Plasma osmolality, volume, and renin activity at the "anaerobic threshold"

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GLEIM, GILBERT W., PAUL M. ZABETAKIS, EUGENE E. DEPASQUALE, MICHAEL F. MICHELIS, AND JAMES A. NICHOLAS. *Plasma osmolality, volume, and renin activity at the "anaerobic threshold."* J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 56(1): 57–63, 1984.—Plasma renin activity (PRA), volume (PV), osmolality, and hemodynamic parameters were examined in relation to the anaerobic threshold (AT) during progressive cycle ergometry (PE) and repetitive bouts of unilateral isokinetic knee extension-flexion (LE) at 50% maximum voluntary contractions in eight normotensive males. During PE, the observed rise in PRA paralleled that of lactate with abrupt increases occurring at the AT. Correlation of %Δ lactate (La), %Δ osmolality, and %Δ PV with %Δ PRA were $r = 0.65$, 0.36, and −0.51, respectively (all $P < 0.01$). In addition, when mean arterial pressure was plotted as a function of $\dot{V}O_2$, the rate of rise was greater below the AT than above the AT (11.5 vs. −2.4 mmHg·l^{-1}·min, $P < 0.001$). A time control study (TC) exercising subjects for the same duration but at work rates maintained below the AT resulted in significantly lower values for both PRA and La (7.18 vs. 11.27 mg angiotensin I (ANG I)·ml^{-1}·min and 3.16 vs. 9.93 mM, $P < 0.05$ for TC vs. PE) while producing a similar fall in %Δ PV and rise in osmolality. During LE, a high correlation was obtained for %Δ PRA and %Δ La ($r = 0.86$, $P < 0.01$) but not for %Δ PRA with %Δ PV or %Δ osmolality. The data demonstrate that PRA parallels lactate during exercise and that mean arterial pressure rises more slowly beyond the AT despite a more rapid rise in PRA.

plasma renin activity; mean arterial pressure; dynamic exercise; isokinetic exercise

DURING PROGRESSIVE DYNAMIC EXERCISE, an abrupt increase in the rate of rise of blood lactate, minute ventilation, and CO_2 production may denote the recruitment of additional anaerobic systems; this point was designated the "anaerobic threshold" (AT) by Wasserman et al. (28). Although it has been demonstrated that there is a shift in metabolic substrate availability about the AT with less free fatty acid and more glycogen being consumed (10, 12), the relationship of the AT to the endocrine and hemodynamic responses of dynamic exercise has yet to be precisely defined.

Furthermore, there is some controversy as to the interpretation of the AT (15). Patients with McCardle's syndrome demonstrate a nonlinear increase in minute ventilation at 70–85% of maximum O_2 consumption despite no increase in mixed venous lactate (9). Also, studies have shown that the ventilatory threshold and lactate threshold can occur at different times (8, 11) and that the AT can be altered by changes in acid-base status (17).

Recently, Lehmann et al. (18) observed that, at work rates above the AT, catecholamine levels increased at rates comparable to that of lactate. Although not addressing the AT per se, Wade and Claybaugh (26) and Kotchen et al. (16) observed a significant rise in plasma renin activity at 70 and 100% of maximum O_2 consumption ($\dot{V}O_{2\,max}$) but not at lower work rates of 35 and 40% $\dot{V}O_{2\,max}$. As a result, it is possible that during dynamic exercise the release of renin as well as catecholamine may be intimately linked to the attainment of the AT.

The present study was undertaken to investigate the response of renin during progressive dynamic exercise and isokinetic exercise. Plasma volume and osmolality changes were also evaluated during both dynamic and isokinetic exercise to identify the relative contribution of these factors to renin release. The purpose of the study was to define *1*) the relationship of lactate, plasma volume, and plasma osmolality to renin release during dynamic and isokinetic exercise, and *2*) the interrelationship of these changes with the cardiovascular events occurring at the AT.

MATERIALS AND METHODS

Eight normotensive nontrained male volunteers (aged 25–30 yr) who were in good health and not taking medication agreed to participate in the study. Informed written consent was obtained, and the protocol was approved by the Research and Publications Committee of Lenox Hill Hospital.

The testing consisted of four separate testing periods, each separated by at least 2 days but occurring within a 2-wk period. Progressive exercise (PE) and time control (TC) were always performed between 0800 and 1000 h, whereas the isokinetic leg exercise (LE) was performed between 1100 and 1400 h. The progressive exercise was always performed first, but the order of the other tests

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was randomized.

