Influence of angiotensin on the early progression of heart failure

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Lohmeier, Thomas E., H. Leland Mizelle, Glenn A. Reinhart, and Jean-Pierre Montani. Influence of angiotensin on the early progression of heart failure. Am. J. Physiol. Regulatory Integrative Comp. Physiol. 278: R74–R86, 2000.—The purpose of this study was to elucidate the role of circulating ANG II in mediating changes in systemic and renal hemodynamics, salt and water balance, and neurohormonal activation during the early progression of heart failure. This objective was achieved by subjecting six dogs to 14 days of rapid ventricular pacing (240 beats/min) while fixing plasma ANG II concentration (by infusion of captopril + ANG II) either at approximately normal (days 1–8, 13–14) or at high physiological (days 9–12) levels. Salt and water retention occurred during the initial days of pacing before sodium and fluid balance was achieved by day 8. At this time, cardiac output and mean arterial pressure were reduced to ~55 and 75% of control, respectively; compared with cardiac output, reductions in renal blood flow were less pronounced. Although plasma ANG II concentration was maintained at approximately normal levels, there were sustained elevations in total peripheral resistance (to ~135% of control), filtration fraction (to ~118% of control), and plasma norepinephrine concentration (to 2–3 times control). During the subsequent high rate of ANG II infusion on days 9–12, there were no additional sustained long-term changes in either systemic or renal hemodynamics other than a further rise in right atrial pressure. However, high plasma levels of ANG II induced sustained antinatriuretic, sympathoexcitatory, and dipsogenic responses. Because these same long-term changes occur in association with activation of the renin-angiotensin system during the natural evolution of this disease, these results suggest that increased plasma levels of ANG II play a critical role in the spontaneous transition from compensated to decompensated heart failure.

sodium excretion; sympathetic nervous system; cardiac output; systemic and renal hemodynamics; drinking; atrial natriuretic peptide

NEUROHORMONAL ACTIVATION PLAYS an important role in the pathophysiology and prognosis of heart failure (5, 6, 9, 10, 12, 33). Because angiotensin-converting enzyme inhibitors have been shown to delay the progression of heart failure and to improve symptoms and prolong life in patients with ventricular dysfunction (5, 9, 33), there has been considerable interest in the mechanisms whereby the renin-angiotensin system contributes to the pathogenesis of congestive heart failure. Of particular importance to the pathogenesis and treatment of heart failure are the actions of ANG II, which lead to the early progression of this disease. Unfortunately, there is a limited understanding of the role of the renin-angiotensin system in the early progression of heart failure for several reasons. First, most experimental and clinical studies have been conducted in subjects with advanced heart failure. From these studies, one cannot determine the role of ANG II in the early progression of the disease. Secondly, in most heart failure studies designed to elucidate the influence of ANG II on systemic and renal hemodynamics and sodium excretion, acute responses to blockade of the renin-angiotensin system have been determined. However, short-term responses to alterations in ANG II activity do not necessarily reflect long-term actions of ANG II. Additionally, most measurements of systemic hemodynamics in subjects with heart failure have been made only under resting conditions, which may not reflect the hemodynamic actions and consequences of elevated circulating levels of ANG II during daily activity. Finally, there are few longitudinal studies that have combined measurements of systemic and renal hemodynamics, salt and water balance, and neurohormonal responses throughout the evolution of heart failure. Studies that incorporate all of these factors are necessary to elucidate the relative importance of the multiple actions of ANG II on the progression of heart failure.

Neurohormonal determinations under resting conditions indicate that increased sympathetic activity, but not activation of the renin-angiotensin system, is characteristically associated with the early stages of ventricular dysfunction when salt and water balance is maintained; protracted fluid retention occurs only later in the disease process when plasma norepinephrine (NE) concentration increases further in association with elevations in plasma renin activity (8, 10, 28). These neurohormonal measurements under resting conditions suggest the following. First, because plasma renin activity (PRA) is normal in the early stages of ventricular dysfunction, it would appear that circulating ANG II has little influence on hemodynamics and sodium excretion in the compensated phase of heart failure when salt and water balance is achieved. However,
ever, this notion does not account for the possibility that impaired hemodynamic responses and excessive sympathetic stimulation during daily activity result in periods of abnormally high plasma ANG II concentration that may have significant hemodynamic and antinatriuretic consequences. Secondly, because the progression of heart failure is associated with activation of the renin-angiotensin system, it is conceivable that ANG II plays a causal role in promoting salt and water retention and inducing further sympathoexcitation during the transition from compensated to decompensated heart failure. There is little direct evidence, however, to support this notion, and little is known about the critical neurohormonal mechanisms that initiate the protracted retention of salt and water in the decompensated phase of heart failure.

 Accordingly, the goal of the current study was to elucidate the influence of circulating ANG II on the progressive changes in systemic and renal hemodynamics, salt and water balance, and sympathetic activation that are present both in the early stages of cardiac dysfunction and in the early transition from compensated to decompensated heart failure. To accomplish this goal, heart failure was achieved by rapid ventricular pacing. We used a protocol of pacing-induced heart failure that is both reproducible and predictable and one that mimics the systemic and renal hemodynamic, the neurohormonal, and the water and electrolyte changes that occur in the early stages of asymptomatic heart failure in humans (8, 10, 28). In the present study, however, the influence of ANG II on the early progression of heart failure was elucidated by maintaining plasma ANG II concentration either at approximately normal levels or the elevated physiological levels expected during the spontaneous transition from compensated to decompensated heart failure. This was achieved by chronic infusion of both captopril and ANG II throughout the entire progression of heart failure. Finally, to determine the integrated daily effects of ANG II on systemic hemodynamics and salt and water balance rather than the less-relevant cardiovascular influences of ANG II under basal conditions, arterial pressure, cardiac output, right atrial pressure, and salt and water balance were monitored 24 h/day.

