for at least 48 hours. CAFA treatment resulted in a reduction in PCWP, pulmonary artery pressure, and systemic vascular resistance (SVR) and an increase in CI. As shown in Figure 2, for US patients (in whom measurements were obtained for 24 hours before device implantation), initiation of CAFA treatment resulted in an abrupt and progressive reduction in PCWP relative to a stable baseline over the preceding 24 hours. Data for all 23 patients are shown in Figure 3. Improvements in all parameters were sustained and progressive over 72 hours of treatment. At 12 and 24 hours after removal of the device, all hemodynamic benefits were still present. Mean arterial pressure decreased from baseline during the first several hours of treatment and remained stable during the remainder of device treatment and after removal. Figure 4 plots PCWP versus CI at baseline, after 24 and 72 hours of CAFA, and at 24 hours after device removal for the 20 patients who received treatment for at least 48 hours. The findings are consistent with an improvement (upward shift) in the Starling curve, which persisted 24 hours after discontinuation of treatment.

Weak inverse correlations were observed between the 24-hour change from baseline in both SVR ($r=0.42$; $P=0.048$) and PCWP ($r=0.40$; $P=0.056$) with baseline CI. Patients with lower baseline CI tended to show greater reductions in SVR and PCWP with treatment.

Serum creatinine trended downward from baseline over the first 48 hours of treatment, with the effect sustained at 72 hours (overall $P=0.095$; Figure 5). In the US patients only, serum creatinine levels were repeated an average of 3 days after discontinuation of treatment, and at that time, levels had increased again from 1.21±0.35 mg% on treatment day 3 to 1.43±0.39 mg%.

TABLE 1. Baseline Characteristics

Patient	Age, y	Gender	Diagnosis	EF, %	Medicines
1	64	M	Ischemic cardiomyopathy	25	Dobutamine
2	53	M	Graft arteriosclerosis	20	Dopamine
3	70	M	Dilated cardiomyopathy	8	Dopamine
4	40	M	Dilated cardiomyopathy	15	Dobutamine, milrinone
5	51	M	Ischemic cardiomyopathy	15	Dobutamine, milrinone
6	67	M	Ischemic cardiomyopathy	NA	Dobutamine, dopamine
7	65	F	Valvular heart disease	20	Dobutamine, dopamine
8	60	M	Ischemic cardiomyopathy	28	Dobutamine, milrinone
9	52	M	Dilated cardiomyopathy	19	Dobutamine
10	51	M	Ischemic cardiomyopathy	20	Dobutamine, nitroprusside
11	69	M	Ischemic cardiomyopathy	15	Dobutamine
12	52	M	Dilated cardiomyopathy	22	Dobutamine
13	51	F	Dilated cardiomyopathy	17	Milrinone
14	60	M	Ischemic cardiomyopathy	25	Milrinone
15	54	M	Dilated cardiomyopathy	22	Milrinone
16	35	M	Dilated cardiomyopathy	8	Dobutamine, milrinone
17	46	M	Dilated cardiomyopathy	10	Dobutamine
18	49	M	Dilated cardiomyopathy	15	Dobutamine, milrinone, nesiritide
19	53	M	Ischemic cardiomyopathy	19	Dobutamine, dopamine, milrinone, nesiritide
20	26	M	Dilated cardiomyopathy	12	Dobutamine, milrinone
21	75	M	Dilated cardiomyopathy	18	Milrinone
22	44	F	Dilated cardiomyopathy	24	Dobutamine, milrinone
23	70	M	Dilated cardiomyopathy	13	Dobutamine, milrinone
24	49	M	Dilated cardiomyopathy	12	Milrinone

NA indicates not available.

Adverse Effects

A total of 8 patients experienced complications during treatment. One death (described above) was not considered related to the device. The remaining 7 patients had no lasting sequelae. In 2 patients, the percutaneous device was removed on the second day because of bleeding from the insertion site. In both cases, bleeding was controlled by manual compression after device removal. In 1 patient, during surgical inflow cannula insertion, there was dissection of the profunda femoris artery, which was surgically repaired without sequela. In 1 patient, the right iliac artery was dissected during sheath exchange after removal of the pigtail cannula. This event was managed conservatively, without sequela. In 1 patient, the percutaneous device was removed on the fourth day because of loss of left pedal pulse, which returned immediately after device removal. In 2 patients, the device was removed owing to thrombosis within the cannulas, which resulted in reduced flow. In both patients, 1 of whom had deficiency of antithrombin III, anticoagulation was subtherapeutic. Neither patient experienced any clinical embolic events.

