The renin–angiotensin–aldosterone system, antidiuretic hormone and sympathetic nerve activity in an experimental model of congestive heart failure in the dog

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Summary

1. Congestive heart failure was induced in dogs by rapid pacemaker stimulation of the heart (240–280/min) for 14 days. This represents a model of low output heart failure which permits the study of the development and reversal of congestive heart failure in an anatomically intact circulation in the unanaesthetised animal.

2. Cardiac output was reduced by 54%. Pulmonary artery pressure gradually increased by a factor of 2.4 and pulmonary capillary pressure rose to 4.6 times basal values. The animals retained a mean of 1.1 litres of fluid.

3. At the same time there was a gradual increase of plasma levels of renin, angiotension II, aldosterone, noradrenaline and adrenaline. After the pacemaker stimulation was discontinued all hormone levels returned to normal, the retained fluid was excreted, and intracardiac pressures and cardiac output returned to baseline values.

4. When heart failure was established at the end of the pacemaker stimulation period an inappropriately high secretion of antidiuretic hormone in relation to plasma osmolality was observed in five of six dogs.

5. It is concluded that beside the well-known non-hormonal renal factors, these hormone systems may be involved in the formation of oedema in congestive heart failure. The inappropriately high levels of antidiuretic hormone may cause hyponatraemia by water retention, representing a state of ‘dilutional hypo-osmolality’.

Key words: adrenaline, aldosterone, angiotensin II, antidiuretic hormone, experimental congestive heart failure, noradrenaline, oedema, renin.

Introduction

The roles of the renin–angiotensin–aldosterone system, sympathetic nerve activity and antidiuretic hormone in the development of oedema in congestive heart failure are still unclear. In addition to haemodynamic changes which influence renal function and increase tubular reabsorption of sodium and water [1, 2] there are hormone systems (both pressor and nonpressor) involved in the regulation of electrolyte and water balance. It is known that the secretion of both renin [3] and aldosterone [4] is increased in severe heart failure and there is evidence that an inappropriately high secretion of antidiuretic hormone may participate in fluid retention by excessive water reabsorption, resulting in a clinical state of ‘dilutional hypo-osmolality’ [5]. Nonetheless there is controversy about the precise role of the renin–angiotensin–aldosterone system in heart failure [6–9]. Also, no experimental procedure has been described which produces heart failure in unanaesthetised animals with an anatomically intact circulation. In order to investigate the course of this disease experimental congestive heart failure was produced in the dog. This model not only allowed us to study the development of chronic heart failure but also allowed us to reverse the changes which occurred, permitting the study of both the haemodynamic and hormonal changes which take place during both processes.

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Methods
The experiments were performed in nine beagle dogs (14–16 kg) of which six went through the whole procedure. Under general anaesthesia (pentobarbitone sodium, 30 mg/kg) an external jugular vein was exposed and a Swan-Ganz thermodilution flow catheter 7F was positioned in the pulmonary artery. A second catheter was positioned in the right atrium and a pacemaker lead was implanted into the right ventricle. The positions of the catheters were checked by fluoroscopic control and by pressure recording. Control measurements were made 48 h later.

Pressures were obtained with a Statham P 23 Db pressure transducer and were registered on a polygraph recorder. Cardiac output was measured by thermodilution after injection of 10 ml of 0.9% sodium chloride solution (saline) at about 0°C into the right atrium. Control blood samples were withdrawn from the pulmonary artery for the measurement of the pressor hormones and plasma osmolality. The animals were given a standard diet with free access to water. All unanaesthetized procedures were done with the animal, which had been previously trained, lying in an unrestrained position on a table.

After control measurements the external pacemaker (Elema Siemens), which was worn by the animal in a small bag, was set at a rate of 240–280 beats/min for 14 days. After this time the pacemakers were stopped and the dogs were observed for a further 6 days. All experimental procedures were carried out with the permission of the appropriate governmental authorities and were under the regular supervision and control of an official veterinary surgeon. Pulmonary capillary pressure and pulmonary artery pressure were recorded daily, cardiac output was measured on days 0, 2, 4, 7, 14, 15, 17 and 20. During the pacing period all measurements were made at the high heart rate.

Blood for the determination of plasma renin concentration, angiotensin II, aldosterone, antiuretic hormone, noradrenaline, adrenaline and plasma osmolality was taken from the pulmonary artery on days 0, 3, 5, 8, 14, 15, 17 and 20. Plasma renin concentration was measured by radioimmunoassay with a commercially available kit (Becton Dickinson) by incubating plasma for 60 min at 37°C with sheep angiotensinogen. Angiotensin II was measured by radioimmunoassay by the method of Disterdieck & McElwee [10], aldosterone by radioimmunoassay kit (Sorin), antiuretic hormone by radioimmunoassay similar to that described previously [11], with a modification of the extraction procedure [12], and noradrenaline and adrenaline radioenzymatically by the method of Da Prada et al. [13]. Except for antiuretic hormone all measurements were carried out in duplicate. All these methods are routinely used in our laboratory and are well established standardized methods. In all assays used, the within-assay coefficient of variation does not exceed 10% and the inter-assay coefficient of variation does not exceed 14.9%. Plasma osmolality was measured by the freezing-point method (Knauer osmometer).

Statistical analysis was performed by Student’s t-test for paired samples. Data are given as means ± SEM and were considered significant at the P < 0.05 level.

