Chronic Amlodipine Treatment During the Development of Heart Failure

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**Background**—This study examined the effects of chronic amlodipine treatment on left ventricular (LV) pump function, systemic hemodynamics, neurohormonal status, and regional blood flow distribution in an animal model of congestive heart failure (CHF) both at rest and with treadmill exercise. In an additional series of in vitro studies, LV myocyte contractile function was examined.

**Methods and Results**—Sixteen pigs were studied under normal control conditions and after the development of chronic pacing–induced CHF (240 bpm, 3 weeks, n=8) or chronic pacing and amlodipine (1.5 mg · kg⁻¹ · d⁻¹, n=8). Under ambient resting conditions, LV stroke volume (mL) was reduced with CHF compared with the normal control state (16±2 versus 31±2, P<0.05) and increased with concomitant amlodipine treatment (29±2, P<0.05). At rest, systemic and pulmonary vascular resistance (dyne · s⁻¹ · cm⁻⁵) increased with CHF compared with the normal control state (3102±251 versus 2156±66 and 1066±140 versus 253±24, respectively, both P<0.05) and were reduced with amlodipine treatment (2108±199 and 480±74, respectively, P<0.05). With CHF, LV stroke volume remained reduced and was associated with a 40% reduction in myocardial blood flow during treadmill exercise, whereas chronic amlodipine treatment normalized LV stroke volume and improved myocardial blood flow. Resting and exercise-induced plasma norepinephrine levels were increased by >5-fold in the CHF group and were reduced by 50% from CHF values with chronic amlodipine treatment. Resting plasma endothelin (fmol/mL) increased with CHF compared with the normal state (10.4±0.9 versus 3.1±0.3, P<0.05) and was reduced with amlodipine treatment (6.6±1.1, P<0.05). With CHF, LV myocyte velocity of shortening (μm/s) was reduced compared with normal controls (39±1 versus 64±1, P<0.05) and was increased with chronic amlodipine treatment (52±1, P<0.05).

**Conclusions**—Chronic amlodipine treatment in this model of developing CHF produced favorable hemodynamic, neurohormonal, and contractile effects in the setting of developing CHF. (Circulation. 1998;98:1666-1674.)

Key Words: calcium channel blockers ▪ heart failure ▪ blood flow ▪ hormones

Therapeutic modalities for the syndrome of congestive heart failure (CHF) have included a reduction in left ventricular (LV) afterload by vasodilation and/or neurohormonal modulation. However, previously performed clinical trials with calcium (Ca²⁺) channel antagonists, which effectively reduce systemic vascular resistance and thereby LV afterload, have reported deleterious effects in patients with CHF.¹⁻⁴ However, newer compounds of the dihydropyridine subclass of Ca²⁺ channel antagonists, such as amlodipine, have been shown to significantly reduce vascular resistance properties without significant effects on myocardial contractility.⁵⁻⁷ In a recent clinical trial, amlodipine therapy was associated with no adverse effects on morbidity or mortality in patients with severe CHF.⁴ The fundamental mechanisms by which amlodipine treatment may influence LV function and hemodynamics during the development of CHF warrant investigation. The overall goal of the present study was to examine LV pump function, systemic hemodynamics, regional blood flow, neurohormonal activity, and myocyte contractility after chronic amlodipine treatment with developing CHF.

**Methods**

Sixteen pigs (25 kg, male, Hambone Farms, SC) were chronically instrumented with aortic, pulmonary, and left atrial catheters (model GPV, 9F, Access Technologies), a pulmonary artery flow probe (20 mm, Transonics), and a modified atrial pacemaker (model 8329, Medtronic, Inc) as described previously.⁵⁻¹¹ After a 10-day recovery from surgery, baseline studies were performed at rest and with exercise, and the pigs were then assigned to the following treatments: (1) rapid pacing at 240 bpm for 21 days or (2) treatment with amlodipine (1.5 mg · kg⁻¹ · d⁻¹) for the entire pacing period (n=8). This laboratory has demonstrated previously that this rate and
duration of rapid atrial pacing reliably causes LV dilation and pump
dysfunction.9–11 The amlodipine treatment was given every morning
in an oral formulation that has been shown previously to maintain
steady-state blood levels for this compound and to have pharmaco-
logical activity against the vascular smooth muscle L-type Ca2+
channel.6,12 At the completion of the pacing protocol, the animals
were returned to the laboratory, and the pacemaker was deactivated.
After a 1-hour stabilization period, resting and treadmill data
were collected.

