Combined Treatment with Vessel Dilator and Kaliuretic Hormone in Persons with Congestive Heart Failure

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Vessel dilator and kaliuretic hormone, two cardiovascular peptide hormones, enhance urine flow 2- to 13-fold and 4-fold, respectively, in persons with class III New York Heart Association congestive heart failure (CHF). The natriuresis and diuresis secondary to vessel dilator and kaliuretic hormone are not blunted as are atrial natriuretic peptide and brain natriuretic peptide effects in persons with CHF compared with healthy individuals. The present investigation determined if the two peptide hormones that do not have blunted effects in persons with CHF may have added beneficial effects when given simultaneously to individuals with class III CHF. Together with each at 100 ng/kg of body weight per minute, vessel dilator and kaliuretic hormone increased urine flow rate 3.5-fold ($P < 0.05$) compared with their 60-min baseline and control CHF subjects' urine flow rates. Combined, they enhanced the excretion rate of sodium a maximum of 3.6-fold ($P < 0.05$) with 2.5- and 2-fold enhancement 2 and 3 hrs after infusion. These data indicate that vessel dilator and kaliuretic hormone have diuretic and natriuretic effects when used in combination, but these effects are not additive over their individual effects in persons with CHF. Exp Biol Med 229:521-527, 2004

Key words: congestive heart failure; atrial natriuretic peptides; treatment; diuresis; natriuresis

This work was supported in part by Grants-in-Aid from the American Heart Association, Florida/Puerto Rico Affiliate, St. Petersburg, Florida (J.R.D., D.D.S., D.L.V.), National Institutes of Health Grant, Bethesda, Maryland (J.R.D., D.L.V.), and a Merit Award from the Department of Veterans Affairs, Washington, DC (D.L.V.).

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Received December 23, 2003.
Accepted March 4, 2004.

1535-3702/04/2296-0001$15.00

Introduction

Vessel dilator and kaliuretic hormone, consisting of amino acids 31–67 and 79–98, respectively, of the 126-amino acid atrial natriuretic peptide (ANP) prohormone are hormones synthesized primarily within the heart (1, 2). Having more than one peptide hormone synthesized by the same gene and stored within the same prohormone for release is common with respect to peptide hormones (1, 2). In congestive heart failure (CHF), both vessel dilator and kaliuretic hormone increase in the circulation in an apparent adaptive response to overcome the sodium and water retention that characterizes CHF (3–5). These peptide hormones enhance sodium and/or water excretion in animals (6–8) and healthy humans (9). We have found that vessel dilator enhances urine flow 2- to 13-fold and sodium excretion 3-fold in persons with New York Heart Association (NYHA) class III CHF (10). Kaliuretic hormone increases urine flow 4-fold and sodium excretion 3-fold in persons with CHF (11). The natriuresis and diuresis secondary to vessel dilator and kaliuretic hormone are not blunted in persons with CHF compared with healthy individuals (10, 11). Other cardiac peptide hormones, such as ANP (11,12), long-acting natriuretic peptide (13), and brain natriuretic peptide (14–16), on the other hand, have blunted natriuretic and diuretic effects in persons with CHF compared with healthy humans. The observation that vessel dilator and ANP have additive effects in healthy monkeys (17) forms the rationale of the present investigation. The current study was designed to determine if the two cardiac hormones that do not have blunted effects when given separately to persons with CHF (i.e., vessel dilator and kaliuretic hormone) might have additive or even synergistic effects when given simultaneously to patients with CHF.

Materials and Methods

CHF Volunteers. Twelve men (aged 35 to 80 years; average age, 57 ± 6 years) at the James A. Haley Veterans Medical Center (Tampa, FL) with compensated CHF were

Table 1. Characteristics of CHF Patients Receiving Vessel Dilator Plus Kaliuretic Hormone[a]

Patient No.	Age (years)	Weight (kg)	Blood pressure (mm Hg)	Heart Rate (bpm)	Na^+ (m*M*/l)	K^+ (m*M*/l)	EF (%)
Vessel dilator and kaliuretic hormone							
1	51	75.0	122/60	85	141	4.3	20
2	40	81.4	97/68	87	133	4.7	15
3	61	77.3	117/59	60	137	4.0	40
4	58	109.0	116/72	74	136	4.2	25
5	49	90.9	130/78	76	134	3.8	15
6	80	118.0	126/52	70	141	4.8	25
Mean ± SEM	57 ± 6	92±7	118/65 ± 5/4	75 ± 4	137 ± 1	4.3 ± 0.2	23 ± 4
CHF controls							
1	70	89.1	116/76	96	131	3.9	38
2	63	79.6	101/57	80	134	4.1	15
3	42	95.5	125/71	88	133	4.6	23
4	35	84.0	144/90	98	137	4.8	20
5	75	84.0	117/54	83	136	4.7	26
6	64	93.2	107/50	72	137	4.5	28
Mean ± SEM	58 ± 7	88 ± 2	118/66 ± 6/6	86 ± 4	135 ± 1	4.4 ± 0.1	25 ± 3

