Urocortin 2 infusion in human heart failure

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Received 28 February 2007; revised 5 July 2007; accepted 17 July 2007; online publish-ahead-of-print 25 August 2007

See page 2561 for the editorial comment on this article (doi:10.1093/eurheartj/ehm413)

**KEYWORDS**
Hormones; Cardiac output; Haemodynamics; Echocardiography; Vasodilation

**Aims** To document the haemodynamic, neurohormonal, and renal responses to Urocortin 2 (UCN2) infused in human heart failure (HF).

**Methods and results** Eight male patients with HF [left ventricular ejection fraction (LVEF) < 40%, NYHA class II–III] received placebo and 25 [low dose (LD)] and 100 μg [high dose (HD)] of UCN2 intravenously over 1 h in a single-blind, placebo-controlled, dose-escalation design.

UCN2 increased cardiac output (CO) (mean peak increments ± SEM; placebo 0.3 ± 0.1; LD 1.0 ± 0.3; HD 2.0 ± 0.2 L/min; P < 0.001) and LVEF (0.0 ± 1.5; LD 5.9 ± 2.1; HD 14.1 ± 2.7%; P = 0.001) and decreased mean arterial pressure (placebo 6.7 ± 1.3; LD 11.4 ± 1.7; HD 19.4 ± 3.3 mmHg; P = 0.001), systemic vascular resistance (SVR) (placebo 104 ± 37; LD 281 ± 64; HD 476 ± 79 dynes s/cm²; P = 0.003), and cardiac work (CW) (placebo 48 ± 12; LD 66 ± 22; HD 94 ± 13 mmHg/L/min; P < 0.001). No significant effect on vasoconstrictor/volume-retaining neurohormones was noted. UCN2 decreased urinary volume (P = 0.035) but not creatinine excretion (P = 0.962).

**Conclusion** Intravenous UCN2 in HF induced increases in CO and LVEF with falls in SVR and CW. No hormone response occurred. The role of UCN2 in circulatory regulation and its potential therapeutic application in heart disease warrant further investigation.

**Introduction**
Urocortin 2 (UCN2) is a vasoactive peptide belonging to the corticotrophin-releasing factor (CRF) peptide family.1 CRF and the urocorins (UCNs) 1, 2, and 3 act through G-protein-coupled receptor subtypes, CRF₁ and CRF₂.2 CRF activates CRF₁ receptors, urocortin 1 (UCN1) binds to both CRF₁ and CRF₂ receptors, whereas UCN2 and urocortin 3 (UCN3) are selective agonists for the CRF₂ receptors, of which there are at least two variants, termed CRF₂(a) and CRF₂(b). The CRF₂(a) receptor is found in high concentration in the human left ventricle, intramyocardial blood vessels, and medial layers of internal mammary arteries.3–5

Recent reports indicate that the UCNs exert effects beyond the hypothalmo-pituitary-adrenal axis, directly upon cardiac, vascular, and vaso-humoral function in health and cardiac disease.6–11 UCN2 infusion in healthy humans induces increases in cardiac output (CO) and left ventricular ejection fraction (LVEF) and decreases systemic vascular resistance (SVR).12 Activation of renin, angiotensin II, and norepinephrine occurred only with high-dose UCN2, with its more powerful haemodynamic effects in company with a modest fall-off in urine volume and sodium and potassium excretion. This parallels effects reported in normal sheep but contrasts with the pronounced suppression of volume retaining, vasoconstrictor/neurohormonal systems, and augmentation of renal function observed in experimental ovine heart failure (HF).7 In intact mice, both wild type and in the muscle-specific LIM protein-deficient HF model, UCN2 is positively inotropic, chronotropic, and lusitropic.10 In isolated rat heart, UCN1, UCN2, and UCN3 reduce infarct size in cardiac ischaemia/reperfusion experiments.11,13 These reports suggest that UCN has an important role in volume/pressure homeostasis in health and heart disease.