METHODS

Animal preparation. Six male dogs weighing 18–26 kg were used in this study, and all procedures were in accordance with National Institutes of Health Guidelines and approved by the Institutional Animal Care and Use Committee. Prior to surgery, the dogs were administered atropine (0.05 mg/kg sc), sedated with acapromazine (0.15 mg/kg sc), and then anesthetized with isoflurane (1.5–2.5%) after induction with thiopental (10 mg/kg iv). All surgical procedures have been described previously (28, 29). In short, catheters made of Tygon microbore tubing were implanted in the lower abdominal aorta and inferior vena cava via the femoral arteries and veins, respectively. Through an incision in the left fourth intercostal space, the pericardium was incised, an electromagnetic flow probe (Carolina Medical Electronics, King, NC) was placed around the ascending aorta, and screw-in bipolar epicardial pacemaker leads (Medtronic, Minneapolis, MN) were implanted near the apex of the left ventricle. Finally, a Tygon catheter was placed in the right atrium through the atrial appendage. The flow probe, pacemaker leads, and catheters were then externalized infrascapularly, and the thoracotomy was closed. Postoperatively, the dogs were treated with antibiotics (Cefazolin sodium, 0.5 g two times per day) for 5 days and analgesics for the first 24–48 h (buprenorphine hydrochloride, 0.015 mg/kg im 2 times/day). Patency of the atrial catheters was maintained by flushing daily with isotonic saline and by filling the catheters with heparin (1,000 U/ml); the femoral catheters were flushed 2–3 times per week and filled with heparin.

Approximately 2 wk after surgery, the dogs were placed in metabolic pens in a room maintained at 22 ± 2°C with a 12:12-h light-dark cycle. They were fitted with a specially designed harness containing two blood pressure transducers (model P23 ID, Statham Laboratories, Hato Rey, Puerto Rico) that were mounted on opposite sides of the chest at the level of the tricuspid valve (28–30, 40). These transducers were used for measurement of right atrial pressure (RAP). An additional transducer mounted at heart level was used for measurement of arterial pressure. Isotonic saline (500 ml/day) was infused continuously in one of the femoral vein catheters by means of a Wiz peristaltic pump (Isco, Lincoln, NE). A disposable filter (Cathivex, Millipore, Bedford, MA) was connected in series with the infusion to prevent passage of bacteria and other contaminants.

During a 10-day training and equilibration period and throughout the entire experiment, the dogs were given free access to water and maintained on a fixed daily diet of two 15.5-oz cans of prescription heart diet (HD; Hill’s Pet Products, Topeka, KS) supplemented with 5 ml of vitamin syrup (V.A.L. Syrup, Fort Dodge Laboratories, Fort Dodge, IA). Two cans of HD provide ~5 meq of sodium and ~60 meq of potassium. Thus, with the intravenous saline infusion, sodium intake was ~80 mg/day. Water consumption was monitored, and 24-h urine samples were collected at noon, ~15 min after feeding. Body temperature was measured each morning, and amoxicillin (250 mg 2 times/day) and dicyclomycin (250 mg 2 times/day) were given prophylactically. During the 10-day period that commenced after harnessing, the dogs were trained to lie quietly in their cages for 2–3 h each morning for collection of blood samples and for determination of renal clearances. On the last few days of the equilibration period, renal function was determined and blood samples were taken; additionally, 24-h measurements of hemodynamics and fluid and electrolyte balance were begun. After these measurements, plasma ANG II concentration was chronically fixed at approximate control levels by continuous intravenous infusion of the angiotensin-converting enzyme inhibitor cap-
topril (Bristol-Meyers Squibb Pharmaceutical Research Institute, Princeton, NJ) and ANG II ([Asp1, Val5]ANG II, Ciba-Geigy, Summit, NJ) at 14 µg·kg⁻¹·min⁻¹ and 0.5 ng·kg⁻¹·min⁻¹, respectively. This rate of captopril infusion chronically inhibits endogenous ANG II formation in the dog (30, 37), whereas the rate of ANG II infusion would be expected to produce approximately normal plasma levels of the peptide (36). Accordingly, this infusion rate of ANG II maintains MAP, glomerular filtration rate (GFR), renal plasma flow (RPF), filtration fraction, and sodium excretion at control levels during captopril administration (37). If small changes in MAP did occur during the first 48 h of captopril + ANG II infusion, the rate of ANG II infusion was adjusted slightly (range = 0.3–0.8 ng·kg⁻¹·min⁻¹) to return MAP to the 24-h control value for that dog. The average infusion rate for all six dogs was 0.63 ± 0.09 ng ANG II·kg⁻¹·min⁻¹. As indicated in RESULTS, by using MAP as an index for the rate of ANG II infusion during captopril administration, all values for systemic and renal hemodynamics, salt and water excretion, and plasma levels of hormones and catecholamines remained at the levels observed prior to blockade of the renin-angiotensin system. To insure steady-state conditions, the captopril + ANG II infusion was maintained for a total of 5–6 days before initiating rapid ventricular pacing. Finally, to verify that the captopril infusion blocked conversion of endogenous ANG I to ANG II, the pressor effects of intravenous bolus injections of ANG I (2 µg) on MAP were determined before and after chronic administration of captopril + ANG II. Prior to captopril infusion, ANG I increased MAP 41 mmHg; in contrast, during captopril administration, there were no discernible changes in MAP in response to ANG I.

On the day before pacing, blood samples were taken and renal function was measured once again to establish control values for the subsequent experimental period. After these control measurements, a modified pulse generator (model 5984 or 8420, Medtronic, Minneapolis, MN) was connected to the epicardial pacemaker leads and the heart rate was increased to 240 beats/min for 14 days (28). Plasma ANG II concentration was fixed at approximately normal levels throughout the 2 wk of pacing except on days 9–12 when the rate of ANG II infusion was increased to 5 ng·kg⁻¹·min⁻¹. This higher rate of ANG II infusion during this 4-day period would be expected to produce an approximately eightfold increase in plasma ANG II concentration (36) and, therefore, mimic the activation of the renin-angiotensin system that is normally associated with the spontaneous transition from compensated to decompensated heart failure (28). Renal function was determined on days 1, 8, and 12 of pacing.

Before each renal clearance determination and on intermittent days throughout the control and experimental periods, 8-ml arterial blood samples were taken for measurement of hematocrit, PRA, and the plasma concentrations of atrial natriuretic peptide (ANP), NE, sodium, potassium, and protein. Blood samples were taken between 9:15 and 10:00 AM after the dogs had been in a recumbent position for ~45 min and MAP and heart rate were stable. All blood pressure transducers were calibrated each morning between 8:00 and 8:30 AM before blood sampling.

Analytical methods. Plasma ANP concentration and PRA were measured in 1.0- and 0.5-ml plasma samples by radioimmunoassay, as previously described (28, 40). Plasma NE concentration was determined by HPLC (BAS 200, Bioanalytical Systems, West Lafayette, IN) from 2-ml plasma samples (28, 37, 40). Plasma and urine concentrations of sodium and potassium were determined by flame photometry (model IL 943, Instrumentation Laboratories, Lexington, MA), plasma protein concentration was determined by refractometry (American Optical, Buffalo, NY), and hematocrit was determined by a micromethod (Autocrit II, Clay Adams, Franklin, NJ).

