Circulating Angiotensin Converting Enzyme Activity Is Correlated with Muscle Strength

ALUN G. WILLIAMS[1], STEPHEN H. DAY[2], JONATHAN P. FOLLAND[3], PETER GOHLKE[4], SUKHBIR DHAMRAIT[5], and HUGH E. MONTGOMERY[5]

[1]Institute for Biophysical and Clinical Research into Human Movement, Manchester Metropolitan University, UNITED KINGDOM; [2]School of Sport, Performing Arts and Leisure, University of Wolverhampton, UNITED KINGDOM; [3]School of Sport and Exercise Sciences, Loughborough University, UNITED KINGDOM; [4]Institute of Pharmacology, Kiel University, GERMANY; and [5]UCL Centre for Cardiovascular Genetics, BHF Laboratories, London, UNITED KINGDOM

ABSTRACT

WILLIAMS, A. G., S. H. DAY, J. P. FOLLAND, P. GOHLKE, S. DHAMRAIT, and H. E. MONTGOMERY. Circulating Angiotensin Converting Enzyme Activity Is Correlated with Muscle Strength. *Med. Sci. Sports Exerc.*, Vol. 37, No. 6, pp. 944–948, 2005. **Purpose:** The D-variant of the angiotensin-1 converting enzyme (ACE) gene is associated with higher circulating and tissue ACE activity. Some studies have suggested a similar association of genotype with muscle strength or the gain in strength in response to training. This study has assessed the relationship between circulating ACE activity, strength, and the response to training. **Methods:** Eighty-one untrained men were tested for quadriceps muscle strength, and 44 of these performed an 8-wk program of dynamic strength training of the quadriceps muscle group. Venous blood was obtained for assessment of circulating ACE activity before and after the training program. ACE genotype was also determined. **Results:** At baseline, circulating ACE activity was significantly correlated with isometric ($r = 0.25–0.29$, $P < 0.02$) and isokinetic ($r = 0.38$, $P < 0.0005$) quadriceps muscle strength. ACE genotype also seemed to be related to pretraining muscle strength. However, circulating ACE activity showed no significant association with the 9–14% mean increases of muscle strength in response to the training intervention. ACE genotype also showed no association with the training-induced change in muscle strength. Circulating ACE activity did not change significantly after the training program. **Conclusions:** The data support a role for ACE in the regulation of human skeletal muscle strength, but do not confirm a role in altering the response to short-term training. **Key Words:** FORCE, TRAINING, GENETICS

Angiotensin converting enzyme (ACE, kininase II) is a key component of the circulating human renin-angiotensin system (RAS), generating vasopressor angiotensin II (ANG II), and degrading vasodilator kinins (6). Local RAS also exist in diverse tissues (7) including human muscle (24). ACE may modulate tissue growth processes: both angiotensin II and kinins have growth regulatory effects (11,14), whereas ANG II seems axial in mediating the skeletal muscle growth to mechanical load (12). However, no study has yet evaluated directly the role of ACE in the regulation of skeletal muscle strength or growth in humans.

A functional polymorphism of the ACE gene has been identified in humans, with the absence (deletion allele, D) rather than the presence (insertion allele, I) of a 287 base pair fragment being associated with higher tissue (1) and serum (25) ACE activity. Hopkinson and colleagues (13) recently reported an association of the ACE D-allele with baseline (untrained) skeletal muscle strength among patients with chronic lung disease. However, neither they nor Folland et al. (10) could identify this association among healthy untrained individuals, although Folland et al. did demonstrate an association of the ACE D-allele with a greater gain in quadriceps strength in response to a strength-training program, an effect not confirmed by Thomis et al. (28) in a study of elbow flexors.

