Chronic congestive heart failure is a syndrome with a poor prognosis. Currently, the only therapy providing the possibility of long term survival is heart transplantation. Therefore, new therapeutic strategies continue to be investigated. One such new approach may be the application of recombinant human insulin-like growth factor (IGF)-I. IGF-1 has both acute and long term cardiovascular effects. Acute administration of IGF-1 resulted in a reduction in afterload and positive inotropic effects in patients with heart failure. In vitro and animal studies have demonstrated that IGF-1 can stimulate myofibril formation. In addition, IGF-1 administration has beneficial metabolic effects. The benefits of prolonged IGF-1 therapy have yet to be investigated.

1. Long Term Cardiac Effects

In vitro, IGF-I induces hypertrophy of cultured neonatal rat cardiac cells by inducing the synthesis of cardio-specific proteins. In cultured adult rat cardiomyocytes, IGF-I, but not GH, increases the expression of contractile elements (myofibrils). In vivo, IGF-I selectively stimulates heart but not skeletal muscle growth in rats, whereas GH stimulates both. Moreover, IGF-I stimulates major components (such as β-myosin heavy chain) of the myofibrils in rat heart.

Although early coronary artery reperfusion of the ischaemic myocardium is a desired therapeutic goal, reperfusion itself may contribute to additional myocardial cell injury (i.e. reperfusion injury). A key factor for this phenomenon includes programmed cell death (apoptosis) of cardiac myocytes. IGF-I has been shown to inhibit apoptosis both in vitro and in vivo. Buerke et al. showed that IGF-I limited myocardial reperfusion injury in rats, possibly by the inhibition of apoptosis and of leucocyte-induced cardiac necrosis. Further investigations have demonstrated a cardioprotective effect of IGF-I in doxorubicin-treated rats and improved myocardial function in rats after myocardial infarction.
2. Acute Cardiovascular Effects

IGF-I increases contractility of cultured neonatal rat cardiomyocytes,[22] and has positive inotropic effects on the isolated rat heart.[23,24] The limited data available on the acute cardiovascular effects of IGF-I in humans show that IGF-I has vasodilatory effects.[25-27] Furthermore, Russell-Jones et al.[28] have demonstrated that an intravenous infusion of IGF-I increases the cardiac output and stroke volume in healthy volunteers, as assessed by impedance cardiography.

We have investigated the systemic cardiovascular effects of IGF-I at rest and during exercise in 8 healthy adults.[29] Individuals were randomised to receive recombinant human IGF-I 60 μg/kg or saline subcutaneously in a crossover, double-blind trial, with an interval of 6 days between the 2 injections. Cardiac function and performance were evaluated by echocardiography and exercise tests. IGF-I treatment improved cardiac performance, with a 14% increase in stroke volume and an 18% increase in cardiac output compared with untreated controls. Left ventricular ejection fraction increased by 9% following IGF-I administration (68 vs 62%). Left ventricular diastolic function was not affected by IGF-I compared with controls. Exercise was uneventful, with no pathological changes observed on electrocardiogram. No changes in heart rate or blood pressure were found during rest or exercise. Neither maximal exercise duration nor peak oxygen consumption were influenced by IGF-I treatment.

The acute haemodynamic effects of IGF-I were then evaluated in patients with CHF New York Heart Association Stage II and III.[30] Eight patients were randomised to receive recombinant human IGF-I 60 μg/kg or placebo intravenously over 4 hours in a crossover, double-blind study on 2 consecutive days. Using heart catheterisation, IGF-I treatment was shown to increase cardiac index and stroke volume index, and to decrease systemic vascular resistance, right atrial pressure and pulmonary artery wedged pressure. Mean systemic and pulmonary artery pressure, as well as heart rate and pulmonary vascular resistance were not significantly influenced by IGF-I. Urinary levels of norepinephrine (norepinephrine) decreased significantly during IGF-I infusion, which may indicate a beneficial effect of IGF-I on neurohumoral activation in patients with CHF. IGF-I was well tolerated in all patients, and no pathological electrocardiogram changes were recorded during treatment.

The increase in cardiac output following IGF-I treatment could be caused by a direct cardiac effect or it could reflect peripheral vasodilatation. In the absence of direct measurements of myocardial inotropy, it is not possible to differentiate between these 2 mechanisms.

3. Growth Hormone or Insulin-Like Growth Factor I?

IGF-I mediates many of the effects of pituitary GH.[31,32] The relationship between GH and the cardiovascular system has been extensively investigated. Patients with acromegaly have an increased incidence of cardiovascular disease.[33,34] On the other hand, individuals with GH deficiency tend to exhibit impaired cardiac performance.[35-37] Beneficial effects of GH in the treatment of idiopathic dilated cardiomyopathy[38] and of ischaemic cardiomyopathy have been reported.[39] Part of these GH-induced cardiovascular effects may be promoted by GH stimulation of circulating IGF-I levels and/or of locally produced IGF-I in the heart.[40-42] In line with this explanation, we[4] did not observe direct GH effects on cultured cardiomyocytes and nor did other investigators.[3] On the other hand, IGF-I induces cardiomyocyte hypertrophy and myofibril development in vitro[2-4] and in vivo.[6,7] Nevertheless, sequelae of GH excess such as hypertension, hyperinsulinaemia, insulin resistance and hyperlipidaemia[43-46] are not mediated by GH-induced IGF-I. On the contrary, IGF-I administration diminishes GH secretion, and lowers plasma levels of insulin, very low density lipoprotein (VLDL) and low density lipoprotein (LDL) cholesterol, and increases insulin sensitivity,[47-51] thereby reducing risk factors of cardiovascular disease.