[a] There was no significant difference in age, weight, blood pressure, heart rate, sodium, potassium, or medications between the two CHF groups when evaluated by within-group, repeated-measures of analysis of variance. CHF, congestive heart failure; EF, ejection fraction; bpm, beats per minute.

studied. These volunteers were divided into 2 similar groups; their ages, weights, blood pressures, and heart rates are given in Table 1. All patients had chronic left ventricular systolic dysfunction and dilatation documented by cardiac catheterization, echocardiography, and/or radionuclide angiography. The left ventricular ejection fraction of each subject is listed in Table 1. Each subject had NYHA class III CHF for at least 6 months (range, 6–36 months). Exclusion criteria included anyone with a creatinine level above 1.5 mg/dl, because these cardiac hormones increase in the circulation of persons with renal failure (18, 19). Also excluded was anyone with cirrhosis and ascites, because these peptide hormones also increase in their circulation in this disease state (20, 21). Patients' prescribed medications were not taken the day of the study. All of the CHF patients were using diuretics but stopped taking them the night before the study. The use of nonsteroidals, including aspirin, were stopped 24 hrs before the study, because part of the beneficial natriuretic effects of kaliuretic hormone and vessel dilator is via stimulation of the synthesis of prostaglandin E_2, which, in turn, inhibits Na^+-K^+-ATPase in the kidney (7, 22). Nonsteroidals block this effect (7, 22). Each patient was receiving digoxin and an angiotensin-converting enzyme inhibitor. All of the patients were also receiving a vasodilator except for experimental patient 2 (Table 1), who could not tolerate any of the vasodilators. The use of all of these medications was stopped for at least 12 hrs before the study.

This investigation was conducted in accordance with the guidelines in the Declaration of Helsinki. Informed consent was obtained from each volunteer 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, the Research Committee of the James A. Haley Veterans Medical Center, and by the U.S. Food and Drug Administration (FDA IND No. 32,119). The control CHF subjects in the present study were used in a previous study of the evaluation of vessel dilator used alone in subjects with CHF (10) Details regarding the present study population are outlined in Table 1.

Experimental Protocol. An Insyte-w, 20-gauge, 1.5-in. catheter (Becton Dickinson Infusion Therapy Systems, Inc., Sandy, UT) was placed in one forearm of each subject for infusion, and an identical catheter was placed in the opposite forearm of each subject for blood sampling. A 60-min baseline period preceded any infusion. A total volume of 20 ml of normal saline (0.9% sodium chloride), with or without (i.e., control subjects) kaliuretic hormone and vessel dilator, was infused by a constant-rate infusion pump for a 60-min period. Urine volume was measured with graduated cylinders. A total of 100 ng/kg of body weight per minute was chosen for the infusion dosage of kaliuretic hormone and vessel dilator, because this infusion dose is identical to the dose of vessel dilator (10) and kaliuretic hormone (11) used, respectively, in our previous nonadditive studies. Before using these peptides at this concentration, we performed dose-response curves at 5-fold and 10-fold lower doses and found that in persons with CHF the 5-fold and 10-fold reduction of vessel dilator had no consistent significant natriuretic and/or diuretic effects (data not shown).

All subjects were studied in the morning after an overnight fast, beginning their baseline period at 0800 hr. After completion of the 60-min baseline period, to maintain a similar plasma volume throughout the study, water was given orally in milliliters for each milliliter of urine output.