A greater understanding of the role of ACE (and the ACE gene) in the regulation of muscle strength would be useful for scientists and practitioners working in various fields such as aging, rehabilitation, space travel, and sports performance. The ability to identify good and poor "responders" before a training program might help the design and prescription of training programs, or even assist in selection procedures. In addition, an improved understanding of the mechanisms involved in the development of muscle strength may eventually lead to the development of pharmaceuticals for use in a clinical setting. One means to strengthen study power with regards to muscle strength and ACE might be to compare strength phenotype (and its training response) by ACE activity (as a continuous variable) in addition to that by ACE genotype (a categorical variable). Therefore, the aims of this study were to examine the relationships between circulating ACE activity (as indicated by direct measurement and ACE genotype), muscle strength, and the strength response to resistance training. It was hypothesized that

Address for correspondence: Alun G. Williams, Institute for Biophysical and Clinical Research into Human Movement, Manchester Metropolitan University, Hassall Road, Alsager, ST7 2HL, United Kingdom; E-mail: a.g.williams@mmu.ac.uk.
Submitted for publication October 2004.
Accepted for publication February 2005.

0195-9131/05/3706-0944/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/01.mss.0000166577.42935.4e

greater circulating ACE activity would be related to greater initial muscle strength and a greater response to strength training.

METHODS

The study had appropriate ethics committee approval (the sport, health and exercise ethics committee at Staffordshire University). Written informed consent was obtained from all participants. The study was conducted with both assessors and subjects blind to the subjects' ACE genotype and activity.

Subjects. Subjects comprised male Caucasian recreationally active volunteers drawn from the student and staff populations of Staffordshire University. Only subjects who had not been involved in any structured strength-training program of the quadriceps muscle group during the previous 6 months were eligible to participate. Exclusion criteria were medical problems (such as knee pathology or other orthopedic conditions) that would confound their participation in the study, or the use of any nutritional supplements or anabolic compounds.

We aimed to have at least 80% power to detect a significant one-tailed correlation of magnitude $r = 0.40$ (which would require 40 subjects) for both baseline and training analyses. In the initial phase of the study, 52 subjects were recruited. This gave us 80% power to detect a significant correlation of $r = 0.35$ at the pretraining stage. Eight subjects, whose baseline characteristics did not differ from those who continued, subsequently withdrew from the study before reaching the end of the training program. Thus, 44 subjects completed the training, giving us 80% power to detect a significant correlation of $r = 0.38$. Initial data analyses showed correlations of approximately $r = 0.30$ approaching statistical significance on the 52 subjects tested at the pretraining stage. Therefore, we recruited a further 29 subjects from the same population (who in no way differed significantly from the original 52) for baseline testing only, giving us a power of 80% to detect a significant correlation of $r = 0.28$.

Strength testing. One leg of each subject was randomly chosen for strength training and testing. Subjects were asked to refrain from exercise and alcohol intake for 24 h before testing. Baseline measurements were taken twice within a 7-d period (at least 3 d apart), and posttraining measurements were taken once between 3 and 7 d after the final training session. The reported baseline strength data are the highest values observed on either of the two test days. On all test days, isometric strength at knee angles of 1.57 and 1.05 rad, and isokinetic strength at an angular velocity of 1.05 rad·s^{-1} were assessed using a Kin-Com 125AP dynamometer (Rehab World, Chattanooga, TN). Each isometric measurement involved at least 3 practice trials, and then at least three maximum voluntary contractions (MVC) with at least 30 s of rest between each. If values were seen to increase during the test session, more than 3 MVC were used until values reached a plateau. The isokinetic measurement involved at least three practice trials, and then one set of three consecutive repetitions. For each maximal trial, subjects were given verbal encouragement and instructed to produce as much force as possible for at least 3 s (isometric) or throughout the duration of the contraction (isokinetic).

In addition, on the first pretraining test day and posttraining, percutaneous electrical stimulation was used during isometric testing of unilateral leg extension strength at 1.57 rad on a conventional strength-testing chair (21) to calculate the level of voluntary muscle activation (26). Twitches were 50-μs square wave pulses delivered automatically at 1 Hz via two carbon rubber electrodes placed over the proximal and distal anterior surface of the thigh, and were generated by a Digitimer DS7AH stimulator (Digitimer, UK). Use of a linear reciprocal extrapolation of the twitch force–voluntary force relationship facilitated calculation of muscle activation levels and true muscle strength (TMS) from the MVC measurements (20). Both MVC and TMS data at 1.57 rad were used for analysis.