We report the haemodynamic, echocardiographic, neuro-humoral, and renal effects of UCN2 infused in human HF.

**Methods**

**Subjects**
We studied eight males with stable congestive cardiac failure (six with ischaemic heart disease and two with idiopathic dilated cardiomyopathy, all with LVEF ≤ 40%, NYHA functional class II–III (seven class II and one class III)], plasma creatinine < 1.7 mg/dL (<0.15 mmol/L, range 0.08–0.11; mean 0.10 ± 0.01 mmol/L), aged 43–69 (mean ± SD, 61.2 ± 9.8) years, weighing 78–112 (mean 97 ± 11) kg, with body mass index of 26–39 (mean 33.1 ± 4.3), echo-cardiographic LVEF of 21–39 (mean 32.9 ± 5.7%), and amino terminal pro-brain natriuretic peptide (NTproBNP) of 338 ± 279 pg/mL.

Subjects were taking an angiotensin-converting enzyme-inhibitor (ACE-I) (n = 6) or angiotensin II receptor blocker (n = 1), or both
(n = 1). Seven were receiving a beta-blocker, six a loop diuretic, and one spironolactone. Medications were taken at breakfast ~2-3 h prior to infusion.

Study protocol

The protocol was approved by the Ethics Committee of the New Zealand Ministry of Health (Upper South B, Canterbury). Participants gave written informed consent. Human UCN2 (the 38 amino acid sequence predicted by Reyes et al.14) was provided by Neurocrine Biosciences Inc. (San Diego, CA, USA), manufactured by Bioserv Corporation (San Diego, CA, USA). Subjects were studied using a single-blind dose-escalation design, receiving placebo and 25 and 100 μg UCN2 sequentially with a washout period of 2-5 weeks between each dose. On day 3 of metabolic diets (sodium 120 and potassium 100 mmol per day), subjects ate breakfast and one spironolactone. Medications were taken at breakfast and presented to the study room by 0700 h. A 24 h urine collection was completed at 0800 h. The subjects fasted until lunch at 1300 h. Participants were weighed and 5 mL/kg water was given orally at 0800 h followed by 100 mL/h between 0900 and 1800 h. Subjects were seated except when standing to collect urine samples. At 0815 h, venous cannulae were placed in each forearm, one for the infusion of UCN2 or placebo, and the other for blood sampling. All subjects received vehicle placebo (dissolved in 1 mL water, then made up to 60 mL in normal saline with 50 mL administered), 25 μg UCN2 [1 mg dissolved in 6.6 mL water, then 0.2 mL of that solution made up to 60 mL in normal saline (0.5 μg/mL) with 50 mL administered], and finally 100 μg UCN2 [1 mg dissolved in 5 mL water, then 0.6 mL of that solution made up to 60 mL in normal saline (2 μg/mL) with 50 mL administered] over 1 h commencing at 0900 h.

Blood for hormone assays (drawn at 0830, 0900, 0930, 1000, 1100, 1200, and 1800 h) was collected into chilled tubes containing EDTA except for cortisol (heparin) and angiotensin II (0.125 M EDTA, 0.05 M o-phenanthroline, 2% ethanol, 0.2% neomycin sulphate, and 0.03 mg/mL enalikren) samples. Samples were centrifuged at 4°C and plasma stored at ~8°C before assay for UCN2, cAMP, cyclic guanosine monophosphate (cGMP), adrenocorticotropic hormone (ACTH), cortisol, plasma renin activity (PRA), angiotensin II, aldosterone, arginine vasopressin (AVP), NTPproBNP, epinephrine, norepinephrine, endothelin 1, adrenomedullin, insulin, and ghrelin according to our published methods.15

At the conclusion of infusions, additional samples (for UCN2 pharmacokinetics) were taken at 1005, 1010, 1015, and 1020 h. For each hormone, all samples from an individual were analysed in a single assay. Numbers of UCN2 samples were too great to fit into one assay but samples from the 25 and 100 μg UCN2 active phases were assayed together. Intra and inter-assay coefficients of variation (CVs) were all <18.5%.