On the day of the study, the animals were placed in a custom-
designed sling, and LV echocardiographic measurements were per-
formed (ATL Ultramark VI, 2.25-MHz transducer). Pressures from
the access ports were obtained with calibrated transducers (Statham
P23ID, Gould) and digitized to the computer at a sampling frequency
of 250 Hz (80486 processor, Zenith Data Systems). The flow probe
was connected to a digital flowmeter (T106, Transonics) as well as
being digitized. From the arterial catheter, 30 mL of blood was
drawn into chilled tubes containing EDTA (1.5 mg/mL) and centri-
fuged (2000g, 10 minutes, 4°C). Pulmonary artery and left atrial
samples were measured for oxygen saturation and hemoglobin
content (CO-Oximeter, Instruments Laboratory), and oxygen con-
sumption was computed.13 Fluorescent microspheres (3×10^6,
 Molecular Probes) were injected into the left atrium, and aortic samples
were collected for blood flow measurements. The pigs were then
exercised at a treadmill workload of 3 miles/h at a 15° incline for a
10-minute interval, and measurements were repeated. After the final
set of measurements, the animals were euthanized with an overdose
of pentobarbital (1000 mg), and tissue was harvested. All animals
were treated and cared for in accordance with the National Institutes
of Health Guide for the Care and Use of Laboratory Animals

The plasma samples were assayed for renin activity, endothelin
concentration, and catecholamine levels by methods described pre-
viously.10,11 Blood flow was determined in the LV free wall endocar-
dium and epicardium, lung, kidney, diaphragmatic muscle, latissi-
mus dorsi, and gluteus maximus by spectrofluorimetry (Gilford
Fluoroor IV).14 Coronary vascular resistance was determined as the
mean aortic pressure divided by LV myocardial blood flow and
expressed as mm Hg · min⁻¹ · mL⁻¹ · g⁻¹.

LV Myocyte Contractile Function

For these studies, LV myocytes were harvested from 3 pigs that
underwent concomitant amlodipine treatment and rapid pacing, 3
pigs with rapid pacing only, and 4 control pigs by methods described
previously.10,11 Isolated LV myocyte contractility was then examined
by computer-assisted videomicroscopy.10,11 After baseline measure-
ments, contractile function was examined after a specific inotropic
stimulus in each myocyte in 1 of 3 ways: (1) after β-adrenergic
receptor stimulation with 25 nmol/L isoproterenol (−isoproterenol,
Sigma Chemical Co), (2) after direct stimulation of the L-type Ca2+
channel with 10 nmol/L of the Ca2+ channel agonist
BayK 8644 (Research Biochemicals International), or (3) in the presence
of 8 mmol/L extracellular Ca2+.

Data Analysis

Indices of LV function, systemic hemodynamics, neurohormonal
profiles, and regional blood flow were compared among the treat-
ment groups by ANOVA for repeated measures. For the myocyte
function studies, an ANOVA with a randomized-block split-plot
design was used. If the ANOVA revealed significant differences,
pairwise tests of individual group means were compared by use of
Bonferroni probabilities. All statistical procedures were performed
with the BMDP statistical software package (BMDP Statistical
Software Inc). Results are presented as mean±SEM. Values of
P<0.05 were considered to be statistically significant.

Results

In the CHF plus amlodipine group, plasma levels of amlo-
dipine obtained at the terminal study were 22±2 ng/mL
(range, 15 to 28 ng/mL). In the CHF-only group, LV end-
diastolic dimension increased by 60% and fractional
shortening decreased by 65% from normal control values
(Figure 1). In the CHF plus amlodipine group, LV end-dia-
static dimension was reduced from untreated CHF values,
and LV fractional shortening increased by 76%.

Figure 1. LV end-diastolic dimension increased with pacing CHF and was
reduced from CHF values in which amloidipine was given throughout the
pacing protocol. LV fractional shortening fell in CHF group and was
increased in chronic amlodipine group. *P<0.05 vs control state, +P<0.05 vs
CHF-only group.
LV Function and Hemodynamics

Resting State

In the untreated CHF group, stroke volume and cardiac output were reduced compared with the normal control state (Table 1). In the CHF plus amlodipine group, stroke volume and cardiac output were not different from normal control-state values. In the untreated CHF group, mean aortic pressure was reduced and pulmonary artery pressure and left atrial pressures were increased compared with the normal control state. Systemic and pulmonary vascular resistances were increased in the untreated CHF group. Systemic vascular resistance was normalized and pulmonary vascular resistance reduced in the CHF plus amlodipine group compared with untreated CHF values. Left atrial oxygen saturation levels were lower than in the normal control state. Basal, resting systemic oxygen consumption (VO2) was 6.8±0.6 mL O2·min⁻¹·kg⁻¹ in the normal control state and was unchanged in either CHF group.

