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Effects of acute hexarelin administration on cardiac performance in patients with coronary artery disease during by-pass surgery

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Abstract

Growth hormone (GH) secretagogues are synthetic molecules with neuroendocrine but also cardiovascular activities mediated by specific GH secretagogue-receptors. The acute administration of hexarelin, a peptidyl GH secretagogue, increases left ventricular ejection fraction in normal subjects and even in patients with severe GH deficiency. We evaluated cardiac performances in patients with coronary artery disease after acute administration of hexarelin (2.0 μg/kg, i.v.) compared to that in patients given with GH-releasing hormone (GHRH; 2.0 μg/kg, i.v.), recombinant human (rh)-GH (10.0 μg/kg, i.v.) or placebo. Cardiac performance was studied in 24 male patients (age [mean ± S.E.M.]: 59.5 ± 1.1 years; body mass index: 24.6 ± 0.9 kg/m^2; left ventricular ejection fraction: 57.2 ± 1.4%) with coronary artery disease undergoing by-pass surgery during general anesthesia. Left ventricular ejection fraction, left ventricular end diastolic volume, cardiac index and cardiac output were evaluated by intraoperative omniplane transoesophageal echocardiography while wedge pressure, central venous pressure, mean arterial pressure and systemic vascular resistance index were evaluated by systemic and pulmonary arterial catheterization. RhGH, GHRH and placebo did not exert any hemodynamic effect while hexarelin induced a prompt (after +10 min) increase in left ventricular ejection fraction ($P<0.001$), cardiac index ($P<0.001$) and cardiac output ($P<0.001$) lasting up to +90 min without any variation in left ventricular end diastolic volume. Accordingly, hexarelin induced a reduction of wedge pressure ($P<0.01$). These changes occurred in the presence of increased mean arterial pressure ($P<0.05$) and transient decrease of central venous pressure ($P<0.05$ at +30 min only) but no change in systemic vascular resistance index. Heart rate after hexarelin was similar to that after placebo. Hexarelin induced a slight increase in GH levels which was similar to that after GHRH but far lower ($P<0.01$) than that after rhGH. Thus, in patients with coronary artery disease undergoing by-pass surgery, the acute administration of hexarelin clearly improves cardiac performance without any relevant variation in systemic vascular resistance. The cardiotropic effect of hexarelin is not shared by GHRH or by rhGH, indicating that it is not mediated by the increase in circulating GH levels but more likely reflects activation of specific cardiovascular GH secretagogue receptors.

Keywords: Hexarelin; GH Secretagogue; Ghrelin; GHRH (growth hormone-releasing hormone); Cardiac performance; Coronary artery disease

1. Introduction

Growth hormone (GH) and Insulin-like Growth Factor I (IGF-I) influence myocardial morphology and function, acting on specific receptors in the myocardium in both animal and humans (Hussain, 1998; Isgaard et al., 1999; Colao et al., 2001). Moreover, in patients with cardiovascular disease, peculiar hypoactivity of the GH/IGF-I axis has been reported (Mangieri et al., 1996; Giustina et al., 1996, 1999; Anker et al., 1997; Niebauer et al., 1998; Lee et al., 1999; Broglio et al., 1999, 2000a,b; Friberg et al., 2000; Osterziel et al., 2000a,b; Anker et al., 2001).

GH secretagogues are a family of non-natural, peptidyl and non-peptidyl molecules which markedly stimulate GH secretion, acting on specific GH secretagogue-receptors type

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1a mostly distributed within the hypothalamus–pituitary unit (Smith et al., 1997; Muccioli et al., 1998, 2000; Ghigo et al., 2001). Note that the GH-releasing activity of GH secretagogues and GH-releasing hormone (GHRH) is mediated by distinct receptors as also shown by evidence that GH secretagogues and GHRH have a synergic effect (Ghigo et al., 2001). Indeed, a natural GH secretagogue has been recently identified in ghrelin, a peptide predominantly produced by the stomach (Kojima et al., 1999). GH secretagogue-receptor type 1a and other subtypes are also present in peripheral, endocrine and non-endocrine tissues, particularly in the heart where both classical GH secretagogue-receptors type 1a and specific high-affinity binding sites for peptidyl GH secretagogues only are present (Ong et al., 1998; Bodart et al., 1999; Muccioli et al., 2000; Papotti et al., 2000; Ghigo et al., 2001). In the human myocardium, unlabeled hexarelin as well as other peptidyl GH secretagogues such as GH Releasing Peptide-1 (GHRP-1), GH Releasing Peptide-2 (GHRP-2) and GH Releasing Peptide-6 (GHRP-6) completely inhibit the binding of radiolabeled Tyr-Ala-hexarelin that is unaffected by non-peptidyl GH secretagogues and human ghrelin (Bodart et al., 1999; Papotti et al., 2000; Muccioli et al., 2000). Similarly, this binding is unaffected by various cardioactive substances such as angiotensin II, endothelin-1, IGF-I, epinephrine, acetylcholine, neurotensin, calcitonin gene-related peptide (CGRP), substance P, and neuropeptide Y (NPY) and arginine–vasopressin (Bodart et al., 1999; Muccioli et al., 2000).

