Cardiac Effects of Growth Hormone in Adults With Growth Hormone Deficiency
A Meta-Analysis

Patrick Maison, MD; Philippe Chanson, MD

Background—Growth hormone (GH) treatment may improve morphological and functional cardiac parameters in adults with GH deficiency (GHD). However, clinical trials reported to date involved few patients and yielded variable effects.

Methods and Results—We systematically reviewed blinded, placebo-controlled, randomized clinical trials of GH treatment in adults with GHD and open studies in patients with GHD before and after GH treatment, evaluating the effects of GH on cardiac parameters assessed by echocardiography. Sixteen trials (9 blinded and 7 open), involving a total of 468 patients, were identified in 3 bibliographic databases. GH dosage, duration of treatment, and study populations varied among the studies. We conducted a combined analysis of effects on left ventricular mass (LVM), interventricular septum thickness (IVS), left ventricular posterior wall (LVPW), left ventricular end-systolic (LVESD) and diastolic (LVEDD) diameters, stroke volume, E/A ratio, isovolumic relaxation time (IRT), and fractional shortening. Overall effect size was used to evaluate significance, and weighted mean difference between GH and control was given to appreciate size of the effect. GH treatment was associated with a significant increase in LVM: +10.8 (SD: 9.3) g (P=0.02); IVS: +0.28 (0.38) mm (P<0.001), LVPW: 0.98 (0.22) mm (P=0.05), LVEDD: +1.34 (1.13) mm (P<0.001), and stroke volume: +10.3 (8.7) mL (P<0.001). A trend toward a difference in fractional shortening was observed: +1.1 (1.1%) (P=0.06). Overall effect sizes were not significant for LVESD, E/A, and IRT.

Conclusions—GH treatment is associated with a significant positive effect on LVM, IVS, LVPW, LVEDD, and stroke volume, as assessed by echocardiography, in adults with GHD. (Circulation. 2003;108:2648-2652.)

Key Words: heart failure ▪ echocardiography ▪ growth substances ▪ hormones ▪ meta-analysis

Recent epidemiological studies have shown that hypopituitarism in adults may be associated with increased cardiovascular death.1,2 The role of growth hormone deficiency (GHD) in this increased cardiovascular risk is controversial.3 Nevertheless, experimental evidence supports a role of GH and its effector insulin-like growth factor I (IGF-I) in heart function and morphology.4,5 Some clinical studies have also shown specific cardiac alterations in patients with childhood- and adulthood-onset GHD. Relative to matched control subjects, patients with GHD had impaired left ventricular mass (LVM) and ejection fraction6—8 on echocardiography or equilibrium radionuclide angiography.9—11 However, other studies did not show such alterations in patients with GHD.12,13

GH treatment of GHD is associated with a correction of body composition and changes in bone mineral density,14 but its effects on cardiac parameters are less consistent. LVM was increased in some studies7,8,11,15—19 but not in others,13,20—24 Interventricular septum (IVS) and left ventricular posterior wall (LVPW) thickness increased in only 4 studies,7,11,17,24 Heterogeneous results were also obtained for cardiac output13,16,17,20,23 and ejection fraction (EF), which can be used to measure systolic function.7,11,13,15—23 Most of these trials involved small numbers of adults with GHD. We therefore conducted a systematic review of GH trials in adults with GHD to obtain a more reliable evaluation of the effect of GH treatment on cardiac parameters assessed by echocardiography.

Methods

Identification of Relevant Trials
We searched three electronic databases—Medline (Ovid), Biosis, and Experta Medica (EMBASE)—from their year of inception to June 2002. The medical literature was searched for all reports on the

Received March 13, 2003; de novo received July 17, 2003; revision received August 27, 2003; accepted August 27, 2003.

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Dr Chanson has been an investigator in clinical trials sponsored by manufacturers (Pharmacia, Lilly, Novo-Nordisk), has received funds for organizing education, and is a member of the International Advisory Board of HYPOCSS (Hypopituitary Control and Complication Study), which is sponsored by Lilly.

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Circulation is available at http://www.circulationaha.org DOI: 10.1161/01.CIR.0000100720.01867.1D
effect of GH on heart function in human adults with GH deficiency. The search strategy was not limited by study design or language.

