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Associations between cardiorespiratory responses to exercise and the C34T *AMPD1* gene polymorphism in the HERITAGE Family study

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Rico-Sanz, J., T. Rankinen, D. R. Joanisse, A. S. Leon, J. S. Skinner, J. H. Wilmore, D. C. Rao, and C. Bouchard. Associations between cardiorespiratory responses to exercise and the C34T *AMPD1* gene polymorphism in the HERITAGE Family study. *Physiol Genomics* 14: 161–166, 2003. First published June 3, 2003; 10.1152/physiolgenomics.00165.2002.—The associations of the C34T polymorphism of the adenosine monophosphate deaminase 1 (*AMPD1*) gene with cardiorespiratory phenotypes were tested during cycling exercise at absolute and relative power outputs progressing to exhaustion before and after endurance training for 20 wk in the HERITAGE Family Study cohort ($n = 779$). Since no blacks were mutant homozygotes (TT), only whites were considered for analysis (400 normal homozygotes, CC; 97 heterozygotes, CT; and 6 TT). For sedentary state, cycling at the absolute power output of 50 W resulted in a higher rating of perceived exertion in TT ($P < 0.0001$). At the relative intensity of 60% of $\dot{V}O_{2\,max}$, stroke volume was lower in TT ($P < 0.05$). Maximal values for power output, systolic blood pressure, heart rate, $\dot{V}CO_2$, and respiratory exchange ratio were lower in TT ($P < 0.05$). The cardiorespiratory training response at 50 W and at 60% of $\dot{V}O_{2\,max}$ was similar across C34T-AMPD1 genotypes. However, the maximal values for ventilation, $\dot{V}O_2$, and $\dot{V}CO_2$ during exercise increased less in TT ($P < 0.01$). The results indicate that subjects with the TT genotype at the C34T *AMPD1* gene have diminished exercise capacity and cardiorespiratory responses to exercise in the sedentary state. Furthermore, the training response of ventilatory phenotypes during maximal exercise is more limited in TT.

adenosine; human muscle; myoadenylate deaminase

DURING INTENSE EXERCISE CAUSING AMP accumulation, the enzyme adenosine monophosphate deaminase (AMPD; EC 3.5.4.6) is activated in skeletal muscle. AMP accumulation also activates AMP-activated protein kinase, which enhances fat oxidation and glucose transport (35). By converting AMP to IMP, AMPD displaces the equilibrium of the myokinase reaction toward ATP production. The AMPD reaction is also the major contributor to the production of ammonia, a biochemical indicator of the intensity of exercise (12, 19). Moreover, AMPD is the initial reaction of the purine nucleotide cycle (PNC), which plays a central role in the salvage of adenine nucleotides and in determining energy charge (19). Thus AMPD might be an important regulator of muscle energy metabolism during exercise.

The skeletal muscle-specific isoform (M) of AMPD is encoded by the *AMPD1* gene, located on the short arm of chromosome 1 (26). This isoform accounts for more than 95% of the total AMPD in muscle (13). It is mainly located in type II muscle fibers particularly at the neuromuscular junction, but also in capillaries (32).

In addition to highly variable skeletal muscle AMPD levels in a wide range of neuromuscular disorders, ~2% of human skeletal muscle biopsies are reported to be AMPD deficient (14, 15). AMPD deficiency has been attributed to a nonsense mutation (C to T transition in nucleotide 34) in exon 2 of *AMPD1* converting a glutamine codon into a premature stop codon (21). Not surprisingly, the nonsense mutation has been shown to dramatically affect the activity of AMPD in skeletal muscle. Norman et al. (22) showed that homozygotes for the mutation had less than 1% of the AMPD activity found in wild-type individuals.

In early studies, Fishbein et al. (11) proposed that a deficiency of AMPD causes muscular weakness or cramping after exercise. Since then, several studies have tried to elucidate the mechanisms by which AMPD deficiency might regulate muscle metabolism and cause premature onset of fatigue (27). Sinkeler et al. (28) showed that AMPD deficiency caused a lower rate of ATP degradation but similar phosphocreatine (PCr) hydrolysis and lactate accumulation during ischemic isometric exercise. More recently, Norman et

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al. (23) proposed that AMPD deficiency causes higher oxidative metabolism during exercise, as a result of the increased adenosine levels enhancing blood flow, and increased ADP levels stimulating oxidative phosphorylation and thereby compensating for the decreased purine nucleotide cycling. However, similar levels of aspartate and tricarboxylic acid (TCA) cycle intermediates in muscle after exercise among genotypes led Tarnopolsky et al. (30) to conclude that the C34T mutation might be a harmless genetic variant. Power output was not significantly different between TT and the CC homozygotes or CT heterozygotes in both previous studies (23, 30). More recently, however, force-generating capacity during repetitive submaximal isometric muscle contractions was shown to be reduced in subjects with AMPD deficiency compared with sedentary controls (8).

