Long-Term Effects of Growth Hormone on Infarct Size and Left Ventricular Function in Sheep With Coronary Artery Occlusion

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Abstract: The effects of growth hormone (GH) on infarct size and left ventricular (LV) function in experimental acute myocardial infarction (AMI) have been controversial. Moreover, little, if any, information exists regarding long-term evaluation of therapeutic doses of GH in large mammalian models of AMI. We therefore aimed to assess the effect of therapeutic doses of GH over 3.5 months on infarct size and heart function in sheep with AMI. After coronary artery ligation, sheep received subcutaneous human GH 8 IU/d (n = 8) or vehicle (n = 8) over 100 days. Infarct area was similar in GH (16.9% ± 3% of LV area) and placebo (16.5% ± 3.7%, P = not significant) sheep. At 3 days of treatment onset, but not at later times, GH sheep had higher LV shortening fraction (30.7% ± 3.5% vs. 24.8% ± 6.1%, $P < 0.04$), systolic anterior wall thickness (10.1 ± 0.8 vs. 8.6 ± 1.2 mm, $P < 0.02$), and cardiac index (3.8 ± 0.6 vs. 2.8 ± 0.7 $L \cdot min^{-1} \cdot m^{-2}$, $P < 0.01$). This evolution of function parameters paralleled that of serum insulin-like growth factor 1 levels, which differed significantly only during the first week, suggesting a direct effect of GH on LV contractility. These results may suggest the usefulness of therapeutic doses of GH at the early phases of AMI but do not support maintaining the treatment for longer time.

Key Words: growth hormone, acute myocardial infarction, infarct size, sheep

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INTRODUCTION

Coronary artery disease is the leading cause of morbidity and mortality worldwide, and the expected largest single cause of disease economic burden by 2020.[1] Its most severe complication, acute myocardial infarction (AMI), often results in left ventricular (LV) remodeling which, in turn, leads to LV failure. Because the severity of the remodeling process is associated with the size of the infarct,[2] limiting the extent of the necrotic area at the time of coronary occlusion would attenuate functional deterioration and improve the outcome.[3]

On account that growth hormone (GH) is a key mediator of heart structure and function, numerous studies have assessed the effects of GH on infarct size and LV function in experimental animals. The results of such studies have been controversial.

In rodents and isolated rat hearts, infarct size reduction has been achieved with GH,[4–6] GH-releasing hormone,[7,8] GH secretagogues,[9] and skeletal myoblasts transfected with the GH gene.[10] In contrast, no such effect was observed with GH[11] or insulin-like growth factor 1 (IGF-1)[12] in normal or hypophysectomized rats.[13] In rats with chronic high-dose ACE inhibition, additive short-term high-dose GH was beneficial with moderate infarcts but detrimental with large infarcts.[14] Negative effects of after-AMI GH treatment on LV function have been also reported.[15]

With regard to studies on large mammalian models of AMI, the data available are scarce. In pigs with 1-hour coronary occlusion followed by reperfusion, GH-releasing peptide 6 administration reduced infarct size and myocardial oxidative stress.[16] In sheep, after 30 days of coronary occlusion, high-dose GH increased cardiac IGF-1, leading to cardiomyocyte hypertrophy. However, infarct size and LV function were not measured.[17]

To our knowledge, no studies have assessed the effect of therapeutic doses of GH on infarct size and cardiac function in large mammals in the long-term. Accordingly, we assessed in an ovine model of AMI whether daily GH

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administration in doses used in the clinical setting would reduce the fibrotic scar area and improve LV function over a 3.5-month follow-up time.

MATERIALS AND METHODS

Surgical Preparation

All procedures were done in accordance with the Guide for Care and Use of Laboratory Animals, published by the US National Institutes of Health (NIH publication No 85-23, revised 1996) and approved by the Laboratory Animal Care and Use Committee of the Favaloro University. Sixteen male Corriedale sheep weighing 32 ± 2.8 kg were operated. Animals were premedicated with intramuscular acepromazine maleate (5 mg). Anesthesia was induced with intravenous sodium thiopental (20 mg/kg) and maintained with halothane 1.5% in pure oxygen under mechanical ventilation (Neumovent 910; Tecme, Córdoba, Argentina). After a sterile thoracotomy at the fourth intercostal space, the second and third (or first and second, depending on the coronary anatomy of each individual sheep) diagonal branches of the left anterior descending artery were ligated at their origin. An infarct comprising approximately 20% of the LV mass was thus generated. To reduce the incidence of ventricular arrhythmias, lidocaine (3 bolus injections of 2 mg each and a 2 mg/kg infusion), amiodarone (150 mg infusion in 2 hours), and atenolol (2 mg) were administered. Finally, the thoracotomy was repaired and intravenous cephalotin (30 mg/kg) was administered.

