Four-day urocortin-I administration has sustained beneficial haemodynamic, hormonal, and renal effects in experimental heart failure


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Aims To investigate the subacute effects of a sustained intravenous infusion of urocortin-I (Ucn-I) in experimental heart failure (HF).

Methods and results In eight sheep with pacing-induced HF, a 4-day infusion of Ucn-I (0.3 μg/kg/h) induced prompt (30 min) and sustained (4-day) increases in cardiac output (CO; Day 4: 1.8 ± 0.2 vs. 2.3 ± 0.2 L/min, P < 0.001) and stroke volume (7.8 ± 0.8 vs. 10.2 ± 1.0 mL/beat, P = 0.0011), and reductions in mean arterial pressure (MAP; 72 ± 3 vs. 70 ± 3 mmHg, P = 0.0305), left atrial pressure (26 ± 1 vs. 11 ± 2 mmHg, P < 0.001), and total calculated peripheral resistance (43 ± 6 vs. 32 ± 4 mmHg/L/min, P < 0.001). Ucn-I also induced persistent falls in plasma renin (1.34 ± 0.23 vs. 0.77 ± 0.10 mmol/L/min, P = 0.048), aldosterone (327 ± 1172 vs. 382 ± 44 pmol/L, P = 0.0098), endothelin-1 (4.6 ± 0.3 vs. 2.7 ± 0.3 pmol/L, P < 0.001), vasopressin (24 ± 4 vs. 14 ± 2 pmol/L, P = 0.0226) and atrial (184 ± 14 vs. 154 ± 29 pmol/L, P = 0.0226) and brain (43 ± 5 vs. 32 ± 6 pmol/L, P = 0.0016) natriuretic peptides. Plasma adrenocorticotrophic hormone and cortisol rose transiently on Day 0. Ucn-I enhanced urinary sodium excretion (5.3-fold, P = 0.0001) and creatinine clearance (1.3-fold, P = 0.0055) long-term, and tended to increase urine output (P = 0.0748). Food intake was attenuated over the first 2 days of treatment (P = 0.0283).

Conclusion Four-day administration of Ucn-I induces sustained reductions in cardiac preload and MAP, improvements in CO and renal function, and inhibition of a range of vasoconstrictor/volume-retaining factors. These findings support Ucn-I’s therapeutic potential in HF.
the haemodynamic, hormonal, and renal effects of prolonged (days) administration of Ucn-I in experimental ovine HF.

Methods

Surgical preparation

Eight Coopworth ewes (43–52 kg) were instrumented via a left lateral thoracotomy under general anesthesia (induced by 17 mg/kg thiopentone; maintained with halothane/nitrous oxide). Two polyvinyl chloride catheters were inserted in the left atrium for blood sampling and left atrial pressure (LAP) determination; a Konigsberg pressure-tip transducer inserted in the aorta to record mean arterial pressure (MAP); 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 seven French His-bundle electrode stitched subepicardially to the wall of the left ventricle for pacing. A bladder catheter was inserted per rectum for urine collections. Animals recovered for 14 days before commencing the study protocol. During the experiments the animals were kept in metabolic cages, fed a standard laboratory diet (500 g sheep nuts and 250 g chaff/day—containing 80 mmol sodium; 200 mmol potassium) and had free access to water.

Study protocol

Each sheep received a continuous 4-day intravenous infusion of ovine Ucn-I (0.3 µg/kg/h) (American Peptide Company Inc., USA) and a vehicle control (0.9% saline) in a balanced, randomized, and crossover design (four animals to each sequence). Following induction of HF by rapid left ventricular pacing (225 b.p.m.) for 7 days, treatments were then administered over Days 8–12 of pacing. A week without pacing between phases allowed recovery to normal pre-pacing parameters. Infusions commenced at 1000 h on study Day 0 and were administered via the pulmonary artery catheter in a total volume of 50 mL/day.

