Prolonged Urocortin 2 Administration in Experimental Heart Failure
Sustained Hemodynamic, Endocrine, and Renal Effects

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Abstract—Although acute administration of urocortin 2 has beneficial actions in heart failure, the integrated hemodynamic, hormonal, and renal effects of sustained urocortin 2 treatment in this disease have not been investigated. In the current study, we administered a 4-day infusion of a vehicle control (0.9% saline; n = 6) or urocortin 2 (0.75 µg/kg per hour; n = 6) to sheep with pacing-induced heart failure. Compared with time-matched controls, infusion of urocortin 2 produced rapid (30-minute) and persistent (4-day) improvements in cardiac contractility (day 4: control 905 ± 73 mm Hg/s; P < 0.001) and output (2.6 ± 0.1 versus 3.8 ± 0.3 L/min; P < 0.001), together with reductions in left atrial pressure (28 ± 1 versus 12 ± 1 mm Hg; P < 0.001) and peripheral resistance (30 ± 2 versus 20 ± 2 mm Hg/L per min; P < 0.001). In contrast, urocortin 2–induced falls in mean arterial pressure were not established until the second day (day 4: 74 ± 2 versus 72 ± 2 mm Hg; P < 0.05). Prolonged urocortin 2 administration was associated with sustained (days 0 to 4) declines in plasma renin activity (day 4: 1.33 ± 0.27 versus 0.73 ± 0.20 nmol/L per hour; P < 0.001), aldosterone (970 ± 383 versus 396 ± 96 pmol/L; P < 0.05), vasopressin (2.4 ± 0.8 versus 1.3 ± 0.1 pmol/L; P < 0.05), endothelin 1 (7.2 ± 0.7 versus 4.5 ± 0.4 pmol/L; P < 0.01), and atrial (269 ± 27 versus 150 ± 19 pmol/L; P < 0.001) and B-type (65 ± 9 versus 29 ± 6 pmol/L; P < 0.001) natriuretic peptides, as well as an acute transient rise in plasma cortisol (day 1: 150 ± 11006 versus 67 ± 27 pmol/L; P < 0.001). Chronic urocortin 2 also persistently augmented urinary sodium (day 4: 4-fold increase; P < 0.001) and creatinine (1.4-fold; P < 0.01) excretion and creatinine clearance (1.5-fold; P < 0.01) compared with control. Food consumption was temporarily suppressed (P < 0.05). In conclusion, 4-day urocortin 2 administration induces sustained improvements in hemodynamics and renal function, in association with inhibition of multiple vasoconstrictor/volume-retaining systems. These findings support the therapeutic potential for urocortin 2 in heart failure. (Hypertension. 2011;57:1136-1144.)

Key Words: urocortin 2 ■ heart failure ■ hemodynamics ■ hormones ■ renal function

Urocortin (Ucn)-1 and Ucn2 belong to a family of peptides sharing structural similarities with corticotropin-releasing factor (CRF), a hormone pivotal in regulating the response to stress. The Ucn peptides signal through the 2 G protein–coupled CRF receptors, CRFR1 and CRFR2. Although both receptors are found in the central nervous system, CRFR2 is also widespread throughout the periphery, including strong expression in the heart and in endothelial and smooth muscle cells of the systemic vasculature. The overlap of Ucn2 and the CRF-R2 receptor subtype suggests the peptide may function largely in a paracrine/autocrine fashion in the periphery, at least in normal health. Whether levels are significantly elevated in diseased states (and, thus, may also partially function in an endocrine fashion) is unknown. In addition to some differences in distribution, variances in ligand-receptor affinities also exist, with Ucn1 binding equally to both receptor subtypes and Ucn2 highly selective for CRFR2. It is relatively well established that CRFR1 mediates activation of the hypothalamic-pituitary-adrenal (HPA) stress axis, leading to the release of adrenocorticotropic hormone and thence cortisol, whereas CRFR2 (the only receptor subtype found in cardiac tissue) appears to mediate the majority of the cardiovascular actions reported for the Ucn peptides to date. These include vasodilation and positive inotropic and chronotropic effects after systemic administration in normal animals. In light of this evidence of a likely role for the Ucn peptides in circulatory homeostasis, a number of studies subsequently investigated the acute effects of Ucn1 and Ucn2 in the setting of heart failure (HF; experimental and clinical) and demonstrated that both peptides have beneficial effects including dose-dependent reductions in cardiac preload and afterload and increases in ejection fraction and cardiac output (CO), together with attenuation of a number of vasoconstrictor/volume-retaining systems.
factors and improvements in renal function.\textsuperscript{5–9} That endoge-
nous production of the Ucns play a role in the pathogenesis of HF is supported by work investigating the effects of selective
antagonism of the CRF-R2 receptor in sheep both before and
after induction of HF.\textsuperscript{10} This study found that CRF-R2 antagonism in the HF setting significantly increased periph-
eral resistance, blood pressure, and cardiac preload, in con-
junction with elevations in plasma renin-aldosterone and
endothelin 1 levels, effects opposite those seen after admin-
istration of Ucn1/Ucn2. In contrast, responses in the normal
state were blunted and largely nonsignificant. These findings
suggest that the endogenous Ucn peptides offer some protec-
tion to the failing heart.

