Effects of ramipril on renal function during progressive overpacing-induced heart failure in dogs

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Objective—To investigate the effects of preventive angiotensin converting enzyme inhibitor treatment with ramipril in dogs with progressively severe experimentally induced heart failure.

Animals—20 dogs.

Procedures—Dogs were randomly allocated to receive no treatment (control) or ramipril (0.125 mg/kg, PO, daily) for 7 weeks. Physical examination, repetitive catheterization of the right side of the heart, and echocardiography were performed before the study (day 0) and weekly for 7 weeks. Renal plasma flow (RPF) as determined by para-aminohippuric acid clearance and glomerular filtration rate (GFR) as determined by creatinine and iohexol clearances were measured on day 0 and at weeks 4 and 7.

Results—Overpacing induced a progressive increase in right atrial pressure (RAP) and pulmonary artery pressure, occluded (PAPO), with a decrease in systemic arterial pressure. There were progressive alterations of echocardiographic indices of diastolic and systolic ventricular function. The RPF and GFR decreased before cardiac output decreased, and filtration fraction increased. The logarithm of the urinary sodium-to-potassium concentration ratio (log10(Na+/K+)) decreased. Significant effects of ramipril included a delay in clinical signs of heart failure, a late decrease in RAP and PAPO, and increases in the sodium excretion fraction and log10(Na+/K+). There was a satisfactory agreement between the creatinine and iohexol clearance measurements.

Conclusions and Clinical Relevance—Results suggest that, in this rapid-evolving, dilated cardiomyopathy, activation of the renin-angiotensin system contributes to the pathophysiology of heart failure late in the disease and essentially by an activation of renal salt and water retention. (Am J Vet Res 2006;67:1236–1243)

ABBREVIATIONS

RPF Renal plasma flow
GFR Glomerular filtration rate
ACE Angiotensin converting enzyme
FS Fraction shortening
LAD Left atrial diameter
Ao Aortic root diameter
PEP Pre-ejection period
LVET Left ventricular ejection time
IVRT Isovolumetric relaxation time
PAPO Pulmonary artery pressure, occluded
RAP Right atrial pressure
Clcr Creatinine clearance
CIi iohexol clearance
ClPAH Para-aminohippuric acid clearance
log10(Na+/K+) Logarithm of the urinary sodium-to-potassium concentration ratio
ClOsm Osmolar clearance
ClH2O Free water clearance
EF Excretion fraction

Activation of the renin-angiotensin system contributes to clinical signs and prognosis of heart failure through a complex interaction of effects, which include myocardial and vascular remodeling, renal vasoconstriction with decreases in RPF and GFR, sodium and water retention, potassium depletion, and positive interaction with the sympathetic nervous system.1-5 Accordingly, ACE inhibitors, angiotensin II receptor blockers, and anti-aldosterone treatments reportedly improve clinical state and survival in humans with heart failure.6-9 However, essentially all of these studies have been performed in humans with established disease, and exactly how the renin-angiotensin system contributes to the progression of heart failure is not completely understood.

The purpose of the study reported here was to investigate the effects of preventive ACE inhibitor treatment with ramipril in dogs with progressively severe, experimentally induced heart failure. For this purpose, we used the overpacing-induced heart failure model in dogs, titrated to observe all stages of disease progression during a period of 7 weeks.10 Angiotensin converting enzyme inhibition was induced with ramipril at a dose recommended in veterinary practice.11,12 Cardiac function was monitored by repetitive catheterization of the right side of the heart and echocardiography, and renal func-
tion was monitored by RPF, GFR, and plasma and urinary electrolyte determinations. We specifically asked whether, and at what stage of disease progression, ACE inhibition would improve cardiovascular function. We investigated if this improvement was due to changes in renal hemodynamics and in sodium reabsorption or through direct changes in systolic or diastolic function and cardiac output.

**Materials and Methods**

The study was approved by the Animal Care and Use Committee of the Free University of Brussels and was conducted in accordance with the *Guide for the Care and Use of Laboratory Animals.*

**Dogs**—Twenty male Beagles weighing between 13 and 17 kg were included in the study. Dogs had free access to water and were fed a dry maintenance diet; sodium was not restricted. During general anesthesia, a bipolar pacemaker lead was surgically inserted in the right jugular vein and implanted in the right ventricular apex during fluoroscopy. A multiprogrammable pulse generator was inserted in the subcutaneous tissues of the cervical region and connected to the pacemaker lead.

