Intact Negative Feedback of Four Cardiac Hormones in Congestive Heart Failure

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In 30 individuals with class III congestive heart failure (CHF), negative feedback of 4 cardiac peptide hormones, ie, long-acting natriuretic peptide (LANP), vessel dilator, kaliuretic peptide, and atrial natriuretic factor (ANF) from the same 126-amino acid (aa) prohormone were studied with the infusion of 100 ng/kg body weight (BW) for 60 minutes of each of the 4 cardiac hormones and a saline control (n = 6 for each). LANP decreased the circulating concentrations of vessel dilator, kaliuretic peptide, and ANF by 24%, 55%, and 30%, respectively. Vessel dilator decreased the circulating concentrations of ANF, kaliuretic peptide, and LANP 27%, 12%, and 62%, respectively. Kaliuretic peptide decreased the circulating concentrations of LANP, ANF, and vessel dilator 89%, 67%, and 70%, respectively. ANF decreased the circulating concentrations of LANP, vessel dilator, and kaliuretic peptide 88%, 59%, and 98%, respectively. Infusion of each of these 4 cardiac hormones decreased the excretion of the other 3 hormones into the urine by 11% to 92%. These results suggest that the respective cardiac hormones inhibit the release of each other rather than their breakdown, which would have increased their urinary concentrations. The feedback regulation of these hormones found previously in healthy humans is, thus, preserved in persons with CHF despite their increased endogenous circulating concentrations.

IN CONGESTIVE HEART failure (CHF), circulating concentrations of atrial natriuretic peptides (ANPs) increase in the circulation.[1,2] Their increase in the circulation of persons with CHF suggests that these cardiac hormones may have lost their normal feedback regulation,[3] but this possibility has never been examined experimentally. The ANP hormonal system consists of a 126-amino acid (aa) prohormone synthesized within myocytes of the heart and stored in storage granules within the heart for release into the circulation.[4] This hormonal system contains several peptide hormones from the same 126-aa prohormone with blood pressure-lowering, natriuretic, diuretic, and/or kaliuretic (ie, potassium-excreting) properties.[5-7] Thus, peptides consisting of aa 1 to 30 (proANF 1 to 30; long-acting natriuretic peptide), aa 31 to 67 (proANF 31 to 67; vessel dilator), aa 79 to 98 (proANF 79 to 98; kaliuretic peptide), and aa 99 to 126 (proANF 99 to 126; atrial natriuretic factor [ANF]) each have blood pressure-lowering, diuretic, natriuretic, and/or kaliuretic properties in both humans[6,7] and animals.[5,8-11] When released into the circulation, these peptides circulate as a 98 aa N-terminus and a 28-aa C-terminus (ie, ANF) of this prohormone.[12-18] In addition, vessel dilator, long-acting natriuretic peptide (LANP), and kaliuretic peptide circulate as distinct entities after having been proteolytically cleaved from the rest of the N-terminus by proteases.[1,19] Utilizing reverse phase high-pressure liquid chromatography, Hunter et al[20] have confirmed that vessel dilator, kaliuretic peptide, and proANF 99 to 126 circulate as distinct peptide hormones.

In 30 healthy humans studied with infusion of 100 ng/kg body weight (BW) · min for 60 minutes of each of the respective peptides, LANP decreased the circulating concentrations of vessel dilator and ANF 51% and 89%, respectively.[3] Vessel dilator decreased the circulating concentration of ANF by 55% and the peptides immunologically recognized by LANP radioimmunoassay (RIA) by 58%.[3] The antibodies to LANP in this assay recognize LANP (50%) and proANF (1 to 98), ie, N-terminus of the ANF prohormone (50%).[19] Kaliuretic peptide decreased the circulating concentration of ANF by 40%, vessel dilator by 31%, and the peptides recognized by the LANP RIA by 46%.[3] ANF decreased the circulating concentration of vessel dilator by 40% and the peptides recognized by LANP RIA by 38%.[3] Infusion of vessel dilator, LANP, kaliuretic peptide, and ANF also decreased the excretion of the other ANPs measured in the urine by 32% to 84%.[3] These data taken together indicate that each of the respective ANPs inhibits the release, rather than breakdown, of each other, as increased breakdown would have resulted in their urinary concentrations being increased.[3] This study further indicated that because proANF 1 to 98 was decreased in the circulation secondary to vessel dilator and kaliuretic peptide infusions, they inhibit their own release, as they are both derived from proANF 1 to 98, ie, the 98-aa N-terminus of the ANF prohormone.