Increasingly, focus is being directed at Ucn2 (over Ucn1) as a potential treatment strategy in HF because this peptide selectively binds CRFR2 and, thus, presumably, avoids del-
terious activation of the HPA axis (via CRFR1). Indeed,
Ucn2 is currently being trialed as a short-term (4-hour intravenous infusion) parenteral therapy in patients hospital-
ized for acute decompensated HF.\textsuperscript{11} However, recent studies in both experimental\textsuperscript{7} and human\textsuperscript{9} HF have observed signif-
ificant HPA activation (rises in plasma adrenocorticotropic
hormone and/or cortisol levels) after short-lived Ucn2 admin-
istration. Given these findings, together with evidence that the CRFR2 subtype may be involved in sustained appetite suppression,\textsuperscript{4} it is essential that the effects of more chronic Ucn2 treatment be investigated before the full therapeutic
potential of the peptide can be discerned. The present study
examines for the first time the integrated hemodynamic,
hormonal, and renal effects of prolonged (4-day) administra-
tion of Ucn2 in HF using an experimental ovine model.

Methods
Surgical Preparation
Twelve Coopworth ewes (39 to 59 kg) were instrumented via a left
lateral thoracotomy under general anesthesia (induced by 17 mg/kg of
thiopentone; maintained with halothane/nitrous oxide).\textsuperscript{12} Two
polyvinyl chloride catheters were inserted in the left atrium for blood
sampling and left atrial pressure (LAP) determination; a Konigsberg
pressure-tip transducer was inserted into the aorta to record mean
arterial pressure (MAP) and into the apex of the left ventricle to
obtain maximum derivatives of pressure over time (dP/dt[max]) as
an index of contractility; an electromagnetic flow probe placed
around the ascending aorta to measure CO; a Swan-Ganz catheter
inserted in the pulmonary artery for infusions, and a 7 French
His-bundle electrode stitched subepicardially to the wall of the left
ventricle for pacing. A Foley catheter was inserted per urethra in the
bladder and left in place chronically to allow continuous and timed
collections of urine. Animals recovered for 14 days before com-
mitting the study protocol. During the experiments the animals
were held in metabolic cages with free access to water and fed a
standard laboratory diet (500 g of food pellets and 250 g of lucerne
chaff per day providing 80 mmol of sodium and 200 mmol of
potassium).

Study Protocol
HF was induced by 7 days of rapid left ventricular pacing at 220
bpm\textsuperscript{12,13} and maintained by continuous pacing for the duration of the
study. On days 8 to 12 of pacing, the sheep received a continuous
4-day intravenous infusion of either a vehicle control (0.9% saline;
n=6) or murine Ucn2 (25 μg bolus +0.75 μg/kg per hour; n=6;
American Peptide Company Inc.). Both treatments commenced at
10:00 a.m on study day 0 and were administered via the pulmonary
artery catheter in a total volume of 50 mL/d. The Ucn2 dose chosen
in the present study was based on findings observed after dose-
ranging studies with acute administration of Ucn2\textsuperscript{2} and likely to
achieve significant effects in all of the indices measured.

Hemodynamic measurements (MAP, LAP, CO, dP/dt[max], and
calculated total peripheral resistance [CTPR=MAP/CO]) were rec-
corded using an online data acquisition system (PowerLab Systems,
ADInstruments, Dunedin, New Zealand) at 15-minute intervals in the
hour preceding infusion on study day 0 (baseline), at 0.5, 1.0, 1.5,
2.0, 4.0, and 6.0 hours after commencement of treatment, and then
daily on study days 1 to 4. All of the measurements were made with
the animals standing quietly in their crates.