**Experimental design**—The experiment was a longitudinal repeated-measures study. The dogs underwent a modified pacing protocol with a stepwise increase of stimulation frequencies. After a 2-week period of recovery, the multiprogrammable pulse generator was activated on day 0. The rate of stimulation was 180 beats/min and was continued for 1 week (week 1), followed by 200 beats/min during the second week (week 2), 220 beats/min during the third week (week 3), and finally, 240 beats/min during the last 4 weeks (weeks 4 to 7). Dogs were randomly allocated to receive ramipril (0.125 mg/kg, PO, daily beginning on day 0) or no treatment (control group). All investigations were performed when dogs were in sinus rhythm with the pacemaker turned off and after a stabilization period of 30 minutes. A physical examination, Doppler echocardiography, and catheterization of the right side of the heart were performed on day 0, before the start of overpacing, and then weekly until week 7. Measurements of RPF, GFR, and plasma and urinary electrolytes were obtained on day 0 and at weeks 4 and 7. At the end of the study, dogs were euthanized by IV injection of pentobarbital (200 mg/kg).

**Physical examinations**—Physical examinations included evaluation of general clinical signs (such as lethargy and anorexia) and clinical signs of heart failure (edema, ascites, pulmonary rales, and heart murmurs), as well as measurements of heart rate, respiratory rate, and blood pressure (measured with a Doppler sphygmomanometer).

**Doppler echocardiography**—Doppler echocardiography was performed during continuous ECG monitoring with a 3.5- to 5-MHz sector probe, as described. All measurements were performed in triplicate irrespective of the respiratory phase. End diastolic and systolic left ventricular internal diameters were measured from the M-mode right short-axis view of the left ventricle at the level of the chordae tendineae to calculate FS of the left ventricle. The E-point septal separation was measured from the M-mode right short-axis view of the left ventricle at the level of the mitral valve. The LAD and Ao were measured from the 2-dimensional short-axis view. To calculate their ratio, the PEP and the LVET were measured from the left side by pulsed Doppler examination of the aortic flow. Mitral peak flow velocities of the E and A waves were measured from the left apical position by pulsed Doppler examination of the mitral flow, and the mitral E wave-to-A wave ratio was calculated. The IVRT of the left ventricle was measured from the left apical position by simultaneous pulsed Doppler examination of the aortic and mitral flows.

**Hemodynamics**—A pediatric 5-F thermodilution Swan-Ganz catheter was inserted via the left jugular vein during fluoroscopy for measurements of pulmonary artery pressure, PAPO, RAP, and cardiac index.

**Renal function and hydroelectrolytic balance assessment**—All clearance measurements were performed on conscious dogs trained to rest calmly on a table with minimal restraint. All clearance measurements were performed on conscious dogs trained to rest calmly on a table with minimal restraint.

