Patients with dilated cardiomyopathy show reduction of the somatotroph responsiveness to GHRH both alone and combined with arginine

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Abstract

Objective: Altered function of the GH/IGF-I axis in patients with dilated cardiomyopathy (DCM) has been reported. In fact, DCM patients show reduction of IGF-I levels, which could reflect slight peripheral GH resistance or, alternatively, reduced somatotroph secretion. Spontaneous GH secretion has been reported to be altered by some but not by other authors, whereas the GH response to GHRH, but not that to GH-releasing peptides, seems reduced in DCM patients. On the other hand, it is well known that the GH response to GHRH in humans is markedly potentiated by arginine (ARG), which probably acts via inhibition of hypothalamic somatostatin release; in fact the GHRH+ARG test is known as one of the most reliable to evaluate the maximal secretory capacity of somatotroph cells.

Methods: In order to further clarify the somatotroph function in DCM, in well-nourished patients with DCM (34 male, 4 female; age (mean ± S.E.M.) 57.8 ± 1.1 years; body mass index (BMI) 24.6 ± 0.6 kg/m²; left ventricular ejection fraction 23.2 ± 1.6%; New York Heart Association classification I/1, II/17, III/18, IV/2) we studied the GH response to GHRH (1.0 μg/kg i.v.) alone or combined with ARG (0.5 g/kg i.v.). The results in DCM patients were compared with those in age-matched control subjects (CS) (39 male, 7 female; age 58.9 ± 1.0 years; BMI 23.2 ± 0.3 kg/m²).

Results: Mean IGF-I levels in DCM patients were lower than in CS (144.3 ± 6.9 vs 175.1 ± 8.4 μg/l, P < 0.05) whereas basal GH levels were similar in both groups (1.7 ± 0.3 vs 1.7 ± 0.3 μg/l). The GH response to GHRH in DCM patients was lower (P < 0.05) than that in CS (GH peak 6.5 ± 1.2 vs 10.7 ± 2.1 μg/l). In both groups the GH response to GHRH + ARG was higher (P < 0.001) than that to GHRH alone. However, the GH response to GHRH + ARG in DCM patients remained clearly lower (P < 0.01) than in CS (18.3 ± 3.2 vs 34.1 ± 4.6 μg/l). The GH response to GHRH alone and combined with ARG was not associated with the severity of the disease.

Conclusion: DCM patients show blunted GH responses to GHRH both alone and combined with ARG. Evidence that ARG does not restore the GH response to GHRH in DCM patients makes it unlikely that the somatotroph hyporesponsiveness to the neurohormone reflects hyperactivity of hypothalamic somatostatinergic neurons.

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Introduction

Growth hormone (GH) has both direct and insulin-like growth factor-I (IGF-I)-mediated effects on myocardial structure and function in animals (1–8) and such cardiotropic activities of GH and IGF-I possibly explain in humans the cardiac abnormalities observed in excessive or defective GH secretion (3, 9–14). Particularly, in patients with severe GH deficiency (GHD), reduced cardiac mass and performances parallel the decreased GH secretion and IGF-I activity and are restored during recombinant human GH (rhGH) replacement therapy (3, 12, 14–21).

Some but not other authors (22, 23) reported cardiac benefit from rhGH treatment even in patients with idiopathic dilated cardiomyopathy (DCM). However, the functional profile of the GH/IGF-I axis in DCM has still to be definitively clarified, though some peculiar alterations have been reported (24–31).

In fact, well-nourished DCM patients show a reduction of IGF-I levels, which could reflect slight peripheral GH resistance or, alternatively, reduced somatotroph secretion (31). Spontaneous GH secretion has been reported altered by some but not by other authors (24, 31), whereas the GH response to GH-releasing hormone (GHRH), but not that to GH-releasing peptides
subjects (CS) (39 male, 7 female; age: 58.9 years; body mass index (BMI) 24.6 kg/m²) and 46 age- and sex-matched control subjects. The study had been approved by the local Ethical Committee.

Informed consent to enter the study was obtained from all subjects. The study design was previously described. Patients were classified by history of myocardial infarction and/or coronary artery disease diagnosed by coronary angiography. The NYHA functional classes (New York Heart Association functional classification) were the following: class 1, n = 1; class 2, n = 17; class 3, n = 18; class 4, n = 2.