Cardiac GH secretagogue-receptors likely mediate direct cardiovascular activities of GH secretagogues as indicated by evidence that: (a) prolonged hexarelin treatment protects the heart from ischemia in aged as well as in GH-deficient or hypophysectomized rats (De Gennaro Colonna et al., 1997; Rossoni et al., 1998; Locatelli et al., 1999); (b) hexarelin treatment improves cardiac performance after myocardial infarction in rats (Tivesten et al., 2000) while GH Releasing Peptide-2 (GHRP-2) protects against diastolic dysfunction due to post-ischemic myocardial stunning in rabbits (Weekers et al., 2000); (c) acute hexarelin administration increases left ventricular ejection fraction in normal subjects, in patients with severe GH deficiency (Bisi et al., 1999a,b) and even in patients with dilated cardiomyopathy, at least that due to post-ischemic pathogenesis (Broglio et al., 2000c, 2001); (d) similarly, acute ghrelin administration increases cardiac output in normal subjects and in patients with chronic heart failure (Nagaya et al., 2001a,b).

Based on the foregoing, in patients with coronary artery disease undergoing by-pass surgery we studied cardiac performance by omniplane trans-oesophageal echocardiography and arterial catheterization after the administration of hexarelin in comparison with that recorded after placebo, GHRH or exogenous recombinant human (rh)-GH. After each treatment, circulating GH levels were also evaluated.

2. Materials and methods

2.1. Study design and protocol

Twenty-four male patients (age [mean ± S.E.M.]: 59.5 ± 1.1 years; body mass index: 24.6 ± 0.9 kg/m^2; left ventricular ejection fraction: 57.2 ± 1.4%) with coronary artery disease undergoing by-pass surgery were studied. The diagnosis of coronary artery disease was based on a history of prior myocardial infarction and evidence of coronary artery lesions evaluated by coronaroangiography.

All patients were required to have no endocrinopathy and/or no pathology other than the cardiac disease. None had been treated with drugs known to influence GH/IGF-I secretion.

Table 1
Mean (± S.E.M.) left ventricular ejection fraction, cardiac index, wedge pressure, central venous pressure, mean arterial pressure, heart rate and GH in patients with coronary artery disease at baseline and after acute hexarelin, rhGH, GHRH or placebo administration

	Hexarelin		rhGH		GHRH		Placebo	
	Baseline	Maximum Δ variation from baseline	Baseline	Maximum Δ variation from baseline	Baseline	Maximum Δ variation from baseline	Baseline	Maximum Δ variation from baseline
Left ventricular ejection fraction (%)	57.2 ± 1.4	6.8 ± 0.5[a]	49.5 ± 4.2	− 0.8 ± 1.3	55.3 ± 4.2	− 1.0 ± 1.3	54.3 ± 3.2	− 1.6 ± 0.2
Cardiac index (l/min/m^2)	2.6 ± 0.1	0.2 ± 0.03[a]	2.8 ± 0.1	− 0.1 ± 0.1	2.7 ± 0.1	0.0 ± 0.07	2.7 ± 0.1	− 0.1 ± 0.1
Wedge pressure (mm Hg)	11.0 ± 0.7	− 2.3 ± 0.4[b]	9.0 ± 0.6	− 0.7 ± 0.7	10.2 ± 0.8	− 0.2 ± 0.8	10.4 ± 0.7	− 0.3 ± 0.5
Central venous pressure (mm Hg)	10.8 ± 1.2	− 2.0 ± 0.8[b]	7.7 ± 0.7	− 0.5 ± 0.5	8.5 ± 0.9	0.8 ± 0.4	8.6 ± 0.7	0.6 ± 0.7
Mean arterial pressure (mm Hg)	76.7 ± 4.1	5.3 ± 0.9[b]	75.2 ± 2.2	0.3 ± 1.9	74.3 ± 3.0	− 0.8 ± 1.6	74.4 ± 2.6	− 1.1 ± 1.0
Heart rate (bpm)	65.8 ± 2.7	1.0 ± 2.0[b]	71.3 ± 3.3	− 0.3 ± 1.7	62.7 ± 3.2	0.8 ± 1.1	60.9 ± 2.4	0.7 ± 1.2
GH (μg/l)	0.8 ± 0.3	5.1 ± 3.3[b]	0.8 ± 0.2	74.5 ± 9.6[a]	0.9 ± 0.1	2.3 ± 0.9[b]	0.8 ± 0.2	0.3 ± 0.2

