Sympathetic deactivation by growth hormone treatment in patients with dilated cardiomyopathy


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Aims We examined the effects of growth hormone administration on the sympathetic nervous system in patients with idiopathic dilated cardiomyopathy.

Background Growth factor therapy is emerging as a new potential option in the treatment of heart failure. Although growth hormone provides functional benefit in the short term, it is unknown whether it affects the sympathetic nervous system, which plays a role in the progression of heart failure.

Methods Seven patients with idiopathic cardiomyopathy received 3 months treatment with recombinant human growth hormone (0.15–0.20 IU kg⁻¹ week⁻¹). Standard medical therapy was unchanged. Myocardial norepinephrine release, both at rest and during submaximal physical exercise, plasma aldosterone, and plasma volume were measured before and after growth hormone treatment. Myocardial norepinephrine release was assessed from arterial and coronary venous plasma concentrations of unlabelled and tritiated norepinephrine and coronary plasma flow (thermodilution).

Results Growth hormone induced a significant fall in myocardial norepinephrine release in response to physical exercise (from 180 ± 64 to 99 ± 34 ng min⁻¹; P < 0.05). Basally, plasma aldosterone was 189 ± 28 and 311 ± 48 pg ml⁻¹ in the supine and upright position, respectively, and fell to 106 ± 16 (P < 0.01) and 182 ± 29 pg ml⁻¹ (P < 0.05) after growth hormone therapy. Growth hormone increased plasma volume from 3115 ± 493 ml to 3876 ± 336 ml (P < 0.05), whereas serum sodium and potassium concentrations were unaffected.

Conclusions The data demonstrate that growth hormone administration to patients with idiopathic cardiomyopathy reduces myocardial sympathetic drive and circulating aldosterone levels. This neurohormonal deactivation may be relevant to the potential, long-term use of growth hormone in the treatment of patients with heart failure.

Key Words: Growth hormone, cardiomyopathy, sympathetic nervous system.

Introduction

Growth factor therapy is emerging as a new potential strategy in the treatment of heart failure. Administration of growth hormone or insulin-like growth factor I attenuates left ventricular dysfunction in rats with heart failure secondary to doxorubicin administration or left coronary artery ligation. Preliminary data from our laboratory showed that 3 months treatment with growth hormone in patients with idiopathic dilated cardiomyopathy produced substantial haemodynamic and clinical improvement. In line with these observations, when patients with severe heart failure secondary to growth hormone deficiency were treated with replacement therapy, there was a prompt cardiac growth response followed by an impressive improvement of their clinical status.

Whereas the immediate functional benefit of growth factor therapy in heart failure is unequivocal, it is not known whether growth factors affect such long-term outcomes as disease progression and survival. A definite answer will probably only be provided by appropriate clinical trials. In the meantime, it may be important to examine the impact of growth factors on laboratory variables that are regarded as significant predictors of cardiovascular morbidity and mortality in patients with heart failure. Among these variables, it is largely accepted that activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system plays a relevant role.
In this report, we describe the changes in myocardial norepinephrine kinetics and plasma aldosterone concentration induced by growth hormone therapy in a group of patients affected by idiopathic cardiomyopathy and symptomatic heart failure.

Methods

Study patients

The study was performed on seven patients (five men, two women) with chronic heart failure caused by idiopathic cardiomyopathy. The clinical duration of their disease was 3.5 ± 1.5 years, and their mean age was 46 ± 9 years (range 36 to 57 years). Five patients were in NYHA functional class III and two were in class II. The mean left ventricular ejection fraction was 34 ± 1-5%. Additional clinical and haemodynamic parameters of these patients are reported elsewhere[6].

Study protocol

All patients were studied before and after 3 months treatment with recombinant human growth hormone (Genotropin, Pharmacia & Upjohn, Milan) administered subcutaneously at a dose of 41U every other day (0.15–0.20IU per kg of body weight per week). Standard medical therapy for heart failure, including digoxin, diuretics, and ACE inhibitors (ramipril 2.5 mg.day\(^{-1}\)) of 1.5%.