Whether these cardiac peptide hormones have lost their negative feedback (ie, ability to decrease each other's release into the circulation) in persons with CHF has never been investigated. These cardiac peptide hormones are released from the heart with atrial stretch,[21] and the increased plasma volume in CHF appears to be the mechanism of these cardiac peptides' enhanced release into the circulation in CHF indivduals.[1,2] Vessel dilator, LANP, kaliuretic peptide, and ANF do have natriuretic and diuretic effects in persons with CHF.[7,22,23] The present investigation was designed to determine whether the infusion of vessel dilator, LANP, kaliuretic peptide, and/or ANF in CHF individuals decreases the release of each other by

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Submitted April 30, 2001; accepted November 14, 2001.

Supported in part by a Merit Review Grant from the United States Department of Veteran Affairs (to D.L.V.) and a grant-in-aid from the American Heart Association, Florida Affiliate (to D.L.V., D.D.S.).

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0026-0495/02/5105-0009$35.00/0

doi:10.1053/meta.2002.31983

measuring their circulating concentrations before, during, and for 3 hours after their infusion at their respective 100 ng/kg · BW · min concentrations for 60 minutes (ie, same concentration that was used in healthy individuals that demonstrated a negative feedback.[3])

SUBJECTS AND METHODS

Thirty men with clinically stable class III New York Heart Association congestive heart failure aged 33 to 75 years; average, 57 ± 6 years; all normotensive with blood pressures less than 125/80 mm Hg were studied. These subjects had heart rates ranging from 68 to 102 bpm, with respiration rates between 12 and 18 per minute. The volunteers were divided into 5 similar groups based upon age, weight, blood pressure, heart rate, and ejection fractions, which were as follows for each group: the means for the CHF controls were 58 ± 6 years, 88 ± 2 kg, 118/66 ± 6/6 mm Hg, 86 ± 4 bpm, and 25% ± 3%. The vessel dilator CHF group averages were 60 ± 6 years, 85 ± 5 kg, 119/69 ± 8/6 mm Hg, 81 ± 8 bpm, and 19% ± 6%. The LANP patients with CHF means were 54 ± 6 years, 91 ± 5 kg, 126/75 ± 9/4 mm Hg, 75 ± 5 bpm, and 23% ± 3%. The kaliuretic peptide CHF group averaged 56 ± 4 years, 93 ± 4 kg, 118/71 ± 4/2 mm Hg, 75 ± 4 bpm, and 30% ± 3%. The ANF group of patients with CHF averaged 58 ± 6 years, 82 ± 2 kg, 124/72 ± 6/3 mm Hg, 73 ± 5 bpm, and 26% ± 4%. These parameters were not statistically different between the groups. Subjectively, all patients had a history of heart failure, including 1 or more of the following symptoms: dyspnea on mild exertion, paroxysmal nocturnal dyspnea, ankle swelling, or effort-related fatigue. Objectively, chronic left ventricular systolic dysfunction and dilation were documented by cardiac catheterization, echocardiography, and/or radionuclide angiography. Each subject had a left ventricular ejection fraction of 30% or less. Patients with a myocardial infarction within the preceding 6 months were excluded. The underlying cause of the CHF was ischemic for all the subjects except for control subject 4, in whom the cause was idiopathic. Each subject had class III New York Heart Association CHF for at least 6 months (range, 6 months to 3 years). All of the subjects in this study were in normal sinus rhythm with heart rates of ≤ 102 bpm. None of the patients had primary valvular disease.

Subjects with a creatinine level greater than 1.5 mg/dL were excluded because ANF, vessel dilator, and LANP increase in the circulation of humans with kidney failure.[13,24] LANP and vessel dilator increase in the circulation of persons with ascites,[25] therefore, the subjects with ascites were excluded from the current study. None of the patients' prescribed medications were taken the day of the study or for 12 hours before the study. All over-the-counter medications were stopped at least 24 hours before the study. Specifically, nonsteroidal anti-inflammatory agents, including aspirin, were stopped 24 hours before the study because part of vessel dilator, kaliuretic peptide, and LANP's natriuretic effects work by increasing the synthesis of prostaglandin E_2, which in turn, inhibits Na^+-K^+-adenosine triphosphatase (ATPase) in the kidney.[26,27] Nonsteroidal agents block this effect in vitro[26,27] and in vivo.[7]

