lar, there was a significant correlation between therapy-induced variations in dipyridamole time (i.e. the time from onset of exercise to 0.1 mV of ST segment depression) in the 38 patients with positivity of both tests off treatment[5]. Recently, these findings have been reproduced using beta-blocker therapy alone. Ferrara et al[6] have also documented that the anti-ischaemic effect of beta-blockade is largely independent of the effect on heart rate and is probably linked to a direct 'anti-steal' effect of beta-blockade.

These data should be contrasted with those obtained with dobutamine stress. Beta-blocker therapy reduces the sensitivity of dobutamine stress echocardiography[7] much less than dobutamine stress perfusion. However, this does not reflect a physiological anti-ischaemic action of beta-blockade, but rather a rightward shift in receptor stimulation. As shown by Fioretti et al., atropine coadministration restores an acceptable sensitivity of dobutamine stress[8]. The present paper by Dodi et al. moves along this line, providing useful information to the clinical cardiologist. In contrast to what happens with dipyridamole stress, calcium antagonists and nitrates do not significantly lower the sensitivity of dobutamine-atropine, and mild changes induced by these drugs are not mirrored by changes in exercise testing.

**Conclusion**

For exercise-independent assessment of therapy efficacy, data support the use of dipyridamole rather than dobutamine stress echocardiography.

For primary diagnosis of coronary artery disease, dobutamine sensitivity is less affected by medical therapy than dipyridamole stress echocardiography. No test is 'exercise simulating', although fancy marketing definitions are frequently and inappropriately bandied about in scientific debates.

**References**


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**Growth hormone in the treatment of heart failure: a new tool for the future?**

See page 340 for the article to which this Editorial refers

Severe impairment of left ventricular pump function leads to the clinical syndrome of heart failure. Initial myocardial damage induces a process of remodelling, which is a combination of dilatation and compensatory, but mainly inadequate, hypertrophy of the left ventricle. Dilatation of the cardiac cavity increases wall stress, which accelerates cardiac remodelling in a vicious circle of cardiovascular deterioration[11]. Until recently, clinicians approached heart failure as a disturbance of haemodynamic regulation. Reduction of preload (diuretics, nitrates, ACE inhibitors) and afterload (ACE inhibitors, hydralazine) would reduce wall stress and thereby prevent further progression of cardiac dysfunction.

Since the 1980s, many details on the role of the neurohumoral system and on the pathophysiology of heart failure have been revealed. Neurohumoral...
Progress in molecular biology established greater understanding of the mechanisms and substrates of heart failure, related to the above regulatory systems. Hypertrophy, apoptosis (programmed cell death without signs of inflammation) and changes in intracellular calcium and energy handling, affecting excitation-contraction coupling, were observed in myocytes. Furthermore, functional changes in the sympathetic nerve system, such as attenuation of the efficacy of the cardiac β1-adrenoceptor/second messenger cAMP complex, have been described. In addition, non-myocyte adaptations, such as increased fibroblastic activity with production of large quantities of collagen and loss of capillary density, contribute to the changes in myocardial architecture in the pathogenesis of cardiac failure. Various cell growth modulating factors, such as angiotensin II, aldosterone, catecholamines, endothelin and many cytokines appear to play a key role in the translation of increased cardiac wall stress into this inadequate cardiac adaptation. In addition to haemodynamic and neurohumoral factors, the role of growth hormone in the maintenance of normal cardiac function has long been a matter of speculation, after the description of abnormal cardiac function both in states of growth hormone excess (acromegaly) and growth hormone deficiency. In acromegaly, various cardiovascular diseases are highly prevalent and in untreated acromegals account for the major share of increased mortality. Several clinical and pathological cardiovascular features have been described as associated with this disease, such as an enormous increase in cardiac mass (hearts sized up to 1400 g have been reported), arterial hypertension, coronary artery disease, ventricular arrhythmias and congestive heart failure. In growth hormone deficiency, impairments vary from marginally reduced exercise tolerance to severely diluted cardiomyopathy, with reduced ventricular mass and impairment of systolic function.

