Association of Blood Pressure and Fitness With Levels of Atherosclerotic Risk Markers Pre-Exercise and Post-exercise

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Background: Physical fitness may attenuate the increased atherosclerotic risk in patients with systemic hypertension. We investigated the association of screening blood pressure (BP) and cardiorespiratory fitness with baseline levels and exercise-induced changes in levels of soluble atherosclerotic risk markers.

Methods: Twenty-six otherwise healthy and unmedicated subjects with elevated BP (systolic BP and/or diastolic BP ≥130/85 mm Hg) and 40 subjects with normal BP underwent 20-min treadmill exercise at 65% to 70% of predetermined peak oxygen consumption (VO_{2peak}). Interleukin (IL)-6, soluble intercellular adhesion molecule (sICAM)-1, von Willebrand factor (VWF) antigen, and plasminogen activator inhibitor (PAI)-1 antigen were measured at baseline (ie, pre-exercise), early postexercise, and late postexercise (ie, 25 min after exercise).

Results: At baseline, higher screening mean arterial BP (MAP) independently predicted higher sICAM-1 levels ($P = .031$), and lower VO_{2peak} independently predicted higher IL-6 ($P = .016$) and PAI-1 ($P < .001$) levels. Early and late postexercise lower VO_{2peak} was associated with higher mean PAI-1 ($P \leq .072$) and IL-6 ($P \leq .026$) levels, and higher screening MAP was associated with higher mean sICAM-1 levels ($P \leq .035$). Higher VO_{2peak} was associated with a greater PAI-1 increase from baseline to early postexercise in subjects with elevated BP ($P = .045$) but not in those with normal BP.

Conclusions: Circulating levels of some atherosclerotic risk markers at baseline and with exercise were higher with elevated BP and lower with better fitness. Greater fitness did not particularly protect subjects with elevated BP from potentially harmful responses of atherosclerotic risk markers to acute physical exercise. Am J Hypertens 2007;20:670–675 © 2007 American Journal of Hypertension, Ltd.

Key Words: Cellular adhesion, exercise, fitness, hemostasis, hypertension, inflammation.

Elevated plasma levels of proinflammatory and prothrombotic markers contribute to the increased risk of atherosclerosis and atherothrombotic events in individuals with elevated systemic blood pressure (BP).[1,2] Increased cardiorespiratory fitness attenuates the risk of atherosclerotic cardiovascular diseases.[3] Among hypertensive men, physical fitness was inversely associated with plasma levels of C-reactive protein and soluble intercellular adhesion molecule (sICAM)-1.[4] Atherosclerotic risk increases linearly with higher BP and moreover is predicted by both systolic and diastolic BP.[5] We therefore hypothesized that in a sample of subjects with and without elevated BP, higher mean arterial BP (MAP) and poorer fitness would show associations with higher plasma baseline levels of atherosclerotic markers of inflammation and thrombogenicity. We further hypothesized that the positive relationship between MAP and atherosclerotic markers would be attenuated by good fitness.

In patients with coronary heart disease and hypertension, short-term strenuous physical activity is a triggering factor for an acute coronary event commonly initiated by the rupture of an atherosclerotic plaque.[6,7] Subsequently, an exercise-induced prothrombotic and proinflammatory milieu may contribute to the rapid growth of a coronary thrombus.[8] Whether fitness affects the exercise-induced acute change in proatherogenic factors in hypertension has not been studied. We hypothesized that increases in proinflammatory and prothrombotic activity with exercise are associated with a higher screening MAP and lower fitness level. We further hypothesized that the positive associa-

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tion between MAP and the exercise-induced increase in levels of inflammation and thrombogenesis is less pronounced in fit individuals.

