Does a hypertonic saline load predict fluid retention in pacing induced heart failure?

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Abstract

Objective: We examined the response to hypertonic saline challenge (SC) as a potential predictor of fluid retention during heart failure induced by rapid ventricular pacing. Methods: Twelve dogs (22 ± 4 kg) were given an intra-arterial bolus of 30 ml of 20% saline after establishing baseline fluid intake and urine output (24 h). Dogs were classified according to whether they drank more (Group A) or less (Group B) than the amount required to dilute the SC to isotonicity. Fluid retention was then assessed during heart failure after rapid ventricular pacing according to a graded ordinal scale and correlated with the responses to SC. Results: No difference was noted in baseline fluid intake (1112 ± 236 ml in Group A vs. 809 ± 129 ml in Group B). Five hours after SC cumulative water intake was significantly greater in Group A than in Group B (1018 ± 136 vs. 591 ± 17 ml) (P < 0.01). Urine sodium concentration was 113 ± 11 and 124 ± 28 mmol/l at baseline in Group A and B, respectively; increased to 190 ± 21 and 295 ± 59 mmol/l at 5 h and remained elevated 24 h after SC, 177 ± 60 and 274 ± 55 mmol/l (both P < 0.01 for within-group comparisons vs. baseline). Urine sodium concentration was less in Group A than in Group B at 5 and 24 h (P < 0.05). The fluid retention score was greater in Group A (3.6 ± 0.5) than in Group B (0.8 ± 0.4) (P < 0.01). Fluid retention in heart failure correlated with water intake after the pre-pacing SC (r = 0.68, P < 0.025) and inversely with urine concentrating ability (r = −0.58, P < 0.05). Furthermore, water intake and urine concentrating ability following the SC were inversely related (r = −0.67, P < 0.02). Conclusions: We conclude that normal dogs may be classified according to their fluid intake after SC. Those dogs that drank excessively and produced a dilute urine were more likely to retain fluid during pacing-induced heart failure. Hence, fluid intake and the ability to excrete a concentrated urine after a saline challenge may be useful variables to predict fluid retention in pacing-induced heart failure.

Keywords: Hypertonic saline; Fluid retention; Heart failure; Isotonicity; Dog, conscious

1. Introduction

Fluid retention characterized by edema and ascites is a common manifestation of congestive heart failure (CHF) and has been attributed to activation of neurohormonal mechanisms that promote sodium and water reabsorption by the kidneys. These mechanisms, in combination with Starling forces, such as increased venous capillary pressure and decreased plasma oncotic pressure, promote expansion of extracellular fluid and fluid extravasation [1–8].

Previous studies of CHF in the canine rapid ventricular pacing model [9,10] have shown substantial variability in the development of fluid retention, ascites and weight gain despite similar degrees of cardiac dysfunction. Neuroendocrine responses to pacing-induced heart failure in dogs have also revealed elevation in vasodilator and natriuretic peptides which appear insufficient to maintain circulatory homeostasis [11]. However, neurohormonal studies have failed to explain the variability evident in the development of fluid retention during pacing-induced heart failure [12].
We theorized that the observation of Kanter [13], who described two types of drinking and urinary excretion responses to salt-loading in normal dogs, might be relevant to this issue. One type—the minimal internal regulator—was characterized as drinking to the point of producing an isotonic urine in response to a salt load, whereas the second type—the maximal internal regulator—drank less water after the same salt load and excreted a hypertonic urine. In this regard Ramsay et al. [14] have reported that increases in fluid intake following constriction of the thoracic inferior vena cava in the dog were a potentially important factor in the edema formation associated with the development of CHF.

Against this background we assessed the response to a hypertonic saline challenge (SC) in normal male mongrel dogs in order to explore: (1) whether the classification described by Kanter [13] could be validated, and (2) whether this response would provide insight into the propensity for fluid retention after rapid ventricular pacing.

2. Methods

Twelve male mongrel dogs weighing 22 ± 4 kg were studied. All dogs were preconditioned to the laboratory environment at least 2 days before the experiments. Specifically, each dog was housed in an individual cage in a room with a temperature of 20°C and a light cycle of 07:00–18:00 h. The dogs were fed on a fixed diet of commercial dog food (Tuffy Chunks) once per day in the morning and had free access to tap water. The sodium intake in this diet was 1–1.5 g per day. The study was approved and conducted in accordance with the Health Sciences Animal Welfare Committee of the University of Alberta and the Canadian Council of Animal Care and conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1985).

