In this issue of Circulation, Tajima et al report that recombinant human growth hormone (GH) (3.5 mg · kg⁻¹ · d⁻¹) given for 2 weeks, while not affecting baseline function, restored myocardial contractile reserve in cardiomyocytes isolated from rats 4 to 6 weeks after myocardial infarction (MI) compared with vehicle-treated post-MI rats. In addition, the peak of the Ca²⁺ transient, which was normal at baseline in both GH- and vehicle-treated rats, was depressed in response to increased external Ca²⁺ (3.5 mm/L) in vehicle-treated rats, whereas in the GH-treated group, increased Ca²⁺ restored the peak at the Ca²⁺ transient, as well as cardiomyocyte contractile function. Also, in the GH-treated post-MI hearts, mRNA and protein levels of sarcoplasmic reticulum Ca²⁺ ATPase 2 (SERCA-2) were increased, which lends support to the proposed mechanism for restoration of contractile reserve, because only a small increase in the expression of SERCA-2 protein was reported to enhance myocardial contractility in transgenic mice. The authors indicate that cardiomyocytes were used to obviate effects of altered loading on the heart by the vasodilator actions of GH, and the dose of GH used was said to be sufficiently low to avoid myocardial hypertrophy. This study is the first to analyze the effects of GH in cardiomyocytes from postinfarction rats and provides convincing data concerning a beneficial effect of GH on contractile reserve. It also begins to shed light on mechanisms involved in the effects of GH on myocardial function. However, some of the findings in this study raise questions about GH effects under differing study conditions.

See p 127

In recent years, interest in studying GH as a possible adjunctive treatment for severe heart failure has emerged as a result of a number of observations, including clinical studies showing marked improvements in cardiac function and structure with GH treatment for severe heart failure resulting from GH deficiency, depressed nocturnal GH secretion with low levels of insulin-like growth factor-1 (IGF-1) in patients with severe heart failure, improved cardiac and skeletal muscle mass and function with GH treatment in individuals with chronic GH deficiency without heart failure, and a number of studies in laboratory animals showing that GH and IGF-1 can have beneficial effects on systemic vascular resistance, left ventricular function, and cardiac growth in animal models of heart failure, as cited by the authors. Thus, the study by Tajima et al is relevant and timely.

Two aspects in particular of the study by Tajima et al deserve further discussion: (1) comparison of the findings in normal (sham-operated) hearts with those of other studies and (2) whether the present findings are relevant to the setting of cardiac failure.

GH and the Normal Heart

Tajima et al report no myocardial effects of GH in the sham-operated rats. Thus, in vivo hemodynamic studies, including left ventricular (LV) peak positive dP/dt as well as body weight and LV weight, showed no significant changes; also, cardiomyocyte shortening extent and the velocities of shortening and relaxation, as well as the Ca²⁺ transients, were unaffected by long-term GH treatment of the sham-operated rats.

Previous in vitro studies are generally in agreement with these findings. For instance, experiments in cultured neonatal cardiomyocytes showed no effect of acutely administered GH on protein synthesis, although IGF-1 stimulated it. Strömmer et al gave normal rats GH for 4 weeks (3.5 mg · kg⁻¹ · d⁻¹; twice-daily dosing) and then studied isovolumetric contraction of the isolated hearts. The relation between LV diastolic volume and LV systolic pressure was shifted upward by GH (and IGF-1) compared with untreated control hearts, and LV peak positive dP/dt/developed pressure was slightly increased at baseline; however, the relation between LV diastolic volume and LV systolic wall stress was unchanged by GH, which suggests that GH had no effect on baseline contractility and that the effect on systolic pressure was due to LV hypertrophy. Ca²⁺ transients were unaffected by GH treatment, but the maximal contractile response to high external Ca²⁺ was increased by GH treatment. Cittadini et al also recently reported no effect of acutely administered GH on the function of isolated ferret papillary muscles and isolated dog hearts.

On the other hand, GH (and IGF-1) given in vivo have been shown to produce increased LV function and mass by echocardiography in normal rats treated for 2 weeks, which persisted at 4 weeks of treatment, accompanied by increased peak positive LV dp/dt, enhanced LV performance by echocardiography, and augmented LV and body weights. These findings with GH differ from the in vivo measurements of Tajima et al in sham-operated rats, in which 2 weeks of GH treatment produced no significant hemodynamic changes. Tajima et al argue that their studies were free from effects of...
hypertrophy due to the dose of GH used, yet the same dose (3.5 mg·kg$^{-1}$·d$^{-1}$) was given in the study by Cittadini et al.$^{10}$ Despite this discrepancy between studies performed in vivo, the absence of direct effects of GH in vitro in normal adult rat cardiomyocytes,$^{1}$ neonatal cardiomyocytes in tissue culture,$^{2}$ and isolated perfused normal rat$^{6}$ and dog$^{7}$ hearts, together with the pronounced effects of GH and IGF-1 on cardiac function in the normal rat heart in vivo in 1 of the above studies$^{10}$ and in normal human subjects$^{11}$ (as well as in heart failure in vivo, as discussed below), may lend credence to the possibility that in vivo actions of GH on the heart are mediated at least in part by IGF-1, as observed in other organs and tissues.$^{11,12}$ Clearly, the responses to GH, or lack thereof, in normal myocardium exhibit some variability depending on the preparation (isolated cells, isolated muscle, isolated heart), type of GH administration (acute versus chronic), duration of treatment, serum GH and IGF-1 levels, and the presence or absence of cardiac hypertrophy.