To test the above hypotheses, we measured interleukin (IL)-6, sICAM-1, von Willebrand factor (VWF), and plasminogen activator inhibitor (PAI)-1 in plasma. We selected these molecules because they were previously shown to be increased with elevated BP;[9–11] were predictive of first-time myocardial infarction;[12–15] and, except for PAI-1, were responsive to physical exercise.[16–19] Also, they all define paramount processes in atherosclerosis initiation and progression. Although also having antiinflammatory properties, IL-6 is a potent initiator of the acute-phase response with sympathetic activation.[20] Soluble ICAM-1 reflects the endothelial expression of ICAM-1 that facilitates leukocyte transmigration and thereby vascular inflammation.[21] The VWF mediates platelet adhesion to endothelial lesions; elevated VWF levels reflect a procoagulant state and endothelial activation or damage.[22] High levels of antifibrinolytic PAI-1 give rise to intravascular fibrin accumulation.[23]

Materials and Methods

Study Participants and Screening BP Assessments

This study was approved by the Institutional Review Board of the University of California at San Diego (UCSD). We recruited 66 healthy volunteers from the community who responded to a newspaper advertisement, other printed material (flyers and pamphlets), or word-of-mouth referral. All participants provided written, informed consent to participate in a study on the effects of fitness and exercise on cardiovascular risk in hypertension. Exclusion criteria included history of heart, liver, or renal disease; diabetes; severe asthma; psychosis; and current use of prescribed medication. These were questioned by self-report during the initial screening visit and verified by a history and physical examination performed by a licensed physician. Current pregnancy was verified by human chorionic gonadotropin screening, and obesity was determined by >150% ideal body weight.[24] Signs of heart disease were examined by electrocardiogram (ECG), and signs of liver or renal disease and diabetes were examined by laboratory liver, metabolic, and thyroid panels before a subject's eligibility was determined. If subjects were taking antihypertensive medication, this was tapered, followed by a 3-week washout period, under close monitoring of BP throughout the duration of the study to ensure safety.

Screening BP was measured three times on two separate days, using a Dinamap vital signs monitor (model 845XT; Critikon, Inc., Tampa, FL), and the mean was computed. We applied an appropriately sized cuff and typically allowed 1 min between readings after subject sat resting for approximately 10 min. We used either screening systolic and/or diastolic BP ≥130/85 mm Hg as the partition for the designation of hypertension, corresponding to recently published criteria for the definition of "high normal BP levels."[25] We selected this cutoff because it yielded two reasonably sized groups of subjects with either "normal BP" (n = 40) or "elevated BP" (n = 26), allowing us to meaningfully illustrate continuous associations between MAP and outcome variables.

Exercise Test Procedure

Exercise tests were performed at the UCSD Clinical Trials Center and Pulmonary Function Laboratory by a certified cardiopulmonary technician supervised by a physician. To determine the peak oxygen consumption (VO_{2peak} [mL/kg/min]), subjects underwent a VO_{2peak} test on a treadmill. Termination of the test was based on subjects' indication that they had reached their maximum capacity. The guidelines for verifying obtaining VO_{2peak}, such as perceived exertion, respiratory exchange ratio >1.0, or peak heart rate (HR) similar to an age-predicted maximum (220 bpm − age in years), were used to confirm that VO_{2peak} had been obtained. We applied the standard Bruce protocol, where the speed and grade of the treadmill are increased by 1.7 mph and 10%, respectively, every 3 min. Expired gas was analyzed by use of a Sensormedics metabolic cart (Viasys Healthcare Inc., Conshohocken, PA) equipped with Vmax software (version 6-2A; Viasys Healthcare Inc., Conshohocken, PA), and ECG leads were recorded with Marquette CardioSoft version 3 (GE Medical Systems, Milwaukee, WI). Oxyhemoglobin saturation was monitored with pulse oximetry (Ohmeda; Datex, Louisville, CO). During exercise, BP was assessed by a trained nurse practitioner using a hand sphygmomanometer.