The present study investigated the effects of *AMPD1* genotypes on cardiorespiratory and performance phenotypes during cycling to exhaustion in the sedentary state and in response to training. It was hypothesized that subjects with the T allele at C34T in the *AMPD1* gene would show a lower performance capacity in the sedentary state and a reduced ability to adapt to the exercise-training program.

METHODS

Subjects

The study cohort consisted of 503 white subjects from 99 nuclear families and 276 black subjects from 105 families. Subjects of both genders were between the ages of 17 and 40 yr for offspring and 65 yr of age or younger for parents. They were required to have been sedentary for at least 6 mo. The study protocol was approved by each of the institutional review boards of the HERITAGE Family Study research consortium. Subjects gave written consent to participate in the study. A more detailed description of the HERITAGE Family Study protocol is provided in Bouchard et al. (3).

Experimental Design and Exercise Test Protocols

Subjects completed a total of three exercise tests, each on a different day, both before and after a period of exercise training (see below). These included a maximal test, a submaximal test, and a submaximal-to-maximal test. All exercise tests were conducted on a cycle ergometer (Ergo-Metrics 800S; SensorMedics, Yorba Linda, CA). Subjects completed the maximal test using a graded exercise test protocol, starting at 50 W for 3 min. The power output was increased by 25 W every 2 min thereafter to the point of exhaustion. On a different day, subjects exercised for 8–12 min at an absolute power output of 50 W, rested 4 min, and exercised for 8–12 min at a relative power output equivalent to 60% of maximal oxygen consumption ($\dot{V}O_{2\,max}$). The submaximal-to-maximal test was performed on a third day, starting with the submaximal protocol, i.e., 50 W and 60% of the initial $\dot{V}O_{2\,max}$, followed by 3 min at 80% of $\dot{V}O_{2\,max}$. The test then progressed to a maximal level of exertion (34).

Cardiovascular Measurements

Blood pressure was obtained by using Colin STBP-780 automated units. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 50 W and at the power output eliciting 60% of $\dot{V}O_{2\,max}$ were measured twice at each steady-state power output in the submaximal and submaximal-to-maximal tests, whereas only one recording was obtained at maximal exertion. Thus both the pretraining and posttraining blood pressures are the means of four measurements at 50 W and 60% of $\dot{V}O_{2\,max}$, whereas the value at exertion represents two measurements. Heart rate (HR) was monitored with an electrocardiogram, and values were recorded during the last 15 s of each exercise stage of the maximal test and once steady state was achieved at each of the submaximal-maximal tests (34). Subjects reported their rating of perceived exertion (RPE) (2) during the last 5 s of exercise at each power output.

For the submaximal and submaximal/maximal tests, two HR and cardiac output values were obtained and averaged both at 50 W and at 60% of the initial $\dot{V}O_{2\,max}$, pre- and posttraining. Cardiac output was determined by using the Collier CO_2 rebreathing technique (6), as described by Wilmore et al. (33). Stroke volume was derived by dividing the estimated cardiac output by the measured HR at the time of the cardiac output determination (34). Gas exchange variables [$\dot{V}O_2$, $\dot{V}CO_2$, ventilation rate (V_E), and respiratory exchange ratio (RER)] were recorded using a SensorMedics 2900 metabolic measurement cart throughout each exercise test and reported as the rolling average of the last three 20-s intervals of each exercise stage. The criteria for $\dot{V}O_{2\,max}$ were RER > 1.1, plateau in $\dot{V}O_2$ (changes of <100 ml/min in the last three 20-s intervals), and a HR within 10 beats/min of the maximal HR predicted by age (29).