**Table 1**—Mean ± SEM values for physical examination and hemodynamic parameters during progression of overpacing-induced heart failure in dogs receiving ramipril (0.125 mg/kg, PO, daily; n = 10) or no treatment (control group; 10) for 7 weeks.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Baseline</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAP (mm Hg)</strong></td>
<td>Control</td>
<td>152 ± 8</td>
<td>138 ± 8</td>
<td>126 ± 9</td>
<td>124 ± 8</td>
<td>122 ± 7</td>
<td>126 ± 5</td>
<td>126 ± 5</td>
<td>124 ± 5</td>
<td>124 ± 5</td>
</tr>
<tr>
<td></td>
<td>Ramipril</td>
<td>159 ± 9</td>
<td>138 ± 10*</td>
<td>139 ± 15*</td>
<td>123 ± 8</td>
<td>114 ± 6</td>
<td>123 ± 12</td>
<td>117 ± 11</td>
<td>119 ± 11</td>
<td>119 ± 11</td>
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<tr>
<td><strong>HR (beats/min)</strong></td>
<td>Control</td>
<td>103 ± 6.9</td>
<td>128 ± 7</td>
<td>130 ± 8</td>
<td>143 ± 9</td>
<td>140 ± 3</td>
<td>141 ± 6</td>
<td>150 ± 4</td>
<td>149 ± 6</td>
<td>149 ± 6</td>
</tr>
<tr>
<td></td>
<td>Ramipril</td>
<td>106 ± 6.7</td>
<td>129 ± 7</td>
<td>138 ± 6</td>
<td>145 ± 6</td>
<td>145 ± 1</td>
<td>150 ± 4</td>
<td>152 ± 10</td>
<td>160 ± 8</td>
<td>160 ± 8</td>
</tr>
<tr>
<td><strong>RR (breaths/min)</strong></td>
<td>Control</td>
<td>24 ± 2.2</td>
<td>26 ± 2.6</td>
<td>23 ± 1.6</td>
<td>28 ± 3.0</td>
<td>33 ± 4*</td>
<td>37 ± 4</td>
<td>50 ± 5</td>
<td>47 ± 6</td>
<td>47 ± 6</td>
</tr>
<tr>
<td></td>
<td>Ramipril</td>
<td>21 ± 2.0</td>
<td>24 ± 1.6</td>
<td>26 ± 2.2</td>
<td>27 ± 3.2</td>
<td>35 ± 4</td>
<td>30 ± 1</td>
<td>39 ± 5</td>
<td>42 ± 3</td>
<td>42 ± 3</td>
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<tr>
<td><strong>PAPs (mm Hg)</strong></td>
<td>Control</td>
<td>20.5 ± 1.3</td>
<td>17.6 ± 1.1*</td>
<td>20.7 ± 1.0</td>
<td>19.5 ± 1.3</td>
<td>22.3 ± 1.2</td>
<td>25.0 ± 1.5</td>
<td>27.0 ± 2.2</td>
<td>31.0 ± 2.2</td>
<td>31.0 ± 2.2</td>
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<tr>
<td></td>
<td>Ramipril</td>
<td>19.5 ± 1.9</td>
<td>18.6 ± 1.5</td>
<td>19.6 ± 1.4</td>
<td>20.6 ± 1.1</td>
<td>23.1 ± 1.2</td>
<td>23.7 ± 0.7</td>
<td>26.0 ± 1.0</td>
<td>27.4 ± 1.7</td>
<td>27.4 ± 1.7</td>
</tr>
<tr>
<td><strong>PAPd (mm Hg)</strong></td>
<td>Control</td>
<td>10 ± 1.0</td>
<td>11 ± 1.1</td>
<td>11 ± 0.9</td>
<td>12 ± 0.5*</td>
<td>14 ± 0.7</td>
<td>16 ± 0.6</td>
<td>17 ± 1.2</td>
<td>19 ± 1.0</td>
<td>19 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>Ramipril</td>
<td>9 ± 1.2</td>
<td>10 ± 1.3</td>
<td>10 ± 0.8</td>
<td>12 ± 0.9*</td>
<td>13 ± 0.8</td>
<td>14 ± 0.9</td>
<td>14 ± 1.1</td>
<td>16 ± 1.6</td>
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</tr>
<tr>
<td><strong>PAPm (mm Hg)</strong></td>
<td>Control</td>
<td>14.3 ± 1.1</td>
<td>13.3 ± 1.0</td>
<td>14.7 ± 1.0</td>
<td>14.6 ± 1.2</td>
<td>17.3 ± 1.1</td>
<td>18.3 ± 0.9</td>
<td>20.5 ± 1.6</td>
<td>22.4 ± 1.8</td>
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</tr>
<tr>
<td></td>
<td>Ramipril</td>
<td>14.5 ± 1.1</td>
<td>13.6 ± 1.4</td>
<td>13.8 ± 1.1</td>
<td>15.1 ± 0.9</td>
<td>16.9 ± 1.0</td>
<td>17.3 ± 0.8</td>
<td>18.7 ± 1.2</td>
<td>20.1 ± 1.7</td>
<td>20.1 ± 1.7</td>
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<tr>
<td><strong>CI (L/min/m²)</strong></td>
<td>Control</td>
<td>3.6 ± 0.2</td>
<td>3.7 ± 0.3</td>
<td>3.4 ± 0.1</td>
<td>3.1 ± 0.1</td>
<td>3.1 ± 0.1</td>
<td>3.1 ± 0.2</td>
<td>3.0 ± 0.1</td>
<td>3.0 ± 0.1</td>
<td>3.0 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>Ramipril</td>
<td>4.1 ± 0.2</td>
<td>3.4 ± 0.1</td>
<td>3.2 ± 0.1</td>
<td>3.1 ± 0.2</td>
<td>3.1 ± 0.1</td>
<td>3.0 ± 0.1</td>
<td>3.2 ± 0.2</td>
<td>3.1 ± 0.2</td>
<td>3.1 ± 0.2</td>
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</tbody>
</table>

*Significantly (P < 0.05, P < 0.01, and P < 0.001, respectively) different from baseline.