Each of the subjects was receiving digoxin, an angiotensin-converting enzyme inhibitor, a vasodilator, and a diuretic. Informed consent was obtained from each of the volunteers after the nature and possible consequences of the studies were fully explained. This study was approved by the Institutional Review Board of the University of South Florida Health Sciences Center and the Research Committee of the James A. Haley Veterans Hospital. This study was also approved by the United States Food and Drug Administration (FDA IND No. 32,119). This investigation conforms with the principles outlined in the Declaration of Helsinki for investigation involving human subjects. Some of the CHF subjects in this investigation are the same subjects utilized previously in an investigation of potassium and sodium excretion following the administration of vessel dilator,[7] LANP,[22] and kaliuretic peptide.[23]

Experimental Protocol

The experimental protocol consisted of a 60-minute baseline period preceding any infusion. A total volume of 20 mL normal saline (0.9% sodium chloride, with or without peptide hormones) was infused by a constant-rate infusion pump over a 60-minute time period. Urine and blood samples were obtained every 20 minutes during the infusion and at 30-minute time intervals during the 1-hour baseline and 3-hour postinfusion time periods. The control subjects received vehicle only, but otherwise adhered to an identical protocol of a 1-hour equilibration period followed by a 1-hour infusion period with a 3-hour recovery period of evaluation. A total of 100 ng/kg · BW · min was chosen for the infusion dosage of the ANPs because the release rates of these cardiac peptides from dog hearts with physiologic stimuli is 138 to 292 ng/kg · BW · min.[28] The 100 ng/kg · BW · min concentration utilized in the present investigation is at the lower end of the amount of these peptides released per minute with physiologic stimuli. This is also the same concentration used in the study of negative feedback in healthy humans[3] enabling one to compare with healthy humans the data obtained in the CHF subjects. Further rationale for using the respective 0.1 μg concentrations of these peptides is that a 10-fold lower concentration, ie, 0.01 μg/kg · BW · min for 60 minutes does not consistently cause a natriuresis and diuresis (unpublished observation), and for the present investigation, we wanted to use a concentration of the peptide hormones that causes a biologic effect.

Each of the subjects ingested their usual diet until the evening before the study. All subjects were studied in the morning after an overnight fast, beginning their baseline period at 8 AM. Each volunteer was studied in the seated position. To maintain a similar plasma volume throughout the study, water was given orally in milliliters for each mL of urine output at the above time periods. Each volunteer received only 1 peptide infusion.

Purity of ANPs

The human forms of LANP, vessel dilator, and kaliuretic peptide were synthesized by Peninsula Laboratories (Belmont, CA). Before their use in these studies, samples of these commercially synthesized peptides were subjected to high-pressure liquid chromatography as described previously[1] to determine that they were pure.

Measurement of ANPs

Each of the blood and urine samples were collected into chilled 5-mL EDTA tubes to prevent proteolytic breakdown of any peptides that might be present. RIAs to measure peptides from the N-terminus of the ANF prohormone were devised to aa 1 to 30 (ie, LANP), aa 31 to 67 (ie, vessel dilator), and aa 79 to 98 (ie, kaliuretic peptide) of the 126-aa prohormone, whereas the C-terminal ANF prohormone assay measures aa 99 to 126 of the prohormone, ie, ANF, as described previously by our laboratory.[1] The interassay coefficient of variation for LANP, vessel dilator, kaliuretic peptide, and ANF RIAs were 4.8%, 5.3%, 5.5%, and 5.7%, respectively. The interassay coefficient(s) of variation were 8%, 8%, 7.6%, and 6.9%, respectively.

Statistical Analysis

All data are expressed as the mean ± SE. Statistical analysis was performed using 1-way analysis of variance (ANOVA) for comparisons with the same group and 2-way ANOVA for comparisons between groups with 1 repeated measure (repeated measurements over time) and 1 group factor. To be considered statistically significant, we required a probability value of $P < .05$ (95% confidence limits).