Progressive exercise. The subject reported to the laboratory at 0800 h having been instructed to eat nothing more than clear fluids and toast for breakfast. Caffeinated beverages were excluded. The subject's height and nude weight were obtained. An 18-gauge Medicut intravenous cannula was inserted into a forearm vein and connected to a 250-ml solution of 5% dextrose in water with 2,000 U of heparin added. This served as a flush for the intravenous line and was closed after each flush was completed. Subjects were then prepared for electrocardiographic (ECG) monitoring (V5, aVF). A full resting 12-lead ECG was obtained. Subjects sat next to a mechanically calibrated Collins Pedalmate cycle ergometer (Collins, Braintree, MA) for 20 min, after which a resting blood pressure and blood sample were obtained. For this and all subsequent samples the line was cleared by removing 3–4 ml (dead space 1.5 ml) and 20 ml for blood analyses. The line was flushed with approximately 10 ml of the 5% dextrose in water-heparin solution. Average sampling time was 45 s. The subject next mounted the ergometer and began breathing into a Beckman metabolic measurement cart (Beckman, Fullerton, CA) previously calibrated with standardized gases. After baseline values were obtained, the subject began pedaling at 25 W and 60 rpm. After 3 min, blood pressure was obtained by auscultation, and a blood sample was taken. At 4 min the work rate was increased by 25 W. This procedure was continued until the subject could not maintain the 60-rpm speed. At termination of exercise, the subject sat on the ergometer until a 5-min recovery blood pressure and blood sample were obtained. Dry nude weight was measured to assess weight loss.

Thirty minutes later the subject was tested on a Cybex II isokinetic dynamometer (Lumex, Ronkonkoma, NY) at 180°/s in the motions of knee extension and knee flexion. The strength in knee extension and knee flexion was determined for each leg so that 50% of this value could be used in dictating the work for the isokinetic leg exercise tests.

Isokinetic leg exercise. On a different testing day the subject reported to the laboratory at 1100 h to perform isokinetic leg exercise with one leg. This procedure was repeated on a separate testing day for the opposite leg. The subject sat resting for a period of 20 min. A venipuncture was performed, and 20 ml of blood was obtained. Heart rate was obtained by palpation, and blood pressure was obtained by auscultation. The subject then performed knee extension and flexion at 180°/s on an Orthotron single-joint isokinetic machine (Lumex) at 50% of the maximum measured previously for that leg on the Cybex dynamometer. The subject exercised continuously for 1 min and then rested for 30 s. This was repeated until five sets had been completed. Both the subject and investigator could see the torque register on a dial, and the subject was careful not to perform any obvious isometric work with the upper body. Heart rate and blood pressure were obtained immediately after the test, and another blood sample was taken within 2 min after the test.

Time control. The protocol for this test was identical in every manner to PE except that each patient exercised to the work rate at which his AT had occurred during the PE study. The AT was defined as the point during exercise after which a nonlinear increase in lactate occurred. The subject maintained this work rate for the remaining time previously spent in the progressive exercise test. Blood samples were obtained in the same manner as PE.

Analytical methods. Plasma renin activity (normal range 1.0–5.0 ng angiotensin I (ANG I)·ml^{-1}·h) was determined using the method of Sealey et al. (23). Samples were analyzed for osmolality by freezing-point depression (model 3DII, Advanced Digimatic Osmometer) and for hematocrit in triplicate by the microcapillary method. Blood lactate was measured by a Roche 640 lactate analyzer (Roche Bio-Electronics, Basel, Switzerland).

Calculations and statistics. The percent change plasma volume (%Δ PV) at each work load was calculated from the resting preexercise hematocrit (Hct_{pre}) and subsequent determinations (Hct_{n+1}) using the following equation (1)

$$\%\Delta\ PV = \frac{100}{(100 - Hct_{pre})} \times \frac{100\ (Hct_{n+1})}{Hct_{n+1}}$$

Mean arterial pressure (MAP) was calculated using the following equation

MAP = ⅔ diastolic blood pressure + ⅓ systolic blood pressure

Multiple comparisons were first analyzed by a one-way analysis of variance. When significance was obtained, means were compared using a modified *t* statistic with the critical value obtained by the Bonferroni method (27). Comparisons between two means were analyzed by paired Student's *t* tests. Linear regression and multiple regression were performed by standard techniques (25). Comparisons of regression line slopes were compared by a *t* test for regression coefficients (21).

RESULTS

Oxygen consumption and blood pressure. Values for $\dot{V}O_2$, heart rate (HR), and blood pressure are shown in Table 1. During both PE and the TC study, $\dot{V}O_2$, HR, and systolic pressure all rose. Notably, none of the values at the AT differed significantly between PE and TC or from those values obtained at the end of TC (final work rate). These data comply with our study design that proposed to exercise subjects during TC for the same total length of time as during PE but at a maximum work load equal to their previously determined AT.