2.1. Saline challenge study

Prior to SC the dogs were placed in a metabolic cage for 36 h to allow for acclimation. Fluid intake and urine volume were monitored and recorded for 24 h prior to, during and 24 h after SC. Prior to the experiment, dogs were fasted overnight, but access to water was maintained. Since previous studies [16,17] had shown that intra-arterial infusion of hypertonic saline was a more effective stimulus for drinking than a gastric or intravenous infusion, an intra-arterial bolus of 30 ml of 20% saline was given within 2 min followed by 5 ml of normal saline flush. The time to drink and time to void were carefully monitored for 5 h following SC. Previous studies by Kanter [13] and Di Salvo [15] suggested that dogs usually drink within 10 min of receiving a saltload and that water intake and output in response to SC is complete within 2 h. Accordingly, intervals during which water intake and urine output were assessed included: 0–5, 5–10, 10–20, 20–30, 30–60 and 60–120 min. In preliminary studies we found some dogs who did not void within 2 h and therefore extended the duration of monitoring for a full 24 h. These studies also indicated that whereas dogs continued to drink after 5 h, no differences were observed with respect to the interval water intake between 5 h and 24 h. Since in these studies no differences were found with respect to interval water intake from 5–24 h, we classified dogs into two groups depending on whether their water intake by 5 h after SC was greater than that required to dilute injected salt to isotonicity (Group A: i.e., maximal drinkers) or less than this amount (Group B: i.e., minimal drinkers). Since 30 ml of 20% saline contains 6 g of sodium, a dog requires an additional 667 ml of water to restore osmotic equilibrium.

Arterial blood was sampled just before and at 30, 60 and 120 min following SC and immediately placed on ice. Blood for ANF determination (2 ml for each sample) were put in vacutainer tubes containing EDTA and were centrifuged at 3000 rpm for 7 min. The plasma was separated and stored at −86°C until radioimmunoassay. Plasma was extracted on Sep Pak C-18 columns (Waters, Milford, MA) with acetic acid and ethanol, and the dried eluate stored at −20°C. Peptide levels were measured using a kit supplied by Peninsula Laboratories, Belmont, CA. An additional 3 ml of blood was deposited in a vacutainer tube containing no additive and the resultant serum decanted for determination of sodium concentration. The concentration of serum sodium was measured using Kodak Ektachem 700 utilizing ion-selective (Na⁺) electrodes for potentiometric measurements of ionic sodium. Urine samples of 5 ml each at baseline, 5 and 24 h after SC were placed in airtight containers for later electrolyte analysis. Dogs were kept in a metabolic cage overnight in order to record water intake, urine volume, and acquire urine samples for 24 h after SC.

The SC study was undertaken prior to and was independent of the rapid ventricular pacing study. The pacing study had pre-determined end-points of either 1 (n = 4) or 3 (n = 8) weeks of pacing in order to assess alterations in left ventricular performance and structure at various points in the evolution of heart failure. Assessment of fluid retention during these pacing studies was systematically undertaken by investigators blinded as to the results of the previously performed SC study. Once pacing was initiated, daily clinical and weekly echocardiographic assessments were performed. Clinical evaluation included observation of behaviour, body weight, heart rate, respiratory rate, anorexia, dyspnea, gingival cyanosis, and ascites [12]. An ordinal fluid retention scale was developed for this study as follows: subclinical ascites detected by ultrasound technique was assessed 1 point; ascites detected by both ultrasound technique and clinical assessment received 2 points; advanced ascites with obvious visible abdominal distention scored 3 points. Increased body weight, > 1 kg
(from control to end hemodynamic studies) and pleural effusion observed at autopsy each scored 1 point.

2.2. Induction of heart failure

The method of inducing heart failure has previously been described in detail [10–12]. Briefly, following a general anesthesia with oxygen and halothane, a unipolar pacemaker lead was advanced through the external jugular vein into the right ventricular apex and attached to a programmable pulse generator (Medtronic Minex-8341; Medtronic, Inc.) which was placed in a subcutaneous cervical pocket for a subsequent rapid ventricular pacing study. Each dog was implanted with an externalized chronic indwelling catheter which was positioned in the aortic arch and used for injection of the saltload, blood sampling and pressure measurement during hemodynamic studies. Heparin, 1.5 ml (1000 IU/ml) was injected into the catheter every other day to maintain patency. Dogs were recovered from the effects of surgery for 5 ± 1 days before SC. At least 3 days elapsed after SC and prior to ventricular pacing. For the induction of heart failure by rapid ventricular pacing the generator was programmed to 250 beats/min using a Medtronic 9710A Programmer. Dogs were sacrificed after final hemodynamic and echocardiographic assessments with a 20 ml bolus of 100 mM potassium chloride.