Approximately 1 week after the VO_{2peak} test, subjects returned to the laboratory after having abstained from caffeine, vigorous exercise, alcohol, and smoking for 24 h. A 19-gauge venous forearm catheter was inserted, followed by a supine rest period to establish baseline values for the ECG and BP. After a warm-up period, 20 min of exercise were performed on the treadmill at a calculated (ie, 65–70% VO_{2peak} assessed) steady-state/submaximal intensity. The VO_2 was monitored throughout the steady-state exercise, to maintain the predetermined intensity, and the subjective exertion was also monitored by Borg's 6–20 scale ratings of perceived exertion (RPE). The BP and RPE were recorded every 3 min during exercise. After the 20-min treadmill test, there was a 2-min cool-down phase, during which subjects walked slowly. Blood samples to assess atherosclerotic markers were obtained with the subject in supine position at "baseline" (ie, pre-exercise), "early postexercise" (ie, levels immediately after the 20-min exercise bout), and "late postexercise" (ie, levels 25 min after termination of the exercise bout).

Measurement of Atherosclerotic Markers

Whole blood was drawn into Vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ) containing either EDTA

(for the IL-6 and sICAM-1 assay), buffered sodium citrate 3.8% (for the VWF antigen assay), or buffered sodium citrate supplemented with theophylline, adenosine, and dipyridamole (CTAD) 3.8% (for the PAI-1 antigen assay). The EDTA blood and CTAD blood were spun in a refrigerated centrifuge for 10 min at 2500 × *g*. Sodium citrate blood was spun twice at room temperature for 10 min at 3000 × *g*. Plasma aliquots were stored in polypropylene tubes at −80°C until further analysis. Plasma concentrations of high-sensitivity IL-6 and sICAM-1 (both R&D Systems, Minneapolis, MN) and of VWF and PAI-1 (both Asserachrom Stago, Parsippany, NJ) were determined by ELISA. The lower detection limits of assays were 0.04 pg/mL for IL-6, 0.35 ng/mL for sICAM-1, 1 ng/mL for PAI-1, and 1% for VWF.

There were missing data as following: one sICAM-1 and VWF and 3 IL-6 and PAI-1 values for baseline levels; and 6 IL-6 and PAI-1, 5 sICAM-1, and 4 VWF values for postexercise levels. The intraassay coefficient of variation (CV) was 5.0% for sICAM-1, 13.0% for IL-6, 3.3% for VWF, and 4.7% for PAI-1. The interassay CV was 5.6% for sICAM-1, 8.6% for VWF, and 3.2% for PAI-1. The interassay CV was not assessed for IL-6 because internal control samples were unavailable. The CVs were in accordance with current standards.

Statistical Analyses

Data were analyzed using SPSS version 12.0 for Windows (SPSS, Inc., Chicago, IL). All tests were two-tailed, with $P < .05$. To obtain a normal distribution, IL-6 and VWF values were logarithmically transformed. Log_{10}-transformed IL-6 and VWF values were used for all analyses. Data are given as mean ± SEM of raw values for sICAM-1 and PAI-1, and as geometric means (antilog of the logs' arithmetic mean) ± SEM for IL-6 and VWF. An independent-samples *t*-test and Pearson χ^2 test were applied to investigate group differences in continuous and categorical measures, respectively. Pearson correlations were used to estimate the relationship between 2 continuous variables.

We performed multiple linear regression analyses to determine the independent predictive value of screening MAP, VO_{2peak}, and their interaction for *baseline* (ie, preexercise) levels of each atherosclerotic marker. To build the models, we entered the variables' age, sex, MAP, VO_{2peak}, and the MAP-by-VO_{2peak} interaction in one block into the equations. We applied repeated-measures ANOVA to investigate whether changes in levels of atherosclerotic markers across time points (ie, from baseline to early postexercise and to late postexercise) were significant. Repeated-measures ANCOVA was used to investigate the association of screening MAP, VO_{2peak}, and their interaction with *acute exercise responses* in atherosclerotic markers adjusted for age and sex. This analysis was used when several measurements of the same type were examined on the same subject. Post hoc analysis was performed to identify the direction of a significant interaction between screening MAP and VO_{2peak}, applying Fisher's least significant difference. Assumptions of multiple regression and repeated-measures ANOVA and ANCOVA were met.