Treatment

The sheep were randomized to receive 8 IU (equivalent to 2.66 mg) recombinant human GH (GH group) or vehicle (placebo group) subcutaneously starting at the moment of coronary ligation and every 24 hours at 5 PM thereafter over 105 days. The nature of the injectates was kept blind for all investigators until the end of data processing.

LV Function

Under sedation with intramuscular diazepam (10 mg), each animal underwent M mode and bidimensional echocardiography (Sonos 5500; Hewlett Packard, Boston, MA) at preinfarction (baseline) condition and at 3, 15, 40, 60, and 100 days postinfarction. LV end diastolic volume (LVEDV) and LV end systolic volume (LVESV) were calculated using the area length formula, in a 3-chamber view, obtained from a low parasternal window. Systolic wall thickness and diastolic wall thickness at the peri-infarct zone and in a zone remote to the left anterior descending artery bed, LV ejection fraction, LV fractional shortening, and cardiac output were assessed. The s wave of the tissue Doppler echo (sW) was recorded at the middle segments of the anterolateral wall, proximal, but outside, to the diskynetic zone. To evaluate diastolic function, the E wave to A wave ratio (E/A) and the isovolumic relaxation time were measured. To obtain cardiac index, body surface area was calculated using the equation[18]:

$$BSA = 0.084 \cdot BW^{0.66},$$

where BSA is body surface area (in square meters) and BW is body weight (in kilograms).

Resting LV Perfusion

At 105 days, the animals were sedated (sodium thiopental 20 mg/kg) and submitted to gated single-photon emission computed tomography. Studies were done in an ADAC Vertex Dual Detector Camera System (Milpitas, CA) using 99mTc-sestamibi. The sestamibi injection was done at conscious resting condition 1 hour before acquisition. Regional perfusion was visually evaluated by 2 independent observers using the 20-segment model[19] and a score in which 0 corresponds to normoperfusion; 1, 2, and 3 to mild, moderate, and severe perfusion defects, respectively; and 4 to absence of perfusion. The final score (summed rest score) results from the sum of the individual segmental scores.

Hemodynamics

On day 108 ± 0.9 after surgery, the sheep were weighed and, immediately before sacrifice, a pressure tip catheter was advanced through the carotid artery into the LV chamber under sedation with sodium thiopental, as previously described.[20]

Heart rate, LV peak systolic pressure, LV end diastolic pressure, and the peak rates of LV pressure increase and decay (dP/dt_{max} and dP/dt_{min}, respectively) were calculated using software developed in our laboratory. For each variable, we averaged the values for all beats recorded during a fixed 5-second acquisition time. At the end of LV catheterization, the sheep were killed with an overdose of sodium thiopental followed by a bolus injection of potassium chloride to arrest the heart in diastole.

Measurements of Troponin I

On account that one major objective was to study GH effects on infarct size, we attempted to assess for intergroup homogeneity in the amount of infarcted tissue at the beginning of the study by measuring a variable specific for myocardial tissue necrosis. We therefore determined serum cardiac troponin-I at 4 and 48 hours after AMI by a microparticle enzyme immunoassay using the AxSYM Troponin-I ADV (Abbott laboratories, Buenos Aires, Argentina).

Measurements of IGF-1

Serum IGF-1 concentrations were determined by an immunoradiometric assay using the DSL-5600 Active kit (Diagnostic System Laboratories, Inc, Webster, TX), at basal conditions and at 1, 3, 30, 60, and 100 days after AMI. To avoid confusions derived from circadian variations, samples were always taken at 5 PM, just before GH administration.