Plasma sodium (Na⁺), potassium (K⁺), creatinine, glucose, venous bicarbonate, and chloride (Cl⁻) were measured at 0900, 1000, 1100, 1200, 1400, 1500, and 1800 h with measurement of calcium (Ca²⁺), magnesium, phosphate, total protein, albumin, aspartate transaminase (ALT), alanine transaminase (ALT), amylase, creatine kinase (CK), CK-MB fraction, and troponin T (TnT) at the 0900 and 1800 h time points.

After blood sampling, subjects stood to collect urine (0900, 1000, 1100, 1200, 1400, and 1800 h) for measurement of volume, cAMP, cGMP, Na⁺, K⁺, and creatinine. Systolic and diastolic blood pressure (SBP and DBP), heart rate (HR), and pulse oximetry were recorded at 0830 h, every 15 min from 0900–1100 h, then hourly until 1800 h, with an automatic sphygmomanometer and pulse oximeter (Pro 300 monitor, Dinamap, Critikon, Tampa, Florida, USA). CO was measured by the thoracic impedance method (Minnesota impedance cardiography, model 304B, Surcom Inc., Minneapolis, MN, USA) every 30 min from 0830 to 1100 h, and then hourly until 1800 h.

Echocardiography was performed 1 h before and immediately after infusions (Vivid 3 echocardiogram; General Electric, Fairfield, CT, USA). Left ventricular volume was measured in the four-chamber view, using the modified Simpson’s rule. Data were stored digitally for subsequent analysis of left ventricular volumes (diastolic and systolic) and LVEF, transmirtal early diastolic flow velocity (E), transmirtal deceleration time (DT), early diastolic myocardial velocity (Em), diastolic myocardial velocity during atrial contraction (Am), and systolic myocardial velocity (Sm). Transmirtal flow was measured by pulse wave Doppler at the mitral valve leaflet tips in the four-chamber view. Tissue Doppler myocardial velocities at the medial mitral valve annulus were measured using the machine presets. Left ventricular wall motion score index (LVWMSI) was obtained using the established 16-segment method.14 Cardiac work (CW) was calculated as the product of CO and mean arterial pressure (MAP).

Twelve-lead electrocardiograms (ECGs) (Angilent Pagewriter 200, Angilent Technologies, Andover, MA, USA) were recorded at 0900, 1000, 1400, and 1800 h. PR interval, QRS duration, and QT interval, both uncorrected and corrected (QTc using Fridericia’s method, QT/ RR¹⁄₂), were assessed.

Human urocortin 2 two-site ELISA assay

UCN2 was measured in a two-site chemiluminescent ELISA, using an N-terminal-directed monoclonal antibody for plate coating and a C-terminal-directed rabbit polyclonal antibody. Antiserum was donated by Neurocrine Biosciences Incorporated. Mouse anti-rabbit IgG-Alkaline Phosphatase conjugate plus CSPD² substrate (Applied Biosystems, Foster City, CA, USA) were used to generate the chemiluminescent signal. Samples diluted parallel to the standard curve. Mean recovery of UCN2 was 107% at 2.43 ng/mL, 100% at 1.21 ng/mL, and 100% at 0.61 ng/mL. The lower limit of quantitation (LOQ) was 0.3 ng/mL. The assay detection limit (upper 95% CI for the zero standard) was 0.11 ng/mL (n = 36). We have used all the assay data for statistical calculations and reported 95% CI. The intra and (inter) assay CVs (n = 36) were 5.0% (5.7%) at 0.68 ng/mL, 2.8% (5.7%) at 1.34 ng/mL, and 2.8% (3.9%) at 2.45 ng/mL.

Cross-reactivities were determined by measurement of human UCN1, UCN3, and CRF at 510, 670, and 500 ng/mL, respectively, all evoking assay responses at or below the LOQ (0.3 ng/mL). UCN1 and CRF responses were also at or below the 95% CI for the zero standard.