TABLE 2. Hemodynamics Over the Initial 24 Hours of Treatment (n=23; Mean±SD)

		Hours After Implantation								Overall
	Baseline	1	2	4	8	12	16	20	24	Significance†
PCWP, mm Hg	28.4±4.9	24.8±7.2*	24.3±8.6*	24.5±8.3*	24.3±8.9	21.8±8.1*	21.7±7.2*	21.1±6.6*	21.8±8.6*	P=0.0014
PAP, mm Hg	40.9±6.1	37.3±8.8*	38.5±9.9	38.4±9.5	37.8±10.7	34.9±8.4*	34.5±8.9*	34.8±8.7*	34.6±9.8*	P=0.0005
CI, $L \cdot min^{-1} \cdot m^{-2}$	1.94±0.42	2.06±0.46	2.09±0.44	2.12±0.41	2.13±0.58	2.17±0.56*	2.03±0.45	2.18±0.55*	2.10±0.43*	NS
HR, bpm	89±18	90±17	90±16	88±17	92±16	92±18	89±18	89±18	88±18	NS
BP, mm Hg	76.9±9.3	72.4±10.5*	72.7±9.9	70.3±9.2*	69.9±9.4*	67.3±8.1*	70.1±8.9*	68.5±10.8*	68.7±12.5*	P=0.01
SVR, $dyne \cdot s \cdot cm^{-5}$	1454±486	1352±500	1289±508*	1233±500*	1230±456*	1179±429*	1323±498	1203±478*	1195±421*	NS
PVR, $dyne \cdot s \cdot cm^{-5}$	276±115	262±108	265±128	278±116	302±196	272±114	284±102	283±140	267±138	NS

BP indicates mean arterial pressure; HR, heart rate; PAP, mean pulmonary artery pressure; and PVR, pulmonary vascular resistance.

*$P<0.05$ vs baseline.

†By repeated-measures linear trend analysis.

TABLE 3. Hemodynamics Over 72 Hours of Treatment and After Device Removal for Those Patients With at Least 48 Hours of Device Treatment (n=20; Mean±SD)

		Hours After Implantation											
	Baseline	8	16	24	32	40	48	56	64	72	x+12	x+24	Overall Significance†
PCWP, mm Hg	28.5±4.9	25.8±8.3	22.8±6.7*	22.3±9.0*	23.6±6.1*	25.0±7.0*	23.8±7.6*	22.6±7.7*	21.8±6.5*	19.8±7.0*	19.7±6.8*	21.2±6.6*	$P<0.0001$
PAP, mm Hg	41.3±6.1	39.9±9.8	36.1±8.4*	35.7±9.6*	34.9±7.9*	37.4±8.4*	37.3±9.7*	37.9±9.2	35.9±10.4*	35.2±9.3*	33.2±6.1*	36.2±8.0*	$P<0.0001$
CI, $L \cdot min^{-1} \cdot m^{-2}$	1.97±0.44	2.10±0.55	2.03±0.35	2.09±0.45	2.08±0.37	2.23±0.50*	2.19±0.51	2.22±0.52	2.24±0.50*	2.27±0.43*	2.37±0.50*	2.34±0.54*	$P=0.0013$
HR, bpm	89±18	93±17	89±18	90±19	90±16	89±17	90±18	90±17	90±15	90±15	93±16	90±17	NS
BP, mm Hg	74.7±6.6	70.7±8.9	69.8±8.2*	67.9±11.6*	69.2±6.6*	70.4±11.2	69.1±8.3*	66.0±9.0*	68.7±9.7*	69.2±10.9*	67.5±5.4*	68.4±8.5*	$P=0.0014$
SVR, $dyne \cdot s \cdot cm^{-5}$	1413±453	1224±419	1268±383	1177±382*	1208±350	1186±412*	1170±396*	1086±350*	1142±386*	1136±381*	1051±326*	1037±292*	$P=0.0008$
PVR, $dyne \cdot s \cdot cm^{-5}$	274±114	288±142	284±92	282±138	231±104	236±73	235±106	250±92	258±109	272±107	242±66	256±78	NS

BP indicates mean arterial pressure; HR, heart rate; PAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; x+12, 12 hours after device removal; and x+24, 24 hours after device removal.

