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Urocortin-2 Infusion in Acute Decompensated Heart Failure

Findings From the UNICORN Study (Urocortin-2 in the Treatment of Acute Heart Failure as an Adjunct Over Conventional Therapy)

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Objectives The purpose of this study is to investigate the effects of urocortin-2 as adjunct therapy in acute decompensated heart failure (ADHF).

Background Urocortin-2 produced favorable integrated effects in experimental heart failure but there are no equivalent human data. We describe the first therapeutic study of urocortin-2 infusion in ADHF.

Methods Fifty-three patients with ADHF were randomly assigned to 5 ng/kg/min of urocortin-2 or placebo infusion for 4 h as an adjunct therapy. Changes in vital signs, plasma neurohormonal and renal indices during treatment were compared using repeated-measures analysis of covariance. Ten patients in each arm underwent more detailed invasive hemodynamic evaluation.

Results Urocortin-2 produced greater falls in systolic blood pressure compared to placebo (16 ± 5.8 mm Hg, $p < 0.001$) with nonsignificant increases in heart rate (5.7 ± 3.8 beats/min, $p = 0.07$) and increased cardiac output (2.1 ± 0.4 l/min vs. −0.1 ± 0.4 l/min, $p < 0.001$) associated with a 47% reduction in calculated total peripheral resistance ($p = 0.015$). Falls in pulmonary artery and pulmonary capillary wedge pressures did not differ significantly between groups. Urocortin-2 reduced urine volume and creatinine clearance during infusion but these returned to above baseline level in the 8 h after infusion. Plasma renin activity rose briefly with urocortin-2 coinciding with reductions in blood pressure ($p < 0.001$). B-type natriuretic peptide levels fell significantly over 24 h with urocortin-2 ($p < 0.01$) but not with placebo.

Conclusions Urocortin-2 infusion in ADHF markedly augmented cardiac output without significant reflex tachycardia. Renal indices fell transiently concurrent with urocortin-2-induced reductions in blood pressure. Further investigations are required to uncover the full potential of urocortin-2 in treating ADHF. (J Am Coll Cardiol HF 2013;1:433–41)

Acute decompensated heart failure (ADHF) is a major cause of hospitalization, mortality, and morbidity (1). Conventional treatment for ADHF is frequently limited by compromised hemodynamic status including hypotension (2,3) and renal dysfunction (4). Recent trials of new therapies in ADHF have been largely disappointing (5–8). Hence, there is a need for pharmacotherapy in ADHF that can provide concurrent beneficial effects on hemodynamics—including optimizing filling pressures and cardiac output, and on neurohormonal activation while preserving renal function.

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Urocortin-2 is an endogenous vasoactive peptide that belongs to the corticotrophin-releasing factor (CRF) family (9). It has selective affinity for the CRF_2 receptor and has predominant effects on the cardiovascular system (9). Urocortin-2 is an arterial vasodilator with positive inotropic and lusitropic properties (10–12); it is protective against

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Abbreviations and Acronyms

ADHF = acute decompensated heart failure

ANP = atrial natriuretic peptide

BNP = brain natriuretic peptide

CRF = corticotrophin-releasing factor

cTPR = calculated total peripheral resistance

GFR = glomerular filtration rate

NT-proBNP = N-terminal pro-brain natriuretic peptide

PCWP = pulmonary capillary wedge pressure

PRA = plasma renin activity

ischemia-reperfusion injury and suppresses cardiac sympathetic nerve activity (13,14). Intravenous boluses and constant infusions of urocortin-2 exhibit a powerful combination of beneficial hemodynamic, neurohormonal and renal effects in severe experimental heart failure (15,16). Although consistent hemodynamic effects were seen in stable heart failure patients, renal and neurohormonal effects were minor in comparison with those observed in the pre-clinical studies (12). We hypothesized that treatment with urocortin-2 would be beneficial in ADHF, and we undertook a pilot trial comparing symptomatic, hemodynamic, neurohormonal, and renal responses to a 4-h infusion of urocortin-2 or placebo in addition to standard therapy for ADHF.