2.3. Echocardiographic and hemodynamic measurements

Hemodynamic and echocardiographic measurements were performed simultaneously at baseline during sinus rhythm just before initiation of pacing and subsequently ≥ 30 min after cessation of pacing.

Thoracic echocardiographic studies were carried out using a Sonos 1000 Phased Array Imaging System (HP 77030A) with a 3.5 or 5 MHZ transducer. According to a previous study [18] cross-sectional images of the left ventricle were taken at the level of the mid-papillary muscles and apical 4 chamber view images were obtained with attention taken to include the longest left ventricular cavity as well as a clear view of the mitral and tricuspid valves. Images were stored on an optical disk for analysis. Ejection fraction (EF) was calculated using Simpson’s single plane method.

Hemodynamic studies were performed on conscious animals which were trained to lie quietly in the right decubitus position. Intravenous morphine boluses of 1–2 mg each (total dose 4–14 mg) were given as necessary for sedation. A Swan-Ganz balloon-tipped thermodilution catheter (7F) and a high-fidelity, microtransducer-tipped pigtail Millar catheter (Millar Instruments Inc., Houston, TX) were introduced via the femoral vein and femoral artery to the pulmonary artery and left ventricle, respectively. Right atrial pressure and left ventricular end-diastolic pressure were recorded on a data acquisition system (Dataq Instruments Inc., Akron, OH). Cardiac output, as reported previously [9], was determined by the thermodilution technique (COM-2, Baxter-Edwards, Santa Ana, CA). Cardiac index was expressed as the cardiac output divided by the dog's body weight at the time of the control study.

2.4. Statistical analysis

An unpaired t-test or one-way analysis of variance was used to identify the significant differences between the two groups for parametric data and a Kruskal-Wallis test was used for comparison of ordinal data (i.e., fluid retention scores). Results are shown as means ± s.e.m. unless otherwise stated. Linear regression analysis was used for correlations between the results of SC and quantification of fluid retention. A probability of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Water intake and urine output

Seven dogs were classified as Group A (i.e., within 5 h of the SC they drank more than was required to achieve plasma isotonicity) and 5 were classified as Group B, i.e. they drank less than what was required to achieve plasma isotonicity. Water intake and urine output are shown in Fig. 1 for the dogs separated into Groups A and B. There was no significant difference in cumulative water intake at baseline (24 h intake prior to SC) in Groups A and B (1112 ± 236 to 809 ± 129 ml, n.s.). Eleven of 12 dogs drank within 10 min after administration of the SC. At 5 h after SC cumulative water intake was significantly greater in Group A than in Group B (1018 ± 136 vs. 591 ± 17 ml,

![Fig. 1. Cumulative water intake for Group A (solid bars) and Group B (open bars) and cumulative urine output for Group A (diagonal hatching) and Group B (cross-hatching) are shown at baseline (over 24 h prior to SC), at 5 h and 24 h following SC. * $P < 0.05$, ** $P < 0.01$ for one-way ANOVA, Group A vs. Group B.](https://academic.oup.com/cardiovascres/article-abstract/33/1/172/296171)
Fig. 2. Non-cumulative water intake for Group A (solid bars) and Group B (open bars) is shown for each interval from 0–5, 5–10, 10–20, 20–30, 30–60, 60–120, 120–300, and 300–1440 min after SC. No intergroup differences were seen at any point except from 120–300 min (P < 0.001).

P < 0.01) and again at 24 h (1559 ± 191 vs. 1143 ± 106 ml, P < 0.05). Twenty-four hour output prior to the SC was higher in Group A than in Group B (382 ± 71 vs. 222 ± 42 ml, P < 0.05); cumulative urine output after SC was similar at 5, but greater in Group A than in Group B after 24 h (765 ± 167 vs. 510 ± 86 ml, respectively, P < 0.05).

In Fig. 2, the interval drinking profile after SC is shown for each time period as described previously for Groups A and B. In the period from 120–300 min Group A dogs drank 486 ± 103 ml, which contrasted with Group B which drank 34 ± 32 ml of water (P < 0.001). There was no significant difference in interval water intake during any other period following SC.