[a] $P < 0.01$ (see text for details).
[b] $P < 0.05$ (see text for details).

Informed consent to participate in the study had been obtained from all the subjects and the study protocol had been approved by an independent Ethical Committee.

Biochemical screening tests of hepatic, renal and haematological function as well as evaluation of nutritional parameters had been performed in all subjects.

On the day of the study, after overnight fasting, all the patients underwent by-pass surgery (starting between 7:00 and 8:30 a.m.) under general anesthesia induced by remifentanil (1.5 μg/kg/min), a μ-opioid receptor agonist, cisatracurium (0.2 mg/kg), a nicotinic receptor antagonist, and propofol (0.5 mg/kg), a hypnotic sedative, and maintained with remifentanil (0.5–1.0 μg/kg/min) and propofol (2–4 mg/kg/h).

Left ventricular ejection fraction, left ventricular end-diastolic volume, left ventricular end-systolic volume, cardiac index and cardiac output were monitored by intraoperative omniplane transoesophageal echocardiography. Intraoperative transoesophageal echocardiography was performed in the standard manner with a Hewlett Packard 5500 Sonos echocardiographic system and a Hewlett Packard Omniplane 5-MHz phased-array transducer.

Wedge pressure, central venous pressure, mean arterial pressure, pulmonary arterial pressure, systemic vascular resistance index and pulmonary vascular resistance index were evaluated by arterial catheterization after positioning a Swan-Ganz catheter in the pulmunary artery through a jugular vein and 20-gauge cannula into a radial artery.

Then, at least 20 min after the induction of the general anesthesia, all the patients randomly underwent the acute administration of either of the following.

(1) Hexarelin ([His-D-2Methyl-Trp-Ala-Trp-D-Phe-Lys-NH_2]; Europeptides, France; $t_{1/2} \cong 110$ min [data available for beagles only]; 2.0 μg/kg injected i.v. at 0 min in about 15 s). Each vial containing 100 μg lyophilized hexarelin active substance was diluted in 3 ml isotonic saline 5 min before i.v. injection.

(2) GHRH ([H-Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2]; $t_{1/2} \cong 40$ min; 2.0 μg/kg injected i.v. at 0 min in about 15 s) as commercially available GHRH Ferring, Italia. Each vial containing 50 μg lyophilized GHRH active substance was diluted in 3 ml isotonic saline 5 min before i.v. injection.

(3) rhGH ([H-Phe-Pro-Thr-Ile-Pro-Leu-Ser-Arg-Leu-Phe-Asp-Asn-Ala-Met-Leu-Arg-Ala-His-Arg-Leu-His-Gln-Leu-Ala-Phe-Asp-Thr-Tyr-Gln-Glu-Phe-Glu-Glu-Ala-Tyr-Ile-Pro-Lys-Glu-Gln-Lys-Tyr-Ser-OH]; $t_{1/2} \cong 20$ min; 10.0 μg/kg injected i.v. at 0 min in about 15 s) as commercially available Humatrope, Eli Lilly, Italy. Each vial containing 1.33 mg rhGH active substance with glycine, mannitol and dibasic sodium phosphate as excipients was diluted in 3 ml isotonic saline 5 min before i.v. injection.

(4) Placebo (isotonic saline 3 ml injected i.v. at 0 min in about 15 s).