Water balance was calculated as fluid intake minus urine volume excretion. Fluid intake was considered to be water drunk plus the volume of isotonic saline infused each day (500 ml). The negative values for water balance during the control period reflect the fact that the water content of the food, which was constant from day to day, was not included in the calculation.

Measurements of GFR and RPF were made from the plasma clearances of [¹²⁵I]iothalamate (Glofil, Isotex Diagnostics, Friendswood, TX) and [¹³¹I]iodohippurate (Hippuran, Syncor International, Jackson, MS), respectively, using methods previously described (14, 15, 28). Renal blood flow was calculated from RPF and hematocrit. Renal vascular resistance was calculated as (MAP – RAP)/renal blood flow.

Statistics. Results are expressed as means ± SE. A two-way ANOVA was used to compare the responses during days 1–8 of pacing in the present study with the same responses in dogs with an intact renin-angiotensin system (28). Additionally, to determine whether high plasma levels of ANG II influenced the responses to pacing, all values during the high rate of ANG II infusion (days 9–12 of pacing) and the subsequent 2 days of recovery (days 13–14 of pacing) were compared with day 8 of pacing using one-way ANOVA followed by the Bonferroni t-test for multiple comparisons. Finally, values on the day prior to pacing (after 5–6 days of captopril + ANG II infusion) were taken as control. A paired t-test was used to compare values prior to captopril + ANG II with this control. Differences were considered statistically significant at a value of P < 0.05.

RESULTS

The results of the present study in dogs with plasma ANG II concentration fixed at approximately normal levels are superimposed in Figs. 1–3 with the results of an earlier study from our laboratory in which the renin-angiotensin system was functional during pacing (28); otherwise, the conditions of the two experiments were identical. In this earlier study, measurements of PRA under resting conditions indicated little or no activation of the renin-angiotensin system during 14 days of rapid ventricular pacing at 240 beats/min. Additionally, in dogs with an intact renin-angiotensin system (indicated as control in Figs. 1–3), there were no further significant changes in systemic or renal hemodynamics, salt and water balance, plasma concentrations of ANP, NE, sodium, potassium, or protein, or hematocrit after day 8 of pacing. That is, all responses were stable during the second week of pacing in dogs with an intact renin-angiotensin system (28).

Effects of captopril + ANG II infusion on baseline values. As illustrated in Tables 1 and 2, there were no significant changes in baseline values for systemic and renal hemodynamics during captopril + ANG II infusion. Furthermore, on the 2 days prior to pacing (after 5–6 days of captopril + ANG II infusion), urinary sodium and potassium excretion and water consumption were similar to values preceding infusion of captopril + ANG II (sodium excretion = 84 ± 5 meq/day, potassium excretion = 57 ± 3 meq/day, and water consumption = 85 ± 17 ml/day). Similarly, the plasma concentrations of ANP (107 ± 4 pg/ml), NE (85.0 ± 10.4
pg/ml), sodium (147 ± 1 meq/l), potassium (4.2 ± 0.1 meq/l), protein (6.4 ± 0.2 g/dl), and hematocrit (37 ± 1%) were unchanged during infusion of captopril + ANG II. Thus there were no significant changes in any baseline values when the renin-angiotensin system was fixed at normal levels by infusion of captopril + ANG II. Finally, prior to captopril + ANG II infusion, PRA was 0.56 ± 0.08 ng ANG I·kg⁻¹·min⁻¹. For the six dogs, an infusion rate of 0.63 ± 0.09 ng ANG II·kg⁻¹·min⁻¹ was required to prevent changes in baseline values during captopril infusion.

Systemic hemodynamics. With the renin-angiotensin system fixed at approximately normal levels, the most pronounced changes in systemic hemodynamics occurred prior to day 5 of pacing (Figs. 1 and 2). Thereafter, MAP, cardiac output, total peripheral resistance, and RAP were fairly stable until the rate of ANG II was increased on day 9. By day 4 of pacing, cardiac output fell to ~55% of control and remained at this level for the duration of pacing. In association with this fall in cardiac output, MAP decreased to ~75% of control on days 4–8 of pacing. Additionally, the greatest increase in central venous pressure occurred during days 2–4 when RAP increased from a control level of 0.9 ± 0.4 to 5.9 ± 1.4 mmHg (day 4). As a result of these hemodynamic changes, total peripheral resistance increased to ~135% of control on days 4–8 of pacing. The above relative changes in systemic hemodynamics in the present study during the first 8 days of pacing were not significantly different from those in control dogs with a functional renin-angiotensin system. Thus the renin-angiotensin system had little influence on systemic hemodynamics in the early stages of pacing-induced heart failure. Clearly, the rise in total peripheral resistance during pacing was independent of physiologically significant increments in plasma ANG II concentration.

During pacing, the high rate of ANG II infusion produced only transient changes in systemic hemodynamics, except for RAP (Figs. 1 and 2). Although there

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**Fig. 1.** Effects of rapid ventricular pacing on 24-h values for systemic hemodynamics in controls and in dogs with plasma ANG II concentration fixed at either normal or high levels. A: mean arterial pressure; B: cardiac output; C: total peripheral resistance. Values are means ± SE; n = 6 dogs. *P < 0.05 vs. day 8 of pacing.

**Fig. 2.** Effects of rapid ventricular pacing on 24-h values for right atrial pressure (A) and plasma concentrations of atrial natriuretic peptide (ANP; B) and norepinephrine (NE; C) in controls and in dogs with plasma ANG II concentration fixed at either normal or high levels. Values are means ± SE; n = 6 dogs. *P < 0.05 vs. day 8 of pacing.
were no further significant changes in cardiac output at high plasma levels of ANG II, MAP and total peripheral resistance did increase for 1–2 days before returning to the levels achieved prior to the high rate of ANG II infusion on day 8 (increments in MAP did persist after 4 days of high ANG II in all but one dog with the greatest impairment of cardiac output; in this dog, MAP actually decreased ~10 mmHg). In contrast to these transient changes, RAP increased progressively from 7.6 ± 1.2 to 11.1 ± 1.2 mmHg during the 4 days ANG II was infused at the high rate. Thus the most significant sustained systemic hemodynamic effect of high plasma levels of ANG II was an increase in RAP. As discussed next, this reflected the pronounced effects of ANG II on salt and water balance.