**GH and the Failing Heart**

An attempt to generalize the findings of Tajima et al$^{1}$ to disease conditions should include a discussion of the lack of convincing evidence for heart failure in their postinfarction rats under basal, untreated conditions either in vivo or in vitro. Catheterization of the whole heart in untreated rats with MI at the end of the study (by use of a needle inserted into the LV with a short catheter and conventional strain gage) showed no differences in peak LV pressure or peak positive and negative LV dP/dt compared with sham-operated rats, although LV end-diastolic pressure was higher (12 mm Hg) in the MI group. Also, isolated myocytes from the untreated post-MI hearts showed no significant depression of the extent of cell shortening or the rate of cell shortening and lengthening compared with cardiomyocytes from sham-operated control rats. Baseline SERCA-2 mRNA and protein levels were not decreased in the MI rats, as is sometimes seen in failing hearts. It is possible that the lack of evidence for LV and myocardial failure in the post-MI rats relates to the relatively small average myocardial infarct size (29%) reported by Tajima et al.$^{1}$ The possibility exists that the findings would be the same in cardiomyocytes from postinfarction hearts that do have clear-cut evidence of heart failure, but additional studies will be needed to settle this issue.

Tajima et al report no significant effects of GH treatment on LV function in vivo in the post-MI rats compared with the vehicle-treated MI group; thus, LV peak positive and negative dP/dt, LV systolic pressure, LV end-diastolic pressure, and body and LV weights were not significantly affected by GH.$^{1}$ In addition, cardiomyocytes from GH-treated post-MI rats showed no significant differences in baseline myocyte function or baseline Ca$^{2+}$ transients compared with those in vehicle-treated MI rats. This study is the first to provide such information on cardiomyocytes in the post-MI setting, but the accompanying in vivo findings differ from other observations in the whole heart. In other studies in rats with heart failure treated with GH early$^{13}$ and late$^{14}$ after MI, GH (2.5 to 3.0 mg · kg$^{-1}$ · d$^{-1}$ for 2 or 3 weeks) has been reported to increase LV function and contractility (peak positive dP/dt of the LV) and to augment LV weight and body weight compared with untreated rats with MI. Such effects were also seen in rats given GH alone for 2 weeks after a period of chronic treatment with losartan to produce initial cardiac remodeling$^{15}$; in that study, vasodilation with altered systolic loading, increased wall thickness, enhanced LV contractility, and elevated cardiac filling pressure all appeared to contribute to improved LV function with GH administration in the failing heart late after MI. However, none of these in vivo studies in the rat MI model has examined the effects of GH on contractile reserve in the postinfarction setting, as in the cardiomyocytes studied by Tajima et al.$^{1}$

Several factors might be involved in the findings by Tajima et al that indicated a lack of any effect of GH on baseline myocardial contractility and function in vitro and in vivo in post-MI rats. Isolated myocytes are not subject to altered loading or changed neurohumoral conditions, which could indirectly influence LV function in vivo in both normal and postinfarction conditions, and cardiomyocyte function might provide a better assessment of myocardial contractility and function than in vivo studies, although if this were the case, such indirect effects should have been observed in the in vivo studies of Tajima et al. A dosing effect seems possible, because it was not reported whether the GH was given in divided doses daily (as in most previous studies) or whether plasma GH and IGF-1 levels were elevated.$^{1}$ Finally, the in vivo responses to GH observed by others showing increased LV peak positive dP/dt and LV function as well as augmented LV weight could be due to responses of the failing heart to GH that are different from those in post-MI hearts without evident heart failure.

Whether or not GH will prove useful as an adjunctive agent in the treatment of human heart failure remains uncertain. In the preliminary study by Fazio et al$^{16}$ in patients with idiopathic dilated cardiomyopathy who were receiving low-dose ACE inhibition, cardiac responses were examined before, during, and after 3 months of GH treatment (but not in a randomized control group), and beneficial cardiac actions of GH were observed, including improved LV function and increased LV mass. However, a more recent randomized, blinded study$^{17}$ in older patients with idiopathic dilated cardiomyopathy who were receiving high-dose ACE inhibition showed no benefit of GH treatment for 3 months. Therefore, many questions remain to be answered, not only about the level of ACE inhibition, but also about safety, duration of treatment, dose of GH, and type of cardiac disease in which GH might be effective, because most experimental studies have been in a post-MI rather than a cardiomyopathic setting. In this connection, ongoing studies in cardiomyopathic hamsters with late, end-stage heart failure indicate that GH has reduced effects on the LV compared with those in younger hamsters.$^{18}$ and preliminary studies suggest that GH given in combination with high-dose ACE inhibition in the late phase may not be effective in improving cardiac function. In addition to these factors, if additional clinical trials of GH in heart failure are performed, the potential for resistance to exogenous GH should be considered, along with a number of other features found to be important in the response to treatment of GH-deficient patients, including age, sex, body mass index, and GH binding protein level.$^{19}$ The mechanisms
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References


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