The growth hormone and insulin-like growth factor 1 axis in heart failure

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Experimental data suggests that growth hormone and IGF-1 have beneficial effects on myocardial function in animal models of heart failure. Preliminary evidence suggests an abnormality in the growth hormone-IGF-1 axis in heart failure with relative growth hormone resistance. Beneficial effects of growth hormone and IGF-1 include vasodilatation, stimulation of cardiac hypertrophy, increase in calcium sensitivity of cardiac myofilaments and prevention of apoptosis. Recently, cardiac cachexia has been shown to be a powerful negative predictive factor in heart failure. Cachectic patients have higher angiotensin II levels. In the rat there is an interaction between the renin-angiotensin system and IGF-1. Thus, angiotensin II infusion causes weight loss in part through a catabolic effect. This effect results from increased protein degradation. Angiotensin II reduces circulating and skeletal muscle IGF-1 but increases IGF-1 and the IGF-IR expression in cardiac muscle. Preliminary data suggest a potential beneficial effect of growth hormone in heart failure. Further trials are necessary to test the potential beneficial effect of growth hormone and/or IGF-1 in heart failure.

Key words: Growth hormone, IGF-1, heart failure, cachexia, renin-angiotensin system.

There has been increasing recent interest in the potential use of growth hormone in the treatment of congestive heart failure.

Growth hormone plays a decisive role in somatic growth, acting largely through induction of insulin-like growth factor 1 (IGF-1) synthesis by the liver (the primary determinant of circulating IGF-1), and by peripheral tissues (yielding autocrine/paracrine effects) [33]. Some evidence supports direct tissue effects of growth hormone. Evidence for cardiac effects of growth hormone include the observations that growth hormone excess (acromegaly) may produce a spectrum of cardiovascular abnormalities including hyperkinesis and peripheral vasodilation progressing to severe systolic and diastolic dysfunction [44]. On the other hand, growth hormone deficiency may be accompanied by significant cardiac dysfunction, which is at least partially reversible by growth hormone therapy [23]. Experimental evidence indicates that both growth hormone and IGF1 have beneficial effects on cardiac function in models of heart failure.

Relatively little is known about the growth hormone-IGF-1 axis in heart failure but there is data suggesting dysregulation of this axis with some degree of growth hormone resistance [2]. If this is the case one can hypothesize that dysregulation of this axis plays a potentially important pathogenetic role in heart failure, and more particularly contributes to...
the skeletal muscle abnormalities which are frequent in this syndrome [43]. The prognostic importance of muscle wasting and cachexia in heart failure has only recently been appreciated. Mechanisms whereby the growth hormone-IGF-1 axis may be altered in heart failure are not understood but recent studies in the rat have indicated that there is a profound interaction in vivo between the renin-angiotensin system and endocrine and autocrine IGF-1 [5]. Thus the renin-angiotensin system (which is one of multiple neuroendocrine systems activated in heart failure) is an attractive candidate as a potential trigger of growth hormone/IGF-1 dysregulation in heart failure. This brief review addresses some of the issues relating to the role of growth hormone and IGF-1 in heart failure.

**EXPERIMENTAL EVIDENCE FOR CARDIAC EFFECTS OF GH AND IGF1**

There is good evidence for cardiac hypertrophic effects of both growth hormone and IGF-1 administered chronically in the rat [10, 46, 52]. In the setting of myocardial infarction in the rat, growth hormone and IGF-1 (or their combination) have beneficial effects on ventricular growth and cardiac function, particularly in the case of large infarctions [8, 20, 21, 30]. It is of note, however, that transgenic mice with severe (but not complete) IGF-1 deficiency, have increased blood pressure, increased left ventricular contractility, and preserved ventricular hypertrophy following aortic constriction [35].

Potential beneficial effects of growth hormone/IGF-1 include peripheral vasodilation [11, 21], stimulation of hypertrophy in the absence of fibrosis [20], increased calcium sensitivity of cardiac myofilaments [47] and prevention of both necrotic and apoptotic cell death as demonstrated in a transgenic model in which IGF-1 was overexpressed in mouse myocardium using the alpha-myosin heavy chain promoter [36]. The mechanisms whereby IGF-1 prevents cardiomyocyte apoptosis include blunting of Bax expression and inhibition of caspase 3 activation [51]. Recently it has been demonstrated that IGF-1, but not growth hormone, increases contractility by augmenting myofilament Ca\(^{2+}\) sensitivity through a phosphatidylinositol 3-kinase dependent mechanism [9].

In vitro studies have shown that IGF-1 produces hypertrophy of neonatal and adult rat cardiocytes [17, 32]. The signaling pathways whereby IGF-1 stimulates cardiomyocyte growth are poorly understood but may include activation of ERK1, ERK2 and p90 S6 kinase [25]. It is of note that left ventricular IGF-1 expression is increased in models of pressure-overload hypertrophy [19, 28, 50].

Recent studies have addressed the pattern of gene expression induced by growth hormone/IGF-1 in the rodent heart. In a murine model it has been shown that co-administration of growth hormone/IGF-1 produces left ventricular hypertrophy without induction of atrial natriuretic factor, alpha-skeletal actin or collagen III expression, contrary to the pattern seen in pressure-overload hypertrophy [48]. In rats both growth hormone and IGF-1 have been shown to decrease ventricular expression of atrial natriuretic factor [14]. Interestingly, the fetal pattern of left ventricular gene expression induced by renal artery constriction in the rat (a model of pressure-overload hypertrophy) is markedly altered by IGF-1 infusion, with notably a sustained decrease in β-myosin heavy chain expression and a transient decrease in atrial natriuretic factor expression [18].