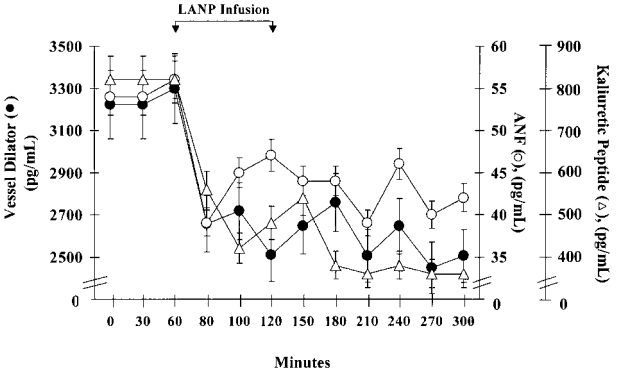

Fig 1. LANP decreases the circulating concentration of ANF (○), vessel dilator (●), and kaliuretic peptide (△). LANP infused intravenously at 100 ng/kg · BW · min for 60 minutes decreased the circulating concentrations of ANF ($P < .05$), kaliuretic peptide ($P < .05$), and vessel dilator ($P < .01$) during the infusion and 3 hours after ceasing the infusion when evaluated by ANOVA; n = 6 for each group.

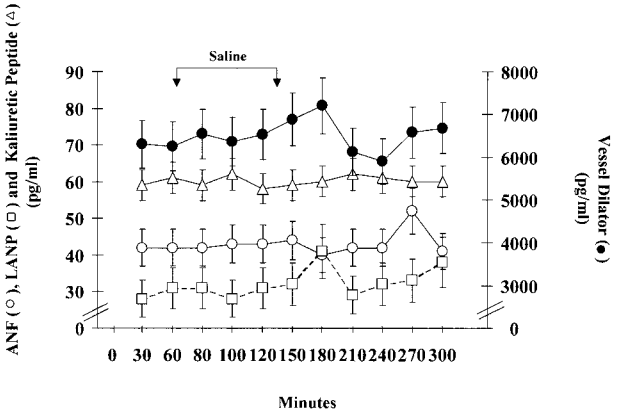

Fig 3. Effect of vehicle (0.9% saline) on the excretion of ANPs into urine. There was no significant enhancement or inhibition of the excretion of ANF (○), LANP (□), vessel dilator (●), or kaliuretic peptide (△) when evaluated by ANOVA; n = 6 for each group.

RESULTS

LANP Decreases the Circulating Concentration of Vessel Dilator, Kaliuretic Peptide, and ANF

Infusion of 100 ng of LANP/kg · BW · min for 60 minutes in persons with CHF decreased the circulating concentration of vessel dilator 24%, ANF 30%, and kaliuretic peptide 55%. These decreases in the circulating concentrations of vessel dilator, kaliuretic peptide, and ANF began within 20 minutes of beginning the LANP infusion with the time course illustrated in Fig 1. The circulating concentrations of vessel dilator, kaliuretic peptide, and ANF remained significantly ($P < .01$) decreased for 3 hours after stopping the LANP infusion (Fig 1). The amounts of ANF, kaliuretic peptide, and vessel dilator excreted into the urine were also decreased 13%, 40%, and 24%, respectively, secondary to LANP infusion (Fig 2). The excretion of vessel dilator and kaliuretic peptide remained significantly decreased ($P < .05$) for 3 hours after cessation of the LANP infusion (Fig 2). In the CHF control subjects who received vehicle (ie, 0.9% saline) infusions only, there was no significant change in the excretion of the respective peptides (Fig 3). Likewise, there was no significant change in the circulating concentration of these peptides with vehicle only. The urine volume of the CHF individuals before, during, and after their respective peptide and vehicle infusions is summarized in Table 1.

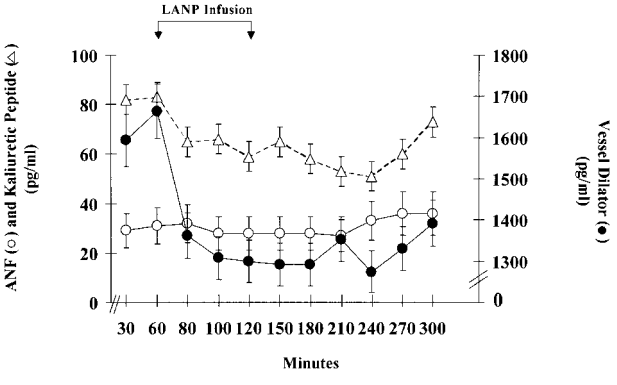

Fig 2. LANP decreases the excretion of ANF (○), vessel dilator (●), and kaliuretic peptide (△). The decrease in the excretion of the vessel dilator and kaliuretic peptide into urine secondary to LANP was significant ($P < .05$), while ANF's excretion was not significant when evaluated by ANOVA; n = 6 for each group.

