Treatment With a Growth Hormone Secretagogue in a Model of Developing Heart Failure
Effects on Ventricular and Myocyte Function

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Background—Exogenous administration of growth hormone (GH) and subsequently increased production of insulin-like growth factor-1 can influence left ventricular (LV) myocardial growth and geometry in the setting of congestive heart failure (CHF). This study determined the effects of an orally active GH secretagogue (GHS) treatment that causes a release of endogenous GH on LV function and myocyte contractility in a model of developing CHF.

Methods and Results—Pigs were randomly assigned to the following treatment groups: (1) chronic rapid pacing at 240 bpm for 3 weeks (n = 11); (2) chronic rapid pacing and GHS (CP-424,391 at 10 mg·kg⁻¹·d⁻¹, n = 9); and (3) sham controls (n = 8). In the untreated pacing CHF group, LV fractional shortening was reduced (21 ± 6 versus 47 ± 2%), and peak wall stress increased (364 ± 21 versus 141 ± 5 g/cm²) from normal control values (P < 0.05). In the GHS group, LV fractional shortening was higher (29 ± 2%) and LV peak wall stress lower (187 ± 126 g/cm²) than untreated CHF values (P < 0.05). With GHS treatment, the ratio of LV mass to body weight increased by 44% from untreated values. Steady-state myocyte velocity of shortening was reduced with pacing CHF compared with controls (38 ± 1 versus 78 ± 1 mm/s, P < 0.05) and was increased from pacing CHF values with GHS treatment (55 ± 7 mm/s, P < 0.05).

Conclusions—The improved LV pump function that occurred with GHS treatment in this model of CHF was most likely a result of favorable effects on LV myocardial remodeling and contractile processes. On the basis of these results, further studies are warranted to determine the potential role of GH secretagogues in the treatment of CHF. (Circulation. 2001;103:308-313.)

Key Words: ventricles ■ myocytes ■ contractility ■ growth substances

The progression of congestive heart failure (CHF) is accompanied by left ventricular (LV) remodeling and worsening pump function. The LV remodeling in CHF often results in chamber dilation, which in turn causes increased LV wall stress. This increased LV wall stress further exacerbates LV performance through both increased LV afterload and potentially compromising myocardial contractile function. One approach in the regulation of LV remodeling with CHF would be to augment the failing myocardium with growth factors. Several studies have demonstrated that administration of growth hormone (GH) or insulin-like growth factor-1 (IGF-1) can directly influence LV myocardial structure and function.1-6 The results from clinical studies, in which recombinant GH was delivered through subcutaneous injections, provide support for the concept that GH can influence LV geometry with CHF.6-7 Exogenous administration of GH, however, can be difficult for applications in the clinical treatment of CHF. An alternative approach for increasing systemic levels of GH would be to directly stimulate the pituitary to augment the synthesis and release of GH. The production of GH from the pituitary is influenced by the release of GH-releasing hormone from the hypothalamus. Past studies have demonstrated that the release of GH from the pituitary can be mediated by stimulation of the GH-releasing hormone receptor through the use of peptidomimetic agonist, or GH secretagogue (GHS).6,7 Accordingly, the overall goal of this study was to determine whether administration of GHS during the progression of a CHF process would provide beneficial effects on LV structure and function.

Methods
Chronic rapid pacing in pigs causes a reproducible phenotype of CHF, which includes LV pump dysfunction, neurohormonal system activation, and myocyte contractile dysfunction.8-11 Accordingly, this pacing CHF model was used to examine the effects of GHS treatment. This study used an orally bioavailable GHS (CP-424,391,
GHS treatment was instituted before the onset of chronic rapid pacing and continued throughout the pacing period.

Instrumentation and Induction of Pacing CHF
Twenty Yorkshire pigs (20 kg, male, Hambo Farms, Orangeburg, SC) were chronically instrumented with an atrial catheter and a modified atrial pacemaker, as described previously. After a 14- to 21-day recovery from the surgical procedure, the pigs were randomly assigned to 1 of the following treatment groups: (1) chronic rapid pacing at 240 bpm for 3 weeks with placebo treatment (n=11), (2) chronic rapid pacing and GHS supplementation (n=9), and (3) sham controls (n=8). GHS treatment (8:00 AM daily) was started 7 days before the activation of the pacemaker and continued throughout the 21-day pacing protocol. At each week after enrollment in the study, the animals were returned to the laboratory for evaluation of LV function and plasma collection, as described in the following section. All animals were treated and cared for in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (National Research Council, Washington, DC, 1996).

