Progressive Cardiac Dysfunction and Fibrosis in the Cardiomyopathic Hamster and Effects of Growth Hormone and Angiotensin-Converting Enzyme Inhibition

Tsutomu Ryoke, MD, PhD; Yusu Gu, MD; Lan Mao, MD; Minoru Hongo, MD, PhD; Ross G. Clark, PhD; Kirk L. Peterson, MD; John Ross, Jr, MD

Background—Growth hormone (GH) improves cardiac function in the rat with myocardial infarction, but its effects in a model of primary dilated cardiomyopathy have not been reported. GH effects were examined at early (4 months) and late (10 months) phases of disease in the cardiomyopathic (CM) hamster, and the combination of GH with chronic ACE inhibition was assessed in late-phase heart failure.

Methods and Results—CM hamsters (CHF 147 line) at 4 months showed severe systolic left ventricular (LV) dysfunction with normal LV filling pressure, and at 10 months there was more severe systolic as well as diastolic dysfunction with increasing myocardial fibrosis. Recombinant human GH alone for 3 weeks at age 4 months increased LV wall thickness and reduced systolic wall stress without altering diastolic wall stress, whereas at 10 months, wall stress and fractional shortening did not improve. The LV dP/dt max was enhanced at both ages by GH, which at 4 months reflected increased contractility, but at 10 months was most likely caused by elevation of the LV filling pressure. The increasing degree of fibrosis correlated inversely with LV function but was unaffected by GH. In other CM hamsters, high-dose ACE inhibition alone (quinapril), started at 8 months and continued for 11 weeks, improved LV function and inhibited unfavorable remodeling, but the addition of GH for 3 weeks at age 10 months produced increased wall thickness with little additional functional benefit and increased the LV filling pressure and diastolic wall stress.

Conclusions—GH treatment alone improved LV dysfunction at 4 months of age in CM hamsters by increasing contractility and reducing wall stress but had few beneficial effects at 10 months in severe LV failure. After chronic ACE inhibition, addition of GH at 10 months had no additional beneficial effects and further increased LV diastolic pressure. These differing effects of GH may relate to the progressive increase of LV fibrosis in the CM hamster. (Circulation. 1999;100:1734-1743.)

Key Words: myocardium • collagen • ventricles • hypertrophy • cardiomyopathy

Chronic myocardial dysfunction leads to progressive cardiac dilation with increased systolic wall stress and afterload mismatch, resulting in reduced cardiac output (CO) and congestive heart failure despite the occurrence of compensatory hypertrophy.1 When compensatory cardiac hypertrophy is adequate in other cardiac overload states, left ventricular (LV) wall stress can be normalized and LV performance maintained.2 Growth factors can be important mediators of normal cardiac growth and adaptive cardiac hypertrophy, and recombinant human growth hormone (rhGH; GH) and its local effector insulin-like growth factor-1 (IGF-1) have been shown to be essential not only for cardiac development but also for maintaining cardiac mass and performance in adult life.3 In subjects with GH deficiency, cardiac performance is impaired, and the administration of GH increases ventricular wall thickness and normalizes cardiac function at rest and during exercise.4

In heart failure secondary to myocardial infarction in the rat, exogenous administration of IGF-1, GH, and the combination of IGF-1 and GH leads to improved global cardiac function accompanied by cardiac hypertrophy in proportion to body growth, improved cardiac performance, peripheral vasodilation,5–7 and in some studies, a positive inotropic effect.5–7 In some but not all initial clinical studies, GH has caused increased LV wall thickness with enhanced CO and function in patients with dilated cardiomyopathy (DCM)6 and

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cardiomyopathy due to coronary artery disease or increased cardiac mass, but no enhancement of function in another study of patients with DCM. Thus, further laboratory investigation is needed on the potential role of GH administration under various conditions in different forms of heart failure.

The cardiomyopathic (CM) hamster is a naturally occurring, genetically transmitted model in which DCM with progressive heart failure is caused by an inherited autosomal recessive mutation in the gene coding for δ-sarcoglycan, a component of the dystrophin complex. This animal model has many phenotypic features of idiopathic DCM in humans, and therefore the present study was designed to assess the pathophysiological features of the CM hamster heart at early and late stages of progression, to determine whether treatment with GH alone can affect LV remodeling and function at these stages, and to examine the effects of adding GH to chronic ACE inhibition in the late stage of heart failure.