Strength training. During a familiarization session, each subject's 10-repetition maximum (10-RM) load for unilateral knee extension on the training device (WLCE-365, Body-Solid Inc., IL) was determined. Each training session consisted of one warm-up set of 10 repetitions at 75% 10-RM load followed by four sets of 10 repetitions at 100% 10-RM load, with 1-min rest periods between sets. Each repetition required 1 s to lift the weight, and 1 s to lower the weight. The resistance was adjusted appropriately on each set so that, as much as possible, 10 repetitions (i.e., 10-RM) could be performed for all sets. The training was performed 3 wk^{-1} for 8 wk, that is, a total of 24 training sessions. All training sessions were supervised, with continual verbal encouragement given throughout. Daily performance was recorded.

Determination of plasma ACE activity. Fasting 10-mL blood samples were obtained from a superficial forearm vein before and after the training program. All subjects abstained from alcohol and caffeine intake, and from exercise, for at least 24 h before blood sampling. Plasma was separated immediately from 10 mL of the whole blood by centrifugation at 1500 *g* for 10 min, and stored at below −20°C until analysis. ACE activity was assayed using a modified fluorometric method using carbobenzoxy-phenyl-alanyl-histidyl-leucine (Z-phe-his-leu) as a substrate (3,29).

Determination of ACE genotype. An additional 5-mL EDTA sample of whole blood was drawn pretraining, from which leukocyte DNA was extracted by salting out. ACE genotype was determined using a three-primer polymerase chain reaction (PCR) amplification as previously described (18), with products resolved on a 7.5% polyacrylamide gel by two independent staff blind to all subject data.

Statistical analysis. All data were analyzed using the SPSS for Windows (Release 11.0) statistical software package (SPSS Inc., Chicago, IL). The effects of the strength-training program on muscle strength and circulating ACE activity were assessed using Student's paired *t*-tests. One-tailed partial correlations were used to investigate the rela-

tionships between baseline ACE activity and baseline muscle strength (controlling for baseline body mass, stature, and body mass index (BMI)), and baseline ACE activity and the adaptations to strength training (controlling for baseline body mass, stature, BMI, and strength). The effects of ACE genotype on baseline characteristics (with baseline body mass, stature, and BMI as covariates) and on the adaptations to strength training (with baseline body mass, stature, BMI, and strength as covariates) were assessed for linear trend using ANCOVA. The accepted level of significance was set at $P = 0.05$ for all statistical tests. The partial eta squared effect size statistic (which indicates the proportion of the effect and error variance that is attributable to the effect) was obtained during ANCOVA. Data are expressed as mean ± SD unless otherwise stated.

RESULTS

A total of 81 subjects were studied, whose mean ± SD baseline characteristics were: age, 22.2 ± 3.9 yr; body mass, 77.2 ± 12.5 kg; stature, 1.80 ± 0.08 m; body mass index, 23.9 ± 3.6 kg·m^{-2}; activity level, 5.2 ± 3.5 h of exercise per week; ACE genotype II, 23 (28%); ID, 35 (43%); and DD, 23 (28%), ACE activity 33.3 ± 8.7 nM His-Leu-mL^{-1}. ACE genotype distribution was in Hardy–Weinberg equilibrium (a fact also true of the subset that underwent the training program). Subject characteristics were independent of ACE genotype or activity.

For those completing the training program, baseline ACE activity (31.0 ± 8.0 nM His-Leu-mL^{-1}) did not alter with training (31.0 ± 8.5 posttraining, $P = 0.885$ by paired *t*-test). As a result, analyses were performed with regard to pretraining ACE activity alone.