Salt and water balance. During the last 2 days of the control period just prior to pacing, urinary sodium, potassium, and volume excretion averaged 83 ± 4, 55 ± 3, and 865 ± 29 ml/day, respectively. Water consumption was 56 ± 13 ml/day, and water balance averaged ~325 ± 43 ml/day. As illustrated in Fig. 3, on day 1 of pacing there was a net loss of ~40 meq sodium and ~250 ml fluid. Subsequently, salt and water were retained for several days before sodium and fluid excretion returned toward control levels on day 8 of pacing. For the initial 8 days of pacing, there was a cumulative retention of ~140 meq sodium and ~950 ml water in the absence of a change in drinking. In the present study, the time-dependent changes in salt and water balance during days 1–8 of pacing were similar to those that occurred in control animals, indicating that the renin-angiotensin system had little influence on sodium and volume homeostasis in the early stages of pacing-induced heart failure.

In marked contrast to control animals that maintained salt and water balance during the last week of pacing, dogs with high plasma levels of ANG II on days 9–12 of pacing exhibited pronounced and protracted salt and water retention and increased drinking. During this 4-day period, the dogs retained ~275 meq sodium and ~2,300 ml water, and water consumption increased from 65 ± 19 (day 8) to 312 ± 81 ml/day on day 12 of high ANG II (Fig. 3). In association with the marked fluid retention (and increase in RAP), there were signs of lethargy, dyspnea, and ascites, which improved somewhat on days 13 and 14 of pacing when the rate of ANG II infusion was returned to basal levels. During this 2-day period, there was a net negative sodium and water balance of ~55 meq sodium and ~320 ml water, respectively, and water consumption (100 ± 34 ml/day) returned to basal levels. However, during these 2 days, the dogs excreted <20% of the salt and water retained when plasma ANG II levels were elevated. Finally, there were no significant changes in urinary potassium excretion during pacing. In summary, high plasma levels of ANG II during pacing.

Table 1. Systemic hemodynamics before and during chronic infusion of captopril + ANG II

<table>
<thead>
<tr>
<th></th>
<th>MAP, mmHg</th>
<th>CO, l/min</th>
<th>TPR, mmHg l·min⁻¹</th>
<th>RAP, mmHg</th>
<th>HR, beats/min</th>
</tr>
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<tbody>
<tr>
<td>Preinfusion</td>
<td>99 ± 3</td>
<td>2.6 ± 0.1</td>
<td>39.3 ± 2.2</td>
<td>0.9 ± 0.3</td>
<td>73 ± 3</td>
</tr>
<tr>
<td>Captopril + ANG II</td>
<td>101 ± 4</td>
<td>2.7 ± 0.1</td>
<td>38.9 ± 2.1</td>
<td>0.9 ± 0.4</td>
<td>76 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 6. MAP, mean arterial pressure; CO, cardiac output; TPR, total peripheral resistance; RAP, right atrial pressure; HR, heart rate. There were no significant changes in the baseline values during captopril + ANG II infusion.

Table 2. Renal hemodynamics before and during chronic infusion of captopril + ANG II

<table>
<thead>
<tr>
<th></th>
<th>GFR, ml/min</th>
<th>RPF, ml/min</th>
<th>FF</th>
<th>RBF, ml/min</th>
<th>RR, mmHg·min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preinfusion</td>
<td>76.1 ± 6.0</td>
<td>203 ± 20</td>
<td>0.38 ± 0.02</td>
<td>320 ± 29</td>
<td>0.33 ± 0.03</td>
</tr>
<tr>
<td>Captopril + ANG II</td>
<td>73.2 ± 7.0</td>
<td>188 ± 17</td>
<td>0.39 ± 0.01</td>
<td>290 ± 25</td>
<td>0.36 ± 0.03</td>
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Values are means ± SE; n = 6. GFR, glomerular filtration rate; RPF, renal plasma flow; FF, filtration fraction; RBF, renal blood flow; RR, renal resistance. There were no significant changes in the baseline values during captopril + ANG II infusion.

Fig. 3. Effects of rapid ventricular pacing on 24-h values for urinary sodium excretion (A), water balance (B), and water consumption (C) in controls and in dogs with plasma ANG II concentration fixed at either normal or high levels. Values are means ± SE; n = 6 dogs. *P < 0.05 vs. day 8 of pacing.
induced substantial salt and water retention and increased drinking.

Neurohormonal responses. The neurohormonal responses to rapid ventricular pacing are shown in Fig. 2. After day 1, plasma ANP concentration increased in parallel with RAP until day 8 of pacing. On day 8 of pacing, there was an approximately six- to sevenfold increase in plasma ANP concentration (control = 121 ± 12 pg/ml). Additionally, on days 2–8 of pacing, plasma NE concentration was two- to threefold greater than control (control = 84.0 ± 9.6 pg/ml). Importantly, these neurohormonal changes occurred in the absence of physiologically significant increments in plasma ANG II concentration and were similar to those that occurred previously in dogs with a functional renin-angiotensin system.

During pacing, plasma NE but not ANP concentration increased further in the presence of high plasma levels of ANG II. Despite additional increments in RAP, plasma concentrations of ANP failed to increase above day 8 pacing levels during the high rate of ANG II infusion. Furthermore, during the high rate of ANG II infusion, plasma levels of ANP were similar to those that occurred in controls not exhibiting further increments in RAP during week 2 of pacing. In contrast, plasma NE concentration increased progressively during the 4 days ANG II was infused at the high rate, reaching 6–7 times control on day 12. Because this additional two- to threefold increase in plasma NE concentration during the second week of pacing did not occur in control animals with normal PRA (28), this additional sympathoexcitation was a result of either the direct or indirect effects of elevated plasma levels of ANG II.

Renal hemodynamics. The most prominent changes in renal function during the first 8 days of pacing were reductions in RPF and increments in filtration fraction, which on day 8 reached values of ~75 and 118% of control, respectively (Table 3); decreases in GFR were relatively small, and on day 8 GFR was −88% of control. In addition, although filtration fraction increased in all but one dog during the high rate of ANG II infusion (the dog with the greatest fall in cardiac output and RPF on day 8 of pacing), there were no further statistically significant changes in GFR, RPF, or filtration fraction during high ANG II (day 12). These changes were comparable to those that occurred previously in control dogs with an intact renin-angiotensin system (28), as illustrated in Table 3. Thus elevated plasma levels of ANG II, while causing pronounced salt and water retention, had little sustained influence on renal hemodynamics during pacing.

The calculated values for renal blood flow and renal resistance as well as the recorded values for systemic hemodynamics during measurement of renal function (vs. the 24-h values in Fig. 1) are presented in Table 4. Most importantly, this table illustrates that in contrast to total peripheral resistance, which was elevated throughout the entire 2-wk period of pacing, renal resistance either decreased (day 1) or was unchanged from control levels during pacing. Thus, during pacing, renal blood flow was better preserved than blood flow throughout the remainder of the body. High plasma levels of ANG II did increase renal resistance in all but one dog (the dog with the greatest impairment in cardiac output and RPF during pacing). However, for the group as a whole, there were no significant changes in systemic blood flow or cardiac output during pacing.