At baseline and at +10, 20, 30, 60 and 90 min, cardiovascular variables were recorded and serum samples were withdrawn for GH assay.

Serum GH levels (μg/l) were measured by immunoradiometric assay (hGH-CTK, Sorin Biomedica, Saluggia, Italy). The sensitivity of the assay was 0.15 μg/1. The inter- and the intra-assay coefficients of variation were 2.9–4.5% and 2.4–4.0%, respectively.

The procedures related to this protocol did not affect the normal procedures related to the by-pass surgery.

2.2. Statistical analysis

Haemodynamic and hormonal parameters are expressed as absolute values or as absolute changes from baseline.

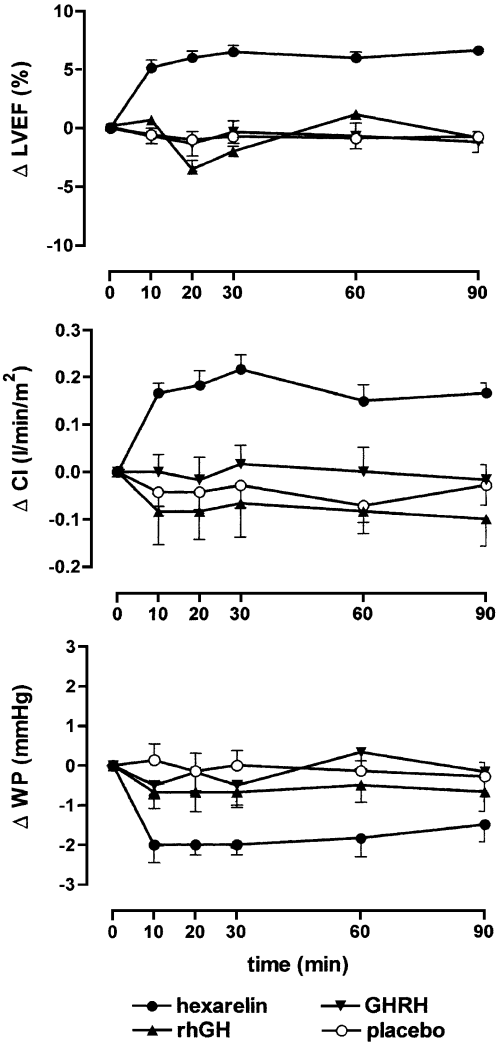

Fig. 1. Mean (±S.E.M.) Δ left ventricular ejection fraction, Δ cardiac index and Δ wedge pressure variations after hexarelin (2.0 μg/kg, i.v. at 0′ as a bolus) or GHRH (2.0 μg/kg, i.v. at 0′ as a bolus) or rhGH (10.0 μg/kg, i.v. at 0′ as a bolus) or placebo (saline 3 ml at 0′ as a bolus) administration in patients with coronary artery disease undergoing by-pass surgery under general anesthesia.

The statistical analysis of the data was performed by analysis of variance (ANOVA, Kruskal–Wallis or Friedman two way tests) followed by Wilcoxon signed rank test or Mann–Whitney *U*-test as appropriate.

Pearson correlation analysis was also performed where indicated. The results are expressed as means ± S.E.M.

3. Results

Cardiovascular parameters at baseline were similar in all groups (Table 1). The administration of rhGH, GHRH as well as of placebo did not modify any of the hemodynamic parameters (Table 1 and Figs. 1 and 2).

On the contrary, hexarelin administration induced a striking increase of left ventricular ejection fraction ($P<0.001$), cardiac index ($P<0.001$) and cardiac output ($P<0.001$) (Tables 1 and 2 and Fig. 1). Left ventricular ejection fraction, cardiac index and cardiac output promptly increased, the increase being significant from 10 min ($P<0.05$ vs. baseline) after hexarelin administration and persisting elevated up to 90 min ($P<0.05$ vs. baseline) (Fig. 1).

Such hemodynamic effects were accompanied by a significant reduction of left ventricular end systolic volume ($P<0.01$), from 10 min ($P<0.05$ vs. baseline) up to 90 min ($P<0.05$ vs. baseline) after hexarelin administration, in the absence of any significant variation of left ventricular end diastolic volume (Table 2).