Methods

The experimental protocol was approved by the Animal Subjects Committee of the University of California San Diego. Male CM Syrian hamsters 4, 8, and 10 months of age of the CHF 147 line (a derivative of the UM-X7.1 strain) and 10-month-old male golden hamsters were obtained from Canadian Hybrid Farms (Halls Harbor, Nova Scotia, Canada). The life span of the CHF 147 line averages 350 days, and the 10-month hamsters represent a preterminal phase of heart failure. The hamsters were maintained at 20 ± 2°C, 55 ± 20% humidity, with 12/12-hour light/dark cycles and free access to food and water.

rhGH Dose and Duration of Treatment in Normal Hamsters

Normal 10-month-old hamsters were divided into placebo and treatment groups (n=8 each). For comparison with subsequent CM groups, the placebo group underwent echocardiography and cardiac catheterization. rhGH treatment for 14 days (2 mg/kg BID SC) did not significantly increase LV weight (LVW) but increased body weight (BW) by 11%, whereas GH for 28 days significantly increased both LVW (14%) and BW (38%), reducing the LVW/BW ratio. Therefore, an intermediate treatment period of 3 weeks was selected for the study.

rhGH Alone in CM Hamsters

CM hamsters at 4 and 10 months of age were randomly assigned to placebo or rhGH 2 mg/kg BID SC for 21 days (at 4 months, n=16 for placebo, n=19 for GH; at 10 months, n=17 for placebo, n=19 for GH).

Quinapril and Quinapril+rhGH in CM Hamsters

Quinapril was chosen for ACE inhibition because its effectiveness in improving cardiac performance and survival in CM hamsters has been shown, with highly effective ACE inhibition at an optimum maximum dosage of 100 mg · kg⁻¹ · d⁻¹. CM hamsters 8 months of age were randomly assigned to 3 groups (n=20 each): placebo, quinapril alone (Q group), and quinapril+GH (Q/GH group). The quinapril was added to drinking water with 10% honey, placebo was 10% honey water, and both were administered for 11 weeks. Solutions were prepared and residual volumes measured daily, and hamsters were weighed weekly, with adjustment of the volume administered; the daily dose of quinapril averaged 117.3 mg · kg⁻¹ · d⁻¹. For the final 3 weeks of quinapril treatment (starting at 10 months of age), the placebo and Q groups received normal saline injections, while the Q/GH group received rhGH 2 mg/kg BID.

Figure 1. Representative transthoracic LV M-mode echocardiograms in a normal saline-treated hamster (left), a 4-month saline-treated CHF 147 hamster (middle), and a 10-month saline-treated CHF 147 hamster (right).
Echocardiographic Studies

Echocardiography was performed just before randomization and at the completion of treatment, as previously described. Normal hamsters were anesthetized with 65 mg/kg and CM hamsters with 50 mg/kg of sodium pentobarbital IP. A 7.5-MHz transducer was used. All measurements were made in a blinded manner.

Hemodynamic Studies

At the end of treatment, hamsters were anesthetized with pentobarbital 80 mg/kg IP for normal hamsters and 65 mg/kg IP for CM hamsters, intubated, and ventilated; a bilateral vagotomy was performed, and the left femoral artery was cannulated, as described. The CO was determined with a thermocouple (placed in the aorta via the carotid artery), an injector, and a computer system (Columbus Instruments Co) using 3 to 5 right atrial injections of room-temperature saline to achieve 3 computations of CO that agreed within 10%. The thermocouple was then removed and replaced by a 2F high-fidelity catheter-tip micromanometer (model SPR-407, Millar) that was advanced into the LV to assess LV pressure, as described previously.

Meridional stress of the LV wall ($\sigma$) was calculated as $\sigma = PR_i/2h(1+h/2R_i)$, where $P$ is LV pressure, $R_i$ is inner LV minor-axis radius, and $h$ is wall thickness. Peak-systolic LV pressure and end-systolic LV wall thickness, and LV end-diastolic pressure and end-diastolic LV wall thickness were used to determine systolic and diastolic wall stress, respectively.

GH and IGF-1 levels

Total plasma rhGH was measured by a specific and sensitive ELISA, and total IGF-1 by radioimmunoassay using an antibody to rat IGF-1.