Table 3. Changes in renal hemodynamics during rapid ventricular pacing in control dogs with an intact renin-angiotensin system (28) and in dogs with fixed plasma levels of ANG II.

<table>
<thead>
<tr>
<th>Day</th>
<th>Control</th>
<th>Fixed ANG II</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR, ml/min</td>
<td>74.1 ± 3.6</td>
<td>73.2 ± 7.0</td>
</tr>
<tr>
<td>RPF, ml/min</td>
<td>188 ± 12</td>
<td>188 ± 17</td>
</tr>
<tr>
<td>FF</td>
<td>0.40 ± 0.02</td>
<td>0.57 ± 0.02</td>
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</table>

Values are means ± SE; n = 6. Days 1 and 8 were compared with day 0 (prepacing), *P < 0.05. In addition, days 12–14 were compared with day 8. There were no significant differences between 2 groups. Also, there were no significant differences between day 8 and days 12–14 in either group.

Table 4. Changes in systemic and renal hemodynamics during rapid ventricular pacing in dogs with fixed plasma levels of ANG II.

<table>
<thead>
<tr>
<th>Day</th>
<th>Fixed ANG II</th>
</tr>
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<tbody>
<tr>
<td>MAP, mmHg</td>
<td>101 ± 4</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>86 ± 3*</td>
</tr>
<tr>
<td>TPR, mmHg·l⁻¹·min⁻¹</td>
<td>76 ± 4*</td>
</tr>
<tr>
<td>RBF, ml/min</td>
<td>89 ± 6</td>
</tr>
<tr>
<td>RR, mmHg·l⁻¹·min⁻¹</td>
<td>86 ± 6</td>
</tr>
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</table>

Values are means ± SE; n = 6. Days 1 and 8 were compared with day 0 (prepacing), *P < 0.05. In addition, day 12 was compared with day 8. There were no significant differences between days 8 and 12.
in MAP, renal blood flow, or renal resistance after 4 days of high plasma levels of ANG II (day 12).

Plasma concentrations of electrolytes and protein and hematocrit. During the first 8 days of pacing, the time-dependent changes in the plasma concentrations of electrolytes and protein and hematocrit were similar to those described for control animals (28) with one exception: plasma potassium concentration increased from 4.2 ± 0.1 to 4.6 ± 0.1 meq/l in the present study when plasma ANG II concentration was fixed at approximately normal levels, whereas it was unchanged in controls with an intact renin-angiotensin system. By day 8 of pacing there were no significant changes in either plasma sodium concentration (control = 147 ± 1 meq/l) or hematocrit (control = 35 ± 1%), whereas plasma protein concentration decreased from a control level of 6.4 ± 0.2 to 5.6 ± 0.2 g/dl (on day 8). In the present study, as in control animals (28), there were no further changes in either plasma sodium or potassium concentration or hematocrit during week 2 of pacing. In contrast, in the present study, the marked fluid retention induced by high plasma levels of ANG II was associated with further reductions in plasma protein concentration to 4.8 ± 0.2 g/dl on day 12. In control animals, neither fluid retention nor additional reductions in plasma protein concentration occurred during week 2 of pacing.

DISCUSSION

The present study elucidates the role of ANG II in mediating derangements in systemic and renal hemodynamics, neurohormonal activation, and alterations in salt and water balance during the early progression of heart failure. These results suggest that increased plasma levels of ANG II do not contribute importantly to the above responses in the early phase of heart failure when salt and water balance is achieved, and neurohormonal measurements under resting conditions indicate normal PRA. Furthermore, the current findings demonstrate that pathophysiological increases in plasma ANG II concentration have a profound effect on the early progression of heart failure by inducing pronounced and protracted salt and water retention, increased drinking, and further activation of the sympathetic nervous system. Because these same cardiovascular changes are normally associated with activation of the renin-angiotensin system during the natural transition from compensated to decompensated heart failure, these results support the hypothesis that ANG II plays a critical role in the early progression of this disease.

One of the goals of this study was to determine whether increments in plasma ANG II concentration contribute to the early events associated with the development of compensated heart failure. To accomplish this objective, it was necessary to maintain approximately normal plasma levels of ANG II during the initial 8 days of pacing. This was achieved by chronic infusion of captopril and a fixed rate of ANG II. Because ANG II is metabolized by tissue as well as circulating proteases and cardiac output decreased during pacing, one potential concern with our approach might be that plasma levels of ANG II actually increased on days 1–8 as a result of a fall in the metabolic clearance rate of ANG II. However, the decrease in cardiac output by almost 50% during pacing would be expected to produce a less than twofold increase in plasma ANG II concentration. Although not investigated in the present study, elevations in plasma levels of ANG II of this magnitude have very little or no effect on systemic or renal hemodynamics, sodium excretion, drinking, or neurohormonal activation in normal dogs (3, 16, 35, 36, 44). Furthermore, if sustained increments in plasma levels of ANG II on days 1–8 of pacing had contributed to the above responses, we would not have expected all of the measured responses during this initial period of pacing to be quantitatively comparable to those in paced dogs with a functional renin-angiotensin system, normal PRA under basal conditions, and possibly even episodic exacerbations in renin secretion and plasma levels of ANG II during periods of activity (28). Therefore, it is unlikely that increments in plasma ANG II concentration, as a result of decreased metabolic clearance rate of ANG II, contributed significantly to the responses that occurred during the initial days of pacing when approximately normal plasma levels of ANG II were maintained.