*$P<0.05$ vs baseline.

†By repeated-measures linear trend analysis, including all values from baseline through 72 hours.

Discussion

Despite substantial advances in medical treatment for heart failure, hospitalizations for this condition continue to be common, representing a major source of morbidity and cost.[1] Heart failure exacerbations are characterized by manifestations of volume overload, low cardiac output, or both.[10,11] Medical treatment, including intravenous diuretics, vasodilators, and inotropic agents, are not uniformly successful in achieving the desired clinical improvement and are suspected of contributing to adverse clinical outcomes.[12–18] In the present study of patients with severe heart failure exacerbation and persistent hemodynamic derangement despite intravenous diuretic and inotropic and/or vasodilator therapy, we observed that CAFA, with the Cancion system, markedly improved PCWP, pulmonary artery pressure, and CI in association with reduced SVR. Hemodynamic improvement was still present after discontinuation of flow augmentation. Serum creatinine trended downward during treatment. This initial human investigation provides encouraging evidence for a potentially important clinical role for this novel treatment. Ongoing investigation is directed toward determining a role for CAFA in facilitating recovery from heart failure exacerbation refractory to conventional medical treatment.

CAFA differs from all previously applied forms of circulatory assistance. With an arterial-to-arterial flow circuit, drawing blood from the iliac artery and returning it to the descending thoracic aorta, the Cancion system does not assume or directly augment cardiac output. Previous devices, including one that is percutaneously implanted with 15F to 21F cannulas (CardiacAssist, Inc),[19] are designed to directly augment cardiac output, in parallel with the intrinsic circulation. These auxiliary flow systems require high-flow pumps, large-bore cannulas, and surgical or highly invasive implantation techniques. They are, therefore, reserved for the most severely ill patients who are, however, candidates for complex, invasive procedures. Although the initial 5 patients enrolled in the present study had surgically implanted cannulas, in the subsequent 19 patients, CAFA was achieved with a simple percutaneous procedure, performed in the catheterization laboratory. CAFA was provided by a centrifugal pump that generates up to 1.5 L/min of flow.

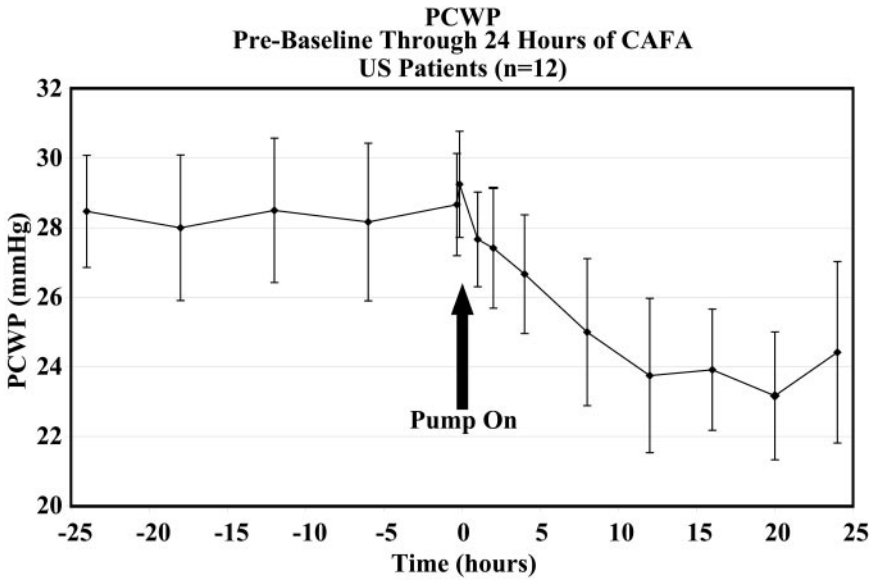

Figure 2. Effects of CAFA on PCWP (mean±SEM) during the first 24 hours of treatment in US patients (n=12), in whom serial measurements were made during the 24 hours preceding device implantation. Measurements remained stable before initiation of device treatment, after which PCWP decreased rapidly and continued to decrease over the subsequent 12 hours.