Heart Weight, Other Organ Weights, and Fluid Volume

After blood sampling, hamsters were euthanized with an overdose of pentobarbital (150 mg/kg), pleural and abdominal effusions were measured, and the wet weight of the heart and other selected organs was determined.

Collagen Volume Fraction

In 4- and 10-month-old CM hamsters, 4 to 5 hearts were fixed in 10% buffered formalin, and paraffin sections were cut perpendicular to the long axis and stained with Masson’s trichrome. LV myocardial collagen volume fraction (VF) was evaluated in a representative cross section from each heart by use of morphometric point-counting. Histological sections were viewed at $\times 400$ under a microscope with a color video camera, and 12 randomly selected fields from each transmural quadrant were analyzed by computer with a grid. The LV collagen VF was calculated as the sum of collagen points in all 12 fields divided by the sum of myocyte points minus calcification, vasculature, and empty points.

mRNA Measurements

From each group of CM and normal hamsters, 4 to 5 LVs were rapidly frozen and used for mRNA analyses, as described elsewhere. cDNA probes were specific for mRNAs encoding atrial natriuretic peptide (ANF), collagen I and collagen III (gift of Dr Francisco Villareal, University of California, San Diego), and sarcoplasmic reticulum Ca$^{2+}$-ATPase. The densitometric values of the collagen I doublet (which reflects alternative splicing) were averaged.

Statistics

Intergroup comparisons between normal and CM hamsters at 4 and 10 months and between the placebo, Q, and Q/GH groups and analysis of mRNA levels was done by ANOVA with post hoc tests by the Newman-Keuls multiple-range method. Echocardiographic data at baseline and after treatment from the same hamsters in each group were compared by 2-tailed paired $t$ tests. The collagen VF did not differ statistically without and with GH treatment, and therefore the data were combined in analyzing the effects of collagen on LV function by linear regression analysis. A probability value of $P<0.05$ was accepted as statistically significant.

Results

Studies in Normal Versus Placebo-Treated CM Hamsters

Figure 1 shows echocardiograms of normal and placebo-treated CM hamsters. Placebo CM hamsters at 4 and 10 months were significantly abnormal compared with normals, the LV chamber being dilated (LVDd), the LV wall thinned (posterior wall thickness, PWT), and LV systolic function (% fractional shortening [FS]) depressed (Figure 2) (detailed comparison data not shown; normals: LVDd 5.27±0.42 mm, PWT 1.33±0.06 mm, %FS 48.6±4.2). The LV systolic pressure (LVSP), LV dP/dt max, and CO also were significantly abnormal in both CM groups compared with normals (normals: LVSP 141±11.2 mm Hg, LV dP/dt max 11 033±2059 mm Hg/s, CO 45.4±5.9 mL/min, and cardiac index [CI] 279±35 mL/mm Hg) (Table 1). At 4 months, LV
relaxation (τ) (normal: 9.9 ± 1.4 ms) and LV end-diastolic pressure (LVEDP) were not different from normals, but at 10 months both were abnormal and LV diastolic and systolic wall stress (normal: 40.2 ± 9.1 × 10^3 dyn/cm^2) values also became markedly elevated (Figure 3; Table 1).

Studies With rhGH Treatment Alone in 4- and 10-Month CM Hamsters
GH alone in both age groups caused elevations of plasma GH and IGF-1 levels (Table 2). In the 10-month group, 2 GH-treated hamsters died, 1 during treatment (unknown cause) and 1 after anesthesia before the second echocardiogram. GH caused an increase in BW in 4- and 10-month hamsters (39% and 28%, respectively) and in selected organ weights (data not shown) compared with the placebo groups (Table 2). Heart weight and LVW were increased in both the 4- and 10-month GH-treated hamsters (LVW by 27% and 21%, respectively) (Table 2). The LVW/tibial length (TL) ratio also increased, but because of the large increase in BW, the LVW/BW decreased in both groups (Table 2). The volume of effusions in CM hamsters at 4 and 10 months was not significantly affected by GH (Table 2).