Statistics

Data were analysed by repeated measures analysis of variance (ANOVA), using SPSS version 11.5 statistical package (SPSS Inc., Chicago, IL, USA). The significance reported for both overall dose effect and between pairs of study phases (i.e. placebo vs. 25 μg, placebo vs. 100 μg, and 25 vs. 100 μg) is the time-by-dose interaction from commencement of infusion to 1 h post-infusion unless otherwise stated. This period represents the infusion time plus four times the UCN2 half life (t½). Where significant differences between doses were identified, pairwise comparisons were undertaken using Fisher’s protected LSD test. UCN2 t½, metabolic clearance rate (MCR), and volume of distribution (VD) were calculated using a one-compartment model (WinNonLin Professional 3.1, Pharsight Corporation, Mountain View, CA, USA). Geometric means and 95% CI are tabulated for non-normally distributed hormone measures. Other results are presented as mean ± SEM. For clarity, pooled 95% CI are displayed for the graphed hormones and pooled SEM for the graphed haemodynamics. A value of P < 0.05 was taken to indicate statistical significance.

Results

Urocortin 2 infusion

Plasma UCN2 concentrations increased in a dose-related fashion from 230 (40–420) to 1390 (1210–1590) pg/mL and 5360 (4650–6070) pg/mL with placebo and 25 and 100 μg doses, respectively (P < 0.001 for both doses compared with time-matched placebo control values). Plasma cAMP
tended to increase \( (P = 0.087; \) placebo compared with 100 \( \mu \)g dose) (Figure 1).

**Pharmacokinetics**

The \( t_{1/2} \); for immunoreactive UCN2 (median, IQR) was 15.5 (11.4–125.4) min, MCR 0.09 (0.02–0.32) L/min, and VD 3.4 (1.9–5.4) L.

**Haemodynamics and echocardiography**

UCN2 increased CO (maximal increments from pre-infusion levels were 0.3 ± 0.1, and 1.0 ± 0.3 and 2.0 ± 0.2 L/min for placebo, 25 and 100 \( \mu \)g doses, respectively, \( P < 0.001 \) for both doses compared with placebo). Corresponding increments in HR were 1.8 ± 0.8, and 4.1 ± 0.9 and 6.8 ± 1.0 b.p.m., \( P < 0.001 \). UCN2 decreased SBP (maximal

![Graphs showing changes in various parameters over time](https://example.com/graph.png)

**Figure 1** Change from commencement of urocortin 2 infusion in plasma urocortin 2, cyclic adenosine monophosphate, N-terminal pro-brain natriuretic peptide, ACTH, and adrenomedullin (geometric mean and pooled 95% confidence intervals) to urocortin 2 infusion in eight male humans with mild heart failure. Urocortin 2 infusion occurred between time 0 and 1 h. ‘Dose comparison’ refers to overall assessment of differences between doses by ANOVA of time by dose interaction. Placebo vs. 25 \( \mu \)g, placebo vs. 100 \( \mu \)g, and 25 vs. 100 \( \mu \)g refer to comparison of placebo with individual active doses and between the two active doses (25 and 100 \( \mu \)g). Pooled 95% confidence intervals are displayed at the right upper corner in each panel.
decrements $-10.6 \pm 1.9$, and $-11.9 \pm 2.5$ and $-22.6 \pm 4.6 \text{mmHg}, P < 0.001$, DBP $(-5.9 \pm 1.3$, and $-11.6 \pm 1.6$ and $-18.6 \pm 2.7 \text{mmHg}, P < 0.001$), and MAP $(-6.7 \pm 1.3$, and $-11.4 \pm 1.7$ and $-19.4 \pm 3.3 \text{mmHg}, P < 0.001$). SVR fell $-104 \pm 37$, and $-281 \pm 64$ and $-476 \pm 79 \text{dynes s/cm}^5, P = 0.003$, as did CW $36 \pm 5$, and $-54 \pm 25$ and $-77 \pm 17 \text{L mmHg/min}, P < 0.001$. Sustained post-infusion decreases in SVR, CW, and arterial pressure were observed, with longer lasting and more clear-cut effects from the 100 µg compared with the 25 µg dose (Figures 2 and 3).