Training program. The training was conducted on cycle ergometers (Universal Aerobicycle, Cedar Rapids, IA). Subjects were endurance trained, three times a week, for 20 wk. The intensity of the exercise progressively increased from a HR corresponding to 55% of $\dot{V}O_{2\,max}$ during the first 4 wk to 75% during the last 8 wk. The duration was also progressively increased from 30 min/day during the first 2 wk to 50 min/day, which was maintained from the 14th week to the end of the program. A more detailed description of the training program can be found elsewhere (29). To maintain constant training HR, the ergometers were interfaced with a computer system (Universal Gym Mednet, Cedar Rapids, IA) that adjusted automatically the power output to each individual's target HR. All training sessions were supervised on site.

Genotype Determination

To detect the C→T transition at nucleotide +34 at the exon 2/intron 2 boundary of the *AMPD1* gene, the region surrounding exon 2 was amplified as described in Norman et al. (22), creating a *Nsp*I site in the presence of the mutant allele. Normal and mutant alleles were identified following digestion with *Nsp*I and separation on agarose gels, yielding visible fragments of 214 bp and 191 bp, respectively.

Statistical analysis. Associations between phenotypes and genotypes were analyzed using the MIXED procedure in the SAS Version 8.1 software package. Nonindependence among family members was adjusted for by using a "sandwich estimator," which asymptotically yields the same parameter estimates as ordinary least squares or regression methods, but the standard errors and consequently hypothesis testing are adjusted for the dependencies. The method is general, assuming the same degree of dependency among all members within a family. Adjustments for age, gender, and body mass index were made for the baseline values, and for age, gender, body mass index, and baseline value for the response to training by including these variables as covariates in the

Table 1. *Distribution of AMPD1 genotypes in the HERITAGE Family Study cohort*

	Black	White
CC	98.9(273)	79.5(400)
CT	1.1(3)	19.3(97)
TT	0(0)	1.2(6)
T allelic frequency	0.5%	10.8%

Values are in percent; number people is in parentheses. The mutant allele (T) corresponds to the C34T transition in the gene.

MIXED model. Cardiac output and stroke volume were statistically adjusted for size using body surface area as determined by the equation of DuBois and DuBois (9).

RESULTS

Allelic Distribution and Subjects Characteristics

Table 1 shows the distribution of the alleles among blacks and whites. The genotype frequencies were in Hardy-Weinberg equilibrium in whites in whom it could be tested. The T allele frequency reached 0.5% in blacks and 11% in whites. The low frequency of the T allele in the black population precluded any meaningful analysis in this ethnic group. Table 2 shows the basic characteristics of whites. There were no significant differences in age, height, and body weight across genotypes.

Sedentary state

Absolute power output (50 W). DBP and SBP responses to 50 W were not affected by genotype (Table 3). The RPE was higher in TT compared with CC and CT ($P = 0.0002$). This was likely due to the fact that 50 W represented a 7% higher relative intensity in TT (37 ± 3% of maximal power output, $P < 0.05$) than in CC and CT genotypes (30% and 30%, respectively).

Relative submaximal intensity (60% $\dot{V}O_{2\ max}$). At the power output eliciting 60% of $\dot{V}O_{2\ max}$, SBP was higher ($P < 0.05$) in CT compared with TT and CC homozygotes (Table 4). Stroke volume was 13% lower in TT ($P < 0.05$). Ventilatory phenotypes and RPEs were similar across genotypes.

Metabolic responses at maximal intensity. Table 5 shows the values of the cardiorespiratory and performance phenotypes at exhaustion. SBP was lower ($P < 0.01$) in TT compared with CT and CC, whereas DBP was similar. The ventilation was identical across the three genotypes. There was a tendency for the $\dot{V}O_{2\ max}$ to be lower in TT ($P = 0.10$), while the maximal values for $\dot{V}CO_2$ and RER were significantly lower in TT compared with the other genotypes ($P < 0.05$ and $P < 0.01$, respectively). Moreover, the maximal power output was ~14% lower in TT ($P < 0.05$).

