EXPERIMENTAL STUDIES

Beneficial Hemodynamic, Endocrine, and Renal Effects of Urocortin in Experimental Heart Failure: Comparison With Normal Sheep

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OBJECTIVES
The goal of this study was to determine the bioactivity of urocortin (Ucn) in experimental heart failure (HF).

BACKGROUND
Urocortin may participate in cardiovascular function and pressure/volume homeostasis. Its effects in HF are unknown.

METHODS
Eight normal sheep and eight sheep with pacing-induced HF received ovine Ucn (10, 50, and 100 mg intravenous boluses at 2-h intervals) in vehicle-controlled studies.

RESULTS
Urocortin boluses dose-dependently increased plasma Ucn (p < 0.001). Pharmacokinetics were similar in normal and HF sheep with half-lives approximating 1.3 and 19.5 h for the first and second phases, respectively. In HF, cardiac output increased (twofold), while peripheral resistance, left atrial pressure (both 50% falls: p < 0.001), and mean arterial pressure (p < 0.05) fell. In normal sheep, changes in peripheral resistance and atrial pressure were blunted and in arterial pressure were directionally opposite. Urocortin induced persistent, dose-dependent falls (30% to 50%) in plasma vasopressin, renin activity, aldosterone, natriuretic peptides (all p < 0.001), and endothelin-1 (p < 0.05) in HF sheep, while adrenocorticotrophic hormone and cortisol levels rose acutely (both p < 0.001). In comparison, Ucn in normal sheep resulted in a similar rise in cortisol and fall in aldosterone, no significant effects on plasma renin activity and natriuretic peptides, and a rise in vasopressin. Urocortin produced dose-dependent, sustained increases in urine volume (twofold, p < 0.01), sodium excretion (9-fold rise, p < 0.001), and creatinine clearance (p < 0.001) in HF sheep. No significant renal effects were observed in normal sheep.

CONCLUSIONS
Urocortin has profound and sustained hemodynamic, hormonal, and renal effects in experimental HF. Urocortin may have a role in pressure/volume homeostasis in HF and may provide a novel therapeutic approach to this disease. (J Am Coll Cardiol 2002;40:1495–505) © 2002 by the American College of Cardiology Foundation

Urocortin (Ucn), a recently isolated 40-amino acid peptide member of the corticotropin–releasing factor (CRF) family (1), may play a role in cardiovascular and volume homeostasis. Originally identified in rat midbrain (1), Ucn has subsequently been detected in the heart, brain, vasculature, kidney, and digestive system (2–6). The distribution of Ucn's proposed endogenous receptor, CRF-R2 (7,8), functionally linked to adenylate cyclase, overlaps with that of Ucn in both the central nervous system and periphery (2,3,8,9). In the rat, cerebral Ucn immunoreactivity is increased by dehydration (10) and salt loading (11), while cardiac Ucn messenger RNA expression is raised in left ventricular (LV) hypertrophy (2) and in cardiac myocytes after ischemia (12). In humans, immunoreactivity is increased in the ventricles of patients with dilated cardiomyopathy (2).

A number of actions have been attributed to Ucn. It stimulates secretion of adrenocorticotropic hormone (ACTH) from isolated rat pituitary cells (1), and atrial and brain natriuretic peptide (ANP and BNP) from rat cardiac myocytes (13). Central administration of Ucn attenuates hyperosmolality-induced arginine vasopressin (AVP) release in the rat (14), and subcutaneous Ucn inhibits lipopolysaccharide-induced serum tumor necrosis factor in mice (15). Urocortin is also reported to protect cardiac myocytes from cell death induced by hypoxia (16) and reduce damage in isolated rat hearts subjected to regional ischemia/reperfusion (17). Hemodynamic effects of peripherally administered Ucn include vasodilation in the rat (1) and increases in cardiac contractility, coronary blood flow and conductance, cardiac output, and heart rate (HR) in normal sheep (18).

In view of the potential roles that Ucn may play in cardiovascular/volume homeostasis and the pathophysiology
of heart failure (HF), we have conducted the first controlled studies of the integrated hemodynamic, endocrine, and renal effects of Ucn in experimental HF.