Pretraining strength measures correlated significantly with circulating ACE activity. This applied to isometric strength at 1.57 rad (687 ± 156 N) and at 1.05 rad (809 ± 155 N) (r = 0.253, $P = 0.013$; and r = 0.289, $P = 0.005$, respectively; Fig. 1), isokinetic strength at 1.05 rad·s^{-1} (178 ± 34 N·m) (r = 0.375, $P < 0.0005$; Fig. 2), and TMS at 1.57 rad (r = 0.252, $P = 0.014$).

The characteristics of the 44 subjects who completed the training program (mean ± SD age, 22.6 ± 3.8 yr; body mass, 76.8 ± 11.8 kg; stature, 1.80 ± 0.07 m; body mass index, 23.8 ± 3.3 kg·m^{-2}; activity level, 4.8 ± 3.9 h of exercise per week, ACE genotypes II, 16 (36%); ID, 17 (39%); and DD, 11 (25%)) did not differ from the group overall. Among these, training produced significant increases in isometric strength at both 1.57 and 1.05 rad and isokinetic strength (Table 1). Similarly, quadriceps muscle activation was 94.3 ± 4.1% before training and rose significantly (to 96.0 ± 2.8%, $P = 0.008$) after training. The changes in strength were unrelated to circulating ACE activity (Table 1).

The distribution of ACE genotypes for the 81 subjects tested at baseline was II 23 (28%), ID 35 (43%), and DD 23 (28%), which is in Hardy–Weinberg equilibrium. As anticipated, ACE activity was significantly associated with ACE genotype, being 26.3 ± 7.6, 33.5 ± 6.4, and 39.9 ± 7.5 nM

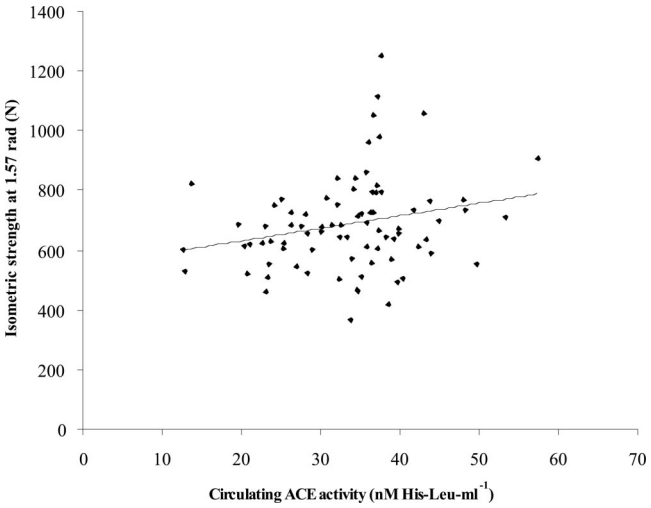

FIGURE 1—Relationship between pretraining circulating ACE activity and isometric strength (MVC data) at 1.57 rad ($N = 81$, r = 0.253, $P = 0.013$).

His-Leu-mL^{-1} for those of II, ID, and DD genotype, respectively ($P < 0.0005$, partial eta squared = 0.354). Linear trend analysis showed that ACE genotype had a significant effect on baseline isometric strength at 1.05 rad ($P = 0.026$, partial Eta squared = 0.067; Fig. 3). The linear trend effect of ACE genotype on baseline isometric strength at 1.57 rad approached statistical significance whether expressed as MVC data ($P = 0.081$, partial eta squared = 0.042; Fig. 3) or TMS data ($P = 0.096$). Similarly, the linear trend effect of ACE genotype on isokinetic strength approached statistical significance ($P = 0.052$, partial eta squared = 0.050; Fig. 3). Training-related changes in muscle strength were independent of ACE genotype ($0.147 < P < 0.757$), corresponding with the results for ACE activity.

DISCUSSION

Circulating ACE activity is positively correlated with both static and dynamic muscle strength measures of the quadriceps muscle in healthy Caucasian males naïve to strength training.

