Abstract—Unlike healthy subjects, overt congestive heart failure cannot “escape” the sodium- and water-retaining actions of mineralocorticoid excess. It is undefined whether escape occurs in asymptomatic left ventricular dysfunction (ALVD), which is characterized by preserved sodium homeostasis, natriuretic peptide activation, and normal circulating aldosterone. We hypothesized that, in ALVD, mineralocorticoid excess with exogenous deoxycorticosterone acetate (DOCA) would overwhelm renal compensatory mechanisms, resulting in sodium and water retention, and promote renal and cardiac collagen deposition. ALVD was induced in 2 groups (N=5 each) of dogs by tachypacing at 180 bpm. Urine was collected daily and blood drawn at baseline and days 2, 5, 8, and 11. One group served as control (ALVD), and the other received DOCA (ALVD+DOCA) starting at day 2 of pacing. Urine flow and sodium excretion were unchanged in the ALVD group. In ALVD+DOCA, urine flow and sodium excretion decreased on the first 2 days DOCA was given but normalized starting day 4. Urine flow and urinary cGMP excretion increased in ALVD+DOCA after DOCA escape. Plasma atrial natriuretic peptide, B-type natriuretic peptide, and cGMP increased equally in both groups. There were no differences in cardiorenal and hemodynamic parameters in an acute study on day 11. Although renal collagen area fraction was similar, left ventricular collagen area fraction in ALVD+DOCA was significantly higher than in ALVD (3.3±0.4% versus 2.0±0.2%; P=0.012). We conclude that ALVD can escape the sodium- and water-retaining effects of mineralocorticoid excess. Despite renal escape, increased left ventricular collagen deposition suggests that the heart but not the kidney failed to escape the tissue effects of DOCA. (Hypertension. 2007;50:481-488.)

Key Words: basic science ■ experimental models ■ extracellular matrix ■ heart failure ■ kidney physiology/pathophysiology ■ mineralocorticoids

The kidney plays a key role in the syndrome of congestive heart failure (CHF), especially with respect to the congestive symptoms associated with overt CHF.1 It is increasingly appreciated that the syndrome of overt CHF is frequently preceded by a chronic stage in which ≈50% of subjects with decreased left ventricular (LV) ejection fraction have no heart failure (HF) symptoms, termed “asymptomatic LV dysfunction” (ALVD).2-3 Importantly, patients with ALVD are at increased risk for progression to overt CHF and show increased mortality.4,5

In contrast to overt CHF, ALVD is characterized by the kidney’s ability to preserve urinary sodium excretion despite ventricular dysfunction. This occurs in the setting of increased plasma levels of atrial and B-type natriuretic peptide (ANP and BNP, respectively) and, in the absence of diuretic therapy, lack of activation of the renin-angiotensin-aldosterone system.6,7 The mechanism of progression from ALVD and sodium balance to clinical symptoms of congestion and sodium retention remains unclear, although studies in experimental HF suggest that it may involve the activation of aldosterone, which promotes sodium reabsorption in the inner medullary collecting duct and which has been implicated in contributing to renal and cardiac fibrosis.8-14

It has long been known that when healthy individuals are given excessive doses of exogenous mineralocorticoid (eg, aldosterone or the aldosterone precursor deoxycorticosterone acetate [DOCA]), they escape the sodium- and water-retaining effects after a few days despite continuing mineralocorticoid administration.15 This phenomenon is called “mineralocorticoid escape.”16 In contrast to healthy individuals, patients and animals with symptomatic CHF cannot escape mineralocorticoid excess and continue to retain sodium and suffer from increasing edema and symptoms of congestion.17-20 To date, it is unknown whether mineralocorticoid escape occurs in ALVD. Defining whether mineralocorticoid escape by the kidney is preserved in ALVD provides the opportunity to define further cardiorenal interactions and the biology of aldosterone in the earliest stages of evolving CHF.

The current study uses a canine model of ALVD that closely mimics the cardiorenal and neurohumoral characteristics of human ALVD.21,22 We hypothesized that exogenous...
mineralocorticoid excess in experimental ALVD produced by DOCA would overwhelm sodium and water homeostatic mechanisms of escape and result in sodium and water retention and aggravated cardiac dysfunction. In addition, we also defined the collagen content of the kidney and left ventricle in the setting of mineralocorticoid excess in this model of early ventricular dysfunction.