### METHODS

**Surgical preparation.** A total of 16 Coopworth ewes (43 to 55 kg) were instrumented under general anesthesia (induced by 17 mg/kg thiopentone; maintained with halothane/nitrous oxide). In eight sheep (normal group) a carotid artery was cannulated (16 G Angiocath) for direct measurement of mean arterial pressure (MAP) and HR, and a polyethylene catheter was placed in the jugular vein for recording of right atrial pressure (RAP) and blood sampling. A Swan-Ganz thermodilution catheter (American Edwards, Irvine, California) was placed in the pulmonary artery via the jugular vein for the measurement of cardiac output (CO).

The other eight sheep (HF group) were instrumented via a left lateral thoracotomy (19). Two polyvinyl chloride catheters were inserted in the left atrium for blood sampling and left atrial pressure (LAP) determination; a Königsgberg pressure-tip transducer was inserted in the aorta to record MAP; an electromagnetic flow probe was placed around the ascending aorta to measure CO, and a 7F His-bundle electrode was stitched subepicardially to the wall of the LV for LV pacing.

In both groups a bladder catheter was inserted for urine collections. Animals recovered for 7 (normals) or 14 days (HF) before studies commenced. During experiments, the animals, held in metabolic cages, had free access to water and food (containing 80 mmol/day sodium; 200 mmol/day potassium).

**Study protocol.** Heart failure was induced by seven days of rapid LV pacing (225 beats/min) (19). Pacing was continued throughout the study period. In both groups, each sheep received intravenous boluses of ovine Ucn (10, 50, and 100 mg at 2-h intervals) (American Peptide Company, Sunnyvale, California) or a vehicle control (10 ml 0.9% saline) administered two days apart in a balanced random order.

Mean arterial pressure, RAP/LAP, and calculated total peripheral resistance (CTPR = MAP/CO) were recorded at 15-min intervals in the hour preceding the first bolus at 10:00 AM (baseline); at 15, 30, 45, 60, 90, and 120 min succeeding each bolus; and at 10:00 AM the following day. Hemodynamic measurements were determined by online computer-assisted analysis using established methods (20,21).

Blood samples (25 ml) were drawn from the jugular vein (normal group) or left atrium (HF group) at 30 min; and immediately preceding the first bolus at 10:00 AM (baseline); at 30, 60, and 120 min succeeding each bolus; and at 10:00 AM the following day. Samples were taken into tubes on ice, centrifuged at 4°C, and stored at either −20°C or −80°C before assay for immunoreactive Ucn, cyclic adenosine monophosphate (cAMP), AVP, ACTH, cortisol, endothelin-1, plasma renin activity (PRA), angiotensin II (AngII-HF sheep only), aldosterone, ANP, BNP, and catecholamines (19–22). All samples of each hormone from individual animals were measured in the same assay to avoid inter-assay variability. Plasma electrolytes, glucose, and hematocrit were measured with every blood sample taken.

Plasma Ucn concentrations were determined via radioimmunoassay. The samples initially underwent methanol extraction where 1 ml plasma was mixed with 2 ml methanol (100%), centrifuged to remove precipitated proteins, and the supernatant dried down and reconstituted in 0.5 ml assay buffer. One hundred microliters of the extract or rat Ucn standard (Bachem, Torrance, California) were then incubated with 100 µl anti-serum (raised in rabbit to rat Ucn [identical to ovine Ucn] [23] coupled to human α-globulins [2.5 mg/ml serum] via glutaraldehyde [The Salk Institute, La Jolla, California]) and 100 µl radiolabeled (125I) rat Ucn. Bound and free labeled Ucn were separated using a solid phase second antibody. Recovery of unlabeled Ucn standard was 65% to 75%. The detection limit of the assay was 3.8 pmol/l, and the IC50 was 90.4 pmol/l. Intra-assay coefficients of variation (CV) were 7.7% and 6.2% over the ranges of 0 to 100 and 100 to 250 pmol/l, respectively, and inter-assay CVs were 14.1% and 11.9% at 30 and 80 pmol/l, respectively. Cross reactivity to ovine Ucn and human UCN-II (Phoenix Pharmaceuticals, Belmont, California) was <0.001% and to murine Ucn-II was <0.026%.

Urocortin plasma half-life, clearance, and volume of distribution were calculated using a two-compartment model (WinNonLin Professional 3.1, Pharsight Corporation, Mountain View, California).

Urine volume and samples for the measurement of urine cAMP, sodium, potassium, and creatinine excretion were collected at two hourly intervals before (baseline) and after each bolus and overnight (4:00 PM to 10:00 AM).
The study protocol was approved by the local Animal Ethics Committee.