MAP, LAP, CO, stroke volume (SV = CO/heart rate), and calculated total peripheral resistance (CTPR = MAP/CO) were recorded at 15 min intervals in the hour preceding infusion on study Day 0 (baseline), at 0.5, 1, 1.5, 2, 4, and 6 h following commencement of treatment, and then daily on study Days 1–4. Haemodynamic measurements were determined by on-line computer assisted analysis using established methods. Blood samples were drawn from the left atrium (immediately following haemodynamic measurements) into tubes on ice, centrifuged at 4°C and stored at –20°C

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Non-paced</th>
<th>Paced</th>
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<tbody>
<tr>
<td>CO (L/min)</td>
<td>4.2 ± 0.4</td>
<td>2.0 ± 0.2***</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>83 ± 2</td>
<td>74 ± 3***</td>
</tr>
<tr>
<td>LAP (mmHg)</td>
<td>4.1 ± 0.3</td>
<td>22.4 ± 0.6***</td>
</tr>
<tr>
<td>SV (mL/beat)</td>
<td>45 ± 4</td>
<td>8.9 ± 0.8***</td>
</tr>
<tr>
<td>CTPR (mmHg/L/min)</td>
<td>20 ± 3</td>
<td>39 ± 5***</td>
</tr>
<tr>
<td>Ucn-I (pmol/L)</td>
<td>11.8 ± 0.3</td>
<td>16.9 ± 0.5*</td>
</tr>
<tr>
<td>cAMP (pmol/L)</td>
<td>21.5 ± 1.1</td>
<td>33.2 ± 2.1**</td>
</tr>
<tr>
<td>ANP (pmol/L)</td>
<td>17 ± 2</td>
<td>184 ± 11***</td>
</tr>
<tr>
<td>BNP (pmol/L)</td>
<td>3 ± 1</td>
<td>37 ± 4***</td>
</tr>
<tr>
<td>PRA (nmol/L/h)</td>
<td>0.39 ± 0.06</td>
<td>1.24 ± 0.24***</td>
</tr>
<tr>
<td>Aldosterone (pmol/L)</td>
<td>225 ± 24</td>
<td>1897 ± 829***</td>
</tr>
<tr>
<td>Endothelin-1 (pmol/L)</td>
<td>1.68 ± 0.08</td>
<td>3.81 ± 0.42***</td>
</tr>
<tr>
<td>AVP (pmol/L)</td>
<td>1.7 ± 0.1</td>
<td>23.6 ± 3.7***</td>
</tr>
<tr>
<td>Norepinephrine (pmol/L)</td>
<td>2683 ± 507</td>
<td>12186 ± 4932***</td>
</tr>
<tr>
<td>Epinephrine (pmol/L)</td>
<td>490 ± 88</td>
<td>1551 ± 684***</td>
</tr>
<tr>
<td>Urine output (mL/h)</td>
<td>81 ± 12</td>
<td>37 ± 5 ***</td>
</tr>
<tr>
<td>Urinary sodium excretion (mmol/L)</td>
<td>2.62 ± 0.30</td>
<td>0.70 ± 0.25***</td>
</tr>
<tr>
<td>Urinary potassium excretion (mmol/L)</td>
<td>9.0 ± 0.6</td>
<td>6.1 ± 0.6**</td>
</tr>
<tr>
<td>Urinary creatinine excretion (mmol/L)</td>
<td>0.50 ± 0.02</td>
<td>0.44 ± 0.04***</td>
</tr>
<tr>
<td>Urinary AMP excretion (mmol/L)</td>
<td>94 ± 11</td>
<td>155 ± 15**</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>121 ± 9</td>
<td>96 ± 8**</td>
</tr>
</tbody>
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Significant differences are shown: **P < 0.01, †P < 0.001.
Seven days of rapid left ventricular pacing induced the haemodynamic, hormonal, and sodium-retaining hallmarks of established HF—with reduced MAP, CO, SV, and renal function, increased CTPR and LAP, and ubiquitous hormone activation. A comparison of measurements made in sheep before (laboratory normal data, n = 20) and after the development of pacing-induced HF (control baseline data) can be seen in Table 1.

