Gene–environment interactions and the response to exercise

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Summary. Many of the symptoms of heart failure (breathlessness and fatigue) are not primarily due to reduced cardiac output, but relate to an impairment of peripheral muscle performance and metabolic efficiency. With regular training it is possible to increase skeletal muscle performance through improvements in muscle efficiency. Recent data suggest that such improvements may be modulated by local tissue renin-angiotensin systems and, in particular, by the local activity of angiotensin-converting enzyme (ACE). These findings might explain the remarkable benefits of ACE inhibition in the treatment of heart failure.

Skeletal muscle function and heart failure

The mechanisms that lead to exercise-limiting fatigue and breathlessness in chronic heart failure (CHF) remain obscure. Symptoms persist in the absence of pulmonary congestion (Coats 1996) and correlate poorly with measures of left ventricular dysfunction (Sullivan & Hawthorne 1995). Patients suffer restriction in their exercise capacity long before they have reached the limits of their cardiopulmonary reserve (Jondeau *et al.* 1992). Factors other than central haemodynamic performance thus predominantly limit physical performance in heart failure (Katsuki *et al.* 1995; McKelvie *et al.* 1995; Coats 1996a, b). Recent data suggest that abnormalities in skeletal muscle function are responsible for much of the symptomatic limitation attributed to CHF (Minotti *et al.* 1991; Harridge *et al.* 1996), and that the functional capacity of patients with CHF is restricted to a large degree by peripheral (skeletal muscle) metabolic effects rather than through central (cardio-respiratory) effects (Jondeau *et al.* 1997). Muscles become less resistant to

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fatigue (Harridge *et al.* 1996), and this impaired endurance performance (reduced by up to 30%) (Minotti *et al.* 1991; Magnusson *et al.* 1996), correlates closely with both functional capacity (Minotti *et al.* 1991) and with maximal oxygen uptake (VO2max) (Magnusson *et al.* 1996).

It is not widely appreciated that the metabolic efficiency of skeletal muscle can be modulated in health and disease. It can be increased in response to physiological situations in which achieving 'more external work for less energy utilization' might be advantageous, such as lactation (Spurr *et al.* 1998), dietary energy deficiency (Kulkarni & Shetty 1992) and exercise training (Gissane *et al.* 1991). In contrast, decreased metabolic efficiency may be a crucial contributor to the abnormal skeletal muscle function of CHF (Massie *et al.* 1988; Kemp *et al.* 1996). Several findings support this contention, including some limited data from animal experimentation. Firstly, oxidative capacity is reduced in patients with CHF by 30%, but 'effective muscle mass' by up to 65% (Kemp *et al.* 1996). Secondly, resting lower-limb oxygen consumption is higher than that seen in controls (Opasich *et al.* 1997). Thirdly, data derived from work on a rat model has shown that prolonged

submaximal exercise in the rat is associated with greater glycogen utilization in the oxidative muscles of CHF animals than of controls, suggesting increased use of local energy stores to achieve the same external work (Musch *et al.* 1990). In contrast, energy consumption per unit of external contractile work is increased in the diaphragmatic muscle of rats with CHF when compared to controls (Lecarpentier *et al.* 1998). Such metabolic inefficiency may be even greater with exercise than at rest, and such defects in metabolic efficiency may be sufficient to limit exercise capacity (Opasich *et al.* 1997).

Interventions that benefit function or survival in CHF may do so through impact on metabolic efficiency. Regular moderate exercise training leads to improved exercise tolerance and symptoms in CHF patients (Afzal *et al.* 1998; Group EHFT 1998; Tyni-Lenne *et al.* 1998). Such improvement is related not to changes in limb blood flow (Belardinelli *et al.* 1995; Hambrecht *et al.* 1997; Maillefert *et al.* 1998), but to improvements in muscle metabolism (Stratton *et al.* 1994; Brunotte *et al.* 1995) and, more specifically, metabolic efficiency (Kemp *et al.* 1996; Hare *et al.* 1999). Meanwhile, the administration of a class of drugs known as angiotensin-converting enzyme (ACE) inhibitors has remarkable beneficial effects on the functional capacity, morbidity and mortality of patients with chronic heart failure (CHF) (AIRE Study Investigators 1993). ACE inhibitors have been the sole agents found to substantially modify disease progression and outcome, and prevent the development of heart failure in asymptomatic patients. These effects have yet to be adequately explained (Coats 1996), and certainly cannot be attributed to the simple natriuresis and vasodilatation expected from a reduction in angiotensin II synthesis (Cohn *et al.* 1991). It seems that the limiting role of peripheral (muscle) factors to exercise in CHF is reduced by treatment with ACE inhibitors (Jondeau *et al.* 1997). Given that the functional limitations in CHF seem to relate to impaired skeletal muscle metabolic efficiency, the benefits of exercise training in heart failure may be partly due to some measure of rectification of this deficit. It is possible that the benefits of ACE inhibitors might similarly be mediated through an enhancement of skeletal muscle metabolic efficiency.