Table 2
Mean (± S.E.M.) left ventricular ejection fraction, cardiac output, end diastolic volume, end systolic volume, systemic vascular resistance index, pulmonary vascular resistance index and pulmonary arterial pressure in patients with coronary artery disease at baseline and at the individual left ventricular ejection fraction peak after hexarelin administration

	Baseline	Value at individual left ventricular ejection fraction peak
Left ventricular ejection fraction (%)	57.2 ± 1.4	64.0 ± 1.1[a]
Cardiac output (ml)	4.9 ± 0.3	5.2 ± 0.3[a]
Left ventricular end diastolic volume (ml)	96.8 ± 4.8	95.5 ± 4.0
Left ventricular end sistolic volume (ml)	41.0 ± 1.7	34.0 ± 1.7[b]
Systemic vascular resistance index (dyn s cm^{-5} m^2)	2053.3 ± 157.6	2025.0 ± 120.7
Pulmonary vascular resistance index (dyn s cm^{-5} m^2)	299.0 ± 27.1	311.8 ± 24.3
Pulmonary arterial pressure (mm Hg)	20.8 ± 1.1	21.2 ± 1.2

[a] $P<0.001$ (see text for details).
[b] $P<0.01$ (see text for details).

Accordingly, a clear reduction of wedge pressure ($P<0.01$) from 10 min ($P<0.05$ vs. baseline) up to 90 min ($P<0.05$ vs. baseline) after hexarelin administration was observed (Table 1 and Fig. 1).

Such cardiovascular effects of hexarelin occurred in presence of an increase in mean arterial pressure ($P<0.05$ from 30 min up to 90 min vs. baseline and vs. placebo)

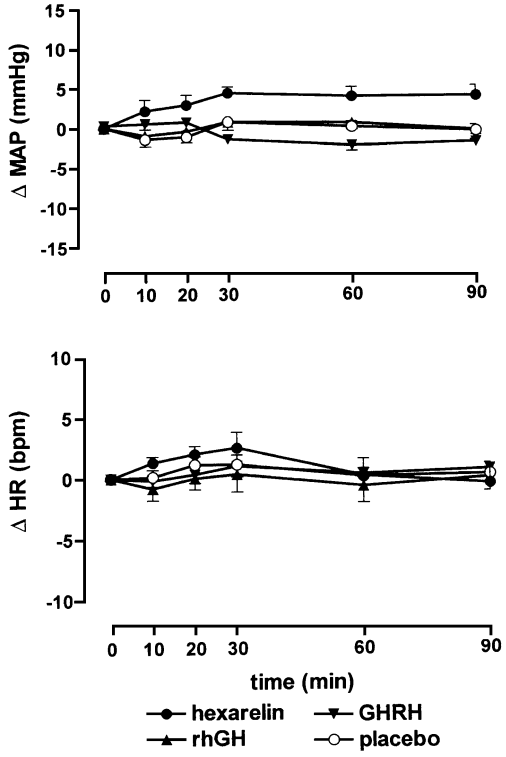

Fig. 2. Mean (± S.E.M.) Δ mean arterial pressure and Δ heart rate variations after hexarelin (2.0 μg/kg, i.v. at 0′ as a bolus) or GHRH (2.0 μg/kg, i.v. at 0′ as a bolus) or rhGH (10.0 μg/kg, i.v. at 0′ as a bolus) or placebo (saline 3 ml at 0′ as a bolus) administration in patients with coronary artery disease undergoing by-pass surgery under general anesthesia.

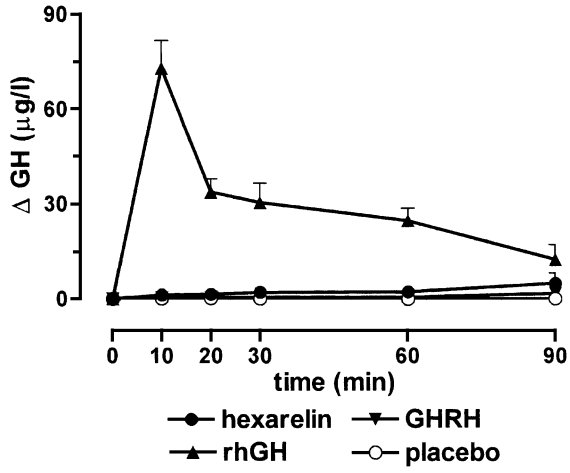

Fig. 3. Mean (± S.E.M.) Δ GH variations after hexarelin (2.0 μg/kg, i.v. at 0′ as a bolus) or GHRH (2.0 μg/kg, i.v. at 0′ as a bolus) or rhGH (10.0 μg/kg, i.v. at 0′ as a bolus) or placebo (saline 3 ml at 0′ as a bolus) administration in patients with coronary artery disease undergoing by-pass surgery under general anesthesia.