Methods

The UNICORN (Urocortin-2 in the Treatment of Acute Heart Failure as an Adjunct Over Conventional Therapy) study was a single-center, randomized, double-blind, placebo-controlled trial (Australian New Zealand Clinical Trials Registry number ACTRN12609000508279). The study protocol was approved by the ethics committee of the New Zealand Ministry of Health (Upper South B, Canterbury), and the Standing Committee on Therapeutic Trials. The study was conducted under the oversight of the Data Monitoring Committee of the Health Research Council of New Zealand. Although Neurocrine Biosciences Inc. provided the trial peptide and the initial toxicology information for assessment by the Standing Committee on Therapeutic Trials, they made no other financial or intellectual contribution, and the trial was entirely designed by the investigators and funded by a grant from the Health Research Council. All participants gave signed written informed consent to take part in the trial. All participants were invited to take part in the right heart catheter substudy for more detailed hemodynamic observations with additional consent until 20 right heart catheter studies were completed.

Patient eligibility. Inclusion criteria were as follows: patients ≥18 years of age were eligible if they were recruited within 36 h of admission for ADHF and less than 24 h from first dose of intravenous loop diuretic agents, had dyspnea at rest or with minimal exertion, with at least 1 clinical sign of heart failure (specifically, either respiratory rate >20/min or pulmonary edema with crackles to at least one-third above lung bases), and at least 1 objective measurement consistent with heart failure (either chest x-ray film showing pulmonary congestion, brain natriuretic peptide [BNP] >115 pmol/l or N-terminal-pro brain natriuretic peptide [NT-proBNP] >120 pmol/l, or left ventricular ejection fraction <40% on echocardiogram).

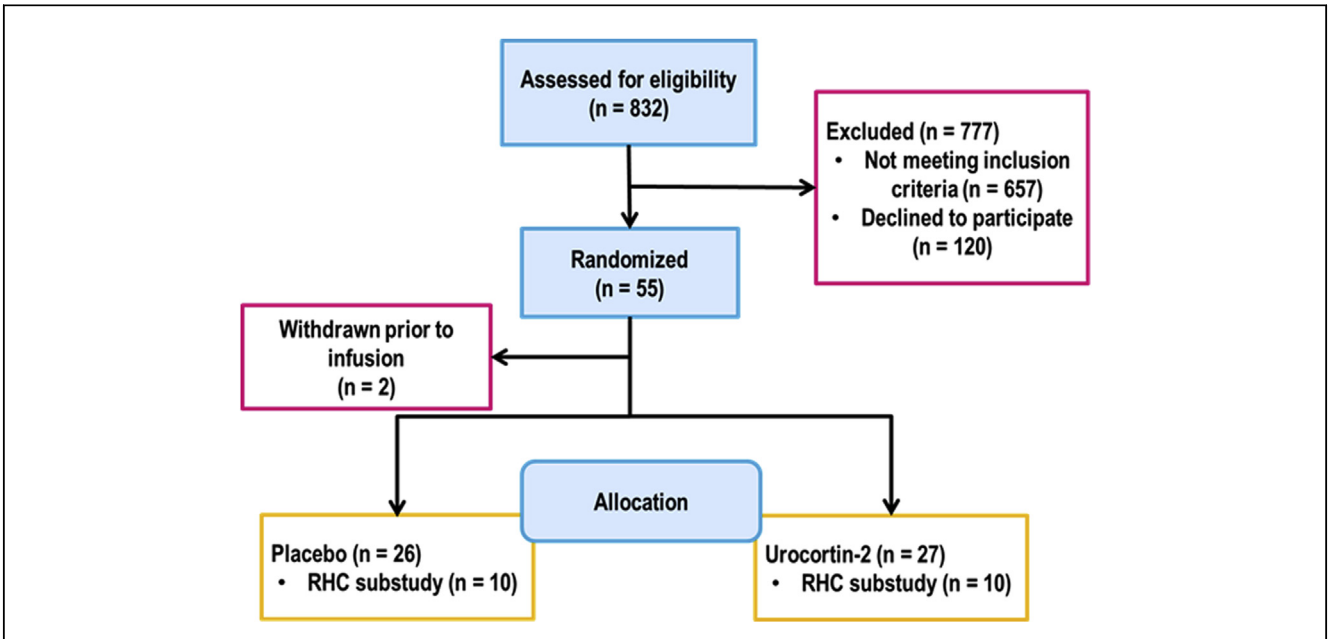

Figure 1 Recruitment and Treatment Allocation Flow Diagram

RHC = right heart catheterization.