Because all the VO_{2peak} used in our data analyses were adjusted for body weight (mL/kg/min) rather than absolute oxygen consumption (L/min), we made no additional adjustments for body mass index (BMI). Because the four atherosclerotic risk markers clearly differ in their biological functions, no statistical adjustment for multiple comparisons was performed.

Results

Subjects' Characteristics

Table 1 presents comparisons of the demographic and cardiovascular characteristics of the 66 subjects categorized into the elevated BP versus normal BP groups. Individuals with elevated BP were older and had a higher BMI compared with those with normal BP. Partly as a consequence of higher weight, individuals with elevated BP also had lower VO_{2peak} (mL/kg/min) than those with normal BP.

Bivariate Associations with Atherosclerotic Markers at Baseline

Subjects with elevated BP had higher levels of PAI-1 (62.6 ± 7.4 ng/mL *v* 39.5 ± 5.4 ng/mL; $P = .013$) and sICAM-1 (283.8 ± 18.3 ng/mL *v* 245.3 ± 9.1 ng/mL; $P = .043$) than the normal BP group. Accordingly, MAP correlated with PAI-1 ($r = 0.30$, $P = .017$) and with sICAM-1 ($r = 0.36$, $P = .003$). Although showing a

Table 1. Characteristics in 66 subjects by blood-pressure categorization

Variable	Elevated blood pressure* (*n* = 26)	Normal blood pressure (*n* = 40)	*P* value
Sex (male/female)	15/11	19/21	.418
Age (y)	46.7 ± 1.5	33.7 ± 1.4	<.001
Screening mean arterial blood pressure (mm Hg)	106 ± 2	85 ± 1	<.001
Body mass index (kg/m^2)	28.4 ± 0.8	24.4 ± 0.7	.001
VO_{2peak} (mL/kg/min)	30.6 ± 1.9	37.5 ± 1.4	.004

VO_{2peak} = peak oxygen consumption during exercise. Analyses were by Student's *t*-test or Pearson χ^2 test. Values are mean ± SEM.
* Screening systolic blood pressure and/or diastolic blood pressure ≥130 mm Hg or ≥85 mm Hg.

Table 2. Multiple linear regression analyses of baseline levels of atherosclerotic risk markers

Predictors entered	IL-6 (pg/mL)	sICAM-1 (ng/mL)	VWF (%)	PAI-1 (ng/mL)
Sex	−0.16 (−0.31/0.15)	−5.50 (−46.5/35.5)	−13.1 (−30.9/11.0)	−38.0 (−55.3/−20.7)*
Age (y)	−0.01 (−0.05/0.05)	−.53 (−3.06/1.99)	0.55 (−1.08/2.18)	−.80 (−1.84/0.23)
MAP (mm Hg)	0.01 (−0.01/0.03)	2.05 (0.20/3.91)†	0.28 (−0.81/1.63)	0.50 (−0.26/1.26)
VO_{2peak} (mL/kg/min)	−0.03 (−0.04/−0.01)†	−1.47 (−3.85/0.90)	−0.26 (−1.87/1.08)	−2.09 (−3.07/−1.11)*
Interaction term	0.00 (−0.00/0.00)	0.10 (−0.13/0.15)	−0.17 (−0.18/0.30)	−0.05 (−0.10/0.01)

IL-6 = interleukin-6; interaction term = MAP-by-VO_{2peak} interaction; MAP = mean arterial blood pressure; PAI-1 = plasminogen activator inhibitor; sICAM-1 = soluble intercellular adhesion molecule-1; VWF = von Willebrand factor.