A number of variables changed significantly over the 4 days of control treatment (with continued pacing) including decreases in CO (P < 0.001), SV (P < 0.001), MAP (P = 0.0009), haematocrit (P < 0.001), creatinine clearance (P < 0.001), urine creatinine (P = 0.0009) and urine potassium excretion (P < 0.001), and in rises in LAP (P < 0.001), norepinephrine (P = 0.0006), aldosterone (P = 0.0265), endothelin-1 (P = 0.0201), BNP (P = 0.0188), and plasma creatinine (P = 0.033). In addition, on Day 1 of the control phase plasma cAMP (P = 0.0057) and drinking (P = 0.044) fell, and plasma ACTH (P = 0.0014) and cortisol (P = 0.039) rose acutely (Figures 1–4, Table 2). There was no statistical evidence of significant carry-over effects for any of the variables tested (P > 0.05 for all sequence by treatment interactions), or of significant differences between pre-treatment control and Ucn-I baseline data.

When compared with vehicle control data, infusion of Ucn-I induced prompt (30 min) and sustained (4 day) increases in CO (Day 4: 1.8 ± 0.2 vs. 2.3 ± 0.2 L/min, P < 0.001) and SV (7.8 ± 0.8 vs. 10.2 ± 1.0 mL/beat, P = 0.0011), and reductions in MAP (72 ± 3 vs. 70 ± 3 mmHg, P = 0.0305), LAP (26 ± 1 vs. 11 ± 2 mmHg, P < 0.001), and CTPR (43 ± 6 vs. 32 ± 4 mmHg/L/min, P < 0.001) (Figure 1). Haematocrit was elevated relative to control over Days 1–4 (P < 0.001, Table 2).

Infusion of Ucn-I gradually increased circulating concentrations of the peptide from a baseline of 14 pmol/L to a plateau of ~7500 pmol/L on Day 3 (P < 0.001) (Figure 2). Plasma concentrations of Ucn-I’s intracellular second messenger, cAMP, were unchanged during the first 24 h but were elevated when compared with control over Days 2–4 (Day 4: 30 ± 2 vs. 35 ± 2 nmol/L, P = 0.0143). Ucn-I administration produced rapid but short-lived increases in plasma AVP (P = 0.0129), ACTH (P = 0.0057), and cortisol (P = 0.046) on Day 0 (Figure 2), and while the latter two hormones remained close to control levels during Days 1–4, AVP concentrations were significantly reduced over this time compared with control (Day 4: 24 ± 4 vs. 14 ± 2 pmol/L, P = 0.0028).

Although PRA was not significantly altered by Ucn-I administration acutely, plasma aldosterone levels fell (6 h: 2221 ± 762 vs. 994 ± 588 pmol/L, P = 0.0412), and persistent reductions in both factors were observed over the following 4 days of treatment (Day 4: PRA 1.34 ± 0.23 vs. 0.77 ± 0.10 nmol/L/min, P = 0.048; aldosterone 3273 ± 1172 vs. 382 ± 44 pmol/L P = 0.0098) (Figure 3). Plasma...
endothelin-1 was also markedly diminished during this period (Day 4: \(4.6 \pm 0.3\) vs. \(2.7 \pm 0.3\) pmol/L, \(P < 0.001\)), as were natriuretic peptide levels (ANP: \(184 \pm 14\) vs. \(154 \pm 29\) pmol/L, \(P = 0.0226\); BNP: \(43 \pm 5\) vs. \(32 \pm 6\) pmol/L, \(P = 0.0016\)) (Figure 3).

Circulating levels of norepinephrine, epinephrine, glucose (Table 2), sodium, and potassium (data not shown) were not significantly altered by protracted Ucn-I administration, while plasma creatinine tended to decline (\(P = 0.0735\)) (Table 2).

Ucn-I infusion acutely increased urine output (4–6h: 2-fold, \(P = 0.0254\)), urinary potassium excretion (1.8-fold, \(P = 0.001\)), sodium excretion (5.5-fold, \(P = 0.0007\)), creatinine excretion (1.4-fold, \(P = 0.0046\)), and creatinine clearance (1.3-fold, \(P = 0.0031\)) (Figure 4 and Table 2), with the latter three variables remaining elevated compared with control over the following 4 days of treatment (Day 4: sodium excretion 5.3-fold, \(P = 0.0001\); creatinine excretion 1.2-fold, \(P = 0.005\); creatinine clearance 1.3-fold, \(P = 0.0055\)). Urine output and urine cAMP excretion tended to be raised over this period (\(P = 0.0748\) and \(P = 0.0619\), respectively). Water intake was reduced short-term (\(P = 0.0491\)) but was not significantly lower than control over the remaining 4 days, whereas food intake was attenuated over the first 2 days of Ucn-I infusion (\(P = 0.0283\)), before returning to pre-treatment levels over Days 3 and 4 (Figure 4).

