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Cardiovascular and renal effects of conivaptan hydrochloride (YM087), a vasopressin V_{1A} and V_2 receptor antagonist, in dogs with pacing-induced congestive heart failure

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Abstract

The systemic hemodynamic and renal responses to conivaptan hydrochloride (YM087; 4′-(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzoazepine-6-carbonyl)-2-phenylbenzanilide monohydrochloride), a vasopressin V_{1A} and V_2 receptor antagonist, were determined in pentobarbital-anesthetized dogs after 2 to 3 weeks of rapid right ventricular pacing. Congestive heart failure, characterized by decreases in first derivative of left ventricular pressure (left ventricular dP/dt_{max}) and cardiac output, and increases in left ventricular end-diastolic pressure and total peripheral vascular resistance, was induced by chronic rapid right ventricular pacing at 260–280 beats/min. Intravenous administration of conivaptan (0.1 mg/kg) significantly increased left ventricular dP/dt_{max} and cardiac output and significantly decreased left ventricular end-diastolic pressure and total peripheral vascular resistance. Conivaptan also increased urine flow and reduced urine osmolality by markedly increasing free water clearance. These results indicate that conivaptan produced hemodynamic improvement and marked aquaresis in dogs with congestive heart failure. Therefore, conivaptan may find clinical use in treating patients with congestive heart failure.

Keywords: Conivaptan hydrochloride; Congestive heart failure; Vasopressin receptor antagonist, non-peptide; Vasoconstriction; Water retention

1. Introduction

Traditionally, chronic heart failure has been regarded as a disorder in which the ventricles fail to pump adequate quantities of blood for the needs of peripheral organs. However, heart failure is now thought of as a disorder of the total circulatory system, not merely a disease of the heart (Packer, 1992a). A number of neurohormonal mechanisms such as the sympathetic nervous system, the renin–angiotensin system and vasopressin, are activated to compensate for an impaired cardiac function. These neurohumoral mechanisms act to maintain blood flow to vital organs by peripheral vasoconstriction, as well as to increase preload and maintain cardiac output by promoting renal sodium and water retention. Ultimately, these compensatory mechanisms fail, due to physiological adaptation, leading to a vicious cycle of compensation and adaptation, terminating in congestive heart failure (Francis, 1988; Parmley, 1989). Drugs which antagonize the actions of these neurohormonal factors and block this vicious cycle offer a promising approach to the treatment of heart failure (Cohn, 1988; Packer, 1989, 1992b; Yatsu et al., 1998).

The neurohormone, vasopressin, exerts a potent vasoconstrictive effect via the cardiovascular V_{1A} receptor and induces water retention via the renal V_2 receptors. Conivaptan (YM087) is an orally active, non-peptide, vasopressin V_{1A} and V_2 receptor antagonist (Yatsu et al., 1997; Tahara et al., 1997a,b, 1998a,b,c). It has already been demonstrated that conivaptan (0.01 to 0.1 mg/kg i.v.) exerts a dose-dependent diuretic effect in dogs without an increase in the urinary excretion of electrolytes, inhibits the pressor effect of exogenous vasopressin in a dose-de-

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pendent manner (0.003 to 0.1 mg/kg i.v.) and, at the highest dose (0.1 mg/kg i.v.), almost completely blocks vasoconstriction caused by exogenous vasopressin (Yatsu et al., 1997). Based on these findings, the effects of conivaptan (0.1 mg/kg i.v.) on systemic hemodynamics and diuresis of pentobarbital-anesthetized dogs with congestive heart failure was examined. Congestive heart failure was induced by rapid right ventricular pacing, which has been previously reported to produce hemodynamic, structural and neurohumoral changes very similar to those observed in patients with congestive heart failure (Riegger and Liebau, 1982; Armstrong et al., 1986; Moe et al., 1989; Spinale et al., 1991).