Treadmill Exercise

In both CHF groups, heart rate increased significantly from resting values with exercise but remained lower than that achieved in the normal control state. In the normal control state, cardiac output increased 2-fold with treadmill exercise (Table 1). In the untreated CHF group, cardiac output increased from resting values but remained reduced from normal control values. In the CHF-plus-amlodipine group, cardiac output was similar to normal control values. Systemic and pulmonary vascular resistance fell significantly with treadmill exercise in the normal control state and in both CHF

### TABLE 1. Systemic Hemodynamics and LV Pump Function With Pacing-Induced CHF: Effects of Chronic Amlodipine Treatment

<table>
<thead>
<tr>
<th></th>
<th>Control Rest</th>
<th>Exercise</th>
<th>CHF Rest</th>
<th>Exercise</th>
<th>CHF + Amlodipine Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>119±4</td>
<td>267±8‡</td>
<td>157±7*</td>
<td>214±9‡</td>
<td>133±6†</td>
<td>223±8‡</td>
</tr>
<tr>
<td>Pump function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>31.4±1.8</td>
<td>32.0±1.2</td>
<td>15.7±1.4*</td>
<td>27.7±2.0†</td>
<td>29.0±2.4†</td>
<td>35.6±3.0†</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>3.7±0.2</td>
<td>8.5±0.4‡</td>
<td>2.4±0.2*</td>
<td>6.0±0.4‡</td>
<td>3.8±0.2†</td>
<td>7.9±0.7†</td>
</tr>
<tr>
<td>Pressures, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aorta</td>
<td>97±2</td>
<td>105±2‡</td>
<td>91±2*</td>
<td>90±2*</td>
<td>96±4</td>
<td>93±3*</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>16±1</td>
<td>25±2‡</td>
<td>31±3*</td>
<td>31±3*</td>
<td>25±2*</td>
<td>24±2*</td>
</tr>
<tr>
<td>Left atrium</td>
<td>11±1</td>
<td>13±1</td>
<td>31±3*</td>
<td>28±2*</td>
<td>21±2†</td>
<td>18±3†</td>
</tr>
<tr>
<td>Resistances</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic, dyne·s·cm⁻⁵</td>
<td>2156±66</td>
<td>1016±46‡</td>
<td>3102±251*</td>
<td>1216±104‡</td>
<td>2108±199†</td>
<td>978±73‡</td>
</tr>
<tr>
<td>Pulmonary, dyne·s·cm⁻⁵</td>
<td>253±24</td>
<td>127±13‡</td>
<td>1066±140*</td>
<td>386±53‡</td>
<td>480±74‡</td>
<td>198±38‡</td>
</tr>
<tr>
<td>Rate x pressure, 10⁴ bpm×mm Hg</td>
<td>11.6±0.6</td>
<td>28.1±1.2‡</td>
<td>14.0±0.7*</td>
<td>19.2±0.9‡</td>
<td>12.7±0.6</td>
<td>20.9±1.4‡</td>
</tr>
<tr>
<td>Oxygen saturations, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrium</td>
<td>95.9±0.3</td>
<td>94.3±0.9</td>
<td>95.2±0.8</td>
<td>93.0±1.5</td>
<td>92.5±1.0†</td>
<td>86.8±2.5†</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>63.1±1.9</td>
<td>38.8±3.0‡</td>
<td>41.2±4.8*</td>
<td>23.0±3.6‡</td>
<td>52.4±2.5†</td>
<td>24.5±1.2†</td>
</tr>
<tr>
<td>Sample size (n)</td>
<td>16</td>
<td>16</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
*P<0.05 vs control.
†P<0.05 vs CHF.
‡P<0.05 vs resting state.