Methods

The study and all of the procedures were in accordance with the Animal Welfare Act and were approved by the Mayo Clinic Institutional Animal Care and Use Committee.

Model of ALVD

Ten male mongrel dogs (19 to 26 kg) had pacemakers with a right ventricular epicardial lead implanted under general anesthesia as described previously in detail.23 Ports for blood sampling were implanted subcutaneously in the left flank and connected to the left femoral artery. After surgery, dogs were allowed 2 weeks to recover. This model is characterized by systolic ventricular dysfunction, preserved sodium and water homeostasis, and activation of the natriuretic peptide system but without activation of the renin-angiotensin-aldosterone system.21,24

Chronic Study

For the chronic 11-day study, dogs were placed in metabolic cages that allowed 24-hour urine collection. Dogs were fed a diet that contained a fixed amount of sodium (Hill’s canned Canine i/d diet [50 mEq of sodium per day; Hill’s Pet Nutrition) and were allowed ad libitum access to water. Twenty-four-hour urines and blood samples (33 mL) were collected on 2 baseline days. ALVD was then induced by rapid ventricular pacing at 180 bpm as reported previously.21,24 Daily urine collections were continued until the end of the study. Mean arterial pressure was measured, and blood samples were drawn on days 2, 5, 8, and 11 of pacing. Urine and blood samples were harvested, and weights of the cardiac chambers and the kidneys were determined.

Data are presented as mean±SEM or as percentage of change from baseline ±SEM. Data not normally distributed were analyzed with nonparametric tests. Within groups, comparisons to baseline were done with 1-way ANOVA for repeated measurements with posthoc Dunnet’s test or with nonparametric Wilcoxon’s signed rank test. Between groups, values were compared with 2-way ANOVA for repeated measurements when they were normally distributed. Alternatively, differences to baseline were calculated, and groups were compared with the appropriate t-test.

Electrolyte and Neurohumoral Assays

Electrolyte measurements of urine and plasma were done by flame photometry (IL943, Instrumentation Laboratory). All of the blood and urine samples used for neurohumoral assays were stored at −80°C until analysis. Urine for cGMP analysis was heated to 90°C before storage to inhibit degradative enzymatic activity. Aldosterone, plasma renin activity, cGMP, ANP, BNP, C-type natriuretic peptide (CNP), and arginine vasopressin were determined by commercially available radioimmunoassays as described previously.24 If assay results were below the lower level of detection of the respective assay, this lower level was assigned.

Renal and Myocardial Collagen Area

Fraction Determination

Renal slices containing cortex and medulla were fixed in 10% formalin as were slides from the LV free wall. Tissues were embedded in paraffin and sectioned at 6-μm thickness. Collagen-area fraction was quantified in slides stained with picrosirius red (Direct Red 80, Sigma). Briefly, paraffin was removed with xylene and then decreasing concentrations of ethanol. Slides were stained with hematoxylin followed by staining for 30 minutes with 0.1% (weight/volume) picrosirius red dissolved in saturated picric acid. Absolute alcohol and xylene were used to dehydrate the sections, and coverslips were then mounted onto the slides with Permount (Fisher Scientific). Quantification of the collagen-area fraction was performed with a digital imaging system (KS 400, Kontron Electronics). Fifteen images each were randomly selected from the LV-free wall, renal cortex, and outer and inner medulla.

Statistics

Data are presented as mean±SEM or as percentage of change from baseline ±SEM. Data not normally distributed were analyzed with nonparametric tests. Within groups, comparisons to baseline were done with 1-way ANOVA for repeated measurements with posthoc Dunnet’s test or with nonparametric Wilcoxon’s signed rank test. Between groups, values were compared with 2-way ANOVA for repeated measurements when they were normally distributed. Alternatively, differences to baseline were calculated, and groups were compared with the appropriate t-test.
Compared with unpaired Student’s t test or Mann-Whitney U test. Measurements from the acute study were compared with unpaired Student’s t test or Mann-Whitney U test. A P ≤0.05 was considered significant.