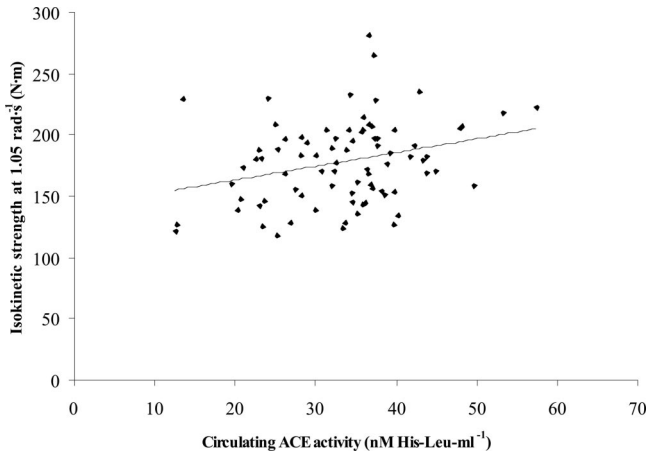

FIGURE 2—Relationship between pretraining circulating ACE activity and isokinetic strength at 1.05 rad·s^{-1} ($N = 81$, r = 0.375, $P < 0.0005$).

TABLE 1. Pre- and posttraining values of isometric strength and isokinetic strength for the 44 subjects who completed the training.

	Pre	Post	Change	% Change	*P* pre-post	Pearson Correlation between Strength Change and ACE Activity
MVC at 1.57 rad (N)	701 ± 161	787 ± 184	86 ± 130	13.8 ± 18.8	< 0.0005	$r = -0.0495$ $P = 0.381$
TMS at 1.57 rad (N)	746 ± 180	822 ± 196	75 ± 138	11.9 ± 19.3	0.001	$r = -0.0280$ $P = 0.432$
MVC at 1.05 rad (N)	798 ± 152	861 ± 170	63 ± 120	8.8 ± 16.1	0.001	$r = -0.1379$ $P = 0.198$
Isokinetic strength at 1.05 rad·s^{-1} (N·m)	174 ± 36	195 ± 41	21 ± 23	13.1 ± 14.5	< 0.0005	$r = 0.0167$ $P = 0.459$

P values pre-post are from Student's paired *t*-test; data are mean SD.

This small to moderate correlation is significant, with ACE activity associated with 6–14% of the observed variation in baseline strength. These findings have value for two reasons.

First, these data help clarify the association of ACE genotype and activity with skeletal muscle performance characteristics, an issue subject to some considerable debate. Neither Folland et al. (10) nor Thomis et al. (28) could identify an association of ACE genotype with pretraining strength of quadriceps and elbow flexors, respectively. However, neither study was powered to detect such an association. Conversely, Hopkinson et al. (13) showed quadriceps strength to be associated with the D-allele, but only among patients with chronic obstructive lung disease. Our data suggest that ACE activity is associated with quadriceps strength, and extend the observation by Hopkinson et al. to the young and healthy.

Second, in keeping with the established literature, ACE genotype was associated with circulating ACE activity. Given that ACE activity is associated with strength, we might expect genotype to be similarly associated. This was indeed observed, with the partial Eta squared statistic indicating that 4–7% of the variation in strength could be attributed to ACE genotype. However, the tighter statistical association of ACE activity (rather than genotype) with strength reflects the added power of seeking association with a continuous variable (ACE activity) rather than a categorical surrogate of ACE activity (ACE genotype) and support the use of ACE activity measures over genotype in the conduct of such studies (17). This view is emphasized by