**Statistics.** Results are expressed as mean ± SEM. To test for baseline differences between normal and HF sheep, baseline data from each state (mean of measurements made within the hour before treatment) were compared using paired t tests. To test for the effects of Ucn, control and Ucn study limbs (in both normal and HF sheep separately) were compared using repeated measures analysis of variance (ANOVA). Where significant differences were noted, the level of significance at individual time points on figures and tables was determined using pairwise least-significant-difference tests with the appropriate mean-square error term from the ANOVA (Fisher protected least-significant-difference test). To test for differences in the response to Ucn between normal and HF states, Ucn study limbs in each state were compared by covariate ANOVA using baseline data as the covariates. Significance was assumed at p < 0.05.

**RESULTS**

Pacing induced the hemodynamic, hormonal, and sodium retaining hallmarks of congestive HF, with significantly reduced MAP and CO and increased LAP and hormone levels (Figs. 1 to 5).

**Hemodynamics.** In HF, Ucn doubled CO and halved CTPR and LAP (all p < 0.001), restoring these indexes toward normal levels. These effects were still evident at 24 h (Fig. 1). Reductions in MAP were small (p < 0.05) and not dose-dependent. Hematocrit was elevated the day after Ucn administration (p < 0.05) (Table 1).

In normal sheep, Ucn also increased CO (p < 0.001), but downward trends in CTPR and atrial pressures were not significant. In contrast with HF sheep, Ucn increased MAP (p < 0.001). Heart rate (fixed at 225 beats/min in the HF group) increased twofold with Ucn (p < 0.001) in normal sheep and remained elevated at 24 h (Table 1).
Comparing HF and normal groups, CTPR and atrial pressures fell more in HF sheep (both p < 0.001), and effects on MAP were directionally opposite (p < 0.001).

Hormones. In HF sheep, Ucn dose-dependently increased plasma Ucn (p < 0.001) from 20 ± 2 to 336 ± 45, 1,900 ± 143, and 4,836 ± 355 pmol/l, respectively, 30 min after each bolus (Fig. 2). Concentrations remained elevated at 24 h (1,405 ± 239 pmol/l). Urocortin plasma half-life was calculated as 1.23 ± 0.60 and 20.1 ± 3.35 h for the first and second phases, respectively, clearance as 0.43 ± 0.06 and 3.09 ± 0.86 l/h, and volume of distribution as 10.05 ± 1.05 and 5.39 ± 0.72 l. Urocortin substantially and dose-dependently reduced plasma AVP (p < 0.001), PRA (p < 0.001), aldosterone (p < 0.001), ET-1 (p < 0.05), AngII (p < 0.001), ANP (p < 0.001), and BNP (p < 0.001) concentrations (Figs. 2 to 4, Table 1). These factors were still decreased relative to control at 10:00 AM the following day. Conversely, Ucn induced acute rises in plasma ACTH (p < 0.001) and cortisol (p < 0.001) (Fig. 2) that were not dose-related. Circulating cAMP (Table 1) and catecholamine levels (Fig. 4) were unchanged compared with control.

In normal sheep, plasma Ucn levels and pharmacokinetics were similar to those in HF. Plasma Ucn increased from 12.3 ± 1.3 to 219 ± 19; 1,777 ± 91; and 4,142 ± 175 pmol/l, respectively, 30 min after each bolus (p < 0.001). Plasma half-life was calculated as 1.32 ± 0.39 and 19.1 ± 1.96 h for the first and second phases, respectively, clearance as 0.38 ± 0.05 and 2.18 ± 0.71 l/h, and volume of distribution as 9.44 ± 0.41 and 3.40 ± 0.48 l. Compared with control, Ucn in normals increased plasma AVP (p < 0.05) and cortisol levels (p < 0.001), reduced plasma aldosterone (p < 0.05) and ET-1 levels (p < 0.05), but had no significant effects on PRA, plasma ACTH, ANP, BNP, catecholamines (Figs. 2 to 4), or cAMP levels (Table 1).

Comparison between groups showed significantly different effects on PRA (p < 0.01), ANP (p < 0.001), and BNP (p < 0.001), which all fell in HF sheep but did not change.

![Figure 2](image-url)

Figure 2. Mean ± SEM plasma urocortin, arginine vasopressin, adrenocorticotropic hormone (ACTH), and cortisol responses to incremental boluses of urocortin and a vehicle control in eight normal sheep (left panel) and eight heart failure sheep (right panel). Significant differences are shown by: *p < 0.05; **p < 0.01; †p < 0.001.
significantly in normal sheep, and directionally opposite effects on plasma AVP (p < 0.001). Second phase volume of distribution was greater in HF sheep (p < 0.05).