Results

Baseline parameters were not significantly different between the 2 groups (Table 1). After the start of pacing, ALVD showed a significant increase in plasma ANP and cGMP (Table 2). In contrast, plasma renin activity, aldosterone, arginine vasopressin, BNP, CNP, plasma sodium, potassium, and hematocrit were unchanged. Mean arterial pressure was decreased only on day 11. ALVD+DOCA showed an increase in ANP, cGMP, and BNP, whereas plasma renin activity (lower level of detection: 0.1 ng/mL per hour) and aldosterone (lower level of detection of assay: 2.5 ng/dL) were suppressed. Plasma sodium and CNP were unchanged, whereas potassium levels decreased. Mean arterial pressure and plasma arginine vasopressin (lower level of detection: 1.25 pg/mL) decreased, but this was not significant between groups. Hematocrit decreased, and this was significant between groups on days 5 and 8. Plasma cGMP was significantly lower on day 2 in the ALVD+DOCA group (before the start of DOCA administration), but this was not the case on any other day.

As reported in Table 3 and shown in Figure 1, in the ALVD group, urinary sodium excretion, urine flow, and urinary

| TABLE 2. Mean Arterial Pressure, Hematocrit, and Humoral Data |
|-------------------|----------------|----------------|----------------|----------------|----------------|
| Parameter         | Baseline       | Day 2          | Day 5          | Day 8          | Day 11         |
| Plasma Na⁺, mmol/L| ALVD 153±5     | 147±3          | 154±6          | 145±4          | 150±2          |
|                   | ALVD+DOCA 155±5| 147±4          | 146±3          | 146±3          | 151±2          |
| Plasma K⁺, mmol/L | ALVD 4.5±0.2  | 4.4±0.1        | 4.7±0.3        | 4.4±0.2        | 4.6±0.2        |
|                   | ALVD+DOCA 4.7±0.2| 4.6±0.2      | 3.9±0.2*       | 3.6±0.1†       | 3.7±0.2†       |
| MAP, mm Hg        | ALVD 106±3     | 96±3           | 96±6           | 91±3           | 85±4‡          |
|                   | ALVD+DOCA 127±11| 117±6         | 108±7*         | 107±6          | 110±5*         |
| ANP, pg/mL        | ALVD 69±12     | 158±23‡        | 221±40‡        | 273±46‡        | 364±127‡       |
|                   | ALVD+DOCA 72±22| 139±39         | 222±45*        | 528±220*       | 380±79*        |
| BNP, pg/mL        | ALVD 44±16     | 78±29          | 73±29          | 99±49          | 89±36          |
|                   | ALVD+DOCA 25±8 | 37±15          | 56±24          | 66±23*         | 108±44*        |
| CNP, pg/mL        | ALVD 14.0±2.5  | 10.3±1.2       | 13.2±4.1       | 21.6±2.4       | 10.2±1.3       |
|                   | ALVD+DOCA 9.1±1.7| 8.2±1.2      | 8.3±1.5        | 12.5±4.8       | 9.6±1.5        |
| cGMP, pmol/mL     | ALVD 9.7±0.4   | 17.0±0.7†      | 20.2±1.7†      | 17.3±1.3‡      | 19.6±1.0†      |
|                   | ALVD+DOCA 10.6±1.7| 10.3±2.4†    | 18.4±3.3*      | 21.6±4.1*      | 21.2±2.0*      |
| Aldosterone, ng/dL| ALVD 6.3±2.8   | 3.2±0.5        | 4.0±0.8        | 4.6±0.9        | 3.7±0.8        |
|                   | ALVD+DOCA 3.2±0.4| 3.1±0.6       | 2.5±0.0        | 2.5±0.0        | 2.5±0.0        |
| PRA, ng/mL per hour| ALVD 1.8±0.3  | 2.0±0.3        | 3.8±1.2        | 3.5±1.0        | 2.8±0.8        |
|                   | ALVD+DOCA 3.1±1.1| 1.4±0.4       | 0.3±0.1†       | 0.3±0.1†       | 0.2±0.1†       |
| AVP, pg/mL        | ALVD 0.27±0.09 | 0.31±0.08      | 0.23±0.07      | 0.26±0.09      | 0.28±0.08      |
|                   | ALVD+DOCA 0.41±0.06| 0.27±0.11    | 0.34±0.11      | 0.17±0.01*     | 0.31±0.09      |
| Hematocrit, %     | ALVD 43±1      | 46±1           | 47±1           | 45±1           | 42±2           |
|                   | ALVD+DOCA 44±2  | 44±1           | 40±1†          | 39±1†          | 39±2*          |

Values are expressed as mean±SEM. AVP indicates arginine vasopressin; MAP, mean arterial pressure; PRA, plasma renin activity.

