

## Introduction

Congestive heart failure (CHF) is a clinical syndrome in which systolic or diastolic cardiac dysfunction leads to activation of the renin-angiotensin-aldosterone and sympathetic nervous systems, producing hypervolemia and vasoconstriction, followed by vascular congestion and pulmonary edema.

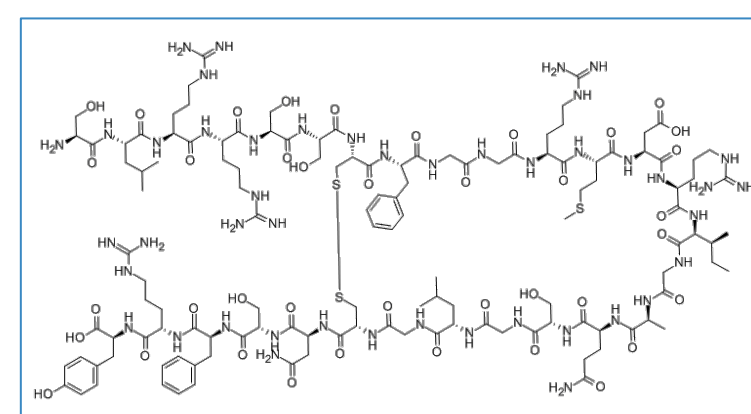
Loop diuretics are recommended as a first-line therapy in the management of CHF and are important in the symptomatic treatment. But, furosemide activates the renin-angiotensin-aldosterone system (RAAS).

In Japan, carperitide which is a human atrial natriuretic peptide (hANP) preparation is clinically applied

and reported to be useful as a therapeutic agent for acute heart failure in human medicine. Studies in human trials have shown that carperitide has multiple effects such as vasodilation, sodium diuresis, and inhibition of the RAAS. And, it is considered that these effects improve heart failure.

There is also a report that improving congestion by intravenously administering carperitide to MR model dogs due to vasodilating action. It has already been clinically applied to veterinary patients with pulmonary edema.

However, as far as we know, there is no report on the therapeutic effect of carperitide in clinical cases. In this study, we examined the effect of carperitide on neurohumoral factors in clinical cases.



## Purpose

- Effects of carperitide in clinical cases
- Observing changes in plasma concentration of neurohumoral factors (ANP, NT-proBNP, Aldosterone) in acute congestive heart failure dogs treated with carperitide

## Materials & Methods

### Inclusion criteria

- Dog exhibited pulmonary edema due to mitral regurgitation
- Mean blood pressure : 80mmHg<
- Hypotension in dogs  
Mean blood pressure : 60mmHg>  
or Systolic blood pressure : 80mmHg>
- When carperitide is administered to dogs with congestive heart failure, the maximum mean blood pressure decreases by 18mmHg.

Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat, ed 5, 183-186, 2000

J Vet Med. 63:243-250, 2001

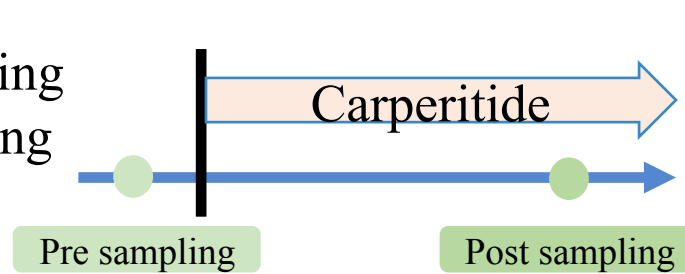
## Materials & Methods

### Animals

- A total of 19 patients visited during the study period. From these cases, 9 patients fulfilled the criteria of the study. The 9 patients were 1 female, 1 spayed female, 4 neutered males, and 4 intact males. The breeds were Chihuahua (5), CKCS (1), Shih Tzu (1), Papillon (1), and Shetland Sheepdog (1). Median age of the patients was 11 years (9-13). Median body weight of the patients was 3.8kg (2.1-9.2).