Table 3. *Cardiorespiratory phenotypes during bicycle exercise at 50 W for the three C34T AMPD1 genotypes*

	CC	CT	TT	*P*
50 W, % of MPO	30 ± 1	30 ± 1	37 ± 4	0.12
DBP, mmHg	71 ± 1	71 ± 1	72 ± 3	0.85
SBP, mmHg	145 ± 2	150 ± 2	146 ± 4	0.05
HR, beats/min	118 ± 2	119 ± 2	128 ± 6	0.34
SV, ml	98 ± 1	98 ± 2	88 ± 7	0.33
Q, l/min	11.4 ± 0.1	11.4 ± 0.2	11.1 ± 0.7	0.92
V_E, l/min	30 ± 1	31 ± 1	34 ± 2	0.13
$\dot{V}O_2$, ml/min	1,027 ± 9	1,035 ± 12	1,070 ± 39	0.45
$\dot{V}CO_2$, ml/min	944 ± 12	948 ± 13	997 ± 47	0.54
RER	0.92 ± 0.01	0.91 ± 0.01	0.93 ± 0.01	0.24
RPE	9.9 ± 0.2	10.1 ± 0.2	11.9 ± 0.4	0.0002*

Values are adjusted means ± SE. Adjustments were made for age, gender, and BMI. Body size adjustment for stroke volume (SV) and cardiac output (Q) was done using body surface area. DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate; V_E = ventilation rate; $\dot{V}O_2$, oxygen consumption rate; $\dot{V}CO_2$, carbon dioxide production rate; RER, respiratory exchange ratio; RPE, rating of perceived exertion; MPO, maximal power output. *$P < 0.0001$ vs. CC and CT.

Response to Training

The changes during exercise at 50 W and 60% of $\dot{V}O_{2\ max}$ in response to the endurance-training program indicated similar adaptation among the three genotypes. However, the decrease in RPE at 50 W as a result of the training program was larger in TT ($P < 0.05$). Maximal DBP decreased after training in CC and CT, whereas it remained the same in TT ($P < 0.03$). Maximal ventilation, $\dot{V}O_{2\ max}$, and $\dot{V}CO_{2max}$ increased less in TT ($P < 0.01$) (Table 6).

DISCUSSION

In the present study, we examined the associations of the C34T *AMPD1* genotype with cardiorespiratory, metabolic, and performance phenotypes during submaximal cycle exercise at an absolute and a relative intensity and at exhaustion in the sedentary state and in response to 20 wk of exercise training. In this study, we found a T allele frequency of 11% in whites but only of 0.5% in blacks. As there were only three CT and no TT in blacks, the study focused on the data of whites alone. One of the limitations of this study is the fact that the low number of homozygotes for the TT allele made it impossible to stratify the cohort by age and

Table 2. *Basic characteristics of the white subjects from the HERITAGE Family Study cohort*

Genotype	*n*	Age, yr	Height, cm	Weight, kg	BMI, kg/m^2
CC	187 M, 213 F	35.5 ± 14.4	170.2 ± 9.5	75.2 ± 17.6	25.8 ± 5.1
CT	54 M, 43 F	37.0 ± 15.2	171.6 ± 9.3	77.0 ± 16.7	26.0 ± 4.5
TT	4 M, 2 F	36.7 ± 12.5	177.5 ± 13.3	80.3 ± 9.7	25.7 ± 4.2
		$P = 0.39$	$P = 0.60$	$P = 0.77$	$P = 0.99$

Values are means ± SD. M, male; F, female; BMI, body mass index.

Table 4. *Cardiorespiratory phenotypes during bicycle exercise at 60% of maximal oxygen uptake for the three C34T AMPD1 genotypes*

	CC	CT	TT	*P*
DBP, mmHg	73 ± 1	72 ± 1	74 ± 3	0.49
SBP, mmHg	165 ± 1	168 ± 2	162 ± 1	0.03*
HR, beats/min	141 ± 1	142 ± 2	145 ± 2	0.46
SV, ml	104 ± 2	104 ± 2	92 ± 5	0.03†
Q, L/min	14.5 ± 0.3	14.5 ± 0.3	13.2 ± 0.7	0.11
$\dot{V}_E$, l/min	45 ± 1	45 ± 1	43 ± 3	0.61
$\dot{V}O_2$, ml/min	1,529 ± 26	1,545 ± 31	1,428 ± 59	0.17
$\dot{V}CO_2$, ml/min	1,488 ± 29	1,492 ± 32	1,370 ± 76	0.30
RER	0.97 ± 0.00	0.96 ± 0.01	0.96 ± 0.02	0.31
RPE	13.0 ± 0.2	13.3 ± 0.3	13.4 ± 0.8	0.37

Values are adjusted means ± SE. Adjustments were made for age, gender, and BMI. Body size adjustment for SV and Q was done using body surface area. RPE, rate of perceived exertion. *$P < 0.05$ vs. CT. †$P < 0.01$ vs. CC, and $P < 0.05$ vs. CT.