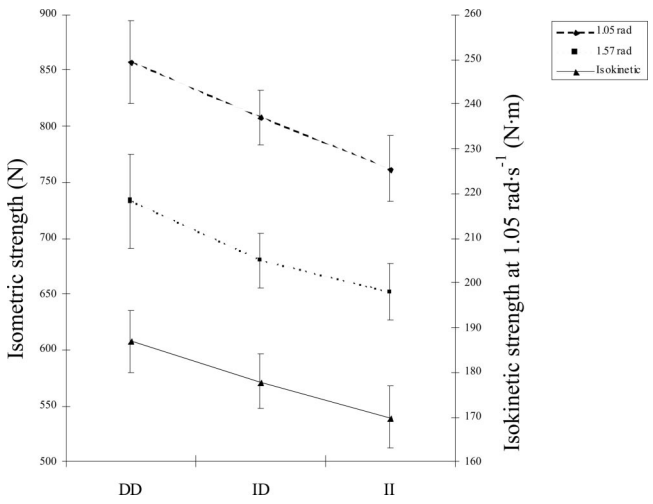

FIGURE 3—Effect of ACE genotype on pretraining isometric strength at 1.05 rad (linear trend $P = 0.026$), isometric strength at 1.57 rad (MVC data; linear trend $P = 0.081$) and isokinetic strength at 1.05 rad·s^{-1} (linear trend $P = 0.052$). $N = 81$ ($N_{II} = 23$, $N_{ID} = 35$, $N_{DD} = 23$). Data are mean ± SE.

the stability in circulating ACE activity over the training period, a finding that fits well with similar stability over time identified by other investigators (2,5).

The association of circulating ACE activity with strength may be mediated through circulating ACE activity itself. However, ACE genotype influences both circulating and tissue ACE activity (1,25), and ACE is expressed in human skeletal muscle (24). Thus, the strength differences might be mediated through the effects of skeletal muscle ACE expression.

Such effects may be mediated through ACE-dependent synthesis of Ang II and subsequent differences in muscle size. Ang II is a potent growth factor in cardiac muscle (4) and, in skeletal muscle, seems necessary for the transduction of mechanical forces to yield growth (12). Such effects are probably mediated through the Ang II Type 1 (AT_1) receptor (4,12). Second, such effects may be mediated through alterations in skeletal muscle fiber type: Zhang and colleagues (31) have recently demonstrated an association of the ACE D allele with a greater proportion of Type II fibers in human vastus lateralis. Such fibers may produce greater force per unit of cross-sectional area (27). Third, it currently remains possible (although unlikely in our opinion) that any effect of ACE via Ang II on muscle strength may occur via neural mechanisms (30).

ACE may also influence muscle strength through the degradation of kinins. Indeed, skeletal muscle contains a complete kallikrein–kinin system (16), can liberate kinins locally (15), and expresses functional bradykinin B_2 receptors (9,23). Kinins inhibit growth processes (8,14), and thus elevated circulating ACE for a prolonged period may influence muscle strength via this alternative pathway.

We were unable to identify an association of the training response with ACE activity ($-0.14 < r < 0.02$, all $P \geq 0.198$), or indeed genotype, thus agreeing with previous nonsignificant results from studies that have used dynamic training (10,28). With our 44 subjects who completed the training, we were powered statistically at the 80% level to detect a significant moderate correlation coefficient of 0.38 between circulating ACE activity and the responses of strength to training. However, our interim power calculation (of the original 44 individuals) showed that more than 300 subjects would be required to establish statistical significance for correlations of the magnitudes we observed. Therefore, it is possible that a very weak correlation exists between circulating ACE activity and the response of muscle strength to training, although a study of substantially larger scale would be required to identify this given our initial data. Moreover, the added power of seeking association with a continuous variable (ACE activity) rather than

a categorical surrogate of ACE activity (ACE genotype) suggests that a sample size of much greater than 300 would be required to identify a very weak effect of ACE genotype on the training response. Either isometric training (10) or a longer duration of dynamic training (19), including periodization, may assist by producing a greater degree of hypertrophy that would facilitate a prospective examination of the effect of ACE on training-induced changes in skeletal muscle strength and size. Given the substantial evidence base demonstrating the role of ANG II as a growth factor in muscle tissue (4,11,12,22) and our own positive findings regarding ACE activity and baseline strength, further such research is indeed warranted.