### Measurements

- Plasma concentration of neurohumoral factors
  - ANP (CLEIA: Chemiluminescence Enzyme Immunoassay)
  - NT-proBNP (ELISA: Enzyme-Linked ImmunoSorbent Assay)
  - Aldosterone (IRMA: Immuno radio metric assay)
- Blood pressure (Systolic, Mean)
- Chest radiography (VHS, pulmonary permeability)
- Echocardiography (LA/Ao, E wave)
- Measurement time point
  - Before carperitide administration: pre sampling
  - After carperitide administration: post sampling
- Treatment
  - Carperitide 0.05µg/kg/min CRI (Carperitide was administered to all patients)
  - Other medications
  - Furosemide 2.0mg/kg SC or 1.0mg/kg/h CRI
  - Dobutamine 5µg/kg/min CRI



### Statistical analysis

- The data of plasma ANP, NT-proBNP, and aldosterone concentration are expressed as median (Minimum - Maximum). The data of blood pressure, VHS, LA/Ao, and E wave are expressed as mean±SD.
- Plasma NT-proBNP concentration were compared by Bonferroni correction. Plasma ANP and aldosterone concentration were compared by Wilcoxon signed-rank test. And Blood pressure, VHS, LA/Ao, and E wave were compared by T test.

## Results & Discussion

### Therapeutic effect

- Side effects were not observed by carperitide and administration of it was safe. At the end of treatment, clinical symptoms improved in all cases and were discharged.

### Blood pressure

- Systolic Pre: 149±25 vs Post: 127±20 \*
- Mean Pre: 105±14 vs Post: 91±9 \*\*
- No significant decrease in blood pressure occurs with furosemide administration

Vet Intern Med. 27:1097-1104, 2013

It can be considered that blood pressure decrease in this study is due to vasodilatory action by carperitide.

- None was observed including hypotension (Systolic) Maximum decrease of 49mmHg (Mean) Maximum decrease of 28mmHg

By setting the administration standard of carperitide to mean blood pressure of 80 mmHg <, no hypotension is observed and it can be administered safely.

### Chest radiography

- 6 of 9 cases showed improvement in pulmonary permeability on chest X-ray after carperitide (post).

- VHS Pre: 11.8±0.88 vs Post: 10.8±0.96 \*\*

### Echocardiography

- LA/Ao Pre: 2.66±0.62 vs Post: 2.24±0.48 \*
- E wave Pre: 151±33 vs Post: 122±25 \*\*