LV Function Measurements
All studies were performed in a conscious state with the pacemaker deactivated. LV dimensions and fractional shortening were obtained by echocardiography, and resting aortic pressure was obtained as previously described. From the LV echocardiographic and blood pressure measurements, LV peak and systolic circumferential wall stress values were computed by use of a spherical model of reference. LV myocardial velocity of circumferential fiber shortening, corrected for heart rate (Vcf), was computed from the LV dimensions and pressure data. Simultaneously drawn blood samples were assayed for norepinephrine, IGF-1, and blood glucose, as previously described.

After the LV function measurements on day 21 of the protocol, the animals were deeply anesthetized with 4% isoflurane, and a sternotomy was performed. The heart was quickly removed and processed for studies as described below.

LV Myocyte Contractile Function and Cross-Sectional Area
Isolated LV myocyte contractility was examined by computer-assisted videomicroscopy. After baseline measurements, contractile function was examined either after β-adrenergic receptor stimulation with 25 nmol/L isoproterenol (–isoproterenol, Sigma Chemical Co) or in the presence of 8 mmol/L extracellular calcium (Ca²⁺). Myocardial sections cut in the circumferential orientation were examined by light microscopy to evaluate the myocyte cross-sectional area by use of computer-assisted methods described previously.

Data Analysis
Indices of LV function, systemic hemodynamics, and neurohormonal profiles were first compared among the treatment groups by ANOVA for repeated measures. For the myocyte function studies, an ANOVA using 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. LV cross-sectional area measurements were examined to ensure a normal gaussian distribution and then subjected to ANOVA and mean separation by the Student-Newman-Keuls test. All statistical procedures were performed with the BMDP statistical software package. Results were presented as mean±SEM. Values of P<0.05 were considered to be statistically significant.

Results
All of the pigs that entered the rapid-pacing protocols were successfully studied. In the GHS-treated group, plasma IGF-1 levels were increased by ~2-fold over untreated pacing values and normal control values (Figure 1).

LV Geometry and Function With Rapid Pacing: Effects of GHS Treatment
LV wall stress measurements and fractional shortening obtained with each week of chronic rapid pacing with and without GHS treatment are summarized in Figure 2. In the untreated rapid-pacing group, LV end-systolic and peak wall stress increased and LV fractional shortening decreased in a time-dependent manner. In the rapid-pacing and GHS-treated group, the change in LV wall stress patterns was markedly attenuated from untreated values and was associated with a significant improvement in LV fractional shortening. In the GHS-treated group, however, LV wall stress increased and LV fractional shortening decreased from baseline values.

Systemic hemodynamics and LV dimensions after the 3-week protocol are summarized in Table 1. In both rapid-pacing groups, ambient resting heart rate was increased and resting blood pressure decreased from control values. LV end-diastolic dimension was increased in both rapid-pacing groups compared with controls but was reduced in the GHS-treated group compared with untreated pacing values. LV end-diastolic wall thickness was decreased from control values in the untreated pacing group but remained unchanged from control values in the GHS-treated group. Vcf was reduced by ~50% in the rapid-pacing group compared with control values. In the GHS-treated group, LV Vcf was also
physiological response to this form of treatment. More importantly, GHS treatment during pacing-induced CHF was associated with a significant improvement in LV pump function. The present study provided a mechanistic basis for this improvement in LV ejection performance with GHS treatment. First, GHS treatment induced LV myocardial growth, which in turn reduced LV afterload through a reduction in wall stress patterns. Second, GHS treatment was associated with an intrinsic improvement in myocyte contractile function and inotropic capacity. Thus, the unique findings from this study demonstrated that it is possible to stimulate the GH-pituitary axis through oral GHS treatment and that this approach provides beneficial effects on LV function and contractile processes with developing CHF.