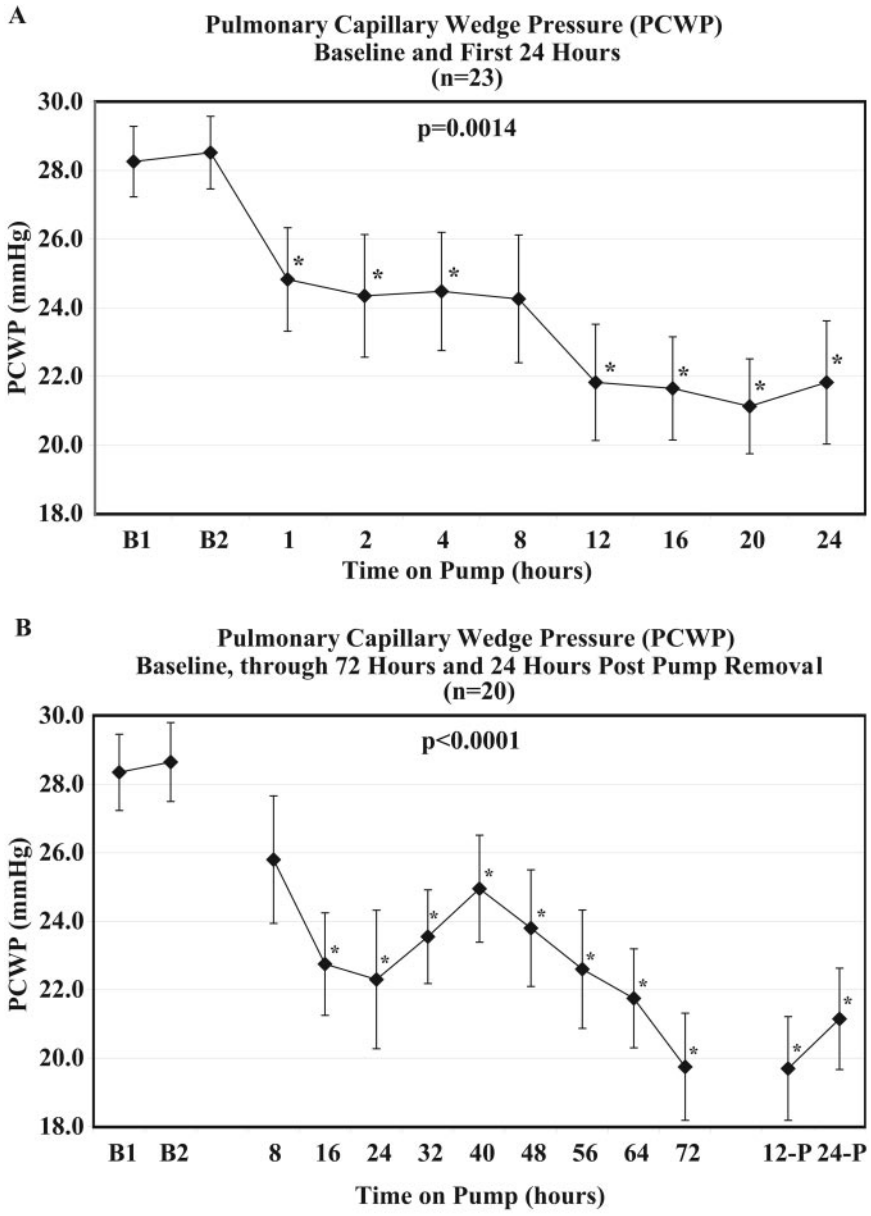

Figure 3. Effects of CAFA on PCWP within the entire patient population. A, Results (mean±SEM) at baseline and during the first 24 hours of treatment in 23 patients. B, Results at baseline, during 72 hours of treatment, and 12 and 24 hours after discontinuation of treatment (12-P, 24-P) for the 20 patients who underwent treatment for at least 48 hours. Asterisks denote significant difference from baseline by *t* test ($P<0.05$). Probability values denote overall significance by repeated-measures linear trend analysis applied to all data through 24 (A) or 72 (B) hours. B1 and B2 are duplicate baseline measurements obtained 10 minutes apart.