Studies on the role of growth hormone in the modulation of cardiac structure and function have followed the availability of recombinant human growth hormone and in the present issue Fazio et al. demonstrate a direct relationship between the level of growth hormone and left ventricle wall thickness in humans, thereby emphasizing the role of growth hormone in maintenance of myocardial structure. Earlier this year the same group reported an increase in myocardial mass and a reduction in the size of left ventricular chamber dimensions, thereby decreasing left ventricular wall stress, after treatment with growth hormone in normopituitaric patients with idiopathic dilated cardiomyopathy. These changes were associated with improvements in haemodynamics, myocardial energy metabolism and clinical status. The limitations of this study were the small number (seven) of treated patients, who had all idiopathic dilated cardiomyopathy, and the duration of treatment of not more than 3 months.

In order to understand the potential therapeutic value of growth hormone in heart failure, an introduction to its complex regulatory system is mandatory. Growth hormone is excreted by cells in the anterior pituitary in response to hypothalamus-derived growth hormone releasing hormone. The peripheral action of growth hormone is dependent on the plasma level of growth hormone, circulating growth hormone binding proteins, the activity of its receptors on cell membranes and the intracellular processing of the signal derived from it. Growth hormone exerts its effects via its receptor, present on all cell types, as well as through the production of insulin-like growth factor I. Insulin-like growth factor I mediates many of the somatotropic effects of growth hormone, such as stimulation of growth and development of bones, organs and muscle in youth, and maintenance of muscle mass and strength in later life. Most circulating insulin-like growth factor I is produced by the liver, but peripheral tissues are also capable of synthesizing additional insulin-like growth factor I, presumably in circumstances of urgent local needs. As yet, two distinct insulin-like growth factor I receptors have been described.

Six different insulin-like growth factor I binding proteins have been identified which modulate the effects of insulin-like growth factor I. Insulin-like growth factor binding protein-3 serves as a carrier of insulin-like growth factor I in plasma and provides some buffer capacity to the system. Insulin-like growth factor binding protein-2 acts as a shuttle between plasma and tissues, while other insulin-like growth factor binding proteins predominantly act as high affinity binding proteins in extracellular fluids. More than 95% of insulin-like growth factor I is bound in heterodimer/trimer complexes with one of the six insulin-like growth factor binding proteins, but only free insulin-like growth factor I is biologically active. Local synthesis, excretion and degradation of insulin-like growth factor binding proteins regulates free, active insulin-like growth factor I.
concentrations at tissue level. Through these combined actions of various elements of the growth hormone/insulin-like growth factor I axis at endocrine, paracrine and autocrine levels the anabolic drive is continuously tailored to both systemic and local demands. Cardiac areas with increased wall stress show a higher expression of growth hormone and insulin-like growth factor I receptors, allowing for locally adjusted higher somatotrophic activity at the same systemic growth hormone concentration. This observation provides a rationale for the involvement of growth hormone in the maintenance of mass and constant remodelling of tissues throughout the body. Failure of the system to adjust properly, both in growth hormone deficiency and in growth hormone excess, leads to unwarranted adaptations of architecture and function.

Growth hormone is physiologically excreted in pulses. Disturbance of this pattern, due to stable high levels, as occurs in acromegaly, interferes with normal growth hormone receptor expression in central and peripheral tissues, increases hepatic insulin-like growth factor I production, rearranges insulin-like growth factor binding protein expression in peripheral tissues and possibly also effects tissue-specific insulin-like growth factor binding protein proteases. The resulting disturbed balance in the somatotropic system at tissue level may induce abnormal remodelling of the organ. In this respect, exogenously administered growth hormone causes, despite normal mean levels of growth hormone in plasma, a similar effect. In the case of primary growth hormone deficiency this is a matter of little concern, as increased survival and quality of life, in particular as a result of improved cardiac function, are undisputed. But the administration of growth hormone to compensate for the physiological decline in growth hormone concentration with ageing, called the somatopause, has to be treated with caution because of the aforementioned disturbances of normal physiology.

In the treatment of type 1 diabetes mellitus by subcutaneous injections of insulin, a similar situation is observed. This therapy has had an enormous impact on survival and quality of life, but does not completely restore normal glucose metabolism. Apart from delivery of the insulin at the wrong site, i.e. not in the portal circulation, insulin is physiologically excreted in regular discrete small pulses, tailored to needs in response to plasma glucose concentrations. As yet, this cannot be mimicked by current administration techniques. Therefore, the disease is still associated with multiple long-term complications and reduced life expectancy.