## Results & Discussion

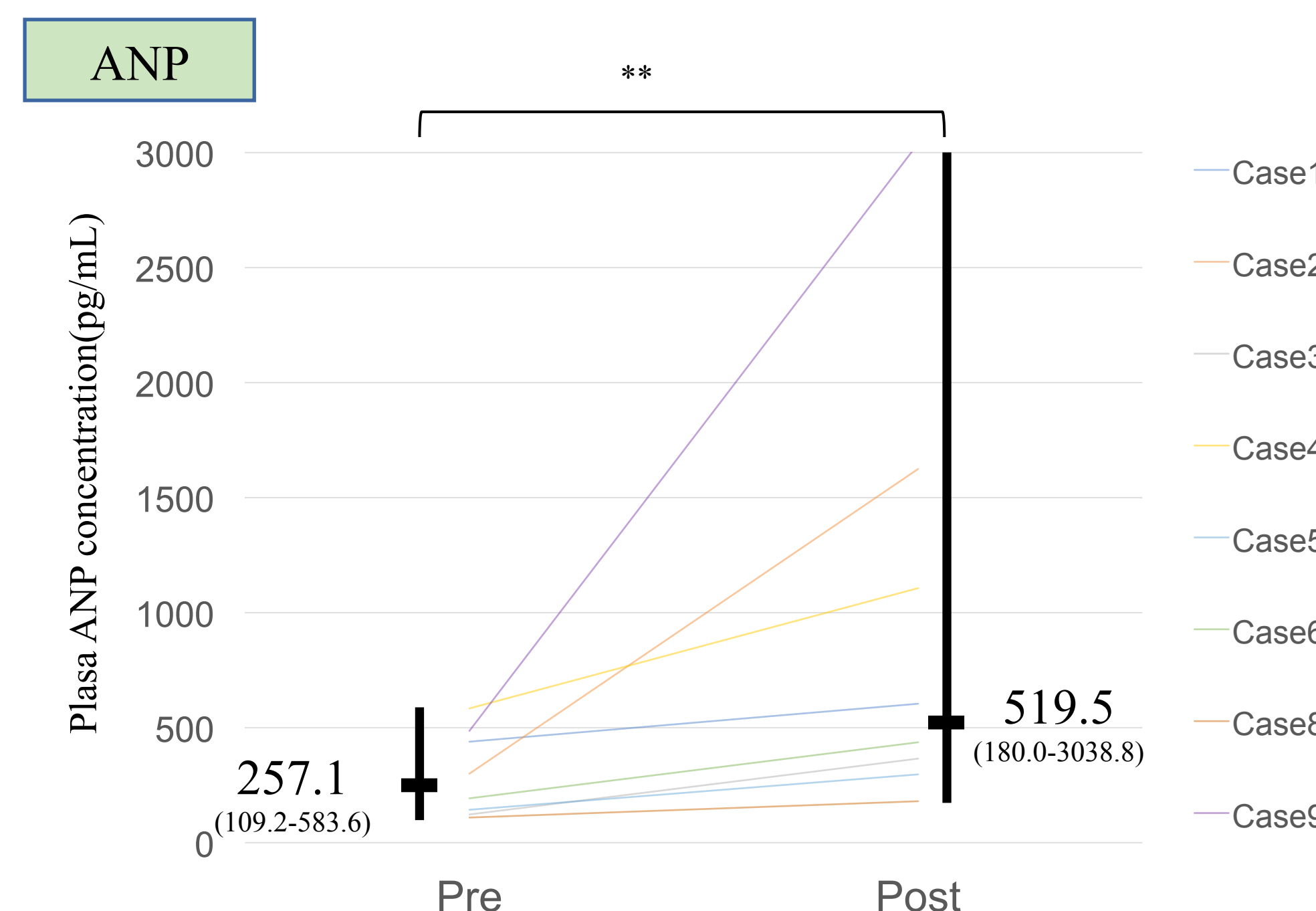


Fig1. Temporal alterations of plasma ANP concentration after administration of carperitide 0.05 µg/kg/min. The median and range are indicated by lines and bars, respectively.

- Plasma ANP concentration significantly elevated with a human atrial natriuretic peptide preparation administration.

It can be considered that pharmacological effects of ANP are also obtained in dog's body by hANP