A plot of rate pressure product (MAP × HR) and lactate measurements obtained during PE revealed a striking relationship (Fig. 1). There was less of an increase in rate pressure product at lactate levels above the AT (mean lactate 2.5 mM). Despite a continued rise of both PRA and lactate as well as heart rate at work loads above the AT, there was a decline in the slope of MAP (−2.4 above the AT vs. 11.5 below the AT, $P < 0.001$) when plotted as a function of $\dot{V}O_2$ (Fig. 2). Consequently there was a less rapid increase in rate pressure product

TABLE 1. *Hemodynamic measurements during progressive exercise and time control protocols*

		Rest	Anaerobic Threshold	Final Work Rate
$\dot{V}O_2$, l/min	PE	0.32 ± 0.04	1.48 ± 0.10	2.74 ± 0.20
	TC	0.28 ± 0.02	1.40 ± 0.09	1.48 ± 0.09
P		NS	NS	0.001
Heart rate, beats/min	PE	78 ± 2	140 ± 7	189 ± 4
	TC	75 ± 2	130 ± 4	148 ± 6
P		NS	NS	0.001
Systolic blood pressure, mmHg	PE	126 ± 4	173 ± 7	192 ± 8
	TC	118 ± 4	166 ± 8	169 ± 8
P		NS	NS	0.05
Diastolic blood pressure, mmHg	PE	82 ± 3	81 ± 5	78 ± 5
	TC	81 ± 3	81 ± 5	78 ± 5
P		NS	NS	NS
Mean arterial pressure, mmHg	PE	97 ± 3	112 ± 5	116 ± 3
	TC	94 ± 2	109 ± 2	108 ± 2
P		NS	NS	0.05

Values are means ± SE; $n = 8$ subjects. $\dot{V}O_2$, O_2 consumption; PE, progressive exercise; TC, time control.

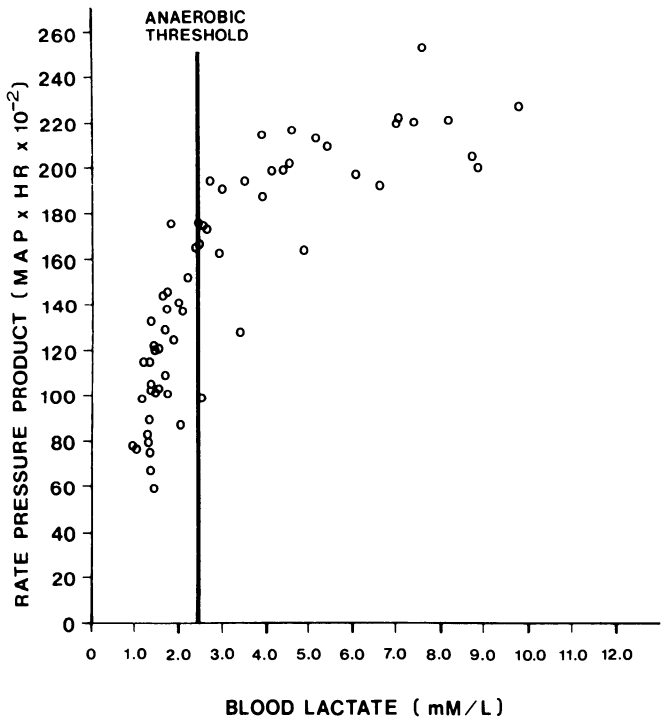

FIG. 1. Relationship of rate pressure product and blood lactate during the progressive exercise protocol in 8 subjects. *Solid vertical line* represents mean anaerobic threshold (2.42 ± 0.20 mM) of 8 subjects. See text for additional information.

above the AT due to a failure of MAP to rise despite increasing amounts of lactate and PRA.

Lactate and renin. There were no significant differences between PE and TC resting values for plasma renin activity (PRA) or blood lactate (Table 2). In contrast, the PE recovery values for both PRA and lactate were significantly higher than those obtained during the TC study. For comparison all further data are expressed as percent change from resting values.