Echocardiographic Studies
Changes were very similar in comparisons between the placebo and GH groups with those using paired echocardiographic data before and after treatment (latter data not

![Figure 3. Selected hemodynamic variables in placebo (open bars) and GH-treated (shaded bars) CM hamsters at 4 and 10 months. LV dP/dt max (A), LVEDP (B), and meridional stress of LV wall at end systole (ES; C) and end diastole (ED; D). Bars represent mean ± SD. *P < 0.05 vs placebo group of same age.](link-to-image)
The mildly prolonged astolic pressure in 10-month hamsters was increased by GH, whereas the LV end-diastolic pressure in the 4-month normals or between groups (data not shown). ATPase mRNA levels were not significantly different from doublet (data not shown). Sarcoplasmic reticulum Ca$^{2+}$-ATPase mRNA levels were not significantly different from normals or between groups (data not shown).

**LV Collagen VF and Cardiac Function in CM Hamsters**

The LV collagen VF was high in CM hamsters (Table 2) and significantly higher, by 42%, in 10-month than in 4-month hamsters ($P<0.01$). The VF was not significantly affected by GH treatment compared with the placebo group at either age (Table 2), and therefore data at both ages were grouped for regression analyses. There were good correlations between the LV collagen VF and the LVDd (Figure 4A) and the LV relaxation rate (LV dP/dt$_{min}$ and $\tau$, Figure 4C and 4D). The LV dP/dt$_{min}$ showed a significant but less strong correlation (Figure 4B).

**Cardiac Gene Expression**

ANF mRNA was increased in all groups compared with normals and was not significantly affected by GH (Figure 5A). Collagen I and III mRNA levels were increased compared with normals at 4 months but not at 10 months (Figure 5B and 5C); GH increased 1 of the bands of the collagen I doublet (data not shown). Sarcoplasmic reticulum Ca$^{2+}$-ATPase mRNA levels were not significantly different from normals or between groups (data not shown).

**Studies With rhGH and Quinapril in Late-Stage CM Hamsters**

Survival rates were 95% in the Q and Q/GH groups and 80% in the placebo group (number of deaths considered too small for valid statistical analysis). The CM hamsters found dead in the placebo group showed pleural effusions and ascites, whereas hamsters that died in the Q and Q/GH groups (1 per group) did not evidence effusions. In the Q group, at the end
of treatment there were decreases in BW, organ weights, LVW, and fluid volume compared with the placebo group (Table 3). In the Q/GH group, BW and liver weight were increased compared with both the Q and placebo groups, although fluid volume and lung weight were reduced compared with the placebo group (Table 3). The LVW/TL was increased in the Q/GH compared with the Q group, although lower than in the placebo group, whereas the absolute LVW was increased compared with the Q group. The LVW normalized to BW was comparable in the Q/GH and Q groups and decreased compared with placebo because of the marked increase in BW induced by GH (Table 3).

**Echocardiographic Studies**

The LVdD was decreased in both the Q and Q/GH groups compared with the placebo group, although it was increased in the Q/GH group compared with the Q group (Figure 6A). The LV PWT was decreased by 10% in the Q group compared with the placebo group, and it was increased by 7% in the Q/GH group compared with the Q group and was not significantly different from the placebo group (Figure 6B). The %FS was increased in both the Q and Q/GH groups compared with placebo, with no difference between Q and Q/GH groups (Figure 6C).

**Hemodynamic Studies**

The heart rate was higher in the Q group than in both the placebo and Q/GH groups, whereas the LV peak-systolic pressure and mean arterial pressure were not significantly different between groups (Table 4). LV dP/dt max in both the Q and Q/GH groups were not different from placebo (Figure 7A). The LV end-diastolic pressure was decreased in the Q group compared with both placebo and Q/GH groups, and in the Q/GH group it was not different from placebo (Figure 7B). The high systolic LV wall stress levels were not different from the placebo group in the Q and Q/GH groups (Figure 7C). However, the diastolic LV wall stress was significantly reduced in the Q group compared with placebo, and the addition of GH to quinapril increased the diastolic wall stress compared with the Q group, so that it did not differ significantly from placebo (Figure 7D). The CO was higher in the Q/GH group than in the other 2 groups, but the CI did not differ between groups because of the large increase in BW (Table 4). Quinapril treatment alone did not affect the SVR, but when GH was added to quinapril, the SVR decreased compared with the placebo and Q groups (Table 4).