**Urine and plasma electrolytes.** In HF sheep, Ucn dose-dependently increased urine volume (twofold, p < 0.01), sodium (ninefold, p < 0.001), creatinine (p < 0.001) and cAMP excretion (p < 0.01) (Fig. 5), and creatinine clearance (p < 0.001) (Table 1). These variables remained elevated above controls at 24 h. Potassium excretion rose after Ucn (p < 0.05). Water intake was unaltered (Table 1). Urocortin reduced plasma potassium (p < 0.001) and creatinine (p < 0.01) concentrations and increased plasma glucose (p < 0.001)—the latter two responses still apparent at 24 h (Table 2). Urocortin did not significantly affect plasma sodium concentrations.

In normal sheep there was no significant effect on any of the urinary parameters measured (Fig. 5, Table 1). Urocortin reduced plasma potassium (p < 0.05) and increased plasma glucose (p < 0.001) but had no effect on water intake, plasma sodium, or creatinine levels (Tables 1 and 2).

Comparison between HF and normal groups showed significantly greater effects of Ucn on sodium and potassium excretion (both p < 0.05) and urinary volume (p < 0.01) in HF sheep.

**DISCUSSION**

This is the first report of the hemodynamic, hormonal, and renal effects of acute intravenous Ucn in experimental HF. In HF, Ucn induced profound reductions in CTPR and ventricular filling pressures, and increases in cardiac output in concert with broad spectrum falls in neurohormonal activation (including inhibition of the renin-angiotensin-aldosterone axis and the vasoconstrictor peptides AVP and ET-1) and pronounced augmentation of renal function. Responses to Ucn in HF sheep—especially MAP, CTPR, atrial pressures, PRA, plasma AVP, ANP and BNP, and renal indexes—differed markedly from those found in normal sheep. This combination of sustained responses incorporates many of the therapeutic goals of HF management where this peptide or similarly acting compounds may ultimately have clinical applications in human HF.
Hemodynamics. Urocortin induced prompt (15 min) and impressive dose-dependent rises in CO in HF. In keeping with the residual levels of Ucn in plasma, CO was still significantly elevated 20 h after the bolus. Similar observations of marked and sustained CO responses were seen in the normal sheep and have been previously reported by Parkes et al. (18). While this effect in HF must at least partially reflect a reduction in cardiac afterload, the previously reported potent positive inotropic actions of Ucn (24) may also play a role. Indeed, inotropic activity is suggested in the present study by marked increments in CO in the face of profound falls in filling pressure (especially as changes in MAP were modest relative to the marked increase in CO and steep fall in CTPR). As with any inotropic agent, there is a potential concern of pro-arrhythmic activity with Ucn. While there have been no reports of pro-arrhythmic effects of either CRF or Ucn, nor has our experience with Ucn in normal or paced sheep (where it is possible that the stress of rapid pacing plus a pro-arrhythmic agent might cause ventricular tachycardia/fibrillation, seen as escape from pacing) indicated any such activity, this possible side effect requires further investigation.

The moderate blood pressure-lowering effects of Ucn in sheep with HF contrasted with the pressor effect we observed in normal sheep as was reported previously by Parkes et al. (18). The difference in MAP responses between HF and normal animals may be due, in part, to the preconstricted state of the arterial vasculature in HF. The hypotensive effect—at least at higher doses of Ucn—in the HF sheep may be mediated to some extent by its actions to substantially reduce elevated plasma levels of the potent vasoconstrictor peptides AngII, endothelin-1, and AVP.

Urocortin also induced striking dose-dependent and persistent reductions in LAP in the HF sheep, presumably a consequence of the large increases in CO, although a possible contribution from reduced venous tone cannot be excluded from our data. A decrease in circulating volume is unlikely to have contributed acutely, although this may have been a contributing factor the following day (when preload was still significantly reduced) as judged by the vigorous

Figure 4. Mean ± SEM plasma atrial natriuretic peptide, brain natriuretic peptide, norepinephrine, and epinephrine responses to incremental boluses of urocortin and a vehicle control in eight normal sheep (left panel) and eight heart failure sheep (right panel). Significant differences are shown by: *p < 0.05; †p < 0.001.
natriuresis/diuresis sustained overnight and the rise in hematocrit. The minor decline in MAP in concert with major falls in LAP and CTPR and increments in CO can be seen as a desirable hemodynamic profile in HF—with enhanced tissue blood flow coupled with sustained perfusion pressure. This pattern contrasts with current standard treatment with angiotensin-converting enzyme inhibition, which can induce profound falls in systemic pressure (with concomitant risks of impaired cerebral and renal perfusion) and only modest increments in CO.