Blood samples were drawn from the left atrium 30 minutes and
immediately before infusion (day 0: baseline); at 0.5, 1.0, 2.0, 4.0,
and 6.0 hours after treatment commencement; and then daily on
study days 1 to 4. Samples were taken into EDTA tubes on ice,
centrifuged at 4°C, and stored at −80°C before assay for plasma
renin activity (PRA), aldosterone, arginine vasopressin, cortisol,
atrial and B-type natriuretic peptide (ANP and BNP, respectively),
endothelin 1, and catecholamines.\textsuperscript{14} All of the samples from indi-
vidual animals were measured in the same assay to avoid interassay
variability. Plasma electrolytes and hematocrit were measured with
every third blood sample taken.

Urine volume and samples for the measurement of urine cAMP,
sodium, potassium, and creatinine excretion were collected over the
2 hours before infusion on study day 0 (baseline); at 2, 4, and 6 hours
after treatment commencement; and then daily on study days 1 to 4.
Creatinine clearance was calculated as urine creatinine
concentration×volume/plasma creatinine. Water intake was mea-
sured as per urine output, and food consumption was calculated
daily.

The study protocol was approved by the animal ethics
committee of the University of Otago.

Statistics
Results are expressed as mean±SEM. Baseline hemodynamic and
hormone values represent the mean of measurements made within
the hour immediately pretreatment. Differences between nonpaced
laboratory normal sheep (n=20) and HF animals (mean of control
and Ucn2 baseline data; n=12) were compared using independent t
tests (Table 1). No significant differences were found between
pretreatment control and Ucn2 baseline data (analyzed using inde-
dendent t tests), indicating a similar level of HF severity for both
groups at the commencement of the study protocol. Differences
between control and Ucn2 treatment arms were determined using
2-way ANOVA with time as a repeated measure. Time×treatment
interactions are quoted in the text. Where significant differences
were identified by ANOVA, the level of significance at individual
time points in Figures 1 through 4 and Table 2 was established by
Fisher protected least-significant difference tests (using the appro-
priate mean-square error term from the ANOVA). Significance was
assumed when P<0.05.

Results
Seven days of rapid left ventricular pacing induced the hemody-
namic, hormonal, and sodium-retaining hallmarks of estab-
lished HF as described previously,\textsuperscript{12,13} with reduced MAP, CO, and
renal function; increased CTPR and LAP; and widespread hormone activation (Table 1). Compared with time-
matched vehicle control data, Ucn2 infusion over 4 days pro-
duced rapid (within 30 minutes of treatment initiation) and
sustained (days 0 to 4) improvements in dP/dt[max] (day 4:
905±73 versus 1424±158 mm Hg/s; P<0.001) and CO (2.6±0.1
versus 3.8±0.3 L/min; P<0.001), together with reduc-
tions in LAP (28±1 versus 12±1 mm Hg; P<0.001) and CTPR (30±2
versus 20±2 mmHg/L per minute; P<0.001; Figure 1).

MAP was unaltered by Ucn2 during the first 6 hours of
Cardiac output, L/min  5.8 ± 0.4  2.9 ± 0.2‡
dP/dt max, mm Hg/s  2089 ± 153  1035 ± 128‡
Mean arterial pressure, mm Hg  88 ± 2  76 ± 2‡
Left atrial pressure, mm Hg  4.1 ± 0.3  25.2 ± 1.0‡
Total peripheral resistance, mm Hg/L per min  15 ± 3  29 ± 3‡
 Plasma atrial natriuretic peptide, pmol/L  17 ± 2  322 ± 32‡
 Plasma B-type natriuretic peptide, pmol/L  3 ± 1  61 ± 6‡
 Plasma renin activity, nmol/L per h  0.32 ± 0.06  1.17 ± 0.23‡
 Plasma aldosterone, pmol/L  225 ± 24  644 ± 230†
 Plasma endothelin 1, pmol/L  1.68 ± 0.08  7.07 ± 0.52‡
 Plasma vasopressin, pmol/L  0.9 ± 0.1  1.9 ± 0.5*
 Plasma norepinephrine, pmol/L  2683 ± 507  8601 ± 2567‡
 Plasma epinephrine, pmol/L  490 ± 88  798 ± 125*†
 Plasma cortisol, nmol/L  120 ± 24  89 ± 18
 Plasma sodium, mmol/L  143 ± 3  144 ± 0.9
 Plasma potassium, mmol/L  4.0 ± 0.6  4.1 ± 0.1
 Plasma creatinine, mmol/L  0.068 ± 0.002  0.084 ± 0.005‡
 Hematocrit, %  31.2 ± 1.2  28.0 ± 1.3†
 Urine volume, mL/h  81 ± 11  54 ± 16
 Urinary sodium excretion, mmol/h  2.62 ± 0.30  0.92 ± 0.31‡
 Urinary potassium excretion, mmol/h  9.0 ± 0.6  6.7 ± 1.8*
 Urinary creatinine excretion, mmol/h  0.50 ± 0.02  0.36 ± 0.03‡
 Creatinine clearance, mL/min  121 ± 9  46 ± 5‡