Vessel Dilator Decreases the Circulating Concentrations of LANP, Kaliuretic Peptide, and ANF

Infusion of 100 ng of vessel dilator/kg · BW · min for 60 minutes decreased the circulating concentrations of ANF, LANP, and kaliuretic peptide 27%, 62%, and 12%, respectively (Fig 4). The infusion of vessel dilator also significantly decreased the excretion of ANF (50%; $P < .001$), LANP (42%; $P < .01$), and kaliuretic peptide (18%; $P < .05$) within urine (Fig 5).

Kaliuretic Peptide Decreases the Circulating Concentrations of ANF, LANP, and Vessel Dilator

Kaliuretic peptide (100 ng/kg · BW · min) infusion for 60 minutes decreased the circulating concentrations of ANF 67%, vessel dilator 70%, and LANP 89% (Fig 6). The decrease in the other ANPs in the circulation secondary to kaliuretic peptide continued to be significant ($P < .001$) throughout the 3-hour postinfusion period (Fig 6). Kaliuretic peptide also decreased the excretion of ANF (34% decrease), vessel dilator (60% decrease), and LANP (62% decrease) into the urine of these subjects (Fig 7).

ANF Decreases the Circulating Concentrations of LANP, Vessel Dilator, and Kaliuretic Peptide and Their Excretion Into Urine

ANF (100 ng/kg · BW · min for 60 minutes) decreased the circulating concentrations of vessel dilator (59% decrease), LANP (88% decrease), and kaliuretic peptide, 98% decrease (Fig 8). ANF also decreased the excretion into urine of vessel

Table 1. Vessel Dilator and Kaliuretic Peptide Enhance Urine Volume and Urine Flow Rate in Patients With CHF

	Infusion Time (min)				
	30	60	80	100	120
CHF control patients					
Mean ± SE	75 ± 34	62 ± 20	38 ± 10	33 ± 7	35 ± 6
V	2.3 ± 0.24	2.0 ± 0.33	1.91 ± 0.27	1.65 ± 0.31	1.75 ± 0.42
LANP					
Mean ± SE	68 ± 18	43 ± 10	36 ± 10	25 ± 13	55 ± 13
V	2.27 ± 0.60	1.43 ± 0.33	1.80 ± 0.50	1.25 ± 0.65	2.75 ± 0.65
Vessel dilator					
Mean ± SE	60 ± 12	51 ± 9	83 ± 13*	75 ± 8*	179 ± 56*
V	2.0 ± 0.40	1.70 ± 0.30	4.15 ± 0.65	3.75 ± 0.40	8.95 ± 2.8
Kaliuretic peptide					
Mean ± SE	31 ± 5	22 ± 5	53 ± 25*	27 ± 6	32 ± 9*
V	1.03 ± 0.17	0.7 ± 0.17	2.65 ± 1.25	1.35 ± 0.3	1.60 ± 0.45
ANF					
Mean ± SE	96 ± 13	35 ± 22	22 ± 14	24 ± 14	18 ± 21
V	3.20 ± 0.43	1.17 ± 0.73	1.10 ± 0.70	1.20 ± 0.70	0.9 ± 1.05

NOTE. Values for urine volume are in milliliters; values for urine flow rate (V) are in milliliters of urine per minute. The 1-hour baseline was used to ensure that each subject was at their baseline. The 60-minute time period is thus the control time period for comparison of any increase in urine volume. Enhancement of urine volume by vessel dilator and kaliuretic peptide was significant (*) at $P < .01$; enhancement of urine flow rate of each time point was significant at $P < .05$; LANP enhanced urine flow rate only between 120 to 210 minutes at $P < .05$ when evaluated by 1-way analysis of variance. ANF did not cause a significant increase in urine volume or flow rate in these CHF subjects. These urine volume and flow rates are a summary of data previously published[7,22,23] (n = 6 for each group).

dilator 92%, kaliuretic peptide 50%, and LANP 22% (Fig 9). The decrease in the excretion of the other ANPs in urine secondary to ANF continued to be significant ($P < .05$) for 3 hours post-ANF infusion. During their respective infusions, the concentration of infused peptides increased 2.6-fold to 3.8-fold. Thus, ANF increased 3.3-fold, LANP 3.8-fold, vessel dilator 3.6-fold, and kaliuretic peptide 2.6-fold during their respective infusions ($P < .01$) (Fig 10).

