

# Effects of performance-enhancing drugs on cardiac structure and energy metabolism

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## Abstract

Due to their potential to increase strength, athletes may consume performance-enhancing drugs (PEDs) such as anabolic androgenic steroids (AAS) and human growth hormone (GH). Despite the controversies surrounding the use of AAS and human GH, the chronic regimes and doses consumed for performance enhancement are markedly higher than those used acutely in clinical situations (with respect to compounds approved for therapeutic use), and may have adverse effects on the myocardium. These include increases in cardiac mass, though whether this hypertrophy is physiological or pathological in nature remains unclear. Regardless, cardiac hypertrophy is associated with secondary changes in cardiac energy metabolism that may contribute to cardiac dysfunction and the progression towards heart failure. As the misuse of PEDs may also result in sudden cardiac death, a better understanding of PED-induced cardiac hypertrophy and energy metabolism is required.

**Keywords:** performance-enhancing drugs; anabolic androgenic steroids; human growth hormone; left ventricular hypertrophy; cardiac energy metabolism.

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## Introduction

The clandestine use (and abuse) of performance-enhancing drugs (PEDs) by athletes is rooted in the expectation that these substances increase strength and athletic performance, and thus have the potential to provide an advantage (albeit clearly unfair) over other competitors in the field. Even though the ability of PEDs to increase athletic performance is controversial, these compounds are used by both competitive and recreational athletes. However, the use of these compounds is not benign, as they can pose serious adverse risks to health, including those pertaining to the cardiovascular system. Indeed, enhanced physical performance must be met by elevated cardiac workload and energy demand. As such, PEDs may directly and/or indirectly influence cardiac energy metabolism. Furthermore, PEDs are associated with an increased risk of left ventricular (LV) hypertrophy. As alterations in cardiac energy metabolism have been demonstrated to contribute to the development of cardiovascular disease [1,2],

and since the hypertrophied heart itself undergoes metabolic maladaptations [1], the potential risks of PED use/abuse on cardiovascular health are of high clinical relevance. Although the list of compounds utilized as PEDs is vast, and their effects numerous, this article will be limited to the discussion of the potential effects of anabolic androgenic steroids (AAS) and human growth hormone (GH) on cardiac structure and energy substrate metabolism.

### AAS and human GH as PEDs

AAS are derivatives of testosterone, which have been chemically modified such that anabolic effects (increased protein synthesis/decreased protein degradation, increased lean body mass/muscle mass) predominate relative to androgenic (masculinizing) effects. Clinically relevant AAS include nandrolone, oxandrolone, oxymetholone, and stanozolol. A number of clinical trials have demonstrated that short-term treatment with AAS is relatively safe, and has utility following major trauma, surgery, prolonged periods of immobilization, and various wasting conditions, settings where AAS attenuate protein loss in otherwise catabolic disease states [3]. It should be noted that a large number of testosterone derivatives have been synthesized (>1000), which has resulted in a market for illicit, “designer” AAS [4]. The chronic abuse of these compounds has serious adverse effects. With respect to the cardiovascular system, AAS abuse has been associated with abnormal lipid profiles (i.e. increased LDL/decreased HDL cholesterol), elevations of blood pressure, LV hypertrophy, acute myocardial infarction, and sudden cardiac death [5,6]. Of these changes, LV hypertrophy may have prominent effects on cardiac energy metabolism (see below) in the setting of chronic AAS abuse.

Human GH is secreted from the anterior pituitary, and circulates predominantly as a 22 kDa peptide. GH has both direct and indirect effects (mediated by insulin-like growth factor I) in a variety of tissues. With respect to potential performance enhancing effects, GH increases cellular amino acid uptake, stimulates skeletal and muscle growth (increases lean body mass), decreases adiposity, and increases heart rate and cardiac output [7]. However, it should be noted that GH promotes a diabetic-like profile of catabolic metabolism, as it increases circulating free fatty acid (FFA) levels, while decreasing skeletal muscle insulin-sensitivity [7]. Interestingly, acute treatment (15 days) with recombinant human

GH increases stroke volume and contractility in experimental heart failure secondary to coronary artery ligation [8]. Although not a consistent finding, a number of small clinical studies have also reported beneficial effects of GH treatment in the settings of non-ischemic [9,10] and ischemic heart failure [11]. On the surface, these findings appear to suggest that acute GH treatment may be cardioprotective. However, chronic GH abuse may elicit pathological alterations in cardiac structure and metabolism, exemplified by hypertrophic cardiac remodeling in the setting of acromegaly (GH excess).

### Cardiac energy metabolism in the healthy heart

In the normal healthy heart, virtually all (~95%) ATP generated arises from mitochondrial oxidative phosphorylation, with the remainder derived from glycolysis. In cardiac muscle, fatty acids account for 60–80% of oxidative energy metabolism, while carbohydrates such as glucose and lactate account for the remaining 20–40%. Despite producing more ATP than carbohydrates, fatty acids are not as oxygen-efficient, requiring ~10% more oxygen to produce an equivalent amount of ATP [12]. In addition, fatty acids directly inhibit the oxidation of carbohydrates through a phenomenon termed the “Randle cycle.” This uncouples glycolysis from glucose oxidation, which increases proton production and reduces cardiac efficiency [12].