Dummy coding of 0 and 1 was used for men and women, respectively, for sex. Columns show unstandardized regression coefficient b (slope) with 95% confidence interval (lower limit/upper limit). The regression coefficient b designates the mean amount the dependent variable (ie, each atherosclerotic risk marker) changes when the predictor variable changes by one unit and the other predictors are held constant. Coefficients with confidence intervals are given in raw values for sICAM-1 and PAI-1 and in antilog values for IL-6 and VWF.

* $P < .001$; † $P < .05$.

medium effect size (d) for being higher in subjects with elevated BP than in those with normal BP, the differences in IL-6 (0.99 ± 0.13 pg/mL *v* 0.75 ± 0.10 pg/mL; $P = .15$, $d = 0.39$) and in VWF (130.2% ± 9.8% *v* 111.0% ± 7.6%; $P = .12$, $d = 0.41$) between BP groups were not significant.

The VO_{2peak} showed inverse correlations with IL-6 ($r = -0.31$, $P = .015$) and with PAI-1 ($r = -0.34$, $P = .007$). The VO_{2peak} also showed a trend toward statistical significance for an inverse correlation with sICAM-1 ($r = -0.24$, $P = .056$) but was not significantly associated with VWF.

Independent Predictors of Atherosclerotic Markers at Baseline

Table 2 shows that physical fitness was inversely associated with levels of PAI-1 ($P < .001$) and IL-6 ($P = .016$) and that MAP was directly associated with levels of sICAM-1 ($P = .031$). More precisely, for a 1 mL/kg/min decrease in VO_{2peak}, there were mean increases in PAI-1 of 2.1 ± 0.5 ng/mL, and in IL-6 of 0.03 ± 0.01 pg/mL. Also, there was a mean increase of 2.1 ± 0.9 ng/mL in sICAM-1, with a 1 mm Hg increase in MAP. In addition, male sex was significantly predictive of higher PAI-1 ($P < .001$). Age and the interaction between MAP and VO_{2peak} were not independent predictors of any atherosclerotic marker at baseline (all $P \geq .10$).

Metabolic Responses to 20-Min Exercise

During 20 min of steady-state exercise, the mean MAP was higher in individuals with elevated BP than in normal BP individuals (120 ± 2 mm Hg *v* 96 ± 2 mm Hg; $P < .001$). At the end of the exercise test, the mean respiratory exchange ratio (1.15 ± 0.1 *v* 1.14 ± 0.1; $P = .80$) and percent heart rate (HR) of the age-predicted maximum HR (97.1% ± 1.6% *v* 95.2% ± 1.5%; $P = .42$) were similar in the elevated and normal BP groups. Both groups similarly perceived their mean exertion during the 20-min exercise period as "somewhat hard" (elevated BP group = 13.2 ± 0.3, normal BP group = 13.2 ± 0.3; $P = .99$), indicative of moderate exertion, which was consistent throughout the exercise period.

Atherosclerotic Marker Responses to 20-Min Exercise

In all subjects, repeated-measures ANOVA showed that crude changes across time points were significant for IL-6, sICAM-1, and VWF but not for PAI-1 (Table 3). The following repeated-measures analyses were all adjusted for age and sex (ANCOVA).

Table 3. Change in atherosclerotic risk marker levels with exercise across all subjects

Marker	Baseline	Early postexercise	Late postexercise	*P* (ANOVA)
IL-6 (pg/mL)	0.83 ± 0.08	1.11 ± 0.10*	1.33 ± 0.12*‡	<.001
sICAM-1 (ng/mL)	259.9 ± 9.8	278.1 ± 9.9*	258.9 ± 9.9‡	<.001
VWF (%)	120.2 ± 6.3	119.1 ± 8.0	102.3 ± 7.6†§	.015
PAI-1 (ng/mL)	49.1 ± 4.8	50.5 ± 3.7	46.5 ± 3.6	.48

Data are given as mean ± SEM for sICAM-1 and PAI-1 and as geometric mean ± SEM for IL-6 and VWF. Sample sizes are $n = 60$ for interleukin (IL)-6 and plasminogen activator inhibitor (PAI)-1, $n = 61$ for soluble intercellular adhesion molecule (sICAM)-1, and $n = 62$ for von Willebrand factor (VWF). A significant *P* value for repeated-measures ANOVA indicates a significant change from baseline to early postexercise and to late postexercise values. Post hoc comparisons were made to examine differences in marker values between individual time points.