Morphometry and Histology

The heart was excised, and after removing the atria and the right ventricle, the LV was weighed for calculation of the LV weight/BSA ratio. The LV was opened from apex to base parallel to the posterior interventricular sulcus and extended flat before fixation. Digital photographs were obtained for image processing (Image-Pro Plus 4.1; Media Cybernetics, Silver Spring, MD) to determine LV and infarct areas. Infarct size was expressed as percent total LV area. After at least 48-hour fixation, a 1-cm thickness slice of the LV was cut perpendicular to the apex–base axis at the mid infarct level. The slice was further divided into 6 pieces that were embedded

in paraffin. Five-micrometer sections were stained with Masson trichrome. In slices from normoperfused myocardium, the diameter of 50 transversally cut cardiomyocytes was measured and the average calculated. Wall thickness (in millimeters) was measured at the center of the infarct and at the normal peri-infarct borders.

Statistical Analysis

An analysis of variance for repeated measures with "treatment" as between-subjects factor and "time" as within-subjects factor was performed for all variables, followed by Bonferroni adjustment for multiple comparisons. All statistical computations were performed using SPSS for Windows software, release 10.0.1. Results are presented as mean ± SD. Values of $P < 0.05$ were considered to indicate statistically significant differences.

RESULTS

No differences were found in either LV weight (GH: 110 ± 13 g and placebo: 103 ± 11 g; P = not significant) or LV weight/BSA ratio (GH: 112.4 ± 12.3 g/m^2 and placebo: 107.9 ± 10.8 g/m^2; P = not significant), suggesting absence of LV hypertrophy in GH-treated animals.

At 3 days after starting the treatment, GH animals showed an increase in BSA (0.89 ± 0.05 m^2) that was marginally significant (P = 0.058) with regard to placebo sheep (0.84 ± 0.05 m^2). This trend disappeared over time, with no differences in either total body weight or BSA being observed at the end of the study.

Infarct Size

Troponin-I levels did not differ between groups at 4 hours (GH: 8.14 ± 3.1 ng/mL and placebo: 10.5 ± 2.5 ng/mL; P = not significant) and 48 hours (GH: 64.5 ± 18 ng/mL and placebo: 71.1 ± 7.6 ng/mL; P = not significant) after AMI, suggesting homogeneity in the induction of experimental infarcts. Three and a half months after treatment onset, no differences in infarct size were observed (GH: 16.9% ± 3% of LV area and placebo: 16.5% ± 3.7%; P = not significant) (Fig. 1).

Wall thickness at the mid infarct zone was significantly higher in the GH group (10.1 ± 1.5 mm) than in the placebo group (6.6 ± 2 mm, $P < 0.01$) (Fig. 1). No differences in