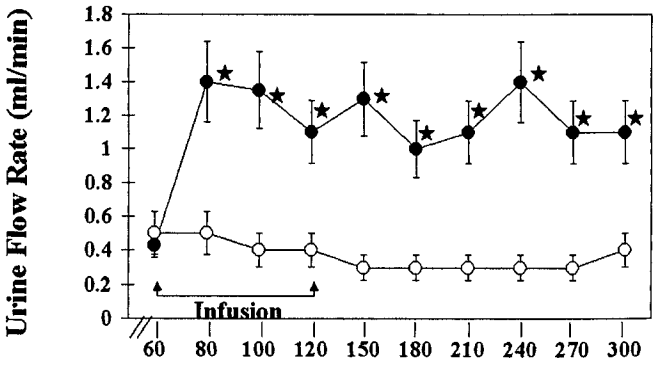

Figure 1. Enhancement of urine flow rate in milliliters of urine per minute by vessel dilator and kaliuretic hormone (•). The enhancement of urine flow rate by vessel dilator and kaliuretic hormone at their 100-ng/kg of body weight concentrations for 60 mins became significant at $P < 0.05$ (★) in the first 20 mins of the infusion (i.e., at 80 mins on this graph) compared with their 60-min baseline point and with the control congestive heart failure subjects (○) who received vehicle only when evaluated by within-group, repeated-measures analysis of variance ($n = 6$ in each group).

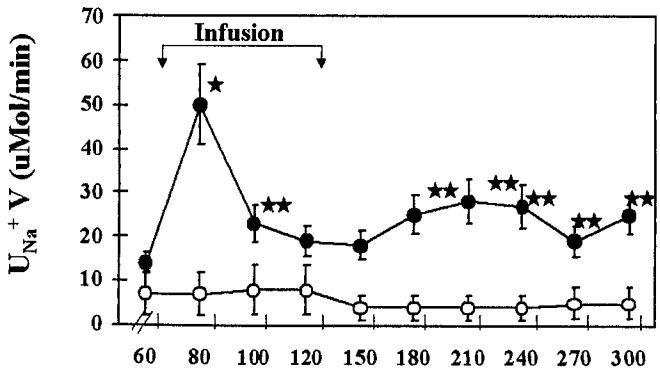

Figure 2. Vessel dilator and kaliuretic hormone at their 100-ng/kg of body weight concentrations (•) for 60 mins enhance the sodium excretion rate 3.6-fold ($P < 0.01$) (★) during the first 20 mins of their infusion in persons with congestive heart failure (CHF). Other points during the infusion and up to 3 hrs after infusion of these two peptide hormones where sodium excretion rates were significant by at least $P < 0.05$ are marked by . This significance is compared with both their 60-min baseline point and the control CHF subjects (○) who received vehicle only when evaluated by within-group, repeated-measures analysis of variance ($n = 6$ for each group).

Each volunteer received only one vehicle or kaliuretic peptide and vessel dilator infusion.

Purity of Kaliuretic Hormone and Vessel Dilator. The human forms of kaliuretic hormone and vessel dilator were synthesized by Peninsula Laboratories (Belmont, CA). Before their use in these studies, samples of these commercially synthesized peptides were subjected to high-performance liquid chromatography to verify purity and authenticity by use of a Novapak C_{18} (5-μm) cartridge column (Waters Chromatomography Division, Millipore Corporation, Milford, MA) as described in detail previously (3).

Measurement of Sodium, Potassium, Creatinine, and Osmolality. Sodium and potassium concentrations in the study were measured by flame photometry (Model 943; Instrumentation Laboratories, Lexington, MA). Osmolality was measured by freezing point depression (Micro-Osmette 5004; Precision Systems, Inc., Sadbury, MA). Urine Na^+ and K^+ excretion rates were calculated as follows: electrolyte (Na^+ or K^+) measured at specific time points by flame photometry × liters of urine output divided by minutes between samples × 1000 = μEq/Na^+ or K^+/min.

Urine Flow Rate. Urine flow rate was calculated from the volume of urine produced (in milliliters) divided by the number of minutes (20 or 30 mins) for the subject to produce the specific amount of urine measured.

Statistical Analysis. Data obtained in this investigation are given as mean ± SD. Differences were evaluated by repeated-measures analysis of variance within groups. To be considered statistically significant, we required a probability value <0.05.

Results

The combination of vessel dilator and kaliuretic hormone increased urine volume 2-fold ($P < 0.05$) and urine flow rate 3.5-fold ($P < 0.05$; Fig. 1) within 20 mins of beginning their simultaneous infusions. All of the patients with CHF except one (No. 3) had a diuretic response to the combination of vessel dilator and kaliuretic hormone, with the maximal diuresis (3-fold increase) occurring 30 mins and 2 hrs after stopping their infusion. Three hours after