* $P < 0.001$ and † $P < 0.01$, compared with values at baseline; ‡ $P < 0.001$ and § $P < 0.05$, compared with values at early postexercise.

Interleukin-6 Mean VO_{2peak} was significantly associated with mean IL-6 at all time points ($P = .012$, effect size/partial eta squared [η_p^2] = 0.11). Mean VO_{2peak} showed inverse associations with mean IL-6 at baseline (0.82 ± 0.08 pg/mL; $r = -0.31$, $P = .020$), early postexercise (1.11 ± 0.10 pg/mL; $r = -0.31$, $P = .019$), and late postexercise (1.34 ± 0.34 pg/mL; $r = -0.30$, $P = .026$).

Soluble ICAM-1 Mean screening MAP was significantly associated with mean sICAM-1 levels at all time points ($P = .011$, $\eta_p^2 = 0.11$). Mean screening MAP showed direct associations with mean sICAM-1 at baseline (259.8 ± 9.8 ng/mL; $r = 0.28$, $P = .035$), early postexercise (277.9 ± 9.9 ng/mL; $r = 35$, $P = .007$), and late postexercise (256.9 ± 9.7 ng/mL; $r = 0.35$, $P = .008$).

The interaction between MAP and VO_{2peak} showed a significant association with an exercise-induced change in sICAM-1 across all time points ($P = .047$, $\eta_p^2 = 0.07$). Across all time points, the association between VO_{2peak} and change in sICAM-1 was significant in subjects with normal BP ($P = .024$, $\eta_p^2 = 0.15$) but not in those with elevated BP ($P = .86$, $\eta_p^2 < 0.01$). However, associations between VO_{2peak} and increase in sICAM-1 from baseline to early postexercise (+20.8 ± 5.1 ng/mL; $P = .15$) and between VO_{2peak} and decrease in sICAM-1 from early to late postexercise (−19.8 ± 4.0 ng/mL; $P = .23$) were not significant in the normal BP group.

Plasminogen Activator Inhibitor-1 Mean VO_{2peak} was significantly associated with mean PAI-1 levels at all time points ($P = .001$, $\eta_p^2 = 0.18$). Mean VO_{2peak} showed inverse associations with mean PAI-1 levels at baseline (47.3 ± 4.0 ng/mL; $r = -0.48$, $P < .001$), early postexercise (50.0 ± 3.4 ng/mL; $r = -0.36$, $P = .006$), and, at borderline significance, late postexercise (47.2 ± 3.5 ng/mL; $r = -0.24$, $P = .072$).

The MAP-by-VO_{2peak} interaction showed a significant association with exercise-induced change in PAI-1 across all time points ($P = .004$, $\eta_p^2 = 0.15$). Across all time points, VO_{2peak} was significantly associated with exercise-induced change in PAI-1 in subjects with elevated BP ($P = .004$, $\eta_p^2 = 0.35$) but not in those with normal BP ($P = .73$, $\eta_p^2 < 0.01$). In subjects with elevated BP, there was a significant increase of 1.3 ± 0.6 ng/mL ($P = .045$) in PAI-1 from baseline to early postexercise, with one unit of increase in VO_{2peak}.

von Willebrand Factor Exercise-induced changes in VWF levels across all time points and mean VWF levels at all three time points were similar in subjects with different levels of MAP and VO_{2peak}.