Data show mean ± SEM measurements in sheep before (nonpaced: laboratory normal data; n = 20) and after induction of heart failure by 7 d of rapid left ventricular pacing at 220 bpm (paced: mean control and Ucn2 baseline data; n = 12).

*P<0.05 shows significant differences.
†P<0.01 shows significant differences.
‡P<0.001 shows significant differences.

Ucn2 infusion markedly increased urine output (2 to 4 hours: >4-fold; P<0.01), urinary sodium (5.5-fold; P<0.001), and creatine excretion (1.6-fold; P<0.001), as well as creatine clearance (1.5-fold; P<0.01) acutely, with the latter 3 indices remaining significantly raised compared with vehicle control over the following 4 days of treatment (day 4: sodium excretion, 4-fold higher; creatine excretion, 1.4-fold; and creatine clearance, 1.5-fold; Figure 4 and Table 2). Urine cAMP excretion also tended to be elevated relative to control (0.10>P>0.05; Figure 4), whereas potassium excretion was not significantly changed (Table 2).

Food consumption declined over the first 2 days of Ucn2 administration (P<0.05) before returning to pretreatment levels over days 3 to 4 (Figure 4), with a similar trend observed for drinking (P value not significant; Table 2). The transient reduction in food intake observed during Ucn2 treatment translated into a corresponding temporary fall in daily sodium intake (based on a calculation of 80 mmol of sodium per 750 g of food per day) compared with the controls (P<0.05), which, in conjunction with the increase in daily sodium excretion (P<0.001), produced an overall decrease in daily sodium balance in the Ucn2-treated animals (P<0.001; Table 2). The resulting cumulative sodium balance at day 4 of the study came to 98±15 mmol for the control group and to −449±47 mmol for the Ucn2 group.

### Discussion

The present study is the first to report the integrated hemodynamic, hormonal, and renal effects of long-term Ucn2 administration in HF, demonstrating that 4-day infusion of the peptide produces significant and sustained improvements in cardiac contractility and output and reductions in LAP, CTPR, and MAP, together with suppression of adverse circulating vasoconstrictor/volume-retaining factors (PRA, aldosterone, arginine vasopressin, and endothelin 1) and augmentation of renal function. In contrast, effects to increase plasma cortisol and curb feeding were transient.

The initial hemodynamic responses to prolonged Ucn2 infusion in the present study are identical to those we reported previously after acute administration of the peptide in experimental ovine HF. It is important, in this more chronic setting, these Ucn2-induced effects were sustained for the duration of the 4-day treatment period, suggesting that there was no desensitization to protracted administration of the peptide, at least over this time span. This finding is in keeping with work in rats showing negligible downregulation of CRFR2 mRNA expression in the left ventricle and aorta even after 5 weeks of Ucn2 delivery. The range and the persistence of Ucn2’s cardiovascular effects are comparable to those seen in response to 4-day infusion of Ucn1 in experimental HF, although the onset of effect appears to be more rapid with Ucn2. Of note, the magnitude of the effects produced by these 2 peptides by day 4 of treatment were essentially similar despite a >2-fold higher dose of Ucn2 being used (Ucn2: 0.75 µg/kg per hour; Ucn1 0.3 µg/kg per hour), indicating, as suggested in earlier acute administration studies, differ
ences in Ucn1 and Ucn2 pharmacokinetics, especially in metabolic clearance rates.