### TABLE 2. Plasma Neurohormones With Pacing-Induced CHF: Effects of Chronic Amlodipine Treatment

<table>
<thead>
<tr>
<th></th>
<th>Control Rest</th>
<th>Exercise</th>
<th>CHF Rest</th>
<th>Exercise</th>
<th>CHF + Amlodipine Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>124±11</td>
<td>798±153‡</td>
<td>638±126*</td>
<td>3789±1334‡</td>
<td>323±57†</td>
<td>1742±192†‡</td>
</tr>
<tr>
<td>Epinephrine, pg/mL</td>
<td>87±32</td>
<td>297±42‡</td>
<td>211±26*</td>
<td>603±234‡</td>
<td>224±31†</td>
<td>407±64‡</td>
</tr>
<tr>
<td>Renin activity, ng·mL⁻¹·h⁻¹</td>
<td>4.0±0.6</td>
<td>10.1±1.2</td>
<td>25.0±5.0*</td>
<td>26.8±5.8*</td>
<td>12.6±3.5†</td>
<td>25.7±5.3‡</td>
</tr>
<tr>
<td>Endothelin, fmol/mL</td>
<td>31±0.3</td>
<td>35±0.2</td>
<td>10.4±0.9*</td>
<td>12.2±1.8*</td>
<td>6.6±1.1†</td>
<td>6.4±1.1†</td>
</tr>
<tr>
<td>Sample size (n)</td>
<td>16</td>
<td>16</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
*P<0.05 vs control.
†P<0.05 vs CHF.
‡P<0.05 vs resting state.
groups. In the CHF-plus-amlodipine group, left atrial oxygen saturation values were reduced from resting values as well as from normal control values. Systemic \( \text{VO}_2 \) increased significantly in the normal control state with exercise (6.8 ± 0.6 to 34.2 ± 2.5 mL O\(_2\) • min\(^{-1}\) • kg\(^{-1}\), \( P<0.05 \)). In the untreated CHF group, systemic \( \text{VO}_2 \) increased from resting values with exercise (5.7 ± 0.5 to 19.7 ± 1.1 mL O\(_2\) • min\(^{-1}\) • kg\(^{-1}\), \( P<0.05 \)) but was significantly reduced from that achieved in the normal state (\( P<0.05 \)). In the CHF-plus-amlodipine group, systemic \( \text{VO}_2 \) was similar to untreated CHF values at rest (5.9 ± 0.3 mL O\(_2\) • min\(^{-1}\) • kg\(^{-1}\)) and with exercise (23.9 ± 3.0 mL O\(_2\) • min\(^{-1}\) • kg\(^{-1}\), \( P<0.05 \)).

**Neurohormonal System Activity**

**Resting State**

In both CHF groups, plasma norepinephrine and epinephrine values were significantly increased from normal control state levels (Table 2). In the resting state, chronic amlodipine treatment with the development of pacing CHF significantly reduced plasma norepinephrine levels compared with untreated CHF values. Plasma renin activity increased by 4-fold in the untreated CHF group compared with normal control values and was significantly reduced in the CHF-plus-amlodipine group. Plasma endothelin levels increased by 4-fold in the untreated CHF group compared with normal control values. In the CHF-plus-amlodipine group, plasma endothelin levels were reduced by >40% from untreated CHF values. Plasma lactate levels were increased by 3-fold in the untreated CHF group and were similar to control values in the CHF-plus-amlodipine group.

**Treadmill Exercise**

Plasma catecholamines increased significantly in all 3 groups with treadmill exercise (Table 2). Chronic amlodipine treatment during developing CHF significantly blunted the rise in both plasma norepinephrine and epinephrine after treadmill-induced exercise. Plasma endothelin values were lower in the CHF-plus-amlodipine group compared with untreated CHF values.

**Regional Blood Flow**

**Resting State**

LV myocardial blood flow was reduced in the untreated CHF group compared with normal control values (Table 3). In the CHF-plus-amlodipine group, resting ambient LV myocardial blood flow was normalized. Coronary vascular resistance was increased in the untreated CHF group but was normalized in the CHF-plus-amlodipine group. Pulmonary parenchymal flow was reduced by >65% from normal control values in the untreated CHF group. Pulmonary parenchymal flow increased by >50% in the CHF-plus-amlodipine group compared with CHF-only values. Renal blood flow was reduced in both CHF groups compared with normal control values. Representative resting skeletal muscle blood flow, as determined by blood flow to the latissimus dorsi and gluteus maximus muscles, was similar between the normal control and CHF groups.