Inclusion Criteria
We selected reports independent of the inclusion criteria. We included all randomized, blind, placebo-controlled trials in patients over 17 years of age with the diagnosis of GHD performed by insulin tolerance test (except two12,23) and a GH peak <5 µg/L. In 1998, Consensus Guidelines for the diagnosis and treatment of adults with GHD recommended the use of the insulin tolerance test (ITT) as a reference test for evaluating GHD and stated that “most normal subjects respond to ITT with a peak GH concentration of >5 µg/L.” The reasons for using different stimulation tests were contraindications to ITT or preference of researchers who previously validated their tests versus ITT. Because only 9 such trials were found, we also included 7 open studies. Cardiopulmonary investigations were based on 2-dimensional echocardiography, and at least 1 of the following outcome measures was included: LVM, IVS, LVPW, left ventricular end-systolic (LVESD) and diastolic (LVEDD) diameters, stroke volume, ratio of E-wave and A-wave peak velocities of the mitral flow profile (E/A), isovolumic relaxation time (IRT), and fractional shortening.

Data Extraction
Data were extracted from published reports onto a standardized form. The authors were contacted to obtain unpublished data and to verify extracted data when necessary. Discrepancies were resolved by discussion between the authors. The following data were extracted: mean age, sex, number of patients included, number lost to follow-up, target GH dose, treatment duration, study quality (design, blindness, statistical methods), losses to follow-up for each outcome measure, baseline and follow-up values in both groups (means and standard deviation or standard error of the mean), and methods used to measure outcomes.

Statistical Methods
The effect size was calculated differently for parallel-group, crossover, and open study designs to reflect the intergroup and intragroup variances.26 The effect size was computed as the mean difference (GH minus placebo) in the changes (follow-up minus baseline) for each outcome measure. In the case of crossover trials, effect sizes were calculated by using mean difference between the ends of each period. For open studies, effect sizes were calculated with mean differences between baseline and follow-up. A positive effect size means an increase with GH treatment and a negative effect size a decrease. To calculate the overall effect size, each study was weighted by the reciprocal of its variance. Because the variance of changes was not stated in all the articles, they were calculated, when necessary, from the r statistic, the probability value, or confidence intervals (variances, standard error of the mean).26 These values had to be estimated from the figures in the study by ter Maaten et al.21 We explored heterogeneity between studies by using the Q test. The analyses were repeated, using a random-effects model when the effect size was significant in a fixed model to confirm the result.27 A funnel plot was drawn, and its asymmetry was measured to assess the possible influence of publication and location biases.28 The intercept of linear regression, where the effect size divided by the standard error is regressed against the reciprocal of the standard error, provides a measure of asymmetry. To assess sensitivity, when the effect size was drawn by one or two trials (eg, a large trial), these studies were dropped from the analysis. To quantify the size of the effect, we calculated weighted mean (and standard deviation) change between the groups or periods for each outcome measure when data were available.

The effects of the GH dose, the IGF-I increase, the treatment duration, and the study design on the overall estimates were assessed by stratification or meta-regression. Weighted least-squares regres-
0.63]) with high target doses and only for LVM (0.23 [0.09; 0.38]) with low doses, suggesting a dose-effect relation. Dose distribution between studies was too restricted to confirm this dose-effect relation by meta-regression. The relation between distribution between studies was too restricted to confirm this dose-effect relation. Dose distribution between studies was too restricted to confirm this dose-effect relation. Dose distribution between studies was too restricted to confirm this dose-effect relation.

**Discussion**

The anabolic effects of the GH/IGF-I axis are well established, together with its role in the regulation of heart function and morphology. IGF-I directly causes cardiac hypertrophy.4 Cittadini et al,5 using isolated rat and ferret muscles, found evidence that IGF-I, contrary to GH, augmented myocardial contractility by sensitizing myofilaments to Ca2+. IGF-I also retards cardiomyocyte apoptosis.29 These findings suggest that GH administration may have a marked trophic effect on the heart, particularly in patients with GHD. However, although some studies showed an increase in LVM during GH therapy of GH-deficient patients,28,11,15–19 others did not.13,20–24

As in all systematic overviews, publication is a potentially major source of bias because trials with positive and significant results are more likely to be published than those with neutral or negative results. Nevertheless, as significant reported parameters were rarely identical in selected trials, such bias seems unlikely.