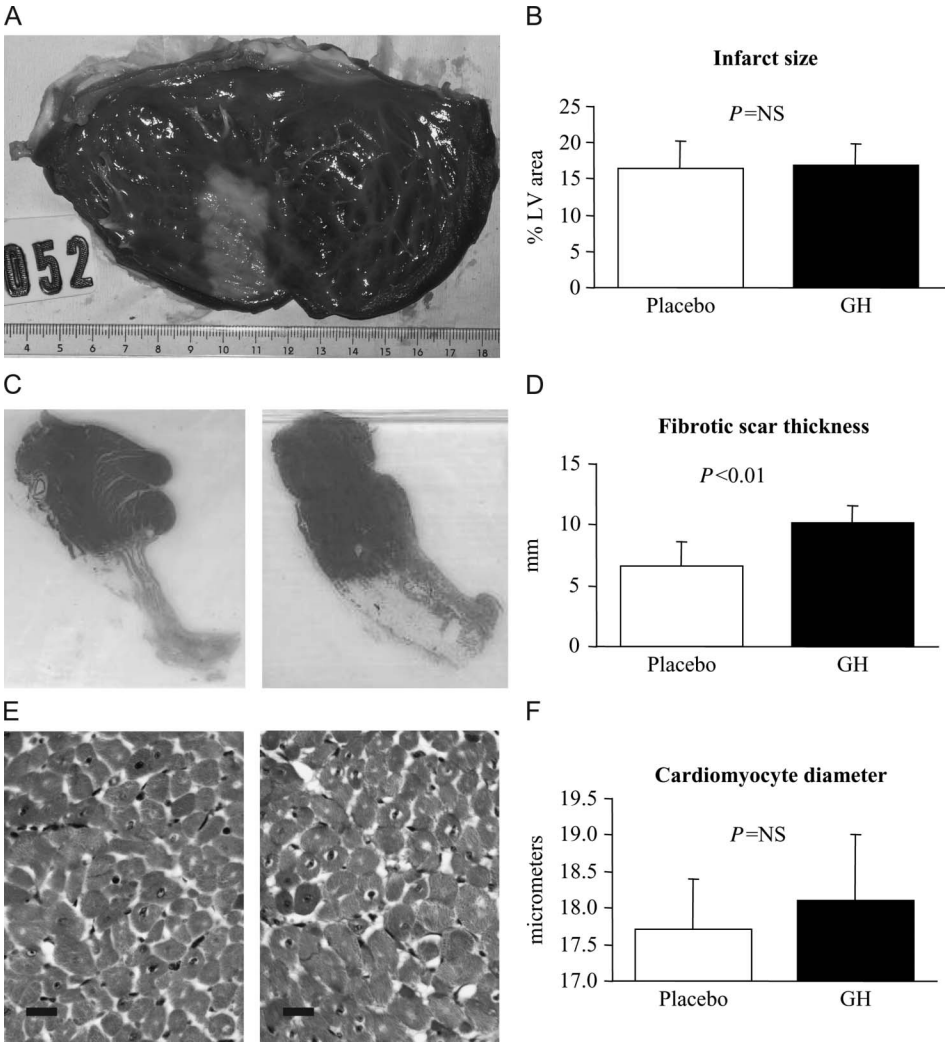

FIGURE 1. Morphometry. A, An example of the endocardial aspect of a LV extended flat before fixation. The pale area with well-defined borders is the infarct scar. The image corresponds to a GH-treated sheep. B, Infarct size. No intergroup differences were found in the size of the fibrotic scar 3.5 months after treatment onset. C, Examples of the infarct and the infarct border zone in placebo-treated (left) and GH-treated (right) sheep (Masson trichrome, magnification: ×4). The collagen scar was significantly thicker in the GH-treated group (D). E, myocardial tissue sections stained with Masson trichrome from a placebo-treated animal (left) and a GH-treated animal (right). Bars = 20 μm. F, Cardiomyocyte diameter. No intergroup differences in cardiomyocyte diameter were found at 3.5-month follow-up.

peri-infarct wall thickness were observed. Neither did cardiomyocyte diameter differ between groups (GH: 18.1 ± 0.9 μm and placebo: 17.7 ± 0.7 μm; P = not significant) (Fig. 1).

Left Ventricular Function

Table 1 lists the echocardiographic measures of LV systolic and diastolic performance. Three days after treatment onset, the GH group displayed higher values for LV fractional shortening (30.7% ± 3.5% vs. 24.8% ± 6.1%, $P < 0.03$), systolic anterior wall thickness (10.1 ± 0.8 vs. 8.6 ± 1.2 mm, $P < 0.02$), sW (8.2 ± 2.5 vs. 5.7 ± 1.2 cm/s, $P < 0.04$), and cardiac index (3.8 ± 0.6 $L{\cdot}min^{-1}{\cdot}m^{-2}$ vs. 2.8 ± 0.7 $L{\cdot}min^{-1}{\cdot}m^{-2}$; $P < 0.01$). However, these differences progressively disappeared in later echocardiograms (except for the isolated case of sW at 30 days). Both groups displayed sinus tachycardia during the echocardiogram recorded at 3 days after AMI, but heart rate did not differ between groups at any times. At the end of the follow-up, LVEDV and LVESV were marginally increased ($P = 0.06$) in GH-treated sheep. No intergroup differences were found in LV ejection fraction throughout the study. Table 2 shows the values for variables recorded by LV catheterization at the end of the study (LV peak systolic pressure, LV end diastolic pressure, dP/dt_{max} and dP/dt_{min}). No differences were observed.

Resting LV Perfusion

At 105 days after treatment, the perfusion defect did not differ between groups (SRS for GH group: 19.6 ± 4.2; summed rest score for placebo group: 18.4 ± 5.9; P = not significant).