The impressive and persistent improvements in CO observed in the HF animals in the current study likely reflect Ucn2's potent inotropic activity\(^5\)\(^,\)\(^17\) given the concomitant rise in \(dP/dt(\text{max})\), as well as falls in cardiac afterload (CTPR). The CO increase presumably contributed to the marked decline in LAP (\(\sim 15\ \text{mm Hg} \) drop by day 4), although the lusitropic\(^5\) and venodilator actions of the peptide (the latter decreasing circulatory filling pressures)\(^18\) may also have participated. Four-day infusion of Ucn2 also produced sustained reductions in CTPR and MAP that are consistent with the peptide’s reported vasodilatory actions.\(^3\)\(^,\)\(^10\) In addition to direct vascular effects, other actions of Ucn2 to suppress vasoconstrictor neurohumoral factors, such as angiotensin II (Ang II; evidenced here by reductions in PRA), endothelin 1, and arginine vasopressin; to inhibit endothelin 1–induced arterial constriction\(^3\); and to contract plasma volume (as indicated by the increase in hematocrit) are also likely to have contributed to the resulting vasodilation/fall in arterial pressure. These latter mechanisms might be expected to play a larger role in a setting such as congestive HF, which is characterized by hormone activation, global vasoconstriction, and volume overload. Indeed, recent work by Yang et al\(^19\) in

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**Figure 1.** Mean±SEM hemodynamic responses to a 4-day infusion of urocortin 2 (0.75 µg/kg per hour; \(n=6\)) and a vehicle control (\(n=6\)) in sheep with heart failure. Significant differences shown by \#P<0.001.
spontaneously hypertensive rats (a model also marked by vasoconstriction, as well as an activated renin-angiotensin system) demonstrated that not only does intravenous Ucn1 reduce serum angiotensin-converting enzyme (ACE) and Ang II levels, but a significant positive relationship exists between circulating ACE and systolic blood pressure. In agreement with our study, Dieterle et al.\textsuperscript{15} have shown sustained blood pressure lowering by Ucn2 in hypertensive salt-sensitive Dahl rats after chronic treatment. This occurred in conjunction with the preservation of left ventricular function (in contrast to the deterioration exhibited in untreated controls) and in the absence of any heart rate increase.

As with hemodynamic responses, Ucn2-induced endocrine effects were qualitatively similar to those observed previously after bolus or short-term administration\textsuperscript{7} and were also maintained throughout the 4 days of treatment. Increasing evidence is pointing toward active opposition of the renin-angiotensin system by the Ucn system, with extended sup-

<table>
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<td>Hematocrit, %</td>
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Data show mean±SEM measurements before (d 0) and during (d 1 to 4) continuous infusions of a vehicle control (n=6) and Ucn2 (0.75 \(\mu\)g/kg per h; n=6) in sheep with heart failure.

*P<0.05 shows significant differences between control and Ucn2.
†P<0.01 shows significant differences between control and Ucn2.
‡P<0.001 shows significant differences between control and Ucn2.
pression of serum ACE and Ang II concentrations already noted above,\(^19\) and mitigation of both PRA and Ang II demonstrated by us formerly with acute Ucn1/Ucn2 delivery.\(^6,7\) In the present study we additionally report the long-term inhibition of PRA by Ucn2 in the setting of HF. It is conceivable that this is attributed to direct inhibition of renin secretion by Ucn2 given that we did not observe the expected compensatory rise in PRA usually seen with inhibition of ACE activity.\(^20\) Pertinent to this, we have recently shown significant attenuation of captopril-induced increases in PRA by acute Ucn2 in experimental HF.\(^21\) Although a direct inhibitory effect of Ucn2 on PRA is in keeping with the presence of Ucn2 in the kidney,\(^2\) the natriuretic effect of Ucn2, likewise evident for the duration of the 4 days of treatment, is also likely to have had renin-suppressive activity (via increased delivery of sodium [and chloride] to the macula densa). Interestingly, Yang et al\(^19\) likewise observed that, in contrast to the decline in ACE and Ang II seen with chronic Ucn1 treatment in hypertensive rats, serum (and tissue) levels of angiotensin 1-7 (an angiotensin I metabolite that counters many of the actions of Ang II including vasoconstriction)\(^22\) were elevated, perhaps further adding to the vasodilatory effects of Ucn2.