Intervention in subjects with normal somatotropic function is disputable on similar grounds. The decline in many endocrine systems that occurs in the course of life may also be protective in some respects. There is a longstanding unease about the effect of exogenous growth hormone on the development of malignant tumours, as these may also respond to growth hormone. Added to this, and in line with the above, there is also concern about the long-term effects of exogenously administered growth hormone on normal tissue organisation. In the heart, this might be counterproductive since the positive effects, such as the increase in cardiomyocyte mass, may be outweighed by a simultaneous overgrowth of interstitial fibrous tissue, proliferative wall thickening of intramural vessels and inadequate remodelling leading to disarray of hypertrophied myocardial fibres, as has been shown in individuals with longstanding acromegaly.

In conclusion, the preliminary results in patients with heart failure on the relationship between cardiac wall stress and growth hormone plasma levels and the effects of growth hormone on myocardial levels by the group of Fazio et al. are interesting. These results are consistent with previous animal studies on experimental heart failure, which have proven that growth hormone can improve cardiac function. Some experimental findings even suggest that the hypertrophic response is not accompanied by fibrosis or loss of capillary density. However, nothing is known about the possible harmful effects of chronic administration of growth hormone in normopituitary subjects. Prospective studies of longer duration on the value of growth hormone treatment in patients with severe heart failure, particularly in those with normal growth hormone level, are needed before this can be instituted in general practice. Theoretically, those who need a limited period of treatment would most likely strike a positive balance between short-term effects and long-term complications. Patients waiting for heart transplantation, victims of acute myocarditis during the convalescence period and patients that cannot be weaned from mechanical ventilators as result of concomitant heart failure, would fit this description.

Finally, one should keep in mind that malnutrition and malabsorption may render growth hormone treatment ineffective in congestive heart failure. In addition to the effect of hepatic stasis on hepatocyte metabolism, protein malnutrition in particular has been shown to interfere with the coupling of growth hormone to insulin-like growth factor I production, providing a glimpse of the molecular basis for the effects of congestive heart failure on the organism as a whole, with the possibility of leading to cardiac cachexia. The nutrition of these groups of patients needs greater attention; its effectiveness may
be as helpful as drug treatment and help reduce the costs of such therapy.

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Future of paediatric cardiology and its patients

See page 198 for the article to which this Editorial refers

The paper by Dr Jane Somerville, based on an invited lecture to the First World Congress of Paediatric Cardiology and Cardiac Surgery, makes some very interesting and thought provoking points. The future of paediatric cardiology and its patients can be looked at from several viewpoints which include the views of a fetal cardiologist, a paediatric cardiologist, a paediatric cardiac surgeon, a cardiologist dealing with adolescents with congenital heart disease or an adult cardiologist. Each one of these will see the future in a different light and so it would not be surprising if there were disagreements with Dr Somerville’s views.

Dr Somerville deals with multiple aspects of the service of paediatric cardiology, but she takes too pessimistic a view of its future. She implies that our small specialty is shrinking and will have to make strenuous efforts to survive by taking over other areas of practice, such as fetal cardiology and adolescent congenital heart disease. The opposing view would be offered by several paediatric cardiologists in the U.K. that the main problem at present is an increasing workload.

We strongly support the view that the specialty dealing with adolescents and adults with congenital heart disease needs to be recognised in its own right. It is important that these patients are not passed around to a completely different adult cardiology team with little insight or experience of dealing with such patients. However, such a specialty should be part of a team that offers complete and comprehensive care of patients from fetal diagnosis of congenital heart disease to old age. It is only with this approach that those caring for babies with congenital heart disease are likely to discover the long-term problems of surgical or interventional or conservative treatment and thus would be able to modify treatment options and improve their knowledge and the future of the patients. The emphasis on such comprehensive management should be on a cooperative and not a competitive approach. Dr Somerville’s views seem to verge on the paranoia about her area of interest being taken over by paediatric cardiologists.

In a paper such as Dr Somerville’s, it would be surprising if it were not influenced by political