SAP = Systolic artery pressure, HR = Heart rate, RR = Respiratory rate, PAPs = Systolic pulmonary artery pressure, PAPd = Diastolic pulmonary artery pressure, PAPm = Mean pulmonary artery pressure, CI = Cardiac index.
The clearance value on each dog. The GFR of iohexol (GFRI) during the 3-point elimination phase was required for acceptance of the data. 

obtained 2, 3, and 4 hours after iohexol injection and placed in tubes containing sodium heparin. 

Creatinine (50 mg/mL) and PAH (12.5 mg/mL) were dissolved in sterile water and stored at –20°C until use. For ClCr and the ClPAH, a 1-minute IV bolus (creatinine, 50 mg/kg; PAH, 2 mg/kg) followed by a 2-hour constant infusion (creatinine, 0.3 mg/kg/min; PAH, 0.1 mg/kg/min at a rate of 0.4 mL/min) were administered with lactated Ringer’s solution at a rate of 3 mL/min. For ClI, a 1-minute IV bolus of iohexol at a dose of 240 mg/kg was injected. After an equilibration period of 50 minutes, a rubber catheter was placed to empty and rinse the urinary bladder 3 times with 10 mL of sterile water. Three successive urine collection periods of 20 minutes were performed; a 5-mL sample of venous blood was obtained at the midpoint of each period. The bladder was carefully rinsed with sterile water (10 mL) after each period, and the rinsing solution was added to the urine volume of the preceding collection. To measure ClI, blood samples were obtained 2, 3, and 4 hours after iohexol injection and placed in tubes containing sodium heparin.

Creatinine concentrations in urine and serum were determined according to the Jaffe method. Urine and serum concentrations of PAH were analyzed by a spectrophotometric assay, whereas plasma concentrations of iohexol were determined by high-performance liquid chromatography.

Calculations—The ClCr, was calculated by use of the following equation:

$$\text{ClCr (mL/kg/min)} = \frac{(U_{\text{Cr}} \times UO)}{P_{\text{Cr}}}$$

where $U_{\text{Cr}}$ and $P_{\text{Cr}}$ are urinary and serum concentrations of creatinine, respectively, and $UO$ is urinary output. Urinary output was calculated as $UO = \text{urinary volume/(body weight \times time of collection)}$. The GFR of creatinine (GFRCr) was calculated as the mean of 3 successive clearances.

The ClI was calculated by use of the following equation:

$$\text{ClI (mL/kg/min)} = \frac{D}{(AUC \times \text{body weight})}$$

where D is the dose of iohexol injected and AUC is the area under the curve. The area under the curve was calculated by use of the following mono-compartmental model:

$$AUC = \frac{C_0}{k}$$

where $C_0$ is the plasma iohexol concentration at zero time as determined by extrapolation of the line of best fit from 120-, 180-, and 240-minute samples, and k is the elimination rate constant (slope) of the decay curve. An $R^2$ value of $\geq 0.97$ for the 3-point elimination phase was required for acceptance of the clearance value on each dog. The GFR of iohexol (GFRI) was then corrected by use of the Brochner-Mortensen formula as follows:

$$\text{GFR} = 0.990778 \times (\text{ClI}) - 0.001218 \times (\text{ClI})^2$$

The ClPAH was calculated by use of the following equation:

$$\text{ClPAH (mL/kg/min)} = \frac{(U_{\text{PAH}} \times UO)}{P_{\text{PAH}}}$$

where $U_{\text{PAH}}$ and $P_{\text{PAH}}$ are urinary and serum concentrations of PAH, respectively. The RPF was calculated as the mean of 3 successive clearances.