2. Materials and methods

2.1. Surgical procedures

Beagle dogs of both sexes weighing 8 to 14 kg were used. The animals were anesthetized with sodium pentobarbital (30 mg/kg). Under sterile conditions, a pacemaker lead (BT-60, STAR MEDICAL) was inserted through the right axillary vein into the apex of the right ventricle using fluoroscopy. The lead was connected to a programmable pacemaker (SIP-501, STAR MEDICAL) that was held in a subcutaneous pocket located dorsally at the neck. The animals were allowed to recover for 2 to 3 weeks before rapid right ventricular pacing was begun. Chronic rapid right ventricular pacing at 260 to 280 beats/min was initiated and continued for 2 to 3 weeks. For study, dogs were anesthetized with sodium pentobarbital (15 mg/kg i.v.). A constant level of anesthesia was maintained by intravenous infusion of sodium pentobarbital with an infusion pump at a rate of 1 to 3 mg/kg/h through the right cephalic vein. After endotracheal intubation, artificial respiration was initiated by means of a respiration pump (SN-480-4; Shinano Seisakusho, Tokyo, Japan) using room air at 18 strokes/min (20 ml/kg tidal volume). Body temperature was maintained at 37 to 38°C on a thermostatically controlled heating table (SN-662; Shinano Seisakusho, Tokyo, Japan). The right femoral artery was catheterized to allow measurement of systemic blood pressure with a pressure transducer (AP-200T; Nihon Kohden, Tokyo, Japan) and of heart rate with a tachometer (AP-600G; Nihon Kohden, Tokyo, Japan) triggered by the arterial pulse wave. After thoracotomy at the left third intercostal space, an electromagnetic flow probe was attached to the aortic arch to measure cardiac output with an electromagnetic blood flowmeter (MFV-3100; Nihon Kohden, Tokyo, Japan). A catheter-tip manometer (TCP2RN136F30; Tokai Rikadenki, Tokyo, Japan) was inserted into the left ventricle through the left common carotid artery to measure left ventricular pressure. The first derivative of left ventricular pressure (left ventricular dP/dt_{max}) was obtained with an electrodifferentiator (EQ-600 G; Nihon Kohden, Tokyo, Japan). Changes in all parameters were recorded on a polygraph (RM-6000; Nihon Kohden, Tokyo, Japan). A catheter was inserted in the right femoral vein for the intravenous infusion of either conivaptan or the vehicle. A urinary bladder catheter (Foley Pediatric 8 Fr) was inserted to collect urine. These experiments were approved by the Animal Ethical Committee of Yamanouchi Pharmaceutical, and conducted humanely.

2.2. Experimental protocol

After the completion of surgery, the pacemaker was turned off, and the animals were allowed to stabilize for approximately 60 min. As illustrated in the protocol (Fig. 1), a blood sample (3 ml) and 10-min urine samples were collected, and hemodynamic parameters were measured. Similar procedures were conducted and these parameters were measured in anesthetized healthy dogs ($n = 6$) to compare basal values with those from dogs with congestive heart failure ($n = 8$). Dogs with congestive heart failure were placed into either the conivaptan (0.1 mg/kg i.v., $n = 5$) group or the vehicle ($n = 3$) group. The hemodynamic and renal effects of this compound were assessed in dogs with congestive heart failure.

2.3. Analytical procedures

Stroke volume (stroke volume = cardiac output/heart rate) and total peripheral vascular resistance (total peripheral vascular resistance = mean blood pressure/cardiac output) were calculated. Plasma and urine osmolality were determined by the freezing point depression method, using an osmometer (Model 3C2, Advanced Instruments). Free water clearance was calculated as the urine flow minus osmolal clearance [C_{osm} = (urine flow rate) × (urine osmolality/plasma osmolality)].