DISCUSSION

Infusion of ANF into human subjects with CHF decreased the circulating concentration of vessel dilator, kaliuretic peptide, and the N-terminal ANF prohormone peptides recognized by the LANP RIA. ANF also decreased the excretion of these peptides into the urine of these CHF volunteers. These data taken together suggest that the decreased concentration of ANPs observed in the circulation secondary to ANF infusion was due to their decreased release into the circulation rather than to their increased excretion (ie, breakdown), which would have resulted in their concentrations being increased in urine. One other theoretical interpretation of the data is that ANF caused the other ANF prohormone-derived peptides to be taken up by the ANF clearance receptor, resulting in a decrease in their plasma concentrations. This possibility is ruled out by the fact that the peptides derived from the N-terminus of the ANF prohormone are linear peptides and are not cleared by the

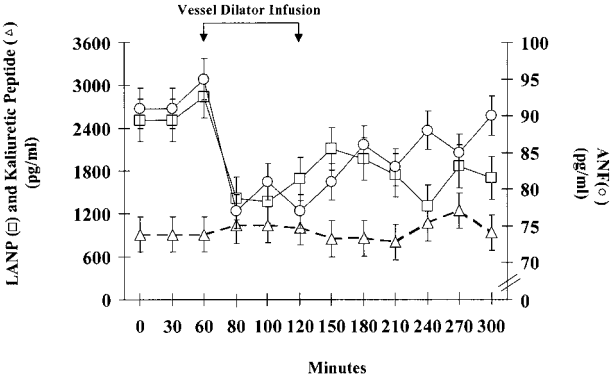

Fig 4. Vessel dilator infusion (100 ng/kg · BW · min) for 60 minutes decreases the concentrations of ANF (○), kaliuretic peptide (△), and LANP (□). The decrease in ANF was significant at $P < .05$, while the decrease in LANP was significant at $P < .001$ during the infusion of vessel dilator and for 3 hours after ceasing this infusion when evaluated by ANOVA. The decrease in kaliuretic peptide did not reach statistical significance when evaluated by ANOVA; n = 6 for each group.

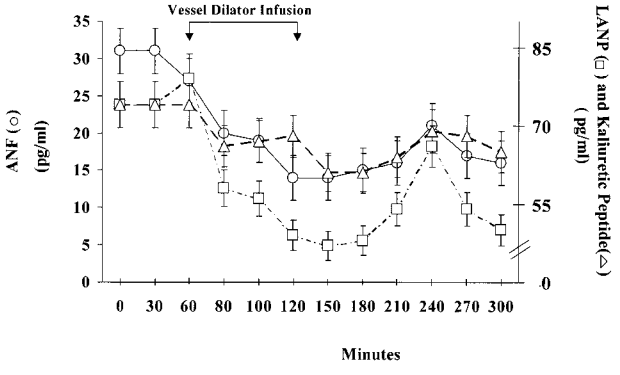

Fig 5. Vessel dilator decreases the excretion of ANF (○), kaliuretic peptide (△), and LANP (□). The decrease in the excretion of ANF and LANP by vessel dilator was significant at $P < .001$ and $P < .01$, while kaliuretic peptide's decrease was significant at $P < .05$ when evaluated by ANOVA; n = 6 for each group.

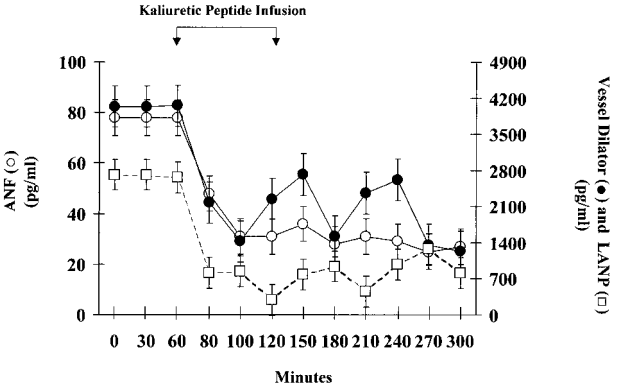

Fig 6. Kaliuretic peptide infusion (100 ng/kg · BW · min for 60 minutes) significantly ($P < .001$) decreases the circulating concentrations of ANF (○), vessel dilator (●), and LANP (□) during the kaliuretic peptide infusion and for 3 hours after ceasing the infusion when evaluated by ANOVA; n = 6 for each group.