Urocortin significantly increased HR in normal sheep, confirming the positive chronotrophic effects of this peptide previously reported (18). It was not possible to assess changes in HR in the HF sheep as the pacemaker must remain on at 225 beats/min throughout the study period to maintain the stable HF profile. This represents a drawback of the pacing-induced model of HF. Thus, the effects of Ucn on HR in HF remain to be determined.

Hormones. Baseline plasma Ucn levels tended to be elevated in these sheep with HF (20 ± 2 pmol/l) compared with normal animals (12.3 ± 1.3 pmol/l, p = NS). Although Ucn has been detected in a wide variety of tissues (2–6), the source of circulating Ucn is unknown (in either physiological or pathophysiological conditions). It is possible, however, that there may be some cardiac contribution to the raised plasma levels of the peptide observed in this model of HF, given the augmented Ucn immunoreactivity and gene expression demonstrated in the cardiac ventricles of animals and patients with heart disease (2). Cytokines (interleukins-1β and -6, tumor necrosis factor-α) (25) and ischemia (12), both of which have been shown to stimulate Ucn secretion from rat cardiomyocytes, may play a regula-

Figure 5. Mean ± SEM urine volume, sodium, potassium, creatinine, and cyclic adenosine monophosphate (AMP) excretion in response to incremental boluses of urocortin (striped bars) and a vehicle control (open bars) in eight normal sheep (left panel) and eight heart failure sheep (right panel). The overnight sample was collected from 4:00 PM to 10:00 AM. Significant differences are shown by: *p < 0.05; **p < 0.01; †p < 0.001.
tory role in this setting. To our knowledge, only a single study has previously measured Ucn in plasma (26), reporting concentrations of approximately 15 pg/ml (3.2 pmol/l) in normal humans. It remains to be seen whether plasma Ucn levels are elevated in human HF. The current study documents for the first time the pharmacokinetics of Ucn, which were similar in normal and HF sheep. Half-lives for first and second phases were approximately 1.3 and 19.5 h, respectively. The pharmacokinetics of Ucn in humans remain unknown. Despite marked increases in plasma Ucn, plasma levels of cAMP, a proposed second messenger (8), remained unchanged, and any response in urine cAMP was inconsistent. However, significant hemodynamic and hormonal effects were observed within 15 to 30 min after the lowest dose bolus, indicating Ucn is a rapidly acting hormone. It is possible that Ucn stimulated cAMP sufficiently at the tissue level to induce a biological response but insufficiently to induce a measurable rise in circulating concentrations. There is, however, evidence that alternative pathways for Ucn exist, for example, via prostaglandin generation (24).

Despite falls in arterial pressure (and plasma concentrations of AVP and the natriuretic peptides) in the HF sheep, PRA (and AngII) was dose-dependently reduced by Ucn. Whether this was due to direct inhibition of renin release from the juxtaglomerulus by Ucn, increased delivery of sodium (and chloride) to the macula densa (reflected in the significant rise in sodium excretion), or some other PRA-inhibitory mechanism, remains to be seen. Trends for PRA to fall in normal sheep were not significant in the current study but have been reported previously (18). Aldosterone concentrations were also reduced (more apparent in HF sheep), presumably as a result of the decline in circulating AngII (and perhaps plasma potassium) and notwithstanding the substantial rise in ACTH. However, a direct effect of Ucn on the adrenal glomerulosa cannot be excluded from

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Values are mean ± SEM. Significant differences (compared with time-matched control) are shown by: *p < 0.05; †p < 0.001.

cAMP = cyclic adenosine monophosphate; HF = heart failure; Ucn = urocortin.
our data. The present study reports for the first time that Ucn dose-dependently decreases plasma endothelin-1 concentrations—an effect even more apparent 20 h after bolus in HF sheep. Such a response has not been observed by the authors previously following administration of other vasodilator peptides such as ANP/BNP or adrenomedullin (unpublished data).