3.2. Urine sodium and total sodium excreted

Table 1 shows urine sodium concentration in mmol/l which was similar at baseline in both Groups. After SC, urine sodium increased significantly from baseline in Groups A and B at 5 h (P < 0.01) and remained elevated at 24 h (P < 0.01) compared to baseline values for each group. Urine was more dilute in Group A than in Group B at 5 h and similarly after 24 h following SC (P < 0.05 for both). Cumulative sodium excretion in grams was not different at any time point between the groups.

3.3. Serum sodium and chloride levels

Serum sodium levels at baseline in Groups A and B were 141 ± 2 and 141 ± 1 mmol/l, respectively, and at 30 min 144 ± 1 in Group A and 143 ± 1 mmol/l in Group B (n.s.). At 120 min after SC serum sodium concentrations were similar to baseline in both groups (142 ± 1 for Group A and 140 ± 1 mmol/l for Group B).

Serum chloride levels followed a similar pattern, being 114 ± 1 for Group A and 113 ± 1 mmol/l for Group B at baseline, increasing by 30 min to 121 ± 1 and 121 ± 2 mmol/l, respectively (P < 0.01 for each). At 120 min after SC, serum chloride levels were 117 ± 1 and 116 ± 1 mmol/l (similar to baseline). There were no intergroup differences.
3.4. Atrial natriuretic factor during SC

In Fig. 3, plasma ANF data are shown. No change was evident from baseline over the subsequent 120 min after the saline challenge. At 120 min after SC Group A ANF (i.e., 9.8 ± 1.4 pg/ml) was greater than Group B (7.2 pg/ml, \( P < 0.02 \)).

3.5. Fluid retention

In Group A the average fluid retention score was 3.6 ± 0.5, which was higher than the Group B average score of 0.8 ± 0.4 (out of a possible maximum score of 5) \( P < 0.01 \). In Group A dogs, 6 had been paced for 3 weeks whereas one was paced for 1 week. In Group B, 3 dogs were paced for 1 week and 2 dogs for 3 weeks.

3.6. Relationships of water intake, urine volume, plasma ANF, serum Na\(^+\) and fluid retention

Following completion of the pacing study, water intake between 2 and 5 h (where the differences between Groups A and B were evident) was correlated with the fluid retention assessment (Fig. 4). As is evident, fluid retention after pacing bore a significant linear relationship with water intake after SC \( (r = 0.68, \ P < 0.025) \). We also correlated fluid retention with the ability to excrete a concentrated urine as indicated by urine sodium difference from baseline to 24 h following the SC (Fig. 5). The

**Table 2**

<table>
<thead>
<tr>
<th>Time period</th>
<th>RAP (mmHg)</th>
<th>LVEDP (mmHg)</th>
<th>Fluid retention (units)</th>
<th>Fluid intake 5 h (ml)</th>
<th>Fluid intake 2–5 h (ml)</th>
<th>Assignment to Group A or B At end of SC</th>
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RAP (right atrial pressure) and LVEDP (left ventricular end-diastolic pressure) measured during control hemodynamic studies (Con) and at the end of the pacing period (End). Fluid retention, assessed at the time of the end hemodynamic study, fluid intake recorded during the SC study at 5 h (used to assign the subjects to Group A or B) and fluid intake during 2–5 h which was significantly different in Group A compared to B (Fig. 2) is also shown for each dog.
ability to produce a concentrated urine after the saltload study was inversely correlated with the degree of fluid retention seen after rapid ventricular pacing ($r = -0.58$, $P < 0.05$).

Since water intake and the ability to produce a concentrated urine were found to be predictive of fluid retention in experimental heart failure, the relationship between these variables was tested as shown in Fig. 6. Water intake 2–5 h after the SC was inversely related ($r = -0.67$, $P < 0.02$) to the dog’s ability to produce a concentrated urine. Therefore those dogs which drank excessively (maximal drinkers) after the SC produced a dilute urine, whereas those that drank less (minimal drinkers) produced a more concentrated urine. Those dogs that were able to tolerate the SC without excessive drinking were less inclined to retain fluid during the development of rapid pacing-induced experimental heart failure.

Serum sodium and chloride levels, which were not different at 120 min after SC, did not provide any further insight into the differences observed in drinking in the two groups of dogs. Similarly, baseline water intake and urine volume did not correlate with fluid retention. Neither sodium nor chloride nor ANF concentrations correlated with fluid retention scores.