With higher dose UCN2, increases in LVEF and E were observed while LVWMSi decreased (Figures 4 and 5). No significant changes were seen in A, DT, Em, Am, Sm, or E/Em (data not shown).

**Neurohormones**

UCN2 infusion induced significant increases in NTproBNP, ACTH, and ADM (Figure 1). UCN1, PRA, angiotensin II, AVP, aldosterone, epinephrine, norepinephrine, cortisol, cAMP, ghrelin, insulin, or endothelin-1 was not significantly altered by either dose of UCN2 (Figure 1 and Table 1).

**Plasma biochemistry**

A subtle elevation (from $0.09 \pm 0.01$ to $0.10 \pm 0.01 \text{mmol/L}, P = 0.045$) in plasma creatinine was observed during and in the hour after the 100 µg UCN2 infusion. UCN2 infusion did not alter plasma Na$^+$, K$^+$, glucose, venous bicarbonate, Cl$^-$, Ca$^{2+}$, magnesium, phosphate, total protein, albumin, AST, ALT, amylase, CK, CK-MB, and TnT during this period (results not shown).

**Urinalysis**

UCN2 infusion induced no change for the period of infusion and for the subsequent hour in urinary volume, excretion of sodium, potassium, creatinine, cAMP, or cGMP. If the whole observation period was considered, UCN2 infusion induced subtle but significant dose-related decreases in urinary volume ($P = 0.005$) and sodium excretion ($P < 0.001$) (Table 2).

**Electrocardiogram**

UCN2 did not change PR interval, QRS duration, and QT or QTc intervals. No arrhythmic effect of UCN2 was observed.

**Observed events**

All volunteers flushed during infusions of UCN2. This subsided within 2 h of the end of infusions.

**Discussion**

We provide the first report on UCN2 infused in human HF. Infusions of 25 and 100 µg UCN2 markedly elevated plasma UCN2, which had a $t_2$ of 15 min, MCR of 0.09 L/min, and a VD of 3.4 L.

**Haemodynamic status**

We observed a dose-related increase in CO substantially secondary to decreased after-load through vasodilatation (as evidenced by decreases in SVR and flushing in all subjects at both doses) and a small increase in HR. Whether a positive inotropic effect by UCN2 also contributed to the increase in CO is uncertain. Our data cannot address this question as loading conditions and HR were not fixed. However, UCN2 has a positive inotropic effect in the isolated mouse heart,
and in rabbit ventricular myocytes via CRF(2) receptor-mediated stimulation of protein kinase A (PKA).\textsuperscript{10,17} The CO increment is less marked than previously observed with the same dosing regimen in healthy volunteers.\textsuperscript{12} Presumably, this reflects underlying ventricular impairment and the effects of drug therapy.

The marked decreases in SBP and DBP with only minor increments in HR reflected a vasodilator effect on a background of HF-related blunting of baroreceptor responses together with medications (e.g. beta blockade) that may also reduce reflex responses to falls in blood pressure. This contrasts with our findings in normal humans in whom there was no change in SBP, with UCN2 infusion at the same doses. It is possible that the greater increase in CO in normal subjects counterbalanced the effect of the vasodilatory response on systolic pressures, the net result being minimal change in SBP.\textsuperscript{12} The sustained nature of the falls in arterial pressure and SVR suggests changes in intracellular signaling with longer activity than the period of elevated plasma UCN2. Multiple vasodilator mechanisms are reported for the UCNs. UCN2 acts via cAMP/PKA and p38 mitogen-activated protein kinase in rat aortic ring\textsuperscript{18} and causes endothelium-independent vasodilatation in human internal mammary artery \textit{in vitro}.\textsuperscript{5} UCN1 induces vasodilatation in rat coronary artery via activation of PKA-dependent vascular Ca\textsuperscript{2+}-activated K\textsuperscript{+} channels\textsuperscript{19} (although a conflicting report suggests a PKC-mediated mechanism\textsuperscript{20}), and in human