2.4. Drugs and data analysis

Conivaptan hydrochloride (YM087; 4′-(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzoazepine-6-carbonyl)-2-

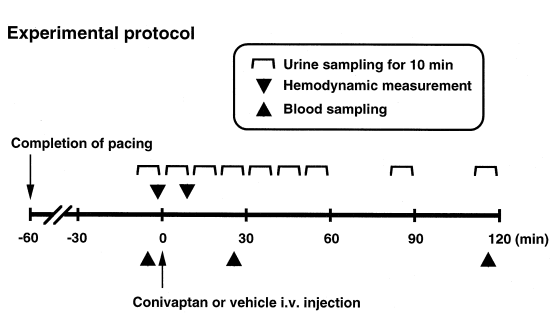

Fig. 1. Experimental protocol.

phenylbenzanilide monohydrochloride) was synthesized by Yamanouchi Pharmaceutical (Ibaraki, Japan). All other chemicals were of the best grade commercially available. Conivaptan was dissolved in dimethylformamide and diluted with distilled water. The final concentration of dimethylformamide was 5% and the drug solution was administered i.v. at a volume of 0.2 ml/kg. All data are expressed as the means ± S.E.M. Between-group differences were analyzed using Student's unpaired *t*-test. Within-group changes were analyzed using Student's paired *t*-test. Differences were considered significant at a *P*-value of less than 5%.

3. Results

Fig. 2 illustrates the basal values of hemodynamic parameters in the healthy (Normal) and congestive heart failure dog groups. Left ventricular dP/dt_{max}, an index of cardiac contractility, cardiac output and stroke volume were significantly reduced and total peripheral vascular resistance and left ventricular end-diastolic pressure were significantly elevated in the congestive heart failure group compared to the values of these indices from the Normal group. In the congestive heart failure group, there was a slight decrease in mean blood pressure and a slight in-