Tissue renin-angiotensin systems (RAS) and skeletal muscle function

Tissue RAS

The circulating human renin-angiotensin system (RAS) has long been recognized to play an important role in circulatory homeostasis. Angiotensinogen produced by the liver is acted upon by renin (produced by the kidney) to produce angiotensin I (Ang I). This is cleaved by circulating (and membrane-bound) ACE, to generate the potent vasoconstrictor angiotensin II (Ang II). Ang II also stimulates adrenal aldosterone release (leading to salt and water retention), and degrades vasodilator kinins. In this way, increasing RAS activity raises blood pressure. However, it has become increasingly clear that evolutionarily ancient local renin-angiotensin systems exist in diverse tissues including human myocardium (Dzau 1988), adipose tissue (Jonsson *et al.* 1994), and skeletal muscle (Dragovic *et al.* 1996), for which a metabolic role has been suggested.

Modification of skeletal muscle metabolic efficiency might provide one explanation for the remarkable beneficial effects of ACE-inhibitor treatment in those with CHF. We have investigated such a peripheral metabolic role for tissue RAS, through the utilization of a common genetic variant in the human ACE gene. In the human ACE gene, the absence (Deletion, *D* allele) rather than the presence (Insertion, *I* allele) of a 287 base pair fragment at intron 16 is associated with higher tissue ACE activity (Danser *et al.* 1995). The I and D alleles are equally common, meaning that we can divide the British population into 25% who are 'II' (with low tissue ACE activity), 50% who are 'ID' (with intermediate tissue ACE activity), and 25% who are DD (and have the higher tissue ACE activity). We have examined the responses of humans to various physiological stimuli according to their ACE genotype. These studies strongly support a metabolic role for tissue RAS and demonstrate a remarkable, and previously unreported, role in the regulation of human skeletal muscle performance and metabolism. These data may account for many of the beneficial effects of ACE inhibition in the treatment of cardiac failure, and pave the way for the development of more specific drug classes with even greater efficacy.

ACE genotype and exercise-induced left ventricular growth

Initial studies were performed in young male army recruits before and after a 10-week physical training programme (Montgomery *et al.* 1997). Left ventricular (LV) mass measured by echocardiography, altered by $+ 2.0$ g, $+ 38.5$ g and $+ 42.3$ g for II, ID and DD genotypes, respectively ($P < 0.0001$). The prevalence of electrocardiographically defined LVH rose from 6/24 before training to 11/24 afterwards in those of DD genotype ($P < 0.01$), but from 8/30 to only 9/30 in those of II genotype. Clearly, one might explain these data in

one of two ways: either that the DD genotype is associated with an excessive growth response to any given burden, or that the burden on the heart (in terms of cardiac work performed per unit of external skeletal muscular work) is greater. Early data suggested that, in fact, the D allele was associated with increased cardiac work in order to achieve similar external skeletal muscle mechanical work. Certainly, there is evidence to suggest an effect of local RAS activity on cardiac growth responses. Consistent with this suggestion, analysis of data for 460 consecutive recruits at the end of 10 weeks training revealed a trend towards poorer performance in a 1.5 mile run being associated with the D allele (mean $\pm$ SD time in minutes 9.76 ± 0.63 *vs.* 9.83 ± 0.62 *vs.* 9.90 ± 0.69 min for II, ID and DD, respectively) (unpublished data).

Physical performance and ACE genotype

The results from our work with military recruits (Montgomery *et al.* 1997) would suggest that, for any given external work load, those of II genotype (a marker of lower ACE activity) might have to perform less cardiac work. In other words, at any given level of *cardiac* work, *external work* (or *performance*) might be lower. We examined this hypothesis. Seventy-eight recruits (mean $\pm$ SEM, age 19.0 ± 0.2 years: ACE genotype 20 [25.6%] II, 46 [62.8%] ID, 12 [15.4%] DD) completed an identical 10-week general physical training programme. The maximum duration (in seconds) for which they could perform repetitive elbow flexion whilst holding a 15-kg barbell was assessed. Exercise duration, independent of genotype at baseline, improved in a genotype-dependent fashion after 10-weeks of training (79.4 ± 25.2 *vs.* 24.7 ± 8.8 *vs.* 7.1 ± 14.9 s for II *vs.* ID *vs.* DD, respectively) Improvement was thus 11-fold greater (p 0.001) for those of II than DD genotype (Montgomery *et al.* 1998).