**Discussion**

Placebo-treated CM hamsters exhibited features resembling those of DCM in humans, including progressive LV dilatation and wall thinning, increasing wall stress, and by 10 months, congestive heart failure and diastolic dysfunction characterized by elevated LVEDP, increased diastolic wall stress, and impaired LV relaxation (prolonged $\tau$).

**Growth Hormone Alone, Cardiac Hypertrophy, and Diastolic LV Function**

The increase of BW with GH alone in CM hamsters at 4 months and 10 months was probably primarily a result of soft-tissue and organ growth, because large BW increases occurred with GH in the normal hamsters, although some fluid retention also was likely, particularly in the 10-month CM group. Although absolute heart and LV weights (and LVW normalized to TL) increased with GH, the relatively larger increase in BW lowered the HW/BW and LVW/BW. The observed cardiotoxic effect of GH was accompanied by an increase of LV wall thickness and further mild
dilatation of the LV chamber in both age groups. This pattern is suggestive of eccentric hypertrophy, consistent with increased LV myocyte length in rats with GH-secreting tumors. The sodium- and volume-retaining effects of GH as well as the requirement for enhanced CO probably also contributed to the LV dilation.

In the 4-month group, there were no changes in LVEDP or diastolic LV wall stress, but GH improved LV relaxation ($\tau$). However, in the 10-month group, the LVEDP and diastolic LV wall stress were increased by GH and $\tau$ was not improved; this response was probably due to several factors, including fluid retention (see pleural and ascitic fluid, Table 2) and operation of the LV on a steep portion of the diastolic pressure-volume curve (due to increased fibrosis and perhaps also to the increased LV mass).

**Growth Hormone Alone and Systolic LV Function**

In the 4-month group, the increased %FS with GH was related in part to the reduced LV systolic wall stress consequent to increased wall thickness and the known vasodilator effect of GH. The LV $\frac{dP}{dt}_{max}$ was augmented by GH without any increase in the preload (LVEDP and end-diastolic wall stress), indicating enhanced myocardial contractility, resulting in the decreased $\tau$ and contributing to the increased %FS. Thus, at 4 months, GH produced a form of LV remodeling characterized by increased LV wall thickness with favorable functional effects.

In the 10-month group, GH did not affect systolic wall stress or %FS. A small but significant increase in LV $\frac{dP}{dt}_{max}$ was associated with increased LV end-diastolic dimension and end-diastolic wall stress, which could have been causative in view of the positive relation between preload and LV $\frac{dP}{dt}_{max}$.

GH has been reported to enhance myocardial contractility in vivo in rats in several settings, as recently reviewed. Although the mechanism of increased contractility produced by GH treatment in the 4-month group with LV systolic dysfunction remains uncertain, it has been reported that short-term GH treatment in CM hamsters enhances LV function and preserves the density of sarcoplasmic reticulum Ca$^{2+}$ release channels.

**Gene Expression and Cardiac Fibrosis**

Despite the increasing LV fibrosis between 4 and 10 months, the mRNA levels for collagen I and III were elevated only at 4 months. Collagen III mRNA is generally elevated in early stages of hypertrophy, and these findings suggest that in end-stage preterminal disease, when fibrosis was extensive, there was little synthesis and turnover of collagen.
Effects of ACE Inhibition Alone and With Added GH

ACE inhibition with quinapril caused an abrupt and sustained decrease of BW in the 10-month CM hamsters during the first week, undoubtedly a result of the reduction of retained fluid volume, whereas BW increased steadily in the placebo group. A marked increase of BW occurred when GH was added to quinapril after 8 weeks in the Q/GH group, although sustained ACE inhibition–induced reduction of excess fluid retention due to heart failure was reflected by lowered fluid effusion volumes in the Q/GH as well as the Q groups. Sodium retention and extracellular volume expansion due to GH administration can occur in GH-deficient patients and in normal human subjects, and in the CHF147 CM hamster, activation of the renin-angiotensin system was reduced by ACE inhibition.

As expected, LVW, LVDd, and LV PWT were significantly decreased by quinapril alone, and in the Q/GH group, LV PWT and LVW were increased, although the quinapril effect on LVDd was retained; however, the increase in LVEDP in the Q/GH group caused the LV end-diastolic wall stress to rise, and GH was ineffective in lowering LV systolic wall stress or further improving the LV %FS. Quinapril alone did not change the systolic LV pressure or the SVR in this hamster model, which might be explained by excess sympathetic tone under anesthesia, as suggested by significantly increased heart rate in the Q group. However, GH had a consistent vasodilating action, increasing the CO and decreasing the SVR when used alone at 4 and 10 months and in the presence of quinapril.