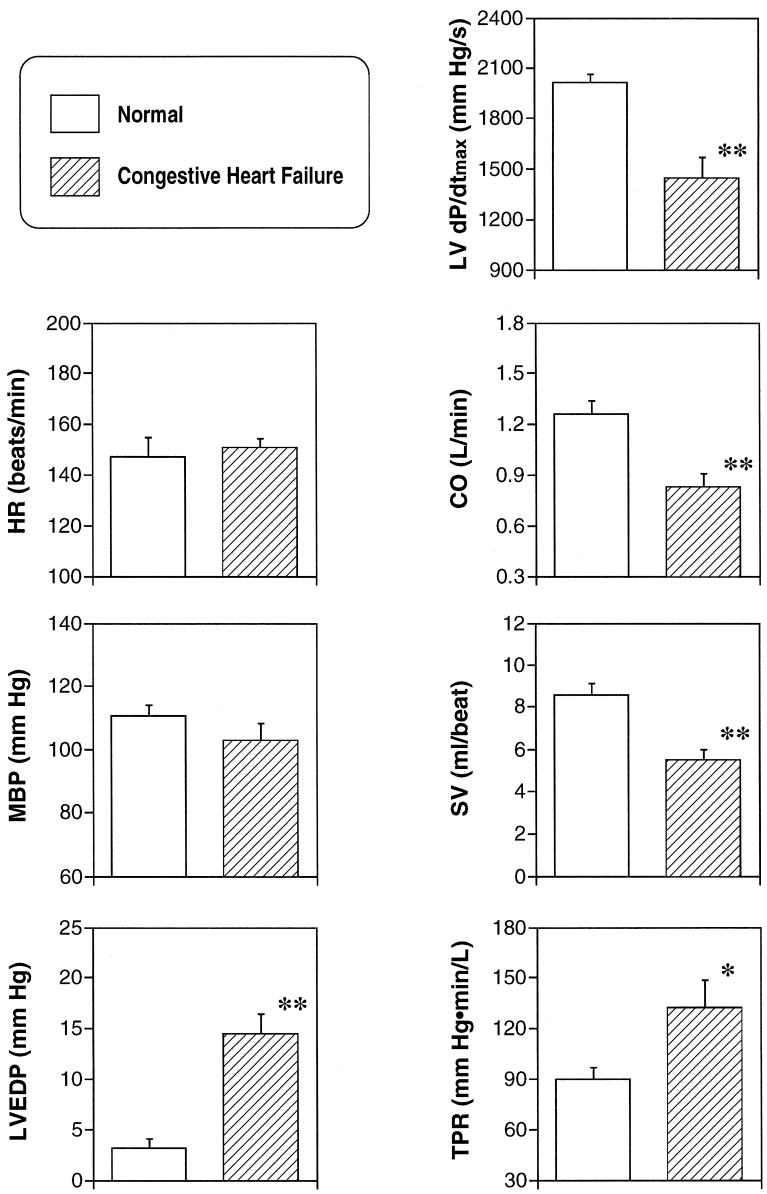

Fig. 2. Basal hemodynamic measurements in normal ($n = 6$) dogs and in dogs with congestive heart failure ($n = 8$). Columns represent the means ± S.E.M. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with value in normal dogs, as determined by Student's unpaired *t*-test. HR, heart rate; MBP, mean blood pressure; LVEDP, left ventricular end-diastolic pressure; LV dP/dt_{max}, first derivative of left ventricular pressure; CO, cardiac output; SV, stroke volume; TPR, total peripheral vascular resistance.

crease in heart rate. These states are consistent with hemodynamics characteristic of patients with congestive heart failure.

Fig. 3 illustrates the basal values of urinary parameters from the Normal and congestive heart failure groups. Urine could not be collected in two animals in the Normal group because the tip of the catheter for urine sampling was not inserted in the bladder. Although not significantly so, urine flow decreased in the congestive heart failure group compared with that in the Normal group but urine osmolality increased significantly, showing an impairment of water excretion similar to water retention characteristic of patients with advanced heart failure.

Conivaptan (0.1 mg/kg i.v.) improved cardiac function, as evidenced by significant increases in left ventricular dP/dt_{max}, cardiac output and stroke volume, and reduced preload and afterload, as evidenced by significant decreases in left ventricular end-diastolic pressure and total peripheral vascular resistance in dogs with congestive heart failure (Fig. 4). Simultaneously, there was a slight but significant increase in heart rate probably accompanied by vasodilation. These parameters were almost stable before and after vehicle injection in the vehicle group (Fig. 5).

Fig. 6 illustrates the effects of conivaptan on urine flow, urine osmolality and free water clearance. In dogs with congestive heart failure, urine flow gradually increased following conivaptan injection (0.1 mg/kg, i.v.) and reached the maximum response 50 to 60 min after administration. Urine flow was still increased 110 to 120 min after administration. Urine osmolality gradually decreased following conivaptan injection, reaching the minimum concentration 50 to 60 min after administration. Urine osmolality was still decreased 110 to 120 min after administration. Free water clearance gradually increased following conivaptan injection (0.1 mg/kg, i.v.) and reached the maximum response 50 to 60 min after dosing. Free water clearance was still increased 110 to 120 min after administration. These results indicate strongly that the increase in urine flow and the decrease in urine osmolality due to conivaptan were based primarily on an increase in free water clearance. In the vehicle group, these parameters were almost stable throughout the study period (Fig. 6).

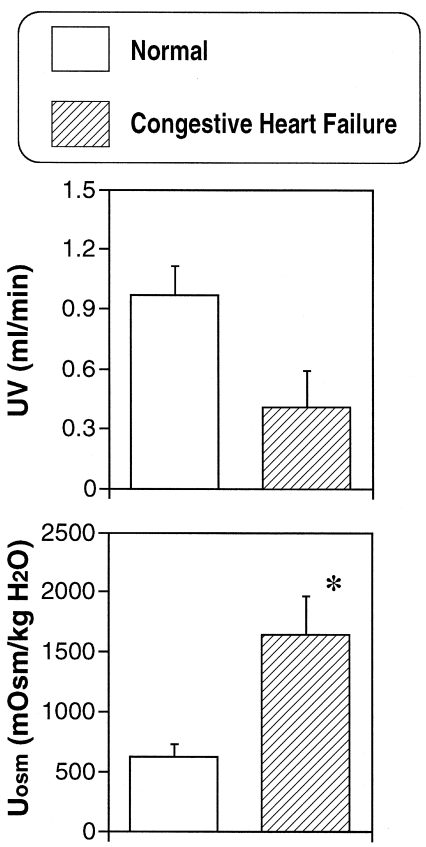

Fig. 3. Basal urinary parameters in normal ($n = 4$) dogs and in dogs with congestive heart failure ($n = 8$). Columns represent the means ± S.E.M. $^{*}P < 0.05$ compared with value in normal dogs, as determined by Student's unpaired *t*-test. UV, urine flow; U_{osm}, urine osmolality.