Systemic hemodynamics. Although chronic administration of angiotensin-converting enzyme inhibitors improves cardiac function in patients with advanced congestive heart failure (9, 33), little is known about the long-term influence of ANG II on systemic hemodynamics in the early phases of cardiac dysfunction. One fundamental issue that confounds this understanding is that there is controversy regarding the basic hemodynamic changes that are associated with the early evolution of heart failure. According to dogma, when cardiac output falls after an insult to the heart, compensatory increases in systemic vascular resistance occur to maintain arterial pressure and organ perfusion. However, despite reduced cardiac output, increased systemic vascular resistance has been observed in some (1, 8, 28, 29, 31, 39), but not all (8, 19, 34, 38, 43), previous studies of experimental heart failure. This variability presumably reflects many differences in experimental design, including: use of anesthesia, method for measurement of cardiac output, stage of heart failure, and state of the subject (resting vs. active). Additionally, one particularly important but often neglected consideration is whether RAP has been included in the calculation of total peripheral resistance. Whereas this is not an important consideration in most physiological states because RAP is negligible with respect to arterial pressure, it is particularly relevant in heart failure because substantial elevations in RAP are associated with the progression of the disease. Consequently, failure to include RAP in the calculation of total peripheral resistance can result in significant overestimation of systemic vascular resistance during the evolution of heart failure. In fact, failure to include RAP in this calculation may even indicate an increase in total peripheral resistance when one does not exist.
The results from the present longitudinal study, in which systemic hemodynamics were monitored 24 h/day, clearly demonstrate that the early progression of pacing-induced heart failure is associated with sustained increments in systemic vascular resistance; furthermore, the present study provides insight into the mechanisms that account for sustained peripheral vasoconstriction during chronic reductions in cardiac output. To our knowledge, the present study and earlier ones from our laboratory (28, 29) are the only experimental investigations that have continuously monitored arterial pressure, cardiac output, and RAP 24 h/day and have used computerized technology to calculate total peripheral resistance on a minute-by-minute basis throughout the early progression of heart failure. Because plasma ANG II concentration was fixed at approximately normal levels during the first 8 days of pacing in the present study and the systemic hemodynamic response was similar to that which occurred previously in dogs with a functional renin-angiotensin system subjected to the same rate of ventricular pacing (28), it is unlikely that increased plasma levels of ANG II exert an important influence on the early systemic hemodynamic events associated with this model of heart failure. These findings differ from those of Rieger et al. (39) and Brands et al. (1), who reported attenuated increments in peripheral resistance (and attenuated reductions in cardiac output) during pacing in dogs administered angiotensin-converting enzyme inhibitors vs. dogs with an intact renin-angiotensin system. However, in these earlier studies (1, 39), the pacing conditions produced more severe reductions in cardiac output and greater activation of the renin-angiotensin system than in the present model of compensated pacing-induced heart failure. Furthermore, another important difference between these earlier studies (1, 39) and ours is that in the present study, plasma ANG II concentration was fixed at approximately normal levels prior to and throughout the initial stages of pacing-induced heart failure to prevent hemodynamic changes associated with complete inhibition of the renin-angiotensin system. Under conditions devoid of baseline changes in systemic (and renal) hemodynamics, the present results indicate that increased plasma levels of ANG II do not account for the long-term increases in systemic vascular resistance and the reductions in cardiac output present in the early stages of compensated heart failure. Furthermore, these data indicate that early sustained increments in peripheral vascular resistance do occur in response to long-term reductions in cardiac output and arterial pressure and that they are mediated by mechanisms other than by activation of the renin-angiotensin system. Possible mechanisms include increased sympathetic activity and decreased nitric oxide production (due to decreased shear stress associated with the fall in cardiac output).

Even when plasma levels of ANG II were increased by infusion during pacing, ANG II had little sustained influence on systemic hemodynamics other than increasing RAP. During increased plasma levels of ANG II, there were no significant changes in cardiac output and sustained arterial pressure responses were either diminished, compared with normal dogs (14, 16, 24, 26), or nonexistent. Because only transient increases in total peripheral resistance occurred at the high rate of ANG II infusion, it would appear that local autoregulatory mechanisms and/or vasodilator factors were sufficient to offset the vasoconstrictor actions of ANG II. These results, however, do not exclude the possibility that local mechanisms may fail in the more chronic phases of advanced heart failure, leading to further increases in peripheral resistance and reductions in cardiac output. For example, it has been shown that endothelium-dependent vasodilation is impaired in advanced heart failure (8).

Salt and water balance. Salt and water retention occurred during the first week of pacing before sodium excretion returned toward control levels. A previous chronic study in dogs with bilateral atrial appendectomy and impaired ANP secretion provided direct evidence that high circulating levels of ANP are essential to the long-term maintenance of sodium balance during sustained reductions in cardiac output and arterial pressure in the compensated phase of pacing-induced heart failure when salt and water balance is achieved (28).

Interestingly, renin secretion does not appear to be elevated in the early stages of heart failure, despite reduced arterial pressure and increased sympathetic activity (1, 8, 10, 28). Thus normal PRA values under resting conditions suggest that the renin-angiotensin system has little influence on salt and water balance in the early stages of ventricular dysfunction. Indeed, direct support for this notion is provided by the present study. In the present study, the temporal pattern of salt and water excretion during the first 8 days of pacing when plasma ANG II concentration was fixed at approximately normal levels was very similar to that which occurred previously in paced dogs with a functional renin-angiotensin system (28).

The normal transition from compensated to decompensated heart failure is associated with activation of the renin-angiotensin system, pronounced salt and water retention, and increased drinking (1, 8, 10, 28, 31). To determine whether pathophysiological levels of ANG II may play a causal role in promoting these changes in salt and water balance, the rate of ANG II infusion was increased during the second week of pacing to achieve physiologically relevant increments in plasma ANG II concentration (1, 27, 30). In contrast to the basal rates of sodium excretion and drinking typically observed in the presence of normal levels of PRA during week 2 of pacing (28), increased ANG II infusion on day 9 of pacing in the present study led to marked and protracted salt and water retention and increased drinking. This is consistent with the hypothesis that activation of renin-angiotensin system plays a causal role in mediating the spontaneous transition from compensated to decompensated heart failure.

In light of the profound influence of arterial pressure on the long-term sodium excretory response to the renin-angiotensin-aldosterone system (14–16), the sus-
tained antinatriuresis induced by increased plasma levels of ANG II during pacing was not too surprising. Under normal conditions, the high infusion rate of ANG II administered in the present study produces transient sodium retention lasting 2–3 days and is associated with a 30–35-mmHg increase in MAP (14, 16, 24, 26). However, when renal perfusion pressure is prevented from increasing during ANG II infusion, there is sustained sodium retention (14, 16). In the present study in dogs with pacing-induced heart failure, MAP not only failed to increase to hypertensive levels, but it actually remained below control during ANG II infusion. Thus the pronounced and protracted sodium retention induced by ANG II during pacing is consistent with the concept that increased renal perfusion pressure plays a major role in permitting the kidneys to escape from the sodium-retaining actions of ANG II (14–16). The results of the present study are also consistent with the observations that either chronic mineralocorticoid administration or chronic infusion of ANG II at doses that normally elevate arterial pressure does not increase MAP to hypertensive levels in dogs with high-output heart failure and is not associated with sodium escape (41, 42).