Measurements of IGF-1

Figure 2 shows the time course of serum IGF-1 levels. Baseline presurgery serum IGF-I values were 68 ± 32.4 ng/mL in the GH group and 50.7 ± 27 ng/mL in the placebo group (P = not significant). One and 3 days after treatment onset, serum levels of IGF-1 were higher in the GH group (1 day: GH: 65.6 ± 20.1 and placebo: 34.7 ± 17.2 ng/mL; $P < 0.01$ and 3 days: 83.8 ± 25.4 ng/mL and placebo: 44.8 ± 22.2 ng/mL; $P < 0.01$). At later time points (30, 60, and 100 days), the significance of the differences disappeared due to a steeper IGF-1 increase in the placebo group than in the GH group. In effect, at 30 days, IGF-I was 92.9 ± 56.9 ng/mL in GH sheep and 70 ± 34 ng/mL in placebo animals (P = not significant); at 60 days, it was 92.8 ± 39.1 ng/mL (GH) and 81.6 ± 36.2 ng/mL (placebo) (P = not significant); and at 100 days, it was 105 ± 63.3 ng/mL (GH) and 86.1 ± 45.9 ng/mL (placebo) (P = not significant).

DISCUSSION

Most studies on the effects of GH on myocardial infarct size have been made on small rodents and have yielded controversial results. Moreover, LV function has not consistently been assessed, the follow-up time has been predominantly short, and in many cases, the doses used have been far higher than those usually applied in patients.

We therefore aimed to assess whether GH treatment in therapeutic doses would limit infarct size and exert long-term benefits on LV function in a large mammalian model of AMI. Our results show that in sheep with acute coronary artery occlusion, daily subcutaneous GH administration at doses

TABLE 1. Echocardiographic Measures of LV Performance

	Groups	Baseline	3 D	15 D	30 D	60 D	100 D	*P*
FS (%)	Placebo	39.1 ± 5.2	24.8 ± 6.1	33.5 ± 7.7	35 ± 5	38 ± 5.4	35.3 ± 7.3	*< 0.03
	GH	40.5 ± 5.6	30.7 ± 3.5*	32.4 ± 4.2	37.2 ± 8.3	35.8 ± 7.1	33.5 ± 5.4	
SAWTh (mm)	Placebo	12.8 ± 0.5	8.6 ± 1.2	10.6 ± 2.2	11.1 ± 1.6	11.7 ± 0.7	12.4 ± 0.9	*< 0.02
	GH	12.9 ± 0.9	10.1 ± 0.8*	9.1 ± 1.6	11.4 ± 2	11.9 ± 1.6	11.8 ± 1.5	
DAWTh (mm)	Placebo	8.8 ± 1.1	7.8 ± 1	7.2 ± 1.1	7.6 ± 1	8.2 ± 0.5	8.3 ± 1.2	—
	GH	8.6 ± 1	8.8 ± 0.9	6.5 ± 1	8 ± 1.2	8.3 ± 10	8.2 ± 1.1	
ESV (mL)	Placebo	25.4 ± 6.2	27.3 ± 9.8	34.7 ± 6.6	35.3 ± 7.6	36.5 ± 6.5	33.1 ± 8.3	*= 0.06
	GH	28.2 ± 9.2	32 ± 11.3	40.7 ± 8.9	40.9 ± 11.3	39.5 ± 13.4	45.4 ± 14.4*	
EDV (mL)	Placebo	56.1 ± 5.2	44.5 ± 10	62 ± 11	71.2 ± 9.3	72.8 ± 9	63.9 ± 12.9	*= 0.06
	GH	56.4 ± 8.7	53.9 ± 15	68.8 ± 15.2	75.7 ± 18.8	68 ± 14.9	78.2 ± 14.6*	
sW (cm/s)	Placebo	9.1 ± 1.1	5.7 ± 1.2	6.2 ± 1.4	6.5 ± 1	8.4 ± 1.5	7.2 ± 1.7	*< 0.04
	GH	10 ± 1.1	8.2 ± 2.5*	8 ± 3.7	8.7 ± 2.3*	8.8 ± 2.7	7.8 ± 1.5	
E/A	Placebo	1.6 ± 0.5	0.67 ± 0.25	0.87 ± 0.14	0.90 ± 0.26	0.81 ± 0.12	0.64 ± 0.08	—
	GH	1.52 ± 0.31	0.62 ± 0.22	0.84 ± 0.22	0.76 ± 0.16	0.81 ± 0.19	0.68 ± 0.11	
IVRT (ms)	Placebo	75 ± 11.9	75.3 ± 11.3	68.1 ± 11.9	70.6 ± 6.8	73.8 ± 6.9	88.8 ± 9.9	—
	GH	67.5 ± 4.6	65.8 ± 8.8	64.4 ± 9.4	73.8 ± 6.4	74.4 ± 10.2	85.9 ± 7.3	
CI ($L{\cdot}min^{-1}{\cdot}m^{-2}$)	Placebo	2.5 ± 0.5	2.8 ± 0.7	3.5 ± 0.8	4.5 ± 1.4	4.3 ± 1.2	3.6 ± 1.3	*< 0.01
	GH	2.3 ± 0.7	3.8 ± 0.6*	3.9 ± 1.5	4.3 ± 1.3	3.8 ± 0.9	4 ± 1	
EF (%)	Placebo	55 ± 8.1	39.9 ± 11	43.6 ± 7.2	50.3 ± 10	50.1 ± 6.2	48.2 ± 8.3	—
	GH	50.7 ± 8.9	41.4 ± 7.4	40.3 ± 10	46.1 ± 5.9	43.4 ±11.3	43 ± 11.5	