*Significant difference vs baseline within the ALVD+DOCA group.
†Significant difference between groups when values are expressed as percentage of baseline.
‡Significant difference vs baseline within the ALVD group.
TABLE 3. Urine Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine flow, mL/min</td>
<td>ALVD</td>
<td>0.88</td>
<td>0.11</td>
<td>0.08</td>
<td>0.06</td>
<td>0.11</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>ALVD + DOCA</td>
<td>0.11</td>
<td>0.05</td>
<td>0.02</td>
<td>0.04</td>
<td>0.09†</td>
<td>0.06†</td>
<td>0.08†</td>
<td>0.11†</td>
<td>0.09†</td>
</tr>
<tr>
<td>UnNa, μEq/min</td>
<td>ALVD</td>
<td>17 ± 3</td>
<td>12 ± 1</td>
<td>12 ± 1</td>
<td>13 ± 1</td>
<td>13 ± 5</td>
<td>14 ± 3</td>
<td>14 ± 2</td>
<td>13 ± 4</td>
<td>17 ± 2</td>
</tr>
<tr>
<td></td>
<td>ALVD + DOCA</td>
<td>16 ± 2</td>
<td>5 ± 1†</td>
<td>5 ± 1†</td>
<td>9 ± 1*</td>
<td>16 ± 4</td>
<td>15 ± 4</td>
<td>15 ± 3</td>
<td>20 ± 4</td>
<td>24 ± 3*</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>ALVD</td>
<td>41 ± 2</td>
<td>40 ± 3</td>
<td>40 ± 3</td>
<td>39 ± 1</td>
<td>30 ± 9</td>
<td>37 ± 7</td>
<td>38 ± 3</td>
<td>31 ± 8</td>
<td>32 ± 3</td>
</tr>
<tr>
<td></td>
<td>ALVD + DOCA</td>
<td>39 ± 5</td>
<td>37 ± 5</td>
<td>30 ± 3</td>
<td>39 ± 1*</td>
<td>31 ± 4</td>
<td>27 ± 6°</td>
<td>22 ± 3*</td>
<td>24 ± 4*</td>
<td>29 ± 1*</td>
</tr>
<tr>
<td>UANPV, pg/min</td>
<td>ALVD</td>
<td>1091 ± 243</td>
<td>1111 ± 155</td>
<td>1046 ± 196</td>
<td>1076 ± 273</td>
<td>1031 ± 237</td>
<td>925 ± 266</td>
<td>855 ± 187</td>
<td>861 ± 297</td>
<td>981 ± 260</td>
</tr>
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<td></td>
<td>ALVD + DOCA</td>
<td>1195 ± 142</td>
<td>903 ± 98</td>
<td>923 ± 95</td>
<td>787 ± 100*</td>
<td>739 ± 100</td>
<td>579 ± 29</td>
<td>527 ± 59</td>
<td>565 ± 84</td>
<td>510 ± 61*</td>
</tr>
<tr>
<td>UCMPV, pmol/min</td>
<td>ALVD</td>
<td>144 ± 21</td>
<td>106 ± 17</td>
<td>320 ± 210</td>
<td>237 ± 68</td>
<td>104 ± 35</td>
<td>112 ± 26</td>
<td>163 ± 16</td>
<td>152 ± 43</td>
<td>171 ± 68</td>
</tr>
<tr>
<td></td>
<td>ALVD + DOCA</td>
<td>79 ± 10</td>
<td>50 ± 16</td>
<td>62 ± 8</td>
<td>149 ± 89</td>
<td>59 ± 21</td>
<td>84 ± 60</td>
<td>80 ± 19</td>
<td>87 ± 20</td>
<td>98 ± 31</td>
</tr>
<tr>
<td>ALVD</td>
<td>1827 ± 530</td>
<td>1131 ± 608</td>
<td>3100 ± 1645</td>
<td>3587 ± 1264</td>
<td>773 ± 381</td>
<td>810 ± 366</td>
<td>1238 ± 477</td>
<td>502 ± 377*</td>
<td>1465 ± 697</td>
<td>2563 ± 1700</td>
</tr>
<tr>
<td>ALVD + DOCA</td>
<td>438 ± 132</td>
<td>171 ± 77*</td>
<td>76 ± 28</td>
<td>1725 ± 504*</td>
<td>380 ± 216</td>
<td>1714 ± 860</td>
<td>441 ± 262</td>
<td>1059 ± 497*</td>
<td>2478 ± 2106</td>
<td>1397 ± 552</td>
</tr>
<tr>
<td>UANPV, pg/min</td>
<td>ALVD</td>
<td>20 ± 10</td>
<td>54 ± 36</td>
<td>13 ± 8</td>
<td>421 ± 389</td>
<td>570 ± 560</td>
<td>16 ± 9</td>
<td>23 ± 13</td>
<td>721 ± 716</td>
<td>405 ± 384</td>
</tr>
<tr>
<td></td>
<td>ALVD + DOCA</td>
<td>6 ± 2</td>
<td>4 ± 1</td>
<td>3 ± 1</td>
<td>34 ± 22</td>
<td>6 ± 2</td>
<td>14 ± 7</td>
<td>5 ± 1</td>
<td>7 ± 3</td>
<td>33 ± 16</td>
</tr>
<tr>
<td>UcGMPV, pmol/min</td>
<td>ALVD</td>
<td>1511 ± 383</td>
<td>1684 ± 685</td>
<td>1643 ± 480</td>
<td>1946 ± 584</td>
<td>2048 ± 790</td>
<td>3132 ± 1729</td>
<td>2004 ± 1074</td>
<td>1468 ± 860</td>
<td>1286 ± 459</td>
</tr>
<tr>
<td></td>
<td>ALVD + DOCA</td>
<td>815 ± 106</td>
<td>2778 ± 1568*</td>
<td>1178 ± 260</td>
<td>1595 ± 257*</td>
<td>2307 ± 568*</td>
<td>1801 ± 274*</td>
<td>2272 ± 552</td>
<td>2719 ± 458*</td>
<td>3568 ± 592*</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM.