![Figure 3](https://academic.oup.com/eurheartj/article-abstract/28/21/2589/533498)  
**Figure 3** Systolic, mean arterial, and diastolic blood pressure responses (mean and pooled standard errors) to urocortin 2 infusion in eight male humans with mild heart failure. Infusion time and statistical comparisons as per Figure 1. Pooled SEM is displayed to the mid-right of each panel.

![Figure 4](https://academic.oup.com/eurheartj/article-abstract/28/21/2589/533498)  
**Figure 4** Left ventricular end-diastolic volume, end-systolic volume, and ejection fraction responses (mean ± SEM) to urocortin 2 infusion in eight male humans with mild heart failure. Infusion time and statistical comparisons as per Figure 1.

![Figure 5](https://academic.oup.com/eurheartj/article-abstract/28/21/2589/533498)  
**Figure 5** Transmitral early diastolic flow velocity (E) and left ventricular wall motion score index responses (mean ± SEM). Infusion time and statistical comparison as per Figure 1.
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<td>Norepinephrine (pmol/L)</td>
<td>Pl</td>
<td>265 (211-334)</td>
<td>250 (205-306)</td>
<td>228 (194-269)</td>
<td>225 (174-291)</td>
<td>203 (175-235)</td>
<td>310 (229-421)</td>
<td>302 (219-416)</td>
<td>200 (140-286)</td>
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<td>25 µg</td>
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<td>Norepinephrine (pmol/L)</td>
<td>Pl</td>
<td>156 (93-260)</td>
<td>136 (87-213)</td>
<td>113 (75-171)</td>
<td>82 (64-125)</td>
<td>104 (71-183)</td>
<td>114 (71-203)</td>
<td>25 (10-63)</td>
<td>179 (122-263)</td>
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<td>25 µg</td>
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<td>Values are displayed as geometric means (95% confidence intervals); time 0 indicates commencement of the infusion; participants ate lunch 3 h post-infusion. Pl, placebo; PRA, plasma renin activity; AVP, arginine vasopressin; NTproBNP, N-terminal pro-brain natriuretic peptide; DC, dose comparison.</td>
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internal mammary artery ring smooth muscle via both endothelium-dependent and -independent mechanisms. Falls in CW and SVR extended beyond the period of increased CO. The effect on calculated CW occurs predominantly post-infusion and reflects longer lasting effects on blood pressure than on HR (Figures 2 and 3). A moiety that increases CO without increased CW over sustained intervals may have therapeutic potential in HF. However, further studies of the relative importance of vasodilation, positive inotropism, lusitropism, and chronotropism are warranted, as the balance between these effects may influence the safety profile of UCN in treating HF.

The echocardiographic findings are consistent with augmented left ventricular systolic function (with a fall in LVWMSI indicating increased contractility within viable, even if diseased, wall segments) and may reflect cardiac unloading, although, again, direct inotropic effects are also plausible. The dose-related increases in ejection fraction were substantial (approximately 6 and 15 absolute per cent for the 25 and 100 µg doses, respectively) despite the underlying myocardial dysfunction. Transmural early diastolic flow velocity (E) increased, which may be due to greater negative pressure induced from more vigorous systolic flow velocity (E) increased, which may be due to underlying myocardial dysfunction. Transmitral early diastolic (E) and late diastolic (A) flow velocities were also increased, suggesting an increase in compliance and an improvement in diastolic function.