4. Discussion

Rapid right ventricular pacing for 2 to 3 weeks induced congestive heart failure, characterized by decreases in left ventricular dP/dt_{max} and cardiac output, and increases left ventricular end-diastolic pressure and total peripheral vascular resistance. There was a slight decrease in mean blood pressure in the congestive heart failure group due to the reduction in cardiac function and a slight reflex increase in heart rate in association with a reduction in systemic perfusion pressure. Urine flow decreased and urine osmolality increased significantly in the congestive heart failure group compared with the Normal group. Water retention, characteristic of patients with advanced heart failure (Schrier, 1988; Martin and Schrier, 1997), was also observed. These changes are similar to those described previously (Brands et al., 1993; Himura et al., 1994; Naitoh et al., 1994; Teranuma et al., 1997) and resemble many of the alterations found in patients with congestive heart failure. Therefore, we used this model to study the effects of conivaptan to relieve the symptoms of congestive heart failure.

The results of this study indicate that short-term administration of conivaptan, a vasopressin V_{1A} and V_2 receptor antagonist, leads to hemodynamic improvement and marked aquaresis in dogs with congestive heart failure. The profile of hemodynamic responses showed increases in left ventricular dP/dt_{max}, cardiac output and stroke volume, and decreases in left ventricular end-diastolic pressure and total peripheral vascular resistance. The renal response to conivaptan is characterized by an increase in urine flow and a decrease in urine osmolality, i.e., aquaresis, on the basis of an increase in free water clearance. These results clearly demonstrate that conivaptan acts as a vasopressin V_{1A} and V_2 receptor antagonist in dogs with congestive heart failure. This result is similar to that previously obtained with healthy dogs (Yatsu et al., 1997).