If the demands of the heart are increased, such as following exercise, the healthy heart can increase LV contractile power and myocardial oxygen consumption 4–6 fold above resting values [13]. Although an acute increase in cardiac workload generally increases myocardial fatty acid uptake and  $\beta$ -oxidation, the relative increase is greater for carbohydrates (glucose and lactate) following exercise, or  $\beta$ -adrenergic stimulation and elevated afterload [13]. The *in vivo* response is highly dependent on the arterial concentrations of energy substrates, as an increase in arterial lactate during exercise markedly enhances its myocardial uptake at the expense of FFAs [14]. Conversely, with prolonged moderate intensity exercise (>30 min), increased adipose tissue lipolysis and the subsequent elevation in plasma FFA levels enhances myocardial FFA uptake and  $\beta$ -oxidation [15].

### Cardiac metabolism in the hypertrophied heart

While physiological hypertrophy and its associated metabolic changes are adaptive to cardiovascular

function, the metabolic alterations following pathological hypertrophy are maladaptive and may contribute towards the progression to overt heart failure (see [1] for in depth review of energy metabolism and its alterations in the hypertrophied heart). These metabolic changes include a reversion to a fetal phenotype of energy substrate metabolism. Specifically, glycolysis increases, while fatty acid  $\beta$ -oxidation decreases and glucose oxidation rates either slightly increase or remain unaltered in response to cardiac hypertrophy [16,17]. Despite these alterations in oxidative energy metabolism, overall tricarboxylic acid cycle activity remains normal, due in part to a marked increase in anaplerotic flux from glycolytically-derived pyruvate (via flux through malic enzyme) in the hypertrophied heart [18]. Another key factor separating physiological from pathological hypertrophy, and potentially contributing to their associated metabolic differences may be due to angiogenesis. Physiological hypertrophy due to exercise is accompanied via matched increases in vascularity such that the myocardium is sufficiently oxygenated, whereas pathological hypertrophy is not accompanied via a similar increase in vascularity, resulting in tissue hypoxia, which likely contributes to the elevation in glycolytic rates [19].

### PEDs & LV hypertrophy

Whereas the therapeutic use of AAS and GH is usually aimed at replacement therapy, and utilizes low doses, abuse of these substances for the purposes of performance enhancement employs doses that can be much greater than those utilized clinically (e.g., use of AAS as performance enhancing drugs can be 40–100-fold greater than therapeutic doses [4]), or the use of untested/novel designer compounds. Due to ethical considerations, the effects of such dosing regimens on aspects of cardiac function (for that matter human health) cannot be assessed using randomized placebo controlled trials. However, the adverse effects of chronic AAS use on cardiac structure and function may be garnered from case reports, as well as non-blinded trials with AAS users, while those of chronic GH use may resemble adverse cardiac remodeling observed in acromegaly (chronic GH excess).

Although not a consistent finding, a number of reports provide echocardiographic evidence of concentric hypertrophy in AAS users (See [5] for review).

While concentric hypertrophy can initially represent physiological hypertrophy, its maladaptive characteristics in the setting of AAS use are evidenced by diastolic dysfunction [20,21], which can also occur in the absence of overt hypertrophy [22], resulting in impaired ventricular relaxation and filling at normal pressures. Clinically, cardiac hypertrophy and diastolic dysfunction, which eventually progress to systolic heart failure are cardinal pathologies observed in growth hormone excess [23]. A potential common underlying mechanism of cardiac hypertrophy in response to AAS and GH may involve activation of the renin-angiotensin aldosterone system [24]; however, this is not firmly established. Regardless of the potential trigger(s), the mediators of cardiac hypertrophy secondary to chronic AAS or GH abuse likely involve one or more of the complex protein kinase cascades implicated in pathological cardiac hypertrophy [25]. Cardiac hypertrophy itself can progress to heart failure, and hypertrophy-induced alterations in cardiac energy metabolism accompany this progression as described above.

### Concluding remarks

Despite the controversies surrounding the use of PEDs to gain competitive advantages, their use and misuse will likely continue amongst both competitive and recreational athletes. However, consumption for performance enhancement involves the use of very high doses, or in other situations the use of “designer” compounds. These facets of PED use may predispose to numerous adverse effects, including cardiac hypertrophy and secondary changes in cardiac energy metabolism, although the data is equivocal as to whether PED-induced LV hypertrophy is truly pathological in nature. In addition, individuals utilizing PEDs are for most part also engaged in regular exercise training regimens. How PEDs and differing exercise training regimens interact and affect cardiac structure, metabolism, and function is not well-characterized. Furthermore, direct assessments of cardiac energy metabolism in response to PEDs are few, illustrating the need to improve our understanding in this area. •

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