Renal function
Urine volume and urine sodium excretion were slightly reduced, although creatinine excretion (and presumably glomerular filtration) were well maintained. Although systemic levels of renin, angiotensin II, and norepinephrine were not perturbed, we cannot rule out selective intra-renal activity of these systems as the mechanism underlying these subtle changes in renal function. Currently no published data clarify this issue. There is a paucity of information on the effect of UCN2 on renal cellular activity. The possibility that the UCNs may have paracrine effects in the kidney is supported by the known secretion of UCN1 in the kidney. The effect of UCN2 on renal cellular activity. The possibility that the UCNs may have paracrine effects in the kidney is supported by the known secretion of UCN1 in the kidney.

Neurohormones
Given the marked haemodynamic changes, we observed remarkably little neurohormonal perturbation with UCN2 infusion. Despite 19 mmHg falls in MAP, there was no effect on PRA, aldosterone, or epinephrine, but only a small initial rise in angiotensin II and elevation in norepinephrine restricted to the higher dose infusion (Figure 1). In normal humans infused with the same doses of UCN2, there was a smaller drop in MAP yet significant elevations in PRA and aldosterone in addition to angiotensin II and norepinephrine. This may be partly explained by HF medication in that beta blockade exerts a potent inhibitory effect upon renin secretion. It is likely that the neurohormonal response to UCN2 differs between normal and HF states. In ovine HF, but not in normal sheep, we observed pronounced suppression of PRA, aldosterone, and epinephrine by UCN2 without elevation of norepinephrine. Although this is not seen in the present work, this probably reflects the stable and relatively mild level of treated HF with only moderate haemodynamic and neurohormonal derangement compared with the extreme dysfunction of our ovine experimental HF model. Nevertheless, given the magnitude of the drop in MAP (and thus renal perfusion pressure) observed in our HF patients, a greater renin-angiotensin system (RAS) activation might be expected. This suggests relative RAS suppression.

Table 2  Effect of urocortin 2 infusion on urine biochemistry in eight human males with mild heart failure

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>−1 to 0</th>
<th>0 to 1</th>
<th>1 to 2</th>
<th>2 to 5</th>
<th>5 to 9</th>
<th>DC 0 to 2 h</th>
<th>DC 0 to 9 h</th>
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<tbody>
<tr>
<td>Infusion</td>
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<tr>
<td>Urocortin (mL/h)</td>
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<td>25 µg</td>
<td>153 ± 37</td>
<td>128 ± 34</td>
<td>196 ± 32</td>
<td>118 ± 31</td>
<td>177 ± 15</td>
<td>109 ± 20</td>
<td>0.504 ± 0.005</td>
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<tr>
<td>100 µg</td>
<td>151 ± 47</td>
<td>72 ± 22</td>
<td>74 ± 25</td>
<td>130 ± 40</td>
<td>170 ± 25</td>
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<td>Sodium (mmol/h)</td>
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<td>25 µg</td>
<td>7.7 ± 3.2</td>
<td>5.8 ± 1.8</td>
<td>8.4 ± 1.8</td>
<td>4.4 ± 1.3</td>
<td>4.6 ± 1.0</td>
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<tr>
<td>100 µg</td>
<td>10.5 ± 4.4</td>
<td>3.8 ± 1.3</td>
<td>2.7 ± 0.7</td>
<td>7.3 ± 2.1</td>
<td>4.3 ± 0.8</td>
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<td>Potassium (mmol/h)</td>
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<td>25 µg</td>
<td>1.7 ± 0.5</td>
<td>1.2 ± 0.3</td>
<td>1.3 ± 0.3</td>
<td>0.6 ± 0.3</td>
<td>0.1 ± 0.1</td>
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<tr>
<td>100 µg</td>
<td>2.7 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>1.4 ± 0.3</td>
<td>0.6 ± 0.2</td>
<td>0.1 ± 0.1</td>
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<tr>
<td>Creatinine (mmol/h)</td>
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<td>25 µg</td>
<td>0.46 ± 0.30</td>
<td>0.38 ± 0.27</td>
<td>0.31 ± 0.20</td>
<td>0.12 ± 0.05</td>
<td>0.03 ± 0.01</td>
<td>0.344 ± 0.936</td>
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<tr>
<td>100 µg</td>
<td>0.37 ± 0.15</td>
<td>0.39 ± 0.17</td>
<td>0.33 ± 0.16</td>
<td>0.12 ± 0.06</td>
<td>0.03 ± 0.01</td>
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</table>