Discussion

We found that MAP was an independent predictor of baseline sICAM-1 and that fitness was an independent predictor of baseline IL-6 and PAI-1. These findings are consistent with the notion that proinflammatory and prothrombotic changes might link poor physical fitness with increased cardiovascular disease mortality over the long term.[3,26,27] Our findings may have clinical relevance. The risk of first-time myocardial infarction was previously increased with increasing quartiles of IL-6 and sICAM-1 concentrations.[12,13] In our group of individuals, second-to-third and third-to-fourth quartile transitions in sICAM-1 levels corresponded with MAP increases of 15 and 18 mm Hg, respectively. Transitions between the second-to-third and third-to-fourth quartiles in IL-6 levels corresponded with decreases in VO_{2peak} of 13 and 18 mL/kg/min, respectively.

Greater fitness did not mitigate the positive relationship between MAP and sICAM-1, suggesting that reduction in inflammation and thrombogenicity occurs with better cardiorespiratory fitness, regardless of BP in our sample. As our groups of individuals had relatively mildly elevated BP, it is possible that this effect of fitness on BP–atherosclerotic marker associations is greater in individuals with severe hypertension. The question remains as to whether a healthy lifestyle, in addition to improving fitness, might help retrain proinflammatory and prothrombotic activity in subjects with elevated BP.

Acute exercise induced significant responses in all subjects in IL-6, sICAM-1, and VWF but not in PAI-1 antigen. Higher MAP was associated with higher sICAM-1, and better fitness was associated with lower IL-6 and PAI-1 at early and late postexercise. Postexercise associations were primarily due to associations of MAP and fitness with baseline levels of atherosclerotic markers. Although MAP and fitness were not individually associated with the magnitude of exercise-induced changes in atherosclerotic markers, there was interaction between MAP and fitness. Contrary to our hypotheses, the interaction between MAP and fitness for sICAM-1 was significant in normotensive subjects, and higher fitness was associated with a PAI-1 increase in hypertensive subjects, suggesting possibly increased cardiovascular risk.[23]

Given the mixed findings in previous studies, these rather unexpected findings should be interpreted with caution. For instance, the VWF response to exercise increased with physical conditioning[28] and was also greater in physically fit than in sedentary individuals.[29] Instead of inferring cardiovascular harm, previous investigators proposed that fitness might physiologically increase endothelial turnover,[29] thereby enhancing the endothelial release of VWF and endothelial antifibrinolytic properties.[28] Unfortunately, we did not measure indicators of fibrinolytic activity above and beyond PAI-1 antigen. Information on the activities of tissue-type plasminogen activator and PAI-1 could have created a more definite picture of overall fibrinolytic activity in our study.[30] Because fitness was also not significantly associated with greater exercise responses in VWF, sICAM-1, and IL-6, we offer a careful interpretation of our exercise data. In spite of good fitness, subjects with elevated BP may not necessarily be protected from short-term, exercise-induced hypercoagulability, a possible con-

tributing factor to the clinical manifestation of acute coronary thrombosis as triggered by exercise bouts.[8]

Our study had several strengths and limitations. Subjects were in good health and unmedicated, so that confounding of levels of atherosclerotic markers was minimized. Moreover, cardiovascular fitness was assessed by a standardized method. However, a retrospective power analysis showed that the differences in baseline IL-6 and VWF levels between BP groups and the association between VO_{2peak} and baseline sICAM-1 in all subjects would only have been statistically significant if we had roughly doubled the sample size. We did not use 24-h BP monitoring to approximate the "real" screening BP, and subjects were not explicitly instructed to refrain from alcohol and coffee before BP screening, so a bias in MAP measurements could have influenced our results. Our findings may not generalize to subjects with more severe hypertension, elderly hypertensive patients, and hypertensive patients with very poor physical fitness.

In conclusion, we found independent associations of higher screening MAP and poorer physical fitness with higher baseline levels of markers of a proinflammatory and prothrombotic state. The exaggerated increase in PAI-1 from baseline to early postexercise in physically fit hypertensive subjects suggests that fitness alone may not readily protect those with elevated screening BP from potentially harmful cardiovascular responses to exercise.

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