**CACHEXIA AND HEART FAILURE**

The syndrome of cardiac cachexia or wasting has long been recognized as one of the features of heart failure, and has been ascribed to malnutrition and to possible metabolic abnormalities [42]. Recently cachexia has been shown to be a powerful independent predictor of mortality [3]. Mechanisms are poorly understood but clearly malnutrition per se or reduced blood flow are insufficient to explain the skeletal muscle atrophy and dysfunction common in heart failure [7, 38, 43]. Furthermore, studies in a rat model of heart failure indicate that reduced locomotor activity does not explain reduced skeletal muscle oxidative enzyme activity [45].

Recently studies have suggested possible abnormalities in the growth hormone/IGF-1 axis in heart failure, specifically increased growth hormone levels (without corresponding increases in IGF-1) in severely ill or cachectic heart failure patients [1, 2, 37]. Other notable differences in cachectic heart failure patients included higher catecholamine, cortisol, tumor necrosis factor-alpha, plasma renin activity and aldosterone levels, and lower sodium levels [3]. There have also been reports of lower IGF1 levels in patients with congestive heart failure due to dilated cardiomyopathy [6, 22].

Because IGF-1 is a potent anabolic factor for muscle [53], one may hypothesize that deficient IGF-1 action may be involved in abnormal skeletal muscle metabolism in heart failure, contributing to the loss of muscle strength that is frequently seen in this syndrome [29]. In this respect it has been demonstrated that low IGF-1 in heart failure is associated with reduced muscle strength and increased neurohormonal activation [39]. Furthermore it has been shown that adenovirally-mediated...
overexpression of IGF-1 in mouse skeletal muscle promotes muscle fiber regeneration and prevents aging-related loss of muscle strength [4].

**ANGIOTENSIN II, IGF1 AND THE HEART**

As noted above, little is known about potential alterations of the growth hormone/IGF-1 axis in heart failure, and about possible mechanisms involved. However, recent studies in the rat have demonstrated a profound interaction between the renin-angiotensin system (which is activated in heart failure) and regulation of both autocrine/paracrine and endocrine IGF-1. This interaction may have far-reaching implications for understanding the pathophysiology of heart failure, and in particular of cardiac cachexia. Thus infusion of angiotensin II in the rat produces weight loss and a marked decrease in circulating (endocrine) IGF-1. This effect is pressor-independent and is inhibited by blocking the angiotensin II AT1 receptor [5]. The angiotensin II-triggered decrease in weight and IGF1 is mediated by at least two mechanisms, an anorexigenic effect and a metabolic effect. It is currently unknown how angiotensin II may reduce appetite, but it is noteworthy that infusion of IGF-1 in humans has recently been shown to decrease levels of the appetite-controlling hormone leptin [13].

Using pair-fed control animals we have studied the metabolic effect of angiotensin II. Compared with controls, angiotensin II decreases hepatic IGF-1 mRNA levels, resulting in lowered circulating (endocrine) IGF-1. Also, skeletal muscle weight decreases in angiotensin II infused animals, and preliminary results indicate that this is not due to altered protein synthesis but rather to increased protein degradation, possibly via the ubiquitin-proteasome pathway, an important regulator of protein metabolism [34]. Importantly, skeletal muscle IGF-1 expression is decreased in angiotensin II infused animals, indicating a depressor effect on muscle autocrine/paracrine IGF-1. Co-infusion of IGF-1 and angiotensin II normalizes circulating IGF-1 but does not block the angiotensin II induced decrease in skeletal muscle mass. These findings suggest that the angiotensin II mediated decrease in endocrine IGF-1 is not involved in stimulating muscle loss, but that local reductions of IGF-1 contribute to this muscle loss. Indeed, when IGF-1 is co-infused with angiotensin II it fails to reverse the angiotensin II-induced decrease in muscle IGF-1 mRNA levels. Contrary to its depressor effect on circulating IGF-1 and on skeletal muscle IGF-1, angiotensin II infusion in the rat increases left ventricular IGF-1 and IGF-1 receptor mRNA levels (Brink et al., manuscript submitted). The upregulation of IGF-1 is a hemodynamically-mediated effect (inhibitable by both an angiotensin II AT1 receptor antagonist and by a vasodilator such as hydralazine), whereas IGF1 receptor upregulation is related to the anorexigenic effect of angiotensin II (fig. 1).

**CLINICAL TRIALS**

There is very limited clinical data on the use of growth hormone in treatment of chronic heart failure. To date there have been 8 reports with a total of 106 patients treated [12, 24, 26, 27, 31, 40, 41, 49]. Clinical benefits have been noted in 5 trials, negative results in the others, with notably the only 2 randomized trials [31, 41] reporting no benefit, treatment periods have been short (maximum 3 months) and it is quite possible that benefits may be limited to patients actually presenting cachexia. Treatment regimens have also varied and it is not clear whether intermittent administration may not be more beneficial. There are no reports of IGF-1 administration in chronic heart failure but IGF-1 given acutely to healthy volunteers or to patients with heart failure has been reported to produce beneficial hemodynamic effects [15, 16].

**CONCLUSIONS**

Although chronic growth hormone excess produces cardiac failure, growth hormone deficiency is also associated with cardiac dysfunction. There is some evidence for dysfunction of the growth hormone/IGF-1 axis in heart failure and experimental evidence indicating that angiotensin II depresses skeletal muscle and circulating IGF-1.
Because muscle wasting and cachexia are important determinants of outcome, there is a rationale to test the potential use of growth hormone and/or IGF-1 as adjuvant therapy in chronic heart failure.

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