Values are displayed as mean ± SEM; time 0 indicates commencement of the infusion; participants ate lunch 3 h post-infusion. Pl, placebo; DC, dose comparison.
Small rises in plasma adrenomedullin were seen in response to the two active doses compared with a drop with placebo. Adrenomedullin is an endothelial product, and the observed increase may reflect increased endothelial shear forces secondary to increased CO and regional blood flows. Adrenomedullin is a potent vasodilator. There has been no literature as yet on any interaction between adrenomedullin and the UCIs, and whether UCN2 exerts a direct effect on adrenomedullin release must await further studies.

**Limitations**

The study sample was limited to eight patients with stable mild HF. The complexity and costs of the protocol with multiple analytes, sampled frequently on three separate occasions, necessarily limit group size. The results indicate adequate power for the detection of dose-related changes in many key haemodynamic variables. Assessment of renal responses from the current data is limited by trends towards unmatched baseline (pre-infusion) sodium excretion between study days. However, the data clearly show that the profound natriuresis previously seen in animal models of very severe decompensated HF is not present.

The sequential nature of dosing and the flushing response means imaging was not blinded. Because it is not possible to fix haemodynamic pre- and after-load in clinical studies of this type, we cannot precisely define the relative contributions of vasodilatory, inotropic, lusitropic, and chronotropic actions of UCN to the observed changes in blood pressure, CO, and CW.

**Conclusion**

UCN2 augments CO and reduces vascular resistance in humans with mild HF. The neutral neurohormonal response (which falls between the activation observed in normal humans and the profound suppression observed in severe experimental HF) despite marked haemodynamic change suggests relative RAS suppression and that the humoral response to exogenous UCN2 is dependent on the neurohormonal and haemodynamic milieu into which it is introduced. Further, natriuresis and hormone suppression may only be apparent in severe HF when neurohormonal activation is pronounced and avid sodium retention is established. Experimental and human preclinical studies to date warrant further investigation of the potentially therapeutic effects of UCN2 across a spectrum of severity of human HF.

**Acknowledgements**

This study was financially supported by Neurocrine Biosciences Inc., the Health Research Council, the National Heart Foundation of New Zealand, and the Canterbury Medical Research Foundation. Secretarial assistance was provided by Barbara Griffin.

This study was supported by the Health Research Council of New Zealand.

Support was also received from Neurocrine Biosciences Inc., San Diego, CA, USA, which supplied the peptide and funded the working expenses.

**Conflict of interest:** none declared.

**References**


Clinical vignette

An unusual cause of left atrial mass

Shih-Hsien Sung1,2, Shou-Dong Lee1,2, and Hao-Min Cheng1,2*

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A 47-year-old woman was hospitalized for the evaluation of non-exertional left chest pain and left upper arm weakness for 1 year. Chest film taken before admission revealed an apparently normal-sized heart (Panel A). A mass was uncovered unexpectedly by transoesophageal echocardiography (Panels B and C, arrows).

Then the patient received open heart surgery during admission. A foreign body, a bamboo chopstick, was noticed after the chest wall was opened (Panel D). An intraparenchymal fistula was created by the foreign body with adhesion to apical lung and left hilum just above the superior pulmonary vein. The foreign body also penetrated into the pericardium over the auricle of the left atrium. The foreign body was removed (Panel E) and fistulectomy was performed. The patient recovered uneventfully. Pathology of the excised left atrial mass demonstrated fibrocalcified nodule (Panel F), suggesting chronic tissue reaction to the foreign body. Re-examining the chest film, a band-shaped mass over the left lung field was noted (Panel A, arrow). Tracing back her history, the patient recalled a fight when she was heavily drunk 10 years before and the chopstick was probably jabbed into her left upper back at that time.