### 3.7. Hemodynamic parameters following rapid ventricular pacing (RVP)

In Table 3, selected hemodynamic and echocardiographic parameters are shown for control, 1 and 3 week pacing studies. Individual data for dogs’ fluid retention scores, fluid intake and assignment to Group A or B are identified in Table 2. These results indicate that the expected increases in RAP (right atrial pressure), LVEDP (left ventricular end-diastolic pressure) and decreases in LVEF (left ventricular ejection fraction) and CI (cardiac index) consistent with the development of pacing-induced heart failure [11]. There was no correlation between the response to the saline load (as measured by water intake from 2–5 h and the ability to produce a concentrated urine from baseline to 24 h after saline challenge) and hemodynamic indices of the severity of heart failure: i.e., right- and left-sided filling pressures, end-systolic volume, cardiac index and ejection fraction ($r$-values all $\leq 0.48$, $P \geq 0.25$).

### 4. Discussion

In the current study we have observed different responses to a hypertonic saline bolus. This allows distinction of normal dogs into two groups according to criteria previously suggested by Kanter [13] (i.e., those that drank more or less than what was required to equilibrate a hypertonic saline bolus to isotonicity within 5 h of its administration). Analysis of the temporal profile of fluid intake revealed that a single time period (i.e., from 2–5 h after SC) accounted for the difference between the two groups. Although there was no difference in water intake over the 24 h prior to SC, urine output was greater in the group which drank more after SC, suggesting an underlying distinction may have existed between the two groups.

A key objective of the current study was to establish whether the drinking pattern and urinary excretion response to saline challenge provided insight into the variability and fluid retention evident in heart failure produced by rapid ventricular pacing. Importantly, we observed that both water intake and urinary sodium concentration assessed during the SC study were significantly related to the extent of fluid retention produced by pacing-induced heart failure. Those dogs drinking the largest quantity of water following SC were more prone to retain fluid. In addition, those with the least ability to concentrate their urine, as indicated by the difference in urinary sodium concentration from baseline to 24 h following SC appeared more susceptible to fluid retention (i.e., an inverse relationship existed). Taken together, these two parameters may provide a useful basis for predicting fluid retention in pacing-induced heart failure. A strength of the current study was the spectrum of fluid retention amongst experimental animals ensured by the fact that two different pacing protocols were under-
taken. In this regard it is noteworthy that animals from each pacing period appeared in both Group A and Group B.

Our results agree with those of Kanter [13] who first reported two drinking patterns amongst dogs responding to an identical saltload challenge. He found that the most distinguishing feature between the groups was the time to drink with rapid drinking defining a minimal internal regulator group, as compared with a maximal internal regulator group whose drinking pattern corresponded more slowly after saltloading. Di Salvo [15] identified 3 categories of drinkers based on time: (1) immediate drinkers, <1 min (after saltload), (2) intermediate, 1–10 min, and (3) delayed, >10 min. In the study of Kanter [13] 2 of 7 dogs were classified as minimal internal regulators, whereas Di Salvo [15] identified 13 of 15 dogs as immediate drinkers (comparable to Kanter’s minimal internal regulators). In the present study we identified 7 minimal internal regulators (or maximal drinkers) and 5 maximal internal regulators (or minimal drinkers). Our results are therefore more comparable with Di Salvo’s with regard to the distribution of the two types of responses to saltload in a sample of normal dogs. In our study, 5 of 7 dogs in Group A (the maximal drinkers) developed ascites as they developed congestive heart failure, whereas none of the dogs in Group B (the minimal drinkers) developed ascites during rapid ventricular pacing to congestive heart failure.

In our study we could not separate dogs on the basis of their time to drink but did find, in contrast to Kanter, that the period from 2–5 h after SC was the window in which differences in drinking were most evident. Our dogs were initially monitored for 2 h, but this was extended to ensure that all drinking in response to the SC was monitored and also to allow for a urine sample to be collected since we found that not all animals voided within 2 h following a hypertonic saline load. However, all animals in the present study voided within 5 h.

Limitation in the follow-up observation period to <3 h after salt load in prior studies as well as differences in the route of administration of the saltload—i.e., stomach tube [13] (Kanter), intravenous [15] (Di Salvo), and intra-arterial [16,17] in the present study—may explain some of the variation in response to saltload amongst these studies. It seems likely based on previous studies that intra-arterial injection of hypertonic saline is a more effective stimulus to thirst than intra-gastric infusion. A strength of our study over previous ones is the availability of a 24 h baseline assessment of fluid intake and output as well as a 24 h follow-up after SC [13,15].