*Significant difference vs baseline within the ALVD + DOCA group.
†Significant difference between groups when values are expressed as percentages of baseline.
‡Significant difference vs baseline within the ALVD group.

On day 11 we assessed fractional shortening and cardiovascular hemodynamics before harvesting of the hearts in both groups. This revealed no significant differences between ALVD and ALVD + DOCA. Of note, there were no significant differences in fractional shortening (16 ± 4% versus 17 ± 4%), cardiac filling pressures (right atrial pressure: 2 ± 1 versus 2 ± 1 mm Hg; pulmonary capillary wedge pressure: 15 ± 1 versus 14 ± 3 mm Hg), or cardiac output (2.4 ± 0.4 versus 2.6 ± 0.6 L/min).

DOCA administration. Specifically, a transient decrease in sodium excretion occurred during the initial 2 days of DOCA but then returned to baseline. Of interest, whereas the kidney escaped the effects of DOCA both physiologically and histologically, there was an increase in the collagen content of the heart. This suggests that the profibrotic actions of DOCA, even over a 10-day period, occur at the level of the myocardium but not in the kidney in this model of ALVD.

The renal response to excess exogenous mineralocorticoid in ALVD was unexpected. Our hypothesis was that exogenous mineralocorticoid excess in ALVD would overwhelm sodium homeostatic mechanisms and result in sodium retention and cardiac decompensation. Although studies of longer duration are needed, these results raise the possibility that unknown mechanisms that under normal conditions oppose the renal sodium-retaining actions of DOCA remain intact in ALVD. If understood, such knowledge could possibly be exploited to delay the progression of HF, particularly from the perspective of the kidney.

Mineralocorticoid escape has been the subject of investigation for decades, and various mechanisms have been
implicated. Hemodynamic mechanisms have been invoked, because sodium and water retention secondary to mineralocorticoid excess results in increased intravascular volume.\textsuperscript{25} This, in turn, may yield increased glomerular filtration and reduced tubular reabsorption. In addition, intravascular volume expansion may also increase renal interstitial hydrostatic pressure with reductions in peritubular Starling forces at the level of the proximal tubule to reduce proximal reabsorption of sodium.\textsuperscript{26} Other studies investigating mineralocorticoid escape have found roles for natriuretic peptides,\textsuperscript{27-30} NO,\textsuperscript{31} and the thiazide-sensitive sodium chloride cotransporter.\textsuperscript{32} Titze et al\textsuperscript{33} reported that administration of DOCA and salt to rats was associated with osmotically inactive sodium storage and osmotically neutral sodium retention balanced by potassium loss.