Our meta-analysis showed a significant positive effect on LVM. This probably is due to the concomitant increase in LVEDD, confirming the results of most published trials,7,13,15,16,18,23 and in LVPW as previously demonstrated in four studies.7,11,17,24 These discrepancies in the effects of GH therapy on LVM may be related to the highly variable degree of basal LVM impairment (and thus the potential increase during treatment). Indeed, the duration and severity of GHD differed from one study to another, as well as the proportion of patients with childhood-onset or adulthood-onset GHD.

**TABLE 1. Characteristics of Studies Included in Meta-Analysis**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of Publication</th>
<th>Study Design</th>
<th>Patients Included</th>
<th>No. Lost</th>
<th>Hypopituitarism, %</th>
<th>Adult-Onset, %</th>
<th>Women, %</th>
<th>Age, y</th>
<th>Target Dose, U/kg per wk</th>
<th>Treatment Duration, mo</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuneo15</td>
<td>1991</td>
<td>Parallel</td>
<td>24</td>
<td>0</td>
<td>NA†</td>
<td>NA</td>
<td>33</td>
<td>38.0 (9.8)</td>
<td>0.5</td>
<td>6</td>
<td>LVM, IFS, LVPW, LEVSD, LVEDD, stroke volume, FS</td>
</tr>
<tr>
<td>Amato7</td>
<td>1993</td>
<td>Open</td>
<td>7</td>
<td>0</td>
<td>100</td>
<td>NA</td>
<td>14</td>
<td>26.0 (1.0)</td>
<td>0.1</td>
<td>6</td>
<td>LVM, IFS, LVPW, LEVSD, LVEDD, FS</td>
</tr>
<tr>
<td>Beshyah23</td>
<td>1994</td>
<td>Parallel</td>
<td>36</td>
<td>0</td>
<td>100</td>
<td>81</td>
<td>41</td>
<td>19–67</td>
<td>0.35</td>
<td>6</td>
<td>LVM, IFS, LVPW, LVEDD, E/A, IVRT</td>
</tr>
<tr>
<td>Caidahl16</td>
<td>1994</td>
<td>Crossover</td>
<td>10</td>
<td>1</td>
<td>100</td>
<td>10</td>
<td>34–58</td>
<td>0.5</td>
<td>6</td>
<td></td>
<td>LVM, IFS, LVPW, LVEDD, stroke volume, E/A, IVRT, FS</td>
</tr>
<tr>
<td>Thuesen12</td>
<td>1994</td>
<td>Crossover</td>
<td>21</td>
<td>0</td>
<td>48</td>
<td>NA</td>
<td>38</td>
<td>23.8 (5.5)</td>
<td>0.45</td>
<td>4</td>
<td>LVM, IFS, LVPW, LEVSD, LVEDD, E/A, FS</td>
</tr>
<tr>
<td>Fort18</td>
<td>1995</td>
<td>Open</td>
<td>19</td>
<td>0</td>
<td>100</td>
<td>95</td>
<td>32</td>
<td>45.9 (10.7)</td>
<td>0.25</td>
<td>6</td>
<td>LVM, IFS, LVPW, LEVSD, LVEDD, E/A, FS</td>
</tr>
<tr>
<td>Nass21</td>
<td>1995</td>
<td>Parallel</td>
<td>20</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>25</td>
<td>(27–60)</td>
<td>0.25</td>
<td>6</td>
<td>LVM, IFS, LVPW, LEVSD, LVEDD, FS</td>
</tr>
<tr>
<td>Valcavi17</td>
<td>1995</td>
<td>Parallel</td>
<td>20</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>30</td>
<td>47.2 (11.6)</td>
<td>0.35</td>
<td>12</td>
<td>LVM, IFS, LVPW, LEVSD, LVEDD, stroke volume, E/A, IVRT</td>
</tr>
<tr>
<td>Baum22</td>
<td>1996</td>
<td>Parallel</td>
<td>32</td>
<td>5*</td>
<td>97</td>
<td>NA</td>
<td>0</td>
<td>50.0 (6.1)</td>
<td>0.2</td>
<td>18</td>
<td>LVM, IFS, LVPW, stroke volume</td>
</tr>
<tr>
<td>Sartorio3</td>
<td>1997</td>
<td>Open</td>
<td>8</td>
<td>0</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>29.4 (4.0)</td>
<td>0.5</td>
<td>6</td>
<td>LVM, IFS, LVPW, LEVSD, LVEDD</td>
</tr>
<tr>
<td>ter Maaten 23</td>
<td>1999</td>
<td>Open</td>
<td>50</td>
<td>13</td>
<td>68</td>
<td>NA</td>
<td>0</td>
<td>28.0 (4.0)</td>
<td>0.45</td>
<td>36</td>
<td>LVM, IFS, LVEDD, stroke volume</td>
</tr>
<tr>
<td>Gillberg33</td>
<td>2001</td>
<td>Open</td>
<td>53</td>
<td>0</td>
<td>100</td>
<td>74</td>
<td>35</td>
<td>27.3 (4.4)</td>
<td>0.05</td>
<td>3</td>
<td>IFS, LVPW, FS</td>
</tr>
<tr>
<td>Link28</td>
<td>2001</td>
<td>Open</td>
<td>11</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>18</td>
<td>24.5 (2.7)</td>
<td>0.14</td>
<td>10</td>
<td>IFS, LVPW, LEVSD, LVEDD, FS</td>
</tr>
<tr>
<td>Colao31</td>
<td>2001</td>
<td>Open</td>
<td>20</td>
<td>0</td>
<td>100</td>
<td>50</td>
<td>45</td>
<td>28 (6.7)</td>
<td>0.25</td>
<td>12</td>
<td>IFS, LVPW</td>
</tr>
<tr>
<td>Sneppen31</td>
<td>2002</td>
<td>Parallel</td>
<td>22</td>
<td>2*</td>
<td>100</td>
<td>90</td>
<td>50</td>
<td>41.5 (11.7)</td>
<td>0.03</td>
<td>18</td>
<td>LEVSD, LVEDD, E/A, IVRT, FS</td>
</tr>
<tr>
<td>Ezzi34</td>
<td>2002</td>
<td>Parallel</td>
<td>115</td>
<td>22</td>
<td>100</td>
<td>92</td>
<td>42</td>
<td>46.5 (12.1)</td>
<td>0.25</td>
<td>6</td>
<td>LVM, IFS, LVEDD, LVEDD, E/A, IVRT, FS</td>
</tr>
</tbody>
</table>