**Discussion**

The present study demonstrates for the first time that long-term Ucn-I administration induces sustained reductions in cardiac preload and MAP, augmentation of CO and renal function, and attenuation of adverse vasoconstrictor/volume-retaining factors in experimental HF. The haemodynamic effects of protracted infusion of Ucn-I in sheep with HF are qualitatively similar to those we have reported formerly in response to bolus administration of the peptide in our ovine HF model. The moderate yet persistent blood pressure-lowering effects of infused Ucn-I in the present study occurred in association with substantial reductions in CTPR, indicating an effect on arterial tone. This is in agreement with *in vitro* studies demonstrating a direct vasodilator action of the peptide in both rat and human vasculature. The persistence of this hypotensive response (4 days) concurs with reports in normal mice where pre-treatment with Ucn-I for 3 days did not diminish the blood-pressure lowering effect of subsequent challenges of the peptide. Other mechanisms possibly contributing to the prolonged hypotensive action of Ucn-I in these HF sheep include plasma volume contraction, as evidenced by the rise in haematocrit, as well as marked suppression of a
number of vasoconstrictor factors (activated in this setting) including endothelin-1, AVP, and renin-angiotensin-aldo... and attenuates CRF-R2 antagonism and absent in CRF-R2 knockout mice. Of note, CRF-R2-deficient animals exhibit hypertension when compared with their wild-type littermates.

Four-day infusion of Ucn-I also resulted in an impressive halving of LAP, presumably a reflection of the substantial increase in CO, concurrent haemoconcentration (due at least in part to a reduction in water intake and rise in urine output), and likely lusitropic actions of Ucn-I (as shown for Ucn-II). A possible contribution from reduced venous tone cannot be excluded from our data. Indeed, recent reports suggest that Ucn-I may be of significance in the regulation of the venous circulation in humans. However, in the absence of direct left ventricular imaging in this experiment, a significant drop in left ventricular end-diastolic volume is conjectural. Our results point towards a role for Ucn-I in both the short- and long-term regulations of haemodynamic function, and demonstrate that extended augmentation of this peptide produces a sustained and desirable haemodynamic profile in experimental HF.

Prolonged elevation of circulating Ucn-I was associated with significant rises in plasma levels of cAMP—a proposed intracellular second messenger of the peptide. Plasma cAMP is elevated in HF in relation to the severity of the disease, and concentrations fall following successful HF treatment (with agents which do not utilize the cAMP pathway). The fact that we observe haemodynamic improvement in conjunction with increased plasma cAMP following Ucn-I treatment in the present study, rather than
a decrease in nucleotide levels, suggests that the rise in cAMP is (directly) attributable to Ucn-I. There was, however, a temporal dissociation between the onset of haemodynamic and hormonal effects (15–30 min) and plasma cAMP increases (2 days), a finding we have observed previously following short-term administration of the peptide, suggesting that cAMP was raised sufficiently at the tissue level to induce the significant responses that ensued. Alternatively, other signalling pathways may be involved.\cite{10,12}

Stimulation of the hypothalamic-pituitary-adrenal (HPA) stress axis via activation of CRF-R1 is a well-documented action of Ucn-I, yet obviously undesirable when considering the peptide’s potential as a therapeutic strategy in cardiovascular disease. Although infused Ucn-I did induce a significant rise in plasma ACTH and cortisol in the present investigation (the former presumably via direct stimulation within the pituitary and potentiation by concomitant increases in AVP),\cite{26} the rises were transient (1–2 h) and both hormones persisted at pre-infusion levels for the following 4 days. This response differs from that observed following intermittent Ucn-I administration in the ovine HF\cite{48} where each bolus resulted in an acute marked rise in ACTH/cortisol. It is likely that deletion of the pituitary ‘pool’ of readily available ACTH and negative feedback by cortisol, followed by receptor down-regulation and desensitization,\cite{27} diminished the ACTH response to further stimulation by Ucn-I. The plasma AVP response appeared to be biphasic—with an acute rise (0.5–2 h) followed by a considerable reduction (from elevated baseline concentrations) over Days 1–4 of the infusion. Significant attenuation of plasma AVP has previously been observed following bolus administration of the Ucn-I in HF sheep,\cite{8} and is likely mediated via improved CO and pressure at sinoaortic volume receptors, and possibly also through reductions in plasma angiotensin-II (as reflected by declining PRA).\cite{28}