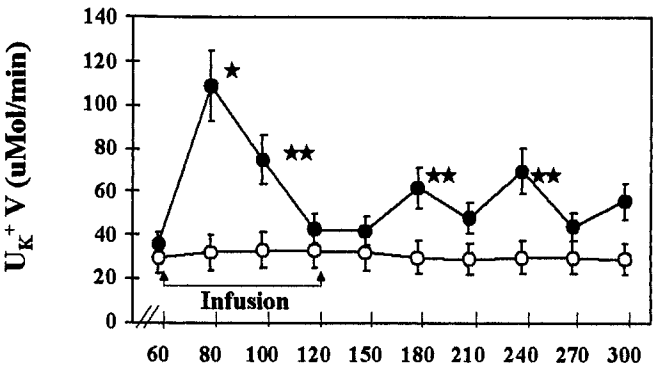

Figure 3. Enhancement of potassium excretion rate with infusion of vessel dilator and kaliuretic hormone (•). The first peak in potassium excretion (3-fold; $P < 0.02$, ★) occurred within 20 mins of beginning the combined infusion of vessel dilator and kaliuretic hormone at their 100-ng/kg of body weight concentration for 60 mins, with the next highest peak (2-fold; $P < 0.05$) occurring 1 hr after cessation of their infusion compared with their 60-min baseline point and the control congestive heart failure subjects (○) who received vehicle only when evaluated by within-group, repeated-measures analysis of variance ($n = 6$ for each group). Each period where there was a significance of at least $P < 0.05$ is marked.

Table 2. No Significant Change in Serum Electrolytes with Combined Vessel Dilator Plus Kaliuretic Hormone from Baseline (60 mins) and End of Infusion (120 mins) and at 1, 2, and 3 hrs After Infusion[a]

Patient No.	60 mins	120 mins	180 mins	240 mins	300 mins
Serum sodium (m*M*/l)					
Vessel dilator and kaliuretic hormone					
1	141	144	142	142	138
2	133	131	135	132	130
3	137	136	138	136	136
4	136	138	138	138	138
5	134	132	133	132	133
6	141	142	143	141	140
Mean ± SEM	137 ± 1	137 ± 2	138 ± 2	137 ± 2	136 ± 2
CHF controls					
1	131	132	132	131	132
2	134	134	135	138	135
3	133	134	134	134	135
4	137	139	137	135	136
5	136	136	136	136	136
6	137	136	136	136	135
Mean ± SEM	135 ± 1	135 ± 1	135 ± 1	135 ± 1	135 ± 1
Serum potassium (m*M*/l)					
Vessel dilator and kaliuretic hormone					
1	4.3	4.4	4.5	4.6	4.5
2	4.7	4.9	4.6	4.5	4.5
3	4.0	4.2	4.3	4.4	4.0
4	4.2	3.5	3.3	3.3	3.5
5	3.8	3.8	3.9	3.9	3.9
6	4.8	4.5	4.2	4.2	4.2
Mean ± SEM	4.3 ± 0.2	4.2 ± 0.2	4.1 ± 0.2	4.2 ± 0.2	4.1 ± 0.2
CHF controls					
1	3.9	4.0	4.1	4.0	3.9
2	4.1	4.1	4.0	3.8	3.7
3	4.6	4.2	4.2	4.0	4.2
4	4.8	5.1	5.1	4.7	4.8
5	4.7	4.2	4.2	4.1	4.0
6	4.5	4.4	4.2	4.1	4.2
Mean ± SEM	4.4 ± 0.1	4.3 ± 0.2	4.3 ± 0.2	4.1 ± 0.1	4.1 ± 0.2

[a] There was no significant difference in serum sodium or serum potassium between the two CHF groups or in individual subjects at different time points when evaluated by within-group, repeated-measures analysis of variance. CHF, congestive heart failure.

cessation of their infusion, urine volume and urine flow (Fig. 1) were still 2.5-fold greater than these subjects' baseline urine volume and urine flow rates. The net cumulative change in urine flow (i.e., change using the 60-min urine collection as a control) was –219 ml for the control CHF group during the experimental period (60–300 mins) and a 169-ml increase ($P < 0.01$) in urine flow with the combination of vessel dilator and kaliuretic hormone during this same period. Vessel dilator plus kaliuretic hormone enhanced sodium excretion rate 3.6-fold ($P < 0.04$) during the first 20 mins of their infusion (Fig. 2). The maximal excretion rate of sodium occurred during the first 20 mins of their infusion. The sodium excretion rate, however, was still increased 2.5-fold ($P = 0.024$) 90 mins after infusion and 2-fold 3 hrs after infusion in these CHF individuals (Fig. 2). The net cumulative change in sodium excretion was an increased excretion of 108 μ*M* with vessel dilator and kaliuretic hormone compared with a decrease of 871 μ*M* in the control CHF subjects in the experimental period (60–300 mins) ($P < 0.01$).