The halving of plasma aldosterone concentrations after 4 days of Ucn2 infusion in our study likely largely reflects the decrease in plasma Ang II (evidenced by decreases in PRA), because no change was noted in circulating potassium concentrations, although a direct effect of Ucn2 on aldosterone secretion cannot be excluded, especially because Ucn2 is expressed in the adrenal gland.\(^2\) The observed decline in plasma arginine vasopressin plausibly relates to the attenuation of arginine vasopressin–stimulatory mechanisms, including improvements in CO (and, thus, pressure to sino-aortic volume receptors), as well as reductions in circulating levels of Ang II and a possible decline in plasma osmolality (as indicated by the concurrent fall in plasma sodium concentrations), which act to overwhelm any positive effect of volume contraction (as assessed by hematocrit falls) on arginine vasopressin secretion.\(^23\) As a secretagogue also of endothelin 1 and ANP/BNP, the fall in levels of Ang II may additionally have contributed to the chronic suppression of these peptides. The major stimulus for secretion of the natriuretic peptides, however, is cardiac transmural pressure,\(^24\) and declines in plasma levels of both ANP and BNP closely paralleled the falls in LAP. Despite the observed falls in circulating natriuretic peptide concentrations observed in our study (peptides...
Ucn2 is reported to stimulate the secretion of ANP and BNP in cardiomyocytes, and ventricular expression of BNP, at least, is reported to be maintained after chronic Ucn2 administration in the rat. Although it is the CRFR1 rather than the CRFR2 subtype responsible for mediating HPA axis activation, the transient rise in plasma cortisol levels seen with chronic infusion of Ucn2 (reportedly selective for CRFR2) was not entirely unexpected given an identical response seen with bolus Ucn2 administration in our previous work. In that earlier study, the concurrent rise in plasma Ucn1 concentrations (and subsequent activation of CRFR1), presumably as a result of competitive inhibition for the CRFR2 by Ucn2, was likely responsible. Moreover, the preservation of the hemodynamic and vasoactive hormone responses relative to the transitory nature of the cortisol rise further indicates that these effects are mediated by disparate mechanisms.

The renal responses to long-term Ucn2, including significant increases in sodium excretion and glomerular filtration rate (creatinine clearance), also persisted over the 4 days of treatment, even in the face of the marked falls in plasma ANP/BNP. It should be noted, however, that, although sodium excretion remained higher in the Ucn2 group at day 4, and although food intake was no longer different from the control group at that stage, this obviously could not persist for long given the marked negative sodium balance. The renal effects in the present study are similar to those seen with
acute Ucn2 administration, and likely underlying mechanisms include renal vasodilation, as well as reductions in the circulating antinatriuretic/antidiuretic factors arginine vasopressin, Ang II, and aldosterone. In addition, reports of Ucn2 expression in the kidney and the trend for urine cAMP excretion to increase in the present study support possible direct tubular actions of the peptide.

In contrast to the sustained improvement in renal function induced by Ucn2, the suppression of food intake was temporary and no longer significant (compared with control) by day 3 of treatment, results similar to findings with prolonged Ucn1 treatment in experimental HF. This occurred despite reports that the CRFR2 subtype may be involved in long-term appetite suppression and transgenic mice lacking the CRF-R2 receptor exhibit normal basal feeding and weight gain. Previous work in rats has demonstrated the appetite-suppressive effects of Ucn2 after intracerebroventricular injection, and, although a direct effect of peripheral Ucn2 at the feeding centers of the brain (especially the hypothalamic ventromedial nucleus, which is suggested to be a key site that transduces CRF receptor-mediated anorexigenic effects), is possible given the report of passive movement of the peptide across the blood-brain barrier, other possible contributory influences may include reduced gastric emptying, as well as interaction with other factors known to regulate appetite, such as leptin, neuropeptide Y, and orexin A.

**Perspectives**

In summary, our study demonstrates for the first time that extended administration of Ucn2 in HF produces sustained
improvements in cardiac function with reductions in cardiac preload and afterload, together with suppression of plasma renin, aldosterone, endothelin 1, and vasopressin, and increases in urine sodium excretion and glomerular filtration rate. Not only does there seem to be no desensitization of cardiovascular effects to prolonged (4-day) Ucn2 administration in HF (an observation reported in normal and hypertensive animal models), but there appears also to be no development of tolerance to the peptide’s actions to suppress the multiple adverse neurohormonal systems activated in this disease and to augment renal function. These findings, not previously noted in any setting, are clearly of benefit and of potential clinical significance for the management of patients with HF. Equally important, other noncardiovascular but possibly undesirable effects of Ucn2 to repress appetite and, indirectly, stimulate the HPA axis were transient. The multiple and sustained beneficial effects of Ucn2 in HF demonstrated in this study further support the therapeutic potential of the peptide in this disease.

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Disclosures

None.

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