In DCM patients, M-mode two-dimensional and Doppler echocardiography (ECHO) was performed with an ultrasonographic phased array with a 2.5 mHz transducer according to the recommendations of the American Society of Echocardiography (39, 40). The following parameters were evaluated: LVDD; left ventricular systolic diameter (LVSD); shortening fraction (SF); and left ventricular ejection fraction (LVEF).

All patients were required to have normal weight, no endocrinopathy and/or nephropathy, inflammatory bowel disease, neoplasm, septic process or other catastrophic states. In fact, all DCM patients were well nourished based on measurement of nutritional parameters such as albumin, prealbumin and transferrin. None of them had been treated with medication known to influence GH/IGF-I secretion. All patients were under standard therapy with diuretics, angiotensin-converting enzyme (ACE) inhibitors and digoxin.

All DCM patients and CS, basal IGF-I levels were evaluated.

All DCM patients and CS (Table 1) were randomly divided into two groups for the acute administration of GHRH (1.0 μg/kg i.v. as a bolus at 0 min) alone or combined with ARG hydrochloride (0.5 μg/kg i.v. over 30 min from 0 min).

Thus, 21 DCM patients and 22 CS underwent GHRH tests whereas 17 DCM patients and 24 CS underwent GHRH+ARG tests (Table 1).

The tests were performed starting between 08.30 and 09.00 h, after an overnight fast and 30 min after cannulation of a cubital vein of the forearm, kept patent by the slow infusion of isotonic saline. Blood samples during tests were taken every 15 min, from −15 min to +90 min.

Serum GH levels were measured in duplicate by IRMA (hGH-CTK; Sorin Biomedica, Saluggia, Italy). The sensitivity of the assay was 0.15 μg/l. The ranges of inter- and intra-assay coefficients of variation were 2.9–4.5 and 2.4–4.0% respectively.

Serum IGF-I levels were measured in duplicate by RIA (Nicholls Institute of Diagnostics, San Juan Capistrano, CA, USA). To avoid interference from binding proteins, all plasma samples were treated with acid–ethanol. The sensitivity of the assay was 0.3 μg/l. The inter- and intra-assay coefficients of variation were 8.8–10.8 and 5.0–9.5% respectively.

All samples from the same subject were analysed together.

The GH secretory responses as well as serum IGF-I levels are expressed as absolute values (μg/l).

The statistical analysis was carried out by non-parametric statistical analysis (Mann–Whitney U test) and a Pearson product–moment correlation test. The results are expressed as mean ± S.E.M.
The GH response to GHRH in DCM patients was lower (P < 0.05) than that in CS (GH peak: 6.5 ± 1.2 vs 10.7 ± 2.1 µg/l) (Fig. 1).

In both groups the GH response to GHRH+ARG was higher (P < 0.001) than that to GHRH alone (Fig. 1).

However, the GH response to GHRH+ARG in DCM patients persisted lower (P < 0.01) than that in CS (18.3 ± 3.2 vs 34.1 ± 4.6 µg/l) (Fig. 1).

The timing of occurrence of the mean GH peak in DCM patients was similar to that in CS after both GHRH and GHRH + ARG.

Analysing individual peak GH responses to GHRH + ARG, 9 out of 17 (52.9%) DCM patients had individual peak GH responses below the third centile of normative values and 6 out of them had GH peak below the first centile (Fig. 2).

The GH response to GHRH alone and combined with ARG was not associated with the ECHO parameters nor with the NYHA classes. Moreover, the somatotroph responsiveness to GHRH either alone or combined with ARG in DCM patients with ischaemic or idiopathic pathogenesis was similar. Both in DCM patients and in CS, no statistically significant differences in the anthropometric, cardiological and hormonal parameters were found between subgroups undergoing GHRH or GHRH + ARG tests (Table 1).

**Side-effects**

Transient facial flushing was recorded in about 25% of DCM patients and CS after GHRH administration.

**Discussion**

The results of the present study demonstrate that patients with DCM show blunted somatotroph responsiveness to GHRH even when given in combination with ARG. In DCM patients as well as in CS the GH response to GHRH + ARG is higher than that to GHRH alone.