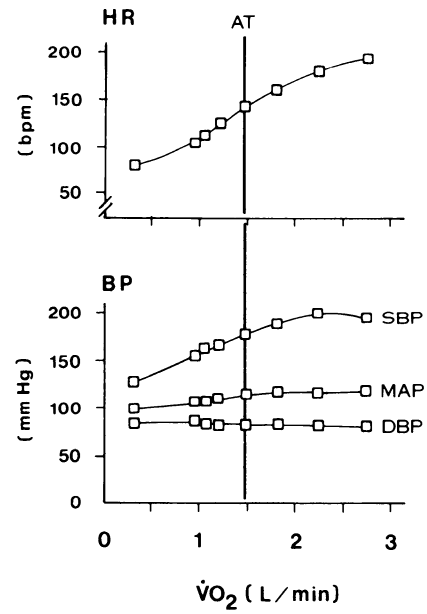

FIG. 2. Heart rate (HR) and blood pressure (BP) levels plotted as function of O_2 consumption ($\dot{V}O_2$). *Each point* represents mean of results from 8 subjects during progressive exercise protocol. *Bottom panel* depicts systolic blood pressure (SBP), mean arterial pressure (MAP), and diastolic blood pressure (DBP), respectively. *Solid vertical line* represents mean anaerobic threshold (AT, 1.48 ± 0.10 l/min). Regression line for mean arterial pressure below AT was $y = 11.5x + 94.2$ compared with $y = -2.4x + 121.2$ above AT.

TABLE 2. *Comparison of progressive exercise and time control values obtained before and 5 min after exercise*

		Rest	After Exercise
PRA, ng ANGI·ml^{-1}·min	PE	3.05 ± 0.91	11.27 ± 2.63
	TC	3.42 ± 0.77	7.18 ± 1.83*
Lactate, mM	PE	1.27 ± 0.06	9.93 ± 0.60
	TC	1.23 ± 0.09	3.16 ± 0.27†
Osmolality, mosmol/kg	PE	287.6 ± 2.8	294.3 ± 2.0
	TC	292.4 ± 3.1	292.0 ± 3.0
Hematocrit, %	PE	41.4 ± 0.6	42.7 ± 1.1
	TC	38.8 ± 0.8*	40.2 ± 1.4
%Δ PV	PE		−3.8 ± 5.0
	TC		−4.9 ± 4.6
Wt, kg	PE	75.8 ± 2.5	75.3 ± 2.5
	TC	75.5 ± 2.5	75.1 ± 2.5

Values are means ± SE; $n = 8$ subjects. PRA, plasma renin activity; PV, plasma volume; PE, progressive exercise; TC, time control. Significant difference between PE and TC: * $P < 0.05$; † $P < 0.001$.

During PE an abrupt increase was observed in the slope of the regression lines at work loads above the AT for both %Δ PRA (66.2 above vs. 19.4 below AT, $P < 0.01$) and %Δ lactate (171.2 above vs. 24.1 below AT, $P < 0.001$) (Figs. 3 and 4). In contrast, PRA and lactate increased constantly during TC; the slopes of the lines were similar to the slopes for PE at work loads below the AT. This relationship resulted in the %Δ PRA and %Δ lactate of PE being significantly different from TC values at two and three work rates above the AT (AT + 2 and AT + 3, respectively), as well as on recovery. A close

