Correspondence

Growth Hormone in Chronic Heart Failure
To the Editor:

Anker et al.\(^1\)\(^2\) reported on the hormonal changes in chronic heart failure (CHF) and their importance for cardiac cachexia. The authors found a trend for increased human growth hormone (hGH) in cachectic patients but similar levels of hGH in noncachectic patients compared with control subjects. No significant differences between patients and the control group were seen for insulin-like growth factor-1 (IGF-1). Nevertheless, the IGF-1/hGH ratio was approximately four times higher in noncachectic CHF patients and control subjects than in cachectic subjects. The authors suggest the presence of hGH-resistance in CHF because the increase in hGH in the cachetic patients was not accompanied by an increase in IGF-1.

With respect to the metabolic hGH-IGF-1-status in CHF, the published data so far are controversial. An exploratory pilot research in nine patients with CHF caused by dilated cardiomyopathy (DCM) and New York Heart Association functional class of dyspnea III-IV investigated hGH metabolism in severe CHF. The study group was compared with a control group matched for age, sex, and body mass index. Patients with CHF had markedly depressed levels of IGF-1, whereas hGH had not been measured. Another metabolic study by Giustina et al.\(^4\) in patients with severe CHF caused by DCM (NYHA functional class of dyspnea III-IV) showed an impaired spontaneous hGH secretion, but Anand et al.\(^5\) found hGH to be greatly increased in untreated patients with severe CHF.

Therefore, hGH appears to be associated with a perturbation of the hGH/IGF-1 axis, leading to a state of functional IGF-1 deficiency.\(^6\) This can be viewed as a state of maladaptation, with the consequence that falling IGF-1 levels either systemic, or locally generated within the myocardium, cause a deleterious effect on myocardial function. The mechanism of the perturbation in the hGH/IGF-1 axis (systemic/local) is unclear; possible mechanisms include reduced hGH secretion from the pituitary or hGH resistance. Perturbation of this axis—either primary, as a result of hGH deficiency, or secondary, as a maladaptive response to CHF—may be responsible for the exacerbation of myocardial dysfunction.

Furthermore, it must be mentioned that DCM is the cause of CHF in which subcutaneous recombinant hGH (r-hGH) is likely to effectively counteract the pathogenetic defect of the disease.\(^7\)\(^8\)

That is why subcutaneous r-hGH in conjunction with the widely accepted drugs for CHF, for example, angiotensin-converting enzyme inhibitors, diuretics, nitrates, calcium antagonists, and digoxin, could become an alternative to cardiac transplantation, as there is a worldwide shortage of donor organs.\(^9\) Further in vivo and in vitro studies with r-hGH in failing myocardial tissue are necessary and awaited.

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Response

Dr Dreifuss raises some interesting issues about growth hormone (GH) and insulin-like growth factor-1 (IGF-1), quoting some previous studies of the GH-IGF-1 axis in patients with chronic heart failure (CHF). Acquired GH resistance is known to occur in patients with severe cachexia and malnutrition after surgery and in critical illnesses such as sepsis (see References 1 and 2 for review). Biochemically it is defined as the presence of high GH but low IGF-1 levels. Additionally, it is important to know about GH and IGF-binding proteins and possibly about the actual bioactive hormone levels. Our study\(^1\) did not aim to study these pathways; it is correct that further detailed studies are needed. The other studies mentioned by Dr Dreifuss did not report the cachectic state of the patients, and therefore it is difficult to compare the results. In any case we would like to emphasize that the possible presence of GH resistance in these patients would not be the first metabolic hormone resistance syndrome in CHF (we have recently shown that insulin resistance is also present\(^1\)) and that the metabolic abnormalities of these patients can only be viewed in conjunction with functional and hemodynamic abnormalities.\(^3\)

We believe that it is important to state that previous studies of GH therapy in patients with dilated cardiomyopathy were small and not placebo controlled. It is far from clear that all patients would benefit from GH therapy and that GH in conjunction with other well-established drugs could become an alternative for cardiac transplantation. There is good reason to predict that patients with GH resistance, that is, patients with an inadequate hormone response on GH administration, are less likely to respond positively to GH administration. As Dr Dreifuss mentioned, recently Fazio et al.\(^6\) have shown in a pilot study of GH treatment of patients with CHF caused by dilated cardiomyopathy (n=7) favorable effects on cardiac function and exercise capacity that corresponded with a positive response of the IGF-1 levels. Frustaci et al.\(^1\) reported contrary results in five patients with dilated cardiomyopathy. Possibly these patients had more severe CHF, but it could well have been the case that these patients were resistant to the action of GH (unfortunately, the change of IGF-1 levels was not reported). The first prospective randomized trials are now

coming through and have failed to demonstrate substantial benefits of GH treatment in patients with CHF due to dilated cardiomyopathy.6

We agree with Dr Dreifuss entirely—more in vivo and in vitro studies must be performed.

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Response
We thank Dr Heller for his comments on our article. After reviewing the original data, we must admit that some statistical data of the in vivo part of the study were reported incorrectly. This was due to a misunderstanding between the statistician and the authors of the manuscript with regard to the probability values. Unfortunately, this error leads to statistical significance that does not exist in reality. However, we want to emphasize that the in vitro data were not affected by this error. The original data, the mean values, and the correct probability values are reported as follows in the Table. The correct probability values are $P = .18$ for mean intimal wall area, $P = .45$ for intimal wall thickness, and $P = .31$ for degree of stenosis. Therefore, paclitaxel applied with the microporous balloon was not able to inhibit intimal growth in this preliminary in vivo study. However, concerning the conclusion of our study, we have completed comprehensive experiments with the double-balloon catheter and paclitaxel in which we could show in vivo efficacy. The results have been submitted for publication. We sincerely apologize for the errors.

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Paclitaxel and Arterial Smooth Muscle Cell Proliferation
To the Editor:
I have recently completed reading “Paclitaxel Inhibits Arterial Smooth Muscle Cell Proliferation and Migration In Vitro and In Vivo Using Local Drug Delivery,” published in the July 15, 1997, issue of Circulation. My questions concerning this study are related to the claimed statistical significance of the in vivo data. According to the published methodology, the data were analyzed by a two-tailed unpaired $t$ test. Having applied this test to verify the significance between the reported means, I find that none of the presented in vivo data have any statistical significance, and I am curious whether Axel et al, in error, might have used a paired $t$ test.

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### Prospective Study of Asymptomatic Aortic Stenosis
To the Editor:
Relevant points were raised in the study of Otto et al1 on 123 adults with asymptomatic aortic stenosis and in the editorial by Caraballo.2 We wish to endorse the crucial but neglected role of exercise testing in the management of patients with “asymptomatic” hemodynamically significant aortic stenosis. Stress testing is particularly pertinent before a decision is made to postpone surgical treatment. It is not only in the United States, as stated by Caraballo, but also in the United Kingdom and in our own environment that there is some reluctance to exercise patients

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Intimal Area</th>
<th>Intimal Wall Thickness</th>
<th>Degree of Stenosis</th>
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<tr>
<td></td>
<td>Paclitaxel</td>
<td>Control</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>1</td>
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<tr>
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</tr>
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<tr>
<td>10</td>
<td>Thrombus</td>
<td>0.21 mm$^2$</td>
<td>Thrombus</td>
</tr>
</tbody>
</table>

Mean±SD: 0.21±0.11 mm$^2$ 0.36±0.29 mm$^2$ 0.11±0.04 mm 0.14±0.09 mm 25.8±8.0% 33.8±20.0%

$P = .18$  $P = .45$  $P = .31$
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