Table 6. *Training response of cardiorespiratory and performance phenotypes during bicycle exercise at exhaustion of progressive intensity bicycle exercise for the three C34T AMPD1 genotypes*

	CC	CT	TT	*P*
DBP, mmHg	−5 ± 1	−4 ± 1	0 ± 2	0.03[a]
SBP, mmHg	17 ± 1	10 ± 2	10 ± 3	0.41
HR, beats/min	0 ± 0	0 ± 1	−2 ± 1	0.39
$\dot{V}_E$, l/min	11.6 ± 0.9	13.9 ± 1.4	3.8 ± 3.7	0.006[b]
$\dot{V}O_2$, ml/min	406 ± 25	422 ± 32	294 ± 39	0.006[c]
$\dot{V}CO_2$, ml/min	471 ± 27	505 ± 35	328 ± 29	<0.0001[d]
RER	0.00 ± 0.00	0.00 ± 0.01	−0.01 ± 0.01	0.23
RPE	0.3 ± 0.1	0.0 ± 0.2	0.9 ± 0.5	0.07
MPO, W	56 ± 2	52 ± 3	66 ± 4	0.06[e]

Values are adjusted means ± SE. Adjustments were made for age, gender, and BMI. [a]$P < 0.01$ vs. CC. [b]$P < 0.05$ vs. CC, and $P < 0.01$ vs. CT. [c]$P < 0.01$ vs. CC and CT. [d]$P < 0.0001$ vs. CC and CT. [e]$P < 0.05$ vs. CC and CT.

gender, and thus the analyses were undertaken on data statistically adjusted for these potential confounders.

Maximal power output in the sedentary state was significantly lower in the TT homozygotes compared with CC and CT genotypes. In contrast, Norman et al. (23) did not observe lower power output in TT during a 30 s all-out sprint cycling exercise. On the other hand, De Ruiter et al. (8) found that force-generating capacity, after 5 min of repetitive voluntary isometric contractions at 40% of quadriceps femoris maximal force, decreased 29.4% in TT, while it decreased significantly less (12.8%) in controls. Moreover, Tarnopolsky et al. (30) found 15% and 26% lower peak power and time to fatigue, respectively, in TT during a progressive intensity exercise protocol. These findings reinforce the idea that the AMPD deficiency observed in TT individuals may reduce exercise capacity, as originally suggested by Fishbein (11). The mechanism by which a lower muscular performance in the range of 15% to 25% occurs in AMPD-deficient subjects remains to be defined. Based on results from several studies, TT homozygotes appear able to maintain muscle ATP levels and energy charge under a variety of exercise conditions (23, 27, 30). Moreover, it does not seem that the anaerobic energy delivery pathways are impaired in TT, since PCr hydrolysis and lactate accumulation are consistently similar to those of CC under a variety of exercise protocols (23, 27, 30).

Table 5. *Cardiorespiratory and performance phenotypes at exhaustion for the three C34T AMPD1 genotypes*

	CC	CT	TT	*P*
DBP, mmHg	83 ± 1	80 ± 1	81 ± 3	0.12
SBP, mmHg	195 ± 2	196 ± 2	185 ± 4	0.003[a]
PP, mmHg	112 ± 2	117 ± 3	104 ± 4	<0.001[b]
HR, beats/min	186 ± 1	184 ± 1	181 ± 3	0.03[c]
$\dot{V}_E$, l/min	106 ± 1	104 ± 2	100 ± 6	0.59
$\dot{V}O_2$, ml/min	2,519 ± 41	2,502 ± 49	2,362 ± 62	0.10[d]
$\dot{V}CO_2$, ml/min	2,977 ± 48	2,923 ± 55	2,721 ± 89	0.04[d]
RER	1.18 ± 0.01	1.17 ± 0.01	1.14 ± 0.01	0.007[e]
RPE	19.2 ± 0.1	19.2 ± 0.1	18.6 ± 0.5	0.49
MPO, W	189 ± 4	187 ± 4	162 ± 8	0.03[f]

Values are adjusted means ± SE. Adjustments were made for age, gender, and BMI. SV and Q were not determined at exhaustion. PP, pulse pressure. [a]$P < 0.01$ vs. CC and CT. [b]$P < 0.05$ vs. CC, and $P < 0.001$ vs. CT. [c]$P < 0.10$ vs. CT, and $P < 0.05$ CC vs. CT. [d]$P < 0.05$ vs. CC, and $P < 0.05$ vs. CT. [e]$P < 0.01$ vs. CC, and $P < 0.05$ vs. CT. [f]$P < 0.01$ vs. CC and CT.