Urocortin induced stepped reductions in plasma ANP and BNP levels in HF sheep. This is likely to reflect reduced cardiac transmural pressures (as judged by the falls in LAP and MAP) leading to reduced stimulus to secretion because Ucn is reported to augment natriuretic peptide secretion from rat cardiac myocytes (2,13). Our findings are in accord with previous studies demonstrating a close parallelism between falls in atrial pressures and plasma natriuretic peptide levels with administration of vasodilator agents in HF (22). Circulating ANP and BNP were still reduced compared with control the following day—consistent with the sustained reduction in LAP.

In contrast with effects observed in normal sheep, intravenous Ucn dose-dependently and persistently reduced plasma AVP levels in sheep with HF. While it is possible that circulating Ucn could affect AVP secretion/release via neural connections that exist between the circumventricular organs (e.g., lamina terminalis, subfornical organ) and hypothalamic paraventricular and supraoptic nuclei, as well as between the median eminence and posterior pituitary, it is more likely that the changes in plasma AVP in HF relate to improved CO and pressure to sinoaortic volume receptors, and possibly to reductions in plasma AngII levels (27). These data, together with evidence of Ucn suppression of water intake (28), and upregulation of Ucn immunoreactivity in the supraoptic nucleus after dehydration (10) and in the hypothalamo-neurohypophysial system after salt loading (11), indicate this peptide is likely to be involved in blood volume regulation, at least under some circumstances. Plasma ACTH and cortisol levels rose acutely after each bolus in HF sheep (not dose-related), suggesting a direct stimulatory effect of Ucn on ACTH release from the pituitary. It is likely that negative feedback of cortisol at the pituitary level dampened the ACTH responses to subsequent doses of Ucn. Urocortin has previously been shown to augment ACTH release from isolated rat pituitary cells and in vivo in conscious rats (1) and sheep (18). The increases in plasma cortisol observed in normal sheep confirm previous findings (18). As demonstrated in rats after central administration (29), intravenous Ucn in the present study increased plasma glucose concentrations in both normal and HF sheep. It is conceivable that the elevation in plasma cortisol may have contributed to this rise (through actions to
increase glycogen storage, stimulate gluconeogenesis, and reduce cellular glucose utilization).

**Renal effects.** This is the first report of the renal effects of Ucn in contrast with the lack of renal effects observed in normal sheep. Ucn markedly increased urine volume and urine sodium and creatinine excretion in HF sheep. These effects—both dose-dependent and sustained overnight—occurred despite falls in arterial pressure (and, hence, renal perfusion pressure) and large reductions in plasma natriuretic peptide concentrations. The significant and persistent decreases in circulating levels of anti-natriuretic/anti-diuretic factors such as AVP, AngII, and aldosterone (and possibly endothelin-1) are likely to have played a role in these renal responses. It is also likely that Ucn has effects on renal hemodynamics, given the major effects on CO and vascular resistance, and reported vasodilator actions in a variety of vascular beds (4,8,24,30). Direct tubular actions may also have occurred given the relative rise in urine cAMP excretion observed in the present study, and reports of Ucn expression within the kidney in the rat (5). Increased glomerular filtration, reflected by the impressive increase in creatinine clearance, may also have contributed to the natriuretic/diuretic effect observed in the HF sheep. These effects were observed notwithstanding the substantial decline in plasma AngII levels that would be expected, under other circumstances, to result in a decrease in efferent arteriolar tone and, hence, in both intraglomerular pressure and glomerular filtration rate. Clearly, the situation is complex, and the exact mechanisms of these renal effects need to be investigated further.

In conclusion, this study is the first to investigate the effects of Ucn in experimental HF. We observed profound and sustained cardiovascular, hormonal, and renal effects—including reductions in peripheral resistance, cardiac preload and afterload, and major increases in CO that were associated with inhibition of a broad spectrum of vasoconstrictor/volume-retaining factors and impressive augmentation of natriuresis, diuresis, and glomerular filtration. While some of these effects were similar to those observed in normal sheep, some were significantly enhanced, for example, falls in CTPR, atrial pressure, PRA, and plasma aldosterone, and others were directionally opposite (MAP and plasma AVP). These data, together with other physiological actions reported for Ucn (protection of cardiac myocytes from hypoxic and ischemia/reperfusion injury, stimulation of natriuretic peptide secretion, and anti-inflammatory properties), suggest this peptide may have protective compensatory actions in cardiovascular disease.

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