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Procedures

Right heart catheterization was performed in the morning after an overnight fast and 24 h without therapy. No premedication was given. The coronary sinus was cannulated with a double-thermistor catheter (Wilton-Webster Laboratories, Baldwin Park, CA, U.S.A.), introduced through the brachial vein. This catheter was used to sample coronary venous blood and to measure coronary blood flow. An 18G catheter was inserted percutaneously into the brachial artery to monitor arterial blood pressure and to obtain arterial blood samples. A contralateral arm vein was cannulated for the administration of a priming dose (27 μCi of L-2,5,6-\(^{3}\)H norepinephrine (New England Nuclear, Boston, MA, U.S.A.) followed by a continuous infusion at the rate of 0.63 μCi.min\(^{-1}\) throughout the experimental period. The norepinephrine infusate was prepared with 0.9% saline with the addition of ascorbic acid to prevent oxidation. After a 20 min equilibration period, two consecutive pairs of blood samples were

Analytical methods

Plasma catecholamines were partially purified by batch alumina extraction[12], separated using ion-pairing reverse phase high pressure liquid chromatography (μBondapak C18-column, Powerline 600A chromatography system, and WISP 700 as autoinjector; Waters Associates, Milpore Corp., Milford, MA, U.S.A.), and quantified by a current produced upon exposure of the column effluent to oxidizing and then reducing potentials connected in series (Coulochem 5100 A; ESA, Inc., Bedford, MA, U.S.A.). Serum levels of potassium and sodium were determined according to standard methods.

Calculations

Myocardial norepinephrine balance was calculated as the product of the arterial (A) – coronary sinus (CS) plasma norepinephrine concentration difference and the
coronary plasma flow. This was obtained by converting coronary blood flow according to the haematocrit. The myocardial fractional extraction (FE) of 3H-norepinephrine was calculated by the equation: \( FE = \frac{A-CS}{A}; \) where \( A \) and \( CS \) are plasma concentrations of tritiated norepinephrine in arterial and coronary venous plasma, respectively. Norepinephrine clearance was obtained by multiplying norepinephrine fractional extraction by coronary plasma flow. Myocardial norepinephrine uptake (MNU) was thus obtained according to the formula: \( MNU = NE \) clearance \( \times \) arterial NE concentration. Once myocardial norepinephrine uptake was calculated, myocardial norepinephrine release was obtained by subtracting myocardial norepinephrine uptake from the norepinephrine myocardial balance.

Statistical analysis to test growth hormone effect was performed by the paired t-test. Results are presented as mean ± SEM.

### Results

The changes in haemodynamic parameters and myocardial norepinephrine kinetics are reported in Table 1. After growth hormone treatment, heart rate was lower at rest and slightly higher during exercise. Arterial blood pressure was not affected by growth hormone. Due to technical problems in the measurement of coronary blood flow in one patient, the data on norepinephrine kinetics refer to six patients. Arterial norepinephrine concentration at rest did not change during treatment. The increase of norepinephrine in response to exercise was reduced after growth hormone, but the difference did not reach statistical significance. Norepinephrine fractional extraction, both at rest and during exercise, was not affected by growth hormone treatment. In the basal study, myocardial norepinephrine release increased five-fold in response to physical exercise (from \( 37 ± 10 \) to \( 180 ± 64 \) ng \( \cdot \) min\(^{-1}\), but much less after growth hormone therapy (from \( 27 ± 4 \) to \( 99 ± 34 \) ng \( \cdot \) min\(^{-1}\); \( P < 0.05 \) vs baseline) (Fig. 1). When myocardial norepinephrine release was expressed per 100 g left ventricular mass, exercise norepinephrine release was \( 64 ± 19 \) ng \( \cdot \) min\(^{-1}\). 100 g\(^{-1}\) left ventricular mass in the basal state and \( 32 ± 10 \) ng \( \cdot \) min\(^{-1}\). 100 g\(^{-1}\) left ventricular mass after growth hormone (\( P < 0.05 \)). Growth hormone did not modify the resting coronary blood flow, but significantly reduced its increase in response to physical exercise (\( P < 0.01 \)). Growth hormone induced a significant increase in plasma volume (from \( 3115 ± 493 \) ml to \( 3876 ± 336 \) ml; \( P < 0.05 \)). In the basal study, the plasma concentrations of aldosterone, measured both in the supine and upright positions, were \( 189 ± 28 \) and \( 311 ± 48 \) pg \( \cdot \) ml\(^{-1}\), respectively, and fell to \( 106 ± 16 \) (\( P < 0.01 \)) and \( 182 ± 29 \) pg \( \cdot \) ml\(^{-1}\) (\( P < 0.05 \) after