**Treadmill Exercise**

LV myocardial blood flow increased by ≈4-fold in the normal control state with treadmill exercise but was reduced in the pacing CHF group (Table 3). With pacing CHF and chronic amlodipine treatment, LV myocardial blood flow was increased from untreated CHF values but remained lower than normal control values. Coronary vascular resistance fell by 4-fold in the normal control state with treadmill-induced exercise. In the untreated CHF group, coronary vascular resistance was reduced from the resting state but remained increased from normal control values. In the CHF-plus-amlodipine group, coronary vascular resistance was similar to normal control values. Pulmonary parenchymal flow increased by 4-fold in the normal control state with treadmill exercise.
exercise and was significantly blunted in the untreated CHF group. In the CHF-plus-amlodipine group, pulmonary flow was not significantly different from the normal control values ($P = 0.12)$. Renal blood flow increased by 50% in the normal control state with exercise but was reduced by 40% in the untreated CHF group. Renal blood flow in the CHF-plus-amlodipine group was similar to untreated CHF values.

**Skeletal muscle blood flow** increased by 5-fold in the control state and was significantly reduced in both CHF groups; this was not affected by chronic amlodipine treatment.

**Myocyte Contractility**

Myocyte contractile function was examined in >500 LV myocytes from the normal control state, with the development of pacing CHF, and with pacing CHF plus concomitant amlodipine treatment. LV myocyte resting length was increased in the untreated CHF group (176 ± 1 versus 126 ± 1 μm, $P < 0.05$). In the CHF-plus-amlodipine group, resting myocyte length remained significantly increased from control values (168 ± 1 μm, $P < 0.05$). Steady-state myocyte contractile function was significantly reduced in the untreated CHF group compared with normal control values (Table 4). In the CHF-plus-amlodipine group, steady-state myocyte contractile function was improved from untreated CHF values. However, steady-state myocyte function in the CHF-plus-amlodipine group remained reduced from normal control values. Although indices of myocyte shortening were improved in the CHF-plus-amlodipine group, certain indices of myocyte relaxation were not improved from untreated CHF values. For example, the time to 50% relaxation was prolonged in both CHF groups compared with normal control values, and this prolongation was not influenced by chronic amlodipine treatment.

In the presence of isoproterenol, myocyte contractile function was significantly blunted in the untreated CHF group (Table 4). In the CHF-plus-amlodipine group, myocyte contractile function with isoproterenol was improved from un-

<table>
<thead>
<tr>
<th>TABLE 4. Isolated Myocyte Contractile Function With Pacing-Induced CHF: Effects of Chronic Amlodipine Treatment</th>
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</thead>
<tbody>
<tr>
<td><strong>Percent shortening, %</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>CHF</td>
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<tr>
<td>CHF + amlodipine</td>
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<tr>
<td><strong>Shortening velocity, μm/s</strong></td>
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<tr>
<td>Control</td>
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<tr>
<td>CHF</td>
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<tr>
<td>CHF + amlodipine</td>
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<tr>
<td><strong>Relengthening velocity, μm/s</strong></td>
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<tr>
<td>Control</td>
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<tr>
<td>CHF</td>
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<tr>
<td>CHF + amlodipine</td>
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<tr>
<td><strong>Time to peak contraction, ms</strong></td>
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<tr>
<td>Control</td>
</tr>
<tr>
<td>CHF</td>
</tr>
<tr>
<td>CHF + amlodipine</td>
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<tr>
<td><strong>Time to 50% relaxation, ms</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>CHF</td>
</tr>
<tr>
<td>CHF + amlodipine</td>
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<tr>
<td><strong>Total duration, ms</strong></td>
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<tr>
<td>Control</td>
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<tr>
<td>CHF</td>
</tr>
<tr>
<td>CHF + amlodipine</td>
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<tr>
<td><strong>Number of myocytes, n</strong></td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>CHF</td>
</tr>
<tr>
<td>CHF + amlodipine</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

* $P < 0.05$ vs control.
† $P < 0.05$ vs CHF.
‡ $P < 0.05$ vs baseline.
treated CHF values. With increased extracellular Ca\(^{2+}\), myocyte contractile function was significantly reduced in the untreated CHF group. In the CHF-plus-amlodipine group, myocyte function was significantly improved from untreated CHF values in the presence of increased extracellular Ca\(^{2+}\). Isolated myocyte contractile function increased in all 3 groups in the presence of the L-type Ca\(^{2+}\) channel agonist \(\text{BayK 8644}\). In the untreated CHF group, myocyte function after \(\text{BayK 8644}\) administration was reduced from normal control values. In the CHF-plus-amlodipine group, indices of myocyte shortening were significantly improved after the addition of \(\text{BayK 8644}\) compared with untreated CHF values. However, indices of active myocyte relaxation, such as time to 50% relaxation, remained significantly prolonged in the CHF-plus-amlodipine group and were similar to untreated CHF values. The absolute change in myocyte velocity of shortening after the addition of isoproterenol, extracellular Ca\(^{2+}\), or \(\text{BayK 8644}\) was computed for each individual myocyte and is shown in Figure 2.