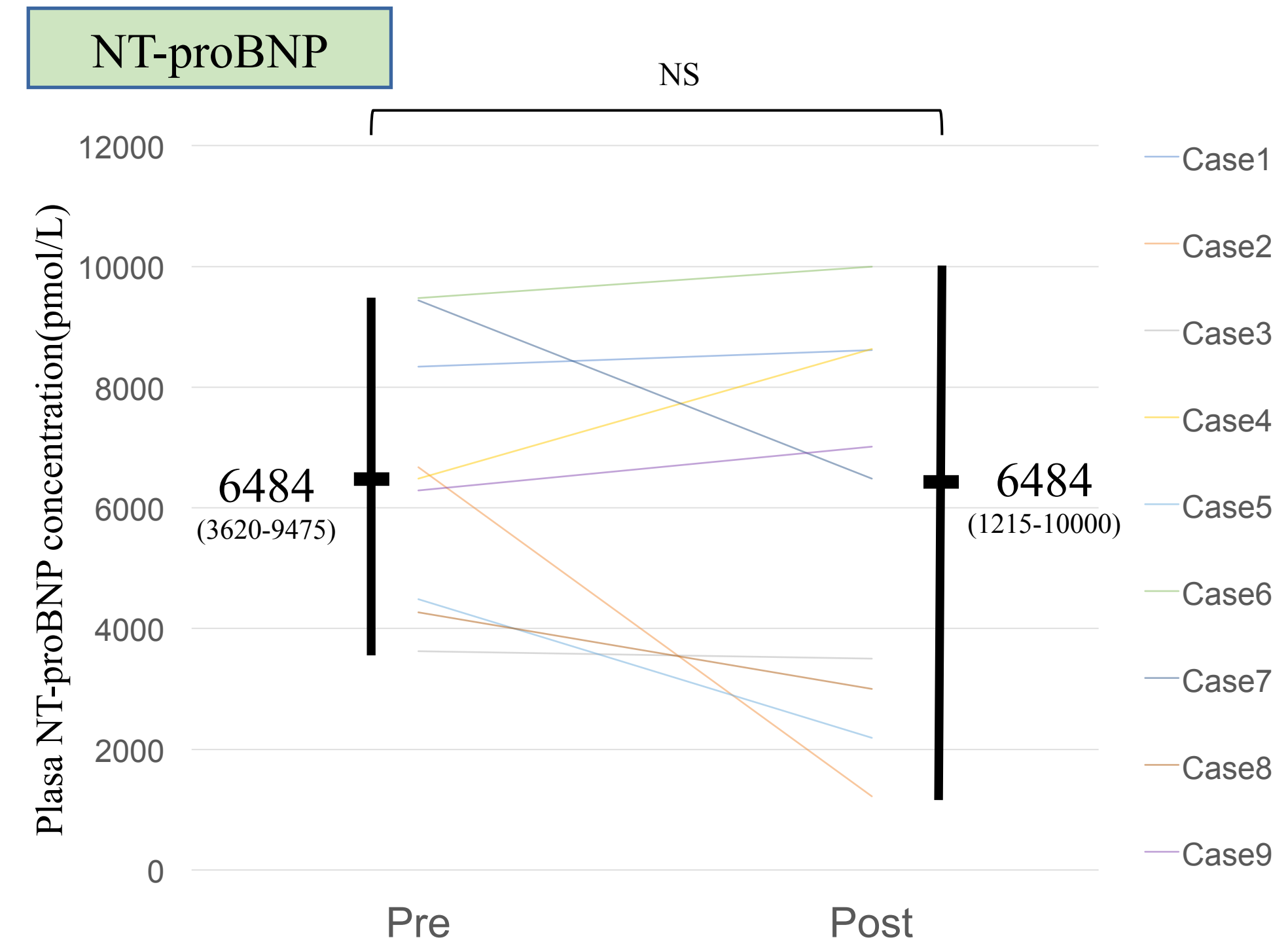


Fig2. Temporal alterations of plasma NT-proBNP concentration after administration of carperitide 0.05 µg/kg/min. The median and range are indicated by lines and bars, respectively.

- NT-proBNP is more useful than BNP as an evaluation of cardiac congestion during carperitide administration.

But,

- There was no significant difference in the median plasma NT-proBNP concentration between Pre and Post.

In this study, it was considered difficult to evaluate cardiac congestion during the administration of carperitide with NT-proBNP