In the present study, the effects of increased plasma levels of ANG II on drinking as well as sodium excretion differed markedly from the response in normal dogs. A number of acute studies have shown that ANG II acts centrally to stimulate drinking (17). However, when high physiological levels of ANG II are achieved in normal dogs by intravenous infusion of ANG II, drinking does not increase either acutely or chronically (26, 36). In contrast, during pacing-induced heart failure in the present study as well as during high-output heart failure (41), increments in plasma levels of ANG II to pathophysiological levels induced a sustained increase in drinking. Because acute studies have shown that activation of cardiopulmonary and arterial baroreceptors inhibits drinking, it has been proposed that the increase in blood pressure normally associated with ANG II infusion counteracts the central dipsogenic effects of ANG II. This hypothesis is supported by the observation that the drinking response to acute infusions of ANG II is enhanced in dogs with cardiac and sinoaortic denervation (20). However, even if baroreflexes prove to have a long-term influence on drinking, they would be expected to be relatively unimportant in offsetting the drinking response to ANG II in heart failure for the following reasons.

1. Cardiopulmonary baroreflex function is impaired in heart failure (7, 8, 45), and therefore, the restraining influence of cardiac reflexes on drinking may be attenuated, despite high cardiac pressures. Secondly, because arterial pressure is reduced and the rise in arterial pressure in response to ANG II is greatly diminished in heart failure, there would be little activation of arterial baroreflexes to oppose the central stimulatory effects of ANG II on drinking. Regardless of mechanism, the results of the present study demonstrate that increased drinking during the spontaneous transition from compensated to decompensated heart failure can be mimicked in dogs with compensated pacing-induced heart failure by infusion of high physiological levels of ANG II.

2. Neurohormonal responses. Sympathetic activation is an early event in the progression of heart failure, and plasma levels of NE are inversely related to cardiac function (10, 23). Despite this, it is not clear whether increased sympathetic activity merely reflects deterioration of cardiac function or whether it contributes to the decline in cardiac performance, either by direct effects on the heart or by indirect actions to increase preload and afterload. Furthermore, the aff erent mechanisms that account for increased sympathetic activity in heart failure remain an enigma. Because arterial and cardiopulmonary baroreflexes inhibit sympathetic activity, it has been suggested that the sympathoexcitation of heart failure may be due to depressed baroreflexes (7, 8, 45). Another hypothesis is that increased sympathetic activity in heart failure is due to the stimulatory actions of ANG II on the sympathetic nervous system (7, 36, 45). However, although baroreflex dysfunction and activation of the renin-angiotensin system are associated with the progression of heart failure (8, 45), there is little direct evidence from studies employing either chronic baroceptor denervation or chronic blockade of the renin-angiotensin system to indicate that either of these mechanisms accounts for sympathetic activation in heart failure.

The present study provides insight into the mechanisms that account for sympathetic activation during the progression of heart failure. Plasma levels of NE increased during the first 8 days of pacing even though plasma ANG II concentration was fixed at approximately normal levels; furthermore, the rise in plasma NE concentration was similar to that which occurred in paced dogs with a functional renin-angiotensin system and normal PRA (28). Thus the present findings indicate that the early activation of the sympathetic nervous system in pacing-induced heart failure is independent of increased circulating levels of ANG II. On the other hand, because plasma NE concentration increased substantially when plasma levels of ANG II were increased by infusion, this finding suggests that activation of the renin-angiotensin system may play a causal role in mediating further sustained increments in sympathetic activity, such as during the spontaneous transition from compensated to decompensated heart failure. Whereas these findings indicate that activation of the renin-angiotensin system may account for concomitant increases in plasma NE concentration during the progression of heart failure, it is not clear whether sympathetic stimulation in the present study was due to direct actions of ANG II on the sympathetic nervous system or whether sympathetic activation merely reflected further deterioration of circulatory (although cardiac output did not decrease further) or respiratory function due to excessive salt and water retention. A recent study, however, supports the former possibility (7). In that study, acute administration of an ANG II antagonist decreased renal sympathetic nerve activity more in rabbits with chronic heart failure and elevated
PRA than in controls. A unique aspect of this earlier study was that the fall in arterial pressure normally associated with ANG II blockade was circumvented by infusion of the α-adrenoreceptor agonist methoxamine. Therefore, in the absence of the confounding influence of hypotension-induced reflex activation of the sympathetic nervous system during ANG II blockade, this study indicates that ANG II has direct sympathoexcitatory effects in the more chronic stages of heart failure when there is increased activity of the renin-angiotensin system.

In the present study, the sustained increase in plasma NE concentration during the high rate of ANG II infusion contrasts markedly with the chronic sympathetic response to ANG II infusion in normal dogs. In normal dogs, infusion of high physiological levels of ANG II causes hypertension and is not associated with an increase in plasma NE concentration (3, 24, 26). In fact, under these conditions, renal sympathetic nerve activity is chronically depressed (3), a response that promotes sodium excretion (24). Although the afferent mechanisms that account for sustained renal sympathoinhibition during chronic ANG II hypertension have not been established, it is conceivable that activation of cardiopulmonary and/or arterial baroreflexes mediates this long-term response as a result of the sodium-retaining and hypertensive effects of ANG II. However, if this is indeed the case, the inhibitory influence of baroreflex activation on renal sympathetic nerve activity would be expected to be minimal in heart failure because of low arterial pressure and impaired cardiopulmonary baroreflex function (7, 8, 45). Consequently, the direct stimulatory effects of ANG II on sympathetic activity may be unopposed by baroreflexes in heart failure. Chronic studies relating to the long-term influence of baroreflexes on sympathetic activity (and thirst) are needed to elucidate the mechanisms that account for the sustained sympathoexcitatory (and dipsogenic) effects of ANG II in heart failure.

The chronic stimulatory effects of ANG II on ANP secretion appear to be dependent on hemodynamic changes that increase atrial pressure (30). In keeping with atrial stretch being the primary stimulus for ANP secretion (2), plasma ANP concentration increased progressively during the first week of pacing in parallel with increments in RAP. As plasma ANG II concentration was maintained at approximately normal levels during this time, the ANP response to pacing was independent of increased plasma levels of ANG II. However, although increased plasma levels of ANG II caused marked fluid retention and further elevations in atrial pressure, plasma ANP concentration failed to increase further during this time. This may reflect a limit to increased synthetic and secretory capabilities for ANP early in the course of pacing-induced heart failure (8, 28, 34).