The potassium excretion rate increased 3-fold from 36–109 μ*M*/min ($P < 0.02$) within 20 mins of starting the combined vessel dilator and kaliuretic hormone infusion (Fig. 3). There was a second peak (2-fold increase, $P < 0.03$) 2 hrs after stopping the combined vessel dilator and kaliuretic hormone infusion (Fig. 3). The net cumulative positive change in potassium excretion was a 219-μ*M* increase with vessel dilator and kaliuretic hormone compared with a 31-μ*M* decrease in the control CHF subjects ($P < 0.01$) during the experimental period (60–300 mins). Serum sodium and potassium never varied by more than 4 or 1 m*M*/l, respectively (not significant), from their baseline values during the 5 hrs of this investigation in either the subjects who received vehicle only or those who received a combination of vessel dilator and kaliuretic hormone (Table 2).

The baseline urine flow, sodium, and potassium (i.e., immediately before beginning the respective infusion at the 60-min time point) of the CHF subjects in the two groups were not significantly different from each other (Figs. 1–3).

Table 3. No Significant Change in Hemodynamics with Combined Vessel Dilator Plus Kaliuretic Hormone from Baseline (60 mins) and End of Infusion (120 mins) and at 1, 2, and 3 hrs After Infusion[a]

Patient No.	60 mins	120 mins	180 mins	240 mins	300 mins
Blood pressure (mm Hg)					
Vessel dilator and kaliuretic hormone					
1	122/60	131/65	120/60	138/70	140/78
2	97/68	121/69	125/73	107/65	111/74
3	117/59	127/59	108/64	113/60	123/60
4	116/72	112/74	104/90	104/76	112/60
5	130/78	126/83	146/86	149/96	129/83
6	126/52	116/50	104/50	120/58	118/48
Mean ± SEM	118/65 ± 5/4	122/67 ± 3/5	118/70 ± 7/6	122/71 ± 7/6	122/67 ± 5/5
CHF controls					
1	116/76	110/76	113/61	121/64	120/61
2	101/57	101/63	89/55	84/50	87/48
3	125/71	134/68	122/64	126/66	113/61
4	144/90	160/90	161/90	158/90	161/90
5	117/54	124/53	115/54	93/47	85/49
6	107/50	105/53	106/46	107/46	114/52
Mean ± SEM	118/66 ± 6/6	122/67 ± 9/6	118/62 ± 10/6	115/61 ± 11/7	113/60 ± 11/6
Heart rate (bpm)					
Vessel dilator and kaliuretic hormone					
1	88	87	85	91	89
2	87	75	78	73	74
3	60	62	64	61	59
4	74	83	76	77	85
5	76	73	77	77	79
6	70	70	70	73	70
Mean ± SEM	76 ± 4	75 ± 4	75 ± 3	75 ± 4	76 ± 4
CHF controls					
1	96	96	105	103	96
2	80	81	80	80	80
3	88	91	95	96	97
4	98	97	96	89	97
5	83	80	71	80	73
6	72	68	67	68	72
Mean ± SEM	86 ± 4	86 ± 5	86 ± 6	86 ± 5	86 ± 5

[a] There was no significant difference in blood pressure or heart rate between the two CHF groups or individual subjects at different time points when evaluated by within-group, repeated-measures analysis of variance. CHF, congestive heart failure; bpm, beats per minute.

Likewise, the baseline urine flow, sodium, and potassium excretion of the subjects in the present investigation were not significantly different from these CHF subjects who received vessel dilator (10) or kaliuretic hormone (11) alone. There were no adverse effects with infusing kaliuretic hormone and vessel dilator together. There was no significant decrease in blood pressure in either the CHF volunteers who received the combination of vessel dilator and kaliuretic hormone or in the persons who received vehicle only (Table 3).

Discussion

In the present investigation, the combination of vessel dilator and kaliuretic hormone caused a 3.6-fold increase in the excretion rate of sodium in the CHF patients. The maximal enhancement of sodium excretion in the first 20 mins of the combined vessel dilator and kaliuretic hormone infusion in the present investigation is similar to what has been observed with kaliuretic hormone (3-fold; Ref. 11) and vessel dilator (2.5-fold; Ref. 10) when used alone at the same concentration in persons with CHF. The data of the present investigation indicate that adding these two cardiac hormones together does not cause an additive enhancement of the excretion rate of sodium in persons who have CHF over and above that caused by the individual hormones alone.