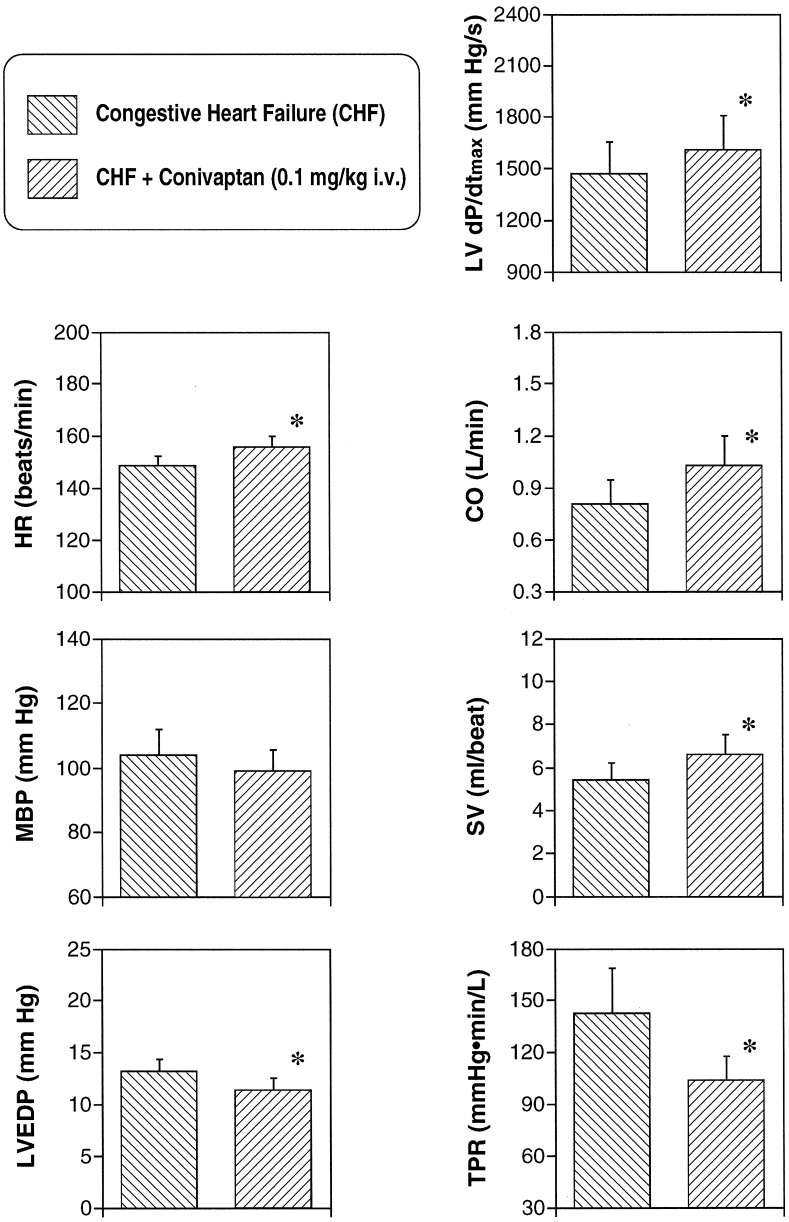

Fig. 4. Changes in heart rate (HR), mean blood pressure (MBP), left ventricular end-diastolic pressure (LVEDP) and (LV dP/dt_{max}) (first derivative of left ventricular pressure), cardiac output (CO), stroke volume (SV) and total peripheral vascular resistance (TPR) in response to conivaptan in dogs with congestive heart failure ($n = 5$). Columns represent the means ± S.E.M. $^*P < 0.05$ compared with value for pretreatment with conivaptan, as determined by Student's paired *t*-test.

These findings are also consistent with other reports that a peptide vasopressin V_{1A} and V_2 receptor antagonist improves cardiohemodynamics and exerts diuretic effects in rat models of heart failure (Mulinari et al., 1990; Wang et al., 1991), and that combined administration of vasopressin V_{1A} and V_2 receptor antagonists produces hemodynamic improvement and aquaretic effects in a canine model of heart failure (Naitoh et al., 1994).

Cardiohemodynamics began improving as little as 10 min after conivaptan injection. Since conivaptan exerted little aquaretic effect at this time point, the hemodynamic improvement is attributed primarily to blockade of vasopressin V_{1A} receptors. This hypothesis is consistent with other reports that a peptide vasopressin V_{1A} receptor antagonist improves hemodynamics in animal experimental models (Arnolda et al., 1986, 1991; Raya et al., 1990) and in patients with congestive heart failure in whom plasma vasopressin levels were elevated (Nicod et al., 1985, 1986; Creager et al., 1986).

Since marked aquaretic effects were observed after conivaptan dosing, conivaptan could prove very useful for the relief of water retention due to impaired renal water excretion in hyponatremic patients with congestive heart failure (Schrier, 1988; Martin and Schrier, 1997). This is