One potential explanation for hemodynamic improvement with CAFA relates to cardiac unloading through conservation of forward flow throughout the cardiac cycle. Additionally, the early and progressive decrease in SVR suggests that augmentation of flow within the aorta in patients with reduced cardiac output stimulates vasodilation within downstream resistance arterial beds through flow-mediated vasodilation. Utilizing an in vitro model of the central arterial circulation, Gharib and Beizaie[20] observed that during low-flow states, the flow pattern is perturbed, with reversal of blood flow along the aortic borders during diastole. CAFA favorably alters this pattern by providing antegrade flow throughout the cardiac cycle. Such changes in arterial flow patterns are likely to have a major influence on endothelial release of vasoactive mediators, such as nitric oxide, as has been demonstrated by Lu and Kassab.[21] Our finding in the present study that the magnitude of the observed decrease in SVR and in PCWP correlated inversely with baseline CI (that is, patients with the lowest baseline CI showed the greatest magnitude of response to CAFA) is consistent with the hypothesis that a low-flow state within the aorta signals downstream vasoconstriction, and augmentation of aortic flow reverses this effect.

In a study by Haithcock et al,[6] 4 hours of CAFA within a microembolic, ischemic, chronic myopathic canine model achieved progressive reduction in left heart filling pressure associated with reductions in LV volumes and increases in stroke volume, cardiac output, and EF. There was no discernible change in heart rate or arterial pressure. Wasler et al[7] previously reported the first human application of this technique in a patient with ischemic cardiomyopathy who was admitted for exacerbation of heart failure. During 3 days of treatment with CAFA, there were substantial decreases in PCWP, LV dimensions, and serum creatinine, with increases in CI and EF.

We enrolled patients with severe exacerbations of chronic heart failure, characterized by high cardiac filling pressures

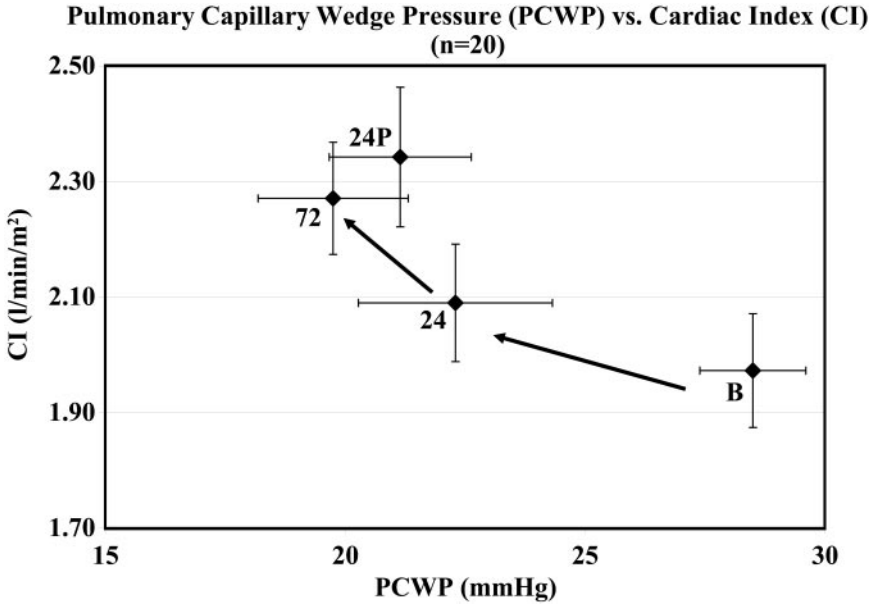

Figure 4. Plot of PCWP vs CI (mean±SEM) at baseline (B), after 24 and 72 hours of CAFA (24 and 72, respectively), and 24 hours after discontinuation of treatment (24P) in the 20 patients who underwent treatment for at least 48 hours. The concomitant reduction in PCWP and increase in CI defines an upward shift in the LV Starling curve.

and low CI, whose conditions were poorly responsive to intravenous diuretics and inotropes and/or vasodilators. Our observations of marked improvement in hemodynamics, which persisted 24 hours after discontinuation of CAFA, support a role for this form of treatment as an adjunct to medical therapy in patients requiring hospitalization because of worsening heart failure. An increase in CI (excluding augmented aortic flow), at a time when PCWP is markedly reduced from baseline, indicates that the LV has moved to a more favorable Starling curve. CAFA treatment is likely to break a vicious circle characterized by reduced aortic flow, worsening peripheral vasoconstriction, increasing filling pressure, and further reduction in cardiac output, providing an opportunity for sustained clinical benefit. Furthermore, a prolonged reduction in filling pressures and SVR, with a reduction in LV volumes (and presumed reduction in wall stress) as observed in animal investigations, may achieve recovery in myocardial function.