In conclusion, circulating ACE activity has been associated directly with human muscle strength for the first time. This new finding supports the idea that ANG II is likely to act as a growth factor in human skeletal muscle. Although circulating ACE activity was assessed in this study, local ACE activity (and ANG II production) in skeletal muscle may be even more important in influencing muscle properties and should be investigated.

S.D. was funded by the British Heart Foundation, from whom the Centre for Cardiovascular Genetics receives core funding. H.M. is funded by the Portex Endowment at the Institute of Child Health, London. The study was funded from an unconditional educational grant from Aventis UK, Ltd.

REFERENCES

1. Danser, A. H., M. A. Schalekamp, W. A. Bax, et al. Angiotensin-converting enzyme in the human heart. Effect of the deletion/insertionpolymorphism. *Circulation* 92:1387–1388, 1995.
2. Day, S. H., C. Williams, J. P. Folland, P. Gohlke, and A. G. Williams. The acute effects of exercise and glucose ingestion on circulating angiotensin-converting enzyme in humans. *Eur. J. Appl. Physiol.* 92:579–583, 2004.
3. Depierre, D., and M. Roth. Fluorimetric determination of dipeptidyl carboxypeptidase. (angiotensin- I-converting enzyme). *Enzyme* 19:65–70, 1975.
4. Dostal, D. E., and K. M. Baker. Angiotensin II stimulation of left ventricular hypertrophy in adult rat heart: mediation by the AT1 receptor. *Am. J. Hypertens.* 5:276–280, 1992.
5. Dux, S., N. Aron, G. Boner, A. Carmel, A. Yaron, and J. B. Rosenfeld. Serum angiotensin converting enzyme activity in normal adults and patients with different types of hypertension. *Isr. J. Med. Sci.* 20:1138–1142, 1984.
6. Dzau, V. J. Tissue renin-angiotensin system: physiologic and pharmacologic implications. Introduction. *Circulation* 77:I1–3, 1988.
7. Dzau, V. J., K. Bernstein, D. Celermajer, et al. The relevance of tissue angiotensin-converting enzyme: manifestations in mechanistic and endpoint data. *Am. J. Cardiol.* 88:1L–20L, 2001.
8. Emanueli, C., R. Maestri, D. Corradi, et al. Dilated and failing cardiomyopathy in bradykinin B(2) receptor knockout mice. *Circulation* 100:2359–2365, 1999.
9. Figueroa, C. D., G. Dietze, and W. Muller-Esterl. Immunolocalization of bradykinin B2 receptors on skeletal muscle cells. *Diabetes 45(Suppl.* 1):S24–28, 1996.
10. Folland, J., B. Leach, T. Little, et al. Angiotensin-converting enzyme genotype affects the response of human skeletal muscle to functional overload. *Exp. Physiol.* 85:575–579, 2000.
11. Geisterfer, A. A., M. J. Peach, and G. K. Owens. Angiotensin II induces hypertrophy, not hyperplasia, of cultured rat aortic smooth muscle cells. *Circ. Res.* 62:749–756, 1988.
12. Gordon, S. E., B. S. Davis, C. J. Carlson, and F. W. Booth. ANG II is required for optimal overload-induced skeletal muscle hypertrophy. *Am. J. Physiol.* 280:E150–159, 2001.
13. Hopkinson, N. S., A. H. Nickol, J. Payne, et al. Angiotensin converting enzyme genotype and strength in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 170:395–399, 2004.
14. Ishigai, Y., T. Mori, T. Ikeda, A. Fukuzawa, and T. Shibano. Role of bradykinin-NO pathway in prevention of cardiac hypertrophy by ACE inhibitor in rat cardiomyocytes. *Am. J. Physiol.* 273: H2659–2663, 1997.