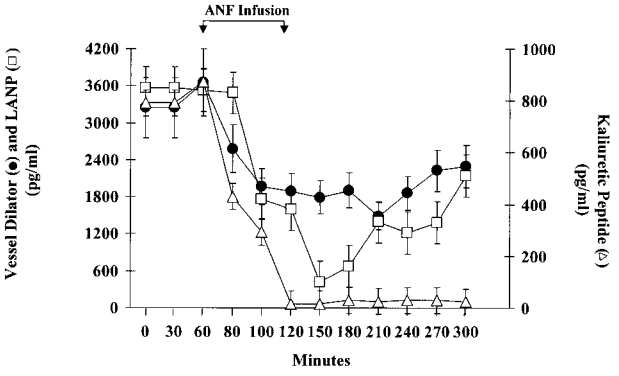

Fig 8. ANF (100 ng/kg · BW · min) for 60 minutes significantly ($P < .001$) decreases the circulating concentrations of vessel dilator (●), kaliuretic peptide (△), and LANP (○) during its infusion and for 90 minutes after ceasing the infusion when evaluated by ANOVA; n = 6 for each group.

clearance receptor (which has affinity only for peptides with a ring structure).[4,29,30] There is also no evidence to suggest that there are specific clearance receptors for each of the different peptides derived from the N-terminus of the ANF prohormone.[4]

Vessel dilator, LANP, and kaliuretic peptide, likewise, all decreased the concentration of ANF in the circulation and its excretion into the urine of the CHF volunteers. These findings suggest that peptides from the N-terminus of the ANF prohormone, whether derived from the amino-terminus (LANP), middle (vessel dilator), or its carboxy-terminus (kaliuretic peptide) of the N-terminus of this prohormone each inhibit the release, rather than the breakdown, of ANF as their mechanism of action of producing a decreased circulating concentration of ANF in persons with CHF.

The peptides derived from the N-terminus of the ANF prohormone (ie, vessel dilator, LANP, and kaliuretic peptide) were also found to inhibit the release of each other in this investigation, suggesting a very intricate set of checks and balances for the release of these peptides dependent upon the circulating concentration of each in persons with CHF. An increase in the circulation of 1 of the peptides from the N-terminus of the ANF prohormone caused their own release into the circulation to be decreased. The ability to inhibit their own release was demonstrated by the ability of vessel dilator, LANP, and kaliuretic peptide to decrease the release of proANF 1 to 98 into the circulation. LANP, vessel dilator, and kaliuretic peptide are derived from proANF 1 to 98 within the circulation,[1,19,20] and their ability to decrease the release of the larger polypeptide from which they are derived indicates that they are, in effect, inhibiting their own release. The ability of these ANPs to inhibit their own release, the release of proANF 1 to 98, and the release of ANF suggests that they are inhibiting all of the peptides that constitute the ANF prohormone. This series of observations suggests that the prohormone itself may be the target of the inhibition by the respective peptides derived from this prohormone.

In the present investigation, the amount of negative feedback of the respective peptides in persons with CHF was similar to

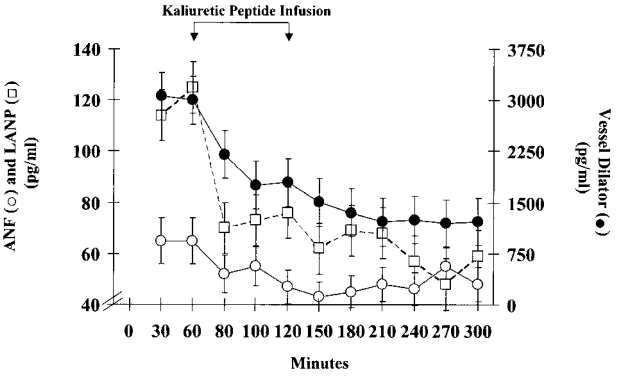

Fig 7. Kaliuretic peptide decreases the excretion rate of ANF (○; $P < .05$), vessel dilator (●; $P < .001$), and LANP (□; $P < .001$) when evaluated by ANOVA; n = 6 for each group.