Similar to acute administration of Ucn-I,\cite{8} we observed marked reductions in the vasoconstrictor renin–angiotensin–aldosterone and endothelin-1 systems with long-term Ucn-I treatment. PRA decreases were sustained over the 4-day infusion period and occurred in the face of falls in arterial pressure (and plasma concentrations of AVP and the natriuretic peptides). Whether PRA reductions were due to increased delivery of sodium to the macula densa (evidenced by the significant rise in sodium excretion), a direct inhibitory effect of the Ucn-I on renin secretion, or some other PRA-inhibitory mechanism remains to be determined. Although attenuation of the plasma aldosterone is likely to be in part a consequence of the declines in circulating PRA/angiotensin-II, it is important to note that the fall preceded that of PRA, suggesting a possible direct inhibitory effect of Ucn-I on aldosterone secretion. The mechanism behind the striking and persistent reductions in plasma endothelin-1 concentrations we observed cannot be established from our data. Although it has been shown that Ucn-I opposes the vasoconstricting actions of endothelin-1,\cite{10,11} the peptide’s effect on endothelin secretion is unknown. Clearly, further investigation into the relationships between Ucn-I and these clinically important vasoactive systems is required.

Despite significant acute falls in LAP (and therefore reduced cardiac transmural pressure and stimulus for secretion), plasma natriuretic peptide levels were unchanged during the first 6 h of the Ucn-I infusion—findings in contrast with previous studies showing close parallelism between falls in atrial pressure and circulating ANP/BNP concentrations following the administration of vasodilator agents.\cite{29} It is conceivable that Ucn-I enhanced natriuretic peptide secretion\cite{2} sufficiently during this time to counteract the opposing effect of falling intracardiac pressure, whereas the significant ANP/BNP reductions over Days 1–4 reflect the substantial and sustained improvements in haemodynamic function. It should also be noted that plasma ANP/BNP tended to rise slowly again during Days 2–4, over which time LAP was observed to be fairly constant.

The renal response to extended Ucn-I treatment in sheep with HF—a sustained natriuresis, increase in creatinine clearance and a trend for augmented urinary output—is similar in type to those observed following acute administration of the peptide,\cite{8} and occurred despite falls in arterial pressure (and therefore renal perfusion pressure) and reductions in plasma ANP/BNP. It is likely that the prominent and persistent reductions in circulating levels of the sodium/volume-retaining factors AVP, angiotensin-II, and aldosterone (and perhaps endothelin-1) contributed to these renal responses. Ucn-I’s effect on renal haemodynamics, a prolonged elevation in the glomerular filtration rate (as assessed by the increase in creatinine clearance) and possibly renal blood flow,\cite{10} may also have contributed to the sustained natriuresis (and diuresis). In addition, direct tubular actions may have been involved, given reports of Ucn-I expression within the kidney\cite{30} and the relative increase in urine cAMP excretion observed in the present study. The maintenance of sodium excretion in conjunction with the extended decrease in renal perfusion pressure points to a shift in the pressure-natriuresis curve with long-term Ucn-I treatment in HF. These renal effects are clearly of benefit in this underperfused, sodium/volume-retaining state.