Results
Three dogs died suddenly during the rapid phase of pacing (fatal arrhythmia). In an autopsy (performed by an independent veterinary surgeon) enlargement of both ventricles was found as well as pleural effusions and ascites. In one dog also a small pericardial effusion was observed.

All of the following results were obtained from the remaining six dogs. There was a gradual increase in mean pulmonary artery and pulmonary capillary pressure during rapid pacing of the heart, reaching a plateau on days 5, 6 and 7 (Fig. 1). Pulmonary capillary pressure rose from 5.5 ± 0.7 to 25.3 ± 0.9 mmHg and pulmonary artery pressure from 13.0 ± 1.9 to 31.8 ± 0.4 mmHg. After the pacemaker stimulation was discontinued there was a slow return of pulmonary capillary and pulmonary artery pressures to normal values within 6 days. During pacemaker
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stimulation, cardiac output dropped from \(3.5 \pm 0.5\) to \(1.6 \pm 0.1\) litres/min. Again, this variable returned to basal levels after pacing was stopped. During pacing, body weight decreased only slightly from \(14.9 \pm 0.9\) to \(14.1 \pm 0.8\) kg (Fig. 2), although the animals reduced their food intake towards the end of the pacing period. After the pacemakers were stopped the dogs excreted a mean of \(1.1\) litres of fluid and their mean body weight dropped to \(13.0 \pm 0.8\) kg (\(P < 0.05\)).

Plasma renin concentration, angiotensin II and aldosterone were all gradually increased during the development of congestive heart failure and there was a reversal to normal after the end of stimulation (Fig. 3).

Antidiuretic hormone levels and plasma osmolality were in the normal range until the last day of pacing, when severe heart failure was established (Fig. 4). Plasma osmolality decreased from \(302.7 \pm 3.7\) (day 0) to \(295.7 \pm 3.0\) (day 14) mosmol/kg of water (\(P < 0.05\)) (Fig. 4). In comparison with basal values, antidiuretic hormone showed an increase in five of six dogs on day 14 (Fig. 5). In these five animals the increase of antidiuretic hormone in relation to the decreased plasma osmolality represents an inappropriately high secretion, which normally would be prevented by the hypothalamic osmoreceptor system. One dog showed an intact regulation of antidiuretic hormone, which decreased according to the fall in plasma osmolality. After stopping ventricular pacing there was a significant suppression of antidiuretic hormone on day 17 compared with control values (\(P < 0.05\)) and plasma osmolality was significantly elevated on days 17 and 20 (\(P < 0.025\)), indicating a water diuresis.

**Fig. 2.** Mean body weight before, during and after pacemaker stimulation (hatched area represents the calculated retained fluid during the development of heart failure).

**Fig. 3.** Plasma renin concentration, angiotensin II (ANG II) and aldosterone before, during and after external pacemaker stimulation (***P < 0.001).

**Fig. 4.** Arginine-vasopressin and plasma osmolality before, during and after rapid pacing (*P < 0.05).
Plasma noradrenaline and adrenaline showed a similar pattern to that for plasma renin concentration, angiotensin II and aldosterone during the development of congestive heart failure and also after stopping the pacemakers (Fig. 6).

Discussion
In addition to the well-established non-hormonal renal mechanisms involved in the development of oedema, by increasing tubular reabsorption of sodium and water [1, 2], hormonal factors may contribute to this process. As has been found previously [14–16] the renin–angiotensin–aldosterone system is activated in heart failure and the renin–angiotensin system is recognized as the major stimulus for the increased aldosterone secretion [17–19]. The stimulation of the renin–angiotensin system in heart failure is probably due both to renal mechanisms [20, 21] and increased sympathetic nerve activity [22]. In the studied animal model of heart failure increased plasma renin concentration, angiotensin II, noradrenaline and adrenaline were found, and cardiac function deteriorated as indicated by a fall in cardiac output and an increase in intracardiac pressures. In the same time fluid retention occurred. It is possible that angiotensin II [23, 24], noradrenaline [25] and adrenaline [26] directly affected renal sodium conservation or indirectly influence it by the stimulation of aldosterone. This is in agreement with data from other animal models of low cardiac output [27, 28] in which the role of the renin–angiotensin–aldosterone system in fluid retention has been demonstrated by using converting-enzyme inhibitors.

In the reported experiments, in five of six animals an inappropriately high secretion of antidiuretic hormone was observed when heart failure was established, resulting in high levels of antidiuretic hormone in relation to plasma osmolality. This means that the normal regulating system, of the secretion of antidiuretic hormone, via hypothalamic osmoreceptors and atrial volume receptors, must have been over-ridden by non-osmolar stimuli [5]. This may be the result of impaired secretion of antidiuretic hormone in response to atrial stretch or volume receptor activity [29] and/or it may be caused by a parasympathetic stimulation via carotid baro-receptors when 'effective' arterial blood volume is reduced [30, 31]. Furthermore angiotensin II may directly influence the release of antidiuretic hormone [32].

This is in accordance with data from patients with severe heart failure both from our laboratory [33] and others [34], in which inappropriately
high levels of antidiuretic hormone were found in patients with low plasma osmolality or hyponatraemia. These findings suggest that antidiuretic hormone contributes to water retention and to the development of hyponatraemia in heart failure, although we certainly cannot exclude the role of intrarenal factors in the development of hyponatraemia in heart failure in these experiments.

References