A bolus injection of hypertonic saline through the intra-arterial catheter stimulated drinking within 10 min in 11 of 12 dogs. The amount of water intake was considerably larger and the latent time for drinking much shorter than the study reported by Kanter [13]. The individual variations in both the amount and rate of drinking after SC deserve comment. In the present study differences in absorption time and mixing [13] were eliminated by the method of saline delivery. An identical saline load should both increase plasma osmolality and cerebral dehydration to a similar degree, resulting in a stimulus for dogs to drink consistent amounts of water. Intra-arterial infusion of hypertonic saline [16] has been previously shown to rapidly increase serum sodium by 7.3 mmol/l which then gradually decreased to normal after 30 min. However, in our study the serum sodium level of both groups was similar and could not account for differences in water intake between the groups. The differences in drinking behaviour between the two groups may represent differences in sensitivity to cellular dehydration, or acute changes in plasma volume, and/or increases in plasma osmolality in each dog. When a hypertonic solution is added to the extracellular fluid, the osmolality increases, causing rapid osmosis of water from cells into the extracellular compartment [8].

Thus, in the present study, infusion of a saltload which was sufficient to cause a 15–20% increase in plasma volume by the rapid influx of water from the cells to balance osmolality would be expected to have resulted in acute suppression of vasopressin release through the stimulation of pressure/volume receptors in the cardiac atria, aorta and carotid sinus. Differences in the sensitivity of osmoreceptors and baroreceptors reacting to increases in osmolality and pressure or volume, respectively, may help explain the drinking responses observed in these dogs. It is known that ANF promotes both natriuresis and diuresis as well as antagonizes the action of vasopressin. Despite the extent of SC no significant elevation in ANF occurred over the subsequent 2 h; however ANF was slightly higher in Group A than B at the onset of the 2 h period where a difference in drinking pattern emerged. Basal ANF levels did not relate to the subsequent occurrence of fluid retention after rapid ventricular pacing. Angiotensin II is known to stimulate the thirst center [19,20] and reduce renal blood flow [23]. The angiotensin system is usually not elevated until congestive heart failure is advanced and both ascites and weight gain are evident in the pacing model [10,23]. It may be that fluid retention in dogs with CHF in Group A was partly related to their sensitivity to a thirst stimulus such as angiotensin II which was not measured in this study.

Serum sodium was shown to decrease in a previous pacing study [10]. Furthermore, it has been suggested that hyponatremia in congestive heart failure may be related to the activation of the renin–angiotensin system [23]. A decrease in serum sodium at advanced heart failure in the presence of increased body weight and edema formation has been suggested to be the result of an impairment in free water clearance [8,25–27]. The mechanism of this impairment has been proposed [8] to be an angiotensin-mediated decrease in renal blood flow with a concomitant increase in osmolality in the inner medulla inhibiting free water excretion. Angiotensin has also been implicated as a modulator of plasma vasopressin increase, thereby promot-
ing water reabsorption in the renal collecting ducts and further reducing free water clearance [28]. Both of these hormonal changes are the result of compensatory efforts to maintain systemic blood pressure in the face of decreasing cardiac function.

Some limitations to this study should be noted. We analyzed plasma ANF only up to 2 h after SC. Since most of the differential drinking between Group A and B occurred after 2 h, additional ANF samples at 5 h and 24 h would have been helpful to delineate the ANF responses in the two groups in response to volume expansion and may have improved the correlation between this variable and the degree of fluid retention. Secondly, although ANF values were significantly different in the two groups at 2 h after SC, the magnitude of the changes were relatively small. In view of these minimal changes, the analysis of other hormonal regulators of fluid homeostasis (in particular, renin, angiotensin II and arginine-vasopressin) may have helped us to gain additional insights.

Changes in right atrial pressure, left ventricular end-diastolic pressure and cardiac index from control to end studies did not correlate with fluid retention scores. This suggests that other factors, possibly humoral or renal-related may play an important role in determining which dogs develop fluid retention despite similar hemodynamic impairment.

In summary, our results suggest that intact normal dogs may be categorized into two groups based on water intake following an intra-arterial saltload. Furthermore, water intake and urine-concentrating ability following the saltload may be useful to predict the development of fluid retention in experimental pacing-induced congestive heart failure.

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