(Fig. 2) and a mild and transient decrease of central venous pressure that reached statistical significance at 30 min only ($P<0.05$ vs. baseline and vs. placebo), whereas no variations in pulmonary arterial pressure, systemic vascular resistance index and pulmonary vascular resistance index were observed (Table 2). Moreover, hexarelin also induced a mild and transient increase in heart rate ($P<0.05$ at 20 min vs. baseline, only), that however did not attain statistical significance versus placebo (Fig. 2).

In the hexarelin group, no significant correlations were found between the hemodynamic responses to hexarelin and the cardiovascular variables at baseline.

Basal GH levels were similar in all groups. The increase of GH levels after acute rhGH administration was marked and significantly greater ($P<0.01$) than that after GHRH which, in turn, was similar to that observed after hexarelin administration. No significant variation of GH levels were observed with the placebo (Table 1 and Fig. 3).

4. Discussion

The results of the present study in patients with coronary artery disease undergoing by-pass surgery demonstrate that the acute administration of hexarelin, a synthetic peptidyl GH secretagogue, clearly improves cardiac performance without any significant variation in systemic vascular resistance. This cardiac effect of hexarelin is shared by neither GHRH nor rhGH.

The presence of GH secretagogue-receptors type 1a and other GH secretagogue-receptor subtypes in the cardiovascular system has been demonstrated (Ong et al., 1998; Bodart et al., 1999; Muccioli et al., 2000; Papotti et al., 2000; Ghigo et al., 2001) and likely explains the cardiovascular activity of synthetic and natural GH secretagogues. Specifically, it had been demonstrated that: (a) prolonged hexarelin treatment protects the heart from ischemia in aged as well as in GH-deficient or hypophysectomized rats (De Gennaro Colonna et al., 1997; Rossoni et al., 1998; Locatelli et al., 1999) though acute exposure of perfused rat heart to very high hexarelin dose induces some coronary vasoconstriction and reduction in cardiac contractility (Bodart et al., 1999); (b) hexarelin treatment improves cardiac performance after myocardial infarction in rats (Tivesten et al., 2000) while GHRP-2 protects against diastolic dysfunction due to post-ischemic myocardial stunning in rabbits (Weekers et al., 2000); (c) acute hexarelin administration increases left ventricular ejection fraction without any change in blood pressure, heart rate or catecholamine levels in normal subjects, in patients with severe GH deficiency (Bisi et al., 1999a,b) and even in patients with dilated cardiomyopathy, at least that due to post-ischemic pathogenesis (Broglio et al., 2000c, 2001). Evidence that GH secretagogues maintain their cardiovascular activity even in animals and humans with hypopituitarism indicated that these actions are GH-independent and likely mediated by specific cardiovascular receptors. This assumption is of relevance when it is considered that the acute administration of ghrelin, a natural GH secretagogue, also increases cardiac output in normal subjects and in patients with chronic heart failure (Nagaya et al., 2001a,b). On the other hand, prolonged treatment of rats with ghrelin seems unable to protect the heart from ischemia (Torsello and Locatelli, personal communication) and this is of relevance when considering the existence in the heart of binding sites specific for synthetic peptidyl GH secretagogues (Muccioli et al., 2000; Papotti et al., 2000).

With this as background, we studied the effects of hexarelin on cardiac performance, using omniplane transoesophageal echocardiography and arterial catheterization in patients with coronary artery disease during general anesthesia for by-pass surgery. The effects of the maximal GH-releasing dose of hexarelin were compared with those of rhGH (administered at a dose known to increase circulating GH levels to an extent similar to that generally recorded after hexarelin administration in normal subjects (Imbimbo et al., 1994)) and of GHRH, the hypophysiotropic GH-releasing neurohormone given at a maximal dose (Gelato et al., 1984). The effects of hexarelin were compared with the effects of these hormones because GH has acute and chronic cardiovascular activities (Volterrani et al., 1997, 2000; Isgaard et al., 1999; Isgaard and Bengtsson, 2000; Colao et al., 2001) and even GHRH seems to exert some cardiovascular activity (Watanabe et al., 1995; Hasegawa et al., 1988).