*Maximum lost (varying with outcome). NA indicates not available.
shown an increase in fractional shortening,7,11,13,17,18 whereas others showed no change.15,16,20–23,30,31 Our meta-analysis showed a trend toward a positive effect of GH on fractional shortening. Even if it occurs, it must be kept in mind that improved LV fractional shortening reflects an increase in contractility only if loading characteristics remain unchanged. In fact, if postloading conditions have been considered as not altered by GH treatment in some studies,10 others have demonstrated that GH treatment was able to modify vascular reactivity in improving endothelium-dependent and non-endothelium-dependent vaso-dilatation, which were impaired in patients with GHD as compared with normal control subjects.33–35 Concerning preloading conditions, LVEDD increases after GH treatment of adults with GHD, probably as a consequence of the documented increase in blood volume.

Echocardiographic studies of systolic function have at least 3 limitations. The first is technical: Echocardiography is probably less sensitive than other techniques such as equilibrium radionuclide angiography for the assessment of systolic function.11 Unfortunately, the small number of published studies using these techniques did not allow a meta-analysis. Second, echocardiography (like radionuclide angiography) may lack sensitivity for detecting the effect of GH at rest, as the LV ejection fraction improvement was not allowed in patients with GHD as compared with normal control subjects.10,23,30,31 Our meta-analysis showed a trend toward a positive effect of GH in patients with cardiac failure and potential effect of GH in patients with childhood-onset GHD whose lack of GH secretion during the developmental period provokes more marked alterations of cardiac structure and function that are more responsive to GH.