The filtration fraction (FF) was calculated as $FF = (\text{GFR}_{\text{Cr}} / \text{RPF})$. The EFs and log10(Na+/K+) were calculated by use of the following equations:

$$EF_x = \frac{[(U_x \times P_{\text{Cr}})/(P_x \times U_{\text{Cr}})]}{\text{log10}(\text{Na}/\text{K})} = \frac{\log(U_{\text{Cr}} \times 10U_x)}{\text{log10}(\text{Na}/\text{K})}$$

where x is the molecule Na+, K+, or urea excreted.

The ClOsm and ClH2O were calculated by use of the following equations:

$$\text{ClOsm} = \frac{U_{\text{Osm}} \times \text{urinary volume}}{(P_{\text{Osm}} \times \text{body weight} \times \text{time of collection})}$$

$$\text{ClH2O} = UO - \text{ClOsm}$$

where $U_{\text{Osm}}$ and $P_{\text{Osm}}$ are urinary and plasma osmolalities, respectively.

Statistical analysis—All values are reported as mean ± SEM. Results of a Shapiro-Wilk test indicated that the variables were normally distributed. The correlation between ClCr and ClI was calculated by use of a least squares linear regression, and the agreement between ClCr and ClI was determined by plotting the differences between the 2 methods against the mean and calculation of the 95% limits of agreement from the mean difference and SD.

Continuous variables were tested by a 2-factor ANOVA for repeated measures. When a time effect was detected, as a result of induction of the disease, we compared week 0 to 7 (for cardiac variables) and weeks 4 and 7 to week 0 (for renal parameters) with a modified t test (ie, t test computed by use of the residual variance of the ANOVA). When a group effect was detected, as a result of treatment, or when the interaction group time was significant, the 2 groups were then compared week by week with a modified t test. All comparisons were performed at a 1-sided significance level of $P = 0.05$.

![Figure 1](image-url)
Time and treatment effects were tested for discontinuous variables with a χ² test.¹⁹

Results
Physical examination findings indicated progressive increases in heart and respiratory rates and a progressive decrease in blood pressure (Table 1). Clinical signs of congestive heart failure such as weakness, apathy, cachexia, heart murmurs, pulmonary crackles, and ascites were detected from weeks 4 to 5. Tricuspid regurgitant murmurs and ascites developed during weeks 4 and 5, respectively (Figure 1).

Doppler echocardiography of the heart revealed a progressive decrease in FS and an increase in the PEP-to-LVET ratio starting at week 1, with progressive increases in LAD and in the LAD-to-Ao ratio (Table 2). Indices of diastolic function (ie, the mitral E wave–to–A wave ratio and IVRT) indicated a progressive evolution with decreased relaxation starting at week 1, a pseudonormal mitral inflow and IVRT at the fourth week, and a restrictive pattern with an increased mitral E wave–to–A wave ratio from the fifth to seventh weeks (Figure 2).

Results of hemodynamic measurements indicated an increase in PAPO from the third to the seventh weeks, whereas RAP increased from the fourth to the seventh weeks (Figure 3). There was a progressive decrease in the cardiac index and a progressive increase in mean pulmonary arterial pressure (Table 1).

There was a significant correlation between ClCr and ClH₂O, with a satisfactory agreement between these 2 methods; the mean difference between the 2 methods was –0.7 mL/kg/min, and the 95% limits of agreement varied from –1.25 to 2.65 mL/kg/min (Figure 4). Heart failure was associated with a decrease in GFR, which was of the same magnitude using the 2 methods of measurement at weeks 4 and 7 (ClGFR evolution vs ClH₂O evolution; the value of P was not significant). Renal plasma flow decreased proportionally more, increasing the filtration fraction (Figure 5).

Serum creatinine concentrations remained unchanged, whereas serum urea concentrations increased; both were within reference ranges (Table 3). The EF of potassium increased, and the EF of sodium and log_{10}(Na/K) decreased (Figure 6). Urinary output, ClOsm, ClH₂O, and the EF of urea all decreased from weeks 4 to 7 (Table 4).

Ramilpril delayed the development of tricuspid regurgitant murmurs and ascites (Figure 1) and limited the increases in RAP and PAPO beginning at the fourth and the fifth weeks, respectively (Figure 3). Ramilpril had no effect on GFR and RPF, but did increase the EF of sodium and the log_{10}(Na/K) (Figures 4–6).