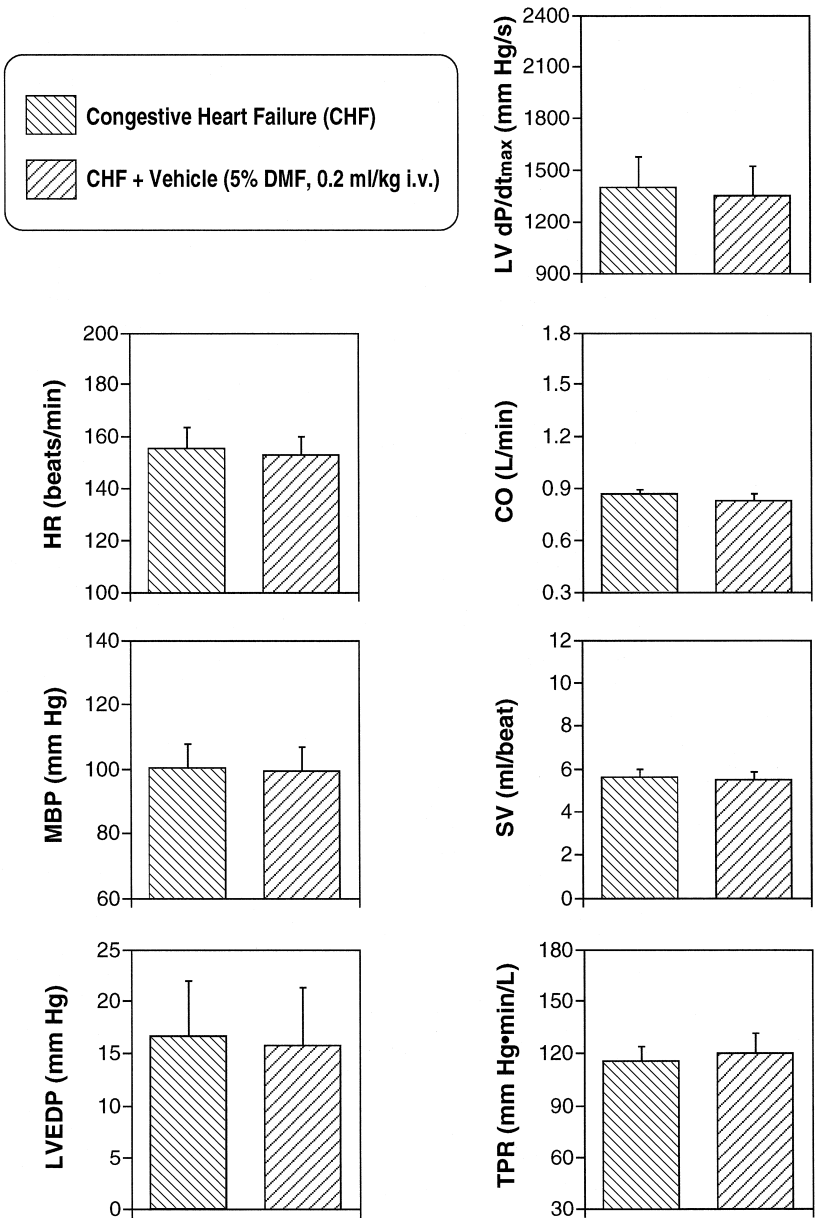

Fig. 5. Changes in heart rate (HR), mean blood pressure (MBP), left ventricular end-diastolic pressure (LVEDP) and (LV dP/dt_{max}) (first derivative of left ventricular pressure), cardiac output (CO), stroke volume (SV) and total peripheral vascular resistance (TPR) in response to vehicle in dogs with congestive heart failure ($n = 3$). Columns represent the means ± S.E.M. DMF, dimethylformamide.

important because water retention-induced dilutional hyponatremia is a well-defined predictor of mortality in patients with congestive heart failure (Dzau and Hollenberg, 1984; Cohn et al., 1984; Lee and Packer, 1986). The important role of vasopressin in inducing hyponatremia associated with congestive heart failure was suggested by results of numerous studies. Szatalowicz et al. (1981) used a sensitive radioimmunoassay for vasopressin to show that congestive heart failure patients with plasma hypoosmolality of a degree sufficient to suppress vasopressin to undetectable levels in healthy subjects had inappropriately high plasma vasopressin levels. A subsequent study confirmed this non-osmotically triggered stimulation of vasopressin secretion associated with decompensated congestive heart failure (Goldsmith et al., 1986). They also showed that these plasma vasopressin levels are not suppressible by acute water loading. Additionally, Kim et al. (1990) showed that expression of vasopressin mRNA increases in the hypothalamus of rats with congestive heart failure. The pivotal importance of vasopressin-mediated water retention has been demonstrated by studies of vasopressin V_2 receptor antagonists. First, it was shown that in rats with low cardiac output heart failure, a peptide vasopressin V_2 receptor antagonist corrected the impaired urinary dilution in response to acute water loading (Ishikawa et al., 1986). Fujisawa et al. (1993) also showed that a non-peptide