The effect of GH dose on the cardiac response in GHD has not been investigated so far. Indeed, the issue of physiological or pharmacological response to treatment is important. Our meta-analysis shows higher overall effect size in trials with high target dose of GH, suggesting a dose-effect relation. Moreover, we have demonstrated that the overall effect size is significantly greater for IVS, LVEDD, and stroke volume in the group with higher increase in IGF-I levels during treatment than in the group with lesser increase. Thus, a relation between response of some cardiac parameters and amplitude of IGF-I response to GH treatment seems likely. This may also indicate that a better cardiac response is obtained in patients with more severe GHD, as assessed by lower basal IGF-I levels. It would have been interesting to study the dose-effect relation in terms of IGF-I Z score, which takes into account the variance of age. Unfortunately, in the majority of studies, IGF-I was given in absolute terms, without any reference to normal age-adjusted ranges that could have permitted calculation of an SD score.

Because the aims of GH substitutive treatment in patients with GHD is to obtain and, thereafter, to maintain IGF-I levels in the normal age- and sex-adjusted range, it is not possible from our data to draw any conclusion about the potential effect of GH in patients with cardiac failure and “normal” GH/IGF-I axis. However, it must be emphasized that even in patients with heart failure, the individual response to GH treatment is a fundamental variable to take into account: The higher the target dose and the increment in IGF-I levels, the higher the changes in cardiac function. This is exemplified by the results of a large double-blind trial showing initially no modifications in cardiac function during GH treatment in patients with heart failure,38 but, when reanalyzed as function of IGF-I increase, demonstrating a

<table>
<thead>
<tr>
<th>Factors</th>
<th>No. of Trials</th>
<th>No. of Patients</th>
<th>Weighted Mean Differences (SD)</th>
<th>Global Effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVM</td>
<td>11</td>
<td>210 211</td>
<td>NS</td>
<td>10.8 g (9.3)</td>
</tr>
<tr>
<td>IVS</td>
<td>15</td>
<td>292 294</td>
<td>&lt;0.001</td>
<td>0.28 mm (0.38)</td>
</tr>
<tr>
<td>LVPW</td>
<td>14</td>
<td>255 256</td>
<td>&lt;0.05</td>
<td>0.98 mm (0.22)</td>
</tr>
<tr>
<td>LVESD</td>
<td>10</td>
<td>153 151</td>
<td>NS</td>
<td>0.32 mm (1.06)</td>
</tr>
<tr>
<td>LVEDD</td>
<td>13</td>
<td>218 218</td>
<td>NS</td>
<td>1.34 mm (1.13)</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>5</td>
<td>81 82</td>
<td>NS</td>
<td>10.3 mL (8.7)</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>7</td>
<td>134 137</td>
<td>NS</td>
<td>0.05 (0.13)</td>
</tr>
<tr>
<td>IVRT</td>
<td>5</td>
<td>95 97</td>
<td>NS</td>
<td>−1.60 ms (7.36)</td>
</tr>
<tr>
<td>FS</td>
<td>9</td>
<td>148 158</td>
<td>NS</td>
<td>1.06 % (1.06)</td>
</tr>
</tbody>
</table>

onset and adulthood-onset GHD is also a limitation of our meta-analysis. Indeed, it probably underestimates the cardiac response to GH in patients with childhood-onset GHD whose lack of GH secretion during the developmental period provokes more marked alterations of cardiac structure and function that are more responsive to GH.
marked increase of LV ejection fraction in those patients who responded to GH therapy with substantial IGF-I generation.99

Finally, it must be underlined that beyond the improvement in echocardiographic parameters reviewed in this meta-analysis, GH treatment is also able to produce clinical benefits, particularly in terms of exercise capacity in patients with GHD, as demonstrated in various trials.11,20 Improvement in cardiac function with GH treatment may be one of the factors contributing to this increase in exercise performance.

In conclusion, this meta-analysis confirms that GH treatment is associated with a significant positive effect on LVM, IVS, LVEDD, and stroke volume, as assessed by echocardiography in adults with GH deficiency. In contrast, GH treatment was not found to have a significant impact on systolic parameters.

Acknowledgments
We thank Dr Anne Klibanski for fruitful discussion during the preparation of the manuscript.

References
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_Circulation_. 2003;108:2648-2652; originally published online November 17, 2003; doi: 10.1161/01.CIR.0000100720.01867.1D
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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