GH treatment and subsequent changes in circulating levels of IGF-1 can influence a number of cardiovascular processes, including LV loading conditions and contractility. Whether and to what degree treatment with a GHS would influence LV geometry and function in the setting of both experimental and clinical forms of CHF has remained unexplored. The present study used an orally active GHS in a porcine model of CHF and demonstrated that circulating IGF-1 levels were increased by 2-fold, indicating a biological response to this form of treatment. More importantly, GHS treatment during pacing-induced CHF was associated with a significant improvement in LV pump function. The present study provided a mechanistic basis for this improvement in LV ejection performance with GHS treatment. First, GHS treatment induced LV myocardial growth, which in turn reduced LV afterload through a reduction in wall stress patterns. Second, GHS treatment was associated with an intrinsic improvement in myocyte contractile function and inotropic capacity. Thus, the unique findings from this study demonstrated that it is possible to stimulate the GH-pituitary axis through oral GHS treatment and that this approach provides beneficial effects on LV function and contractile processes with developing CHF.

Figure 2. LV end-systolic wall stress (top), LV peak wall stress (middle), and LV fractional shortening (bottom) were measured with each week of rapid pacing with and without concomitant GHS treatment (rapid pacing/GHS). All measurements were performed with pacemaker deactivated and pig in a conscious state. In both rapid-pacing groups, LV wall stress patterns increased from baseline values after 1 week of pacing. In GHS-treated group, however, LV wall stress was significantly reduced from untreated pacing values. LV fractional shortening fell in a time-dependent manner in rapid-pacing-only group and GHS-treated group. After 2 and 3 weeks of rapid pacing, however, LV fractional shortening was higher in GHS-treated group than rapid-pacing-only values. #P<0.05 vs baseline values, *P<0.05 vs respective rapid-pacing-only values.

D " reduced from normal control values, myocyte contractile function was significantly blunted in the untreated pacing values. With exposure to extracellular Ca²⁺, indices of myocyte contractile function remained reduced from control values in the untreated rapid-pacing group. In the GHS treatment group, myocyte function after exposure to extracellular Ca²⁺ was increased compared with untreated rapid-pacing values but remained significantly lower than normal control values.

Discussion

The administration of recombinant GH or IGF-1 has been demonstrated to influence LV myocardial growth in the setting of both experimental and clinical forms of CHF.3,4,6,7,14 Whether and to what degree treatment with a GHS would influence LV geometry and function in the setting of a developing CHF process, however, remained unexplored. The present study used an orally active GHS in a porcine model of CHF and demonstrated that circulating IGF-1 levels were increased by 2-fold, indicating a biological response to this form of treatment. More importantly, GHS treatment during pacing-induced CHF was associated with a significant improvement in LV pump function. The present study provided a mechanistic basis for this improvement in LV ejection performance with GHS treatment. First, GHS treatment induced LV myocardial growth, which in turn reduced LV afterload through a reduction in wall stress patterns. Second, GHS treatment was associated with an intrinsic improvement in myocyte contractile function and inotropic capacity. Thus, the unique findings from this study demonstrated that it is possible to stimulate the GH-pituitary axis through oral GHS treatment and that this approach provides beneficial effects on LV function and contractile processes with developing CHF.

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patients with dilated cardiomyopathy, GH treatment that subsequently increased IGF-1 levels reduced LV wall stress and improved LV pump function. Increased IGF-1 levels have been demonstrated to potentially influence vascular resistive properties. For example, recombinant GH treatment in CHF patients was associated with a reduction in resting mean arterial pressure and systemic vascular resistance. In addition, IGF-1 has been demonstrated to induce nitric oxide (NO) production in vitro and has vasodilatory properties consistent with an NO-mediated effect in vivo. The present study did not measure vascular reactivity or NO production with GHS treatment, and this area warrants further investigation. Nevertheless, in the present study, a significant reduction in LV wall stress was observed with GHS treatment, which in turn would provide a favorable effect on LV loading conditions and therefore pump function.