Discussion

Treatment with Ca\(^{2+}\) channel antagonists has been historically associated with a deterioration in hemodynamic status and symptoms in patients with chronic LV dysfunction and CHF.\(^1\)\(^-\)\(^4\) There are significant differences, however, between subclasses of Ca\(^{2+}\) channel antagonists with respect to potency and duration of action, effects on myocardial electrophysiology and contractility, and vascular selectivity.\(^5\)\(^-\)\(^7\)\(^,\)\(^12\) One of the novel Ca\(^{2+}\) channel antagonists with respect to pharmacological profile and vascular selectivity is amlodipine.\(^5\)\(^-\)\(^7\)\(^,\)\(^12\) A recent clinical trial demonstrated that chronic amlodipine treatment in patients with CHF was not associated with adverse effects on symptoms or survival.\(^8\) More importantly, and in contrast to past studies, this clinical study provided results suggesting that amlodipine treatment in patients with CHF due to nonischemic causes was associated with improved survival. In light of these clinical observations, the present study was designed to examine the effects
of chronic amlodipine treatment on LV pump function, systemic hemodynamics and neurohormonal status, regional blood flow distribution, and myocyte contractility in a porcine model of developing CHF due to chronic rapid pacing. The unique and important findings of the present study were 3-fold. First, concomitant amlodipine treatment during the progression of pacing-induced CHF improved LV pump function, increased myocardial blood flow, and reduced systemic and pulmonary vascular resistance compared with untreated CHF animals. Second, under resting conditions and with treadmill-induced exercise, chronic amlodipine treatment during the development of pacing CHF reduced plasma catecholamine and endothelin levels. Third, chronic amlodipine treatment with developing CHF was associated with improved steady-state isolated LV myocyte contractility and improved inotropic capacity compared with untreated CHF values. Thus, in contrast to conventional Ca$^{2+}$ channel antagonists, the findings of the present study suggest that chronic amlodipine treatment during developing CHF results in favorable effects on LV pump function, hemodynamic and neurohormonal systems, and myocyte contractile processes.

Contributory mechanisms for the improvement in LV pump function observed with chronic amlodipine treatment most likely include reduced LV afterload (reduced systemic vascular resistance), improved myocardial blood flow, and a protective effect on myocyte contractility. Chronic amlodipine treatment during the development of pacing CHF also resulted in reduced LV end-diastolic volume and left atrial pressures compared with untreated CHF values. The progressive LV dilation that occurs with chronic rapid pacing results in recruitment of the Frank-Starling mechanism, but this mechanism is exhausted and results in diminished LV stroke volume with prolonged periods of pacing. In the present study, the favorable LV loading conditions and improved contractility that occurred with chronic amlodipine and rapid pacing most likely attenuated the recruitment of the Frank-Starling mechanism and thereby reduced the degree of LV dilation. With treadmill-induced exercise, chronic amlodipine treatment with pacing CHF improved LV pump function. Likely contributory factors for this observation include reduced systemic vascular resistance, improved myocardial blood flow, and increased capacity of LV myocytes to respond to an inotropic stimulus compared with untreated CHF values.

In the present study, ambient resting heart rate was increased and the maximal heart rate achieved with treadmill-induced exercise reduced with the development of pacing CHF. This observation is consistent with clinical forms of CHF in which maximal heart rates are reduced from normal target levels with exercise. In the normal control state, the basic mechanism by which cardiac output was increased with exercise was through increased heart rate, because LV stroke volume remained unchanged. Interestingly, with pacing CHF, contributory factors for the increased cardiac output with exercise included a combination of increased LV stroke volume and heart rate. Concomitant amlodipine treatment during the development of pacing CHF reduced ambient resting heart rate but did not influence the maximal heart rate achieved with treadmill exercise. The observation that chronic amlodipine with pacing CHF did not diminish the maximal heart rate achieved with treadmill exercise is similar to a past report that demonstrated that Ca$^{2+}$ channel antagonists therapy in patients did not reduce maximal heart rates achieved with exercise.