<table>
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<th>Haemodynamic parameters and myocardial norepinephrine (NE) kinetics before and after 3 months of therapy with growth hormone</th>
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<td>Baseline</td>
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<td></td>
<td>Rest</td>
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<td>Heart rate (beats. min(^{-1}))</td>
<td>( 86 ± 5 )</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
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<td>Arterial plasma NE (pg. ml(^{-1}))</td>
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<td>Coronary blood flow (ml. min(^{-1}))</td>
<td>( 153 ± 18 )</td>
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<tr>
<td>Plasma volume (ml)</td>
<td>( 3115 ± 493 )</td>
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Values are mean ± SEM. 
*\( P < 0.05 \); †\( P < 0.01 \) vs baseline

![Figure 1](https://example.com/figure1.png)  
**Figure 1** Effect of growth hormone on myocardial norepinephrine release and plasma aldosterone concentration in patients with idiopathic dilated cardiomyopathy. □ = baseline; ■ = after growth hormone.
growth hormone (Fig. 1). Three months after growth hormone therapy was stopped, plasma aldosterone concentration returned to near-basal values (175 ± 20 and 301 ± 35 pg . ml⁻¹ in the supine and upright position, respectively). Before growth hormone therapy, serum potassium and sodium concentrations were 4.5 ± 0.4 and 138 ± 2 mEq . l⁻¹, respectively, and remained unmodified after growth hormone therapy (4.6 ± 0.5 and 138 ± 2 mEq . l⁻¹, respectively).

Discussion
This study demonstrates that growth hormone administration to patients with idiopathic cardiomyopathy induces marked deactivation of the myocardial sympathetic drive during physical exercise and reduces the circulating aldosterone concentration, both supine and upright. The reduction of sympathetic activity after growth hormone is even more evident if myocardial norepinephrine release is corrected for the increase in myocardial mass. The present data may provide further insights into the mechanisms of growth hormone interaction with cardiac growth and performance.

Growth hormone administration may increase plasma renin activity and aldosterone concentration[13]. Circumstantial evidence also suggests that growth hormone might have an effect on catecholamine synthesis and action[14]. Both the sympathetic nervous system and renin-angiotensin-aldosterone systems act as growth and inotropic factors in the myocardium. Thus, in theory, the effect of growth hormone on the increase in the mass and function of the left ventricle[6] in patients with heart failure could be, in part, mediated by further neurohormonal activation. The present data demonstrate that this was not the case. The fact that growth hormone exerted marked growth and functional effects in the failing heart despite the reduced adrenergic drive and the lowered aldosterone levels supports the idea that growth hormone directly affects cardiac morphology and performance.

There is consensus that, although enhanced sympathetic nervous system and renin-angiotensin-aldosterone activity increases myocardial contractility and thus may benefit patients affected by cardiac dysfunction, it can be harmful in the long-term[10,11]. Thus, the present observation that growth hormone improves cardiac performance with great economy of neurohormonal activation may be of particular relevance to the long-term outcome of growth hormone treatment. Indeed, high cardiac sympathetic activity and aldosterone concentration were shown to be independent predictors of poor survival in patients with congestive heart failure[15,16].