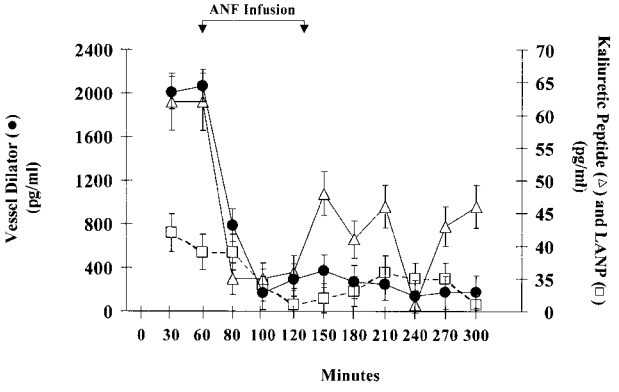

Fig 9. ANF decreases the excretion rate of vessel dilator (●), LANP (□), and kaliuretic peptide (△). The decrease in vessel dilator was significant at $P < .001$ during and for 3 hours postinfusion, while the decrease in LANP and kaliuretic peptide during this time period was significant at $P < .05$ when evaluated by ANOVA; n = 6 for each group.

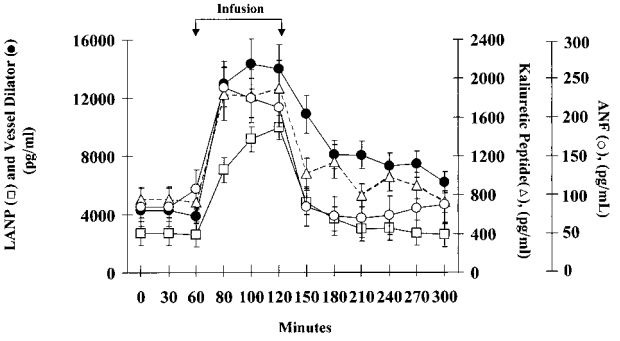

Fig 10. Increase of the respective ANPs in the circulation during their own infusion of 100 ng/kg · BW · min for 60 minutes. LANP (□) and ANF (○) decreased to baseline within 2 hours and 30 minutes, respectively, of stopping their infusions, whereas kaliuretic peptide (△) and vessel dilator (●) were still significantly ($P < .01$) increased 2½ and 3 hours after stopping their infusions, when evaluated by ANOVA. Infusion of vehicle only (ie, 20 mL normal saline) did not cause the circulating concentration of any of these peptides to increase; n = 6 for each group.

that found previously in healthy adults.[3] The data of the present investigation, thus, suggest that the negative feedback system of these cardiac hormones is intact in persons with heart failure. The ability of a hormone to feedback on the gland or tissue from which it is released to inhibit its own release (ie, negative feedback) is a well-recognized method of fine tuning secretion in endocrine physiology.[31] The present investigation indicates that ANPs (ANF, LANP, vessel dilator, and kaliuretic peptide) also have this property, and that this ability remains intact when CHF is present.

The increase in ANPs within the circulation in persons with CHF[1,2] is, thus, not due to lack of negative feedback. Rather, the increase of these cardiac peptides in the circulation in CHF appears to be a response of these natriuretic and diuretic peptides trying to overcome the sodium and water retention that is present in CHF. Evidence for this observation derives from the fact that these cardiac peptides increase proportionately in the circulation in direct relationship to the severity of CHF.[1,2] Although increased in the circulation, 2 of these peptide hormones, ie, ANF[23,32] and LANP,[22] have blunted effects in CHF, which may be due to downregulation of their receptors. These cardiac peptide hormones are released from the heart with atrial stretch,[21] and the increased plasma volume in CHF appears to be the mechanism of these cardiac peptides' enhanced release into the circulation in persons with CHF.[1,2]

In isolated hearts, one only has to increase pressure in the atria 7 mm Hg to cause release of these peptide hormones.[21] A decrease or increase in pressure within the atria is 1 of the main regulators of release of these peptides.[21] Vessel dilator[7] and ANF[4] have both been shown to decrease preload (via decreasing blood volume) and afterload (via decreasing systemic vascular resistance) of heart. Thus, a decrease in filling pressures secondary to the respective ANPs may be an important mechanism mediating their ability to decrease their own and each other's concentrations within the circulation.

ACKNOWLEDGMENT

We thank Charlene Pennington and Rose M. Overton for excellent secretarial and technical assistance, respectively. We thank Drs Mohammed Baig, Ali Nasser, Hamang Patel, and Nadim Khan for their assistance with identifying the CHF subjects and for their assistance with the cardiac peptide infusions.

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