Table 2—Mean ± SEM values for Doppler echocardiographic variables during progression of overpacing-induced heart failure in dogs receiving ramipril (0.125 mg/kg, PO, daily; n = 10) or no treatment (control group; 10) for 7 weeks.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Baseline</th>
<th>Pacing activation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 1</td>
<td>Week 2</td>
</tr>
<tr>
<td>FS (%)</td>
<td>Control</td>
<td>36 ± 1.32</td>
<td>27 ± 1.0*</td>
</tr>
<tr>
<td></td>
<td>Ramipril</td>
<td>35 ± 1.37</td>
<td>28 ± 1.0*</td>
</tr>
<tr>
<td>PEP:LVET</td>
<td>Control</td>
<td>0.33 ± 0.02</td>
<td>0.41 ± 0.01*</td>
</tr>
<tr>
<td></td>
<td>Ramipril</td>
<td>0.30 ± 0.01</td>
<td>0.41 ± 0.03</td>
</tr>
<tr>
<td>LAD (cm)</td>
<td>Control</td>
<td>2.1 ± 0.08</td>
<td>1.9 ± 0.10</td>
</tr>
<tr>
<td></td>
<td>Ramipril</td>
<td>2.0 ± 0.07</td>
<td>2.0 ± 0.04</td>
</tr>
<tr>
<td>LAD:Ao</td>
<td>Control</td>
<td>1.1 ± 0.02</td>
<td>1.0 ± 0.05</td>
</tr>
<tr>
<td></td>
<td>Ramipril</td>
<td>1.1 ± 0.04</td>
<td>1.1 ± 0.03</td>
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</tbody>
</table>

*Significantly (P < 0.001) different from baseline.
Discussion

Results of the study reported here indicated that preventive ACE inhibition with ramipril in overpacing-induced heart failure in dogs improves advanced clinical signs, renal sodium and water handling, and cardiac preload, suggesting an effective but limited and late contribution of the renin-angiotensin system in this heart failure model.

The overpacing-induced heart failure model in dogs is characterized by development, within a few weeks, of dilated cardiomyopathy with impaired cardiac systolic and diastolic function and increased cardiac and pulmonary vascular pressures, with neurohormonal and renin-angiotensin system activation. We adapted the pacing rate such as to detect all stages of heart failure during a period of 7 weeks. Results of
our study verify the early subclinical development of marked alterations in ventricular function as assessed by echocardiography, confirming results of another study in which invasive techniques were used. After only 1 week of pacing in dogs with clinical signs, the Doppler echocardiography revealed a delayed relaxation pattern, with a decreased mitral E wave-to–A wave ratio and an increased IVRT. This was accompanied by early systolic dysfunction as assessed by a decrease in Fs and an increase in the PEP-to-LVET

Table 3—Mean ± SEM values for serum urea and creatinine concentrations during progression of over pacing-induced heart failure in dogs receiving ramipril (0.125 mg/kg, PO, daily; n = 10) or no treatment (control group; 10) for 7 weeks.

<table>
<thead>
<tr>
<th>Parameter (mg/dL)</th>
<th>Group</th>
<th>Baseline (Week 0)</th>
<th>Pacing activation (Week 0)</th>
</tr>
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<tbody>
<tr>
<td>Urea</td>
<td>Control</td>
<td>32 ± 2</td>
<td>40 ± 31</td>
</tr>
<tr>
<td></td>
<td>Ramipril</td>
<td>31 ± 3</td>
<td>43 ± 25</td>
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<tr>
<td>Creatinine</td>
<td>Control</td>
<td>0.82 ± 0.03</td>
<td>0.90 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>Ramipril</td>
<td>0.83 ± 0.04</td>
<td>0.93 ± 0.06</td>
</tr>
</tbody>
</table>

*†‡Significantly (P < 0.05, P < 0.01, and P < 0.001, respectively) different from baseline.
decreased urinary output, ClOsm, EF of sodium, and alteration in renal hemodynamics. There was an avid firming neurohormonal activation-mediated early were decreased after only 4 weeks of overpacing in arrhythmia-related sudden death,27 but exactly how nervous system.23-26 intense hypertensive hormones and the sympathetic in RPF and GFR, all of which suggest activation of potassium depletion, and positive interaction with effects, which include myocardial and vascular remodeling, renal vasoconstriction with decreases in pressures. Results of our study thus confirm the validity of the overpacing-induced heart failure model for studies of clinical, Doppler echocardiographic, and hemodynamic stages of the disease during a reasonable period of several weeks.