The downward trend in serum creatinine also favors clinical usefulness for this technique. There has been substantial recent attention given to the "cardio-renal syndrome" of severe heart failure, with growing evidence that worsening renal function during hospitalization carries a poor prognosis.[22–25] It is possible that CAFA directly augments renal blood flow, or alternatively, that the same signals responsible for downstream vasodilation (eg, nitric oxide) favorably affect glomerular and/or tubular function. Ongoing animal investigations are directed toward further exploration of the mechanisms of CAFA action on central hemodynamics, as well as on renal hemodynamics and glomerular and tubular function.

Observations in the present study justify investigations of the potential for translating the hemodynamic and renal benefits of CAFA treatment into improved symptoms and clinical outcomes. The ongoing Multi-center Trial of the Orqis Medical Cancion System for the Enhanced Treatment

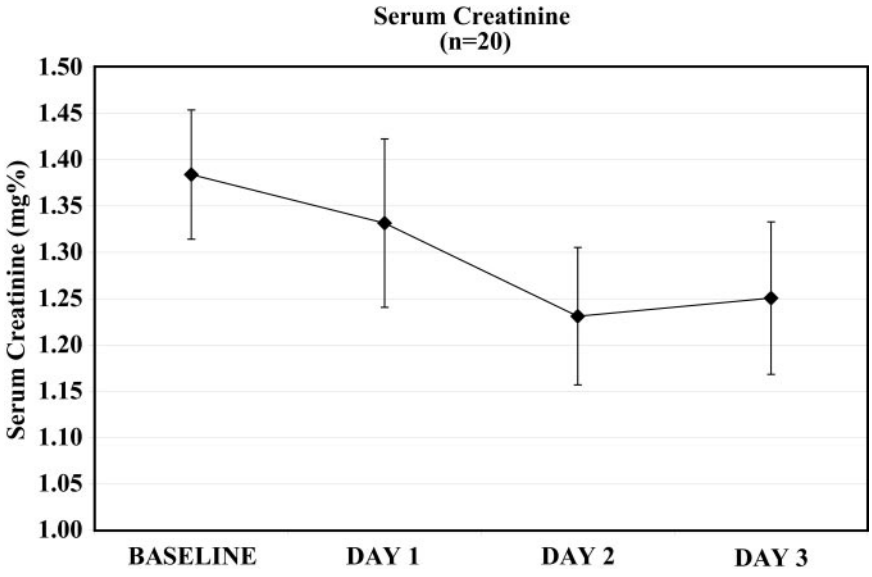

Figure 5. Serum creatinine values (mean±SEM) at baseline and during CAFA. Overall $P=0.095$ by repeated-measures linear trend analysis.

of Heart Failure Unresponsive to Medical Therapy (MOMENTUM) is a randomized, controlled trial of the effects of CAFA therapy added to medical therapy versus medical therapy alone on both hemodynamics and clinical outcomes.

In summary, CAFA therapy with the Orqis Cancion system achieved significant improvement in hemodynamics that were still present after termination of treatment in patients hospitalized with an exacerbation of chronic heart failure that had been inadequately responsive to medical therapy, including intravenous diuretics and inotropes and/or vasodilators. These benefits were most pronounced in patients with lower baseline cardiac indices and were accompanied by beneficial trends in serum creatinine. Although the precise mechanism for CAFA benefit continues to be explored, it is possible that effects derive, at least in part, from modulation of signals emanating from the aorta responsible for downstream vascular effects. An ongoing investigation is exploring a potential role of nitric oxide in mediating such effects. CAFA, achieved through a readily implanted percutaneous device, represents a promising mode of therapy for patients with severe heart failure. The clinical impact of this mode of therapy is currently under investigation.

Acknowledgment

This work was funded by Orqis Medical Corporation, Lake Forest, Calif.

Disclosure

Drs Czerska, Bohm, Oren, Sadowski, Khanal, Abraham, Wasler, Dahm, Gavazzi, Gradinac, Legrand, Mohacsi, Poelzl, Radovancevic, Van Bakel, Zile, Cabuay, and Bartus are Principal Investigators for Orqis Medical Corporation. Dr Jansen was an employee of Orqis Medical. Dr Konstam is a part-time employee of Orqis Medical, serving as Medical Director.