Possible mechanisms
The increased sympathetic activity in congestive heart failure is aimed at raising arterial blood pressure and blood volume in compensation for the reduced cardiac output. Thus, maintenance of blood pressure and volume relies on a constantly elevated sympathetic drive. In addition, in patients with congestive heart failure there is desensitization of the vascular baroceptors, which accounts for their inability to suppress enhanced sympathetic activity. In our patients, growth hormone treatment increased plasma volume and, as previously reported, remarkably improved cardiac output, particularly during physical exercise[6]. These changes by themselves may explain the myocardial sympathetic deactivation. The fact, however, that myocardial norepinephrine release was markedly decreased in response to physical exercise and only marginally decreased at rest suggests that it was the improved cardiac output on effort rather than the expanded plasma volume that induced sympathetic deactivation.

Angiotensin II may affect the neural release of norepinephrine and may therefore potentially affect regional norepinephrine kinetics[17]. In our study, the experimental setting before and after growth hormone was identical in terms of ACE inhibitor regimen and therapy withdrawal before assessment of norepinephrine kinetics. Nevertheless, we could not measure angiotensin II concentration and therefore the possibility that angiotensin II may have been partly responsible for the changes in norepinephrine kinetics cannot be completely excluded.

Another factor that may potentially affect regional norepinephrine kinetics is tissue blood perfusion. However, it is unlikely that the reduction in coronary blood flow after growth hormone therapy affected myocardial norepinephrine kinetics because it is well established that only wide variations in blood flow, far above those observed in our patients, are able to modify norepinephrine spillover[18].

The reduction of myocardial norepinephrine release induced by growth hormone is important not only for the adverse consequences of prolonged sympathetic overactivity on the heart but also because it could prevent the depletion of norepinephrine stores, which is responsible for the insufficient response of the failing heart to inotropic stimuli[19,20].

Because our patients were on ACE inhibitor treatment, we did not measure plasma renin activity but looked at the changes in plasma aldosterone, given the fact that its secretion is only in part dependent on angiotensin II. Monitoring the aldosterone profile in heart failure is also of interest because aldosterone per se plays an important role in myocardial interstitial remodelling and progression of heart failure[21]. The plasma concentration of aldosterone in our patients before growth hormone treatment was above the normal range. This may reflect the secondary increase in aldosterone concentration that is often observed in patients on chronic ACE inhibition, consequent to the fact that aldosterone secretion eludes angiotensin II control[22].

The mechanism responsible for the lowering of aldosterone levels after growth hormone therapy may be related to improved haemodynamics. One of the reasons
for the high aldosterone levels in heart failure is the reduced splanchnic clearance of the hormone\textsuperscript{[23]}. Although hepatic blood flow was not measured in our patients, splanchnic circulation could have benefited from the improved cardiac output after growth hormone therapy. It is also conceivable that the expanded plasma volume and reduced sympathetic activity may have contributed to reducing aldosterone concentration. Plasma potassium was not involved in the fall of aldosterone concentration because no change occurred in this variable. Finally, it is possible that the decrease in aldosterone concentration was beneficial in terms of favouring sympathetic nervous system deactivation. Recent data indicate that aldosterone administration to the carotid sinus reduces baroreflex sensitivity in the dog\textsuperscript{[24]} inducing a situation analogous to that existing in chronic heart failure. Thus, one may speculate that the fall in aldosterone after growth hormone therapy may have helped to re-establish the equilibrium between sympathetic outflow and baroreceptor function.

Limitations

A limitation of this study is the lack of a control group due to ethical concerns about performing two catheterization studies in patients receiving placebo. However, we tried to circumvent this problem by selecting patients who were in a stable haemodynamic condition in the 6 months before the study. In addition, the finding that plasma aldosterone returned to near-basal values after withdrawal of growth hormone therapy supports the conclusion that its changes are specifically related to growth hormone treatment.

References