Well-nourished DCM patients show reduction of IGF-I levels, which could reflect slight peripheral GH resistance or, alternatively, reduced somatotroph secretion (31). Spontaneous GH secretion in DCM has been reported altered by some but not by other authors (24, 31). On the other hand, the GH response to GHRH in DCM patients has been found clearly blunted when compared with that in CS (31). These findings have been confirmed also by the present study.
Interestingly, the GH response to hexarelin, a synthetic GHRP, has been found preserved in DCM patients (31). GHRPs stimulate GH secretion mainly via central actions probably including antagonization of somatostatin activity and enhanced activity of GHRH-secreting neurons (41). Thus, to explain the reduced somatotroph responsiveness to GHRH we hypothesized the existence of somatostatinergic hyperactivity. To verify this hypothesis, we decided to study the GH response to GHRH combined with ARG in DCM patients. In fact, ARG is known to markedly potentiate the somatotroph responsiveness to GHRH in humans, probably via inhibition of hypothalamic somatostatin release (32). In fact, ARG does not modify either basal or GHRH-induced GH rise from rat pituitary, whereas, in vivo, it potentiates the GH response to GHRH (32, 33). In man, ARG counteracts the somatostatin-mediated negative GH auto-feedback mechanism as well as the inhibitory effect of glucose or neuroactive substances acting by stimulation of somatostatin secretion (32, 42–44). ARG totally restores both spontaneous and GHRH-stimulated GH release in ageing, in which the GH hyposecretory state is probably due to a somatostatin hypertone (34, 45). Moreover, ARG does not modify the stimulatory effects of drugs acting by inhibiting somatostatin release (32).

Independently of the mechanisms underlying the effect of ARG, it remains that GHRH+ARG represents one of the most potent and reproducible tests to evaluate the maximal secretory capacity of somatotroph cells (36–38). In fact, it is considered the best alternative to insulin-induced hypoglycaemia for the diagnosis of GHD in adults (38, 46, 47).

Our present findings showing that DCM patients show clear reduction of the GH response to the GHRH + ARG test imply that ARG is unable to restore the somatotroph responsiveness to the neurohormone. Thus, this evidence suggests that the reduced somatotroph responsiveness to GHRH in DCM is unlikely to be due to hypothalamic somatostatinergetic hyperactivity. Based on evidence that GHRPs elicit massive GH release in DCM patients (31), pituitary insufficiency is unlikely in this condition. Other unknown alterations in the neural control of GH secretion in DCM have to be taken into account (48, 49). The possibility that hypoactivity of GHRH-secreting neurons underlies the low somatotroph response to GHRH seems unlikely, again based on the normal GH response to GHRPs (31). In fact it has been shown that normal hypothalamic–pituitary function and, particularly, of GHRH activity is needed for the full GH-releasing effects of GHRPs (41). The existence of a peculiar alteration in the putative, natural GHRP-like ligand in DCM remains to be verified.

An alternative hypothesis can be put forward to explain the low somatotroph responsiveness in DCM. All DCM patients were on digoxin, ACE inhibitor and furosemide treatment; so the possibility that these substances have iatrogenic effects on somatotroph function should not be ruled out. It has already been shown that chronic treatment with cardiotropic and anti-hypertensive drugs may influence neurohormonal activities (50–52). For instance, digoxin possesses modulatory activity on both sympathetic and renin activity independently of the haemodynamic effects (53). Moreover, chronic treatment with ACE inhibitors reduces IGF-I levels in hypertensive patients independently of the anti-hypertensive activity (54).

In the present study, no relationship was found between the GH response to provocative stimuli and the severity of the disease. However, the absence of any correlation between hormonal, metabolic and cardiac...
parameters does not rule out the existence of a functional link between the GH/IGF-I axis and the heart.

In conclusion, patients with DCM show blunted GH responses to GHRH both alone and combined with ARG. Evidence that the GH response to GHRH in DCM patients is clearly reduced even when ARG is coadministered makes unlikely the existence of hyperactivity of hypothalamic somatostatinergic neurons as a cause of low somatotroph responsiveness to the neurohormone.

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