References

1. American Heart Association. *Heart Disease and Stroke Statistics: 2004 Update.* Dallas, Tex: American Heart Association; 2004. Available at: www.americanheart.org. Accessed July 28, 2004.
2. Krumholz HM, Parent EM, Tu N, Vaccarino V, Wang Y, Radford MJ, Hennen J. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med*. 1997;157:99–104.
3. Jain P, Massie BM, Gattis WA, Klein L, Gheorghiade M. Current medical treatment for the exacerbation of chronic heart failure resulting in hospitalization. *Am Heart J*. 2003;145:S3–S17.
4. Frazier OH, Rose EA, Oz MC, Dembitsky W, McCarthy P, Radovancevic B, Poirier VL, Dasse KA, for the HeartMate Investigators. Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation. *J Thorac Cardiovasc Surg*. 2001;122:1186–1195.
5. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meir P, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, Desvigne-Nickens P, Oz MC, Poirier VL. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med*. 2001;345:1435–1443.
6. Haithcock BE, Morita H, Fanous NH, Suzuki G, Sabbah HN. Hemodynamic unloading of the failing left ventricle using an arterial-to-arterial extracorporeal flow circuit. *Ann Thorac Surg*. 2004;77:158–163.
7. Wasler A, Radovancevic B, Fruhwald F, Tripolt M, Tscheliessnigg K. First use of the Cancion cardiac recovery system in a human. *ASAIO J*. 2003;49:136–138.
8. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.
9. Mahon NG, Blackstone EH, Francis GS, Starling RC III, Young JB, Lauer MS. The prognostic value of estimated creatinine clearance alongside functional capacity in ambulatory patients with chronic congestive heart failure. *J Am Coll Cardiol*. 2002;40:1106–1113.
10. Nohria A, Lewis E, Stevenson LW. Medical management of advanced heart failure. *JAMA*. 2002;287:628–640.
11. The ADHERE™ Registry. *First Quarter 2003 National Benchmark Report*. Fremont, Calif: Scios Inc.
12. Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ. Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. *Circulation*. 1999;100:1311–1315.
13. Domanski M, Norman J, Pitt B, Haigney M, Hanlon S, Peyster E. Diuretic use, progressive heart failure, and death in patients in the Studies of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol*. 2003;42:705–708.
14. Cotter G, Metzkor E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, Shaham O, Marghitay D, Koren M, Blatt A, Moshkovitz Y, Zaidenstein R, Golik A. Randomized trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary edema. *Lancet*. 1998;351:389–393.
15. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML, et al, for the PROMISE Study Research Group. Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med*. 1991;325:1468–1475.
16. Cuffe MS, Califf RM, Adams KF Jr, Benza R, Bourge R, Colucci WS, Massie BM, O'Connor CM, Pina I, Quigg R, Silver MA, Gheorghiade M, for the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287:1541–1547.
17. O'Connor CM, Gattis WA, Uretsky BF, Adams KF Jr, McNulty SE, Grossman SH, McKenna WJ, Zannad F, Swedberg K, Gheorghiade M, Califf RM. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flora International Randomized Survival Trial (FIRST). *Am Heart J*. 1999;138:78–86.
18. Bouvy ML, Heerdink ER, De Bruin ML, Herings RM, Leufkens HG, Hoes AW. Use of sympathomimetic drugs leads to increased risk of hospitalization for arrhythmias in patients with congestive heart failure. *Arch Intern Med*. 2000;160:2477–2480.
19. Vranckx P, Foley DP, de Feijter PJ, Vos J, Smits P, Serruys PW. Clinical introduction of the TandemHeart, a percutaneous left ventricular assist device, for circulatory support during high-risk percutaneous coronary intervention. *Int J Cardiovasc Interv*. 2003;5:35–39.
20. Gharib M, Beizaie M. Correlation between negative near-wall shear stress in human aorta and various stages of congestive heart failure. *Ann Biomed Eng*. 2003;3:678–685.
21. Lu X, Kassab GS. Nitric oxide is significantly reduced in ex-vivo porcine arteries during reverse flow because of increased superoxide production. *J Physiol*. 2004;561(pt 2):575–582.
22. Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, Sanak MJ. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol*. 2001;38:955–962.
23. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. *Am Heart J*. 1999;138:285–290.
24. Aronson D. Mittleman MA. Burger AJ. Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure. *Am J Med*. 2004;116:466–473.
25. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB, Krumholz HM. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol*. 2004;43:61–67.