The renin-angiotensin system is known to aggravate heart failure through a complex interaction of effects, which include myocardial and vascular remodeling, renal vasoconstriction with decreases in both RPF and GFR, sodium and water retention, potassium depletion, and positive interaction with the sympathetic nervous system.1-3,5,20,21,23,24 An increased release of angiotensin II is believed to play a major role in the marked decrease in renal perfusion, which develops early in patients with heart failure.35 In the study reported here, both RPF and GFR were decreased after only 4 weeks of overpacing in the presence of still unchanged cardiac output, confirming neurohormonal activation-mediated early alteration in renal hemodynamics. There was an avid sodium and water retention state as indicated by decreased urinary output, ClUM, EF of sodium, and log10(Na+/K+); an increased ClH2O in the presence of an unchanged cardiac output; and marked decreases in RPF and GFR, all of which suggest activation of intense hypertensive hormones and the sympathetic nervous system.23-26

The administration of ACE inhibitors has been found to improve clinical state and survival in patients with heart failure.6,7,11 The improved survival appears to be essentially attributed to a decreased risk of arrhythmia-related sudden death,37 but exactly how and when renin-angiotensin system activation affects the evolution of heart failure from early to late stages is not completely understood.38 Results of our study are in agreement with the notion that beneficial effects of ACE inhibitors in rapidly evolving heart failure, such as in overpacing-induced cardiomyopathy, may be essentially attributed to an improvement in renal function, with a predominant limitation in tubular handling of sodium and water.7 However, this result may not be transposable to chronic and slowly evolving heart failure models or diseases, in which angiotensin II and aldosterone, in combination with activation of the sympathetic nervous system, are more likely to contribute to the disease by major myocardial and arterial remodelling effects.

In the study reported here, administration of ramipril had no effect on RPF or GFR, suggesting limited participation of angiotensin II in altered renal hemodynamics in the overpacing-induced heart failure model. Ramipril was given at a dose previously found to effectively inhibit ACE in dogs and is recommended for treatment of heart failure in dogs. In addition, ramipril treatment was associated with a marked improvement in the EF of sodium and log10(Na+/K+), which are valid indices of the effects of aldosterone on the renal tubules.38 The delayed development of clinical signs of congestive heart failure and the decrease in ventricular filling pressures may be considered direct consequences of the beneficial effects of ramipril on the hydroelectrolytic balance. We therefore believe that the absence of renal hemodynamic effects of ramipril in our study could be explained by insufficient dosage or absorption.

In the study reported here, GFR was measured by use of 2 methods (ClCcr and Clu). Mean values of 3.1 mL/kg/min for Clu and 4.1 mL/kg/min for ClCcr in healthy dogs are in agreement with previously reported reference values in dogs.30-32 However, the correlation between the 2 clearances, although significant, was weak, and results of the Bland-Altman analysis revealed that Clu underestimated ClCcr by approximately 0.7 mL/kg/min, with a difference of as much as 0.98 mL/kg/min, indicating only moderate precision. This may have been attributable to the small number of plasma iohexol concentration measurements used to construct the plasma elimi-
nation curve. Nevertheless, it is of interest that both Cl\textsubscript{a}, and C\textsubscript{d} determinations lead to similar estimations of the mean decrease in GFR (2- and 2.3-fold, respectively) in dogs with heart failure, whereas serum urea and creatinine determinations remained within reference ranges. Additionally, the use of 2 measurements of clearances confirms the observation that ramipril had no effect on GFR in dogs with moderate and severe overpacing-induced heart failure.

Results of our study indicated that cardiac and renal function can be monitored by repetitive catheterization of the right side of the heart and Doppler echocardiography and by use of clearance and electrolyte measurements in dogs with overpacing-induced heart failure. Angiotensin converting enzyme inhibition in this particular type of congestive heart failure has only moderate and late beneficial effects, which appear essentially associated with decreased renal tubular sodium and water reabsorption.

References