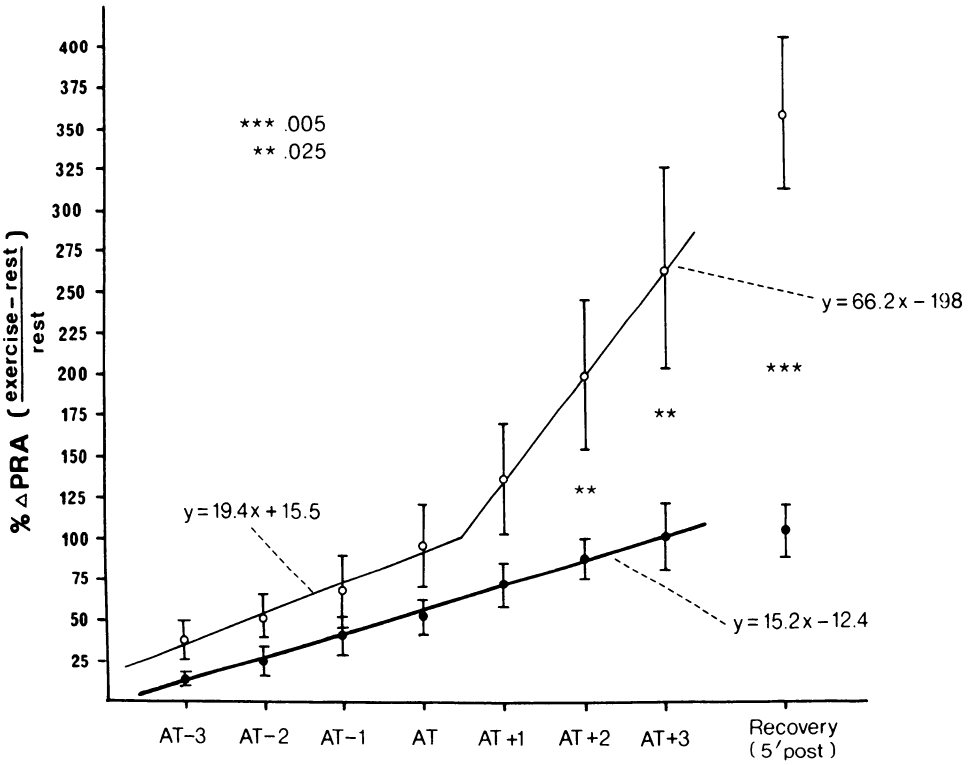

FIG. 3. Percent change in plasma renin activity (PRA) vs. work load normalized for each subject's anaerobic threshold (AT). Rate of rise of PRA is greater at work rates above AT during progressive exercise (PE, *light line*). Slopes of lines for time control study (*heavy line*) and sub-AT for PE are similar. *Each point* represents mean ± SE of results from 8 subjects.

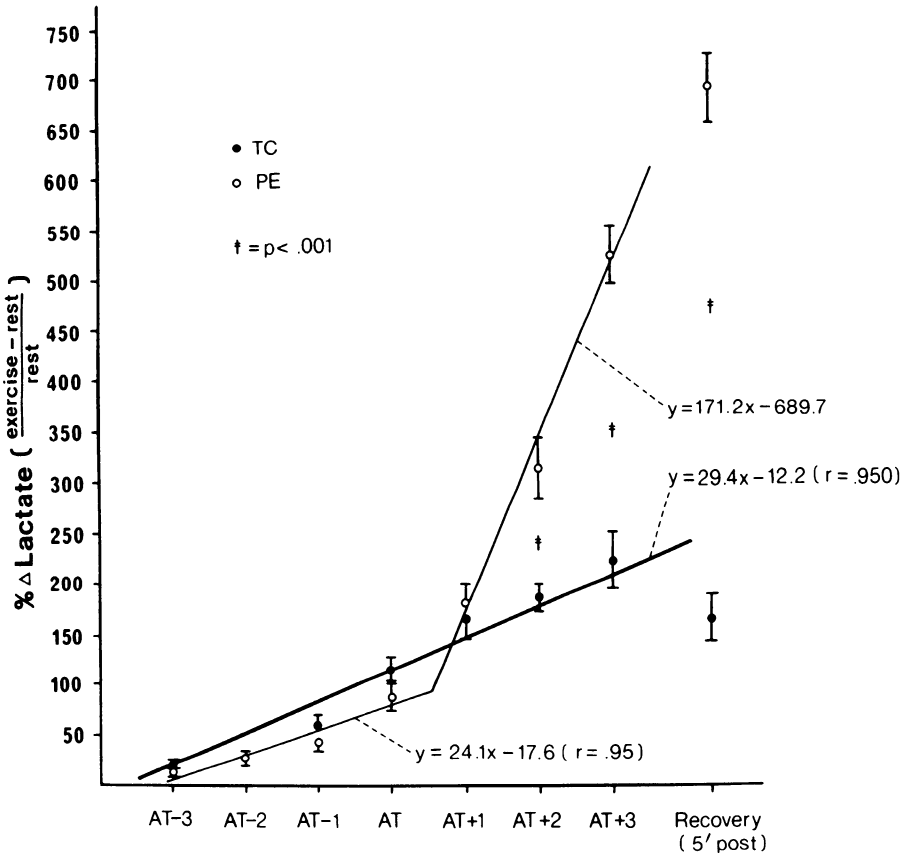

FIG. 4. Percent change in lactate vs. work rate normalized for each subject's anaerobic threshold (AT). By definition, rate of rise of lactate is greater at work rates above AT. Slopes for sub-AT values for progressive exercise (PE, *light line*) and time control studies (TC, *heavy line*) are similar. *Each point* represents mean ± SE of results from 8 subjects.

correlation between exercise-induced alterations in PRA and lactate is apparent. The correlation coefficient for %Δ lactate vs. %Δ PRA during PE for all subjects combined is $r = 0.65$ ($P < 0.001$).