The P values refer to differences between groups.

CI, cardiac index; DAWTh, diastolic anterior wall thickness; E/A, E wave to A wave ratio; EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; FS, fractional shortening; IVRT, isovolumic relaxation time; SAWTh, systolic anterior wall thickness; sW, s wave of the tissue Doppler.

TABLE 2. Measures of Cardiac Performance Obtained by Left Ventricular Catheterization At 3.5-Month Follow-up

	Placebo Group	GH Group
LVPSP (mm Hg)	126 ± 12.5	126.6 ± 12.9
LVEDP (mm Hg)	8.9 ± 7.1	8 ± 4.4
dP/dt_{max} (mm Hg/s)	2326.1 ± 978.8	2312.4 ± 456.6
dP/dt_{min} (mm Hg/s)	–2929.8 ± 943	–2432.2 ± 527.6
HR (beats/min)	124.4 ± 36.6	126.7 ± 18.7

No significant intergroup differences were found for any variable.

LVEDP, LV end diastolic pressure; LVPSP, LV peak systolic pressure; dP/dt_{max}, maximum rate of LV pressure increase; dP/dt_{min}, maximum rate of LV pressure decay; HR, heart rate.

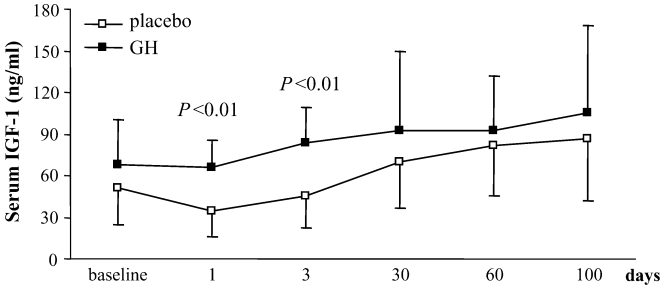

FIGURE 2. Serum levels of IGF-1 in GH-treated and placebo-treated sheep. The significant intergroup differences observed at 1- and 3-day follow-up disappear at later time points due to a steeper increase in the placebo group.

usually used in the clinical setting does not reduce infarct area at 3.5 months of treatment onset.

With regard to cardiac function, GH-treated animals displayed an early, yet transient, improvement of regional LV mechanics and cardiac index. This evolution of function parameters paralleled that of serum IGF-1 levels, which differed significantly during the first week but not later, suggesting a direct effect of GH on myocardial inotropic state.