Such effects on upper limb flexor performance seem to extend to global physical performance. Amongst British Olympic-standard runners, there is a linear trend of increasing *I* allele frequency with distance run, with the proportion of *I* alleles increasing from 0.35 to 0.53 and 0.62 amongst those running ≤ 200 m ($n = 20$: predominantly anaerobic), $400-3000$ m ($n = 37$: mixed aerobic and anaerobic) and ≥ 5000 m ($n = 34$: predominantly aerobic), respectively ($P = 0.009$ for linear trend)(Myerson *et al.* 1999). High altitude mountaineers (who perform extreme hypoxic endurance exercise) also exhibit an excess of the *I* allele when compared to controls − but to a much more marked degree. Twenty-five elite unrelated male British mountaineers with a

history of ascents beyond 7000 m without the use of supplemental inspired oxygen were studied. Genotype distribution was compared to that of 1906 healthy British males. Mean (SD) age was 40.6 (6.5) years in the 25 subjects, and 55.6 (3.2) years amongst the 1906 controls. Both genotype distribution and allele frequency differed significantly between climbers and controls (p 0.02 and 0.003, respectively), with a relative excess of II genotype and deficiency of DD genotype. Amongst the 15 climbers who had ascended beyond 8000 m without oxygen, none was of DD genotype (6 (40%) II and 9 (60%) ID: I allele frequency 0.65). Ranked by number of ascents without oxygen, the top performer climbing over 8000 m was of II genotype (5 ascents, compared to a mean of 2.4 ± 0.3 ascents for the > 8000 m group), as were the top two in this group for number of additional 7000 m ascents (> 100 and 18, compared to a mean of 10.3 ± 6.5 ascents)(Montgomery *et al.* 1998).

The *I* allele thus seems to be associated with enhanced endurance potential in skeletal muscle. We have recently shown that the *I* allele is associated with greater improvements in metabolic efficiency of skeletal muscle with training. Fifty-eight Caucasian male army recruits (35 II and 23 DD) were studied before and after an 11-week programme of (primarily aerobic) physical training. 'Delta efficiency' (the ratio of the change in muscle work performed/min to the change in energy expended/min: the most valid measure of the efficiency of muscular contraction) (Gaesser & Brooks 1975) was calculated. Prior to training, delta efficiency was independent of genotype (24.5% and 24.9%, respectively, $P = 0.59$). However, the response to training was strongly genotype-dependent, with delta efficiency rising significantly only amongst those of II genotype (absolute change of -0.26% for those of DD genotype ($P > 0.05$) and 1.87% for those of II genotype ($P < 0.01$): $P < 0.025$ for II *vs.* DD)(Williams *et al.* 2000).

The administration of Ang II to rodent models is associated with a pressor-independent reduction in metabolic efficiency, and a consequent skeletal muscle cachectic response consistent with an effect of tissue RAS on skeletal muscle metabolic efficiency (Brink *et al.* 1996). Conversely, a reduction in ACE activity through pharmacological means seems to beneficially alter skeletal muscle metabolism, and the benefits of ACE inhibition in patients with CHF thus seem mediated though peripheral (skeletal muscle) metabolic effects rather than through central (cardio-respiratory) effects (Jondeau *et al.* 1997). Forearm oxygen consumption during maximal exercise is lower in patients with severe CHF, and is increased by the administration of the ACE-inhibitor captopril (Imaizumi *et al.* 1990). In rats with

CHF, muscle ATP and creatine phosphate levels decline more quickly with exercise than in control, and lactate levels rise faster. Six weeks of treatment with the ACE inhibitor trandolapril reverses these effects, suggesting that ACE inhibition may restore skeletal muscle metabolic efficiency (Yamaguchi *et al.* 1999).

Mechanism of the beneficial effect of low ACE activity

Improvements in skeletal muscle metabolic function related to low ACE activity may in part relate to changes in muscle composition. Type I (slow twitch) fibres have a maximum velocity of shortening (V_{max}) which is < 5-fold lower than that in type II fibres. Muscular efficiency is maximal at speeds of contraction of approximately 1/3 V_{max} and thus, at slower velocities of contraction, type I fibres are more efficient than type II fibres (Coyle *et al.* 1992). Secondly, alterations in mitochondrial uncoupling protein (UCP) expression may play a critical role. UCP2 and UCP3 are expressed in human skeletal muscle, and uncouple mitochondrial respiration from ATP synthesis (Boss *et al.* 1998). The expression of uncoupling proteins may be modified in order to adjust metabolic efficiency in times of metabolic stress or surplus. Endurance exercise training in rats is associated with a 54% and 76% reduction in skeletal muscle UCP2 and UCP3 expression, respectively, thus allowing for a potentially higher level of metabolic efficiency. Cardiac muscle UCP2 levels also fell by 41%, suggesting that the effects on metabolic efficiency might extend to both cardiac and skeletal muscle (Boss *et al.* 1998).

Conclusions

An intrinsic deficiency in the fatigue resistance and endurance performance of skeletal muscle is responsible for much of the symptomatic limitation attributed to chronic heart failure. This impaired performance also relates in part to defects in muscle metabolic efficiency (Musch *et al.* 1990; Kemp *et al.* 1996; Opasich *et al.* 1996; Opasich *et al.* 1997). Regular moderate exercise training directly improves skeletal muscle performance in heart failure patients through improvements in skeletal muscle metabolic efficiency. There may be a crucial role for renin-angiotensin systems in these findings: Angiotensin II infusion is associated with increased metabolic inefficiency, whilst low ACE activity (as marked by the *I* allele of the ACE gene) is associated with substantially greater improvements in skeletal muscle metabolic efficiency seen with training. It is thus possible that the substantial advantages of ACE inhibition in heart failure

treatment relate to improvements in metabolic performance of skeletal and possibly cardiac muscle.

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