Plasma osmolality and volume. As demonstrated in Fig. 5, a change in the slope of osmolality was also apparent at work rates above the AT during PE, although the difference between PE and TC was not significant until the final work rate of the test. The correlation of the %Δ osmolality with the %Δ PRA was $r = 0.36$ ($P < 0.01$) and that of %Δ plasma volume with %Δ PRA was $r = -0.51$ ($P < 0.001$). Thus PRA varied inversely with %Δ

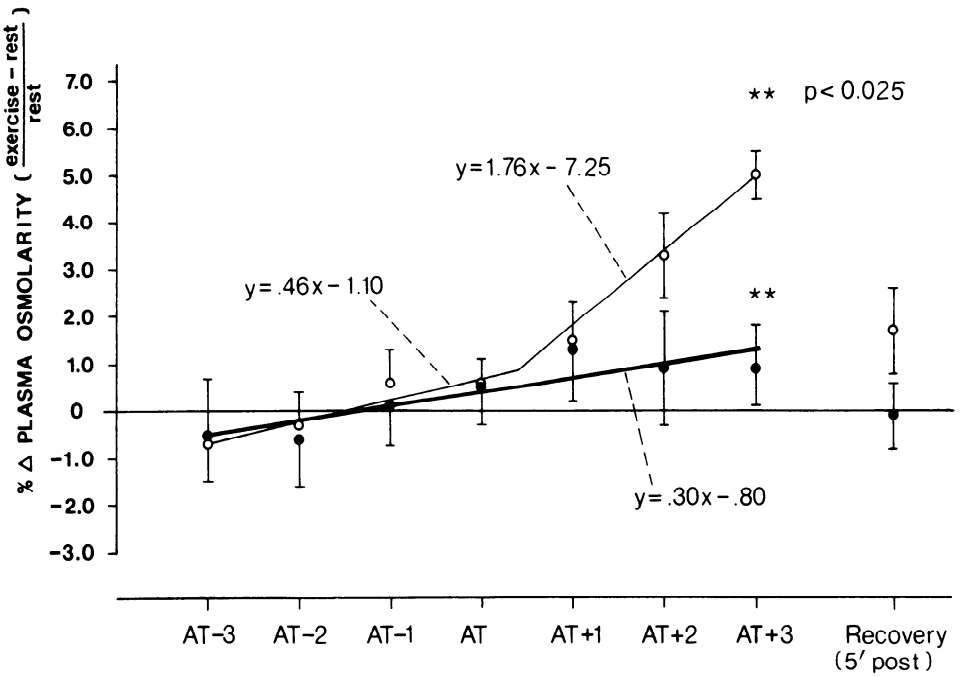

FIG. 5. Percent change in plasma osmolality vs. work rate normalized for each subject's anaerobic threshold (AT). Difference between progressive exercise (*light line*) and time control studies (*heavy line*) is not significant until AT + 3. *Each point* represents mean ± SE of results from 8 subjects.

TABLE 3. *Results of leg exercise responses to isokinetic testing*

	Right leg	Left leg
KE, ft-lb		
Max	149.0 ± 13.2	147.4 ± 14.2
50%	75.0 ± 6.5	73.8 ± 7.1
KF, ft-lb		
Max	99.1 ± 6.7	96.4 ± 7.8
50%	49.4 ± 3.3	48.1 ± 3.8
%Δ Lactate	278 ± 42.4	245.4 ± 36.1
%Δ PRA	31.2 ± 12.0	29.0 ± 10.4
%Δ PV	−7.3 ± 2.2	−5.8 ± 1.6
%Δ Osmolality	1.4 ± 0.8	0.2 ± 0.6

Values are means ± SE; n = 8 subjects. KE, knee extension; KF, knee flexion; PRA, plasma renin activity; PV, plasma volume. No significant difference existed between the right and left leg responses.

TABLE 4. *Hemodynamic responses to isokinetic leg exercise*

	Rest	After Exercise	P
Systolic blood pressure, mmHg	125.7 ± 3.1	169.3 ± 7.3	0.001
Diastolic blood pressure, mmHg	76.6 ± 2.2	74.4 ± 2.4	NS
Mean arterial pressure, mmHg	92.9 ± 1.8	106.8 ± 2.7	0.001
Heart rate, beats/min	75.7 ± 2.2	109.0 ± 6.7	0.005

Values are means ± SE; n = 8 subjects. Pooled data for both legs.

PV and directly with %Δ osmolality. The change in osmolality during exercise appears, in fact, to lag behind the rapid change in lactate. Interestingly multiple regression analysis of %Δ lactate and %Δ PV vs. %Δ PRA during PE yielded a higher multiple correlation (R = 0.70) than either variable alone. Furthermore, the magnitude of PV change in both exercise periods (PE −3.8 ± 5.0 and TC −4.9 ± 4.6) was not different despite a greater rise in PRA during PE (Table 2). Although TC and PE were of the same duration and equal amounts of blood were sampled, subjects did show a significantly greater weight loss in PE (−0.56 ± 0.04 vs. 0.44 ± 0.03 kg, $P < 0.05$), presumably through greater sweat loss.