Renal hemodynamics. The findings in the present study relating to the influence of ANG II on renal hemodynamics are novel in two important ways. First, virtually all previous experimental studies have assessed the effects of acute blockade of the renin-angiotensin system on renal hemodynamics in advanced heart failure, which is characterized by substantial increases in PRA. These studies provide little insight into the role of the renin-angiotensin system in mediating renal hemodynamic changes during the early progression of heart failure when there is little or no elevation in PRA. Secondly, most earlier experimental studies have been acute. Acute studies do not necessarily reflect the long-term renal response to ANG II, which includes the contribution of a number of time-dependent compensatory mechanisms (14, 16).

The renal hemodynamic response to heart failure is characterized by reduced RPF with relatively smaller reductions in GFR; these changes are reflected by an increase in filtration fraction (1, 8, 11, 23, 28, 29, 31). Indeed, these changes in renal function occurred in the present study. However, a new observation in the present study is that these renal hemodynamic changes in the early stages of heart failure are probably independent of increases in plasma ANG II concentration. This is significant because a number of studies have shown that activation of the renin-angiotensin system plays an important role in the preservation of GFR by preferential constriction of efferent arterioles, particularly when renal perfusion pressure is threatened (16). Thus the increase in filtration fraction during the initial days of pacing, in the absence of an appreciable rise in plasma levels of ANG II, indicates that even normal circulating levels of ANG II are sufficient to minimize reductions in GFR in the early stages of heart failure. Alternately, or in addition, it is possible that in heart failure other mechanisms, possibly ANP, contribute to the relative preservation of GFR during reductions in cardiac output and MAP (2).

As in normal dogs (16), the antinatriuretic effects of high physiological plasma levels of ANG II in the present and in an earlier study of pacing-induced heart failure (31) occurred in the absence of a fall in GFR, indicating an important long-term effect of ANG II to increase tubular reabsorption. However, the actions of ANG II that influence tubular reabsorption are complex and include changes in blood pressure, constriction of postglomerular capillaries, which alters peritubular capillary dynamics and medullary blood flow, and direct actions on tubular epithelial cell transport (16). In the present study, there were no consistent long-term changes in either arterial pressure or renal hemodynamics during the protracted sodium retention induced by ANG II. Similarly, no consistent long-term changes in renal hemodynamics have been reported in either experimental animals or human subjects with heart failure during chronic inhibition of the renin-angiotensin system (1, 4, 11, 13, 21, 33). Thus it appears that changes in renal hemodynamics are not essential for mediating the long-term sodium-retaining effects of ANG II in heart failure.

Finally, a few studies have determined the regional distribution of cardiac output in heart failure. It should be emphasized that there are a number of technical and methodological limitations to these studies (22). Nonetheless, early studies in both experimental animals and
human subjects with heart failure indicate that in response to low cardiac output and arterial pressure, there is a proportionally greater reduction in blood flow to a number of organs and tissues, including the kidneys, in an effort to preserve flow to vital organs such as the heart and brain (22, 23). However, the notion that there is a disproportionate reduction in renal blood flow relative to cardiac output in heart failure is incompatible with more recent findings (22, 28, 29, 38), including those in the present study. Throughout the entire progression of pacing-induced heart failure, including the period of increased plasma levels of ANG II, there was an increase in total peripheral resistance, but not renal resistance. Thus the renal fraction of cardiac output was elevated, not depressed, as reported in earlier studies.

Summary and conclusions. The results of the present study suggest that activation of the renin-angiotensin system does not account for the derangements in systemic and renal hemodynamics, the sodium retention, and the neurohormonal activation characteristic of the early stages of cardiac dysfunction. On the other hand, the present findings indicate that, in the compensated phase of heart failure, physiologically relevant increases in plasma ANG II concentration that do not have consistent long-term effects on either systemic or renal hemodynamics can elicit sustained antinatriuretic, sympathoexcitatory, and dipsogenic responses. Furthermore, because these same long-term changes occur in association with activation of the renin-angiotensin system during the spontaneous transition from compensated to decompensated heart failure, it would appear that ANG II plays a critical role in mediating these events in the early progression of this disease. Additional studies are needed, however, to further elucidate the hemodynamic factors and the alterations in the neurohormonal milieu that permit the manifestation of these sustained actions of ANG II when cardiac function is impaired but not when there is normal circulatory function.

Perspectives

Activation of the sympathetic nervous system is consistently observed throughout the progression of heart failure; however, the mechanisms that account for sympathoexcitation are largely unresolved. Although there is little direct evidence from chronic studies, it has been hypothesized that arterial baroreflexes, ANG II, and ANP are important determinants of sympathetic activity in heart failure (7, 8, 45). Another untested possibility is that cardiopulmonary reflexes have a long-term influence on sympathetic activity throughout the evolution of heart failure. It is well established that cardiopulmonary baroreflex suppression of sympathetic nerve activity, including renal sympathetic nerve activity, is impaired in fully developed heart failure (8, 45). Moreover, recent observations in dogs subjected to rapid ventricular pacing indicate that depressed cardiopulmonary baroreflex inhibition of renal sympathetic nerve activity is a relatively early event (week 2 of pacing) associated with the development of ventricular dysfunction (18). Thus cardiopulmonary baroreflex dysfunction could possibly be an important factor that leads to elevations in renal sympathetic nerve activity as heart failure progresses. However, this hypothesis is critically dependent on experiments showing that cardiopulmonary reflexes do in fact chronically influence renal sympathetic nerve activity and sodium excretion under normal conditions in the absence of heart failure. In this regard, recent studies indicate that chronic renal sympathoinhibition is indeed a long-term compensatory response to volume excess and ANG II hypertension (24, 25). Furthermore, preliminary findings indicate that cardiopulmonary reflexes play a dominant role in mediating chronic suppression of renal sympathetic activity in the above states (27). Thus these studies in animals with normal circulatory function support the notion that cardiopulmonary baroreflex dysfunction may contribute to renal sympathoexcitation and attendant salt and water retention during the evolution of heart failure.

It is conceivable that depression of cardiopulmonary reflex inhibition of renal sympathetic nerve activity could play a critical role in the transition from compensated to decompensated heart failure, which is characterized by parallel activation of the renin-angiotensin and sympathetic nervous systems. Impaired sympathetic inhibition would permit the direct stimulatory effects of ANG II on sympathetic activity to be unopposed, resulting in a positive feedback between the renin-angiotensin and sympathetic nervous systems. Thus ANG II would increase renal sympathetic nerve activity, which would stimulate renin secretion further. In turn, higher plasma levels of ANG II would cause further elevations in sympathetic activity and so forth. As a result, there would be progressive fluid retention and progressive cardiac dysfunction.

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