Four-day Ucn-I also suppressed food and water intake in these sheep with HF. Although appetite suppression may be considered an adverse side effect of any potential therapeutic agent in HF, we found that inhibition of feeding was transient, with the peak effect apparent over Days 1 and 2. These data are in agreement with studies investigating more prolonged Ucn-I administration in the normal mouse\cite{31,32} and suggest that tolerance to Ucn-I-induced appetite suppression occurs. Indeed, Cohen et al.\cite{29} reported that repeated administration of Ucn-I resulted in a reduced effect to inhibit food consumption, whereas the hypotensive action of the peptide persisted. Consistent with these findings, transgenic mice lacking the CRF-R2 receptor exhibit elevated basal blood pressure,\cite{23} but normal basal feeding and weight gain,\cite{22} suggesting that the hypotensive and appetite-suppressant effects of Ucn-I are mediated by different mechanisms. Similar to the findings with acute Ucn-I administration,\cite{8,33} we also observed a tendency for plasma glucose levels to be elevated when compared with the control during extended Ucn-I treatment, with the peak effect (Days 1 and 2) matching that of food suppression. The underlying mechanisms by which Ucn-I decreases food intake are unknown but may involve reduced gastric emptying\cite{31} as well as interaction with other factors known to regulate appetite, such as leptin\cite{34} and ghrelin.\cite{35} The repressed drinking response we noted in the present study was also transitory, an observation made previously in mice following 14-day Ucn-I treatment,\cite{36} and thought to be secondary to food intake reductions.\cite{37}
The progressive haemodynamic and renal deterioration and augmented activation of many of the hormones systems noted during the control phase of the present study presumably reflect the increasing severity of HF resulting from continued rapid cardiac pacing. The acute rises in plasma ACTH and cortisol (on Day 1 of the control phase) are likely a consequence of the mild pyrogenic reaction that occurs in some of these chronically instrumented animals following flushing of the fluid-filled lines,37 while the fall in cAMP levels may relate to diurnal variation.38

In addition to the beneficial haemodynamic, hormonal and renal effects demonstrated in the present study, Ucn-I appears to have a direct cardioprotective role. As mentioned earlier, Ucn-I reduces myocyte cell death caused by ischaemia/reperfusion in vitro, ex vivo, and in vivo.14,15 Ucn-I-induced cardioprotection appears to involve several mechanisms including enhanced cardiac expression and production of another cytoprotective peptide, cardiotrophin-1,19 which is also raised in the circulation of the patients with heart disease.40 The protective effects of both peptides involve activation of the p42/p44 MAPK and PI-3 kinase/Akt pathways. Ucn-I cardioprotection may also include stimulation of heat shock protein 9041 and the natriuretic peptides,2 and attenuation of calcium-insensitive phospholipase A2 gene expression.42

Although the cardioprotective actions of Ucn-I undoubtedly enhance its potential as a treatment for HF, reports that the peptide also possesses cardiac hypertrophic activity43 are counter intuitive to Ucn-I’s use in this disease. However, a recent report by Davidson et al.43 demonstrating that Ucn-I induces hypertrophy in cultured rat cardiac myocytes via a pathway distinct from that which mediates its protective actions (following exposure to transient ischaemia) suggests it might be possible to separate these two effects, and thus enhances the survival of cardiomyocytes in hypoxic conditions while avoiding undesirable activation of the hypertrophic pathway. Interestingly, Ucn-I is also reported to attenuate the proliferation of vascular smooth muscle cells.44 Clearly, continued investigation into Ucn-I’s cellular effects is essential.

In 2001, another peptide structurally related to Ucn-I was identified, termed Ucn-II.45 Much interest is currently being directed towards this latter peptide as a potential therapeutic agent in HF due to its specificity for CRF-R2,45 and therefore minimal undesirable activation of the CRFR1-volume-retaining hormone systems and augmentation of renal function seen following Ucn1 treatment in the present study are identified, continued investigation of this peptide is crucial. In addition, the transient nature of the ACTH/cortisol rise induced by sustained Ucn-I administration may suggest that treatment with the more selective CRF-R2 ligand, Ucn-II, may not be all that more advantageous than Ucn-I as a therapy for congestive HF.

In conclusion, we have demonstrated for the first time that extended augmentation of the Ucn-I system in experimental HF induces sustained and beneficial reductions in cardiac preload and MAP, improvements in CO and renal function, and inhibition of a range of adverse vasoconstrictor/volume-retaining factors. In contrast, less desirable stimulation of the HPA axis and appetite suppression were transient events. These findings point towards a role for Ucn-I in long-term pressure/volume regulation and, in combination with its cardioprotective activity, suggest that the peptide has therapeutic potential in HF.

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References