Although we observed no differences in cardiovascular hemodynamics or circulating ANP between groups, our results demonstrate that an increase in urinary cGMP parallels renal escape in ALVD. Interestingly, this occurred in association with no significant increase in the ALVD+DOCA group as compared with the ALVD group with respect to plasma CGMP, plasma ANP, or body weight. Further studies are needed, but we speculate that the increase in urinary cGMP excretion could be achieved by one of the following: (1) a decreased degradation of the natriuretic peptides in the proximal tubule in the ALVD+DOCA group by downregulation of neutral endopeptidase; (2) an increase of the natriuretic peptide type A receptors in the proximal tubule or cortical collecting duct of this group; or (3) by an increase in renal production of uroguanylin, urodilatin, or NO. Given that the ANP assay used cross-reacts with urodilatin, there is less evidence to support its role in renal mineralocorticoid escape, because no differences were detected in ANP levels. Uroguanylin is an intriguing candidate, because it can induce natriuresis, kaliuresis, and diuresis via cGMP-dependent signaling.\textsuperscript{34} It also plays a role in regulating sodium reabsorption in the gut and kidney and warrants further study.

Figure 1. Top, Urinary sodium excretion expressed as percentage of baseline for ALVD (□) and ALVD+DOCA (○). Middle, Urine flow. Bottom, Urinary cGMP excretion. Arrows indicate start of pacing and start of DOCA administration in the ALVD+DOCA group. *P<0.05 vs baseline in ALVD+DOCA group. UcGMPV indicates urinary cyclic guanosine monophosphate excretion; UNaV, urinary sodium excretion; UVoR, urine flow.

Figure 2. Top, Cumulative urinary sodium excretion for ALVD (□) and ALVD+DOCA (○). Middle, Cumulative urine flow, bottom level shows cumulative urinary cGMP excretion. Data are shown as cumulative daily values expressed as percentages of the baseline average. Arrow indicates start of pacing; bracketed vertical line indicates beginning of DOCA administration in the ALVD+DOCA group. *P<0.05 ALVD vs ALVD+DOCA. UcGMPV indicates urinary cyclic guanosine monophosphate excretion; UNaV, urinary sodium excretion; UVoR, urine flow.
The kidney is crucial in sodium and water homeostasis and, via the regulation of intravascular volume, impacts cardiac preload. The importance of the kidney has recently been emphasized by studies that reported that renal function is a powerful independent predictor of subsequent mortality in human HF patients, even in the asymptomatic stage. Our results underscore the importance of the kidney in the compensation of HF, because the kidney was able to restore sodium balance with mineralocorticoid excess despite ALVD. Indeed, despite the excess of a sodium-retaining hormonal factor (ie, DOCA) in a model of reduced cardiac output, no congestion occurred. Clearly, failure to escape would have produced sodium and water retention and symptomatic CHF. Because cardiac function was not different between the ALVD and ALVD/DOCA groups, the kidney played the key role in determining whether congestion secondary to sodium and water retention occurred. This suggests that if one can maintain optimal renal sodium and water handling in evolving CHF, then symptomatic CHF could be delayed. This speculation raises the issue of the importance of pharmacologically targeting the kidney to delay HF progression as advanced by Dries and Stevenson.39

Aldosterone plays an important role in sodium, potassium, and water homeostasis in physiological states. However, in HF, the activation of aldosterone is thought to contribute to the progression of HF.40 Specifically, aldosterone has been associated with edema formation, cardiac hypertrophy, and cardiac fibrosis. Importantly, it has been demonstrated that aldosterone receptor antagonism on top of standard therapy was associated with a substantial improvement in survival in symptomatic CHF41 and in postmyocardial infarction-related CHF.42 This survival benefit may be secondary to the antifibrotic effects associated with aldosterone antagonism, but reducing intravascular volume and decreasing cardiac preload via renal mechanisms or increasing plasma potassium are also possible mechanisms.