In summary, we found GH alone to have favorable functional effects at 4 months when LV systolic dysfunction was severe but diastolic dysfunction was absent. GH alone was less effective at 10 months, late in the course of severe heart failure, when both systolic and diastolic dysfunction were present, which may relate to the progressive LV fibrosis, although increasing age as well as possible resistance to GH could also have been factors. Chronic ACE inhibition alone beginning at 8 months was effective in causing favorable LV remodeling and improving cardiac function, as shown previously, but the addition of GH for the final 3 weeks failed to further improve function and caused elevation of the LV end-diastolic pressure.

These findings might have negative implications concerning the potential for GH to produce beneficial effects in

**TABLE 4. Selected Hemodynamic Variables in CM Hamsters Treated With Q and Q/GH**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Q</th>
<th>Q/GH</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>346.2±48.4</td>
<td>391.2±27.5*</td>
<td>362.4±37.2†</td>
</tr>
<tr>
<td>Mean AoP, mm Hg</td>
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<td>81.5±12.2</td>
<td>77.9±14.6</td>
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<tr>
<td>LVPSP, mm Hg</td>
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<td>LV dp/dtmax, mm Hg/s</td>
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<td>−4626.8±978.1*</td>
<td>−4245.0±1130.9</td>
</tr>
<tr>
<td>t, ms</td>
<td>29.5±9.7</td>
<td>24.8±14.0</td>
<td>24.9±11.0</td>
</tr>
<tr>
<td>CO, mL/min</td>
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<td>31.2±6.0</td>
<td>40.0±10.5†</td>
</tr>
<tr>
<td>CI, mL·min⁻¹·kg⁻¹</td>
<td>208.7±52.6</td>
<td>242.2±45.3</td>
<td>238.5±65.9</td>
</tr>
<tr>
<td>SVR, mm Hg·mL⁻¹·min⁻¹</td>
<td>2.70±0.89</td>
<td>2.68±0.58</td>
<td>2.04±0.56†</td>
</tr>
</tbody>
</table>

Placebo indicates vehicle treatment group. Abbreviations as in Table 1. Values are mean±SD. *P<0.05 vs placebo; †P<0.05 vs Q.
late-stage DCM in humans. However, the extensive fibrosis present in this CM hamster model is not typical of idiopathic DCM, although it may occur in the setting of DCM due to multiple myocardial infarctions. Our findings in the early-phase CM hamster (4 months) and the positive effects of GH and IGF-1 in the rat myocardial infarction model suggest the possibility that GH or IGF-1 might have a clinical role in the particular setting of a large focal scar associated with dysfunction of the remaining noninfarcted myocardium or in cardiomyopathies without extensive fibrosis and before the preterminal phase.

It is uncertain whether or not the marked beneficial effects of GH at rest and exercise in the initial clinical trial, which was uncontrolled by a placebo group but used serial studies including withdrawal in each patient, were due to treatment of relatively early disease and/or relatively low-dose ACE inhibition. In this connection, a recent randomized double-blind trial of GH treatment in older patients having idiopathic DCM but more severe heart failure who received high-dose ACE inhibition did not show improvement in cardiac function or clinical status, although GH caused an increase in LV mass.

In another report using a serial study design in patients with DCM due to coronary artery disease, GH caused improvements in LV diastolic function, CO, and exercise capacity, associated with increased LV wall thickness. It is uncertain whether GH resistance, observed in humans under catabolic conditions, can occur with severe heart failure and cause differing GH responses. The favorable effects of GH alone observed in the 4-month CM hamster group demonstrate that the cardiomyopathic heart can respond to GH, but more experimental studies are needed on GH effects in different causes of DCM, at different stages of heart failure, and with longer GH treatment in the presence of high-dose ACE inhibition.

Acknowledgments

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References


Figure 7. Selected hemodynamic variables in placebo, Q, and Q/GH groups. LV dP/dt max (A), LVEDP (B), and meridional stress of LV wall at end systole (ES; C) and end diastole (ED; D). Bars represent mean ± SD. *P < 0.05 vs placebo group, †P < 0.05 vs Q group.


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