Direct effects of GH on the contractile reserve and intracellular calcium transient of cardiomyocytes have been shown by Tajima et al[21] in rats with postinfarction heart failure. Cittadini et al[22] showed in aequorine-loaded rat whole hearts and ferret papillary muscles that the positive inotropic effects of IGF-1 were not associated with increased intracellular Ca^{2+} availability to the contractile machinery but to a significant increase of myofilament Ca^{2+} sensitivity. Similar positive inotropic effects of IGF-1 in normal and failing canine cardiomyocytes but through the opposite mechanism (increased Ca^{2+} availability with no change in myofilament Ca^{2+} sensitivity) was reported by Kinugawa et al.[23] Further evidence of positive inotropic effects of IGF-1 mediated by increased intracellular Ca^{2+} concentration was provided by Freestone et al[24] in isolated rat cardiac myocytes and von Lewinski et al[25] in human cardiomyocytes from patients with end-stage heart failure. IGF-1 may have also improved diastolic function by increasing the expression of the sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase (SERCA2a), and hence Ca^{2+} reuptake, as shown in senescent rats[26] and bioengineered heart muscle.[27] Alternatively (or concomitantly), GH may have decreased peripheral vascular resistance, as reported for rats with postinfarct chronic LV failure.[28–30] We cannot assert if this was the case for our sheep because pressures were recorded at the end of the study, when neither LV function nor IGF-1 levels differed between groups. A tendency for higher LVEDV and LVESV in GH-treated sheep was observed at the final echocardiogram. To determine if this could represent an early stage of ventricular remodeling induced by GH would require longer follow-up times.

With regard to morphological changes, the only intergroup difference observed at the end of the study was a significantly higher thickness of the fibrotic scar in GH-treated sheep, a feature consistent with the known effect of GH on collagen deposition.[31,32] A similar result was obtained by Mitsi et al[33] in pigs with ischemia–reperfusion injury, in which a single high-dose intracoronary GH injection was made at the time of reperfusion. However, in their pigs, the increased thickness of the scar was accompanied by increased thickness of the nonischemic walls, a feature that was not observed in our sheep. A protective role of GH on postinfarction scars has been reported by Castagnino et al[34] in rats at 25 days after coronary ligation. This consisted of preservation of the collagen network with reduced aneurysm formation. Contrastingly, Bollano et al[35] did not observe differences in aneurysm formation using a 10-fold higher dose of GH. In our sheep, no aneurysms were seen in either group, probably because of the relatively small size of the infarcts. In any case, the higher thickness of the scar was not associated with any differences in LV function between GH- and placebo-treated animals in the long-term.

The small size of the infarcts may in part explain the lack of long-term effects of GH on LV function. It has been reported that the extent of remodeling and hence the chances of evolving toward contractile failure are largely dependent on infarct size.[2] Small infarcts do not lead to substantial remodeling, whereas large ones do.[36] In effect, in most of the studies in which GH treatment attenuated postinfarction LV failure, infarct size ranged from 24% to about 50% of the LV mass.[11,16,21,37,38]

Another reason could be the dose used. Most of the animal studies reporting GH-induced cardioprotection have used doses that are 10- to 40-fold higher than ours.[14,17,29] We aimed to assess if GH was effective in the long-term at doses that could be safely applied in patients. In most human studies of GH replacement, the dose used has ranged from about 0.01 to 0.1 $mg \cdot kg^{-1} \cdot d^{-1}$. We administered 8 IU/d (approximately 0.08 mg/kg), which is within the range and closer to the higher limit. However, it must be acknowledged that our results are only associated to the dose used in the present study, and if doses closer to 1 mg/kg had been applied, long-lasting high serum IGF-1 levels would have been attained, as shown by Matthews et al[17] in sheep. This, in turn, would have probably maintained the improved LV function over a longer time.

As in most other reports, we initiated the treatment at the time of coronary occlusion. Although this approach increases the chances for GH to act on early phenomena associated with myocardial ischemia, it does not reproduce the clinical setting,

in which patients with evolving AMI are usually admitted at later times.

Finally, GH has been found to induce angiogenesis in rats with postinfarct heart failure.[39] We did not assess for microvascular density in our sheep but proved that GH did not modify myocardial perfusion, as indicated by similar scores of ischemic burden at 3.5 months after treatment onset.

CONCLUSIONS

In a large mammalian model of AMI, daily administration of GH in therapeutic doses induced an early, though transient, improvement in LV function associated with significantly higher serum IGF-1 levels. However, it did neither reduce infarct size nor improve LV function in the long-term. These results may suggest the usefulness of therapeutic doses of GH at the early phases of AMI but do not support maintaining the treatment for longer time.

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