In past clinical reports of CHF, the administration of Ca$^{2+}$ channel antagonists caused a significant increase in plasma catecholamine levels. The present study demonstrated that chronic amlodipine treatment during the development of CHF significantly reduced plasma catecholamine levels both at rest and with treadmill-induced exercise. Voltage-dependent Ca$^{2+}$ channels have been identified in sympathetic neurons and the adrenal medulla. The reduced plasma catecholamine levels observed with chronic amlodipine treatment during chronic rapid pacing could be attributed to direct inhibitory effects on sympathetic neuroendocrine activity. Chronic amlodipine treatment with developing CHF improved LV stroke volume and cardiac output and was associated with a reduction in resting ambient heart rate. Thus, a second contributory factor for the reduction in plasma catecholamines that occurred with chronic amlodipine treatment may have been decreased baroreceptor-mediated sympathetic activity.

Endothelin is a potent bioactive peptide that modulates systemic, pulmonary, and coronary vascular tone as well as influencing neurohormonal system activity. For example, Kiowski et al. reported that acute administration of the nonselective endothelin receptor antagonist bosentan significantly reduced systemic and pulmonary vascular resistance in patients with CHF. In a model of CHF induced by chronic caval occlusion, Cannan and colleagues demonstrated that the coronary vasoconstrictor effects of endothelin were increased. Thus, in the present study, the decreased plasma endothelin levels that occurred with chronic amlodipine treatment during developing pacing CHF probably contributed to the concomitant reduction in systemic, pulmonary, and coronary vascular resistance. Plasma endothelin levels have been demonstrated to parallel the severity of symptoms and degree of hemodynamic instability in patients with CHF. Thus, likely contributory factors for the diminished plasma endothelin levels that occurred with chronic amlodipine treatment were improved LV performance and diminished sympathetic activity. However, chronic amlodipine treatment with developing CHF may have selectively modulated endothelin synthesis and/or release. In a study by Nayler et al., amlodipine significantly reduced the expression of endothelin receptor binding sites in ischemic rat hearts.

In past reports, treatment with Ca$^{2+}$ channel antagonists in patients with CHF has been associated with increased plasma renin activity. In the present study, chronic amlodipine treatment reduced resting plasma renin activity from untreated CHF values. This reduction in resting plasma renin activity was probably due to the improved LV pump function and systemic hemodynamics that occurred with chronic amlodipine treatment. Interestingly, with treadmill-induced exercise, plasma renin activity increased in the chronic amlodipine–treated group and was similar to that observed in the untreated CHF group. With treadmill-induced exercise in the chronic amlodipine–treated group, mean arterial pressure fell from resting values and was associated with a persistent
reduction in renal blood flow. Thus, the increased plasma renin activity that occurred in the chronic amlodipine group with exercise was probably due to a reflex response from the juxtaglomerular apparatus of the kidney. However, the mechanisms by which amlodipine influenced resting and exercise plasma renin activity with developing CHF warrants further study.

Although active ischemia and/or infarction is not a feature of the pacing model of CHF, coronary vascular resistance and endothelial control of myocardial blood flow are significantly affected.9,15 Amlodipine has been demonstrated to have a potent vasodilatory effect on coronary vascular smooth muscle.5,6,12 In the present study, chronic amlodipine treatment with developing pacing CHF normalized resting LV myocardial blood flow at rest and improved myocardial blood flow with exercise. Likely contributory mechanisms for the improved LV myocardial blood flow with pacing CHF-plus-amlodipine treatment was a direct effect on Ca\(^{2+}\)-mediated smooth muscle tone and the reduction in circulating levels of endothelin, both of which would reduce coronary vascular resistance. It has been reported previously that in patients with nonischemic cardiomyopathy, abnormalities in myocardial oxygen delivery/demand exist.23 Thus, amlodipine treatment may provide significant coronary vasodilatory effects in the setting of CHF, which may be of particular benefit with respect to myocardial blood flow in patients with relatively normal coronary arteries (no physical obstruction to flow). Although this issue remains speculative, the finding that amlodipine treatment was of particular benefit in CHF patients with apparent nonischemic causes8 supports this hypothesis.

With chronic amlodipine treatment and pacing CHF, pulmonary vascular resistance remained increased and pulmonary parenchymal flow was reduced from normal control values. In addition, chronic amlodipine treatment during the development of pacing CHF reduced left atrial oxygen saturation levels compared with either normal control values or untreated CHF values. These observations suggest that although chronic amlodipine treatment may have provided favorable effects on pulmonary hemodynamics, defects in transcapillary exchange and oxygenation may have occurred. In a past clinical report,8 an increased incidence of pulmonary edema was noted in CHF patients after amlodipine treatment.