Our findings demonstrate that hexarelin induces an increase in cardiac contractility even in patients with coronary artery disease during by-pass surgery. The mechanisms underlying this action are unclear. The increased cardiac contractility would reflect a decrease of the afterload charge following peripheral vasodilatation. Alternatively, it could reflect an increase of coronary blood flow; in fact, hexarelin modulates coronary blood flow in rats (Bodart et al., 1999) and increases left ventricular cardiac contractility in patients with ischemic cardiac disease (Broglio et al., 2000c, 2001 and present data) but not in those with idiopathic dilated cardiomyopathy (Broglio et al., 2000c, 2001). If this was the case, the increase in cardiac contractility should be more marked in coronary artery disease than in normal subjects. Obviously, this comparison was impossible under the present experimental conditions and has to be done in other studies.

As no significant variation was found in either peripheral or pulmonary vascular resistance as evaluated by arterial catheterization, the hypothesis that the effects on cardiac contractility can be explained by decreased vascular resistance seems unlikely to hold. However, ghrelin administration in normal volunteers and patients with chronic heart failure is followed by an increase in cardiac output coupled with a decrease in arterial pressure and systemic vascular resistance without any modification in heart rate or pulmonary capillary wedge pressure (Nagaya et al., 2001a,b). This discrepancy could reflect: (a) the sensitivity of methods

measuring systemic vascular resistance; (b) different cardiovascular patho-physiologic conditions; (c) activation of different cardiovascular GH secretagogue-receptor subtypes (Bodard et al., 1999; Muccioli et al., 2000; Papotti et al., 2000; Cassoni et al., 2001).

Favoring a direct action of hexarelin on cardiac contractility is the evidence that it increases the contractility of papillary muscle likely via actions mediated by endothelial cells or nerve endings (Bedendi et al., 2001).

The effect of hexarelin on cardiac contractility is of interest from the patho-physiological point of view but its clinical impact is unknown. To clarify this point, besides dose–response evaluation, studies addressing the effects of chronic treatment with hexarelin on cardiac performance have to be performed in patients with dilated cardiomyopathy, particularly when this is due to chronic coronary artery disease. It has also to be definitely clarified if these effects are common to all peptidyl GH secretagogues or are specific for hexarelin, although present evidence already favours the former hypothesis (Weekers et al., 2000; Broglio et al., 2001).

As anticipated, while GH and IGF-I clearly exert an effect on myocardial morphology and function, acting on specific receptors in myocardial tissue (Hussain 1998; Isgaard et al., 1999; Isgaard and Bengtsson, 2000; Colao et al., 2001), they are unlikely to mediate the effects of hexarelin that are present even in subjects with hypopituitarism (De Gennaro Colonna et al., 1997; Bisi et al., 1999a; Locatelli et al., 1999). Against this hypothesis, note also that, in the present study, hexarelin displayed cardiac activity despite the slight increase in circulating GH levels which was similar to that after GHRH and far lower than that after rhGH administration. The blunted GH response to hexarelin recorded in this study could reflect an iatrogenic effect of general anesthesia. Though normal spontaneous GH secretion has been reported to be unaffected by general anesthesia induced with cisatracurium, propofol and remifentanil administration (Luger et al., 1989; Murakawa et al., 1998; Brockmann et al., 2000), a potential influence of these drugs on the GH response to provocative stimuli cannot be ruled out.

Finally, though the acute inotropic effect of GH secretagogues cannot be mediated by the increase of circulating IGF-I levels (Ghigo et al., 2001), the possibility that GH secretagogues act via increase of myocardial IGF-I (d'Ercole et al., 1984) cannot be ruled out definitively. In fact, the acute inotropic effect of rhIGF-I has recently been shown either in normal subjects or in patients with dilated cardiomyopathy (Donath et al., 1996, 1998; Bisi et al., 1999c).

In conclusion, this study demonstrated that in patients with coronary artery disease undergoing by-pass surgery, the acute administration of hexarelin, a synthetic peptidyl GH secretagogue, clearly improves cardiac performances without any relevant variation in systemic vascular resistance. This study further supports the hypothesis that hexarelin has direct, GH-independent cardiovascular activity.

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