15. Langberg, H., C. Bjorn, R. Boushel, Y. Hellsten, and M. Kjaer. Exercise-induced increase in interstitial bradykinin and adenosine concentrations in skeletal muscle and peritendinous tissue in humans. *J. Physiol. (Lond.)* 542:977–983, 2002.
16. Mayfield, R. K., N. Shimojo, and A. A. Jaffa. Skeletal muscle kallikrein: potential role in metabolic regulation. *Diabetes* 45(Suppl. 1):S20–23, 1996.
17. Montgomery, H., S. Humphries, and S. Danilov. Is genotype or phenotype the better tool for investigating the role of ACE in human cardiovascular disease? *Eur. Heart J.* 23:1083–1086, 2002.
18. Montgomery, H. E., P. Clarkson, C. M. Dollery, et al. Association of angiotensin-converting enzyme gene I/D polymorphism with change in left ventricular mass in response to physical training. *Circulation* 96:741–747, 1997.
19. Narici, M. V., H. Hoppeler, B. Kayser, et al. Human quadriceps cross-sectional area, torque and neural activation during 6 months strength training. *Acta Physiol. Scand.* 157:175–186, 1996.
20. Norregaard, J., J. J. Lykkegaard, P. M. Bulow, and B. Danneskiold-Samsoe. The twitch interpolation technique for the estimation of true quadriceps muscle strength. *Clin. Physiol.* 17:523–532, 1997.
21. Parker, D. F., J. M. Round, P. Sacco, and D. A. Jones. A cross-sectional survey of upper and lower limb strength in boys and girls during childhood and adolescence. *Ann. Hum. Biol.* 17:199–211, 1990.
22. Pratt, R. E. Angiotensin II and the control of cardiovascular structure. *J. Am. Soc. Nephrol.* 10:S120–128, 1999.
23. Rabito, S. F., R. D. Minshall, F. Nakamura, and L.-X. Wang. Bradykinin B2 receptors on skeletal muscle are coupled to inositol 1,4,5-triphosphate formation. *Diabetes* 45:S29–33, 1996.
24. Reneland, R., and H. Lithell. Angiotensin-converting enzyme in human skeletal muscle: a simple in vitro assay of activity in needle biopsy specimens. *Scand. J. Clin. Lab. Invest.* 54:105–111, 1994.
25. Rigat, B., C., Hubert, F. Alhenc-Gelas, F. Cambien, P. Corvol, and F. Soubrier. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *J. Clin. Invest.* 86:1343–1346, 1990.
26. Rutherford, O. M., D. A. Jones, and D. J. Newham. Clinical and experimental application of the percutaneous twitch superimposition technique for the study of human muscle activation. *J. Neurol. Neurosurg. Psychiatry* 49:1288–1291, 1986.
27. Stienen, G. J., J. L. Kiers, R. Bottinelli, and C. Reggiani. Myofibrillar ATPase activity in skinned human skeletal muscle fibres: fibre type and temperature dependence. *J. Physiol. (Lond.)* 493(Pt 2):299–307, 1996.
28. Thomis, M. A., W. Huygens, S. Heuninckx, et al. Exploration of myostatin polymorphisms and the angiotensin-converting enzyme insertion/deletion genotype in responses of human muscle to strength training. *Eur. J. Appl. Physiol.* 92:267–274, 2004.
29. Unger, T., B. Schull, W. Rascher, R. E. Lang, and D. Ganten. Selective activation of the converting enzyme inhibitor MK 421 and comparison of its active diacid form with captopril in different tissues of the rat. *Biochem. Pharmacol.* 31:3063–3070, 1982.
30. Wali, F. A. Effect of angiotensin II on mechanical and electrical responses of frog, chick and rat skeletal muscle. *Arch. Int. Pharmacodyn. Ther.* 282:314–327, 1986.
31. Zhang, B., H. Tanaka, N. Shono, et al. The I allele of the angiotensin-converting enzyme gene is associated with an increased percentage of slow-twitch type I fibers in human skeletal muscle. *Clin. Genet.* 63:139–144, 2003.