Consistent with past studies, the development of pacing CHF was accompanied by reduced LV myocyte steady-state contractile function and depressed inotropic responsiveness. Past studies have demonstrated that IGF-1 can directly influence contractile function in the setting of a compromised myocardium. With GHS treatment, indices of steady-state myocyte contractile function were improved from CHF values. Thus, a contributory factor for the improved LV pump function with GHS treatment was an intrinsic beneficial effect on myocyte contractile function. GHS treatment resulted in an improvement in myocyte responsiveness to the β-receptor agonist isoproterenol. This effect on myocyte β-adrenergic responsiveness with GHS treatment was achieved in the absence of a reduction in circulating norepinephrine levels. This observation suggests that the improved β-adrenergic response with GHS treatment was probably due to improved inotropic capacity that lay beyond the receptor transduction system itself. In the present study as well as in past reports using GH supplementation, the increased myocyte β-adrenergic response was not associated with an increased incidence of arrhythmias in vivo. Whether chronic GH or GHS supplementation causes a predisposition to arrhythmogenesis, however, warrants further study.

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ate contractile protein synthesis rates in neonatal rat myocyte preparations. Consequently, an important mechanism for the increased LV mass in this model of pacing CHF was probably due to the direct effects of IGF-1 on myocardial contractile protein synthesis and degradative processes. Although a major contributory factor for the effects of GHS treatment in this model of pacing CHF was the augmentation of IGF-1, some recent studies have provided evidence that a GHS may act directly on target tissue, such as the myocardium. Thus, GHS may induce effects on LV myocardial structure that are independent of IGF-1 levels. GH supplementation in the pacing CHF model was not associated with increased collagen accumulation. Moreover, this previous study provided evidence to suggest that GH supplementation may attenuate myocyte loss. In the present study, the basis for the increased LV mass with chronic rapid pacing was myocyte hypertrophy, as evidenced by a significant increase in length and cross-sectional area.

Pituitary dysfunction and a deficiency in GH have historically been associated with cardiovascular disease. Strategies to stimulate normal pituitary function, such as increased GH synthesis and release, may be a useful adjunctive therapy in patients with CHF. It has been demonstrated previously that treatment of normal humans with an orally active GHS provided a robust but pulsatile release of GH from the pituitary. Thus, unlike direct exogenous administration of GH, GHS treatment may afford the advantage of inducing GH levels in a more physiological temporal profile. If this is the case, GHS treatment may be a more appropriate approach to restoring and/or enhancing GH production in the setting of CHF. In GH-deficient patients, oral administration of a GHS for a 4-day period increased serum IGF-1 levels by 50% to 75% and was accompanied by a small rise in plasma glucose levels. In the present study, GHS treatment induced a 2-fold increase in IGF-1 levels compared with untreated pacing CHF values. In the pacing CHF group, plasma glucose levels were reduced from normal values and returned to normal values with GHS treatment. The increase in glucose values with GHS treatment may be due to metabolic effects.

### TABLE 2. Isolated Myocyte Contractile Function With Rapid Pacing Heart Failure: Effects of GHS

<table>
<thead>
<tr>
<th>Baseline</th>
<th>25 nmol/L Isoproterenol</th>
<th>8 mmol/L Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting length, μm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>135 ± 1</td>
<td>131 ± 1†‡</td>
</tr>
<tr>
<td>Rapid pacing</td>
<td>167 ± 1*</td>
<td>162 ± 1*‡</td>
</tr>
<tr>
<td>Rapid pacing and GHS</td>
<td>173 ± 1*†</td>
<td>168 ± 1*‡</td>
</tr>
<tr>
<td>Percent shortening, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4.94 ± 0.05</td>
<td>11.16 ± 0.14‡</td>
</tr>
<tr>
<td>Rapid pacing</td>
<td>2.55 ± 0.04*</td>
<td>5.45 ± 0.15*‡</td>
</tr>
<tr>
<td>Rapid pacing and GHS</td>
<td>3.00 ± 0.03*†</td>
<td>6.39 ± 0.11*‡</td>
</tr>
<tr>
<td>Shortening velocity, μm/s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>78 ± 1</td>
<td>225 ± 4‡</td>
</tr>
<tr>
<td>Rapid pacing</td>
<td>38 ± 1*</td>
<td>120 ± 4*‡</td>
</tr>
<tr>
<td>Rapid pacing and GHS</td>
<td>55 ± 7*†</td>
<td>152 ± 3*‡</td>
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<tr>
<td>Relengthening velocity, μm/s</td>
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<td></td>
</tr>
<tr>
<td>Control</td>
<td>87 ± 1</td>
<td>223 ± 4‡</td>
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<tr>
<td>Rapid pacing</td>
<td>35 ± 1*</td>
<td>94 ± 4*‡</td>
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<tr>
<td>Rapid pacing and GHS</td>
<td>51 ± 11*†</td>
<td>130 ± 3*‡</td>
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<tr>
<td>Time to peak contraction, ms</td>
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<tr>
<td>Control</td>
<td>184 ± 2</td>
<td>164 ± 2‡</td>
</tr>
<tr>
<td>Rapid pacing</td>
<td>244 ± 2*</td>
<td>182 ± 2*‡</td>
</tr>
<tr>
<td>Rapid pacing and GHS</td>
<td>212 ± 1*†</td>
<td>178 ± 2*‡</td>
</tr>
<tr>
<td>Total contraction duration, ms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>447 ± 3</td>
<td>367 ± 5</td>
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<tr>
<td>Rapid pacing</td>
<td>511 ± 4*</td>
<td>463 ± 7*‡</td>
</tr>
<tr>
<td>Rapid pacing and GHS</td>
<td>481 ± 3*†</td>
<td>438 ± 5*‡</td>
</tr>
<tr>
<td>Sample size, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2221 ± 66</td>
<td>666 ± 67</td>
</tr>
<tr>
<td>Rapid pacing</td>
<td>1268 ± 47</td>
<td>477 ± 445</td>
</tr>
<tr>
<td>Rapid pacing plus GHS</td>
<td>2592 ± 1067</td>
<td>1067 ± 1004</td>
</tr>
</tbody>
</table>