In the current study, the ALVD/DOCA group had a slight but significant increase in collagen deposition in the LV-free wall as compared with the ALVD alone group. This profibrotic effect of the mineralocorticoid precursor DOCA was seen despite the fact that the ALVD/DOCA group was able to compensate in terms of renal sodium and water balance during exogenous DOCA administration after the escape phenomenon. At least at day 11 we observed no difference in cardiac filling pressures, which suggests that the fibrotic response was not secondary to mechanical strain induced by volume overload. Although it cannot be excluded that the reduced potassium levels contributed to the fibrosis under the present experimental conditions, it should be noted that potassium supplementation in uninephrectomized, aldosterone-infused rats on 1% NaCl to drink did not affect cardiac fibrosis.43 Thus, the profibrotic action in the heart of DOCA, even in the presence of a normal sodium diet in experimental ALVD, seems to be a direct action of mineralocorticoid excess on the extracellular matrix. Of interest is the observation that the kidney, unlike the heart, did not demonstrate an increase in collagen content. As discussed above with regard to the mechanism of escape from the sodium-retaining effects, cGMP pathways may be involved in this phenomenon.

The current findings may have clinical relevance for our therapeutic strategies in delaying the progression of ALVD to overt HF. As recently discussed in an in-depth review of ALVD,44 American College of Cardiology/American Heart Association guidelines currently do not recommend the use of aldosterone antagonists for ALVD (stage B CHF) on the basis that aldosterone antagonism has only been studied to date in clinical trials with symptomatic CHF. Based on our findings, further proof-of-concept studies may be warranted to test the hypothesis that aldosterone antagonism in ALVD, particularly in those with severely reduced LV ejection fraction who are at greatest risk for disease progression,4 should be considered. Specifically, one could speculate that prompt intervention with an aldosterone antagonist in early HF would help to prevent adverse ventricular remodeling and fibrosis, as well as delay the onset of sodium and water retention as the kidney’s ability to escape the actions of endogenous aldosterone diminishes. Studies of aldosterone antagonism in mild HF suggest some benefit.45,46

![Left Ventricular Collagen Area Fraction](image)

**Figure 3.** LV collagen area fraction as determined in slides stained with picrosirius red. Representative photomicrographs are shown for ALVD (left) and ALVD + DOCA (right).
It should be noted that further mineralocorticoid actions may have been present in this study that were not assessed. Although we did not observe renal collagen deposition, there may have been renal cytokine activation, inflammation, an increase in oxidative stress, and microalbuminuria. Furthermore, we did not assess vascular compliance or endothelial function, which may also have been adversely affected. We also did not investigate the potential influence of glucocorticoids, which can activate the mineralocorticoid receptor unless they are enzymatically modified by 11β-hydroxysteroid dehydrogenase type 2.47,48 Finally, a longer study duration may have resulted in structural changes of the kidney.

In summary, the current study provides new insights into cardiorenal mechanisms in the early stage of CHF in an experimental model of ALVD. Here we demonstrate that, in experimental ALVD, the kidney escapes the sodium- and water-retaining effects of mineralocorticoid excess and prevents congestion. With regard to the mechanisms involved, we provide evidence that DOCA escape is associated with an increase in urinary cGMP excretion. The possible mechanism for escape may use a renal cGMP pathway that will require further studies to be defined. Importantly, we also found that the collagen content of the left ventricle, but not the kidney, increases, underscoring that the kidney but not the heart retains the ability to escape the effects of mineralocorticoid excess in this critical initial period of ventricular dysfunction.

Perspectives
The kidney plays a key role in the syndrome of CHF and in the progression from ALVD, which lacks congestion to overt CHF, in which sodium and water retention with congestion are hallmarks. Little is known about what factors are responsible for the transition of ALVD to overt CHF, but a role for aldosterone has long been advanced. The current study shows that in ALVD the kidney can escape the sodium-retaining effects of mineralocorticoid excess, but the heart does not escape the tissue effects as indicated by increased LV collagen content. Although aldosterone antagonism has been found beneficial in patients with overt CHF, little is known about its value in ALVD. Based on our findings, one could speculate that aldosterone antagonism in ALVD may prevent excessive collagen deposition in the heart and oppose the ultimate onset of sodium retention, which may delay subsequent cardiac decompensation and disease progression. Lastly, understanding renal mechanisms, which mediate mineralocorticoid escape, especially in early ventricular dysfunction, remains a high priority.

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Disclosures
None.

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