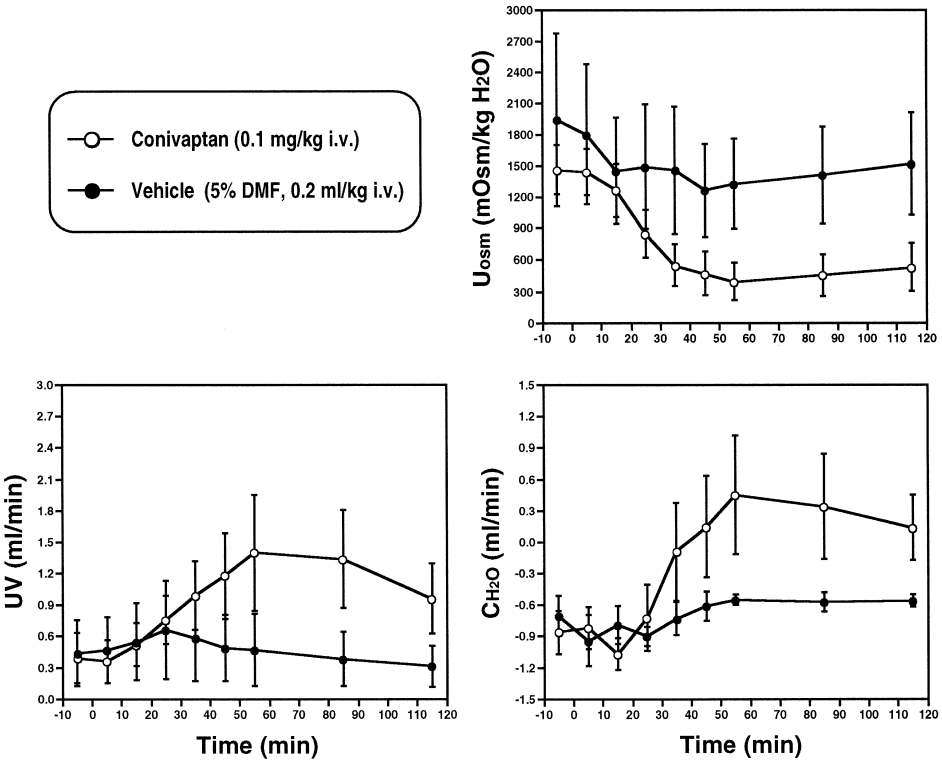

Fig. 6. The time course for changes in urine flow (UV), urine osmolality (U_{osm}) and free water clearance (C_{H_2O}) after the administration of either conivaptan ($n = 5$) or the vehicle ($n = 3$) to dogs with congestive heart failure. Each point represents the means ± S.E.M. DMF, dimethylformamide.

vasopressin V_2 receptor antagonist provoked a normal response to acute water loading in rats with left coronary artery ligation-induced heart failure. Naitoh et al. (1994) also showed that this compound exerted an aquaretic effect in conscious dogs with pacing-induced congestive heart failure. Furthermore, Xu et al. (1997) demonstrated up-regulation of both aquaporin-2 water channel mRNA and protein in rats with congestive heart failure. This effect on collecting-duct water channels in congestive heart failure is associated with an increase in plasma vasopressin levels, and can be reversed with a non-peptide vasopressin V_2 receptor antagonist. Moreover, long-term treatment with the same compound improved survival compared to that of animals with untreated congestive heart failure (Phillips et al., 1995). These findings, together with the present results, clearly demonstrate that vasopressin plays a pivotal role in abnormal renal water retention in congestive heart failure, and show that blockade of both the vasoconstriction and water retention actions of vasopressin exerts beneficial effects on cardiohemodynamics. Consequently, it may improve the prognosis of patients with congestive heart failure. However, further studies are needed to evaluate the long-term effect of conivaptan in heart failure.

In conclusion, the results showed that conivaptan improves cardiohemodynamics and exerts aquauretic effects in dogs with congestive heart failure. This drug shows preliminary promise as a neurohormonal antagonist to treat patients with congestive heart failure.

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