Rapid pacing indicates 21 days of pacing at 240 bpm; rapid pacing and GHS, rapid pacing with concomitant treatment with GHS 10 mg · kg⁻¹ · d⁻¹; and n, number of myocytes. All values are mean ± SEM.

*P<0.05 vs control; †P<0.05 vs rapid pacing only; ‡P<0.05 vs baseline.
secondary to the robust increase in IGF-1. These findings, however, raise an important clinical consideration with respect to the clinical application of GHS treatment in CHF patients with diabetes and poor glucose control.

Although the majority of studies have demonstrated that GH supplementation influences LV pump function in CHF, some past reports have demonstrated that this treatment modality has neutral effects with respect to LV function.\textsuperscript{6,21} For example, in a dog pacing model, there was no significant change in LV mass between the untreated paced dogs and the dogs with GH supplementation, indicating a failure of a myocardial growth response.\textsuperscript{21} In the present study, GHS treatment was used in pigs during chronic rapid pacing and resulted in a significant myocardial hypertrophic response. GH supplementation in patients with CHF has been uniformly associated with a myocardial growth response.\textsuperscript{6,7,22} Results from the present study and past reports suggest that a mechanism by which GH supplementation improves LV pump function is through increased LV wall thickness and a reduction in LV wall stress patterns. In a recent double-blind placebo-controlled trial, short-term GH supplementation induced a directional change in LV wall thickness and wall stress patterns similar to that of the present study. These changes did not reach statistical significance, however.\textsuperscript{7} Another important feature of this past clinical trial was that the CHF patients were treated with high-dose ACE inhibition, which may have influenced the myocardial growth effects of GH treatment. ACE inhibition is now recognized as an important treatment modality for patients with CHF, and new treatment strategies must be considered with respect to this “background therapy.” Thus, the potential additive/synergistic effects on LV and myocyte function by the augmentation of GH levels with ACE inhibition in the setting of CHF warrant further study. Nevertheless, GHS treatment at a dose that significantly increased basal levels of IGF-1 in a model of developing CHF increased LV pump function and improved myocyte contractile performance.

Acknowledgments  
This study was supported in part by National Institutes of Health grant HL-45024, a basic research grant from Pfizer, and an American Heart Association Grant-in-Aid (all to Dr Spinale). Dr Spinale is an Established Investigator of the American Heart Association. The authors wish to express their sincere appreciation to Drs Brent New and Jeffrey Mandel for their surgical assistance during the execution of this project and Michelle Hollowan for assistance in the isolated myocyte studies. The authors also wish to express their appreciation to Melissa Mathews for her assistance in the preparation of the manuscript.

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Circulation. 2001;103:308-313
doi: 10.1161/01.CIR.103.2.308
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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