## Results & Discussion

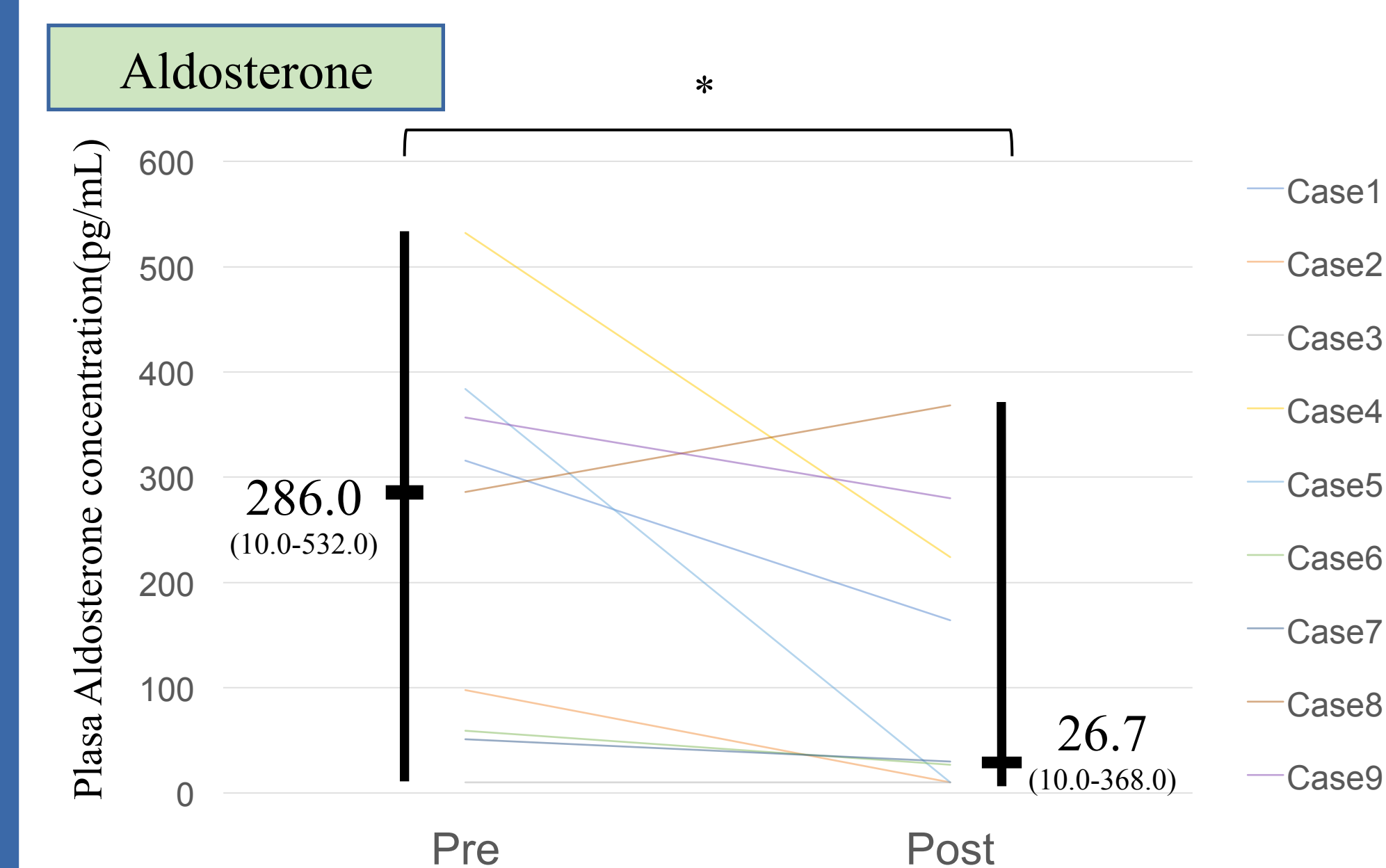


Fig3. Temporal alterations of Aldosterone after administration of carperitide 0.05 µg/kg/min. The median and range are indicated by lines and bars, respectively.

- There is a report that plasma aldosterone concentration significantly elevated with Furosemide administration. Journal of Veterinary Medical Science 72(1), 13-18, 2010
- However, in this study, despite the administration of furosemide to all cases, a dominant decrease of aldosterone was observed.

It can be considered that aldosterone decrease in this study is due to Aldosterone secretion inhibited by Carperitide.

- Aldosterone is a hormone with a strong sodium retention effect and promotes the reabsorption of sodium and water in the kidney, which increases body fluid volume including circulating blood volume, preload increases and cardiac output is increased. Besides that, elevation of plasma aldosterone concentration causes induction of cardiac remodeling, increase in blood pressure by vasoconstriction, and affecting renal function harmfully. Circulation 115 (13) (2007) 1754-1761.
- Higher aldosterone levels were found in patients with chronic HF when compared with controls, and were found to be associated with poor outcome.

Therefore, suppression of aldosterone was thought to lead to improvement of cardiac function and life prognosis.

## Conclusions

It can be expected that administration of carperitide leads to,,,

- Reduction in blood pressure by vasodilating action and decrease in aldosterone due to aldosterone production inhibitory action.
- Improve of symptoms in clinical cases.

**Carperitide is useful for early treatment of pulmonary edema due to mitral valve disease**

## Conflict of Interest Disclosure

### FINANCIAL DISCLOSURE:

No relevant financial relationship exists.

### UNLABELED/ UNAPPROVED USES DISCLOSURE:

I will discuss results of clinical trial for the following agents that are currently NOT approved for use in animals.

– Carperitide(HANP®, DAIICHI SANKYO COMPANY,LIMITED, Japan)