Vessel dilator and kaliuretic hormone when infused simultaneously increased urine volume and urinary flow rate in patients with CHF a maximum of 3-fold. This result is similar to the amount of enhancement of urine flow and urine volume observed when kaliuretic hormone is infused alone in CHF individuals (11). Vessel dilator also enhances urine flow to this extent in persons with CHF when used alone (10). Thus, combining these two cardiac hormones together in persons with CHF does not enhance urine flow over and above what each of these two peptide hormones produce individually.

When used in combination, vessel dilator and kaliuretic hormone enhanced the excretion rate of potassium 3-fold in persons with CHF. Most of this enhanced potassium

excretion is probably secondary to kaliuretic hormone, since vessel dilator does not significantly enhance potassium excretion in either healthy humans (9) or persons with CHF (10): The potassium excretion in the present investigation mirrored that of kaliuretic hormone when used alone at the same concentration in persons with CHF (11).

Why these two peptide hormones do not enhance the excretion rate of water, sodium, and potassium over and above their individual natriuretic effects in persons with CHF when added together may be related to their negative feedback properties (23, 24). In healthy individuals, kaliuretic hormone decreases the circulating concentration of vessel dilator by 31% and vessel dilator's excretion into urine by 32% (23). In persons with CHF, the negative feedback system of these peptide hormones is intact and enhanced (24). Kaliuretic hormone decreases the circulating concentration of vessel dilator by 70% in persons with CHF (24). Vessel dilator decreases the circulating concentration of kaliuretic hormone by 12% in persons with CHF (24). Vessel dilator decreases the excretion of kaliuretic hormone into urine by 18% in persons with CHF, whereas kaliuretic hormone decreases the excretion of vessel dilator into urine by 60% (24). These results suggest that these peptide hormones decrease the release of each other rather than enhancing their breakdown, which would have increased their urinary concentrations (23, 24). Since these peptide hormones are inhibiting each other's endogenous release (23, 24), their endogenous concentrations decrease in the circulation with a resultant decreased natriuresis.

Another contributing reason to why these peptide hormones are not additive is that they have the same (7, 22) and/or saturable mechanism(s) of action. The mechanism of vessel dilator and kaliuretic hormone's induced natriuresis is due to their known ability to inhibit Na^+-K^+-ATPase in the kidney, resulting in a decrease in reabsorption of sodium (7, 22). The reason why there were not additive effects in the present investigation, whereas in the previous investigation vessel dilator and ANP had additive effects in monkeys (17), probably relates to vessel dilator and kaliuretic hormone having the same mechanism of action that can become saturable. Vessel dilator and ANP (used together in the monkeys; Ref. 17) have different mechanisms of action (i.e., ANP does not mediate its effects via inhibiting Na^+-K^+-ATPase in the kidney as vessel dilator and kaliuretic hormone do; Refs. 7, 22). Thus, with ANP and vessel dilator having different mechanisms of action, their effects can be additive, whereas kaliuretic hormone and vessel dilator with the same mechanism of action can "saturate" this mechanism of action, which, in turn, does not allow them to be additive.

The previously demonstrated ability of these peptide hormones to increase the excretion of sodium and filtration fraction of sodium without increasing creatinine clearance suggests that these cardiac hormones' inhibition of reabsorption of sodium is in the distal tubules of persons with CHF (10, 11). Kaliuretic hormone also inhibits aldosterone secretion, whose biologic effects are in the distal tubule, for at least 3 hrs in humans (25). This time course of the decrease in aldosterone correlates directly with the time at which the natriuresis occurred secondary to kaliuretic hormone and vessel dilator together in the present investigation. Vessel dilator, on the other hand, does not appear to have direct effects on aldosterone synthesis, but vessel dilator is a very potent inhibitor of plasma renin activity, decreasing basal activity 66% (26).

In summary, two cardiac hormones (i.e., vessel dilator and kaliuretic hormone) when used together have natriuretic, diuretic, and kaliuretic effects in persons with CHF. Their enhanced excretion rates of sodium and potassium and diuretic effects were not, however, additive over and above their individual effects.

We thank Charlene Pennington for excellent secretarial assistance and Dionne Y. Scott, M.S., Carol S. Landon, B.S., and Imran Hassan, M.D., for excellent technical assistance. We thank David Zaritt, PharmD., and Reinaldo Mercado, B.S., M.S., of Pharmacy Service for their help in the preparation of these peptides for human infusions.

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