Sabina et al. (27) proposed that disruption of the PNC accounted for the 72% lower total work performed during muscle contraction in patients with AMPD deficiency. Tarnopolsky et al. (30) disputed this, as they found similar TCA cycle intermediates in mutant homozygotes as in controls. However, glutamine levels were higher in AMPD-deficient patients and seemed to have decreased during exercise. Since glutamine has been shown to increase TCA intermediates during exercise (4), it might partly compensate for the absent or reduced flux of TCA intermediates generated through the PNC in mutant homozygotes. During intense exercise, muscle adenylosuccinate content decreases and does not recover under ischemic conditions, suggesting that only the deaminating limb of the PNC operates during intense muscle contraction and reamination is dependent on aerobic metabolism (31). Norman et al. (23) suggested that the TT homozygotes compensate their lack of PNC cycling by increasing oxidation of substrates due to ADP and adenosine effects on oxidative metabolism. Furthermore, the higher AMP accumulation in TT can activate AMP-activated protein kinase, which seems to enhance fatty acid oxidation and glucose transport in muscle (35).

Elevated levels of AMP can also lead to adenosine accumulation. Adenosine increases in the interstitium of human muscle with increasing exercise intensity (7, 16, 20), and it increases more in AMPD-deficient compared with normal muscle (23, 27). During exercise at 62% of peak power, infusion of adenosine increased femoral artery blood flow in a dose-dependent manner (25). As the exercise becomes more severe, HR attains a maximal level and stroke volume reaches its maximum and often decreases, resulting in a fall in blood pressure (5). The results reported herein showed that stroke volume was lower in TT at the power output

eliciting 60% of $\dot{V}O_{2\,max}$. In addition, SBP was lower in TT at exhaustion. As the DBP did not change, the pulse pressure was lower in TT at max exercise (Table 5). Since pulse pressure is an indicator of the ejection volume by the heart, these results are consistent with the lower stroke volume observed at 60% of $\dot{V}O_{2\,max}$ in TT.

Although the $\dot{V}O_2$ at exhaustion was not statistically different among the genotypes, the ~5% lower rate of $\dot{V}O_2$ in TT cases could be physiologically relevant at high power outputs. The lower $\dot{V}O_2$ at exhaustion was not due to lack of motivation on the part of the TT subjects, since they fulfilled the criteria for $\dot{V}O_{2\,max}$ (see METHODS). Moreover, the same maximal RPE occurred at a lower power output in TT subjects.

To our knowledge, no study has evaluated the response of *AMPD1* genotypes to exercise training. The TT exhibited cardiorespiratory and metabolic responses to training similar to those of the CC and CT at the submaximal exercise intensities. These are generally characterized by decreased blood pressure, RER, and HR and increased stroke volume and oxygen uptake at a fixed percentage of maximal power output and at exhaustion. As sprint, high-intensity, and endurance training have been shown to decrease the activity of AMPD (10, 17, 24), normal muscle appears to depend less on AMPD. However, the lower increase in the maximal ventilatory response after training in TT is suggestive of reduced ability to perform aerobic exercise at higher intensities. These results on the response to training at maximal power output reinforce the view that TT have a slight impairment potentially caused by increased adenosine levels. On the other hand, the T allele carrier status has been associated with improved survival in patients with coronary artery disease (CAD; Ref. 1) and congestive heart failure (18), effects thought to be mediated by a protective effect of increased myocardial adenosine. In the present study, *AMPD1* TT individuals also benefited significantly from exercise training, as their $\dot{V}O_{2\,max}$ and maximal power output increased significantly. The reasons for this apparent discrepancy between CAD patients and asymptomatic adults remain unclear at this time.

In conclusion, the present results suggest that subjects with the TT genotype of the *AMPD1* gene have reduced exercise capacity. Their ventilatory adaptations to exercise training appear to be limited at higher intensities. They nonetheless exhibited significant cardiorespiratory and performance improvements. Despite the internal consistency of the findings, caution is warranted as there were only six mutant homozygotes available for the association studies.

DISCLOSURES

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