Isokinetic leg exercise. Table 3 shows the results for isokinetic work. There were no significant differences between the legs for any of the variables measured. Therefore the pooled leg exercise data was used for all subsequent analyses. Table 4 shows the changes in blood pressure and heart rate during LE expressed as the mean for both legs.

Linear regression analysis was performed for %Δ PRA vs. %Δ lactate, %Δ PRA vs. %Δ PV, and %Δ PRA vs. %Δ osmolality. A strikingly positive and significant relationship was obtained for %Δ PRA and %Δ lactate (%Δ PRA = 0.24 × %Δ lactate − 33.1, r = 0.86; Fig. 6). In other words, those subjects who liberated the most lactate had the greatest elevations in PRA as well. It should be noted that each subject performed the same relative amount of work (50% of his own maximum). In contrast, the regression lines for %Δ PV vs. %Δ PRA and %Δ osmolality vs. %Δ PRA were not significant and, in fact, were in a direction opposite to that expected; i.e., increasing PRA was associated with less of a decline in PV or a rise in osmolality.

DISCUSSION

As has been previously demonstrated with catecholamines in dynamic exercise (18), changes in PRA correlated directly with changes in lactate during both dynamic and isokinetic exercise. Moreover, work performed at levels above the AT was associated with an abrupt increase in the levels of renin and lactate but with a decreased rate of rise of mean arterial pressure. Under normal physiological conditions a pivotal relationship of

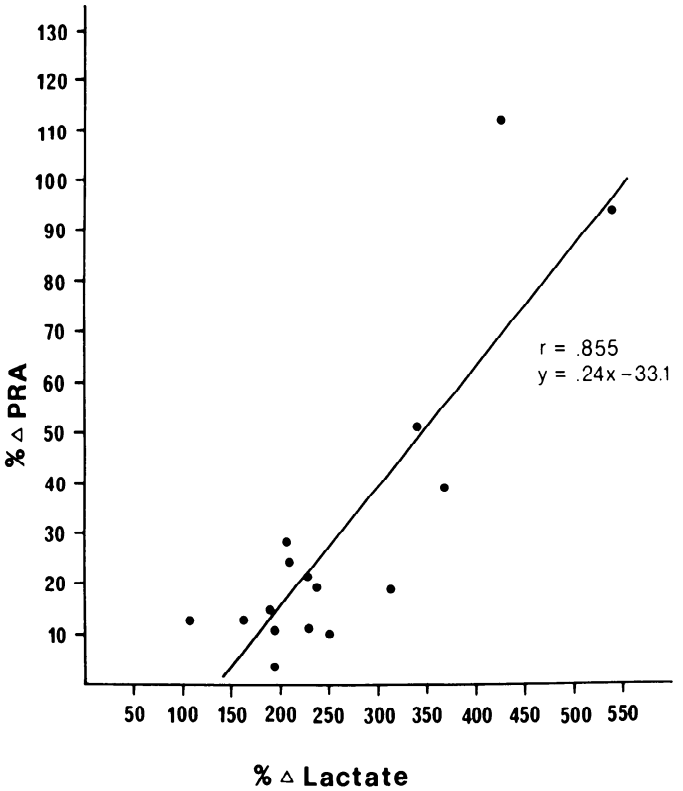

FIG. 6. Relationship of percent change plasma renin activity (PRA) and percent change lactate [(post-pre)/pre] for 8 subjects (16 legs) during isokinetic knee extension-flexion at 50% maximum voluntary contraction.

the AT to indices of sympathetic function and the hemo dynamic events during exercise is suggested by the data.

This observation is consistent with an earlier finding of Wade and Claybaugh (26) who noted that PRA increased only after attainment of 70% $\dot{V}O_{2max}$ after 20 min of exercise. Although lactate levels were not measured, work performed at 35% maximum, presumably below the AT, was not associated with a rise in PRA. Similarly, Kotchen et al. (16) noted that norepinephrine as well as PRA was significantly elevated after 10 min work on a bicycle ergometer at 70 and 100% $\dot{V}O_{2max}$, with no increase at 40% $\dot{V}O_{2max}$. Likewise, Lehmann et al. (18) noted a strong correlation between catecholamines and blood lactate during exercise, whereas Haggendahl, Hartley, and Saltin (10) demonstrated that catecholamine release was related to the intensity of work performed. These studies suggest that the exercise-mediated release of renin and catecholamine is a function of the intensity of work. In light of our findings, during exercise the augmented release of these hormones is commensurate with a nonlinear rise in mixed venous lactate, the point designated as the AT.