The development of pacing CHF was associated with diminished indices of steady-state LV myocyte contractile function. Concomitant amlodipine treatment during the progression of pacing CHF improved myocyte contractility. Thus, a contributory factor for the improved LV pump function that was observed with chronic amlodipine treatment in this model of CHF is a protective effect on intrinsic contractile performance. With the development of pacing-induced CHF, myocyte contractile response after \(\beta\)-receptor stimulation was attenuated. Likely contributory factors for the diminished myocyte \(\beta\)-adrenergic response with pacing-induced CHF are downregulation of \(\beta\)-receptors, alterations in the \(\beta\)-receptor transduction pathway, and diminished cAMP production.10 A likely mechanism for the improved myocyte \(\beta\)-adrenergic response with chronic amlodipine treatment is the reduction in plasma catecholamines, which in turn provided protective effects on the \(\beta\)-adrenergic transduction system. A second contributory factor for the improved \(\beta\)-adrenergic response with chronic amlodipine treatment was a fundamental improvement in the capacity of the myocyte to respond to an inotropic stimulus. This is evidenced by the fact that myocyte responsiveness with extracellular Ca\(^{2+}\) or activation of the L-type Ca\(^{2+}\) channel was improved with amlodipine treatment compared with untreated CHF values.

It was reported previously that a reduction in L-type Ca\(^{2+}\) channel abundance and function occurs with the development of severe CHF.23 With concomitant amlodipine treatment during chronic rapid pacing, the inotropic response after L-type Ca\(^{2+}\) channel activation was significantly improved from untreated CHF values. In a past report, Chapados and colleagues26 reported that chronic treatment with the Ca\(^{2+}\) channel antagonist nifedipine increased L-type Ca\(^{2+}\) channel abundance and myocardial inotropic responsiveness to Ca\(^{2+}\). Thus, contributory mechanisms for the improved inotropic response to L-type Ca\(^{2+}\) channel activation after chronic amlodipine treatment observed in the present study include increased myocyte L-type Ca\(^{2+}\) channel density as well as improved contractile response to Ca\(^{2+}\).

This laboratory has reported increased resting intracellular Ca\(^{2+}\) levels within pacing CHF myocytes, and these alterations in Ca\(^{2+}\) homeostasis were associated with a negative velocity of shortening–frequency response.25 In the present study, the diminished myocyte inotropic response to increased extracellular Ca\(^{2+}\) with pacing CHF was most likely due to an exacerbation of existing defects in Ca\(^{2+}\) homeostatic processes. With concomitant amlodipine treatment during chronic pacing, myocyte inotropic response to extracellular Ca\(^{2+}\) was improved from untreated CHF values. Either with L-type Ca\(^{2+}\) channel activation or in the presence of increased Ca\(^{2+}\), however, indices of active relaxation remained prolonged with chronic amlodipine treatment. Specifically, the time to 50% relaxation and total contraction duration were unchanged with chronic amlodipine treatment compared with untreated CHF values. The time to 50% relaxation reflects the period of cross-bridge release and Ca\(^{2+}\) resequestration by the sarcoplasmic reticulum (SR). Past studies have reported a reduction in the expression and abundance of SR Ca\(^{2+}\)-ATPase with the development of severe CHF.26 Thus, although this remains speculative, the abnormalities in myocyte active relaxation processes that occurred with the development of CHF may be due to abnormalities in SR Ca\(^{2+}\)-ATPase expression and/or function. Furthermore, whether the lusitropic changes observed at the level of the myocyte with the development of pacing CHF, which persisted with amlodipine treatment, are translated to alterations in LV myocardial diastolic properties warrants further study.

The present study did not address whether the hemodynamic effects of amlodipine were dose-dependent or would produce additive effects with other interventions such as ACE inhibition. Furthermore, the direct and potentially novel mechanisms by which amlodipine influenced LV function and contractility with developing CHF remain to be fully established. For example, a recent study by Zhang and Hintze27 reported that amlodipine potentiates nitric oxide levels, similar to those observed with ACE inhibition. Nevertheless, amlodipine treatment in this pacing model of developing...
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CHF improved LV loading conditions and pump function, reduced plasma catecholamine and endothelin levels, and improved LV myocardial blood flow both at rest and with treadmill exercise. Finally, chronic amlodipine treatment with pacing CHF improved contractility and inotropic response at the level of the LV myocyte. These findings suggest that amlodipine may produce favorable hemodynamic, neurohormonal, and contractile effects in the setting of developing CHF.

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