The abrupt rise in renin at work loads above the AT as well as the strong positive correlation between the changes in lactate and PRA support this conclusion. During PE it is also apparent that PRA is directly related to changes in PV. However, based on the available data, PV does not appear to be the primary mediator of renin release. First, although multiple regression analysis demonstrated that changes in PV and changes in lactate together accounted for more variability in PRA than either variable alone, the correlation of %Δ PV with %Δ PRA was not as strong as that for %Δ lactate and %Δ PRA. Secondly, the time control study, during which no subject worked higher than his individual AT, produced changes in PV of similar magnitude to that produced during PE. Yet PRA as well as lactate was significantly lower at the end of the time control study. Finally, using pooled data for the leg exercise, a high correlation was obtained between %Δ PRA and %Δ lactate ($r = 0.86$) despite correlations opposite to that expected for %Δ osmolality and %Δ PV. These data agree with the observation of Convertino et al. (7) that PRA correlates poorly with changes in osmolality and PV during exercise.

Factors other than renal plasma flow may influence the exercise-induced rise in PRA. Despite inhibition of renal vasoconstriction with dihydralazine, Bozovic and Castenfors (2) failed to blunt the rise in PRA in supine exercising subjects. Even after completion of exercise with an increase in renal plasma flow, PRA levels remain elevated (4). Also it appears that alteration in distal tubular sodium delivery during exercise is not a primary regulator of PRA in this setting (5). These studies question the relative importance of a baroreceptor function of the juxtaglomerular apparatus in regulating PRA during acute exercise.

In contrast, the importance of the sympathetic nervous system to the regulation of renin is strongly supported by the observed rise in PRA and catecholamine levels during progressive exercise (7, 16, 18), the reduction in PRA levels with ganglionic blockade in exercising rats (3), and the abolition of PRA through β-blockade in exercising rats (19). The striking relation of PRA and catecholamine levels to the attainment of the AT underscores the importance of sympathetic nervous system activity and concomitant cardiovascular events at this point during exercise. It is of considerable interest that at the AT, the slopes of mean arterial pressure and rate pressure product approach zero in spite of the increases in substances which are largely vasoconstrictors. Such changes have been noted by Clausen (6) with regard to mean arterial pressure, although no relationship with AT was established.

There exists some controversy in the literature regarding the nature of the AT. Green et al. (8) recently demonstrated that a substantial rise in muscle lactate occurs before the blood lactate AT. Since muscle glycolysis occurs before the AT, this data is inconsistent with the assumption that the AT merely represents the onset of anaerobiosis (28). That a breakaway in measurable venous lactate does occur in a reproducible fashion is not at issue. This "anaerobic" or lactate threshold, for want of a better term, may be related to multiple factors including increased production, decreased utilization, alteration in hepatic clearance, or a change in the diffusion of lactate from exercising muscle. It has recently been postulated that catecholamine activation of skeletal muscle phosphorylase may, in fact, contribute to the increase in venous lactate during exercise (24). In view of the correlation of catecholamine levels (18) and PRA with blood lactate, augmented sympathetic outflow at or near the AT may be postulated. Although this data does not permit clarification of all of the questions surrounding

the AT, it does suggest that the AT may be closely linked to an increase in sympathetic activity.

The precise stimulus for this increased sympathetic activity may be localized to the contracting skeletal muscle. Mitchell, Reardon, and McCloskey (20) have reported the existence of a cardiovascular reflex evoked by contracting skeletal muscle. Petrofsky, Phillips, and Lind (22) have shown that the receptor for this reflex may be confined to type II muscle. Our results from LE show that those subjects who liberate the most lactate also demonstrate the greatest increases in PRA. It is well known that type II muscle has a greater glycolytic capacity than type I muscle. Increased mixed venous lactate and PRA may be related to recruitment of type II muscle. This hypothesis is supported by the work of Ivy et al. (14), who demonstrated that fiber composition of the exercising skeletal muscle relates to the level of $\dot{V}O_2$ at which the AT is attained. Subjects or athletes with a higher percentage of type I fiber typically have an AT that is closer to their $\dot{V}O_{2\,max}$ than subjects who have more type II fiber.

In conclusion, our results indicate that the AT represents a pivotal point during exercise associated with an abrupt increase in PRA and with further increases in plasma osmolality. Furthermore, there is less of a rise in mean arterial pressure beyond this point. It is clear that sympathetic activity and hemodynamic events occurring at the AT must not be overlooked in the design of exercise tests and conditioning protocols.

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